The MAK-Collection for Occupational Health and Safety

GMS PUBLISSO ZB MED-Publikationsportal Lebenswissenschaften

Cresyl glycidyl ethers (*o*-isomer, isomer mixture)

MAK Value Documentation – Translation of the German version from 2020

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Keywords

o-cresyl glycidyl ether; cresyl glycidyl ether (isomer mixture); irritation; sensitization; genotoxicity; epoxy resin systems

Abstract

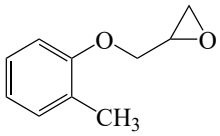
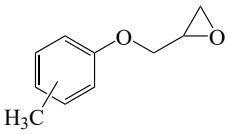
The German Commission for the Investigation of Health Hazards of Chemical Compounds in the Work Area has evaluated cresyl glycidyl ethers (o-isomer [2210-79-9], mixture of isomers [26447-14-3]) considering all toxicological end points. The critical effect of cresyl glycidyl ethers is skin sensitization in humans and animals. In rats, local irritation is observed after inhalation. Cresyl glycidyl ethers are a direct mutagen in bacteria and the mutagenicity is considerably reduced by adding S9-mix. In Big Blue® mice, *o*-cresyl glycidyl ether was not mutagenic in the liver and testes up to oral doses of 500 mg/kg body weight and day. Thus, the substance is not systemically genotoxic. There are no carcinogenicity studies. In rats, the structurally analogous substance phenyl glycidyl ether induced nasal tumours after inhalation of 12 ml/m^3. Based on this structural relationship, cresyl glycidyl ethers are suspected of being locally acting carcinogens. They are therefore assigned to Carcinogen Category 3 B. As they are directly genotoxic in vitro and the local mutagenicity in vivo has not been clarified, a maximum concentration at the workplace (MAK value) cannot be derived. A prenatal toxicity study found no developmental toxicity in rats up to the highest dose tested of 600 mg/kg body weight and day. The contact sensitizing potential is confirmed by new clinical data in humans and animal studies and the previous "Sh" notation is retained. There are no data for respiratory sensitization. Skin contact is not expected to contribute significantly to systemic toxicity.

Citation Note:
Hartwig A, MAK Commission. Cresyl glycidyl ethers (o-isomer, isomer mixture). MAK Value Documentation – Translation of the German version from 2020. MAK Collect Occup Health Saf. 2021 Sep;6(3):Doc055.
DOI: https://doi.org/10.34865/mb221079e6_3or

Manuscript completed:
26 Mar 2019

Publication date:
30 Sep 2021

MAK value	–
Peak limitation	–
Absorption through the skin	–
Sensitization (2013)	**Sh**
Carcinogenicity (2019)	**Category 3 B**
Prenatal toxicity	–
Germ cell mutagenicity	–
BAT value	–

Substance	*o*-cresyl glycidyl ether	cresyl glycidyl ether isomer mixture
Synonyms	2,3-epoxypropyl *o*-tolyl ether glycidyl *o*-tolyl ether [(o-tolyloxy)methyl]oxirane	glycidyl tolyl ether [(tolyloxy)methyl]oxirane
Chemical name	2-[(2-methylphenoxy)methyl]-oxirane	[(methylphenoxy)methyl]-oxirane
CAS number	2210-79-9	26447-14-3
Structural formula		
Molecular formula	$C_{10}H_{12}O_2$	$C_{10}H_{12}O_2$
Molar mass	164.2 g/mol	164.2 g/mol
Melting point	< –69 °C (IFA 2018 a)	< –18 °C (IFA 2018 b)
Boiling point	260 °C at 1013 hPa (ECHA 2018)	170 °C at 100 hPa (IFA 2018 b)
Density	1.09 g/cm³ at 20 °C (IFA 2018 a)	1.14 g/cm³ at 25 °C (IFA 2018 b)
Vapour pressure	0.0514 hPa at 20 °C, 0.0822 hPa at 25 °C (IFA 2018 a)	2 hPa at 20 °C (IFA 2018 b)
log K_{OW}	2.5 (ECHA 2018)	no data
Solubility	840 mg/l water at 21 °C (IFA 2018 a)	practically insoluble in water (IFA 2018 b)
1 ml/m³ (ppm) ≙ 6.813 mg/m³	**1 mg/m³ ≙ 0.147 ml/m³ (ppm)**	

Note: The substance can occur simultaneously as vapour and aerosol.

Documentation for the sensitizing effects of cresyl glycidyl ethers on the skin has already been published. Both *o*-cresyl glycidyl ether and the isomer mixture are used as reactive diluents in epoxy resin systems (Hartwig 2014, available in German only).

1 Toxic Effects and Mode of Action

o-Cresyl glycidyl ether causes slight irritation of the skin in rabbits and no or at most slight irritation of the eyes.

Cresyl glycidyl ethers cause sensitization of the skin in humans and animals.

Head-only inhalation exposure of rats to *o*-cresyl glycidyl ether aerosol for 3 weeks at concentrations of 152 mg/m^3 and above induced irritation of the nasal mucosa; the severity of this effect increased with the concentration. Local irritation was the most sensitive effect in rats given gavage doses of *o*-cresyl glycidyl ether for 90 days and led to ulceration, erosion and inflammatory cell infiltrates in the forestomach at dose levels of 30 mg/kg body weight and day and above.

In a prenatal developmental toxicity study in Sprague Dawley rats, gavage doses of *o*-cresyl glycidyl ether did not induce developmental toxicity up to the high dose of 600 mg/kg body weight and day.

o-Cresyl glycidyl ether and the isomer mixture of cresyl glycidyl ether are directly mutagenic and induce base-pair substitutions in bacteria. The mutagenic activity is reduced considerably by the addition of a metabolic activation system. In the liver and testes of male Big-Blue® mice, *o*-cresyl glycidyl ether did not cause an increase in mutations after gavage doses of up to 500 mg/kg body weight and day for 28 days. Gavage doses of *o*-cresyl glycidyl ether did not induce clastogenic effects in the bone marrow of mice.

There are no studies of carcinogenicity or fertility.

2 Mechanism of Action

The glycerol ether of *o*-cresol is a product of the hydrolysis of the epoxide group of *o*-cresyl glycidyl ether. It was used therapeutically as a muscle relaxant and marketed under the name mephenesin. The formation of this product by hydrolysis may explain the potential effects of *o*-cresyl glycidyl ether and the cresyl glycidyl ether isomer mixture on the nervous system (Gardiner et al. 1992).

The sensitizing, mutagenic and irritant effects are probably caused by the reactivity of the epoxide group of *o*-cresyl glycidyl ether and the cresyl glycidyl ether isomer mixture.

3 Toxicokinetics and Metabolism

3.1 Absorption, distribution, elimination

Male Wistar rats were given single intraperitoneal injections of *o*-cresyl glycidyl ether in arachis oil at dose levels of 0.033 to 1.0 mmol/kg body weight (5.4 to 164.2 mg/kg body weight). Metabolites were identified and quantified in the urine by GC/MS (gas chromatography-mass spectrometry). The urinary excretion of the main metabolite *o*-cresyl glycidyl ether mercapturic acid was linear up to an *o*-cresyl glycidyl ether dose of 0.333 mmol/kg body weight (54.1 mg/kg body weight); above this dose, urinary excretion did not continue to increase with the dose. The percentage of *o*-cresyl glycidyl ether mercapturic acid in the urine decreased from 31% to 11% as the dose level of *o*-cresyl glycidyl ether increased. Within 6 hours after the administration of *o*-cresyl glycidyl ether, 93% of the cumulative amount of *o*-cresyl glycidyl ether mercapturic acid eliminated was recovered in the urine. The authors estimated that the elimination half-life is less than 3 hours (de Rooij et al. 1998).

