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GMS PUBLISSO ZB MED-Publikationsportal Lebenswissenschaften

Bisphenol A diglycidyl ether

MAK Value Documentation, supplement – Translation of the German version from 2020

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Keywords

bisphenol A diglycidyl ether; irritation; sensitization; genotoxicity; spleen; epoxy resin

Abstract

The German Commission for the Investigation of Health Hazards of Chemical Compounds in the Work Area has re-evaluated bisphenol A diglycidyl ether [1675-54-3] considering all toxicological end points. The critical effects of bisphenol A diglycidyl ether in humans and in animals are skin sensitization and spleen toxicity in rats after oral exposure. In several studies in mice, bisphenol A diglycidyl ether was not carcinogenic to the skin. In a guideline study in rats with gavage application of up to 100 mg/kg body weight and day, the substance was not carcinogenic and no effects were observed in the stomach, the site of first contact. After dermal application of bisphenol A diglycidyl ether, the promutagenic DNA adduct hydroxymethylethenodeoxyadenosine-3′-monophosphate was found in the skin of mice. However, as local carcinogenicity was not induced even after the substance was administered as an oral bolus (see above), DNA adduct formation is assumed to be insufficient for tumour induction. This might be due to adequate detoxification of the substance in vivo. There is strong evidence that epoxide hydrolase has a greater detoxification capacity in human skin than in mouse skin. Thus, the assignment to Carcinogen Category 3 A is withdrawn. As aerosol exposure to bisphenol A diglycidyl ether at the workplace is to be assumed and inhalation studies are not available, a maximum concentration at the workplace (MAK value) cannot be derived. In prenatal toxicity studies in rats and rabbits, developmental toxicity was not observed up to the highest doses tested of 540 (rat, oral), 180 (rabbit, oral) and 300 (rabbit, dermal) mg/kg body weight and day. Bisphenol A diglycidyl ether induces mutations in bacteria and is clastogenic to mammalian cells. The substance was neither clastogenic nor mutagenic in several tests in vivo, including 2 dominant lethal tests, and is thus not a systemic genotoxin in vivo. Clinical data from humans and animal experiments show clear evidence of a contact sensitizing potential and the designation with “Sh” is retained. Respiratory sensitizing effects are suspected, but the data are not sufficient to label the substance with “Sa”. The dose taken up via the skin as calculated from in vitro experiments is considerably lower than the tolerable systemic dose extrapolated from chronic oral administration in rats. Hence, the designation with “H” is not retained.

Citation Note:
Hartwig A, MAK Commission. Bisphenol A diglycidyl ether. MAK Value Documentation, supplement – Translation of the German version from 2020. MAK Collect Occup Health Saf. 2023 Dec;8(4):Doc077. https://doi.org/10.34865/mb167554e8_4ad

Manuscript completed:
12 Apr 2019

Publication date:
20 Dec 2023

MAK value	**not yet established, see Section II b of the List of MAK and BAT Values**
Peak limitation	–
Absorption through the skin	–
Sensitization (1997)	**Sh**
Carcinogenicity	–
Prenatal toxicity	–
Germ cell mutagenicity	–
BAT value	–
CAS number	1675-54-3
Vapour pressure at 25 °C	< 0.0001 hPa (Greim 2003)

In 1997, bisphenol A diglycidyl ether was classified in Section III B, which corresponds to the current Carcinogen Category 3 B (Greim 2003). In 2000, the substance was considered as a candidate for Carcinogen Category 5 because the substance itself and structurally related compounds had been shown to cause DNA adduct formation in mouse skin and there was evidence of genotoxicity in vitro. However, as no data were available to derive a NOAEL (no observed adverse effect level) for DNA adduct formation in human skin, the substance was classified in Carcinogen Category 3 A (Greim 2003). Since the supplement was published in 2001 (Greim 2003), new studies relevant to the evaluation have become available that investigated biomonitoring in humans, acute toxicity, toxicity after repeated oral and dermal exposure, skin and respiratory tract sensitization, effects on the skin and eyes, reproductive toxicity, genotoxicity and carcinogenicity. These data are reviewed in this supplement (the documentation from 1997 and supplement from 2001 were combined in one translation from 2003).

Bisphenol A diglycidyl ether is liquid at room temperature. The substance is of very low volatility because of its low vapour pressure, which is below 0.0001 hPa at 25 °C (Greim 2003).

A large number of studies have been carried out with technical grade bisphenol A diglycidyl ether. Due to the manufacturing process, the starting product epichlorohydrin, which is a genotoxic carcinogen, is present as an impurity in technical grade bisphenol A diglycidyl ether (Hartwig 2015). These studies are included in this documentation if their findings are required for the evaluation. The focus of the evaluation is the pure substance; possible impurities are to be evaluated separately.

1 Toxic Effects and Mode of Action

Numerous clinical findings in humans are available for the skin sensitizing effects of epoxy resins containing bisphenol A diglycidyl ether. In addition, the substance had sensitizing effects on the skin of mice and guinea pigs. The clinical findings do not provide sufficient evidence to demonstrate that bisphenol A diglycidyl ether causes sensitization of the airways.

Bisphenol A diglycidyl ether caused slight irritation of the skin, but not of the eyes, in rabbits.

There are no inhalation studies available. Bisphenol A diglycidyl ether has a very low vapour pressure, which is below 0.0001 hPa at 25 °C. The spleen was the target organ in male F344 rats after 2-year gavage administration; histopathological changes were observed at the highest dose tested of 100 mg/kg body weight and day.

Bisphenol A diglycidyl ether is directly alkylating, has marked mutagenic potency in bacteria (base-pair substitutions) and is clastogenic in mammalian cells in vitro. In a large number of in vivo genotoxicity tests, bisphenol A diglycidyl ether did not cause systemic genotoxicity.

After dermal application in mice, bisphenol A diglycidyl ether induced the exocyclic DNA adduct 7-(hydroxymethyl)-1,N^6-ethenoadenosine, which is regarded as promutagenic.

The substance was not carcinogenic in numerous dermal carcinogenicity studies in various mouse strains and in a recent oral carcinogenicity study in male and female F344 rats carried out according to OECD Test Guideline 453.

2 Mechanism of Action

In rats, bisphenol A diglycidyl ether caused effects on the spleen after gavage administration. However, there are no data available for the mechanism of action.

3 Toxicokinetics and Metabolism

No recent data are available, and there are no studies with inhalation exposure.

3.1 Absorption, distribution, elimination

In male F344 rats given an oral 2-^{14}C-propane-labelled bisphenol A diglycidyl ether dose of 2.7 mg/kg body weight, the plasma ^{14}C level reached its maximum 4 hours after administration; less than 10% of the recovered substance was unchanged bisphenol A diglycidyl ether. The half-life in the plasma was 4.8 hours and the highest ^{14}C concentrations in the tissues were found in the liver and intestines. Within 24 hours, 53% of the dose was excreted with the faeces and 8% with the urine. As bisphenol A diglycidyl ether is not very stable in synthetic stomach fluid with a half-life of 70 minutes and the half-life for oral absorption is 42 minutes, it is estimated that more than one third of the orally administered amount is degraded in the gastro-intestinal tract. It was not possible to perform a toxicokinetics study with inhalation exposure because heating bisphenol A diglycidyl ether at room temperature did not achieve a sufficiently high concentration in the air. Therefore, the study was carried out with intravenous injection instead. Twenty-four hours after a dose of 0.43 mg/kg body weight was injected intravenously, the amount of radioactivity in the plasma was 3 times as high as the level determined after the oral administration of 2.7 mg/kg body weight. The relative AUC (area under the concentration–time curve) determined for the radioactivity in the plasma after oral administration was 17% of the AUC calculated after intravenous injection. The plasma half-life was 7.7 hours after the intravenous dose. Within 24 hours, 85% of the dose was excreted with the bile and 9% with the urine. The tissue to plasma concentration ratios in the liver, intestines and lungs were lower than those determined after oral administration. On the basis of the toxicokinetic differences determined after oral administration and intravenous injection and because only small amounts are absorbed after oral administration, it was concluded that studies with oral administration are not suitable for the evaluation of the inhalation toxicity of bisphenol A diglycidyl ether (ECHA 2019 a; Greim 2003).

Percutaneous absorption of bisphenol A diglycidyl ether was slow following application to the skin. When a single dose of 2-^{14}C-propane-labelled bisphenol A diglycidyl ether of 56 mg/kg body weight was applied occlusively to the skin of male mice, 67% of the applied radioactivity was extracted from the skin after 1 day and 11% after 8 days. Within 3 days, 20% of the applied dose was excreted with the faeces and 3% with the urine. However, the same single dose administered orally was absorbed more rapidly. Within 24 hours, 61% was excreted with the faeces and 9% with the urine and after 3 days, total amounts of 80% were excreted with the faeces and 11% with the urine (Climie et al. 1981 a;

Greim 2003). The metabolite profiles in mice were similar after oral administration and dermal application (Climie et al. 1981 a).

