CLH report

Proposal for Harmonised Classification and Labelling

**Based on Regulation (EC) No 1272/2008 (CLP Regulation),
Annex VI, Part 2**

International Chemical Identification:

1,3-bis(2,3-epoxypropoxy)benzene; resorcinol diglycidyl ether

EC Number: **202-987-5**

CAS Number: **101-90-6**

Index Number: **603-065-00-9**

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Note on confidential information

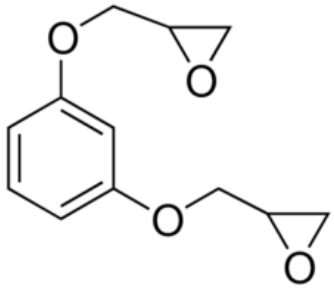
Please be aware that this report is intended to be made publicly available. Therefore it should not contain any confidential information. Such information should be provided in a separate confidential Annex to this report, clearly marked as such.

CONTENTS

1 IDENTITY OF THE SUBSTANCE

1.1 Name and other identifiers of the substance

Table 1: Substance identity and information related to molecular and structural formula of the substance

Name(s) in the IUPAC nomenclature or other international chemical name(s)	1,3-bis(2,3-epoxypropoxy)benzene
Other names (usual name, trade name, abbreviation)	1,3-diglycidyloxybenzene; m-bis(2,3-epoxypropoxy)benzene; 2,2'-(1,3-phenylenebis(oxymethylene))bisoxirane; resorcinol diglycidyl ether; DGRE
ISO common name (if available and appropriate)	-
EC number (if available and appropriate)	202-987-5
EC name (if available and appropriate)	Resorcinol diglycidyl ether
CAS number (if available)	101-90-6
Other identity code (if available)	-
Molecular formula	$C_{12}H_{14}O_4$
Structural formula	
SMILES notation (if available)	-
Molecular weight or molecular weight range	222.2
Information on optical activity and typical ratio of (stereo) isomers (if applicable and appropriate)	Not applicable
Description of the manufacturing process and identity of the source (for UVCB substances only)	Not applicable
Degree of purity (%) (if relevant for the entry in Annex VI)	Not applicable

1.2 Composition of the substance

Table 2: Constituents (non-confidential information)

Constituent (Name and numerical identifier)	Concentration range (% w/w minimum and maximum in multi-constituent substances)	Current CLH in Annex VI Table 3.1 (CLP)	Current self-classification and labelling (CLP)
Resorcinol diglycidyl ether	Not applicable	Acute Tox. 4* (H302) Acute Tox. 4* (H312) Skin Irrit. 2 (H315) Eye Irrit. 2 (H319) Skin Sens. 1 (H317) Muta. 2 (H341) Carc. 2 (H351) Aquatic Chronic 3 (H412)	Acute Tox. 4 (H302) Acute Tox. 4 (H312) Skin Irrit. 2 (H315) Eye Irrit. 2 (H319) Skin Sens. 1 (H317) Muta. 2 (H341) Carc. 2 (H351) Aquatic Chronic 3 (H412)

Table 3: Impurities (non-confidential information) if relevant for the classification of the substance

Impurity (Name and numerical identifier)	Concentration range (% w/w minimum and maximum)	Current CLH in Annex VI Table 3.1 (CLP)	Current self-classification and labelling (CLP)	The impurity contributes to the classification and labelling
No information				

Table 4: Additives (non-confidential information) if relevant for the classification of the substance

Additive (Name and numerical identifier)	Function	Concentration range (% w/w minimum and maximum)	Current CLH in Annex VI Table 3.1 (CLP)	Current self-classification and labelling (CLP)	The additive contributes to the classification and labelling
No information					

Table 5: Test substances (non-confidential information)

Identification of test substance	Purity	Impurities and additives (identity, %, classification if available)	Other information	The study(ies) in which the test substance is used
Resorcinol diglycidyl ether	81%	No information		NTP 1986; Krishna-Murthy et al., 1990
Resorcinol diglycidyl ether	Not specified	No information		Hine et al., 1958; Westrick and Gross (1960), as cited in Gardiner et al., 1992; Van Duuren et al., 1965;

Identification of test substance	**Purity**	**Impurities and additives (identity, %, classification if available)**	**Other information**	**The study(ies) in which the test substance is used**
				Kotin and Falk, 1963; McCammon et al., 1957;
Resorcinol diglycidyl ether	Not specified	No information	Xylene (Acute Tox. 4* (H312); Acute Tox. 4* (H332)) is used as vehicle for dermal and inhalation testing	Westrick and Gross (1960), as cited in Gardiner et al., 1992

2 PROPOSED HARMONISED CLASSIFICATION AND LABELLING

2.1 Proposed harmonised classification and labelling according to the CLP criteria

Table 6:

	Index No	International Chemical Identification	EC No	CAS No	Classification		Labelling			Specific Conc. Limits, M-factors, ATE	Notes
					Hazard Class and Category Code(s)	Hazard statement Code(s)	Pictogram, Signal Word Code(s)	Hazard statement Code(s)	Suppl. Hazard statement Code(s)		
Current Annex VI entry	603-065-00-9	m-bis(2,3-epoxypropoxy)benzene; resorcinol diglycidyl ether	202-987-5	101-90-6	Acute Tox. 4* Acute Tox. 4* Skin Irrit. 2 Eye Irrit. 2 Skin Sens. 1 Muta. 2 Carc. 2 Aquatic Chronic 3	H302 H312 H315 H319 H317 H341 H351 H412	GHS08 GHS07 Wng	H302 H312 H315 H319 H317 H341 H351 H412			
Dossier submitters proposal	603-065-00-9	m-bis(2,3-epoxypropoxy)benzene; resorcinol diglycidyl ether	202-987-5	101-90-6	**Modify** Acute Tox. 4 Acute Tox. 3 Carc. 1B	**Modify** H302 H311 H350	**Add** GHS06 Dgr **Remove** GHS07 Wng	**Modify** H302 H311 H350		ATE-oral: 980 mg/kg bw ATE-dermal: 744 mg/kg bw	
Resulting Annex VI entry if agreed by RAC and COM	603-065-00-9	m-bis(2,3-epoxypropoxy)benzene; resorcinol diglycidyl ether	202-987-5	101-90-6	**Acute Tox. 4** **Acute Tox. 3** Skin Irrit. 2 Eye Irrit. 2	**H302** **H311** H315 H319	GHS08 GHS06 Dgr	**H302** **H311** H315 H319		ATE-oral: 980 mg/kg bw ATE-dermal: 744 mg/kg bw	

					Skin Sens. 1 Muta. 2 **Carc. 1B** Aquatic Chronic 3	H317 H341 **H350** H412		H317 H341 **H350** H412			

In **bold:** the classifications that are proposed to be changed

Table 7: Reason for not proposing harmonised classification and status under public consultation

Hazard class	Reason for no classification	Within the scope of public consultation
Explosives	hazard class not assessed in this dossier	No
Flammable gases (including chemically unstable gases)	hazard class not assessed in this dossier	No
Oxidising gases	hazard class not assessed in this dossier	No
Gases under pressure	hazard class not assessed in this dossier	No
Flammable liquids	hazard class not assessed in this dossier	No
Flammable solids	hazard class not assessed in this dossier	No
Self-reactive substances	hazard class not assessed in this dossier	No
Pyrophoric liquids	hazard class not assessed in this dossier	No
Pyrophoric solids	hazard class not assessed in this dossier	No
Self-heating substances	hazard class not assessed in this dossier	No
Substances which in contact with water emit flammable gases	hazard class not assessed in this dossier	No
Oxidising liquids	hazard class not assessed in this dossier	No
Oxidising solids	hazard class not assessed in this dossier	No
Organic peroxides	hazard class not assessed in this dossier	No
Corrosive to metals	hazard class not assessed in this dossier	No
Acute toxicity via oral route	**harmonised classification proposed**	**Yes**
Acute toxicity via dermal route	**harmonised classification proposed**	**Yes**
Acute toxicity via inhalation route	**conclusive but not sufficient for classification**	**Yes**
Skin corrosion/irritation	hazard class not assessed in this dossier	No
Serious eye damage/eye irritation	hazard class not assessed in this dossier	No
Respiratory sensitisation	hazard class not assessed in this dossier	No
Skin sensitisation	hazard class not assessed in this dossier	No
Germ cell mutagenicity	hazard class not assessed in this dossier	No
Carcinogenicity	**harmonised classification proposed**	**Yes**
Reproductive toxicity	hazard class not assessed in this dossier	No
Specific target organ toxicity-single exposure	hazard class not assessed in this dossier	No
Specific target organ toxicity-repeated exposure	hazard class not assessed in this dossier	No
Aspiration hazard	hazard class not assessed in this dossier	No
Hazardous to the aquatic environment	hazard class not assessed in this dossier	No
Hazardous to the ozone layer	hazard class not assessed in this dossier	No

3 HISTORY OF THE PREVIOUS CLASSIFICATION AND LABELLING

Resorcinol diglycidyl ether has previously been assessed for harmonised classification by TC C&L. Resorcinol diglycidyl ether has an Annex VI entry as Acute Tox. 4* (H302), Acute Tox. 4* (H312), Skin Irrit. 2 (H315), Eye Irrit. 2 (H319), Skin Sens. 1 (H317), Muta. 2 (H341), Carc. 2 (H351), Aquatic Chronic 3 (H412).

Resorcinol diglycidyl ether is not registered under REACH (February 2018).

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 (IARC, 1985+1999). IARC classified resorcinol diglycidyl ether (technical grade) as possibly carcinogenic to humans (Group 2B).

4 JUSTIFICATION THAT ACTION IS NEEDED AT COMMUNITY LEVEL

[B.] Justification that action is needed at Community level is required.

Reason for a need for action at Community level:

Change in existing entry due to changes in the criteria

Further detail on need of action at Community level

The Health Council of the Netherlands published an evaluation of this substance in 1995 and concluded that resorcinol diglycidyl ether should be regarded as a genotoxic carcinogen (Health Council of the Netherlands, 1995). In 1999, it further concluded that the carcinogenicity studies were inappropriate for a quantitative extrapolation for an inhalation based occupational cancer risk value (Health Council of the Netherlands, 1999).

In 2016, the Health Council performed a re-evaluation of the mutagenic and carcinogenic properties of resorcinol diglycidyl ether. In this re-evaluation, the Health Council concluded that resorcinol diglycidyl ether is suspected to be carcinogenic to man and recommended to classify this substance in category 1B. Furthermore, they recommended classifying resorcinol diglycidyl ether as germ cell mutagen in category 2. They considered that the substance acts by a stochastic genotoxic mechanism (Health Council of the Netherlands, 2016).

This 2016 re-evaluation by the Health Council forms the basis for the current proposal for an update of the harmonised classification of resorcinol diglycidyl ether from Cat. 2 to Cat. 1B (H350) for carcinogenicity, taking into account that the criteria under CLP for carcinogenicity are slightly different than under DSD.

Further, the current CLP classification is based on a translation of the harmonised classification under DSD. As a result, the current classification for acute toxicity (oral and dermal) considers a minimum classification.

This CLH proposal is therefore limited to these hazard classes.

Sub-categorisation was considered for Skin Sens. 1. However, the available data did not allow differentiation between category 1A and 1B.

5 IDENTIFIED USES

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.

6 DATA SOURCES

This CLH report is based on a recent report of the Health Council of the Netherlands (2016), "Resorcinol diglycidyl ether. Evaluation of the carcinogenicity and genotoxicity", No. 2016/03, The Hague, February 29, 2016. Starting point of their report was the monograph of the International Agency for Research on Cancer (IARC). Other sources as cited in the text and tables are mentioned in the reference list.

7 PHYSICOCHEMICAL PROPERTIES

Table 8: Summary of physicochemical properties

Property	Value	Reference	Comment (e.g. measured or estimated)
Physical state at 20°C and 101,3 kPa	Straw yellow liquid		
Melting point	32-33 °C	DFG 1992	
Boiling point	172 °C	IARC 1985	
Relative density	1.21	ICSC 1991	
Vapour pressure	Low, $4x10^{-5}$ mm Hg at 25 °C	NTP 2011	
Surface tension	-		
Water solubility	Insoluble in water	Chemiekaarten 2017	
Partition coefficient n-octanol/water	No experimental data (1.23 calculated)		
Flash point	177 °C (open cup)	ICSC 1991	
Flammability			
Explosive properties	Reacts with strong oxidants; presumed to perform explosive peroxides	ICSC 1991	
Self-ignition temperature	-		
Oxidising properties	-		
Granulometry	-		
Stability in organic solvents and identity of relevant degradation products	-		
Dissociation constant	-		
Viscosity	-		

8 EVALUATION OF PHYSICAL HAZARDS

This hazard class has not been evaluated.

9 TOXICOKINETICS (ABSORPTION, METABOLISM, DISTRIBUTION AND ELIMINATION)

9.1 Short summary and overall relevance of the provided toxicokinetic information on the proposed classification(s)

Only limited information on the toxicokinetics of resorcinol diglycidyl ether is available. One study was retrieved.

In a study by Seiler (1984a), 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). 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. No bis-epoxide or diol-epoxide was excreted 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 via the diol-epoxide to the inactive bis-diol substance.

10 EVALUATION OF HEALTH HAZARDS

Acute toxicity

10.1 Acute toxicity - oral route

Table 9: Summary table of animal studies on acute oral toxicity

Method, guideline, deviations if any	Species, strain, sex, no/group	Test substance,	Dose levels, duration of exposure	Value LD_{50}	Reference
Non-guideline, non-GLP	Rat, Long-Evans, male Number of animals/group not specified	Resorcinol diglycidyl ether; propylene glycol was used as vehicle where necessary for ease of administration Intragastric administration	Single exposure, (except for highest dose*); Dose levels not specified; 10-day postexposure observation period	2570 mg/kg bw	Hine et al., 1958 Klimisch score: 2
Non-guideline, non-GLP	Mouse, Webster, male Number of animals/group not specified	Resorcinol diglycidyl ether; propylene glycol was used as vehicle where necessary for ease of administration Intragastric administration	Single exposure; Dose levels not specified; 10-day postexposure observation period	980 mg/kg bw	Hine et al., 1958 Klimisch score: 2
Non-guideline, non-GLP	Rabbit, albino, male	Resorcinol diglycidyl ether;	Single exposure; Dose levels not	1240 mg/kg bw	Hine et al., 1958

Method, guideline, deviations if any	Species, strain, sex, no/group	Test substance,	Dose levels, duration of exposure	Value LD_{50}	Reference
	Number of animals/group not specified	propylene glycol was used as vehicle where necessary for ease of administration Intragastric administration	specified; 10-day postexposure observation period		Klimisch score: 2

** because of the large volume of the highest intragastric dose for rats, the suspension was given in two aliquots, three hours apart, to fasted animals*

10.1.1 Short summary and overall relevance of the provided information on acute oral toxicity

An acute toxicity study via the oral route was conducted in three species, i.e. Long-Evans rat, Webster mouse, and Albino rabbit (Hine et al., 1958). Resorcinol diglycidyl ether was administered via intragastric application. The resultant LD_{50} values were 2570, 980, 1240 mg/kg bw, respectively. In addition to lethality, there was moderate depression, slight dyspnea, and in surviving animals loss of weight and diarrhea observed.