Percutaneous penetration and the metabolism of ^{14}C-labelled *o*-cresyl glycidyl ether dissolved in acetone were investigated in vitro with the skin of C3H mice and F344 rats and with dermatomed human skin. The dose was 5 µmol/cm^2 (0.821 mg/cm^2). About 10%, 18% and 23% of the dose was absorbed by human, rat and mouse skin in 24 hours. With human skin, about 5% had been absorbed after 5 hours and a plateau was reached after about 12 hours. Human skin was found to be the least permeable (apparent permeability constant in 10^{-6} cm/hour: human: 93 ± 11, rat: 134 ± 15, mouse: 176 ± 32, percutaneous penetration after 24 hours in % of the applied dose: human: 10.2 ± 1.6; rat: 17.4 ± 1.8; mouse:

22.7 ± 4.6). The longest lag time was found in human skin (lag time for penetration in hours: human: 0.96 ± 0.23; rat: 0.36 ± 0.26; mouse: 0.51 ± 0.47). Significant losses were determined for all three skin types in the mass balance (recovery in % of the dose applied: human: 13 ± 3, rat: 22 ± 3, mouse: 26 ± 5), which was attributed to the volatility of the substance. Absorption of *o*-cresyl glycidyl ether through the skin was about twice as high after occlusive application; however, this did not have any effect on the extent of metabolism: the same percentage passed through the skin unchanged. The authors suggested that *o*-cresyl glycidyl ether influences its own metabolism over time. In all 3 species, 86% to 88% of *o*-cresyl glycidyl ether was hydrolysed to the diol within the first hours of penetration, but over time, less *o*-cresyl glycidyl ether underwent hydrolysis. Therefore, the percentage of substance that has penetrated the skin, but has not undergone metabolism, increases with time: 0.69% of the applied dose permeated the human skin unchanged during the first 9 hours. Over the next 9 hours, this percentage increased to 2.9% and again to 3.9% during the last 5 hours. The corresponding percentages in the rat and mouse skin were 1.9%, 6.3%, 7.8% (rats) and 2.6%, 4.1%, 6.7% (mice) (Boogaard et al. 2000 a).

These data were used to calculate a flux of 0.821 mg/cm^2 × 0.05 = 0.041 mg/cm^2 in 5 hours or 8.2 µg/cm^2 and hour for human skin. On the basis of this flux and assuming standard conditions (exposure of a 2000 cm^2 area of skin for a period of 1 hour), the total amount absorbed was calculated to be 16.4 mg. On the basis of the permeability constant, or Kp, for human skin of 93 × 10^{-6} cm/h, a flux of 102 × 10^{-3} mg/cm^2 and hour and the absorption of 205 mg under standard conditions were calculated for the undiluted substance (density 1.1 g/cm^3).

3.2 Metabolism

o-Cresyl glycidyl ether is rapidly converted into the diol after incubation with guinea pig liver homogenate in vitro (Gardiner et al. 1992).

Three metabolites were found in the urine of male Wistar rats given a single intraperitoneal injection of *o*-cresyl glycidyl ether in arachis oil at dose levels ranging from 0.033 to 1.0 mmol/kg body weight (5.4 to 164.2 mg/kg body weight): 10% of the dose was identified as 3-(*o*-cresyloxy)lactic acid, 11% to 31% as *o*-cresyl glycidyl ether mercapturic acid and 10% as *N*-acetyl-*O*-(*o*-cresyl)serine (Figure 1; de Rooij et al. 1998).

The toxicokinetic constants determined for humans, rats and mice in an in vitro study are listed in Tables 1 and 2. Metabolic inactivation can occur through the conjugation with glutathione (GSH) by glutathione *S*-transferase or the hydrolysis of the epoxide (epoxide hydrolase).

Both detoxification pathways were investigated in vitro with ^{14}C-labelled *o*-cresyl glycidyl ether in subcellular cytosolic and microsomal fractions from the liver and lungs of humans, F344 rats and C3H mice. The conjugation of *o*-cresyl glycidyl ether with GSH occurred very rapidly and the level of conjugation was much lower in the cytosol of humans than in that of rodents. Therefore, GSH conjugation is a more important detoxification pathway in rodents than in humans. In general, microsomal epoxide hydrolase was more efficient than cytosolic epoxide hydrolase and the epoxide hydrolases were overall more efficient in humans than in rodents (Tables 1 and 2). The authors noted that the efficiency of hepatic clearance by GSH conjugation was similar to that for epoxy butane and diepoxybutane, but that the level of hydrolysis by epoxide hydrolase was greater by two orders of magnitude. For this reason, the genotoxic risk is assumed to be much lower than that of small aliphatic epoxides. Theoretically, glycidaldehyde may be formed by oxidative dealkylation (Boogaard et al. 2000 b). However, this has not been investigated.

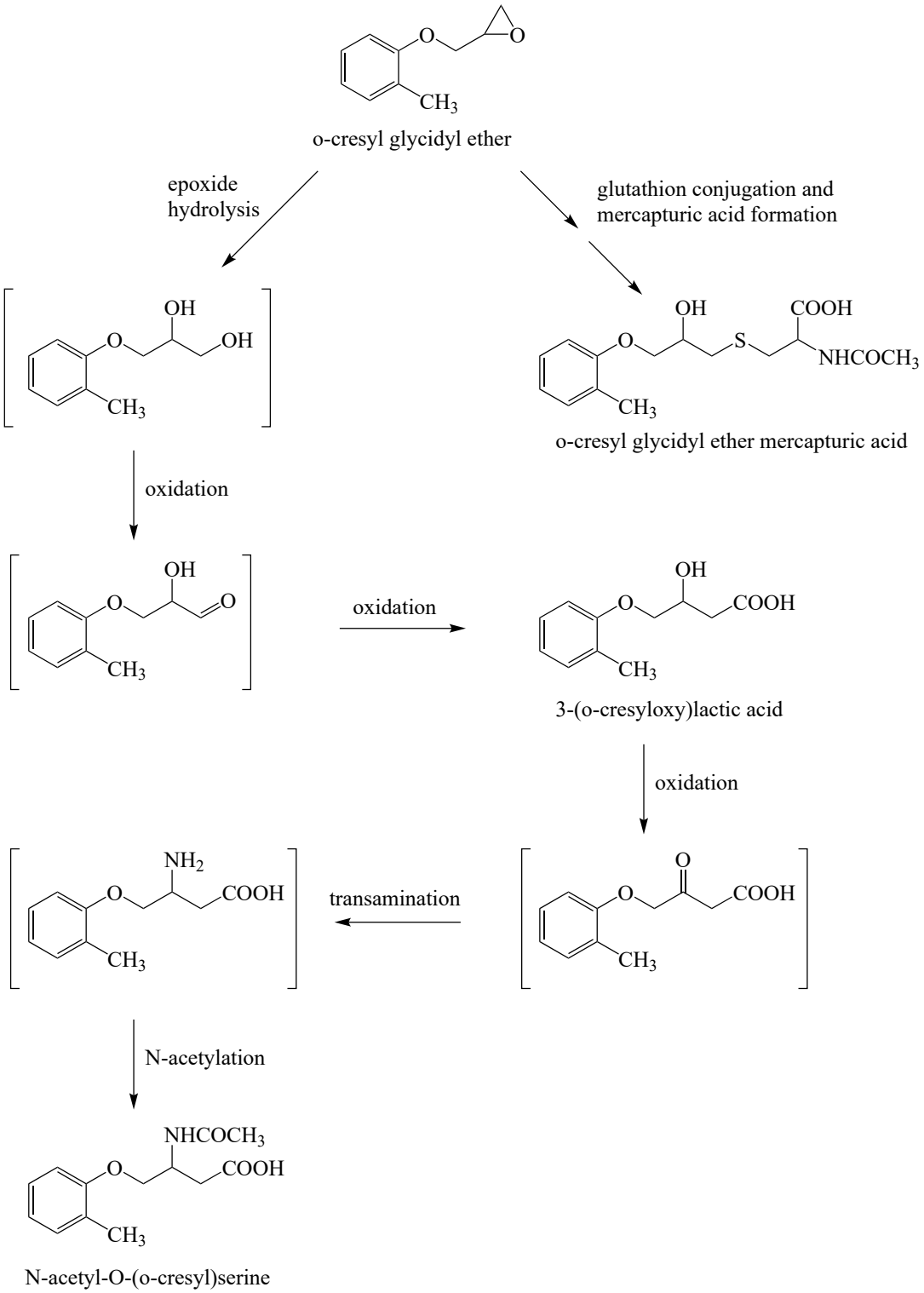


Fig. 1 Postulated metabolism of *o*-cresyl glycidyl ether in rats. The metabolites given in parentheses were not determined (according to de Rooij et al. 1998).