On the basis of the data available for mice (Climie et al. 1981 a), complete oral absorption is assumed because excretion via the faeces was also the main route of elimination after dermal application; therefore, none of the evidence suggests incomplete oral absorption. From the relative AUC of the radioactivity in the plasma determined in the study in rats following oral administration and intravenous injection, oral absorption is calculated to be 17%. However, the relative plasma AUC may underestimate oral absorption because the ratio between the organ and plasma concentrations was higher after oral administration than after intravenous injection. In addition, it has yet to be determined how much unchanged bisphenol A diglycidyl ether is absorbed orally (less than 10% of the radioactivity in the blood after 4 hours) and it is not clear whether the decomposition products in the gastro-intestinal tract or the metabolites formed after absorption also cause systemic toxicity.

The dermal penetration of ^{14}C-ring-labelled bisphenol A diglycidyl ether and its metabolism in dermatomed human skin (mammoplasty), rat skin (F344 rats) and in intact mouse skin (C3H mice) were investigated by means of a flow-through diffusion cell system over a period of 24 hours. A dose of 5 µmol/cm^2 of bisphenol A diglycidyl ether in acetone was used as the test formulation. The apparent permeability constants for human, rat and mouse skin were 0.48 ± 0.22, 5.5 ± 1.5 and 8.6 ± 1.6 (× 10^{-6} cm/h), respectively. It took longer for the substance to penetrate human skin and penetration was less than one tenth of that through rodent skin: the dermal penetration of bisphenol A diglycidyl ether was 0.137% ± 0.005% of the applied dose for human skin, 1.57% ± 0.41% for rat skin and 2.98% ± 0.80% for mouse skin. Bisphenol A diglycidyl ether was metabolized extensively during dermal absorption. In human, rat and mouse skin, 79% ± 8%, 92.9% ± 0.1% and 96% ± 1%, respectively, of the fraction that penetrated the skin was converted into the bis-diol; 10% ± 5%, 3.8% ± 0.1% and 2.0% ± 0.2% was hydrolysed to the mono-diol and 1.1% at most was recovered as unchanged bisphenol A diglycidyl ether. These proportions remained constant for 24 hours (Boogaard et al. 2000 a; Greim 2003). A flux of 2.377 × 10^{-6} g/cm^2 in 24 hours or 9.906 × 10^{-8} g/cm^2 and hour was calculated from the penetration percentage for human skin together with the data for the dose, area of application and duration of the experiment. From this flux, the total absorption of 0.198 mg was calculated based on standard conditions (exposed area of skin of 2000 cm^2 and exposure for 1 hour).

3.2 Metabolism

In mice, hydrolytic ring cleavage of the 2 epoxide rings with the formation of the bis-diol is the most important step in the metabolism of bisphenol A diglycidyl ether after oral or dermal absorption. About 8% of the bis-diol is excreted in free form or as glucuronide and sulfate conjugates. The bis-diol is oxidized at the terminal end to yield α-hydroxycarboxylic acid (about 27% of the dose) and, after decarboxylation, the specific carboxylic acid (about 15% of the dose). The phenol diol (about 5% of the dose) is formed presumably by oxidative dealkylation of the bis-diol and cleavage of glyceraldehyde. Glyceraldehyde can enter the endogenous metabolism (Figure 1; Climie et al. 1981 a, b; Greim 2003).

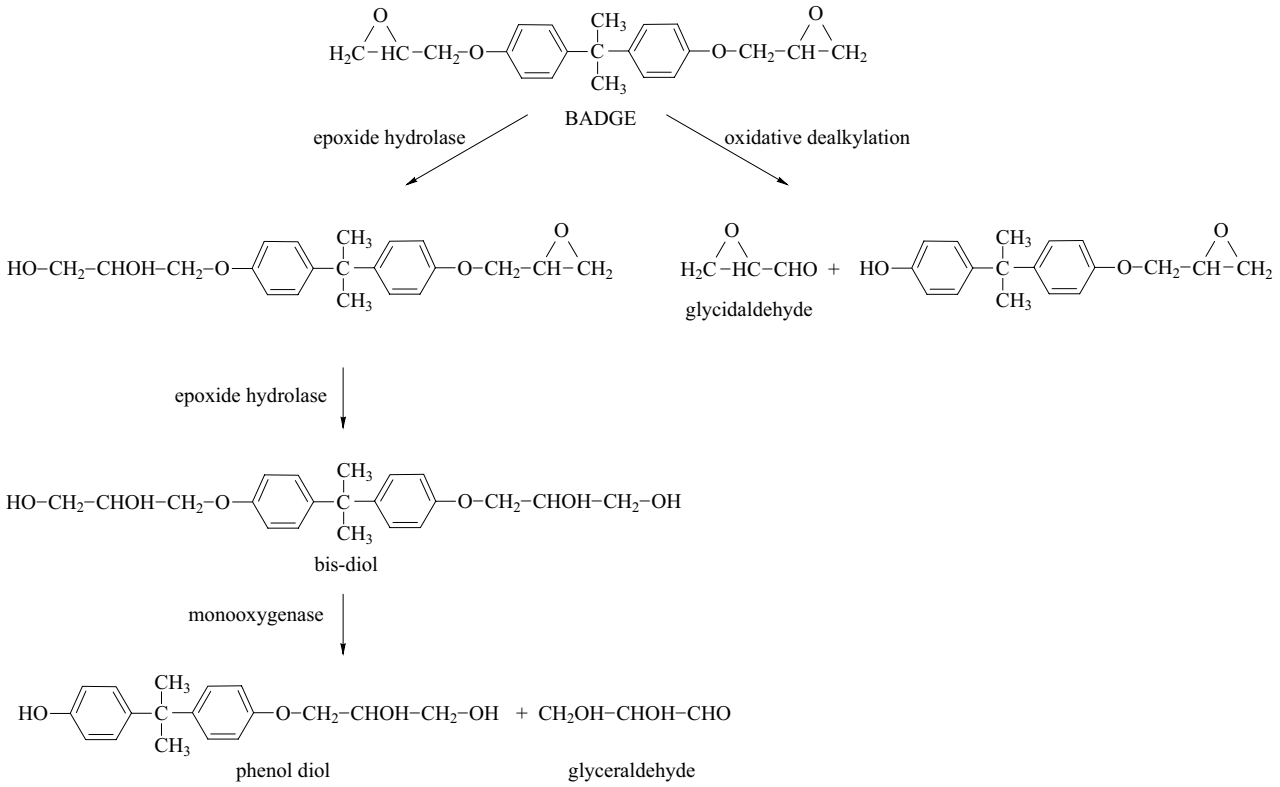

Fig. 1 Metabolism of bisphenol A diglycidyl ether as published in Greim (2003), modified according to Climie et al. (1981 b)

In vitro, the alternative metabolic pathway leading to the formation of the phenol diol, the oxidative dealkylation of bisphenol A diglycidyl ether after cleavage of the reactive glycidaldehyde (see Figure 1), was only a minor pathway (1%) and occurred only after the inhibition of epoxide hydrolase with 1,1,1-trichloro-2,3-epoxypropane in the presence of liver microsomes from CF1 mice. Therefore, the authors assumed that bisphenol A diglycidyl ether is not dealkylated directly to form glycidaldehyde in vivo and that the high level of epoxide hydrolase activity in the liver leads to the more or less complete hydrolysis of bisphenol A diglycidyl ether to the bis-diol (Climie et al. 1981 b; Greim 2003).

Detoxification of bisphenol A diglycidyl ether – species differences: Comparative studies that investigated the metabolism of bisphenol A diglycidyl ether determined much higher levels of hydrolytic activity in human liver microsomes in comparison with those found in rat and mouse liver microsomes: the V_{max} values were 150 nmol/mg and minute (human) compared with 63 nmol/mg and minute (rat) and 46.6 nmol/mg and minute (mouse). The K_m values were 0.63 mM (human) compared with 0.34 mM (rat) and 0.23 mM (mouse). In humans and rodents, epoxide hydrolysis is the main and an efficient route of detoxification of bisphenol A diglycidyl ether. Glutathione conjugation takes place to a lesser extent. Bisphenol A diglycidyl ether and its mono-diol appear to have similar affinities for epoxide hydrolase (Boogaard et al. 2000 b; Greim 2003).

The epoxide hydrolase activity in human skin is higher than that in mouse skin. The specific activities were higher in humans than in mice for the following substrates: phenanthrene-9,10-oxide by a factor of 1.6, benz[a]anthracene-5,6-oxide by a factor of 4.1, benzo[a]pyrene-4,5-oxide by a factor of 2.6, 7-methylbenz[a]anthracene-5,6-oxide by a factor of 2.4, 3-methylcholanthrene-11,12-oxide by a factor of 2.6 and dibenz[a,h]anthracene-5,6-oxide by a factor of 5.4 (Greim 2003; Oesch et al. 1978). Therefore, it is assumed that the bisphenol A diglycidyl ether substrate is likewise detoxified more rapidly in human skin than in mouse skin.