10.1.2 Comparison with the CLP criteria

The LD_{50} value of the rat study (i.e. 2570 mg/kg bw) is outside the border for Acute oral Category 4 of 300-2000 mg/kg bw. The LD_{50} values of the mouse and rabbit studies (i.e. 980 and 1240 mg/kg bw, respectively) fall within the range for Acute oral Category 4 of 300-2000 mg/kg bw. This warrants classification as Acute Tox. 4.

The lowest LD_{50} of 980 mg/kg bw is suggested as ATE for acute oral toxicity.

10.1.3 Conclusion on classification and labelling for acute oral toxicity

Classification of resorcinol diglycidyl ether for acute toxicity via the oral route as Acute Tox. 4 (H302: Harmful if swallowed) is required.

It is proposed to assign an ATE of 980 mg/kg bw for acute oral toxicity.

10.2 Acute toxicity - dermal route

Table 10: Summary table of animal studies on acute dermal toxicity

Method, guideline, deviations if any	Species, strain, sex, no/group	Test substance,	Dose levels duration of exposure	Value LD_{50}	Reference
Non-guideline, non-GLP	Rabbit, strain and sex not specified Number of animals/group not specified	Resorcinol diglycidyl ether	The test substance was applied as a 60% solution in xylene; Non-occlusion conditions; 7 hour exposure period	2420 mg/kg bw (2.0 ml/kg bw) Number of deaths and clinical signs not detailed. Further, it is noted that the contribution of xylene to the	Westrick and Gross (1960), as cited in Gardiner et al., 1992 Klimisch score: 3 (limited details available

Method, guideline, deviations if any	Species, strain, sex, no/group	Test substance,	Dose levels duration of exposure	Value LD_{50}	Reference
				observed effects cannot be excluded.	(secondary literature); co-exposure with xylene which might interfere with the outcome)
Non-guideline, non-GLP	Rabbit, strain and sex not specified Number of animals/group not specified	Resorcinol diglycidyl ether	Dose levels not specified; Continuous exposure, not further specified	744 mg/kg bw (0.64 ml/kg bw) No details provided.	Westrick and Gross (1960), as cited in Gardiner et al., 1992 Klimisch score: 4 (limited details available (secondary literature))

10.2.1 Short summary and overall relevance of the provided information on acute dermal toxicity

An acute toxicity study via the dermal route, only available as secondary source, was available in which rabbits were exposed for 7 hours (under non-occluded conditions) to resorcinol diglycidyl ether as a 60% solution in xylene (Westrick and Gross (1960), as cited in Gardiner et al., 1992). The LD_{50} was reported to be 2420 mg/kg bw. The original study, where this LD_{50} was based on was not available to the Dossier Submitter. Further, it is noted that xylene has a harmonized classification for acute dermal toxicity as Acute Tox. 4* (H312: Harmful in contact with skin). It is not clear what the contribution of xylene to the observed deaths in this study was. Therefore, no conclusion with respect to the acute dermal toxicity of resorcinol diglycidyl ether can be drawn based on this study.

In a second study, only available as secondary source, rabbits were continuously exposed (total exposure period not specified) to resorcinol diglycidyl ether (Westrick and Gross (1960), as cited in Gardiner et al., 1992). The LD_{50} was reported to be 744 mg/kg bw. No further details were provided on the number of animals and decedents and clinical signs. The original study, where this LD_{50} was based on, was not available to the Dossier Submitter. However, the data of this study were previously used by TC C&L to conclude that classification may be appropriate and resorcinol diglycidyl ether was subsequently classified at that time with R21 (The original CLH proposal from 1997 is provided in chapter 15 of this CLH-report.). Therefore, these data will also be used for current classification proposal.

10.2.2 Comparison with the CLP criteria

The reported dermal rabbit LD_{50} of 744 mg/kg bw fall within the range for Acute dermal Category 3 of 200-1000 mg/kg bw. This warrants classification as Acute Tox. 3.

An LD_{50} value of 744 mg/kg bw is suggested as ATE for acute dermal toxicity.

10.2.3 Conclusion on classification and labelling for acute dermal toxicity

Classification of resorcinol diglycidyl ether for acute toxicity via the dermal route as Acute Tox. 3 (H311: Toxic in contact with skin) is required.

It is proposed to assign an ATE of 744 mg/kg bw for acute dermal toxicity.

10.3 Acute toxicity - inhalation route

Table 11: Summary table of animal studies on acute inhalation toxicity

Method, guideline, deviations if any	**Species, strain, sex, no/group**	**Test substance, , form and particle size (MMAD)**	**Dose levels, duration of exposure**	**Value** LC_{50}	**Reference**
Non-guideline, non-GLP	Rat, Long-Evans, male Number of animals/group not specified	Resorcinol diglycidyl ether	Single 8 hour exposure; Saturated air concentration; Concentration level not specified; 10-day postexposure observation period	No deaths observed; LC_{50} was greater than the highest vapour concentration attained	Hine et al., 1958 Klimisch score: 2
Non-guideline, non-GLP	Mouse, Webster, male Number of animals/group not specified	Resorcinol diglycidyl ether	Single 8 hour exposure; Saturated air concentration,; Concentration level not specified; 10-day postexposure observation period	No deaths observed; LC_{50} was greater than the highest vapour concentration attained	Hine et al., 1958 Klimisch score: 2
Non-guideline, non-GLP	Rat, strain and sex not specified Number of animals/group not specified	Resorcinol diglycidyl ether	Single 4 hour exposure; 44.8 mg resorcinol diglycidyl ether (60% in xylene) per liter of air; aerosol.	All rats died within 5 days postexposure. However, it is noted that the contribution of xylene to the observed effects cannot be excluded.	Westrick and Gross (1960), as cited in Gardiner et al., 1992 Klimisch score: 3 (limited details available (secondary literature); co-exposure with xylene which might interfere with the outcome)

10.3.1 Short summary and overall relevance of the provided information on acute inhalation toxicity

An acute toxicity study via the inhalation route was conducted in two species, i.e. Long-Evans rat and Webster mouse (Hine et al., 1958). Animals were exposed during 8 hours to resorcinol diglycidyl ether (as a saturated test atmosphere). No deaths were observed.

In a second study, only available as secondary source, rats were exposed for 4 hours to 44.8 mg resorcinol diglycidyl ether (60% in xylene) per liter of air (Westrick and Gross (1960), as cited in Gardiner et al., 1992). All animals died within 5 days postexposure. It is noted that xylene has a harmonized classification for acute inhalation toxicity as Acute Tox. 4* (H332: Harmful if inhaled). It is not clear what the contribution of xylene to the observed deaths in this study was. Therefore, no conclusion with respect to the acute inhalation toxicity of resorcinol diglycidyl ether can be drawn based on this study.

10.3.2 Comparison with the CLP criteria

As no deaths were observed in an acute inhalation study in rats and mice (Hine et al., 1958) up to the saturated vapour pressure, this does not warrant classification. However, seen the low saturated vapour pressure, it cannot be excluded that testing the mist would result in a requirement for classification but such data is not available. Although deaths were observed in a second inhalation study (Westrick and Gross (1960), as cited in Gardiner et al., 1992), the findings might be confounded by the presence of xylene in the test atmosphere. Therefore, this study cannot be used for classification purposes of resorcinol diglycidyl ether.

10.3.3 Conclusion on classification and labelling for acute inhalation toxicity

Classification of resorcinol diglycidyl ether for acute toxicity via the inhalation route is not required.

10.4 Skin corrosion/irritation

This hazard class has not been evaluated. However, in support of the evaluation of the endpoint carcinogencity, a summary table and a short summary of the skin irritation/corrosion studies are presented below. The individual studies can be found in Annex I.

Table 12: Summary table of animal studies on skin corrosion/irritation

Method, guideline, deviations if any	Species, strain, sex, no/group	Test substance,	Dose levels duration of exposure	Results -Observations and time point of onset -Mean scores/animal -Reversibility	Reference
Draize method Non-guideline, non-GLP	Rabbit, Albino (sex not specified) Number of animals not specified	Resorcinol diglycidyl ether	Concentration not specified 24 h exposure, occlusive, readings at 24 and 72 h	Moderately irritating, with Draize score of 5 out of possible 8	Hine et al., 1958 Klimisch score: 2
Non-guideline, non-GLP	Rabbit, Albino (sex not specified) Four	Resorcinol diglycidyl ether	Concentration not specified; 7 daily applications of 7 h exposure;	Severe irritation reported, score 8 out of possible 8 for erythema and edema (individual daily scores not reported). Three animals died by day 8.	Hine et al., 1958 Klimisch score: 2

Method, guideline, deviations if any	Species, strain, sex, no/group	Test substance,	Dose levels duration of exposure	Results -Observations and time point of onset -Mean scores/animal -Reversibility	Reference
	animals		Readings at 24 h intervals (prior to subsequent application)		
Non-guideline, non-GLP	Rabbit, Five animals	Resorcinol diglycidyl ether	0.01 ml of a 10% solution in acetone; Details on the exposure period and time points of evaluation provided	Scar tissue formation was observed in one animal, and a definite erythema and edema were observed in the other four rabbits	Westrick and Gross, 1960 Klimisch score: 4 (limited details available (secondary literature))
Non-guideline, non-GLP	Rabbit (strain en sex not specified) Number of animals not specified	Resorcinol diglycidyl ether	0.5 ml of a 60% solution in xylene; 24 h exposure	Severe irritation which progressed to necrosis. Further, it is noted that the contribution of xylene to the observed effects cannot be excluded.	Westrick and Gross, 1960 Klimisch score: 3 (limited details available (secondary literature); co-exposure with xylene which might interfere with the outcome)

Summary on skin irritation/corrosion:

In a skin irritation study in which resorcinol diglycidyl ether was applied to rabbit skin for 24h, resorcinol diglycidyl ether was a moderate skin irritant (Draize score 5/8) (Hine et al., 1958). In a second study in which 4 rabbits were treated with 7 daily applications of 7 h each, severe irritation was reported (Draize score 8/8) (Hine et al., 1958). Within this study, 3 deaths, which occurred by treatment-day 8, were attributed to severe irritation. Finally, two studies were described (via secondary source) that reported irritation upon single exposure to resorcinol diglycidyl ether (Westrick and Gross, 1960).

Resorcinol has a current harmonized classification for skin irritation as Skin Irrit. 2 (H315). The original CLH proposal from 1997 is provided in chapter 15 of this CLH-report.

10.5 Serious eye damage/eye irritation

This hazard class has not been evaluated.

10.6 Respiratory sensitisation

This hazard class has not been evaluated.

10.7 Skin sensitisation

This hazard class has not been evaluated.

10.8 Germ cell mutagenicity

This hazard class has not been evaluated.

However, in support of the evaluation of the endpoint carcinogencity, a summary table and a short summary of the *in vitro* and *in vivo* mutagenicity studies are presented below. The individual studies can be found in Annex I.

Table 13: Summary table of mutagenicity/genotoxicity tests *in vitro*

Method, guideline, deviations if any	Test substance, concentration levels, controls, etc	Observations	Reference
Micro-organisms			
Reverse Mutation *Salmonella typhimurium Strains*: TA98, TA100, TA1535, TA1537	*Purity*: 87.9% (analyzed; method not reported) *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), 9-aminoacridine (TA1537), 4-nitro-o-phenylenediamine (TA98); +S9 mix 2-aminoanthracene (all strains) *Statistical analysis*: not used	*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	Canter et al., 1986; NTP, 1986 Klimisch score 2
Reverse Mutation Salmonella typhimurium	*Purity*: >98% (HPLC) *Concentrations*: 0, 50, 100, 200, 500, 1,000 µg/plate	*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	Seiler, 1984b Klimisch score: 3 (only one strain; no metabolic activation;

Method, guideline, deviations if any	**Test substance, concentration levels, controls, etc**	**Observations**	**Reference**
Strains: TA100	*Metabolic system*: not used *Control*: Negative control: not specified, Positive control: not used *Statistical analysis*: not used	highest concentration, resp. *Cytotoxicity*: In 500 and 1000 µg/plate test	no information on potential solvent used; no positive control; not specified negative control; number of replicates unknown)
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	McGregor et al., 1988 Klimisch score 2
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	McGregor et al., 1996 Kimisch score 3 (no metabolic activation, no information on potential solvent used, purity unknown, negative control not specified)
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	*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	Gulati et al., 1989 Klimisch score 2

Method, guideline, deviations if any	**Test substance, concentration levels, controls, etc**	**Observations**	**Reference**
	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	reported	
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): 2 (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	Seiler 1984b Klimisch score 3 (no information on check cell line absence of mycoplasma, 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)
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 *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 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* (+S9, 1st test); 9.4, 8.5, 9.9, 14*, 39* (+S9, 2nd test) *Cytotoxicity*: No information reported	Gulati et al., 1989 Klimisch score 2
Alkylating potency using the 4-(4-	*Method*: According to Friedman and Boger (1961)	*Outcome*: positive; Optical density at 450 nm (measured against negative control): 0.23,	Seiler 1984b

Method, guideline, deviations if any	Test substance, concentration levels, controls, etc	Observations	Reference
nitrobenzyl) pyridine assay Epoxyhydrolase containing rat and mice liver homogenates	*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	0.55, 1.17, 2.18, respectively	

Table 14: Summary table of mutagenicity/genotoxicity tests in mammalian somatic or germ cells *in vivo*

Method, guideline, deviations if any	Test substance, concentration levels, controls, etc	Observations	Reference
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*: %PCEb: 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	Shelby et al., 1993 Kllimisch score 2
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	Shelby et al., 1993 Klimisch score: 2
Micronucleus ICR mice (male	*Method*: single oral dose, 4 animals per dose *Doses*: 300 mg/kg with 24h fixation	*Outcome* Negative: inactive with respect to	Seiler, 1984b

Method, guideline, deviations if any	Test substance, concentration levels, controls, etc	Observations	Reference
and female)	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	micronuclei formation *Toxicity*: 1 out of 4 animals died within 48 h in the experiments with 48h and 72h fixation time	Klimisch score 3 (negative control not specified; no positive controls; no information on toxicity to bone marrow, low number of animals)
Other test systems			
Sex-linked recessive lethal induction *Drosophila melanogaster*	*Exposure*: 3 days to 50,000 ppm in feeding solution *Controls*: Negative: solvent; Positive: nitrosodimethylamine and β-propiolactone *Purity*: 87.9% *Solvent*: 9% ethanol, 1% Tween-80; initial 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)	*Outcome*: Mutagenic: 0.19 and 1.31% lethals for control and exposed groups, resp. *Toxicity*: no mortality or sterility	Valencia et al., 1985; Woodruff et al., 1984 Klimisch score 3 (Classification based on studies in mammalians; no OECD guideline anymore)
Reciprocal translocations induction *Drosophila melanogaster*	*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-nitrosodimethylamine 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%)	Valencia et al., 1985; Woodruff et al., 1984 Klimisch score 3 (Classification based on studies in mammalians; no OECD guideline anymore)

Germ cell genotoxicity

Genotoxicity studies of resorcinol diglycidyl ether in germ cells, which can be considered relevant for humans, are not available.