Tab. 1 Kinetic parameters for the conversion of *o*-cresyl glycidyl ether by the cytosol and microsomes from the liver and lungs of humans, rats and mice (Boogaard et al. 2000 b)

Organ	Fraction	Species	Vmax (nmol/mg/min)	Km (mM)	Vmax / Km (µl/min/mg)	Number of individuals
enzymatic conjugation						
liver	cytosol	human	84.5	14.5	5.84	6
		rat	61.3	2.72	22.5	3
		mouse	150	6.63	22.7	2
lungs	cytosol	human	50.1	20.9	2.40	6
		rat	29.0	5.79	5.01	2
		mouse	29.5	3.95	7.45	2
enzymatic hydrolysis						
liver	cytosol	human	12.7	0.062	204	6
		rat	1.16	0.019	60.2	2
		mouse	45.8	1.60	28.6	2
	microsomes	human	106	0.43	244	6
		rat	61.4	0.26	232	2
		mouse	23.2	0.086	268	2
lungs	cytosol	human	0.40	0.013	30.7	6
		rat	no reaction	–	–	4
		mouse	0.91	3.04	0.30	3
	microsomes	human	6.86	0.036	189	6
		rat	2.68	0.032	84.5	2
		mouse	8.08	0.049	165	2

Tab. 2 Estimated in vivo clearance ($l \times h^{-1} \times kg^{-1}$) of *o*-cresyl glycidyl ether in the liver and lungs (Boogaard et al. 2000 b)

Species	Cytosolic glutathione S-transferase	Epoxide hydrolase
liver		
human	0.45	24
rat	3.6	19
mouse	3.7	10
lungs		
human	0.02	0.40
rat	0.07	0.06
mouse	0.03	0.32

4 Effects in Humans

4.1 Single exposures

There are no data available.

4.2 Repeated exposure

There are no data available.

4.3 Local effects on skin and mucous membranes

There are no data available.

4.4 Allergenic effects

4.4.1 Sensitizing effects on the skin

The sensitizing effects of cresyl glycidyl ethers on the skin have already been evaluated in detail (Hartwig 2014). Relatively few new data have since been published. A 0.25% formulation of the isomer mixture in petrolatum continues to be used for patch testing with cresyl glycidyl ether.

A total of 647 patients that underwent testing at the Finnish Institute of Occupational Health (FIOH) between 1991 and 2014 were tested also with cresyl glycidyl ether; 16 produced positive reactions. Of these 16 patients, 14 exhibited concurrent positive reactions to phenyl glycidyl ether (Aalto-Korte et al. 2015).

In the clinics of the Information Network of Departments of Dermatology (IVDK), a total of 93 406 patients were tested with the standard series epoxy resin in the period from 2002 to 2011; 1453 positive reactions were provoked. In 575 of the patients who had produced positive reactions, a test was performed also with cresyl glycidyl ether, which again yielded positive reactions in 86 (15%) of these patients. In addition, 20 of 8451 tested patients exhibited positive reactions also to cresyl glycidyl ether without a concurrent reaction to the epoxy resin. Simultaneous tests were carried out with phenyl glycidyl ether in 81 patients who had produced a positive reaction to cresyl glycidyl ether; reactions to both substances were observed in 77 cases (Geier et al. 2016 a, b).

4.4.2 Sensitizing effects on the airways

There are no data available.

4.5 Reproductive and developmental toxicity

There are no data available.

4.6 Genotoxicity

In 11 factory workers who were exposed to cresyl glycidyl ether at an average concentration in air below 0.07 mg/m^3 (no other details) for 8 hours per week for 3 weeks, the incidence of chromosomal aberrations in the peripheral blood lymphocytes was not significantly increased (no other details; Gardiner et al. 1992).

4.7 Carcinogenicity

There are no data available.

5 Animal Experiments and in vitro Studies

5.1 Acute toxicity

5.1.1 Inhalation

The studies of acute inhalation toxicity are shown in Table 3.

A study carried out according to OECD Test Guideline 403 with male and female F344 rats yielded a 4-hour LC_{50} value for ***o*-cresyl glycidyl ether** (vapour, whole-body exposure) of greater than 6.1 ml/m³ (40.9 mg/m³) (Dow Chemical Company 1991 a; ECHA 2018).

In another study (aerosol, nose-only exposure) with male and female rats, the 4-hour LC_{50} value for ***o*-cresyl glycidyl ether** was 6090 mg/m³ (Ciba-Geigy Ltd. 1978 b; ECHA 2018). Other 4-hour LC_{50} values reported for cresyl glycidyl ether were in the range from 4800 to 8500 mg/m³ (aerosol) for rats and 310 mg/m³ for mice (no other details; ECB 2000).

Tab. 3 Studies of the acute toxicity of *o*-cresyl glycidyl ether after exposure by inhalation

Species, strain, number per group	Exposure	End point	References
rat, F344, 5 ♂, 5 ♀, OECD Test Guideline 403	6.1 ml/m³ (40.9 mg/m³), theoretical maximum attainable vapour concentration at 20°C: 3.7 ml/m³, vapour, whole-body exposure, 4 hours, purity: > 95% (v/v) (Huntsman BVBA 2006), observation period 14 days	4-hour LC_{50} > 6.1 ml/m³ (40.9 mg/m³); mortality: 0/10; during exposure and at necropsy: no unusual findings	Dow Chemical Company 1991 a; ECHA 2018
rat, Tif: RAIf, 10 ♂, 10 ♀	999 ± 45, 2746 ± 255, 3973 ± 370, 8142 ± 749 mg/m³, gravimetrically determined, aerosol, nose only, 4 hours, composition: 90% *o*-cresyl glycidyl ether, 8% *o*-tolyl-alpha-myanesin, 2% different oligomers, less than 1% in each case (Huntsman Advanced Materials 2019), observation period: 14 days	4-hour LC_{50} 6090 mg/m³; 3973 mg/m³: mortality: 4/20, 8142 mg/m³: mortality: 15/20, ataxia; in all animals within 2–4 hours after the beginning of exposure: dyspnoea, exophthalmos, ruffled fur, ventral or bent posture, deceased animals: small, isolated haemorrhages in the lungs, surviving animals: no unusual findings	Ciba-Geigy Ltd. 1978 b; ECHA 2018

5.1.2 Oral administration

The studies of acute oral toxicity are shown in Table 4.

A study carried out according to OECD Test Guideline 401 (limit test) with male and female Sprague Dawley rats yielded an oral LD_{50} value for ***o*-cresyl glycidyl ether** of more than 5000 mg/kg body weight (ECHA 2018; Safepharm Laboratories Limited 1991 a). In another study carried out according to OECD Test Guideline 401 with male and female Wistar rats, the oral LD_{50} value for ***o*-cresyl glycidyl ether** was about 2800 mg/kg body weight (ECHA 2018).

A study in male and female rats determined an oral LD_{50} value for ***o*-cresyl glycidyl ether** of about 5800 mg/kg body weight (Ciba-Geigy Ltd. 1972 b; ECHA 2018). Other oral LD_{50} values for cresyl glycidyl ether were 4300 and 5140 mg/kg body weight for rats, 1700 mg/kg body weight for mice and 1650 mg/kg body weight for guinea pigs (no other details; ECB 2000).

Tab. 4 Studies of the acute toxicity of *o*-cresyl glycidyl ether after oral administration

Species, strain, number per group	Exposure	End point	References
rat, Sprague Dawley, 5 ♂, 5 ♀, OECD Test Guideline 401, limit test	5000 mg/kg body weight, undiluted test substance, purity: > 95% (v/v) (Huntsman BVBA 2006)	LD_{50} > 5000 mg/kg body weight; 5000 mg/kg body weight: mortality: 3/10; bent posture, piloerection, lethargy, breathing rate ↓, ptosis, ataxia, loss of the righting reflex, in isolated cases: coma, emaciation, dehydration; necropsy: haemorrhages or red-coloured lungs, irregular paleness of the liver, dark-coloured kidneys and haemorrhages in the small intestine; in the animals that survived until the end of the 14-day observation period: isolated foci 1 mm × 1 mm in size, distributed across 25% of the non-glandular region of the stomach	ECHA 2018; Safepharm Laboratories Limited 1991 a
rat, Wistar, 5 ♂, 5 ♀, OECD Test Guideline 401	2000, 3000, 5000 mg/kg body weight, vehicle: 4% carboxymethyl cellulose in distilled water, purity: > 95% (v/v) (Huntsman BVBA 2006)	LD_{50} 2800 mg/kg body weight; mortality within 24 hours: 2000 mg/kg body weight: 0/10, 3000 and 5000 mg/kg body weight: 9/10 in each case; necropsy: 3000 mg/kg body weight and above: red-coloured lungs	ECHA 2018
rat, Tif RAC/f, 5 ♂ and 5 ♀	2150, 3170, 6000 mg/kg body weight, vehicle: polyethylene glycol, composition: 90% *o*-cresyl glycidyl ether, 8% *o*-tolyl-alpha-myanesin, 2% different oligomers, less than 1% in each case (Huntsman Advanced Materials 2019), observation period: 7 days	LD_{50} 5800 mg/kg body weight; mortality: 2150 and 3170 mg/kg body weight: 0/10 in each case, 6000 mg/kg body weight: 2/5 ♂ and 4/5 ♀; dyspnoea, lacrimation, exophthalmos, ruffled fur, bent posture within 2 hours after the beginning of treatment; necropsy of the deceased animals: congestion in the liver	Ciba-Geigy Ltd. 1972 b; ECHA 2018

5.1.3 Dermal application

The studies of acute dermal toxicity are shown in Table 5.