4 Effects in Humans

Biomonitoring: The bisphenol A diglycidyl ether concentrations in urine samples from adult volunteers of the general population were determined. The volunteers came from Albany, New York, in the United States (n = 31; 19 men, 2 male teenagers and 10 women) and from Shanghai, China (n = 26; 15 men and 11 women). The samples were collected between August 2010 and July 2011. No information was provided about the volunteer recruitment process. The geometric mean of the sum of the concentrations of bisphenol A diglycidyl ether and its derivatives (bisphenol A diglycidyl ether mono-diol, bisphenol A (3-chloro-2-hydroxypropyl)-(2,3-dihydroxypropyl) ether and bisphenol A diglycidyl ether bis-diol) was 3 ng/ml in the urine of the volunteers from the United States. In these volunteers, the free bisphenol A diglycidyl ether concentration (after ethyl acetate extraction without the addition of glucuronidase) was 0.121 ng/ml and the total concentration (with the addition of glucuronidase; sum of free and conjugated bisphenol A diglycidyl ether) was 0.599 ng/ml. In the volunteers from China, the urinary concentrations of bisphenol A diglycidyl ether were about one third. The geometric means were 0.204 ng/ml for free and conjugated bisphenol A diglycidyl ether and 0.093 ng/ml for free bisphenol A diglycidyl ether (Wang et al. 2012). This study did not report any effects on health.

Bisphenol A diglycidyl ether concentrations were determined in adipose fat samples from 20 healthy adult volunteers from New York City, United States, who underwent liposuction between 2003 and 2004 (5 men and 15 women) and in plasma samples collected between 2003 and 2004 from 20 male volunteers, also from New York City. The concentrations determined in adipose fat ranged from the limit of detection to a maximum value of 5.16 ng/g wet weight. All values determined in plasma were below the limit of detection. The limits of detection were 0.40 ng/g for the adipose tissue and 0.25 ng/ml for the plasma (Wang et al. 2015). Again, this study did not investigate effects on health.

Allergenic effects

Sensitizing effects on the skin

Bisphenol A diglycidyl ether is the formal monomer in epoxy resins produced from the condensation products of epichlorohydrin and bisphenol A; it probably has the highest sensitizing potential of the low-molecular weight oligomers contained in these resins, but its pure form has not been approved for use as a test formulation for patch testing. However, the international and almost all national standard test series include a 1% formulation of an epoxy resin in petrolatum. The raw materials used for these formulations are non-modified, low-molecular weight epoxy resins based on bisphenol A diglycidyl ether of medium viscosity with a mean molecular mass of 380 to 390 daltons. Comprehensive findings are available for this (these) test formulation(s) because almost all patients with suspected contact allergy are tested with the components of the standard series. The findings confirm that these epoxy resins, which almost exclusively contain bisphenol A diglycidyl ether in addition to other low-molecular weight oligomers, induce sensitizing effects, thereby confirming that bisphenol A diglycidyl ether itself is a sensitizer. Only a few findings from the large number of data available from standard series tests have been included in this documentation by way of example. These have been supplemented with additional findings for the discussion of specific aspects.

The "EPOX 2002" study carried out in the clinics of the Information Network of German Departments of Dermatology (Informationsverbund Dermatologischer Kliniken; IVDK) tested a low-molecular weight epoxy resin based on bisphenol A diglycidyl ether in an extended epoxy resin series; patients with a specific indication in the patch test with suspected contact allergy caused by epoxy resins and those with known positive patch test results from epoxy resins were selected for the study. In the first phase of this study carried out from 2002 to 2003, 50 of a total of 87 patients produced a positive reaction to the low-molecular weight epoxy resin (20 × 1+, 23 × 2+ and 5 × 3+) (Geier et al. 2004).

The test formulation seem to be suitable for patch testing in view of the high reaction index (RI, defined as the quotient: (a – d – i) / (a + d + i); with: a = number of allergic reactions, d = number of questionable reactions, i = number of irritant reactions (Brasch and Henseler 1992)) of 1.0 and the low positivity ratio (PR, percentage of 1+ reactions among the total number of positive reactions (Geier et al. 2003 b)) of 42% (Geier et al. 2003 b, 2004). However, both parameters were probably influenced by the cohort selected and the specific testing because non-specific testing with the standard

series led to a distinctly lower RI and a slightly higher PR (see below). Among the total of 217 patients tested in the first phase and in the subsequent second and third phases from 2003 to 2005, 126 (58%) produced a positive reaction to the low-molecular weight epoxy resin (Geier 2010).

In patch tests, 9 patients who produced a positive reaction to resins based on bisphenol A diglycidyl ether or on bisphenol F diglycidyl ether in an (extended) standard series were tested with graded dilutions of the epoxy resins (in acetone). Four of the 9 test persons reacted to formulations containing the resin based on bisphenol A diglycidyl ether at concentrations as low as 0.01% and 1 of them additionally to a 0.001% formulation (Pontén et al. 2008). Another study used graded concentrations to test 11 patients with initially positive reactions to the 1% formulation of the epoxy resin containing 92% bisphenol A diglycidyl ether. In this test, the 0.32%, 0.1%, 0.032%, 0.01% and 0.0032% formulations of the resin caused at least a 1+ reaction in all 11 patients, in 9 of 11, 5 of 11, 3 of 11 and 1 of 11 patients, respectively. Readings were carried out on days 3 and 7, with 3 patients failing to produce a reaction by day 3 (Hagvall et al. 2016).

In a study carried out by the German Contact Dermatitis Research Group (Deutsche Kontaktallergie-Gruppe; DKG), additional late patch test readings were carried out in 1428 patients who had been tested with the epoxy resin based on bisphenol A diglycidyl ether; 2 late reactions were observed on day 7, 1 late reaction on day 14 and 1 on day 24. The test was repeated in 1 patient who produced a 1+ reaction only on day 7, resulting in a severe reaction on day 3 (Hillen et al. 2006). Thus, sensitization in patch tests with the low-molecular weight epoxy resin based on bisphenol A diglycidyl ether is rare, but may occur in isolated cases.

Reactions were observed in 61 (17.8%) of 343 patients with suspected occupational airborne contact eczema; they had been patch tested with the standard epoxy resin in the IVDK clinics between 1994 and 2013. Of the patients, 31 and 12 produced a positive reaction to reactive thinners and amine hardeners, respectively (Breuer et al. 2015). It is unclear whether the skin reactions, such as those observed in the head or neck area were in fact caused by airborne exposure to bisphenol A diglycidyl ether or by the more volatile reactive thinners and amine hardeners. In other case reports, the eczema was not mediated by the air; contact eczema almost always developed after resin adhering for example to gloved hands was spread across the skin. The (irritant) effects were caused by airborne exposure to reactive thinners, volatile components of hardeners or glass fibres in only a few cases (Schubert et al. 2004).

Frequency of sensitization in clinico-epidemiological studies

From 1992 to 2000, 0.9% to 1.4% (women: 0.6% to 1.2%; men: 1.6% to 2.3%) of the patients tested with the standard series in the clinics of the IVDK produced a positive reaction to low-molecular weight epoxy resin (Geier et al. 2003 a). The evaluation of the test findings from more than 36 500 patients tested with the standard series from 2007 to 2010 yielded similar results. The percentages of sensitization were 1.4% to 1.7% without a uniform trend in terms of time. In this evaluation, men were again affected about twice as frequently as women with a percentage of reactions of about 2.4% (Geier et al. 2011 b, c). In the period from 2002 to 2011, a total of 93 406 patients were tested with the epoxy resin of the standard series in the clinics of the IVDK, yielding 1453 positive reactions (1.6%; 172 3+, 514 2+ and 767 1+), 438 erythematous reactions (0.5%) and 91 irritant reactions (0.1%) (Geier et al. 2016). Based on these values, an RI of 0.46% and a PR of 52.8% were calculated for the test formulation.

In 1997 and 1998, a total of 1299 patients with suspected allergic contact eczema were tested at Malmö University with a resin based on bisphenol A diglycidyl ether as part of the standard series. Positive readings were obtained in 14 patients (1.1%) (Pontén and Bruze 2001).

According to a Swedish study from 2008, this test formulation led to positive reactions in 23 of a total of 2227 patients (1%) between 2001 (month not reported, presumably January) and June 2004 (Pontén et al. 2008).

The North American Contact Dermatitis Group found positive reactions in 2.2% of 3114 and 1.9% of 3438 patients tested with the standard series including epoxy resin based on bisphenol A diglycidyl ether from 1994 to 1996 and 1996 to 1998, respectively. The highest percentage was 2.7% of 5832 patients tested from 1998 to 2000. Positive reactions were obtained in 2.3% of 4909, 1.8% of 5143 and 1.8% of 4439 patients tested from 2001 to 2002, 2003 to 2004 and 2005 to 2006, respectively (Pratt et al. 2004; Zug et al. 2009).

In 2004, 31 dermatology departments from 11 European countries included in the European Surveillance System on Contact Allergies (ESSCA) found positive reactions in about 1.1% of more than 11 000 patients patch tested with epoxy resin based on bisphenol A diglycidyl ether as part of the standard series (ESSCA Writing Group 2008). In 2013 and 2014, the average percentage of positive reactions was also 1.1% of a total of 28 577 patients tested from what were in the meantime 46 clinics in 12 countries (Uter et al. 2017).