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). Exposure to resorcinol diglycidyl ether did also result in an increase in cells with chromosome aberrations with and without metabolic activation. The supporting genotoxicity tests confirmed the positive findings in *in vitro* tests.

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.

The available data are in line with the existing harmonised classification as Muta. 2. The original CLH proposal from 1997 is provided in chapter 15 of this CLH-report.

10.9 Carcinogenicity

Table 15: Summary table of animal studies on carcinogenicity

Method, guideline, deviations if any, species, strain, sex, no/group	Test substance, dose levels duration of exposure	Results	Reference
F344/N rats 50 rats per dose/sex	Resorcinol diglycidyl ether; purity: 81% Gavage, 5 times/week, vehicle corn oil, 0, 25, 50 mg/kg bw/d Exposure period: 103 weeks Observation period: 104-105 weeks 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) (life table test & incidental tumour test).	*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; Krishna-Murthy et al., 1990 Klimisch score: 2
Supplemental to previous study F344/N rats 50 rats per dose/sex	Resorcinol diglycidyl ether; purity: 81% Gavage, 5 times/week, vehicle corn oil, 0, 12 mg/kg bw/d exposure period: 103 weeks	*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.	NTP 1986; Krishna-Murthy et al., 1990 Klimisch score: 2

Method, guideline, deviations if any, species, strain, sex, no/group	Test substance, dose levels duration of exposure	Results	Reference
	observation period: 104-105 weeks 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) (life table test & incidental tumour test).	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%)	
B6C3F1 mice 50 mice per dose/sex	Resorcinol diglycidyl ether; purity: 81% Gavage, 5 times/week, vehicle corn oil, 0, 50, 100 mg/kg bw/d exposure period: 103 weeks observation period: 104-105 weeks 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).	*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; Krishna-Murthy et al., 1990 Klimisch score: 2
Swiss-Millerton female mice 30 treated; 60 untreated controls; 60 vehicle controls	Resorcinol diglycidyl ether Purity: not specified Dermal application (to clipped dorsal skin) 1% in benzene, three times per week, about 100 mg of solution per application Exposure + observation period: life-span The study was continued until there were no survivors	*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 Klimisch score: 3

Method, guideline, deviations if any, species, strain, sex, no/group	Test substance, dose levels duration of exposure	Results	Reference
C57/B1 mice 20 treated	Resorcinol diglycidyl ether Total concentration 0.75 mM Exposure route, frequency and duration, vehicle, purity test material, observation period, method of tumour detection: not specified	*Survival*: 14/20 after 8 months *Tumours*: One skin tumour observed (after 8 months)	Kotin and Falk, 1963 Klimisch score: 3 (not adequate for carcinogenicity asssessment)
C57/B1 mice	Resorcinol diglycidyl ether Purity: not specified Intrascapular painting three times a week	Authors state that substance was carcinogenic; organs not mentioned	McCammon et al., 1957 Klimisch score: 4
Long-Evans rats	Resorcinol diglycidyl ether Purity: not specified Subcutaneous injection	Authors state that substance was carcinogenic; organs not mentioned	McCammon et al., 1957 Klimisch score: 4

The table above 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.

10.9.1 Short summary and overall relevance of the provided information on carcinogenicity

No data on the carcinogenicity of resorcinol diglycidyl ether in humans are available.

The animal 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.

Long-term oral carcinogencity studies were performed with rats and mice (NTP 1986; Krishna-Murhty et al., 1990). In the 2-year oral gavage study in rats (0, 25, 50 mg/kg bw/d, 5 d/wk, 2 year), observed effects included reduced body weight gain and a dose-related reduced survival in both sexes. At the end of the 2-year study, 42/50, 5/50 and 0/50 male and 37/50, 16/50 and 1/50 female rats of the 0, 25 and 50 mg/kg bw/d dose groups, respectively, had survived. Histopathological examination revealed lesions in forestomach. These included non-neoplastic lesions such as basal cell hyperplasia and hyperkeratosis, and statistically increased increased incidences of benign and malignant neoplastic lesion of the epithelium such as squamous cell papilloma (males: 0/50, 17/50 (34%) and 6/49 (12%), females: 0/49, 7/50 (14%) and 1/50 (2%)) and squamous cell carcinoma (males: 0/50, 38/50 (76%) and 4/49 (8%), females: 0/49, 34/50 (68%) and 3/50 (6%)). It is noted that in the high dose animals, the effects were not as striking, which may be explained by the markedly increased number of deaths (Table 16). Adjustment of these numbers for intercurrent mortality, the incidences of squamous papillomas were 0, 40.9 and 33.5% (0, 25 and 50 mg/kg bw/d) for male rats, and 0, 24.2, 14.3% for female rats. Adjusted incidences for squamous carcinomas were 0, 100 and 100% (0, 25 and 50 mg/kg bw/d) for male rats and 0, 97, 100% for female rats. In addition to the increased incidences of

forestomach tumours, some tumour types were observed with reduced incidences (i.e. adrenal pheochromocytoma, leukemia, pituitary adenoma, and thyroid C-cell tumors in males and females; lung adenoma, pancreatic islet cell tumors, and interstitial cell tumors of the testes in males; and mammary glandfibroadenomas and uterine tumors in females). However, none of these decreases were statistically significant when life table analyses were used, and they appeared to be related to the reduced survival observed in the dosed groups relative to those in the controls (NTP, 1986; Krishna-Murthy et al., 1990).

Table 16. Incidences of neoplasms of the stomach in male and female rats administered resorcinol diglycidyl ether in corn oil by gavage for two years (NTP, 1986; Krishna-Murthy, 1990). A: main study, B: supplemental study

A

	Dose resorcinol diglycidyl ether (mg/kg bw/d)					
	0		**25**		**50**	
	m	f	m	f	m	f
Squamous cell papilloma						
Overall incidence	0/50 (0%)	0/49 (0%)	17/50 (34%)	7/50 (14%)	6/49 (12%)	1/50 (2%)
Adjusted incidence[(a)]	0.0%	0.0%	40.9%	24.2%	33.5 %	14.3%
Terminal incidence	0/42 (0%)	0/36 (0%)	0/5 (0%)	1/16 (6%)	0/0 (0%)	0/1 (0%)
Life table test	P<0.001	P<0.001	P<0.001	P=0.002	P<0.001	P=0.125
Cochran-Armitage trend test	P=0.058	P=0.421				
Fischer Exact test			P<0.001	P=0.007	P=0.012	P=0.505
Squamous cell carcinoma						
Overall incidence	0/50 (0%)	0/49 (0%)	38/50 (76%)	34/50 (68%)	4/49 (8%)	3/50 (6%)
Adjusted incidence[(a)]	0.0%	0.0 %	100%	97.0%	100%	100.0%
Terminal incidence	0/42 (0%)	0/36 (0%)	5/5 (100%)	15/16 (94%)	0/0 (0%)	1/1 (100%)
Life table test	P<0.001	P<0.001	P<0.001	P<0.001	P<0.001	P<0.001
Cochran-Armitage trend test	P=0.199	P=0.300				
Fischer Exact test			P<0.001	P=0.001	P=0.056	P=0.125

(a) Kaplan-Meier estimated tumor incidence at the end of the study after adjusting for intercurrent mortality

B

	Dose resorcinol diglycidyl ether (mg/kg bw/d)			
	0		**12**	
	m	f	m	f
Squamous cell papilloma				
Overall incidence	0/50 (0%)	0/50 (0%)	16/50 (32%)	19/50 (38%)
Adjusted incidence[(a)]	0.0%	0.0%	51.7%	48.4%
Terminal incidence	0/39 (0%)	0/39 (0%)	10/23 (43%)	15/35 (43%)
Life table test			P<0.001	P<0.001
Incidental tumour test			P<0.001	P<0.001
Fischer Exact test			P<0.001	P<0.001
Squamous cell carcinoma				
Overall incidence	0/50 (0%)	0/50 (0%)	39/50 (78%)	27/50 (54%)
Adjusted incidence[(a)]	0.0%	0.0 %	92.8%	64.0%
Terminal incidence	0/39 (0%)	0/39 (0%)	20/23 (87%)	20/35 (57%)
Life table test			P<0.001	P<0.001
Incidental tumour test			P<0.001	P<0.001
Fischer Exact test			P<0.001	P<0.001

(a) Kaplan-Meier estimated tumor incidence at the end of the study after adjusting for intercurrent mortality

Due to the excessive mortality at the high dosed rats, a supplemental rat study was performed using resorcinol diglycidyl ether at dose levels of 0 and 12 mg/kg bw/d (5 d/wk, 2 yr). Survival of male but not female rats was significantly reduced compared to the controls. The reduced survival in males was probably due to the increase in squamous cell carcinomas as the incidence of intercurrent mortality without such tumours was comparable between the treated group ((27-19)/50) and the controls (11/50). The body weights were not affected. Similar lesions of the forestomach were observed upon histopathological examination.

Markedly increased incidences of hyperkeratosis and basal cell hyperplasia, and squamous cell papilloma (males: 0/50 (0%), 16/50 (32%); females: 0/50 (0%), 19/50 (38%)) and carcinoma (males: 0/50 (0%), 39/50 (78%); females: 0/50 (0%), 27/50 (54%)) were noticed in both sexes. In addition to the increased incidences of forestomach tumours, some tumour types were observed with reduced incidences (i.e. C-cell tumors of the thyroid in males, and pheochromocytomas of the adrenal medulla in females) (NTP, 1986; Krishna-Murthy et al., 1990).

In the 2-year oral gavage study in mice (0, 50 and 100 mg/kg bw/d, 5 d/wk, 2 year), observed effects included reduced body weight in high dose females. Survival was not significantly affected but survival was low in all female mice groups. Histopathological evaluation revealed treatment-related lesions which were primarily observed in the forestomach of low and high dose mice of both sexes. The incidence of hyperkeratosis and epithelial cell hyperplasia in the forestomach was markedly increased in low- and high-dose mice of both sexes, and squamous cell papillomas and papillomatosis (males: 0/47 (0%), 4/49 (8%), 10/50 (20%); females: 0/47 (0%), 5/49 (10%), 10/49 (20%)) and carcinomas (males: 0/47 (0%), 14/49 (29%), 25/50 (50%); females: 0/47 (0%), 12/49 (24%), 23/49 (47%)) 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. Further, a positive trend was observed for hepatocellular carcinoma in female mice and the incidences of combined adenoma and carcinoma in liver were statistically significantly increased. NTP (1986) considered these as not related to treatment. In comparison with historical control data, the incidence in females dosed with the high dose resorcinol diglycidyl ether (6% for carcinoma, 14% for combined adenoma/carcinoma) was lower than that in historical controls at the same laboratory (upper level 8% for carcinoma and 14% for combined adenoma/carcinoma). Historical control data should preferably be taken from the same laboratory and the same strain, using a time period that is close to the time period at which the study under consideration is conducted. The NTP-study were conducted at Mason lab, which is also included in the historical control data as presented by NTP. It is noted that that the exact time period has not been specified for the individual historical studies. No further details are available on the historical control data from NTP. In addition to the increased incidences of forestomach tumours, some tumour types were observed with reduced incidences (i.e. all types of malignant lymphomas in females, and fibroma, fibrosarcoma, or -carcoma in male mice) (NTP 1986; Krishna-Murthy et al., 1990).

Potential mechanism and human relevance of the forestomach tumours.

The precise underlying mechanism of action for any forestomach carcinogen is at present not fully known. The tumorigenic lesions may be the result of a direct, genotoxic action of the compound on the epithelium, an indirect action (a prolonged proliferation stimulus) or a combination of both (RIVM, 2003).

A working group of IARC concluded 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 (IARC, 2003). 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 nongenotox mechanisms they consider not to be 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 (Proctor et al., 2007).

Further, the CLP-guidance (section 3.6.2.3.2a) states the following with respect to forestomach tumours (i.e. tumours occurring in tissues with no human equivalent): "*Forestomach tumours in rodents following administration by gavage of irritating or corrosive, non mutagenic substances. In rodents, the stomach is divided into two parts by the muco-epidermoid junction separating squamous from glandular epithelium. The proximal part, or forestomach, is non-glandular, forms a continuum with the oesophagus, and is lined by keratinized, stratified squamous epithelium. While 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. See also this Section (k), IARC (2003), and RIVM (2003).*

Tumours occurring in such tissues indicate that the substance has the potential to induce carcinogenic effects in the species tested. It cannot automatically be ruled out that the substance could cause similar tumours of comparable cell/tissue origin (e.g. squamous cell tumours at other epithelial tissues) in humans. Careful consideration and expert judgement of these tumours in the context of the complete tumour response (i.e. if there are also tumours at other sites) and the assumed mode of action is required to decide if these findings would support a classification. However, tumours observed only in these tissues, with no other observed tumours are unlikely to lead to classification. However, such determinations must be evaluated carefully in justifying the carcinogenic potential for humans; any occurrence of other tumours at distant sites must also be considered."

Based on the available *in vitro* and *in vivo* mutagenicity studies, resorcinol diglycidyl ether can be considered a mutagenic subtance. *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. The *in vivo* mouse micronucleus study of Seiler (1984b), applying exposure to resorcinol diglycidyl ether via the oral route, did not find a positive response. The *in vivo* mouse micronucleus of Shelby et al. (1993), applying exposure to resorcinol diglycidyl ether via the intraperitoneal route (which is considered physiologically less relevant to humans), revealed statistically significant increases in cells with micronuclei upon single high exposure only. It is noted that upon a triple-exposure with somewhat lower dose levels, a negative outcome was considered. Shelby et al. (1993) considered that due to the toxicity characteristics of resorcinol diglycidyl ether, a triple-exposure protocol does not permit use of a sufficiently high dose levels to induce observable genetic toxicity.