A test carried out according to OECD Test Guideline 402 with occlusive application of ***o*-cresyl glycidyl ether** to male and female Sprague Dawley rats for 24 hours yielded a dermal LD_{50} value of more than 2000 mg/kg body weight (ECHA 2018; Safepharm Laboratories Limited 1991 c). A study carried out according to OECD Test Guideline 402 with occlusive application of ***o*-cresyl glycidyl ether** to male and female New Zealand White rabbits for 24 hours likewise established a dermal LD_{50} value of more than 2200 mg/kg body weight (ECHA 2018). Another study in male and female rats with occlusive application of ***o*-cresyl glycidyl ether** to the skin for 24 hours yielded a dermal LD_{50} value of more than 2150 mg/kg body weight (Ciba-Geigy Ltd. 1972 a; ECHA 2018). Other LD_{50} values for cresyl glycidyl ethers were 480 mg/kg body weight for mice and more than 2000 mg/kg body weight for rabbits (no other details; ECB 2000).

Tab. 5 Studies of the acute toxicity of *o*-cresyl glycidyl ether after dermal application

Species, strain, number per group	Exposure	End point	References
rat, Sprague Dawley, 5 ♂, 5 ♀, OECD Test Guideline 402	2000 mg/kg body weight, occlusive, 24 hours, undiluted test substance, purity: > 95% (v/v) (Huntsman BVBA 2006)	LD_{50} > 2000 mg/kg body weight; mortality: 0/10; during exposure and necropsy: no unusual findings	ECHA 2018; Safepharm Laboratories Limited 1991 c

Tab. 5 *(continued)*

Species, strain, number per group	Exposure	End point	References
rat, Tif: RAI/f, 3 ♂, 3 ♀	2150 mg/kg body weight, occlusive, 24 hours, composition: 90% *o*-cresyl glycidyl ether, 8% *o*-tolyl-alpha-myanesin, 2% different oligomers, less than 1% in each case (Huntsman Advanced Materials 2019), observation period: 7 days	LD_{50} > 2150 mg/kg body weight; mortality: 0/6; no symptoms and no irritation at the application site, after observation for 7 days, no substance-related changes in the gross-pathological examination of the organs	Ciba-Geigy Ltd. 1972 a; ECHA 2018
rabbit, New Zealand White, 8 ♂, 8 ♀, OECD Test Guideline 402	2200 mg/kg body weight, occlusive, 24 hours, undiluted test substance, purity: > 95% (v/v) (Huntsman BVBA 2006)	LD_{50} > 2200 mg/kg body weight; mortality: 5/16; at all application sites: severe oedema and erythema, which became necrotic after 14 days	ECHA 2018

5.2 Subacute, subchronic and chronic toxicity

5.2.1 Inhalation

The studies with repeated inhalation exposure to *o*-cresyl glycidyl ether are shown in Table 6.

In a study carried out according to OECD Test Guideline 412 with F344 rats, no unusual findings were reported after whole-body exposure to ***o*-cresyl glycidyl ether** concentrations of up to 4 ml/m³ (26.8 mg/m³) for 4 weeks. The NOAEC (no observed adverse effect concentration) was therefore 4 ml/m³ (26.8 mg/m³), the highest concentration tested (Dow Chemical Company 1991 b; ECHA 2018).

In a study with head-only exposure of RAI-f rats to ***o*-cresyl glycidyl ether** aerosol for 3 weeks, transient systemic effects such as reduced body weight gains and feed consumption, dyspnoea and exophthalmos, which is to be interpreted as a marginal effect, were observed at the low concentration of 53 mg/m³ and above. Local irritation of the nasal mucosa was observed at concentrations of 152 mg/m³ and above; the severity of this effect increased with the concentration (Ciba-Geigy Ltd. 1978 a; ECHA 2018). The NOAEC for local irritation of the nasal mucosa was 53 mg/m³.

Tab. 6 Studies of the effects of *o*-cresyl glycidyl ether after repeated exposure by inhalation

Species, strain, number per group	Exposure	Findings	References
rat, F344, 5 ♂, 5 ♀, OECD Test Guideline 412	4 weeks, analysed concentrations: 0, 0.6, 4 ml/m³ (0, 4.0, 26.8 mg/m³), vapour, theoretical maximum achievable vapour concentration at 20°C: 3.7 ml/m³, whole-body exposure, 6 hours/day, 5 days/week, control group: air, purity: 91.06%	**4 ml/m³ (26.8 mg/m³): NOAEC**, no unusual findings	Dow Chemical Company 1991 b; ECHA 2018

Tab. 6 *(continued)*

Species, strain, number per group	Exposure	Findings	References
rat, RAI-f, 10 ♂, 10 ♀	3 weeks, 0, 53 ± 4, 152 ± 4, 305 ± 10 mg/m³, gravimetrically determined, aerosol, 80%–90% of the droplets < 7 µm, head-only exposure, 6 hours/day, 5 days/week, composition: 90% *o*-cresyl glycidyl ether, 8% o-tolyl-alpha-myanesin, 2% different oligomers, less than 1% in each case (Huntsman Advanced Materials 2019), medium concentration group: 21 days recovery	**53 mg/m³: NOAEC for local irritation of the nasal mucosa**; **53 mg/m³ and above**: body weight gains and feed consumption transiently ↓ on 3 days; dyspnoea, exophthalmos; ruffled fur at the beginning of exposure; **152 mg/m³ and above**: congestion and slight purulent inflammation with ulceration of the nasal mucosa (dose-dependent increase in severity, 6/10), after 21 days recovery: in some cases re-epithelialized ulceration, xenobiotic reactions and chronic inflammatory infiltrations (1/10); inhibition of spermatogenesis in one testis (1/10, evaluated as coincidental); **305 mg/m³**: lateral or ventral posture, abdominal swelling, mortality 15/20 (6 ♂ and 9 ♀), deceased animals with acute congestion, bleeding in the myocardium, lungs, liver, kidneys, adrenal glands, pituitary gland, ovaries and brain, marked congestion of the nasal mucosa with purulent inflammation and ulceration, thymocyte depletion in the thymus, spermatogenesis ↓ (♂: 5/10), atrophy of the lymphoid tissue of the spleen (6/20), ulceration of the skin around the mouth (3/20); no unusual findings in the ophthalmologic, haematological, clinico-chemical examinations, organ weights	Ciba-Geigy Ltd. 1978 a; ECHA 2018

5.2.2 Oral administration

In a study carried out according to OECD Test Guideline 408, groups of 10 Wistar Han rats per sex and dose were given ***o*-cresyl glycidyl ether** by gavage for 90 days at dose levels of 0, 30, 100 or 600 mg/kg body weight and day. Local effects of irritation were observed in the stomach and forestomach at the low dose of 30 mg/kg body weight and day and above. At lower dose levels, these effects were characterized by ulceration, erosion and inflammatory cell infiltrates in the forestomach. As the dose levels increased, hyperplasia including hyperkeratosis was induced. No systemic effects were observed up to the high dose (ECHA 2018). The NOAEL (no observed adverse effect level) for the systemic toxicity of *o*-cresyl glycidyl ether was 600 mg/kg body weight and day, the highest dose tested. A NOAEL for local toxicity could not be determined. The LOAEL (lowest observed adverse effect level) was 30 mg/kg body weight and day, the lowest dose tested.

5.2.3 Dermal application

In a Russian study in rats, the dermal application of a **cresyl glycidyl ether** dose of 210 mg/kg body weight and day for 10 days resulted in damage to the nervous system and the liver (no other details; ECB 2000). As a NOAEL of 600 mg/kg body weight was established for oral administration in a study carried out according to OECD Test Guideline 408 and neither neurotoxic effects nor liver effects were observed, the findings of the study with dermal application are implausible and are not included in the evaluation of the absorption of cresyl glycidyl ethers through the skin.

