Diglycidyl resorcinol ether (DGRE)

Health based calculated occupational cancer risk values

Aanbiedingsbrief

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Dutch Expert Committee on Occupational Standards,
a committee of the Health Council of the Netherlands

to

the Minister and State Secretary of Social Affairs and Employment

No. 1999/09OSH, The Hague, 20 December 1999

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Samenvatting

Op verzoek van de Minister van Sociale Zaken en Werkgelegenheid schat de Commissie WGD van de Gezondheidsraad het extra kankerrisico bij beroepsmatige blootstelling aan stoffen die door de Europese Unie of door de Commissie WGD als genotoxisch kankerverwekkend zijn aangemerkt. In dit rapport bekijkt zij of zo'n schatting mogelijk is voor diglycidyl resorcinol ether. Zij heeft daarbij gebruik gemaakt van de methode die is beschreven in het rapport 'Berekening van het risico op kanker' (1995/06WGD) (Hea95).

De commissie is echter van mening dat wegens een gebrek aan voldoende gegevens het niet mogelijk is om het extra kankerrisico voor diglycidyl resorcinol ether te berekenen.

Executive summary

On request of the Minister of Social Affairs and Employment the Dutch Expert Committee on Occupational Standards (DECOS), a committee of the Health Council of the Netherlands, estimates the additional cancer risk associated with occupational exposure to substances that have been classified by the European Union or the DECOS as genotoxic carcinogen. In this report the committee studies if such estimates can calculated for diglycidyl resorcinol ether. It has used the method described in the report 'Calculating cancer risks due to occupational exposure to genotoxic carcinogens' (1995/06WGD) (Hea95).

The committee is of the opinion that due to a lack of sufficient data, it is not possible to estimate the additional cancer risk for diglycidyl resorcinol ether.

Chapter 1

Scope

1.1 Background

In the Netherlands, occupational exposure limits for chemical substances are set using a three-step procedure. In the first step, a scientific evaluation of the data on the toxicity of the substance is made by the Dutch Expert Committee on Occupational Standards (DECOS), a committee of the Health Council of the Netherlands, on request of the Minister of Social Affairs and Employment (annex A). This evaluation should lead to a health-based recommended exposure limit for the concentration of the substance in air. Such an exposure limit cannot be derived if the toxic action cannot be evaluated using a threshold model, as is the case for substances with genotoxic carcinogenic properties.

In this case an exposure-response relationship is recommended for use in regulatory standard setting, ie. the calculation of so-called health-based calculated occupational cancer risk values (HBC-OCRVs). The committee calculates HBC-OCRVs for compounds which are classified as genotoxic carcinogens by the European Union or by the present committee.

For the establishment of the HBC-OCRV's the committee generally uses a linear extrapolation method, as described in the committee's report 'Calculating cancer risk due to occupational exposure to genotoxic carcinogens' (1995/06WGD). The linear model to calculate occupational cancer risk is used as a default method, unless scientific data would indicate that using this model is not appropriate.

In the next phase of the three-step procedure, the Social and Economic Council advises the Minister of Social Affairs and Employment on the feasibility of using the

HBC-OCRVs as regulatory occupational exposure limits. In the final step of the procedure the Minister sets the official occupational exposure limits.

1.2 Committee and procedure

The present document contains the derivation of HBC-OCRV's by the committee for diglycidyl resorcinol ether. The members of the committee are listed in Annex B. The first draft of this report was prepared by H Stouten and MI Willems, from the TNO Nutrition and Food Research Institute in Zeist, by contract with the Ministry of Social Affairs and Employment.

Chapter 2

Diglycidyl resorcinol ether (DGRE)

2.1 Introduction

Diglycidyl resorcinol ether (DGRE) has been classified as a genotoxic carcinogen by DECOS (DEC95).

This evaluation of the carcinogenicity and other toxic effects of diglycidyl resorcinol ether has been based on the reviews by the DFG (Gre95), Gardiner *et al* (Gar92; prepared under the auspices of the US Society of the Plastics Industry, Inc, Epoxy Resin Systems Task Group), and IARC (IARC85). Where relevant, the original publications were reviewed as indicated in the text. In addition, literature was retrieved from the online data bases Chemical Abstracts, Cancerlit, Toxline, and Medline, covering the period 1963-67 to December1995-January 1996.