The data of the toxicokinetic study performed by Seiler (1984a) indicates that oral absorption occurs, which is likely to be followed by systemic distribution (of the parent compound and/or its metabolites). Seiler (1984a) observed that the total amount of radioactivity recovered from urine collected up to 4 hours after a single oral dose of 1000 mg/kg body weight was nearly 50% of the applied dose. Nevertheless, resorcinol diglycidyl ether-induced micronucleus could not be revealed upon oral exposure *in vivo* (Seiler, 1984b), though upon intraperitoneal administration of high doses positive findings were noticed (Shelby et al., 1997). The CLP-guidance states that *"A positive result for somatic or germinal mutagenicity in a test using intraperitoneal administration only shows that the tested substance has an intrinsic mutagenic property, and the fact that negative results are exhibited by other routes of dosage may be related to factors influencing the distribution/ metabolism of the substance which may be characteristic to the tested animal species. It cannot be ruled out that a positive test result in intraperitoneal studies in rodents may be relevant to humans."* Resorcinol diglycidyl ether-induced tumours were only observed in the forestomach, i.e. the site of contact. Tumours in other, systemic, tissues were not observed (NTP 1986; Krishna-Murthy et al., 1990). The toxicokinetic study performed by Seiler (1984a) also 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* mutagenicity results were conclusive. This rapid metabolization to genetically inactive substance 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 active substance is not distributed to other tissues in significant amounts.

The available skin irritation data, the repeated dose studies as well as the carcinogenicity studies point towards an irritative effect at the site of contact upon exposure to resorcinol diglycidyl ether. Resorcinol diglycidyl ether was found to be a moderate skin irritation upon 24h application on rabbit skin (Draize score 5/8) (Hine et al., 1958). Multiple applications (7 daily applications of 7 h each) to rabbit skin resulted in severe irritation (Draize score 8/8), which in some animals even resulted in death (Hine et al., 1958). In the 2-week and 13-week repeated dose studies, resorcinol diglycidyl ether (via oral gavage) was found to induce effects primarily in the forestomach of F344/N rats and B6C3F1 mice of both sexes, causing mucosal cell proliferation, hyperkeratosis, hyperplasia and papillary growth, mucosal ulcers of the forestomach (Ghanayem et al., 1986; NTP, 1986; Krishna-Murthy et al., 1990). When comparing the type/severity of stomach effects in the 2-week and 13-week oral gavage studies with respect to dose levels, mainly local effects with limited severity were noticed in these repeated dose studies. Severe type of effects such as ulceration was only observed at high dose levels (i.e. higher than the dose levels as applied in the

carcinogenicity studies). The data of the NTP carcinogenicity study also point towards local irritation in the forestomach as hyperkeratosis and hyperplasia of the epithelium were observed (NTP 1986; Krishna-Murthy et al., 1990). Taking into account these data, this might suggest that chronic tissue damage with resultant hyperplasia may have contributed to the carcinogenic response in the forestomachs of rats and mice.

Based on the available carcinogenicity data and taking into account the data on toxicokinetics, skin irritation, repeated dose toxicity and mutagenicity, it is considered that resorcinol diglycidyl clearly induces local effects at the site of contact. Upon oral exposure this results in mucosal cell proliferation, hyperkeratosis, hyperplasia, papillary growth, mucosal ulcers and squamous cell papillomas and carcinomas in the forestomach, and by that, it may be considered that resorcinol diglycidyl ether acts (at least partly) via an indirect mode of action (i.e. a prolonged proliferation stimulus). However, as resorcinol diglycidyl ether was also found to be a mutagenic substance, though probably acting at the site of contact and not via systemic exposure due to inactivation, it may be considered that the resorcinol diglcidyl ether-induced forestomach tumours are induced via a (local) genotoxic mechanism.

Taking into account the considerations of RIVM (2003) and IARC (2003), the forestomach tumours as observed in F344/N rats and B6C3F1 mice of both sexes (NTP 1986; Krishna-Murthy et al., 1990) should be taken forward for classification of resorcinol diglycidyl ether for the endpoint carcinogenicity. A potential irrelevance for humans is not clearly demonstrated for the resorcinol diglycidyl ether-induced forestomach tumours.

Read-across with other related substances

As far as known to the Dossier submitter no other resorcinol glycidyl ethers have been tested for carcinogenicity. Several other glycidylethers have been tested for carcinogenicity and a number have a harmonised classification for carcinogenicity and/or mutagenicity but mostly in category 2. Probably the most comparable substance that was tested for carcinogenicity is phenyl glycidyl ether (CAS 122-60-1) as it contains one instead of two glycidylether side chains. Phenyl glycidyl ether is classified as carcinogenic 1B and mutagenic 2. The original CLH proposal from 1997 of phenyl diglycidyl ether is provided in chapter 15 of this CLH-report The carcinogenicity classification was based on an increase in nasal tumours in a inhalation carcinogenicity study in rats. Therefore, it is considered that the read-across to the most comparable substance tested for carcinogenicity, phenyl glycidyl ether, may support the proposed classification as carcinogen category 1b. It is acknowledged that the basis for this read-across may be considered limited. However, in the view of the Dossier Submitter, no other data are available that can be used for read-across.

Table 17: Compilation of factors to be taken into consideration in the hazard assessment

Species and strain	Tumour type and background incidence	Multi-site responses	Progression of lesions to malignancy	Reduced tumour latency	Responses in single or both sexes	Confounding effect by excessive toxicity?	Route of exposure	MoA and relevance to humans
Consistent increase in tumours was observed in both rats and mice	Forestomach tumours; the increase in tumours is limited to the site of exposure in rats and mice	The increase in tumours is limited to the site of exposure in rats and mice	The forestomach tumours in both rats and mice progress to malignancy.	As no forestomach tumours were observed in control rats and mice and in treated animals the tumours were observed partly before the terminal sacrific, the latency period was reduced.	Forestomach tumours were observed in both male and female rats and mice	Local toxicity due to the irritating properties may have contributed to the formation of tumours. Local effects included hyperkeratosis and hyperplasia, indicating no excessive toxicity though these local effects might have contributed to the observed tumour response. In addition, an increase in mortality was observed in the rat and mouse (females) studies. In the rat most early non tumour related mortality were attributable to bronchopneumonia. In female mice the major cause of early dead was necrosuppurative lesion of the ovary. The cause of the lethality is not related to the tumour formation.	The oral route is considered a relevant route of exposure for humans	The available information indicates that both local irritation and (local) mutagencity may have contributed to the increase in forestomach tumours. A genotoxic MoA is considered relevant for humans, while the relevancy of a MoA of local irritation might be questionable. However, no data available to conclude with certainty which MoA is responsible for the forestomach tumours

10.9.2 Comparison with the CLP 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 agent and an increased incidence of malignant neoplasms or of an appropriate combination of benign and malignant neoplasms in (a) two or more species of animals or (b) two or more independent studies in one species carried out at different times*

or in different laboratories or under different protocols. An increased incidence of tumours in both sexes of a single species in a well-conducted study, ideally conducted under Good Laboratory Practices, can also provide sufficient evidence. A single study in one species and sex might be considered to provide sufficient evidence of carcinogenicity when malignant neoplasms occur to an unusual degree with regard to incidence, site, type of tumour or age at onset, or when there are strong findings of tumours at multiple sites".

Adequate studies on carcinogenicity in experimental animals were available for the oral route (NTP 1986; Krishna-Murthy et al., 1990). In these studies resorcinol diglycidyl ether was carcinogenic for two species (i.e. rat and mouse) of both sexes, causing benign and malignant neoplasms of the forestomach. This would basically be sufficient for classification in category 1B (i.e. sufficient evidence for carcinogenity).

An increase in mortality and a reduction in body weight was observed in the chronic study in rats and the tested dose levels could be considered to high. However, an additional dose level was tested without a decrease in body weight and no increase in mortality due to general toxicity showing an increase in the same type of tumours. Therefore, the studies are considered adequate atv least at one or more dose levels for determining the carcinogencity.

With respect to the responsible mode of action, it is known that resorcinol diglycidyl ether is a mutagenic substance. Forestomach tumours, caused by substances that act via a genotoxic mechanism, are considered relevant for humans (IARC, 2003; Proctor, 2007; RIVM, 2003). However, the data of the NTP-study also point towards local irritation in the forestomach as hyperkeratosis and hyperplasia of the epithelium were observed (NTP 1986; Krishna-Murthy et al., 1990). This might also suggest that chronic tissue damage with resultant hyperplasia may have contributed to the carcinogenic response. However, there are currently no data which can exlude a genotoxic mode of action. Therefore, it is assumed that the (local) genotoxicity contributed to the observed tumour response. Consequently, tumour formation at the site of first contact is considered relevant for this substance. Subsequently, the forestomach tumours are considered relevant for humans (IARC, 2003; Proctor, 2007; RIVM, 2003).

Based on these data, it can be concluded that there is sufficient evidence of carcinogenicity. According to the CLP criteria, resorcinol diglycidyl ether should, therefore, be classified in category 1B.

10.9.3 Conclusion on classification and labelling for carcinogenicity

Classification of resorcinol diglycidyl ether for carcinogenicity in category 1B (H350: May cause cancer) is warranted.

10.10 Reproductive toxicity

This hazard class has not been evaluated.

10.11 Specific target organ toxicity-single exposure

This hazard class has not been evaluated.

10.12 Specific target organ toxicity-repeated exposure

This hazard class has not been evaluated.

However, in support of the evaluation of the endpoint carcinogencity, a summary table and a short summary of the oral repeated dose studies are presented below. The individual studies can be found in Annex I.

Table 18: Summary table of animal studies on STOT RE

Method, guideline, deviations if any, species, strain, sex, no/group	**Test substance, route of exposure, dose levels, duration of exposure**	**Results**	**Reference**
Oral route			
Rat, Fischer 344, male 8-16 animals/group Study focussed on forestomach effects Non-guideline, Non-GLP	Resorcinol diglycidyl ether Oral via gavage 0-12-25 mg/kg bw/d 5 days/week, 2 weeks Vehicle: corn oil	Significant increase in the incidence and severity of mucosal cell proliferation and hyperkeratosis at the high dose of 25 mg/kg bw/d.	Ghanayem et al. (1986) Klimisch score 2
Rat, F344/N, male and female 5/sex/dose	Resorcinol diglycidyl ether Oral via gavage 0-190-380-750-1500-3000 mg/kg bw/d Daily for 14 consecutive days Vehicle: corn oil	Mortality: All males and females that received 750, 1500 or 3000 mg/kg bw/d and 2/5 males that received 380 mg/kg bw/d died before the end of the study. BW: All rats receiving 380 mg/kg bw/d and 2/5 males and 1/5 females receiving 190 mg/kg bw/d lost weight during the study. Macroscopy: Kidney: reneal medullae were red and more prominent than usual; Stomach: forestomach showed reddened mucosae and early development of small papillary-like growths. No histopathology performed	NTP (1986); Krishna-Murthy et al., 1990 Klimisch score 2

Rat, F344/N, male and female 10/sex/dose	Resorcinol diglycidyl ether Oral via gavage 0-12.5-25-50-100-200 mg/kg bw/d 5 days per week, for 13 weeks Vehicle: corn oild	Compound-related lesions were observed in the forestomach (squamous cell papilloma, hyperkeratosis, and basal cell hyperplasia) and the liver (minimal to mild centrilobular fatty metamorphosis). Chronic inflammation in the mesenteric lymph nodes was probably secondary to the inflammation or ulceration of the forestomach. Compared with the controls, the three male rats with fatty metamorphosis in the liver had decreased final body weights. However, lower mean body weight gains were also found in other male and female rats administered 200 mg/kg bw/d which did not show hepatic fatty metamorphosis. At necropsy, the wall of the forestomach was sometimes thickened and the mucosal surface contained small, white papillomatous nodules. When examined microscopically, some nodules and squamous papillomata, having localized acanthosis and papillary projections of the epidermis covered by thick layers of keratinized cells. The basal layer of the epithelium was hyperplastic, sometimes showing finger-like projections into the submucosa. Diffuse hyperkeratosis, focal basal cell hyperplasia, or both were usually present in the forestomach of rats without discrete squamous papillomata. In some rats that received 200 mg/kg bw/d, ulceration in the forestomach had completely eroded the epithelium and extended into the muscularis. A few rats without ulcers had circumscribed areas of inflammation in the stomach.	NTP (1986); Krishna-Murthy et al., 1990 Klimisch score 2
Mouse, B6C3F1, male and female 5/sex/dose	Resorcinol diglycidyl ether Oral via gavage 0-90-190-380-750-1500 mg/kg bw/d Daily for 14 consecutive days Vehicle: corn oild	Mortality: Five of five males and 4/5 females receiving 1500 mg/kg bw/d and 2/5 males receiving 750 mg/kg bw/d died BW: Weight loss was observed in all mice that received 750 mg/kg bw/d or more and in 4/5 males en 1/5 females thet received 380 mg/kg bw/d. Weight loss occurred in mice in the 90 mg/kg bw/d groups (4 males and 5 females), but not in animals administered 190 mg/kg bw/d. Macroscopy: kidney: reddened medullae; stomach: reddened mucosae. No histopathology performed	NTP (1986); Krishna-Murthy et al., 1990 Klimisch score 2

Mouse, B6C3F1, male and female 10/sex/dose	Resorcinol diglycidyl ether Oral via gavage 0-25-50-100-200-400 mg/kg bw/d 5 days per week, for 13 weeks Vehicle: corn oild	Mortality: Nine of ten males and 7/10 females receiving 400 mg/kg bw/d died; BW: Final mean body weight compared to controls was depressed 10-25% in groups that received 400 mg/kg bw/d Histopathology: - Forestomach: squamous papillomata, diffuse hyperkeratosis, basal cell hyperplasia, and inflammation, mucosal ulcers (high dose females). - Testis: Slight to mild focal tubular atrophy of the testes in three mice that died during weeks 9 or 10 (Lesion not seen in mice that survived to the end of the study). The testicaly atrophy was, based on accompanying reduced BW, interpreted as being the result of morbidity rather than a direct effect or resorcinol diglycidyl ether. - Liver (high dose): Hepatic necrosis, minimal to mild fatty metamorphosis in periportal areas of the liver (only in animals that died).	NTP (1986); Krishna-Murthy et al., 1990 Klimisch score 2

Summary on repeated dose toxicity data:

For the oral exposure route, multiple gavage studies in rat and mouse were available with exposure periods of 2 weeks and 13 weeks. Resorcinol diglycidyl ether was found to induce mainly effects in the forestomach of F344/N rats and B6C3F1 mice of both sexes, causing mucosal cell proliferation, hyperkeratosis, hyperplasia and papillary growth, mucosal ulcers of the forestomach (Ghanayem et al., 1986; NTP, 1986). When comparing the type/severity of stomach effects with respect to dose levels, mainly local effects with limited severity were noticed in these repeated dose studies. Severe type of effects such as ulceration was only observed at high dose levels (i.e. higher than the dose levels as applied in the carcinogenicity studies).

10.13 Aspiration hazard

This hazard class has not been evaluated.

11 EVALUATION OF ENVIRONMENTAL HAZARDS

This hazard class has not been evaluated.