Tab. 7 Studies of the effects of *o*-cresyl glycidyl ether after repeated oral administration

Species, strain, number per group	Exposure	Findings	References
rat, Wistar Han, 10 ♂, 10 ♀, OECD Test Guideline 408	90 days, 0, 30, 100, 600 mg/kg body weight and day, gavage, vehicle: polyethylene glycol 400, purity: no data	**< 30 mg/kg body weight**: **NOAEL local toxicity in the forestomach/stomach**; **30 mg/kg body weight**: breathing sounds (♀: 1/10); forestomach/stomach: enlargement of the limiting ridge between forestomach and stomach (♂), thickened area in the stomach (♂), sloughing in the stomach (♂), focal inflammatory cell infiltrates in the forestomach (♂), ulceration in the stomach (♂), erosion in the forestomach (♂); **100 mg/kg body weight and above**: salivation ↑; breathing sounds (♂: 2/10); leukocyte count ↑ (♀); forestomach/stomach: hyperkeratosis (♂, ♀); **600 mg/kg body weight**: **NOAEL systemic toxicity**; breathing sounds; 1 death, not substance-related (♀); transient decrease in body weight gains (♂); reddish-brown discoloration of snout (♂: 1/10); leukocyte count ↑ (♂); forestomach/stomach: enlargement of the limiting ridge between forestomach and stomach (♀), thickened area in the stomach (♀), sloughing in the stomach (♀), focal inflammatory cell infiltrates in the forestomach (♀), erosion in the forestomach (♀), hyperplasia in the forestomach (♂, ♀); caecum: inflation (♀: 1/10); no unusual findings: feed and water consumption, ophthalmologic and clinico-chemical examinations, organ weights, behavioural tests, functional performance and sensory reactivity	ECHA 2018

5.3 Local effects on skin and mucous membranes

5.3.1 Skin

In a study carried out according to OECD Test Guideline 404, undiluted ***o*-cresyl glycidyl ether** (0.5 ml; purity: > 95% (v/v); Huntsman BVBA 2006) applied semi-occlusively to the shaved skin of 3 New Zealand White rabbits for 4 hours induced slight erythema and oedema. The average scores were 0.67 (erythema) and 0.27 (oedema) after 1, 24, 48 and 72 hours. The primary irritation index was 1.2 on a scale with a maximum of 8. All effects were reversible within 7 days. The substance was found to cause slight irritation of the skin (ECHA 2018).

In a range-finding study that was not carried out according to valid test guidelines, ***o*-cresyl glycidyl ether** was administered to 6 New Zealand White rabbits either as a single open application to the intact skin or by application to the abraded and unabraded skin under occlusive conditions. Very severe hyperaemia, moderate swelling and superficial exfoliation were observed after open application. The substance was severely corrosive after occlusive application (no other details; Dow Chemical Company 1962; ECHA 2018).

In another study with groups of 3 male and 3 female Russian rabbits, undiluted ***o*-cresyl glycidyl ether** (composition: 90% *o*-cresyl glycidyl ether, 8% *o*-tolyl-alpha-myanesin, 2% different oligomers, less than 1% in each case; Huntsman Advanced Materials 2019) was applied occlusively to the abraded and unabraded skin for 24 hours. The procedure was carried out according to the test method "Appraisal of the Safety of Chemicals in Foods, Drugs and Cosmetics" from 1959. The skin areas were examined after 24 and 72 hours. The primary irritation index was 5.2 on a scale with a maximum of 8. The test substance was found to cause moderate skin irritation (Ciba-Geigy Ltd. 1975; ECHA 2018). In other studies that were not described in more detail, cresyl glycidyl ethers were found to cause moderate to severe irritation of the skin in rabbits (no other details; ECB 2000; Gardiner et al. 1992).

Summary: In studies carried out with rabbits according to valid test guidelines, ***o*-cresyl glycidyl ether** was found to cause slight irritation of the skin.

5.3.2 Eyes

A study carried out according to OECD Test Guideline 405 investigated the eye irritation potential of undiluted ***o*-cresyl glycidyl ether** (0.1 ml; purity: > 95% (v/v); Huntsman BVBA 2006) in 3 New Zealand White rabbits. A score of 0.33 was determined for conjunctival reddening in 2 animals during the observation period of 24 to 72 hours. However, this effect was fully reversible. The mean irritation index over the entire observation period was 0.58. The substance was not found to cause eye irritation (ECHA 2018).

A range-finding study that was not carried out according to valid test guidelines investigated the eye irritation potential of ***o*-cresyl glycidyl ether** (no data for the amount applied) in 1 New Zealand White rabbit. The test substance was applied to 1 eye and rinsed out after 30 seconds. The other eye was used as the control. The test substance caused slight hyperaemia of the conjunctivae, which had fully regressed after 24 hours. Intraocular and corneal effects were not observed. *o*-Cresyl glycidyl ether was not found to cause irritation of the eyes (no data for the irritation index; Dow Chemical Company 1962; ECHA 2018).

In another study, 0.1 g of undiluted ***o*-cresyl glycidyl ether** (composition: 90% *o*-cresyl glycidyl ether, 8% *o*-tolyl-alpha-myanesin, 2% different oligomers, less than 1% in each case; Huntsman Advanced Materials 2019) was applied to groups of 3 male and 3 female English Silver rabbits. The test substance was applied to the lower conjunctival sac of the left eye using a spatula and the eyelids were held open for several seconds. The right eye was used as the control. The treated eyes were rinsed out with 10 ml water after 30 seconds. Examinations were carried out after 24 hours, 2, 3, 4 and 7 days. The mean irritation indices were 0 for the iris and for the cornea and 0.8 for the conjunctivae (maximum values for the cornea: 80, iris: 10, conjunctivae: 20). All changes were reversible within 48 hours. The test substance was found to cause slight irritation of the eyes (Ciba-Geigy Ltd. 1972 c; ECHA 2018). In another study that was not described in detail, cresyl glycidyl ethers caused moderate irritation of the eyes in rabbits (no other details; ECB 2000).

Summary: In studies carried out with rabbits according to valid test guidelines, ***o*-cresyl glycidyl ether** was not found to cause any or at most slight irritation of the eyes.

5.4 Allergenic effects

5.4.1 Sensitizing effects on the skin

In a maximization test in guinea pigs, cresyl glycidyl ethers were found to induce contact sensitization. Conclusions cannot be drawn from the findings of a study with guinea pigs that investigated the cross-reactivity of cresyl glycidyl ethers with *n*-butyl glycidyl ether and C12/C14-monoglycidyl ether (Hartwig 2014).

In a modified local lymph node assay (LLNA) using only 2 concentrations of the test substance in acetone/olive oil (4:1), concentrations of 2% and 10% ***o*-cresyl glycidyl ether** (technical product, purity 91.3%) applied to the skin of groups of 4 female CBA/Ca mice yielded stimulation indices of 4.7 and 16.1, respectively. An EC_3 value (the *o*-cresyl glycidyl ether concentration that leads to a threefold increase in lymphocyte proliferation) of 1.6% was extrapolated from these data (Heine et al. 2016).

In a direct peptide reactivity assay, ***o*-cresyl glycidyl ether** caused an 81.3% depletion of the cysteine peptide and complete depletion of the lysine peptide (Heine et al. 2016).

Positive results were obtained with phenyl glycidyl ether and ***o*-cresyl glycidyl ether** also in the KeratinoSens assay. Concentrations of 16.1 and 15.4 µM (geometric mean of 3 determinations), respectively, led to a 50% increase in luciferase activity. The IC_{50} values (the concentration at which 50% of cells survived) were the concentrations of 187.0 and 151.2 µM, respectively (geometric mean of 3 determinations) (Heine et al. 2016).

By contrast, the isomer mixture of **cresyl glycidyl ether** produced a negative result in the human cell line activation test (h-CLAT) (Heine et al. 2012).

Positive results were likewise obtained with phenyl glycidyl ether in a local lymph node assay carried out with CBA/Ca mice. The substance was applied in 0.01%, 0.1%, 1.0%, 10% and 20% formulations in acetone/olive oil (4:1). An EC_3 value of 0.46% was calculated on the basis of these data (Delaine et al. 2011; Niklasson et al. 2009, 2011).

5.4.2 Sensitizing effects on the airways

There is no information available.

5.5 Reproductive and developmental toxicity

5.5.1 Fertility

There are no fertility studies available.

After exposure of male rats to ***o*-cresyl glycidyl ether** aerosol (head-only exposure) for 3 weeks at a concentration of 305 mg/m³, reduced spermatogenesis was observed in 5 of 10 animals. After exposure to an *o*-cresyl glycidyl ether concentration of 152 mg/m³, spermatogenesis was inhibited in 1 animal, but only in 1 testis; this effect was assessed as coincidental because it occurred only unilaterally. By contrast, no effects were observed in the reproductive organs of the female animals (see Section 5.2.1; Ciba-Geigy Ltd. 1978 a; ECHA 2018).

In another study with exposure of rats to ***o*-cresyl glycidyl ether** vapour by inhalation, no effects on the reproductive organs of male and female animals were observed up to the highest concentration tested of 4 ml/m³ (26.8 mg/m³) (see Section 5.2.1; Dow Chemical Company 1991 b; ECHA 2018).