A number of other studies found similar percentages of reactions after testing epoxy resin as part of the standard series: Coimbra, Portugal: from 1999 to 2008, positive reactions in 24 of 2440 patients (1%) (Canelas et al. 2010); Tel Aviv: from 1998 to 2004, positive reactions in 24 of 2156 patients (1.1%) (Lazarov 2006); Finnish Institute of Occupational Health (FIOH), Helsinki: from 1974 to 1990, positive reactions in 139 of a total of 3731 patients with suspected occupational dermatitis (3.7%; the tested resin contained 89% bisphenol A diglycidyl ether) (Jolanki 1991), from 1991 to 2014: positive reactions in 198 of 4445 patients (4.5%) (Aalto-Korte et al. 2015); Danish Contact Dermatitis Group: from 2005 to 2009, positive reactions in 275 of 20 808 patients (1.7%) (Bangsgaard et al. 2012).

Studies in exposed workers

Sensitization to epoxy resins is very frequently reported by a number of industries requiring the handling of uncured epoxy resins, particularly by plants in which large quantities of epoxy resins are or were applied by hand, for example for the manufacture of wind turbine rotor blades (see below), in pipe relining (see below), in aircraft construction (Hackett 1999) and in ski (and ski-stick) production (Jolanki et al. 1996; Suhonen 1983).

From 1996 to 2001, a total of 763 patients with suspected contact allergy to adhesives were patch tested with low-molecular weight epoxy resin in the clinics of the IVDK. Positive reactions were observed in 67 of 310 patients (21.6%) with occupational dermatitis and in 13 of 332 patients (3.9%) with a non-occupational skin disease (Hillen et al. 2007).

In a study carried out by the IVDK clinics as part of the research project "Frühzeitige Erkennung allergener Stoffe bei beruflicher und nicht-beruflicher Exposition" ("FaSt"; early recognition of allergenic substances during occupational and non-occupational exposure), the men with occupational dermatitis were more frequently sensitized to the low-molecular weight epoxy resin; this was attributed to the specific testing and the selected cohort. The percentages of reactions were highest in the occupational groups of painters and varnishers (41%), plastics processors (30%), and bricklayers and related occupations (10%) (Geier et al. 2002).

Twenty-five of around 70 workers of a plant that made rotor blades with glass-fibre reinforced plastics using the hand lay-up process had to stop work because of occupationally induced contact allergy to epoxy resin based on bisphenol A diglycidyl ether. Initial skin reactions were observed in 6 workers within the first 3 months of beginning work and in 3 other workers within another 3 months (Göring 2001).

In 3 workers with similar occupational exposure, allergic contact dermatitis was manifest as early as 3 to 4 weeks after they had begun to work. In patch tests, the patients reacted to epoxy resin based on bisphenol A diglycidyl ether and to phenyl glycidyl ether (Laskowski and Heise 2000).

In 2001, cases of occupational contact eczema were analysed in a Danish plant manufacturing rotor blades for wind turbines. The workers who used epoxy resins in the hand lay-up process were exposed to epoxy resins based on bisphenol A diglycidyl ether and bisphenol F diglycidyl ether. In patch tests, 34 of 66 tested patients reacted to the resin based on bisphenol A diglycidyl ether (Pontén et al. 2004 a, b; Rasmussen et al. 2005).

Eight workers who repaired damaged water pipes by relining the pipes with coatings of epoxy resin developed work-related contact eczema on their hands, wrists or lower arms after 1 to 42 months of work. Six of the tested workers produced marked to severe reactions to the resin based on bisphenol A diglycidyl ether in the patch test (Berglind et al. 2012).

Studies with workers from the construction industry: Sensitization to epoxy resins is observed relatively frequently among workers in the construction industry (Bock et al. 2003; Geier et al. 2011 a; van Putten et al. 1984), for example in tunnel construction workers (Irvine et al. 1994; Rast 2001), painters (Aalto-Korte et al. 2015; Bangsgaard et al.

2012; Moura et al. 1994; Rømyhr et al. 2006) or floor layers (Aalto-Korte et al. 2015; Bangsgaard et al. 2012; Canelas et al. 2010; Condé-Salazar et al. 1994; Pontén and Bruze 1999).

Of the 74 243 patients who did not work in the construction industry and were tested in the clinics of the IVDK between 1992 and 2000, 1.2% reacted to low-molecular weight epoxy resin. Positive reactions were obtained in 5.9% of the 1238 tested persons working in the construction industry (Uter et al. 2004). Higher non-adjusted sensitization prevalences were determined in plastics processors (13.7% positive reactions) as well as in painters and varnishers (6.9%). A multifactorial Poisson regression analysis yielded increased prevalence ratios for construction and mining industry workers (prevalence ratio = 4.1), painters, carpenters and potters (prevalence ratio = 3.8) and chemical industry workers (prevalence ratio = 2.7) compared with the "service occupations" used as reference (Uter et al. 2002, 2004).

An analysis of the IVDK data for bricklayers and members of related occupations (concrete workers, unskilled construction workers, stucco masons, plasterers, tile setters, screed layers and terrazzo layers) with occupational skin disease revealed that the frequencies of sensitization to epoxy resin had increased in these patients from 8.4% to 12.4% between 1994 and 2008. Very frequently affected were patients who had started to work only after 1999. Evidently, sensitization developed quite rapidly because the highest percentage was observed in patients who had worked in the industry less than 2 years at the time of testing (Geier et al. 2011 a).

Immediate reactions on the skin

There were occasional reports of urticarial reactions after occupational contact with resins based on bisphenol A diglycidyl ether. Pruriginous skin changes developed repeatedly over several years in a worker of a plant manufacturing steel reels. In patch tests, several technical-grade epoxy resins based on bisphenol A diglycidyl ether or bisphenol F diglycidyl ether, but not the hardeners used, produced urticarial reactions after 15 and 30 minutes. This type of reaction to the bisphenol A diglycidyl ether-based resin tested in the standard series was observed both in the non-occlusive and in the occlusive patch test after 30 minutes (Miyamoto and Okamura 1998).

A worker in the aircraft industry reported a 6-month episode of recurrent pruriginous and urticarial reactions on his face and arms that developed within 20 minutes after exposure to epoxy resin components. These reactions were sometimes accompanied by angio-oedema on his lips and tongue and laryngeal symptoms. In the patch test with resin based on bisphenol A diglycidyl ether and with phenyl glycidyl ether and cresyl glycidyl ether, urticarial reactions of up to 40 mm in diameter were observed after 30 minutes. The reactions were reproducible in another test; however, after application of the test substances for 2 days, a late reaction was not observed at the reading taken on day 4 (Sasseville 1998).

A worker developed eczema on his wrists and lower arms after using a two-component epoxy resin in the manufacture of shower cabinets for 2 months. In addition, he developed oedematous changes on his lips and eyelids half a year later. Although he switched to another workplace, occasional exposure to epoxy resin led to a total of 3 episodes with eczematous and oedematous reactions and also to urticarial reactions. Patch tests revealed distinct late reactions to epoxy resin based on bisphenol A diglycidyl ether (1% tested) and to the resins handled by the worker (2% and 4% tested). Prick tests with these resins and with epoxy resin based on bisphenol A diglycidyl ether also yielded positive results. Likewise, open application tests with the two-component resin and with epoxy resin based on bisphenol A diglycidyl ether produced reactions after 20 minutes, whereas the hardener did not cause any reaction (Kanerva et al. 2002).

A patient who might have been sensitized to epoxy resins at his former workplace in a car paint shop, developed laryngeal and buccal swelling followed by unconsciousness while having root canal treatment at a dental practice. The swelling persisted for several days in spite of treatment with high doses of corticosteroids. In the patch test, the epoxy resin tested in the standard series, the components of the root canal filling material (epoxy resins based on bisphenol A diglycidyl ether and bisphenol F diglycidyl ether) and the hardened root canal sealer, but not the hardener, produced marked late reactions. The patient developed marked urticarial reactions to all substances after 20 minutes, and generalized immediate reactions were observed after repeated testing of the filling material and after the second test of the standard epoxy resin (Stutz et al. 2008).

Cross-reactions

Patients sensitized to bisphenol F diglycidyl ether, phenyl glycidyl ether or bisphenol A diglycidyl methacrylate (bis-GMA) and similar substances often produced reactions also to bisphenol A diglycidyl ether in patch tests; most of these were probably immunological cross-reactions (Aalto-Korte et al. 2009; Geier et al. 2016; Greim 2001; Hartwig 2013; Lee et al. 2002).

Sensitizing effects on the airways

Two patients with contact eczema caused by epoxy resin additionally reported respiratory symptoms such as rhinitis and asthma. In both cases, prick tests with 1% formulations of human serum albumin (HSA) conjugates of a commercially available epoxy resin based on bisphenol A diglycidyl ether yielded positive results. Specific IgE as a reaction to this conjugate, and to a lesser extent (possibly because of different conjugates) to the HSA conjugate with purified bisphenol A diglycidyl ether, was likewise detected in both patients. In addition, one of the patients reacted to the prick test and there was evidence of IgE with the HSA conjugate of methyl tetrahydrophthalic anhydride or methyl hexahydrophthalic anhydride. However, there was no indication of an IgE-mediated reaction to HSA conjugates of bisphenol A diglycidyl ether or epoxy resins based on bisphenol A diglycidyl ether in 5 workers who reported occupational rhinitis and were exposed to different epoxy resins (including mainly cyclo-aliphatic epoxy resins) and dicarboxylic anhydride hardeners (Kanerva et al. 1991).