2.2 Identity and physical and chemical properties*

Chemical name	:	Diglycidyl resorcinol ether
CAS registry number	:	101-90-6
CAS name	:	oxirane, 2,2[1]-[1,3-phenylenebis (oxymethylene)]bis-
EEC number	:	603-065-00-9
EINECS number	:	202-987-5
Synonyms	:	meta-bis(2,3-epoxypropoxy)benzene; 1,3-bis-(2,3-epoxypropoxy)benzene; 1,3 diglycidyloxybenzene; NCI-C54966; 1,3-di-(2,3-epoxypropoxy)benzol; 1,3-bis-(2,3-epoxy-propoxy)benzol, 1,3-diglycidyl-oxybenzol; resorcin-bis- (2,3-epoxypropyl)ether; resorcindiglycidylether; araldite ERE 1359
Abbreviation	:	DGRE
Description	:	straw-yellow liquid
Molecular formula	:	$C_{12}H_{14}O_4$
Structure	:	

Molecular weight	:	222.26
Boiling point (0.1 kPa)	:	172ºC
Melting point	:	32ºC
Relative density (25ºC)	:	1.21
Vapour pressure (20ºC)	:	(very low)
Flash point	:	176ºC(open cup)
Solubility in organic solvents	:	miscible with acetone, chloroform, methanol, benzene, and most organic resins
Conversion factors (25ºC, 101.3 kPa)	:	1 ppm = 9.22 mg/m^3 1 mg/m^3 = 0.109 ppm
EEC labeling	:	R: 23/24/25-40-43 S: (1/2-)23-24-25
EEC classification	:	concentration $\geq$ 1%: T; R 23/24/25-40-43 0.1% $\geq$ concentration > 1%: Xn; R 20/21/22

* data from CEG93; Gre95; IARC 1985

2.3 Carcinogenicity studies and selection of study suitable for risk estmation in the occupational situation

The carcinogenicity of DGRE has been evaluated by DFG (Gre95), Gardiner *et al* (Gar92), and IARC (IARC85). No additional data were located.

There were no data from human epidemiological studies. The animal carcinogenicity studies are summarized in Table 1 (annex D).

There were no inhalation carcinogenicity studies available. NTP has examined the carcinogenicity of DGRE in rats and mice. Administration of DGRE in the diet induced squamous cell papillomas and carcinomas in the forestomach of both species. The lowest dose inducing a statistically significant increase in forestomach tumours was 12 mg/kg bw in rats. At this dose, the combined (males plus female) incidences of forestomach squamous cell carcinomas amounted to 66/100. There was no effect on body weight, but male rats had a lower survival rate (46%) than control animals (78%) at w 104. This group of rats receiving 12 mg/kg bw/d was added as a supplementary group to the study one year after the start of the original study because of excessive mortality (50/50 male, 48/50 female dead by week 68-70) in the 50 mg/kg bw group.

In mice, forestomach lesions morphologically similar to those in rats were found at higher dose levels (50, 100 mg/kg bw/d). Treatment did not affect survival rates and only the female mice of the high dose group had significantly lower body weights (from w 20) (Gar92; Kri90).

These studies clearly showed the carcinogenic properties of DGRE. However, only local and no systemic tumours were induced. Therefore, these studies are considered inappropriate for a quantitative extrapolation to an inhalation health-based occupational cancer risk value.

2.4 Existing occupational exposure limits

No occupational exposure limits are listed for DGRE in The Netherlands, Sweden, the UK and the USA (ISZW99). In Germany, DGRE has been classified as an A2 carcinogen and as a sensitizing compound. The A2 carcinogens are not assigned an occupational exposure limit, but a so-called TRK (“Technische Richtkonzentration”, i.e., a concentration feasible with currently technical means). However, no TRK has been established for DGRE (DFG96).

2.5 Toxicity profile of diglycidyl resorcinol ether

The toxicity of DGRE has been reviewed in 1992 by DFG (Gre95) and a task group of the US Society of Plastics Industry (Gar92).

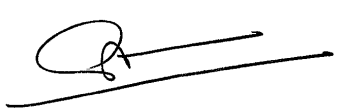
Severe skin irritation and cases of sensitization have been reported to occur in humans. Severe skin and eye irritation was found in rabbits, but in some of the tests, the use of xylene as a solvent of the test material may have influenced the results.

Oral LD_{50}'s were 2570, 980, and 1240 mg/kg bw for rats, mice, and rabbits, respectively, intraperitoneal LD_{50}'s were 178 and 243 for rats and mice, respectively. No deaths were found in rats and mice following an eight-hour exposure to a saturated vapour; rats died within five days following a four-hour exposure to a concentrated aerosol of 44.8 g DGRE (60% in xylene)/m^3. The dermal LD_{50} was 2.0 ml/kg (60% in xylene) for rabbits when applied under not-occluded conditions; when remaining in continuous contact the dermal LD_{50} was 0.64 ml/kg.

Apart from eye irritation, no effects (mortality, body weight, haematology, histology) were observed in male rats exposed to saturated vapours, 7 h/d, 5 d/w, for 10 w.