12 EVALUATION OF ADDITIONAL HAZARDS

Not relevant

13 ADDITIONAL LABELLING

Not relevant

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15 ANNEXES

- *Annex 1 to the CLH report: contains a description of the evaluated studies. See separate document*
- *Original classification proposal of **resorcinol diglycidyl ether** from 1997: see below*
- *Original classification proposal of phenyl diglycidyl ether from 1997: see below*

Original classification proposal of resorcinol diglycidyl ether from 1997

FORM XI/396/93

Commission of the European Communities DG XI

CLASSIFICATION AND LABELLING OF DANGEROUS SUBSTANCES
Recommended form to be used for the proposed classification and labelling of Dangerous Substances in order to update Annex I of Directive 67/548/EEC

Date: 20 March 1997 Prepared by: Health and Safety Executive, UK

The information contained in this form is not regarded as confidential ECBT i.

1. IDENTIFICATION OF THE SUBSTANCE

INDEX No. 603-065-00-9	**EC No.** 202-987-5 **CAS No.** 101-90-6 **ID No.** U043
1.1 EINECS Name	m-bis(2,3-epoxypropoxy)benzene
1.2 Synonyms (state ISO name if available)	**Resorcinyl diglycidyl ether (RDGE)** Diglycidyl resorcinol ether; 1,3-diglycidyloxybenzene; 2,2'-[1,3-phenylenebis(oxymethylene)]bisoxirane; 1,3-bis(2,3-epoxypropoxy)benzene; meta-Bis(2,3-epoxypropoxy)benzene; meta-Bis(glycidyloxy)benzene
1.3 Molecular formula	$C_{12}H_{14}O_4$
1.4 Structural formula	
1.5 Purity (w/w)	
1.6 Significant impurities or additives, their concentrations (w/w)	
1.7 Known uses	**Industrial:** liquid spray epoxy resin, as a dilutant in the production of other epoxy resins used in electrical tooling, adhesive and laminating applications, and as a curing agent for polysulphide rubber (Lee & Neville, 1967) **General public:** Not used
1.8 Proposed classification	Carc Cat 3; Muta Cat 3; R40 Xn; R21/22: Xi; R36/38: R43

EXISTING LABEL	In Annex 1 Yes	Provisional No
Symbol(s)	R-Phrase(s)	S-phrase(s)
T, Xn	R23/24/25-40-43	S(1/2-)23-24-45

2. PHYSICO-CHEMICAL CHARACTERISTICS

From: ICSC: 0193 (1991)

2.1 Physical form	Colourless solid or yellowish viscous liquid, with characteristic odour
2.2 Molecular weight	222.2
2.3 Melting point/range (°C)	32-33
2.4 Boiling point/range (°C)	208-210
2.5 Decomposition temperature	
2.6 Vapour pressure (Pa(°C))	0.05 mm Hg @ 150°C
2.7 Relative density	1.21
2.8 Vapour density (air = 1)	7.95
2.9 Fat solubility (mg/kg, °C)	
2.10 Water solubility (mg/kg, °C)	
2.11 Partition coefficient (log Pow)	
2.12 Flammability **flash point (°C)** **explosivity limits (%,v/v)** **auto-flammability temp. (°C)**	 **open cup:** 177 **closed cup:** **lower limit:** **upper limit:**
2.13 Explosivity **danger of explosion as a result of:** **explosive properties at high temperature**	 Reacts with strong oxidants Presumed to form explosive peroxides.
2.14 Oxidising properties	
2.15 Other physico-chemical properties **(eg. liberates toxic gas on heating or in contact with water or acids)**	Solubility: miscible with acetone, chloroform, methanol, benzene and most organic resins.

3. OBSERVATIONS ON HUMANS

Where available, human data are considered to be of more relevance in determining the potential effects of chemical substances on the human population. (Annex V, Directive 67/548/EEC).

3.1 Occupational exposure

Substance claimed to produce severe skin burns and skin sensitisation in a limited number of cases - however, these data are of doubtful quality and reliability (Hine & Rowe, 1963).

This information is regarded insufficient to justify classification.

3.2 Exposure of the general public

No data available.

4. TOXICOLOGICAL DATA

4.1 ACUTE TOXICITY

4.1.1 Oral

Species	LD_{50} (mg/kg)	Observations and remarks
Rat (Long-Evans) (male)	2,570	(Reported in summary form). No information on the number of animals was provided. Slight dyspnea, and, in surviving animals, loss of weight were reported, although the doses at which these clinical signs were seen were not detailed. Although the cause of death was not established, it was possibly due to irritant effects on the stomach lining. (Hine *et al.*, 1958) **Data support classification as: Harmful if swallowed (R22)** (see Annex A)
Mouse/ Webster (male)	980	
Rabbit/ albino (male)	1,240	

4.1.2 Inhalation

Species	LC_{50} (mg/l)	Exposure time (h/day)	Observations and remarks
Rat	Not determined	4	Concentrated aerosol of 44.8 mg/l (60% RDGE in xylene). It is not clear whether the concentration quoted refers to RDGE or RDGE and xylene. All rats died within 5 days post exposure - number of animals not stated. (Westrick & Gross, 1960; reported in summary form). Xylene is classified for acute toxicity via inhalation (R20). No conclusion with respect to acute toxicity of RDGE can be drawn from this study.
Rat (Long Evans)	Not determined	8	The LC_{50} was greater than the highest vapour concentration attained (exposure concentration not determined analytically, but likely to be very low) - no deaths, number of animals not specified. (Hine *et al.*, 1958). **Data do not support classification**
Mouse (Webster)	Not determined	8	

4. TOXICOLOGICAL DATA (continued)

4.1.3 Dermal

Species	LD50 (mg/kg)	Exposure period	Observations and remarks
Rabbit	2420 (2.0 ml/kg)	7 hours	RDGE applied as a 60 % solution in xylene. Not occluded. Number of animals, decedents, clinical signs not detailed. (Westrick & Gross, 1960; reported in summary form). Xylene is classified for acute toxicity via the dermal route (R21) therefore no conclusion with respect to acute toxicity of RDGE can be drawn from this study.
Rabbit	744 (0.64 ml/kg)	Continuous	No more detail provided. (Westrick & Gross, 1960; reported in summary form). Although it is unclear for how long the RDGE was applied to the skin, this LD_{50} value for acute toxicity suggests that classification may be appropriate. **Classification with R21 is proposed (see Annex A).**

4.1.4 Skin irritation

Species	No. of animals	Exposure time	Conc. (w/w)	Dressing: (semi-occlusive, occlusive, open)	Observations and remarks (specify degree and nature of irritation and reversibility)
Rabbit/ albino	Not stated	24hrs	Unknown concentration	Occlusive	(Reported in summary form, limited details of results provided). Draize method; irritation scored at 24 and 72 h. Moderate irritation with Draize score of 5 out of possible 8. (Hine *et al.*, 1958)
Rabbit	5	Not stated	0.01 ml of 10% solution in acetone	Not stated	(From secondary source, reported in summary form). Scar tissue formation in one animal, with definite erythema and oedema in the other 4 rabbits (Westrick & Gross, 1960)
Rabbit	4	20 daily applications of 7 hr periods (removal with acetone)	1 ml of unknown concentration	Not stated	Irritation scored (Draize) at 24 hour intervals (prior to subsequent application). Severe irritation reported, score 8/8 (individual daily scores not reported). Three animals died by day 8. The authors concluded that death was most likely due to the severe irritation rather than systemic effects. (Hine *et al.*, 1958) **The data support classification with R38 (see Annex A)**

4. TOXICOLOGICAL DATA (continued)

4.1.5 Eye irritation

Species	No. of animals	Exposure time (hours)	Conc. (w/w)	Observations and remarks (specify degree and nature if irritation, any serious lesions, reversibility)
Rabbit	>1 (but actual number not stated)	Not stated	0.1 ml of 20% suspension in propylene glycol	(Reported in summary form, limited details of results provided). Draize method. Average score from readings at 1, 24 and 48 h was 45 (max. possible =110), indicating a moderate effect. (Hine *et al.*, 1958). **Data support classification with R36.**

4.1.6 Irritation of respiratory tract

Species	No. of animals	Exposure time (h/days)	Conc. (w/w)	Observations and remarks (specify degree and nature if irritation, any serious lesions, reversibility)
Rat	Not stated	7 hr/day (50 exp)	Air saturated with vapour; control group	(Reported in summary form, limited details of results provided). Exposure concentration not determined analytically, but likely to be very low. No gross or microscopic lesions seen at necropsy. Although the tissues studied at necropsy were not detailed, since this was an inhalation study it is assumed that the lungs and/or respiratory tract would have been examined. (Hine *et al.*, 1958). ***Data do not support classification***

4.1.7 Skin sensitisation

Species	Type of test	No. of animals	Incidence of reactions observed
			No data available. **Arguments for classification with R43 are given in Annex A.**

4. TOXICOLOGICAL DATA (continued)

4.2 REPEATED OR PROLONGED TOXICITY GROUPED ACCORDING TO SUBACUTE AND SUBCHRONIC TOXICITY

4.2.1 Oral

Species/ strain	Dose (mg/kg bw)	Duration of treatment	Observations and remarks (specify group size, NOAEL, effects of major toxicological significance)
Rat (F344/N) [Males, 8/treatment group, 16 controls]	0, 12, 25 (gavage in corn oil)	5 d/wk for 2 weeks	Limited study in which only the stomach was examined at necropsy. There was no evidence of cell proliferation or hyperkeratosis in rats dosed at 12 mg/kg or in control rats. At the higher dose there was incidence of multifocal forestomach epithelial cell proliferation (4/8 rats) and incidence of multifocal hyperkeratosis (5/8 rats). (Ghanayem *et al.*, 1986).
Rat (F344/N) 5/sex/ treatment group	0, 190, 380, 750, 1500 and 3000	14 consecutive daily doses	All rats dosed at 750 mg/kg or more, and 2/5 males at 380 mg/kg died before end of study. Cause of death was not established; in most cases, stomach lesions seen were not considered severe enough to result in death. Mean body weight decreased in nearly all treatment groups. Reddening of the renal medulla, and lesions and papillary growths in stomach were observed at necropsy in many of the survivors (dose not stated). (NTP, 1986).
Rat (F344/N) 10/sex/ treatment group	0, 12.5, 25, 50, 100, and 200	5 days/ week for 13 weeks	At 200 mg/kg, 1 male died during 8th week of study; cause of death not established but the animal was emaciated. Mean body weight was depressed 10% or more in male rats dosed at 100 mg/kg and above, and in females dosed at 200 mg/kg. Histopathological examination of the stomach was performed on animals dosed at 12.5, 25 or 50 mg/kg. Compound related changes observed in forestomach at 12.5 mg/kg and above, were inflammation, ulceration, squamous cell papilloma, hyperkeratosis and basal cell hyperplasia. Histopathology changes in the liver were necrosis and minimal to mild centrilobular fatty metamorphosis at 200 mg/kg. (NTP, 1986).
Rat (F344/N) 100/sex controls, 50/sex/ treatment group	0, 12, 25, 50	5 days/ week for 103 weeks	Decreased survival was dose-related. None of the males at 50 mg/kg and only 10% of the males at 25 mg/kg survived until the end of the study, compared to 46% at 12 mg/kg and 78% of controls. In females, survival rates were 2%, 32%, 70% and 74%, respectively. Most of the early deaths (occurring from week 30 onwards) were attributable to non-treatment-related bronchopneumonia. Body weight gain was not affected in the low dose group. Wheezing and respiratory distress possibly relating to bronchopneumonia, were the only compound-related clinical signs observed. Histopathology revealed hyperkeratosis, hyperplasia and neoplasms of the squamous epithelium of the forestomach at all dose levels. The squamous epithelium of the oesophagus and nasopharynx was hyperkeratotic in some rats (NTP, 1986).
Mouse ($B6C3F_1$) 5 / sex / group	0, 90, 190, 380, 750 and 1500 mg/kg	14 days	9/10 mice receiving 1500 mg/kg and 2/5 males receiving 750 mg/kg died before the end of the study. The deaths were attributed to RDGE. Mean body weight decreased in all mice dosed at 750 mg/kg and 5/10 dosed at 380 mg/kg. Gross pathology revealed reddening of stomach mucosae and renal medulla (dose-levels not stated) (NTP, 1986).

4.2.1 Oral continued

Species/ strain	Dose (mg/kg bw)	Duration of treatment	Observations and remarks (specify group size, NOAEL, effects of major toxicological significance)
Mouse ($B6C3F_1$) 10 / sex / group	0, 25, 50, 100, 200 and 400	13 weeks	16/20 mice dosed at 400 mg/kg died during the study. The deaths were attributed to RDGE. Mice at 400 mg/kg had depressed body weights (10-25%). Histopathological examination of the stomach, liver kidneys and testes was performed on animals at all doses. Compound related changes in forestomach were inflammation, ulceration, squamous cell papilloma, hyperkeratosis and basal cell hyperplasia at 25 mg/kg and above. Histopathology changes in the liver in mice dosed at 400 mg/kg included focally extensive necrosis and, in decedents only, fatty metamorphosis was seen. Slight to mild focal tubular atrophy of the testes was seen in 3/10 mice dosed at 400 mg/kg that died during weeks 9-10. This lesion was not seen in the mice in this dose level that survived until the end of the study, therefore it is considered to be secondary to general systemic toxicity. (NTP, 1986).
Mouse ($B6C3F_1$) 50/sex/ group	0, 50, 100	5 days/ week for 103 weeks	In males 68% of the mice at 100 mg/kg and 52% at 50 mg/kg survived until the end of the study, compared to 60% of the controls. In females, survival rates were 20%, 26% and 40%, respectively. Most of the deaths in female mice in all groups were attributable to non-treatment-related necrosuppurative lesion of the ovary which spread through the abdomen. Histopathology revealed hyperkeratosis, hyperplasia and neoplasms of the squamous epithelium of the forestomach at both dose levels. Minimal mineralization was found in the kidneys of 30 high dose males, and 18 low dose males compared to 8 control group males.(NTP, 1986).

Note: In the NTP studies, RDGE was administered 81% pure by gavage in corn oil.

4.2.2 Inhalation

Species	Conc. mg/l	Exposure time	Duration of treatment	Observations and remarks (specify group size, NOAEL, effects of major toxicological significance)
Rat	Air saturated with vapour + control group	7 hr/day, (5 day/wk)	10 weeks (50 exp.)	(Study reported in summary form). No treatment-related deaths. No treatment-related clinical effects were seen. No significant gross or microscopic lesions were found in survivors at necropsy. (Hine *et al.*, 1958) **Data do not support classification.**

4.2.3 Dermal

Species	Dose mg/kg	Exposure time	Duration of treatment	Observations and remarks (specify group size, NOAEL, effects of *major toxicological significance)*
				Data presented in section 4.3.3 **Data do not support classification.**

4. TOXICOLOGICAL DATA (continued)

4.3 CARCINOGENICITY (INCLUDING CHRONIC TOXICITY STUDIES)

On the basis of the data presented below it is proposed that this substance be classified as a category 3 carcinogen. See also Annex A.