Also in a study carried out according to OECD Test Guideline 408 with exposure of rats to ***o*-cresyl glycidyl ether** by gavage for 90 days, no effects on the reproductive organs of male and female animals were observed up to the highest dose tested of of 600 mg/kg body weight and day (see Section 5.2.2; ECHA 2018).

In a study that was not described in greater detail with exposure of rats by inhalation to ***o*-cresyl glycidyl ether** concentrations of 0, 2.6 or 19.1 mg/m³, reduced sperm motility, abnormal sperm morphology and an increased number of tubules with desquamated epithelial cells were observed in male rats. Embryolethal effects were observed in the females, particularly during the pre-implantation phase (no other details; IARC 1989).

In a dominant lethal test with dermal application of *o*-cresyl glycidyl ether to mice 3 times a week, the number of implantations per pregnancy was found to be decreased within 8 weeks at a dose level of 1500 mg/kg body weight and application. Also the incidence of pregnancy was reduced, while the number of deaths was similar to that in the control group (see Section 5.6.2; ECHA 2018; Gardiner et al. 1992; University of Texas 1977). Pre-implantation losses can be caused by the death of the embryos or by a treatment-induced reduction in the number of sperm; these are then regarded as cytotoxic effects. However, as further investigation is required to determine which of these possibilities applies, the cause of these effects remains unclear.

5.5.2 Developmental toxicity

In a prenatal developmental toxicity study carried out according to OECD Test Guideline 414, Sprague Dawley rats were given ***o*-cresyl glycidyl ether** by gavage at dose levels of 0, 100, 300 or 600 mg/kg body weight and day (24 animals/group, solvent: polyethylene glycol) from gestation days 5 to 19. Reduced body weight gains and feed consumption were observed in the dams at the dose of 600 mg/kg body weight and day. Other findings were ataxia, bent posture and recumbent position. The increased salivation found at dose levels of 100 mg/kg body weight and day and above and the breathing sounds produced by individual animals in all dose groups and in the control group were attributed to the route of administration. No unusual findings were observed in the foetuses. The NOAEL for developmental toxicity was 600 mg/kg body weight and day, the highest dose, and the NOAEL for maternal toxicity was 300 mg/kg body weight and day (ECHA 2018). *o*-Cresyl glycidyl ether did not induce teratogenic effects.

5.6 Genotoxicity

5.6.1 In vitro

The studies of the genotoxicity of cresyl glycidyl ethers in vitro are shown in Table 8.

o-Cresyl glycidyl ether and the cresyl glycidyl ether isomer mixture induced mutagenic effects in the indicator strains for base-pair substitutions, the Salmonella typhimurium strains TA100 and TA1535, in the absence of a metabolic activation system (Canter et al. 1986; ECHA 2018; Gardiner et al. 1992; Litton Bionetics Inc 1978; University of Texas 1977). After the addition of a metabolic activation system, the mutagenic effect in the two strains was either weaker (ECHA 2018; Litton Bionetics Inc 1978) or no effect at all was observed (Canter et al. 1986; ECHA 2018; Gardiner et al. 1992; University of Texas 1977). An increase in mutations was not observed after exposure of the Salmonella typhimurium strains TA98, TA1537 and TA1538 and the Saccharomyces cerevisiae strain D4 to *o*-cresyl glycidyl ether and the cresyl glycidyl ether isomer mixture at concentrations up to 5000 µg/plate both with and without the addition of a metabolic activation system (Canter et al. 1986; ECHA 2018; Litton Bionetics Inc 1978). In human lymphocytes, *o*-cresyl glycidyl ether led to an increase in DNA repair synthesis at concentrations of 10 µg/ml and above (ECHA 2018; University of Texas 1977).

Summary: *o*-Cresyl glycidyl ether and the cresyl glycidyl ether isomer mixture induced direct mutagenic effects in bacteria in the form of base-pair substitutions. The mutagenic activity was considerably reduced or almost entirely eliminated by the addition of a metabolic activation system.

5.6.2 In vivo

The genotoxicity studies in vivo are shown in Table 9.

o-Cresyl glycidyl ether did not induce mutagenic effects in the host-mediated assay (Gardiner et al. 1992; University of Texas 1977). In male C57BL/6-Big-Blue® mice, *o*-cresyl glycidyl ether did not cause an increase in mutations in the liver and testes in a test carried out according to OECD Test Guideline 488 after gavage doses of up to 500 mg/kg body weight and day for 28 days (BioReliance Corporation 2019). The stomach, as the first tissue to come into contact with *o*-cresyl glycidyl ether after oral administration, should have been investigated, but was not investigated for mutations. In a test with the application of *o*-cresyl glycidyl ether to the skin of Muta™ mice at a dose level of 500 mg/kg body weight and day for 5 days, the incidence of mutations in the skin and liver was not increased 7 and 28 days after the end of treatment. An increased incidence of mutations was found in the bone marrow at the first test reading, but not at the second. This was within the range of the historical controls of the laboratory and was therefore not considered biologically relevant (Covance Laboratories Limited 2000; ECHA 2018). The study is of limited validity because the exposure period was very short at only 5 days, and only the skin, but not the bone marrow and liver, was examined in the positive control group.

In two micronucleus tests, clastogenic effects were not induced in mice given *o*-cresyl glycidyl ether by gavage, either as a single dose of 2000 mg/kg body weight or at doses of 125 mg/kg body weight and day for 5 days (ECHA 2018; Gardiner et al. 1992; Safepharm Laboratories Limited 1991 b; University of Texas 1977). In a dominant lethal test in mice, dermal application of *o*-cresyl glycidyl ether 3 times a week for 8 weeks at a dose of 1500 mg/kg body weight and application caused a decrease in the number of implantations per pregnancy and a reduced incidence of pregnancy. There was no increase in post-implantation losses and the number of deaths was similar to that in the control group (see Section 5.5.1; ECHA 2018; Gardiner et al. 1992; University of Texas 1977). As there was no increase in post-implantation losses, the reduced number of pre-implantations is more likely evidence of systemic toxicity than of a genotoxic effect (Gardiner et al. 1992). Pre-implantation losses may be caused by the death of the embryos or a treatment-related reduction in the number of sperm; these are then regarded as cytotoxic effects. However, as further investigation is required to determine which of these possibilities applies, the pre-implantation losses by themselves do not constitute conclusive evidence of the induction of dominant lethal mutations.

Tab. 8 Genotoxicity of cresyl glycidyl ethers in vitro

End point	Test system	Concentration [µg/plate][a)]	Cytotoxicity[a)]	Effective concentration[a)]	Results		References
					–m.a.	+m.a.	
gene mutation preincubation	Salmonella typhimurium TA98, Salmonella typhimurium TA1537	***o*-cresyl glycidyl ether**, 5 concentrations (no data), up to cytotoxicity or solubility limit, solvent: DMSO, purity: > 95% (v/v) (Huntsman BVBA 2006)	no data		–	–	Canter et al. 1986; ECHA 2018
	Salmonella typhimurium TA100	–m.a.: 0, 3.3, 10, 33, 100, 334; +m.a.: 0, 10, 33, 100, 333, 667	–m.a.: at 100 +m.a.: at 667	revertants ↑: 33: 2-fold and 3-fold, respectively (2 tests)	+	–	
	Salmonella typhimurium TA1535	–m.a.: 0, 3.3, 10, 33, 100, 333; +m.a.: 0, 10, 33, 100, 333, 666	–m.a.: at 333 +m.a.: at 666	revertants ↑: 33: 4-fold, 100: 8.6-fold	+	–	
gene mutation plate incorporation	Salmonella typhimurium TA1535	***o*-cresyl glycidyl ether**, 0, 500, 1000, 2000; no data for solvent, purity: > 95% (v/v) (Huntsman BVBA 2006)	no data	revertants ↑: –m.a.: 500: 23-fold, 1000: 42-fold, 2000: 58-fold, +m.a. (from phenobarbital-treated rats): 500: 0.9-fold, 1000: 0.9-fold, 2000: 1.1-fold, +m.a. (from Aroclor-treated rats): 500: 1.2-fold, 1000: 3.1-fold, 2000: 5.2-fold	+	–/+	Gardiner et al. 1992; University of Texas 1977
	Salmonella typhimurium TA98	see above	no data		–	–	
gene mutation plate incorporation	Salmonella typhimurium TA98	**cresyl glycidyl ether isomer mixture**, 0, 1, 10, 100, 1000, 5000; solvent: DMSO, purity: no data	–m.a.: at 5000 +m.a.: none		–	–	ECHA 2018; Litton Bionetics Inc 1978
	Salmonella typhimurium TA100	see above	–m.a.: at 5000 +m.a.: none	revertants ↑: 100: 1.8-fold and 2.2-fold, respectively, 1000: 6.7-fold and 4.3-fold, respectively (2 tests each)	+	–	