Subacute (14 d) and semichronic (13 w) oral studies in rats and mice preceded the two-year carcinogenicity study presented in table 1 (annex C). In the subacute study (dose range: rats: 190-3000, mice: 90-1500 mg/kg bw/d), body weights were depressed in all treated rats and mice (except at 190 mg/kg bw/d). At higher doses (rats: >380, mice: >750 mg/kg bw/d), partial to complete mortality occurred. At gross examination, lesions of the stomach and renal medulla were observed, with papillary growths in the stomach of many of the surviving treated rats. In the subchronic study (dose range: rats: 12.5-200, mice: 25-400 mg/kg bw/d), the most critical effect was the presence of lesions in the nonglandular stomach (inflammation, ulceration, squamous cell papillomas, hyperkeratosis, basal cell hyperplasia) at doses >12.5 and >25 mg/kg bw/d for rats and mice, respectively. These effect levels are similar to those inducing forestomach squamous cell carcinomas following administration of DGRE for two years.

The Hague, 20 December 1999,
for the committee



dr ASAM van der Burght,
scientific secretary

chairman

References

CEG93 Commissie van de Europese Gemeenschappen (CEG). In: Bijlage bij Richtlijn 93/72/EEG van de Commissie van 1 september tot negentiende aanpassing aan de vooruitgang van de techniek van Richtlijn 67/543/EEG van de Raad betreffende de aanpassing van de wettelijke en bestuursrechtelijke bepalingen inzake de indeling, de verpakking en het kenmerken van gevaarlijke stoffen (vervolg). Maastricht, The Netherlands: Ellis Publications, 1993: 693 (Publicatieblad van de Europese Gemeenschappen L258A, deel I).

DEC95 Dutch Expert Committee on Occupational Standards. Scientific documents on the Dutch list of occupational Carcinogens (I). The Hague, The Netherlands: Sdu Servicecentrum Uitgeverijen, 1995; rep no RA 1/95

DFG96 Deutsche Forschungsgemeinschaft (DFG): Senatskommission zur Prüfung gesundheitsschädlicher Arbeitsstoffe. MAK- und BAT-Werte-Liste 1996. Maximale Arbeitsplatzkonzentrationen und biologische Arbeitsstofftoleranzwerte. Weinheim, FRG: VCH Verlagsgesellschaft mbH, 1996: 48, 108 (Mitteilung 32).

Gar92 Gardiner TH, Waechter JM Jr, Wiedow MA, *et al*. Glycidyloxy compounds used in epoxy resin systems: a toxicology review. Regul Toxicol Pharmacol 1992; 15: S1-S77.

Gre95 Greim H, ed. Diglycidylresorcinether. In: Gesundheitsschädliche Arbeitsstoffe. Toxikologisch-arbeitsmedizinische Begründungen von MAK-Werten (Maximale Arbeitsplatz-Konzentrationen). 1st-21th ed. Weinheim, FRG: VCH Verlagsgesellschaft mbH, 1995.

Hea95 Health Council of the Netherlands, Dutch Expert Committee on Occupational Standards (DECOS). Calculating cancer risks, THe HAgue, The Netherlands. 1995; pub no 1995/06 WGD.

IARC85 International Agency for Research on Cancer (IARC). Diglycidyl resorcinol ether. In: Allyl compounds, aldehydes, epoxides and peroxides. Lyon, France: IARC, 1985: 181-8 (IARC monographs on the evaluation of the carcinogenic risk of chemicals to humans; Vol 36).

ISZW99 Inspectiedienst van het Ministerie van Sociale Zaken en Werkgelegenheid (I-SZW). De nationale MAC-lijst 1999. The Hague, The Netherlands: Sdu Servicecentrum Uitgeverijen, 1999.

Kri90 Krishna Murthy AS, McConnell EE, Huff JE, *et al*. Forestomach neoplasms in Fischer F344/N rats and B6C3F$_1$ mice exposed to diglycidyl resorcinol ether - an epoxy resin. Food Chem Toxicol 1990; 10: 723-9.

A Request for advice

B The committee

C Comments on the public draft

D Animal 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

- GJ Mulder, *chairman*
  professor of toxicology; Leiden University, Leiden
- RB Beems
  toxicologic pathologist; National Institute of Public Health and the Environment, Bilthoven
- PJ Borm
  toxicologist; Heinrich Heine Universität Düsseldorf (Germany)
- JJAM Brokamp, *advisor*
  Social and Economic Council, The Hague
- VJ Feron,
  professor of toxicology; TNO Nutrition and Food Research Institute, Zeist
- DJJ Heederik
  epidemiologist; Wageningen University, Wageningen
- LCMP Hontelez, *advisor*
  Ministry of Social Affairs and Employment, The Hague
- G de Jong
  occupational physician; Shell International Petroleum Maatschappij, The Hague
- J Molier-Bloot
  occupational physician; BMD Akers bv, Amsterdam
- IM Rietjens
  professor in Biochemical toxicology; Wageningen University, Wageningen.