4.3.1 Oral

Species/ strain	D ose mg/kg bw	Duration of treatment	Observations and remarks (specify group size, effects of major toxicological significance)
Rat (F344/N) 50/sex/ treatment group 100 controls/sex	0, 12, 25 & 50	5 days/week for 103 weeks	Survival rates are given under Section 4.2.1. Most of the early deaths were attributable to bronchopneumonia. Wheezing and respiratory distress were the only compound-related clinical signs observed (however, it is not clear whether this was in the same animals that had bronchopneumonia). Histopathology revealed hyperkeratosis, hyperplasia and neoplasms of the stratified squamous epithelium of the forestomach at all dose levels. In some animals (control 0/99, low dose 66/100, mid dose 72/100, high dose 7/99), squamous cell carcinomas were observed on the non-glandular stomach mucosa. The large number of early deaths in high dose animals explains the low incidences of benign and malignant neoplasms found in this group compared with the lower dose groups. (NTP, 1986; Murthy *et al.*, 1990).
Mouse ($B6C3F_1$) 50/sex/group	0, 50 & 100	5 days/ week for 103 weeks	Survival rates are given under Section 4.2.1. Most of the deaths in female mice were attributable to a non-treatment-related necrosuppurative lesion of the ovary which spread through the abdomen. Histopathology revealed hyperkeratosis, hyperplasia and neoplasms (carcinomas: low dose 26/98, high dose 48/99) of the stratified squamous epithelium of the forestomach at both dose levels. The incidences of females with either primary hepatocellular adenomas or carcinomas had a significant positive trend (control 3/48, low dose 1/50, high dose 7/49, historical 6/98); However, liver tumors are not rare in this species of mouse. (NTP, 1986; Murthy *et al.*, 1990). **Data support classification as Carc Cat 3; R40 (see Annex A).**

Note: In these NTP studies, RDGE was administered 81% pure by gavage in corn oil.

4.3.2 Inhalation

Species	conc. mg/l	Exposure time	Duration of treatment	Observations and remarks (specify group size, effects of major toxicological significance)
				No data available.

4. TOXICLOGICAL DATA (continued)

4.3.3 Dermal

Species	Dose	Exposure time	Duration of treatment	Observations and remarks (specify group size, NOEL, effects of major toxicological significance)
Mouse (C57BL)	Not stated	Skin painted 3 times per week	Not stated	Papillomas of the skin were reported. - results only reported in abstract form. (McCammon *et al.*, 1957)
Mouse (C3Hf/Bd)	0.45, 0.9, or 1.8 mg/week	Not stated (skin painting)	2 year 3 applications/ week on shaved skin.	Skin changes included mild hyperkeratosis, depigmentation and follicle depletion. No evidence of skin neoplasms. (Holland *et al.*, 1981)
Mouse (Swiss Mellerton) Groups of 30	100 mg of a solution (1% in benzene)	painted 3 times per week	Lifetime (median survival time, 70 weeks)	No evidence of benign or malignant skin tumors was observed in 30 treated mice. Moderate to severe crusting and/or scarring, and hair loss were observed at the application site. Mean survival times: treated group 70 wk, benzene control 71 wk and untreated control 63 wk. (Van Duuren *et al.*, 1965)
Mouse (C3H) Number unspecified	50 mg/kg (81% pure product as 5% in methyl ethyl ketone)	2/ wk	Assumed lifetime	Preliminary studies identified 50 mg/kg to be MTD. Median survival time was 46 wks. After 36 wks a benign papilloma appeared on one mouse that survived for an additional 15 weeks. In week 48 a subdermal growth that was identified as a squamous cell cancer appeared on another mouse. This study is difficult to interpret since there were no details of a concurrent control group (summary of unpublished study cited by Hine et al, 1958).

4.4 GENOTOXICITY

4.4.1 *In vitro* studies

Test	Cell type	Conc. range	Observations and remarks
Reverse mutation (Ames)	*S.typhimurium* TA 98, TA 100, TA 1535, TA 1537	5-5000 µg/plate	**Positive.** Reproducible, dose-related increases in revertants in strains TA100 and TA1535 observed without metabolic activation and in the presence of Aroclor-induced hamster or rat liver S9 (Canter *et al*, 1986).
Reverse mutation (Ames)	*S.typhimurium* TA100	50-1000 µg/plate	**Positive.** Reproducible, dose-related increases in revertants observed without metabolic activation. (Seiler, 1984).
Cytogenetics-chromosome aberrations	CHO cells	0, 8 and 25 µg/ml	**Positive.** Two separate experiments without metabolic activation performed, with exposure/fixation times 6 hr in first assay and 24 hr in second assay. A statistically significant dose-related increase in aberration frequency (excluding gaps) was observed at both fixation times (mean values of 8, 24 & 44% at 6 hrs, and 9, 48, and 93% at 24 hrs at 0, 8.25 mg/kg respectively). (Seiler, 1984).

4. TOXICOLOGICAL DATA (continued)

4.4.2 *In vivo* studies (somatic cells)

Test	Species	Tissue	Harvest time	Observations and remarks (include route of administration)
Micronucleus	Mouse, (ICR) strain. Male and female. (4 animals / dose group)	Bone marrow	24 h (all doses), 48 & 72 h (controls and top dose only)	**Negative.** Oral gavage (0, 300, 600 mg/kg as aqueous solution in polyethylene glycol-400). Systemic toxicity reported but not detailed, one of 4 in top dose group died. The P/N ratio was unaffected by treatment. No increases in MN frequency observed. A positive result was demonstrated for another substance, diglycidylaniline, within the same study (Seiler, 1984).

4.5 FERTILITY

Species	Route	Dose	Exposure time	Number of gen. exposed	Obsevations and remarks
					No data available.

4.6 DEVELOPMENTAL TOXICITY

Species	Route	Dose	Exposure	Observations and remarks
				No data available.

5. ECOTOXICOLOGICAL STUDIES

Data not reviewed for Health Effects Working Group

6. ENVIRONMENTAL FATE

Data not reviewed for Health Effects Working Group

7. ADDITIONAL ENVIRONMENTAL EFFECTS

Data not reviewed for Health Effects Working Group

8. REFERENCES

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ANNEX A

EC CLASSIFICATION AND LABELLING

RESORCINYL DIGLYCIDYL ETHER (RDGE)
(EINECS name: m-bis(2,3-epoxypropoxy)benzene)

Background information on metabolism of RDGE

Glycidyl ethers, in common with other epoxides, may be metabolised throught the following pathways:

(i) expoxide hydrolase activity, leading to hydrolysis of the epoxide group under formation of the corresponding diol;
(ii) conversion to glutathione conjugates by glutathione-S-epoxide conjugases; and
(iii) non-enzymic covalent binding with proteins, RNA and DNA.

RDGE has been shown to conjugate with glutathione via glutathione-S-epoxide transferase *in vitro*. (Boyland & Williams, 1965). When RDGE was administered (route not detailed) to mice it was metabolised to bis-diol compounds (Seiler, 1984). No further data on the pharmacokinetics and tissue distribution were located in the literature.

Boyland, E. & Williams, K. (1965) An enzyme catalysing the conjugation of epoxides with glutathione. Biochem., 94, 190-197.
Seiler (1984) The mutagenicity of mono- and di-functional aromatic glycidyl compounds. Mutat. Res., 135, 159-167.

Arguments for classification: Physico-chemical effects

No classification is proposed.

Arguments for classification: Health effects

1) *Acute oral toxicity*
A single oral LD_{50} value in the rat, of 2570 mg/kg is available. Although this is outside the range for classification for acute toxicity, LD_{50} values in two other species (mice, 980 mg/kg and rabbits, 1240 mg/kg) support classification with R22. There is no evidence available to support the existing classification with R25.

Acute inhalation toxicity
In rats and mice exposed to a saturated vapour of RDGE for 8 hr there were no signs of toxicity. We propose that no classification is justified.

Acute dermal toxicity
No data are available to support the existing classification with R24. A rabbit LD_{50} value of 744 mg/kg supports our proposal to classify with R21.

2) *Skin irritation*
In a skin irritation study in which RDGE was applied to rabbit skin for 24 hours, RDGE was a moderate irritant (Draize score 5/8). In another study in which 4 rabbits were treated with

20 daily applications, severe irritation was reported (Draize score 8/8). Within this study, 3 deaths, which occurred by treatment-day 8, were attributed to severe irritation. RDGE has been reported to produce "severe skin burns" in humans, although these data are of unreliable quality; the actual exposure circumstances and the precise nature of the effects seen are not clear. Although there are no studies conducted to current regulatory guidelines, overall the available data indicate that RDGE is a skin irritant. These data support R38.

3) *Eye irritation*

In an eye irritation study (reported in summary form), a Draize score of 45/120 was obtained indicating that RDGE is a moderate eye irritant. These data support R36.

4) *Respiratory irritation*

In an inhalation study, fifty 7hr exposures to air saturated with RDGE vapour produced no evidence of respiratory irritation. No classification is proposed for this relatively non-volatile substance.

5) *Skin sensitisation*

RDGE is presently classified with R43. Although, there appear to be no animal studies available to support classification, a single report providing human anecdotal data was found. While the quality of this information is data is limited, it does suggest that RDGE might have skin sensitisation properties. Given that the structurally similar glycidyl ethers (allyl-, *n*-butyl-, and phenyl-) are skin sensitisers, we propose that RDGE is likely to have the same property and propose classification with R43.

6) *Respiratory Sensitisation*

No animal or human data are available. Consequently, classification is not justified.

7) *Repeated Dose Toxicity*

In repeated oral gavage studies in rats and mice, lesions of the forestomach were observed including ulceration, inflammation, hyperplasia and hyperkeratosis. A clear NOAEL for these effects could not be identified from 90-day or 2-year studies; a LOAEL of 12.5 mg/kg was found in rats exposed for 90 days or 2 years; in mice, LOAELs of 25 mg/kg and 50 mg/kg were identified in 90-day and 2 year studies respectively. No stomach lesions were seen in rats at 12 mg/kg in a 14 day oral gavage study.

No other effects indicating serious damage to health were seen at exposure levels within the classification range.

The lesions seen in the forestomach in these experiments are considered to be the result of repeated irritation due to the effect of a concentrated bolus delivery of test substance to forestomach epithelium. The bolus delivery of an irritant test substance is not considered relevant to normal occupational exposure conditions. Therefore, no classification is proposed.

8) *Mutagenicity*

RDGE gave positive results in the absence of exogenous metabolic activation in two bacterial mutagenicity assays and in an *in vitro* cytogenetics assay. From these results it is concluded that this epoxide is a direct-acting mutagen. This electrophilicity is consistent with that of the structurally similar substances, allyl-, *n*-butyl and phenyl- glycidyl ethers.

Only one study in somatic cells *in vivo* is available. In this mouse micronucleus assay, although RDGE gave a negative result following oral administration, it is considered likely that the target tissue (bone marrow) was not adequately exposed and that the result may have been a false negative. Not only were there no signs of systemic toxicity in this assay, but the LD_{50} of RDGE has been shown to be increased 10-fold in rodents when administered by i.p. injection rather than oral gavage (Hine et al, 1958). Either RDGE is poorly absorbed via the gastrointestinal tract or it is metabolised to a less toxic metabolite. The concept that the oral route of administration might have lead to a false negative result is supported by the finding that *n*-butyl glycidyl ether, a structurally similar electrophilic substance, gave a positive result in the bone marrow micronucleus test following i.p. but not oral administration (Gardiner et al, 1992).

Concern remains that RDGE may cause mutagenic effects in somatic cells at sites of initial contact in the body. Classification with Muta Cat 3; R40 is proposed since this substance is a reactive epoxide, mutagenic in vitro without exogenous activation, and has not been tested in a relevant in vivo test (i.e. at a site of initial contact).

Gardiner TH, Waechter JM Jr, Wiedow MA and Solomon WT (1992). Glycidyloxy compounds used in epoxy resin systems: a toxicology review. Regul Toxicol Pharmacol, 15, S1-S77.
Hine CH, Kodama JK, Anderson HH, Simonson DW & Wellington JS (1958). AMA Arch. Ind Health, 17, 129.

9) *Carcinogenicity*

In the absence of observations in humans, a decision regarding classification must be made on the basis of animal carcinogenicity studies.

In an oral gavage NTP study, RDGE was carcinogenic in mice and rats; the stratified squamous epithelium of the proximal alimentary tract was the primary target tissue affected. A high incidence of benign and malignant neoplasms was observed in the non glandular stomach of both male and female mice and rats. In both species, histopathology revealed also hyperkeratosis, hyperplasia and neoplasms of the stratified squamous epithelium of the forestomach at both dose levels tested (12, 25 mg/kg in rats; 50, 100 mg/kg in mice).

The malignant tumours reported in these oral gavage studies developed at the site of initial contact and were associated with hyperkeratosis and hyperplasia of the forestomach epithelium. This suggests that chronic tissue damage with resultant hyperplasia may have contributed to the carcinogenic response seen. As such, there is some uncertainty about the mechanism of tumour induction; both the genotoxic and irritant properties of RDGE may have played a role.

There is no good evidence from skin painting studies in mice that RDGE causes tumours when applied dermally.

Overall, it is possible that genotoxicity and/or chronic cell proliferation may underlie the mechanism of the carcinogenic response seen in rodents in oral gavage studies. We believe that there is considerable uncertainty about the relevance to humans of repeated bolus administration of an irritant substance that results in tumour formation at the site of contact. Furthermore, the tumour formation was in the forestomach, which is also of uncertain

relevance for human health. Therefore, in view of this uncertainty, we propose that classification with Car Cat 2; R45 is not justified. We propose Carc Cat 3; R40.

10) *Reproductive Toxicity*

No data available. No classification proposed.