In the FIOH, prick tests with an HSA conjugate of bisphenol A diglycidyl ether (about 1% in coca solution/glycerol 1:1) were carried out on 1268 patients from January 1991 to May 2011. Reactions with wheals 3 to 7 mm in diameter were observed in 19 tested persons. Epoxy resin caused asthma in 2 patients and allergic contact eczema in another 3 persons tested. An asthmatic reaction (no other details) was observed in 1 of 2 patients (prick test reaction: 3 mm; no specific IgE determined) in the bronchial provocation test with epoxy resin. The findings in the second patient (prick test reaction: 4 mm) were described in a separate publication (see below) (Helaskoski et al. 2015).

The above-mentioned patient was a construction worker who developed contact eczema on the back of his hands shortly after he started work laying floors coated with epoxy resin; the eczema subsequently spread to his lower legs, forearms and face. Later, he also developed work-related respiratory symptoms (shortness of breath, coughing and rhinitis). The total IgE was 245 kU/l and the specific IgE to the HSA conjugate of bisphenol A diglycidyl ether was 20 kU/l. A 2+ reaction was obtained in the patch test with epoxy resin based on bisphenol A diglycidyl ether and a reaction 4 mm in diameter was produced in the prick test, both with the HSA conjugate of bisphenol A diglycidyl ether and with the patch test formulation. A 30-minute bronchial provocation test, during which the patient spread the epoxy resin he had used in a 6-m^3 chamber over a large area, led to a 9% decrease in the forced expiratory volume in one second (FEV_1) 45 minutes after the beginning of the provocation. In a second 45-minute provocation test, a decrease in the FEV_1 of up to 23% was determined after 90 minutes. These reactions were not observed in a control provocation test with a paint that did not contain epoxy resin (Hannu et al. 2009).

A construction worker who filled ruptures in concrete with a two-component epoxy resin inadvertently contaminated his clothing on his right forearm and his left thigh with the resin. Nevertheless, he continued to wear the clothing for the following 2 days. As a result, erythema developed on the areas of skin exposed to the resin and an eczematous skin reaction developed within 2 weeks. Repeated skin contact with epoxy resins caused recurring dermatitis. After 5 years, the worker developed work-related respiratory symptoms (no other details), and occupational asthma was diagnosed after another 2 years. In the bronchial provocation test during which the patient spread an epoxy resin that did not contain a hardener (no other details) on a board for 30 minutes, wheezing and a decrease in the peak expiratory flow (PEF) of 22% were observed after 8 hours. The inhalation of a beta sympathomimetic agent led to a transient normalization of the PEF; however, a maximum decrease of 36% was reached after 17 hours. In addition, pronounced skin reactions developed on the areas of his face, neck, ears and hands exposed to the air about 3 or 4 hours after the provocation (Kanerva et al. 2000).

In other cases in which epoxy resins were suspected of causing respiratory symptoms, the resins that caused the symptoms and may have been used in provocation tests were either not characterized in detail or they included

hardener components and additional glycidyl components (for example Authried et al. 2013; Girao Popolizio et al. 2016; Jacobsen et al. 2015; Solano et al. 2016; Suojalehto et al. 2019). In another case, a provocation test with epoxy resin from the patient's workplace caused a severe "coughing attack", but not a decrease in FEV_1; therefore, the authors assumed that the attack had been caused by irritation (Moulin et al. 2009). Therefore, these studies cannot be used to determine whether bisphenol A diglycidyl ether causes sensitizing effects on the airways.

5 Animal Experiments and in vitro Studies

5.1 Acute toxicity

5.1.1 Inhalation

There are no data available.

5.1.2 Oral administration

The acute oral toxicity of bisphenol A diglycidyl ether is very low. Estimates based on earlier limit tests yielded LD_{50} values higher than 2000 or 4000 mg/kg body weight. The oral LD_{50} values for a commercially available epoxy resin based on bisphenol A diglycidyl ether are 11 400 mg/kg body weight for rats, 15 600 mg/kg body weight for mice and 19 800 mg/kg body weight for rabbits. In addition, an oral LD_{50} of 19.6 ml/kg (about 19 600 mg/kg body weight) was reported in rats for a commercially available epoxy resin based on bisphenol A diglycidyl ether. Unlike the findings of earlier reports, recent studies with pure bisphenol A diglycidyl ether or commercially available epoxy resin based on bisphenol A diglycidyl ether have yielded consistent results (no other details; Dow Chemical Company 2001, 2004).

5.1.3 Dermal application

The dermal LD_{50} values determined for pure bisphenol A diglycidyl ether were higher than 1600 mg/kg body weight for rats and higher than 800 mg/kg body weight for mice. The dermal LD_{50} values for epoxy resins based on commercially available bisphenol A diglycidyl ether were higher than 1200 mg/kg body weight in rats and higher than 800 mg/kg body weight in mice (no other details; Dow Chemical Company 1998 b; Greim 2003).

5.2 Subacute, subchronic and chronic toxicity

5.2.1 Inhalation

There are no data available.

At the time of publication of the 1997 documentation, no relevant data were available for inhalation exposure to bisphenol A diglycidyl ether; this is still the case. Only persons who work with powdered polymers are at risk of being exposed to the substance by inhalation because it has a very low vapour pressure and generally does not occur as an aerosol at the workplace. It was not possible to generate a concentration in air that was high enough to carry out an inhalation study at room temperature by heating bisphenol A diglycidyl ether (Greim 2003).

5.2.2 Oral administration

In a number of studies with oral administration of bisphenol A diglycidyl ether to rats, no organ-specific toxicity was found (Greim 2003).

The new data that have been published since publication of the 2001 supplement are shown in Table 1.

Tab. 1 Effects of bisphenol A diglycidyl ether after repeated oral administration

Species, strain, number per group	Exposure	Findings	References
rat, F344, 65 ♂, 65 ♀	**14** weeks, OECD Test Guideline 408; 0, 50, 250, 1000 mg/kg body weight and day, 7 days/week, gavage, vehicle: Tween® 80 and methyl cellulose, purity: ≥99.32%; the study was planned as a carcinogenicity study, but was discontinued after 99 (♂) or 101 days (♀) because of severe decreases in body weights and feed consumption	**50 mg/kg body weight**: **NOAEL for systemic effects**; **50 mg/kg body weight and above**: body weights ↓ (♀: 3.2%; 250 mg/kg body weight: 5.1%; 1000 mg/kg body weight: 10.9%); blood: erythrocyte count ↓ (♀: 3.4%), haemoglobin concentration ↓ (♀: 3.9%); serum: cholesterol ↑ (♂: 33%; 250 mg/kg body weight: 82%; 1000 mg/kg body weight: 94%; ♀: 2%; 250 mg/kg body weight: 24%; 1000 mg/kg body weight: 26%); **250 mg/kg body weight and above**: body weights ↓ (♂: 10.8%; 1000 mg/kg body weight: 19.2%); blood: erythrocyte count ↓ (♂), haematocrit ↓ (♂, ♀); caecum: enlarged (♂), diffuse hyperplasia of the epithelium (♂); adrenal glands: vacuolation in the cortex ↓ (♂); kidneys: hyaline droplet formation in proximal tubular cells ↓ (♂); liver: eosinophilia of centrilobular hepatocytes ↑ (♂); **1000 mg/kg body weight**: mortality caused by moderate to severe acute necrosis of the proximal cells of the kidneys (2 ♂, 1 ♀); blood: haemoglobin concentration ↓ (♂), number of platelets ↓ (♂, ♀); serum: AST ↑ (♂); caecum: enlarged (♀), diffuse hyperplasia of the epithelium (♀); ileum: diffuse hyperplasia of the epithelium (♂); kidneys: vacuolation of proximal tubular cells (♀); liver: eosinophilia of centrilobular hepatocytes ↑ (♀); testes: focal or multifocal degeneration of the seminiferous tubules; uterus: diffuse atrophy of endometrium and myometrium; control group and high dose group, 10 animals/sex examined: oesophagus, forestomach, stomach without substance-induced findings; DNA adducts not determined	Dow Chemical Company 2001
rat, F344, 65 ♂, 65 ♀	**24** months, OECD Test Guideline 453; 0, 2, 15, 100 mg/kg body weight and day, 7 days/week, gavage, vehicle: Tween® 80 and methyl cellulose, purity: ≥99.32%; interim evaluation of 10 animals/sex and dose after 12 months	**15 mg/kg body weight**: **NOAEL for systemic effects (♂)**; **15 mg/kg body weight and above**: body weights and body weight gains ↓ (♂: body weight gains after 12 months: 4.0%; 100 mg/kg body weight: 12.9% and 24 months: 3.5%; 100 mg/kg body weight: 7.4%); serum: cholesterol ↑ (♀: after 3 months: 15%; 100 mg/kg body weight: 21%; after 12 months: 13%; 100 mg/kg body weight: 32%; not after 24 months); **100 mg/kg body weight**: **NOAEL for systemic effects** (♀); **100 mg/kg body weight**: blood: erythrocyte count ↓ (♂: after 12 months, not after 3 or 24 months); serum: cholesterol ↑ (♂: after 3 months: 24%; after 12 months: 39%; after 24 months: 15%); caecum: enlarged (♂: after 12 and 24 months); spleen: absolute and relative weights ↓ (♂: after 24 months), atrophy, reduction of the red pulp, reduced number of immature haematopoietic cells, less blood in sinusoids, sometimes increased amount of collagenous connective tissue between narrow compressed vascular spaces (♂: after 24 months, 29/55, not after 12 months); interim evaluation after 12 months: control group and high dose group, 10 animals/sex examined: oesophagus, forestomach, stomach without substance-induced findings; end of study: control group (55 animals per sex), 2 mg/kg body weight (15–19 animals per sex) and high dose group (55 animals per sex) examined: oesophagus, forestomach, stomach without substance-induced findings; DNA adducts not determined	Dow Chemical Company 2004 (see Section 5.7)