- H Roelfzema, *advisor*
  Ministry of Health, Welfare and Sport, Den Haag
- T Smid
  occupational hygienist; KLM Health Safety & Environment, Schiphol and professor of working conditions, Free University, Amsterdam
- GMH Swaen
  epidemiologist; Maastricht University, Maastricht
- HG Verschuuren
  toxicologist; DOW Europe, Horgen (Switzerland)
- AAE Wibowo
  toxicologist; Coronel Institute, Amsterdam
- F de Wit
  occupational physician; Labour Inspectorate, Arnhem
- CA Bouwman, *scientific secretary*
  Health Council of the Netherlands, Den Haag
- ASAM van der Burght, *scientific secretary*
  Health Council of the Netherlands, Den Haag

The first draft of the present advisory report was prepared by H Stouten and M Willems, from the Department of Occupational Toxicology of the TNO Nutritionand Food Research Institute, by contract with the Ministry of Social Affairs and Employment.

Secretarial assistance: E Vandenbussche-Parméus.
Lay-out: J van Kan.

Annex **C**

Comments on the public draft

A draft of the present report was relased in 1999 for public review. The following organisations and persons have commented on the draft document:

- mr A Aalto, Tampere, Finland

Annex **D**

Animal studies

Table1 Carcinogenicity studies with diglycidyl resorcinol ether (data from Gar92, Gre95, or IARC85, unless otherwise indicated).

authors	species/route	experimental	findings, tumours	remark
NTP (Kri90)	rat (F344; male/female; n=50/sex/ group) oral (diet)	0, 12, 25, 50 mg/kg bw/d, 7 d/w, 103 w	primary lesions limited to forestomach: hyperkeratosis, hyperplasia, neoplasms: squamous cell papillomas: *male*: 16/50, 17/50, 6/49 vs 0/100; *female*: 19/50, 7/50, 1/50 vs 0/99; squamous cell carcinomas: *male*: 39/50, 38/50, 4/49 vs 0/100; *female*: 27/50, 34/50, 3/50 vs 0/99 no treatment-related tumours were found in other tissues/organs	purity: 88% (contained 30 mainly unidentified impurities; major impurity: 2.8% dihydroxypropoxybenzene) because of increased mortality in high dose group, supplementary groups (0 and 12 mg/kg bw/d) started 1 y after starting the other groups all males and 48/50 females of the high dose group dead by 68-70 w (main cause: broncho-pneumonia), survival rates in other groups (12, 25 mg/kg bw/d): male: 23/50, 5/50 vs 42/50; female: 39/50, 15/50 vs 36/100; decreased body weights in mid and high dose groups

Continuation *table 1*.

authors	species/route	experimental	findings, tumours	remark
NTP (Kri90)	mouse ($B6C3F_1$; male/female; n=50/sex/group) oral (diet)	0, 50, 100 mg/kg bw/d, 7 d/w, 103 w	primary lesions: hyperkeratosis, hyperplasia and neoplasms of forestomach (morphologically similar to those in rats): squamous cell papillomas: *male:* 4/49, 10/50 vs 0/47; *female:* 5/49, 10/49 vs 0/47; squamous cell carcinomas: *male*: 14/49, 25/50 vs 0/47; *female*: 12/49, 23/49 vs 0/47 other: hepatocellular neoplasms: *female*: 1/49, 8/49 vs 3/47	purity: 88% (impurities: see above) no difference in survival between treated and control animals; decreased body weights in all treatment groups
Van Duuren *et al*, 1965	mouse (Swiss-Mellerton; female; n=30) dermal	100 mg of a 1% solution in benzene, 3 times/w, 70 w	no skin tumours induced	control groups included; median survival time: DGRE-treated group: 70 w; benzene-treated control group: 71 w ; untreated control group: 63 w; moderate to severe crusting and/or scaring, hair loss at application site
Kettering Lab, 1958	mouse (C3H; ?; ?) dermal	50 mg of a 5% solution in methyl ethyl ketone, 2 times/w, for life	at w 36: a benign papiloma in one mouse that survived for another 15 w; at w 48: subdermal growth which proved to be a squamous cell cancer in another mouse	purity: 81% apparently, no control group included median survival time: 46 w
Kotin/Falk, 1963	mouse (C57/B1; ?; n=30) dermal	16.6 mg /kg, 3 times/w	a skin tumour in 1/14 mice that survived for 8 mo	