UK proposal

Carc Cat 3; R40: Muta Cat 3; R40: Xn; R21/22: Xi; R36/38: Xi; R43

HSE Toxicology Unit
20 March 1997

Original classification proposal of phenyl diglycidyl ether from 1997

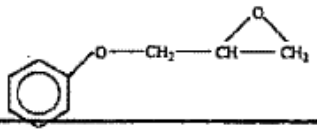
Commission of the European Communities DG XI

CLASSIFICATION AND LABELLING OF DANGEROUS SUBSTANCES
Recommended form to be used for the proposed classification and labelling of Dangerous Substances in order to update Annex 1 of Directive 67/548/EEC

Date: 29th July 1997	Prepared by: Health and Safety Executive, UK

The information contained in this form is not regarded as confidential. ECBI 21 19

1. Identification of the substance

INDEX No. 603-067-00-X	**EC No.** 204-557-2 **CAS No.** 122-60-1 **ID No.** UC40
1.1 EINECS Name **If not in EINECS IUPAC Name**	2,3-epoxypropyl phenyl ether
1.2 Synonyms (state ISO name if available)	**Phenyl glycidyl ether** 1,2-Epoxy-3-phenoxypropane, glycidyl phenyl ether, phenol glycidyl ether, phenoxypropylene oxide, 3-phenoxy-1,2-epoxypropane, phenoxypropene oxide phenyl-2,3-epoxypropyl ether, oxirane (phenoxymethyl)-, PGE
1.3 Molecular formula	$C_9H_{10}O_2$
1.4 Structural formula	
1.5 Purity (w/w)	
1.6 Significant impurities or additives, their concentrations (w/w)	
1.7 Known uses	**Industrial:** A chemical intermediate; a monofunctional reactive modifier. **General public:** Not used.
1.8 Proposed classification	Carc Cat 2; R45 Muta Cat 3; R40 Xn; R20 Xi; R37/38 R43

EXISTING LABEL	In Annex I Yes	Provisional No
Symbol(s)	R-Phrase(s)	S-phrase(s)
Xn	R21-43	S(2-)24/25

2. PHYSICO-CHEMICAL CHARACTERISTICS

(References: IARC, 1989; MAK, 1992)

2.1 Physical form	Colourless liquid
2.2 Molecular weight	150
2.3 Melting point/range (°C)	3.5
2.4 Boiling point/range (°C)	245
2.5 Decomposition temperature	
2.6 Vapour pressure (Pa(°C))	0.013 hPa at 20°C
2.7 Relative density	
2.8 Vapour density (air = 1)	4.37 at 25°C
2.9 Fat solubility (mg/kg, °C)	
2.10 Water solubility (mg/kg, °C)	Nearly insoluble in water
2.11 Partition coefficient (log Pow)	
2.12 Flammability **flash point (°C)** **explosivity limits (%,v/v)** **auto-flammability temp. (°C)**	 **open cup:** **closed cup:** **lower limit:** **upper limit:**
2.13 Explosivity **danger of explosion as a result of:** **explosive properties at high temperature**	 **shock:** **friction:** **ignition:**
2.14 Oxidising properties	
2.15 Other physico-chemical properties **(eg. liberates toxic gas on heating or in contact with water or acids)**	Viscosity: 6cP at 25°C (cited in IARC, 1989) --- Conversion Factor: 1 ppm = 6.23 mg/m^3 (MAK, 1992)

3. OBSERVATIONS ON HUMANS

Where available, human data are considered to be of more relevance in determining the potential effects of chemical substances on the human population. (Annex V, Directive 67/548/EEC).

3.1 Occupational exposure

There are several reports of allergic contact dermatitis caused by occupational exposure to phenyl glycidyl ether.

Three individuals (aged 15, 19 and 45 years, respectively) developed allergic contact dermatitis from PGE used in an adhesive tape (the epoxy adhesive contained approx. 10% PGE). The allergenicity of phenyl glycidyl ether was confirmed by patch testing (Nakagawa et al, 1991).

Among 58 exposed workers with dermatitis, phenyl glycidyl ether was identified as the primary allergen in 9 cases. Sensitivity to both phenyl glycidyl ether and another epoxy resin used in the workplace was observed in an additional 26 workers (Rudzki and Krajewska, 1979).

Fifteen individuals with symptoms suggestive of occupational eczema were patch tested with the suspect allergen, phenyl glycidyl ether. Positive results were obtained with 8 cases. The aetiology of the eczema observed in the remaining 7 cases was not further characterised. Among the 15 cases, there were no responses to another potential sensitiser in the workplace (a chloroparaffin) or a standard series of allergens. Patch testing of phenyl glycidyl ether in 58 non-exposed controls gave negative results (Zschunke and Behrbohm, 1965).

A review of medical records from 1947-1956 indicated 13 cases of dermatitis at one workplace where PGE and other glycidyl ethers were used. In one case, second-degree chemical burns occurred 5 days after an accidental splash of phenyl glycidyl ether on the foot. In 5 of the remaining cases, dermatitis was related to (minimal) phenyl glycidyl ether exposure - clinical signs included itching, erythema, blisters and papules. It is not clear whether the dermatitis was irritant or allergic in nature (Hine et al, 1956).

Seven out of ten marble workers who developed contact dermatitis as a result of handling epoxy resin and cresyl glycidyl ether were found also to have developed skin sensitivity to PGE (Angelini et al, 1996).

These data indicate that PGE has the potential to cause skin sensitisation in humans and, together with the positive evidence from studies in animals (see below), support the existing classification with R43.

3.2 Exposure of the general public

No data available.

4. TOXICOLOGICAL DATA (indicate conclusions and biographical references)

4.1 ACUTE TOXICITY

4.1.1 Oral

Species	LD50 (mg/kg)	Observations and remarks
Rat (Long-Evans) [5 or 6/ dose group]	3850	Males only. (Hine et al, 1956).
Rat	4260	(Smyth et al, 1954; Weil et al, 1963).
Rat	2600	(Czaijkowska and Stetkiewicz, 1972).
Mouse (Webster) [5 or 6/ dose group]	1400	Males only. (Hine et al, 1956). **No classification is proposed.**

4.1.2 Inhalation

Species	LC50 (mg/l)	Exposure time (hours)	Observations and remarks
Rat (Long Evans) [6/ group]	not determined	4	The LC50 was greater than the highest vapour concentration attained (100 ppm*: 0.06 mg/l). Dyspnea, lacrimation, salivation and nasal discharge observed following exposure (Hine et al, 1956).
Mouse (Webster) [5 or 6/ group]	not determined	8	The LC50 was greater than the highest vapour concentration attained (100 ppm*: 0.06 mg/l). Dyspnoea, lacrimation, salivation and nasal discharge observed following exposure (Hine et al, 1956).
Rat (Sprague-Dawley) [6 males/ group]	not determined	4	Rats were exposed to a vapour aerosol mixture and observed for up to 14 days. Approximate lethal concentration of 323 ppm (approx 2 mg/l) was determined. Loss of body weight and severe irritation of the scrotum were observed in surviving rats (Terrill and Lee, 1977). **In view of the deaths reported at approx 2 mg/l, classification with R20 is proposed (see Annex A).**

* There is some doubt about the value of 100 ppm given as the exposure level in this study. Several authors have subsequently noted that Hine et al (1956) misquoted the vapour pressure of phenyl glycidyl ether and suggest that the saturated vapour level employed was probably about 10 ppm (approx 0.06 mg/l).

4. TOXICOLOGICAL DATA (continued)

4.1.3 Dermal

Species	LD50	Exposure period	Observations and remarks
Rabbit	2990 mg/kg	7 hours	Undiluted test substance applied to the skin of rabbits under rubber sleeves. Rabbits wrapped in toweling to further minimise evaporation (Hine et al, 1956).
Rabbit	1500 microlitres/kg		No further details available. (Smyth et al, 1954; Weil et al, 1963).
Rat	2160 mg/kg		Necrotic changes observed at the site of application (Czajkowska and Stetkiewiez, 1972). **These data do not support the existing classification with R21; no classification is proposed.**

4.1.4 Skin irritation

Species	No. of animals	Exposure time (h/day)	Conc. (w/w)	Dressing: (occlusive, semi-occlusive, open)	Observations and remarks (specify degree and nature of irritation and reversibility)
Rabbit	3	4 hours	100%	semi-occlusive	Annex V method. Mean scores at 24, 48 and 72 h for individual animals were 0.67, 0.67 and 1.0 for erythema, and 0, 0 and 0.33 for oedema. Slight scales were observed in all animals at end of study (day 7). (RCC, 1988a)
Rabbit	not stated	24 hours	100%	not stated: 3 layers of gauze were secured by adhesive tape.	Draize method; limited details of results provided. Irritation scores noted at 24 and 72 h. Mild irritation was observed and given an average score (all readings) of 0.7 (max. possible = 8) (Hine et al, 1956).
Rabbit	5	24 hours	various	not stated	Non-standard method designed for potency ranking of irritant substances. Grade 5 (max. possible =10) in at least 1 of 5 rabbits. (Smyth et al (1954; Weil et al, 1963)
Rabbit	4	24 hours	not stated	not stated; 2 layers of gauze were secured by adhesive tape	Draize method; hyperpigmentation and drying of the skin noted together with necrosis of the dermis and subcutaneous tissue. Necrotic changes persisted for up to 2 months, after which scars remained (Czajkowska and Stetkiewiez, 1972) **Classification with R38 is proposed.**

4. TOXICOLOGICAL DATA (continued)

4.1.5 Eye irritation

Species	No. of animals	Exposure time (hours)	Conc. (w/w)	Observations and remarks (specify degree and nature if irritation, any serious lesions, reversibility)
Rabbit	3	>24 hours	100%	Annex V method. No significant ocular lesions were observed. Mean scores of individual animal readings at 24, 48 and 72 h were 0, 0.67 and 1.0 for corneal opacity, zeros for iris lesions, 0, 0.67 and 1.0 for conjunctival redness, and 0, 0.33 and 0.33 for conjunctival oedema. (RCC, 1988b).
Rabbit	not stated	not stated	100%	Draize method; limited details of results provided. Average score from readings at 1, 24 and 48 h was 8 (max. possible =110), indicating a minimal effect (Hine et al, 1956).
Rabbit	not stated	not stated	various	Non-standard method designed to enable potency ranking of potential eye irritants. Score at 18-24 hours was 2 (max. possible=10) (Smyth et al, 1954; Weil et al, 1963).
Rabbit	4	not stated	100%	Three drops of test substance applied to the conjunctival sac. Signs of irritation (congestion of the conjuncti..., lacrimation) were not described fully, although no effects persisted at 4 days post-exposure (Czajkowska and Stetkiewiez, 1972). **No classification is proposed.**

4.1.6 Irritation of respiratory tract

Species	No. of animals	Exposure time (h/days)	Conc. (w/w)	Observations and remarks (specify degree and nature if irritation, any serious lesions, reversibility)
				On the basis of observations in single and repeated exposure (carcinogenicity) studies in rats, **classification with R37 is proposed (see Annex A).**

4. TOXICOLOGICAL DATA (continued)

4.1.7 Skin sensitisation

Species	Type of test	No. of animals	Incidence of reactions observed
Guinea pig	M&K	20	Induction: 3% intradermally and 5% topically. Challenge: 3% topically. One animal died on day 6 and one on day 11; these deaths not substance-related. On challenge, 13/18 animals responded with a positive result (RCC, 1988c).
Guinea pig	non standard	10	Topical induction: 5% solution; non-irritating; 6 days/week; 34 days. All 10 guinea pigs responded to topical challenge with 1% phenyl glycidyl ether (Rudzki and Krajewski, 1979).
Guinea pig	non standard	18	Animals received 8 intradermal injections of diluted phenyl glycidyl ether (conc. not specified) 3 times/week for 3 weeks. Challenge at 24 and 48 hours after the last dose indicated sensitisation in 1/18 animals. From the very limited reporting of this study, no definite conclusions can be reached (Weil et al, 1963).
Guinea pig	non standard	not stated	Topical induction with phenyl glycidyl ether (conc. not stated) daily for 7 days (erythema observed on day 7). On weeks 5, 9 and 12 of the study, single applications of phenyl glycidyl ether to previously untreated skin produced oedema and erythma within 4 days. Although this study was non-standard and poorly reported, the results appear to indicate a sensitisation response (Zschunke and Behrbohm, 1965). **These data and the observations of skin sensitisation in exposed humans, justify retention of the existing classification with R43.**

4. TOXICOLOGICAL DATA (continued)

4.2 REPEATED OR PROLONGED TOXICITY GROUPED ACCORDING TO SUBACUTE AND SUBCHRONIC TOXICITY

4.2.1 Oral

Species/strain	Dose	Duration of treatment	Observations and remarks (specify group size, NOAEL, effects of major toxicological significance)
			No data available.

4.2.2 Inhalation

Species	conc. mg/l	Exposure time	Duration of treatment	Observations and remarks (specify group size, NOAEL, effects of major toxicological significance)
Rat (Long Evans) [10/ dose group]	0 & 100* ppm (0.06 mg/l)	7 hours/ day	50 days	Minimal signs of eye irritation and respiratory distress in exposed animals. No other significant gross or microscopic findings (Hine et al, 1956).
Rat (Sprague-Dawley) [6 males and 6 females/ group]	0 & 29 ppm (0.18 mg/l)	4 hours/ day	14 days	At 29 ppm , rats exposed to a vapour-aerosol mixture. Signs of toxicity included decreased weight gain, "atrophic changes" in kidney, liver, spleen, thymus and testes, and chronic catarrhal tracheitis. The nature and extent of these changes was not further described (Terrill and Lee, 1977).
Rat (Sprague-Dawley) [6 males and 6 females/ group/ time point]	0, 1, 5 & 12 ppm (0.005, 0.03 & 0.07 mg/l)	6 hours/ day	30, 60 or 90 days (maximum of 63 exposures)	At 5 ppm and 12 ppm, mild patchy hair loss predominantly on the head, neck and shoulder region of the animals with perifollicular inflammation, keratotic vesicles and disturbances of keratinization. These effects were more common in female animals. No other clinical signs of toxicity. No changes in biochemical, blood or urinary parameters. No gross or microscopic signs of toxicity in the tissues. (Note: No histological examination of nasal tissue). (Terrill and Lee, 1977; Lee et al, 1977).
Dog (Beagle) [6 males/ dose group]	0, 1, 5 & 12 ppm	6 hours/ day	90 days	No clinical signs of toxicity were observed. No significant haematological, biochemical, gross tissue or microscopic findings (Terrill and Lee, 1977; Lee et al, 1977). **No classification is proposed (see Annex A).**

* There is some doubt about the value of 100 ppm given as the exposure level in this study. Several authors have subsequently noted that Hine et al (1956) misquoted the vapour pressure of phenyl glycidyl ether and suggest that the saturated vapour level employed was probably about 10 ppm (0.06 mg/l).

4.2.3 Dermal

				No data available.	

4. TOXICOLOGICAL DATA (continued)

4.3 CARCINOGENICITY (INCLUDING CHRONIC TOXICITY STUDIES)

4.3.1 Oral

			No data available.

4.3.2 Inhalation

Species	conc. mg/l	Exposure time	Observations and remarks (specify group size, effects of major toxicological significance)
Sprague-Dawley rats (100 males & 100 females per group)	0, 1 & 12 ppm (0, 0.006, 0.07 mg/l)	6 h/ day 5 days/wk 24 months	Carcinomas of the nasal epithelium observed in 1/89 male and 0/87 female controls, 0/83 male and 0/88 female low dose and in 9/85 male and 4/89 female high dose rats. The findings at the high dose were statistically significant. At the high dose only, squamous cell metaplasia, rhinitis, epithelial desquamation, regeneration, hyperplasia and dysplasia of the respiratory epithelium were observed, especially in the anterior regions of the nasal cavity (Lee et al, 1983). The carcinogenic response observed in rats supports the proposal to classify with Carc Cat 2 R45. **Arguments for classification are provided in Annex A.**

4.3.3 Dermal

			No data available.