AST: aspartate aminotransferase

Groups of 65 male and 65 female F344 rats were given gavage doses of bisphenol A diglycidyl ether of 0, 50, 250 or 1000 mg/kg body weight and day. The study was originally planned as a carcinogenicity study, but it was discontinued after about 14 weeks because of severe toxicity. The cholesterol values in serum were increased, body weights were reduced and the erythrocyte count and the haemoglobin concentration were decreased in the blood even at the lowest dose tested of 50 mg/kg body weight and day. In the male animals, histopathological changes were observed in the adrenal glands (reduced vacuolation in the cortex), caecum (diffuse hyperplasia of the epithelium), kidneys (decrease in hyaline droplet formation in the proximal tubular cells) and liver (increased eosinophilia in the centrilobular hepatocytes) at 250 mg/kg body weight and day and above. At 1000 mg/kg body weight and day, degeneration

of the seminiferous tubules was found in all males. At this dose, the histopathological findings in the females included changes in the caecum (diffuse hyperplasia of the epithelium), kidneys (vacuolation of the proximal tubular cells), liver (increased eosinophilia of the centrilobular hepatocytes) and uterus (diffuse atrophy of the endometrium and myometrium). A NOEL (no observed effect level) was not established because the body weights were reduced and the serum cholesterol values were increased at the low dose of 50 mg/kg body weight and day. The authors considered this dose to be the NOAEL because histopathological effects were not detected either in male or in female animals (Dow Chemical Company 2001).

In a 2-year carcinogenicity study in male and female F344 rats, the animals were given gavage doses of bisphenol A diglycidyl ether of 0, 2, 15 or 100 mg/kg body weight and day. At 100 mg/kg body weight and day, histopathological changes were observed in the spleen of the male animals: atrophy with a reduction of the red pulp, a reduced number of immature haematopoietic cells, less blood in the sinusoids and in some cases an increased amount of collagenous connective tissue between narrow compressed vascular spaces. The dose of 2 mg/kg body weight and day was determined by the authors to be the NOEL because body weights were reduced in the males and the serum cholesterol values were increased in the females at 15 mg/kg body weight and day. The authors did not consider these findings to be adverse because the body weights of the males were decreased by only 3.5% and the cholesterol values were only slightly increased (15%) at 15 mg/kg body weight and day. Likewise, no pathological relevance was ascribed to the enlarged caecum that was observed at 100 mg/kg body weight and day. Therefore, a NOAEL for systemic toxicity of 15 mg/kg body weight and day was derived for males and of 100 mg/kg body weight and day for females (see Section 5.7; Dow Chemical Company 2004).

5.2.3 Dermal application

A study with non-occlusive dermal exposure for 90 days was carried out in groups of 10 male and 10 female F344 rats according to OECD Test Guideline 411. The purity of the bisphenol A diglycidyl ether was 99.65%, and acetone was used as the vehicle. The animals were exposed to bisphenol A diglycidyl ether doses of 0, 10, 100 or 1000 mg/kg body weight and day on 5 days a week (another satellite group of 10 females at the high dose 3 days a week). At 1000 mg/kg body weight and day, the body weights and body weight gains were reduced in the male and female rats. Feed consumption was slightly reduced during the entire study period. Epidermal hyperplasia with chronic inflammation, which was characterized as chronic dermatitis, was observed in the male rats at 10 mg/kg body weight and day and above and in the female rats at 100 mg/kg body weight and day and above. A NOAEL of 10 mg/kg body weight and day was derived for local effects in the female animals; a NOAEL could not be established for the male animals (ECHA 2019 a).

Another study carried out according to OECD Test Guideline 411 investigated the specific end point neurotoxicity in groups of 12 male and 12 female F344 rats. The F344 rats were given dermal doses of 0, 10, 100 or 1000 mg/kg body weight and day on 5 days a week over a period of 13 weeks. Reduced body weights were observed in both sexes at 1000 mg/kg body weight and day. In the males, the conduction velocities in the caudal nerves were reduced at both the low and the high doses. This finding was not regarded as treatment-related because a dose–response relationship was not observed, the examinations of neurotoxicity (functional observational battery) and the histopathological examinations of the nerves did not reveal a corresponding toxicological pattern, and the findings were not reversible (ECHA 2019 a).

In a dermal 2-year carcinogenicity study in female F344 rats, slight chronic dermatitis was observed with 99.3% bisphenol A diglycidyl ether in acetone at 100 mg/kg body weight and day and above (5 days a week) (see Section 5.7; Dow Chemical Company 1998 a; Greim 2003).

In a study carried out according to OECD Test Guideline 411 with non-occlusive dermal exposure for 90 days, groups of 10 male B6C3F1 mice were treated with bisphenol A diglycidyl ether doses of 0, 1, 10 or 100 mg/kg body weight and day on 3 days a week (purity: 99.65%; vehicle: acetone). Systemic toxicity was not observed. Mild to moderate chronic active dermatitis was found at 1 mg/kg body weight and day and above; there was a weak dose–response relationship. A NOAEL for local effects was not derived (ECHA 2019 a).

A dermal 2-year carcinogenicity study in male B6C3F1 mice treated with bisphenol A diglycidyl ether on 3 days a week reported chronic dermatitis and histopathologically visible changes in the skin, such as epidermal hyperplasia, scab formation and sporadic cases of ulceration at doses of 10 mg/kg body weight and day and above (see Section 5.7; Dow Chemical Company 1998 b; Greim 2003).

5.3 Local effects on skin and mucous membranes

5.3.1 Skin

In a study in rabbits, bisphenol A diglycidyl ether caused mild irritation of the skin. The undiluted substance (0.5 ml) was applied occlusively (gauze patch, covered with PVC foil, which was fixed with a plaster and covered with lignin and an elastic bandage) to the shaved skin of 3 New Zealand White rabbits for 4 hours. Afterwards, the substance was rinsed off with water. The readings were carried out 1 hour, 24, 48 and 72 hours, and 7 and 14 days after exposure. The mean irritation scores were 0.8 (maximum value: 4) for erythema and 0 (maximum value: 4) for oedema. The erythema was fully reversible within 7 days (ECHA 2019 a).

5.3.2 Eyes

In a study in rabbits carried out according to OECD Test Guideline 405, bisphenol A diglycidyl ether did not cause irritation to the eyes. The undiluted substance (0.1 ml) was instilled in the conjunctival sac of one eye of 3 New Zealand White rabbits. The eyes were examined after 1 hour, 24, 48 and 72 hours and after 7 days. The mean irritation scores were 0 (maximum value: 4) for corneal opacity and 0 (maximum value: 2) for the iris. The irritation scores for the 3 animals were 1, 0.3 and 1.7 (maximum value: 3) for the conjunctivae and 0.7, 0.3 and 1 (maximum value: 4) for chemosis. All changes were fully reversible within 7 days (ECHA 2019 a).

5.4 Allergenic effects

5.4.1 Sensitizing effects on the skin

5.4.1.1 In vivo studies

The 1997 documentation reported positive findings in the maximization test in guinea pigs (Greim 2003). These findings are supported by the clearly positive results obtained by the large number of studies in guinea pigs and mice that are now available.

Bisphenol A diglycidyl ether was shown to be sensitizing in a maximization test in guinea pigs. Intradermal injection and topical induction were carried out with 5% bisphenol A diglycidyl ether (in acetone/propylene glycol) and 10% bisphenol A diglycidyl ether (in acetone after 24-hour pre-treatment with 10% sodium lauryl sulfate in dimethylacetamide/acetone/ethanol; 4:3:3), respectively. A 15% formulation of bisphenol A diglycidyl ether in acetone was used for the 24-hour occlusive challenge treatment. Positive reactions were observed in 18 of 24 animals 1 day after the test patches were removed. After the challenge treatment, no reactions were observed in 12 animals of the control group that had been pre-treated with the vehicle and Freund's complete adjuvant. Twenty-three of 24 animals reacted to a 14% formulation of the p,p′-isomer of bisphenol F diglycidyl ether (Pontén et al. 2002).