Tab. 8 *(continued)*

End point	Test system	Concentration [µg/plate][a)]	Cytotoxicity[a)]	Effective concentration[a)]	Results		References
					–m.a.	+m.a.	
	Salmonella typhimurium TA1535	see above	–m.a.: at 5000 +m.a.: at 5000	–m.a.: revertants ↑: 1: 2.4-fold and 2.0-fold, respectively, 10: 4.4-fold and 3.2-fold, respectively 100: 12.5-fold and 12.7-fold, respectively, 1000: 19.8-fold and 19.8-fold, respectively (2 tests each), +m.a.: revertants ↑: 1: 2.6-fold, 10: 2.9-fold, 100: 3.3-fold, 1000: 8.8-fold	+	+	
	Salmonella typhimurium TA1537	see above	–m.a.: at 1000 and above +m.a.: 5000		–	–	
	Salmonella typhimurium TA1538	see above	–m.a.: at 5000 +m.a.: at 5000		–	–	
	Saccharomyces cerevisiae D4	see above	–m.a.: at 5000 +m.a.: none		–	–	
UDS	human lymphocytes	***o*-cresyl glycidyl ether**, 0, 10, 100, 1000 µg/ml, in DMSO, purity: > 95% (v/v) (Huntsman BVBA 2006)	at 100 µg/ml	10 µg/ml	+	not conducted	ECHA 2018; University of Texas 1977

[a)] if not specified otherwise, the data are given in [µg/plate]
DMSO: dimethyl sulfoxide; m.a.: metabolic activation; UDS: test for the induction of DNA repair synthesis

Tab. 9 Studies of the genotoxicity of cresyl glycidyl ethers in vivo

Test system		Dose	Results	Comments	References
gene mutations host-mediated assay	mouse, ICR, groups of 10 ♀, intraperitoneal inoculation of bacteria, Salmonella typhimurium	*o*-cresyl glycidyl ether, 5 days, 0, 125 mg/kg body weight and day, gavage, no data for vehicle; purity: > 95% (v/v) (Huntsman BVBA 2006)	–		Gardiner et al. 1992; University of Texas 1977

Tab. 9 *(continued)*

Test system		Dose	Results	Comments	References
gene mutation	C57BL/6 Big Blue® mouse, 6 ♂, liver, testes (5 ♂ investigated), OECD Test Guideline 488	o-cresyl glycidyl ether, 0, 125, 250, 500 mg/kg body weight and day, 28 days, investigation on day 56, gavage, 10 ml/kg body weight, vehicle: corn oil, no concurrent positive control group, data from study from the same year with ethyl nitrosourea used as positive control: 40 mg/kg body weight and day, 3 consecutive days (days 1 to 3), examination on day 31; purity: > 85.5%	–	liver, testes: number of mutations in the range of the controls; pilot study: 5 ♂, 250, 500, 1000 mg/kg body weight, 5 days, at 1000 mg/kg body weight: breathing difficulties in 2 animals, no mortality; bone marrow, glandular stomach, duodenum collected, but not analysed for mutations, liver, testes, bone marrow, stomach, duodenum: no gross-pathological findings, no deaths, no clinical findings, as the first tissue to come into contact with *o*-cresyl glycidyl ether after oral administration, the glandular stomach should have been investigated, but was not	BioReliance Corporation 2019
gene mutation	Muta™ mouse, 5 ♂, skin, liver, bone marrow	*o*-cresyl glycidyl ether, 0, 500 mg/kg body weight, 5 consecutive days, 1 application/day, 2 ml/kg body weight dermal application to the shaved dorsal skin (open application), vehicle: acetone, positive control benzo[a]pyrene: 0.25 mg/kg body weight, 5 consecutive days, examination on day 12; exposed animals: examinations on days 12 and 33 (7 and 28 days after the end of application), purity: > 99%	–	bone marrow: statistically significant increase in the incidence of mutations in the rank-transformed and non-transformed analyses at the first test reading (64.9% ± 24.3%; controls: 38.5% ± 4.8%; historical controls from 16 tests: 47.9% ± 23.0%), but not at the second test reading, without biological relevance; skin, liver: incidence of mutations in the range of the controls; range-finding study: 3 ♂, 500, 1000, 2000 mg/kg body weight, 4 days, 1000 mg/kg body weight and above: abdominal swelling, eyes closed, cloudy eyes, piloerection, lethargy, swollen hind legs, severe irritation at the site of application; 1 animal sacrificed in extremis at 1000 mg/kg body weight; limited validity: very short exposure period of 5 days (according to OECD Test Guideline 488 from 2013: daily application for 4 weeks; Test Guideline 488 since 2011); positive control: examination only of the skin, not of the bone marrow and liver	Covance Laboratories Limited 2000; ECHA 2018
micronucleus test	mouse, BKM, 5 ♂ and 5 ♀, bone marrow, OECD Test Guideline 474	*o*-cresyl glycidyl ether, 0, 2000 mg/kg body weight, single, gavage, vehicle: arachis oil, examination after 24, 48, 72 hours, purity: about 95%	–	NCE/PCE unchanged; range-finding study: single application of 2000 mg/kg body weight equivalent to the maximum tolerated dose, positive control: cyclophosphamide	ECHA 2018; Safepharm Laboratories Limited 1991 b
micronucleus test	mouse, B6C3F1, 10 ♀, bone marrow	*o*-cresyl glycidyl ether, 0, 125 mg/kg body weight, 5 days, gavage, vehicle: corn oil, examination after 4 hours, purity: > 95% (v/v) (Huntsman BVBA 2006)	–	NCE/PCE: no data	ECHA 2018; University of Texas 1977

Tab. 9 *(continued)*

Test system		Dose	Results	Comments	References
dominant lethal test	mouse, B6D2F1, 10 ♂ and 60 ♀	*o*-cresyl glycidyl ether, 0, 1500 mg/kg body weight, 8 weeks, 3 times a week, dermal application to ♂: 10%–20% of the body surface, shaved and chemically depilated skin, no data for occlusion, test substance: undiluted, negative control: 0.9% saline solution, positive control: TEM, purity: > 95% (v/v) (Huntsman BVBA 2006)	+/–	number of implantations/pregnancy ↓ (2 weeks after treatment: 6.970; controls: 8.277; signs of pre-implantation losses, no increase in post-implantation losses), pregnancy ↓ (2 weeks after treatment: 63.6%; controls: 83.5%); deaths/pregnancy (2 weeks after treatment: 0.029; controls: 0.020)	ECHA 2018; Gardiner et al. 1992; University of Texas 1977

NCE/PCE: ratio of normochromatic to polychromatic erythrocytes; TEM: triethylene melamine

Summary: *o*-Cresyl glycidyl ether did not induce clastogenic effects in the bone marrow after gavage administration in mice. In a study carried out according to OECD Test Guideline 488, the substance did not cause an increase in mutations in the liver and testes of male Big-Blue® mice after gavage doses of up to 500 mg/kg body weight and day for 28 days. In a study that is of limited validity, dermal application to Muta™ mice for 5 days did not lead to mutagenic effects in the skin, liver and bone marrow. In a dominant lethal test in mice with application to the skin 3 times a week over a period of 8 weeks, pre-implantation losses that were not accompanied by an increase in post-implantation losses were not regarded as conclusive evidence of the induction of dominant lethal mutations.

5.7 Carcinogenicity

There are no data available.

5.8 Other effects

Male C3H/Hej mice (3 animals/group) were given a single intraperitoneal injection of *o*-cresyl glycidyl ether in tricaprylin at dose levels of 0 or 4 mg per animal. After 24 hours, the haemoglobin adduct level in the blood was 1.0 pmol *N*-[2-hydroxy-3-(1-methylphenyloxy)propyl]valine/mg globin. The haemoglobin binding index was 1.3 pmol/g globin per µmol of *o*-cresyl glycidyl ether/kg body weight. The adduct levels of 3 workers involved in styrene lamination who were not exposed to glycidyl ether were below the detection limit of 0.1 pmol/g globin (Pérez et al. 1997).

6 Manifesto (MAK value/classification)

Cresyl glycidyl ethers have sensitizing effects on the skin. In rats, the primary effect after exposure by inhalation is local irritation in the nose. In addition, in vitro studies have found evidence of mutagenic effects.

MAK value and peak limitation. There are no data available in humans.