4.3.4 In vitro transformation assays

Test system	Exposure levels	Observations	Remarks
SA7 virus transformation of primary hamster embryo cells	0, 1.6, 8 and 40 micrograms/ml (toxicity at higher levels)	Dose-dependent enhancement of viral transformation	It is unclear how these non-validated studies performed by Greene et al (1979) should be evaluated. Without validation these results do not contribute to assessment of the carcinogencity of phenyl glycidyl ether.
Transformation of secondary hamster embryo cells.	0, 6.25 and 12.5 micrograms/ml (toxicity at higher levels)	Dose-dependent increase in transformation index.	

4. TOXICOLOGICAL DATA (continued)

4.4 GENOTOXICITY

4.4.1 In vitro studies

Test	Cell type	Conc. range	Observations and remarks
Reverse mutation (Ames)	*S.typhimurium* TA97, TA98, TA100, TA1535	3-1000 micrograms/ plate	**Positive.** Reproducible, dose-related increases in revertants for TA97, TA100 and TA1535 observed without metabolic activation and in the presence of Aroclor-induced hamster or rat liver S9 (Canter et al, 1986).
	S.typhimurium TA100, TA1535,	5-100 micrograms/ plate	**Positive.** Reproducible, dose-related increases in both tester strains in absence of metabolic activation (Neau et al, 1982).
	S.typhimurium TA100	50-1000 micrograms/ plate	**Positive.** Dose-related increase in revertants in absence of metabolic activation (Seiler, 1984).
	S.typhimurium TA98, TA100, TA1535, TA1537, TA1538	0.5-500 micrograms/ plate	**Positive.** Dose-related increases in revertants for TA100 and TA1535 with and without rat liver S9 (Greene et al, 1979).
Cytogenetics-chromosome aberrations	CHO cells	0, 8 & 25 micrograms/ ml	**Positive.** Two experiments without metabolic activation were performed, with exposure/fixation times 6h and 24 h. A slight dose-related increase in aberration frequency at the shorter fixation time was observed (mean values of 1, 5 & 8%). In the other experiment, the mean aberration frequency was 2% in control and exposed cultures. No toxicity reported at top dose. Study included resorcinol diglycidyl ether as a positive control (aberration frequencies > 40%). (Seiler, 1984).
Mammalian cell gene mutations	CHO cells (*hprt* locus)	0, 20, 30, 40 & 50 micrograms/ ml	**Negative.** In the absence of serum (5-6 h exposure), assays with and without Aroclor-induced rat liver S9 showed no increases in mutant fraction. No toxicity reported at top dose. EMS gave a clear positive response. A comparable assay in the presence of serum (18-24 hours exposure) without activation also gave a negative result (Greene et al, 1979).
UDS	Rat hepatocytes	0.45, 4.5, 45 micrograms/ ml	**Negative.** Reproducible result. Exposure time was 20 h. Cytotoxicity prevented assessment of UDS at the top dose. Positive control, 2AAF, gave a clear increase in UDS (Von der Hude et al, 1990).

4. TOXICOLOGICAL DATA (continued)

4.4.2 In vivo studies (somatic cells)

Test	Species (tissue)	Dose groups	Harvest time	Observations and remarks (include route of administration)
Micronucleus	ICR-mice	0, 400, 500, 800 & 1000 mg/kg gavage.	24 h (all doses), 48 & 72 h (top dose only)	Negative. Male and female rats employed. Deaths occurred at the top dose (1 animal/group). No increases in MN frequency observed. Another substance, diglycidylaniline, gave a positive result in the same study (Seiler, 1984). Note that the oral route of administration was employed.
Chromosome aberration	Sprague-Dawley rat (bone marrow)	0, 1, 5 & 12 ppm inhalation (0, 0.006, 0.03 & 0.07 mg/l)	21 h after last exposure	**Negative.** Groups of 6 male rats exposed by inhalation 6 h/day for 19 days. No positive control group. No deaths and no effects on body weight observed. Fifty or more metaphases scored per animal. No significant increases in breaks or rearrangements above relatively high control level of 7.9% of cells with aberrations (Terrill et al, 1982). Note that the dose levels used were low, compared with those that can be administered via orla or parenteral routes. **Despite the negative results obtained in these particular assays, classification with Muta Cat 3; R40 is proposed (see Annex A).**

4.4.3 In vivo studies (germ cells)

Test	Species	Dose groups	Exposure conditions	Observations and remarks
Dominant lethal	Sprague -Dawley rats (8 males and 8 females per group)	0, 2, 6 & 11 ppm	Inhalation exposure of males 6 h/ day for 19 days.	**Negative.** Not performed to current standards. No clinical signs of toxicity in exposed males; no positive control group. Mating in each of 6 consecutive weeks following exposure. No significant effect on the number of litters with early resorptions or on mean postimplantation loss, as determined at gestation day 18 (Terrill et al, 1982).

4. TOXICOLOGICAL DATA (continued)

4.4.4 Other mutagenicity/ genotoxicity studies

Test	Species	Dose groups	Exposure conditions	Observations and remarks
Host-mediated	C57B1/6 x C3H mice	0, 2500 mg/kg (all animals also received S.typhimurium TA1535 by ip. injection).	Oral gavage, intramuscular or ip. injection. Exposure time 3h	A mutagenic response seen in bacteria from 2/5 and 1/5 mice that received phenyl glycidyl ether by oral and intramuscular routes, respectively. No criteria for interpretation of the results were provided and no positive controls were included in this experiment (Greene et al, 1979).
Inhibition of murine testicular DNA synthesis	C57B1/6 x C3H mice	0 or 500 mg/kg	Oral gavage. Exposure time 3.5 hours	5 mice per dose group. No effect on rate of testicular DNA synthesis in this limited investigation (Greene et al, 1979).

4.5 FERTILITY

Species	Dose groups	Exposure conditions	Number of gen. exposed	Obsevations and remarks
Rat (Sprague-Dawley)	0, 2, 6 & 11 ppm	Inhalation exposure of males 6 h/ day for 19 days.	1 F_o males only	A small, non-standard reproductive toxicity test. No clinical signs of toxicity in exposed males (8/ group). Each F_o male mated in each of 6 consecutive weeks following exposure with groups of 3 females (included 1 female for dominant lethal test). For each mating group, 8 F_1 males mated with 24 F_1 females. The percentage of females that became pregnant was significantly reduced in the high dose group in the first breeding week only. No other significant changes in fertility, progeny numbers and survival, or lactational performance. (Terrill et al, 1982). The isolated observation of decreased pregnancy in the high dose group occurred only on the first mating and is believed to have occurred by chance. The functional capacity of all the male rats was demonstrated by subsequent matings. **No classification is proposed.**

4.6 DEVELOPMENTAL TOXICITY

Species	Route	Dose groups	Exposure conditions	Observations and remarks
Rat (Sprague-Dawley)	Inhln.	0, 1, 5 & 12 ppm	25 rats/ group, 6 h/ day gestation days 4-15	**Negative.** Teratogenicity study. No clinical signs of toxicity in dams. Numbers of implantations, live fetuses and resorptions similar in all groups. No effects on fetal length or weight, gross observations or internal and skeletal development. Exposure not continued throughout entire period of organogenesis (Terrill et al, 1982). **No classification is proposed.**

5. ECOTOXICOLOGICAL STUDIES

Data not reviewed for Health Effects Working Group

6. ENVIRONMENTAL FATE

Data not reviewed for Health Effects Working Group

7. ADDITIONAL ENVIRONMENTAL EFFECTS

Data not reviewed for Health Effects Working Group

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ANNEX A

EC CLASSIFICATION AND LABELLING:

PHENYL GLYCIDYL ETHER

(EINECS name: 2,3-epoxypropyl phenyl ether)

Background information on metabolism of phenyl glycidyl ether

Glycidyl ethers, in common with other epoxides, may be metabolised through the following pathways:

(i) epoxide hydrolase activity, leading to hydrolysis of the epoxide group under formation of the corresponding diol;
(ii) conversion to glutathione conjugates by glutathione-S-epoxide conjugases; and
(iii) non-enzymic covalent binding with proteins, RNA and DNA.

The observation of a urinary cysteine conjugate, and the depletion of hepatic glutathione levels in animals exposed to phenyl glycidyl ether via the oral route, confirm that this substance can be metabolised by conjugation with glutathione (MAK, 1992). It is unclear how phenyl glycidyl ether is metabolised in humans. The potential for metabolic detoxication at sites of initial contact in the body has not been established.

MAK (1992). Occupational Toxicants; Critical Data Evaluation for MAK Values and Classification of Carcinogens, 4, 305-311.

Arguments for classification: Physico-chemical effects No classification is proposed.

Arguments for classification: Health effects

1) *Acute oral toxicity*

Acute toxicity studies in rats have consistently given LD_{50} values >2000 mg/kg. A mouse LD_{50} of 1400 mg/kg is available, however we propose that this isolated value does not support any classification given that the rat is the species specified in the criteria for classification.

Acute inhalation toxicity

In rats, deaths have been reported at exposure levels of approx. 2mg/l phenyl glycidyl ether (vapour-aerosol mixture). This supports the proposal to classify with Xn; R20.

Acute dermal toxicity

LD_{50} values of 2160 and 2990 mg/kg in rabbits indicate that no classification is justified. A poorly reported study gives a rabbit LD_{50} of 1500 mg/l; this is insufficient evidence to justify classification.

2) *Skin Irritation*

In the most recent study available, the only one to conform to Annex V, mean erythema and oedema values less that 2.00 were recorded in all animals. Since slight scales were observed in all animals on day 7 at study termination, the complete reversibility of effects was not established. Two relatively old studies also describe signs of only moderate and minimal/mild irritation in rabbits. In contrast to these findings in animals, there is a report of human

exposure to undiluted phenyl glycidyl ether leading to second degree burns (1 individual) or erythema and blisters (5 individuals). There is also a Draize-type study describing necrotic lesions and persistent scaring in rabbit skin.

Given that there is only an isolated report of possible corrosive activity in humans, and the contrasting observations in animals (the majority of studies reporting minimal-moderate skin irritation), we propose that the most appropriate classification is Xi; R38.

3) *Eye Irritation*

In a study conforming to Annex V, there were no significant ocular lesions observed. In addition, in three non-standard studies, extrapolation of the Draize scores suggests that the responses seen were indicative of only minimal eye irritation. These findings suggest that classification is not justified.

4) *Respiratory Irritation*

In single exposure studies, exposure of rats to phenyl glycidyl ether caused dyspnea and nasal discharge. On longer term exposure, rats exhibited rhinitis and histopathological signs of respiratory irritation. On this basis, we propose classification with R37.

5) *Skin Sensitisation*

Observations of allergic responses in exposed humans and in animal tests justify the existing classification of phenyl glycidyl ether with R43.

6) *Respiratory Sensitisation*

No animal or human data available. Consequently, classification is not justified.

7) Repeated dose toxicity

No modern studies performed according to regulatory guidelines are available.

In a study from 1977, rats exposed for 14 days to a vapour-aerosol mixture of 0.18 mg/l (29 ppm) phenyl glycidyl ether for 4 hours/day were reported to show "atrophic changes" in the kidneys, liver, spleen, thymus and testes. Given that the nature and extent of these changes were not further characterised, and that similar findings were not observed in rats exposed at this level for longer periods, this study does not provide sufficient evidence to justify classification.

In a carcinogenicity study, repeated inhalation exposure of rats to 0.07 mg/l produced rhinitis and histopathological signs of upper respiratory tract irritation. We believe that these findings support classification with R37 rather than R48.

Hair loss and associated observations in rats exposed to 0.03 and 0.08 mg/l phenyl glycidyl ether vapour-aerosol mixtures would appear to indicate a local irritant effect and the significance of these findings to humans is unclear. These data do not support classification with R48.

Overall, no classification for repeated dose effects is justified.

5) *Mutagenicity*

Phenyl glycidyl ether consistently gave positive results in bacterial mutagenicity assays both with and without metabolic activation. A weak positive result was also seen in a chromosome aberration test in CHO cells without activation. Negative results have been reported in a CHO *hprt* gene mutation test and a rat liver cell UDS test, although the sensitivity of the gene mutation test might have been increased had higher concentrations of phenyl glycidyl ether been included. Nevertheless, it is concluded that phenyl glycidyl ether is an electrophilic substance with the potential to act as a direct-acting mutagen *in vitro*.

In standard *in vivo* tests (micronucleus, chromosome aberration and dominant lethal), phenyl glycidyl ether administered by either inhalation or oral gavage gave negative results. However given the electrophilicity of this glycidyl ether, and the relatively low doses administered via inhalation, it is most likely that the target tissues (bone marrow, testes) were not adequately exposed in these studies and that the results are false negatives. This concept is supported by the finding that *n*-butyl glycidyl ether, a structurally similar electrophilic substance, gave a positive result in the bone marrow micronucleus test following intraperitoneal injection but not following oral administration (Gardiner et al, 1992).

Concern remains that phenyl glycidyl ether may cause mutagenic effects in somatic cells at sites of initial contact in the body. Classification with Muta Cat 3; R40 is proposed since this substance is a reactive epoxide (an electrophile), mutagenic *in vitro*, and has not been tested in a relevant *in vivo* test (i.e. at a site of initial contact), .

Gardiner TH, Waechter JM Jr, Wiedow MA and Solomon WT (1992). Glycidyloxy compounds used in epoxy resin systems: a toxicology review. Regul Toxicol Pharmacol, 15, S1-S77.

6) *Carcinogenicity*

In the only available carcinogenicity study, a clear increased incidence of nasal epithelial carcinomas in male and female rats was associated with inhalation exposure to phenyl glycidyl ether (0.07 mg/l). No tumours were seen in control animals or in the lower exposure group (0.006 mg/l) in this study. Furthermore, historically, this type of tumour is rare in control rats.

There is some uncertainty about the mechanism of tumour induction in the phenyl glycidyl ether-exposed rats. Both of the genotoxic and irritant properties of this substance may have played a role. From the available information, the exposure level at which tumours were induced appears to have been below a maximum tolerated dose level (MTD) and there is no evidence for a secondary mechanism of action with a practical threshold. However, the findings are considered of relevance to humans.

In view of these considerations, classification with Carc Cat 2; R45 is proposed for phenyl glycidyl ether.

7) *Reproductive toxicology*

There were no toxicologically significant findings in a limited 2-generation reproductive toxicity test in which only F_0 male rats were exposed to phenyl glycidyl ether. No developmental effects were seen in a teratology study in rats. Phenyl glycidyl has not been

demonstrated to pose a reproductive toxicity hazard; no classification is proposed for this endpoint.

UK proposal: Carc Cat 2; R45: Muta Cat 3; R40: Xn; R20: Xi; R37/38: R43

HSE Toxicology Unit
29 July 1997