Of 24 animals pre-treated with bisphenol A diglycidyl ether in the maximization test, 21 likewise reacted to the challenge treatment with 1.7% phenyl glycidyl ether. Reactions were observed also in 5 of 12 control animals. After induction treatment with phenyl glycidyl ether (0.55% intradermal injection and 0.83% topical induction), however, only 3 of 24 animals reacted to bisphenol A diglycidyl ether (Pontén et al. 2009).

Most of the guinea pigs that had been sensitized to bisphenol F diglycidyl ether or bisphenol A diglycidyl methacrylate (BIS-GMA) in maximization tests reacted also to the challenge treatment with bisphenol A diglycidyl ether (Greim

2001; Hartwig 2013; Pontén et al. 2002). However, bisphenol A diglycidyl ether and the p,p′-isomer of bisphenol F diglycidyl ether did not demonstrate any or hardly any cross-reactivity with the o,o′-isomer of bisphenol F diglycidyl ether (Pontén et al. 2002).

Positive reactions were observed in all 20 female Dunkin Hartley guinea pigs that were investigated in another maximization test with a 5% or 10% bisphenol A diglycidyl ether formulation (inconsistent concentration data) in corn oil for intradermal induction and a 50% formulation in corn oil for the topical induction (after non-occlusive pre-treatment with sodium lauryl sulfate) and challenge treatment. No reactions were noted in 10 control animals that had been pre-treated with Freund's complete adjuvant (ECHA 2019 a).

In a Buehler test (induction with 51.4% and challenge treatment with 25% bisphenol A diglycidyl ether in soft paraffin), 10 of 18 animals reacted to bisphenol A diglycidyl ether enriched with epoxy resin (no other details) at the reading carried out immediately after challenge treatment. Positive reactions were observed in 8 of 18 animals at the readings after 24 and 48 hours. In the control group, 1 of 10 animals reacted only at the reading after 24 hours (ECHA 2019 a).

In a split adjuvant test conducted according to Maguirre, 11 of 14 male guinea pigs reacted to the distillate of a low-viscosity epoxy resin (10% formulation in dipropylene glycol methyl ether/polyoxyethylene(20)sorbitan monooleate; 9:1) based on bisphenol A diglycidyl ether (ECHA 2019 a).

In a local lymph node assay (LLNA) carried out according to OECD Test Guideline 429, an EC3 value of 0.1% to 0.2% was estimated for an epoxy resin based on bisphenol A diglycidyl ether and for distilled bisphenol A diglycidyl ether (solvent: acetone). Using acetone/olive oil (4:1) as the vehicle lowered the sensitivity of the test (Gamer et al. 2008).

An LLNA with female CBA/Ca mice likewise yielded positive results. In this assay, bisphenol A diglycidyl ether with 100% purity was tested as 1%, 3% and 10% formulations in acetone/olive oil (4:1). The 3% formulation caused a 6-fold increase in lymphocyte proliferation with an EC3 value of 1.5% (Warbrick et al. 2001).

In another LLNA, 0.01%, 0.1%, 1.0%, 5.0% and 10% concentrations of bisphenol A diglycidyl ether (purity: > 98%) were tested likewise in acetone/olive oil (4:1); the EC3 value was 1.2% (Delaine et al. 2011; O'Boyle et al. 2014).

In an LLNA, female CBA/J mice were treated with 0.3%, 1%, 3%, 10% and 30% formulations of a low-viscosity epoxy resin based on bisphenol A diglycidyl ether in acetone/olive oil (4:1). An EC3 value of 5.7% was calculated from the stimulation indices of 0.9 and 11.8 (ECHA 2019 a).

When 0.003% to 0.3% formulations of bisphenol A diglycidyl ether (purity: 99.3%) in dimethyl formamide were tested in female BALB/c mice, a 3-fold lymphoproliferative response was not produced. In range-finding tests, concentrations of 1% and 3% caused irritation with a 26% and about 3-fold ear swelling, respectively (ECHA 2019 a).

Positive and negative reactions were reported from other animal studies carried out with different technical grade resins; these are included in the registration dataset of the European Chemicals Agency (ECHA) on bisphenol A diglycidyl ether and the oligomeric reaction product of bisphenol A and epichlorohydrin (CAS No.: 25068-38-6) (ECHA 2019 a, b). However, the monomer and oligomer content in the resins was not specified. Furthermore, several of the studies were incompletely documented.

5.4.1.2 In vitro studies

In the direct peptide reactivity assay (DPRA; OECD Test Guideline 442C), bisphenol A diglycidyl ether yielded negative results for lysine peptide depletion (depletion of 1.1% or 3.2%), but positive results for cysteine peptide depletion (42.5% and 25.2%) (Natsch et al. 2013; Takenouchi et al. 2015).

In the KeratinoSens assay (OECD Test Guideline 442D), the I_{max} was 13 µM and the IC_{50} (cytotoxicity marker) was 22 µM. A 50% increase in the luciferase activity (EC1.5) was observed at a concentration of about 5 µM; it was 3-fold at 8.7 µM (Delaine et al. 2011; Natsch et al. 2013).

The human cell line activation test (h-CLAT; OECD Test Guideline 442E) yielded positive results for both CD86 expression (EC150: 18.27 µg/ml) and CD54 expression (EC200: 22.2 µg/ml). At a concentration of 36 µg/ml, 75% of the cells were viable (Takenouchi et al. 2015).

Another positive result (EC150: 26.4 µM) was reported in the U937 cell line activation test (U-SENS™, MUSST; OECD Test Guideline 442E) (Natsch et al. 2013).

Two reviews of in vitro findings described positive results in the genomic allergen rapid detection (GARD) assay. This assay has not (yet) been included in an OECD Test Guideline (Forreryd et al. 2018; Zeller et al. 2017).

5.4.2 Sensitizing effects on the airways

There are no data available.

5.5 Reproductive and developmental toxicity

5.5.1 Fertility

In a 1-generation study in rats with commercially available bisphenol A diglycidyl ether and a 2-generation study in rats with the pure substance (99.7%), effects on fertility or postnatal development were not found up to the highest doses tested of 540 mg/kg body weight and day (commercial substance) and 750 mg/kg body weight and day (pure substance), respectively (Greim 2003).

Groups of 5 male Sprague Dawley rats were given single gavage doses of bisphenol A diglycidyl ether of 0, 500, 750, 1000 or 2000 mg/kg body weight in corn oil. At 750 mg/kg body weight and above, the number of immature sperm was reduced and the number of fully mature sperm in the testis was increased with statistical significance. The treatment did not have any effect on the sperm head count in the testis or epididymis, percentage of positive sperm motility or sperm abnormality (Yang et al. 2010).

5.5.2 Developmental toxicity

The studies below were reviewed in the 1997 documentation:

Prenatal developmental toxicity studies were carried out in rats and rabbits with commercially available, low-molecular weight bisphenol A diglycidyl ether in 0.5% aqueous carboxymethyl cellulose with 0.1% Tween® 80. The rats were given gavage doses of 0, 60, 180 or 540 mg/kg body weight and day from days 6 to 15 of gestation and the rabbits were given gavage doses of 0, 20, 60 or 180 mg/kg body weight and day from days 7 to 19 of gestation. Slight maternal toxicity was observed, but there were no signs of an impairment of embryonic or foetal development or teratogenic effects (Greim 2003).

In another prenatal developmental toxicity study in New Zealand White rabbits, bisphenol A diglycidyl ether doses of 0, 30, 100 or 300 mg/kg body weight and day in polyethylene glycol 400 were applied occlusively to the skin of the animals for 6 hours daily from days 6 to 18 of gestation. Irritation at the application sites was observed at 100 mg/kg body weight and day and above. The treatment did not induce either systemic maternal toxicity or treatment-related changes in the number of implantations, litter size or embryo-foetal development (Greim 2003).

In a new prenatal and postnatal study, groups of 12 female Sprague Dawley rats were treated with gavage doses of bisphenol A diglycidyl ether of 0, 375, 1500 or 3000 mg/kg body weight and day in corn oil from gestation days 6 to 20 and from postnatal days 0 to 21. The male offspring were examined on postnatal days 21, 42 and 63. In the dams, mortality was increased at 1500 mg/kg body weight and day and above (at 3000 mg/kg body weight and day: all dams; at 1500 mg/kg body weight and day: all dams except for 1). At 375 mg/kg body weight and day, the male offspring had lower body weights than the controls. Substance-induced effects on developmental landmarks, the anogenital distance (AGD) and the adjusted AGD (mm/kg) were not observed in the male offspring. While the relative weights of the adrenal glands, lungs, brain, epididymis, prostate and testes were increased at 375 mg/kg body weight and day

compared with the values determined in the controls, no histopathological changes were found in these organs. At 9 weeks of age, the number of spermatids in the seminiferous tubules was reduced at 375 mg/kg body weight and day compared with the levels determined in the controls. In male offspring in the control group, the testosterone levels in the plasma increased with age; this was not observed in the animals treated with 375 mg/kg body weight and day. However, the oestrogen concentrations were not affected by the treatment (Hyoung et al. 2007).