After head-only inhalation exposure of rats to *o*-cresyl glycidyl ether aerosol for 3 weeks, reduced body weight gains and irritation of the nasal mucosa, the severity of which increased with the concentration, were found at concentrations of 152 mg/m^3 and above. The NOAEC was 53 mg/m^3 (Ciba-Geigy Ltd. 1978 a; ECHA 2018). Unusual systemic and local findings were not observed after whole-body exposure of rats to *o*-cresyl glycidyl ether vapour at concentrations of up to 4 ml/m^3 (26.8 mg/m^3) for 4 weeks (Dow Chemical Company 1991 b; ECHA 2018). The most sensitive effect in rats

after exposure by gavage for 90 days was local irritation. Thus, ulceration, erosion and inflammatory cell infiltrates were observed in the forestomach after exposure to *o*-cresyl glycidyl ether at dose levels of 30 mg/kg body weight and day and above. The NOAEL for systemic toxicity in this study was 600 mg/kg body weight and day, the highest dose tested (ECHA 2018). The NOAEL for systemic effects was calculated on the basis of a concentration of 53 mg/m^3 and was about 15 mg/kg body weight (0.8 l/min/kg body weight, 100% absorption, 6 hours/day).

However, a MAK value cannot be derived from the available data because although cresyl glycidyl ethers were conclusively proven to be directly mutagenic in vitro, no conclusions can be drawn with respect to their mutagenicity in vivo. The structurally similar compound phenyl glycidyl ether is mutagenic in vitro and induces tumours of the nose in rats after exposure by inhalation (Henschler 1992).

Classification in a peak limitation category is not applicable.

Prenatal toxicity. In a prenatal developmental toxicity study carried out according to OECD Test Guideline 414 with Sprague Dawley rats, no developmental toxicity was observed after exposure by gavage to *o*-cresyl glycidyl ether up to the highest dose tested of 600 mg/kg body weight and day. Reduced body weight gains and feed consumption were observed in the dams at this dose (ECHA 2018). As no MAK value has been established, the substance has not been classified in a pregnancy risk group.

Carcinogenicity. There are no carcinogenicity studies of cresyl glycidyl ethers.

o-Cresyl glycidyl ether and the cresyl glycidyl ether isomer mixture induce direct mutagenic effects in bacteria (base-pair substitutions). The mutagenic effects are considerably reduced by the addition of a metabolic activation system, which is regarded as evidence of an efficient detoxification mechanism. *o*-Cresyl glycidyl ether does not lead to clastogenic effects in the bone marrow of mice after gavage administration, and in a study carried out according to OECD Test Guideline 488 did not lead to mutagenic effects in the liver and testes of male Big-Blue® mice. The suspected mutagenic effect in vivo is not invalidated by these negative results after gavage administration and the results of a study with application to the skin of Muta™ mice for 5 days because it remains unclear how the substance reacts after inhalation and the application period of only 5 days in the dermal study was very short. Studies in vitro found that GSH conjugation is an important mechanism in the metabolic inactivation of *o*-cresyl glycidyl ether in rats and mice, while epoxide hydrolysis plays a more important role in humans (Boogaard et al. 2000 b). Overall, the data suggest efficient detoxification; however, no quantitative studies have been carried out in vivo, particularly after inhalation. Carcinogenic effects are assumed because of the direct mutagenic effects in vitro. This is also supported by the structural relationship with phenyl glycidyl ether, which is classified in Carcinogen Category 2. Phenyl glycidyl ether induced irritation in the nose and nasal tumours in rats after inhalation exposure to 12 ml/m^3 for 2 years. Histologically, the tumours were carcinomas originating in the epidermis of the anterior nasal cavity. No tumours were observed at 1 ml/m^3 (Henschler 1992). It is assumed that cresyl glycidyl ethers react in a very similar manner because of their structural relationship with phenyl glycidyl ether. Cresyl glycidyl ethers are highly reactive compounds and the type of exposure is an important factor in determining the severity of the effects they induce; this is particularly true for inhalation. Cresyl glycidyl ethers are therefore classified in Carcinogen Category 3 B.

In a comparative study of the mutagenic effects in Salmonella typhimurium strains, the effect strength in TA100 of *o*-cresyl glycidyl ether and phenyl glycidyl ether without metabolic activation was found to be similar (Canter et al. 1986). With the addition of a metabolic activation system, however, as a result of epoxide hydrolases, the mutagenic activity of *o*-cresyl glycidyl ether was considerably reduced. It remains unclear how *o*-cresyl glycidyl ether reacts after inhalation with direct contact with the nasal epithelium, and suspected carcinogenic effects cannot be excluded.

Germ cell mutagenicity. *o*-Cresyl glycidyl ether and the cresyl glycidyl ether isomer mixture induce direct mutagenic effects in bacteria (base-pair substitutions). The mutagenic activity was considerably reduced or almost entirely eliminated by the addition of a metabolic activation system. *o*-Cresyl glycidyl ether did not cause clastogenic effects in the bone marrow of mice after gavage administration. In a study carried out according to OECD Test Guideline 488, the substance did not lead to increased mutations in the liver and testes of male Big-Blue® mice after gavage doses of up to 500 mg/kg body weight and day for 28 days. The study supports the data that there are no mutagenic effects after

gavage administration. However, the glandular stomach, as the first tissue to come into contact with the substance, was not examined. Application to the skin of Muta™ mice for 5 days did not induce mutagenic effects in the skin, liver and bone marrow. The very short period of application was already criticized above. For this reason, this study cannot be used to invalidate the mutagenicity determined in vitro.

In a dominant lethal test in mice with treatment of the skin 3 times a week over a period of 8 weeks, pre-implantation losses that were not accompanied by an increase in post-implantation losses were not regarded as conclusive evidence of the induction of dominant lethal mutations. In a 3-week study with head-only inhalation exposure to *o*-cresyl glycidyl ether, reduced spermatogenesis was observed in 5 of 10 of the male animals at a concentration of 305 mg/m^3 (Ciba-Geigy Ltd. 1978 a; ECHA 2018). This proves that the substance can reach the germ cells.

The structurally similar phenyl glycidyl ether likewise induces direct mutagenic effects in bacteria (base-pair substitutions). In a test for clastogenicity and another for mutagenicity in mammalian cells, phenyl glycidyl ether did not cause clastogenic or mutagenic effects. In a micronucleus test in mice and a dominant lethal test, the substance was not found to be clastogenic in mice at dose levels up to 1000 mg/kg body weight and did not induce dominant lethal mutations in rats after exposure by inhalation to concentrations of up to 12 ml/m^3 (Henschler 1992).

Overall, on the basis of the data available, cresyl glycidyl ethers have not been classified in a category for germ cell mutagens. This decision is supported also by genotoxicity tests carried out with phenyl glycidyl ether, in particular the negative results obtained in the dominant lethal test.

Absorption through the skin. In an in vitro study in human skin, the maximum amount of *o*-cresyl glycidyl ether absorbed was calculated to be 205 mg assuming exposure of 2000 cm^2 of skin for 1 hour.

The systemic NOAEL of *o*-cresyl glycidyl ether in rats after subchronic oral exposure was 600 mg/kg body weight. The following toxicokinetic data are taken into consideration for the extrapolation of this dose as the systemic NOAEL to humans: the corresponding species-specific correction value for the rat (1 : 4), the assumed oral absorption of 100%, the daily exposure of the animals in comparison with the 5 days per week exposure at the workplace (7 : 5), the body weight (70 kg) of the person, a possible intensification of the effect over time (1 : 2) and the extrapolation of the data from the animal study to the human (1 : 2). This results in a systemically tolerable amount of 3675 mg.

As the log K_{OW}, molar mass and solubility in water are similar both for the isomer mixture of cresyl glycidyl ether and for *o*-cresyl glycidyl ether, and similar toxicity can be assumed, the amount calculated can be applied also for the mixture.

Therefore, absorption via the skin is less than 25% of the systemically tolerable amount and *o*-cresyl glycidyl ether and the cresyl glycidyl ether isomer mixture are not designated with an "H" (for substances which can be absorbed through the skin in toxicologically relevant amounts).

Sensitization. Recent clinical findings from clinico-epidemiological studies of allergic reactions to cresyl glycidyl ethers have demonstrated that cresyl glycidyl ethers are sensitizing to the skin. Positive results from experiments likewise confirm that the substances have a sensitizing potential. There are still no data for sensitizing effects on the airways. For this reason, cresyl glycidyl ethers continue to be designated with "Sh" (for substances which cause sensitization of the skin), but not with "Sa" (for substances which cause sensitization of the airways).

Notes

Competing interests

The established rules and measures of the Commission to avoid conflicts of interest (https://www.dfg.de/en/dfg_profile/statutory_bodies/senate/health_hazards/conflicts_interest/index.html) ensure that the content and conclusions of the publication are strictly science-based.

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