5.6 Genotoxicity

5.6.1 In vitro

In the Salmonella mutagenicity test, pure and technical grade bisphenol A diglycidyl ether was mutagenic in the strains TA100 and TA1535, which indicate base-pair substitutions, both without and with the addition of a metabolic activation system. The substance did not lead to an increase in mutations in strains TA98, TA1538 or in Escherichia coli WP2. In human lymphocytes, DNA repair synthesis was not detected with pure bisphenol A diglycidyl ether. Technical grade bisphenol A diglycidyl ether caused sister chromatid exchange in CHO cells (a cell line derived from Chinese hamster ovary) and DNA repair synthesis and chromosomal aberrations in primary rat hepatocytes. The pure substance led to an increase in chromosomal aberrations in rat hepatocytes. Technical grade bisphenol A diglycidyl ether was mutagenic also in mouse lymphoma and CHO cells (Greim 2003).

The new in vitro genotoxicity studies are shown in Table 2. Without the addition of a metabolic activation system, the number of revertants per µg was much higher in the Salmonella typhimurium strain TA100 than in the strain TA1535, whereas with the addition of a metabolic activation system, the number of revertants per µg decreased in TA100 and increased in TA1535 (Sueiro et al. 2001). Strain TA1535 contains a hisG46 mutation, as does strain TA100. The difference between these strains is that strain TA100 contains the plasmid pKM101. TA100 has a higher sensitivity than TA1535 because of increased SOS mutagenesis induced by the *mucAB* gene product of the plasmid mentioned above (Prival and Zeiger 1998). However, it is not known why the number of revertants per µg decreased in strain TA100 and increased in TA1535 with the addition of a metabolic activation system. In a test in peripheral human lymphocytes, bisphenol A diglycidyl ether led to an increased incidence of cells with micronuclei without the addition of a metabolic activation system. No clastogenicity was found in these cells with the addition of a metabolic activation system (Suárez et al. 2000). In addition, the registration data include a chromosomal aberration test in peripheral human lymphocytes, which did not reveal clastogenic effects, and a $TK^{+/-}$ test with a dose-dependent increase in the mutation frequency both with and without the addition of a metabolic activation system (ECHA 2019 a).

Tab. 2 In vitro studies of the genotoxicity of bisphenol A diglycidyl ether

End point	Test system	Concentration [µg/plate][a)]	Cytotoxicity [µg/plate][a)]	Result		Comments	References
				–m. a.	+m. a.		
gene mutation, (plate incorporation)	Salmonella typhimurium TA98, TA100, TA1535, TA1537	vehicle: DMSO, purity: analytical grade	–	–	–	bis-diol and chlorohydrin of bisphenol A diglycidyl ether not mutagenic	Sueiro et al. 2001
	Salmonella typhimurium TA100	0, 10, 50, 100, 250, 500, 1000, 2000	–	+	+	–m. a.: + ≥100 µg/plate; revertants/µg: 2.294; +m. a.: + ≥250 µg/plate; 2% S9: revertants/µg: 0.988; 4% S9: revertants/µg: 0.900; 10% S9: revertants/µg: 0.583	
	Salmonella typhimurium TA1535	0, 10, 50, 100, 250, 500, 1000, 2000	–	+	+	–m. a.: revertants/µg: 0.007; +m. a.: + ≥50 µg/plate; 4% S9: revertants/µg: 0.764; 10% S9: revertants/µg: 1.118; 20% S9: revertants/µg: 1.206	

Tab. 2 *(continued)*

End point	Test system	Concentration [µg/plate][a)]	Cytotoxicity [µg/plate][a)]	Result		Comments	References
				–m. a.	+m. a.		
	Salmonella typhimurium TA98, TA1537	0, 500–5000	–	–	–	no frameshift mutations	
CA	peripheral lymphocytes, humans	0, 5–100 µg/ml, vehicle: DMSO, purity: no data	+ ≥ 100 µg/ml	–	not tested		ECHA 2019 a
MN	peripheral lymphocytes, humans	0, 12.5, 25.0, 50.0, 62.5 µg/ml, vehicle: DMSO, –m. a.: 3, 48 h, +m. a.: 3 h, purity: analytical reagent grade	cytokinesis-block proliferation index ↑: –m. a., 3 h: ≥ 12.5 µg/ml; –m. a., 48 h: ≥ 6.25 µg/ml; +m. a.: –	+	–	–m. a.: + ≥ 12.5 µg/ml	Suárez et al. 2000
$TK^{+/-}$	L5178Y mouse lymphoma cells	0, up to 40 µg/ml vehicle: DMSO, purity: no data	from pretests: –m. a.: ≥ 62.5 µg/ml; +m. a.: ≥ 250 µg/ml	+	+	precipitation of the test substance > 40 µg/ml, dose-dependent increase in the mutation frequency, but concentrations not specified, no individual data included, higher toxicity without m. a.	ECHA 2019 a

[a)] unless otherwise specified
CA: chromosomal aberration test; DMSO: dimethyl sulfoxide; +/–m. a.: with/without the addition of a metabolic activation system; MN: micronucleus test; $TK^{+/-}$: $TK^{+/-}$ mutation test with L5178Y mouse lymphoma cells

5.6.2 In vivo

The in vivo studies that investigated the genotoxicity of bisphenol A diglycidyl ether and were reviewed in the 1997 documentation (Greim 2003) are shown in Table 3. In addition, the table includes a micronucleus test published as part of ECHA's registration dataset (ECHA 2019 a).

Tab. 3 In vivo studies of the genotoxicity of bisphenol A diglycidyl ether

Test system	Dose	Result	Comments	References
somatic cells				
gene mutations, host-mediated assay	mouse, ICR, 10 ♀, intraperitoneally inoculated germs, Salmonella typhimurium	5 days, 0, 1000 mg/kg body weight and day, gavage, vehicle: corn oil, test substances: technical grade and distilled bisphenol A diglycidyl ether	–	Dow Chemical Company 1977; Greim 2003
gene mutations, host-mediated assay	mouse, DBA/2f/Bom, 6 animals, no data for sex, intraperitoneally inoculated germs, mouse lymphoma cells	3 days, 0, 26 000 mg/kg body weight and day, gavage, vehicle: polyethylene glycol 400, test substance: technical grade bisphenol A diglycidyl ether	–	Ciba-Geigy 1978 b; Greim 2003

Tab. 3 *(continued)*

Test system		Dose	Result	Comments	References
DNA strand breaks, alkaline elution, liver	rat, Wistar, 2 ♂, 2 ♀	single, 0, 500 mg/kg body weight, gavage, examination: 6 hours after administration, vehicle: DMSO, purity: 97%	–		Greim 2003; Shell 1981
DNA adducts, skin	mouse, C3H, 4 ♂/time of examination	single, 0.4, 0.8, 2.0 mg/animal, dermal application to the shaved skin, occlusive, 48 hours, examination after end of exposure, ^{14}C-labelled in the glycidyl side chain, vehicle: acetone, purity: > 99.9%	+	0.4 mg/animal: not detected, 0.8 and 2.0 mg/animal: bisphenol A diglycidyl ether equivalents of 2.6 and 6.5 pmol/mg DNA in peak I (elution between deoxyguanosine and deoxyadenosine)	Bentley et al. 1989; Greim 2003
DNA adducts, skin, epidermis	mouse, C3H, 3 ♂/time of examination	single, 2 mg/animal, comparison: glycidaldehyde, dermal application to the shaved skin, occlusive, 48, 96 or 196 hours, examination after end of exposure, vehicle: acetone, purity: high purity, because of recrystallization	+	individual data for DNA adducts/10^6 nucleotides and animal (n = number of animals): 48 hours: 0.15, 0.80 (n = 2); 96 hours: 0.14 (n = 1); 196 hours: 0.22, 0.30 (n = 2); comparison: glycidaldehyde: 24 hours: 136, 195 (n = 2); acetone: no DNA adducts detected; limit of detection: 0.02 DNA adducts/10^6 nucleotides, determination not possible in some cases because of problems in sample preparation and interference during chromatography, no conclusions relating to DNA adduct repair possible; estimated: at most 1.1% of the glycidaldehyde fraction of bisphenol A diglycidyl ether was available for DNA binding	Greim 2003; Steiner et al. 1992
MN, bone marrow	mouse, ICR, 5 ♂, 5 ♀	single, 0, 500, 2500, 5000 mg/kg body weight, gavage, vehicle: corn oil, purity: no data	–	no data for the PCE/NCE ratio, no systemic toxicity, functioning test system verified by positive control cyclophosphamide	ECHA 2019 a
MN, bone marrow	mouse, B6D2F1, 10 ♀	5 days, 0, 1000 mg/kg body weight and day, gavage, vehicle: corn oil, test substances: technical grade and distilled bisphenol A diglycidyl ether	–	no data for PCE/NCE ratio, 1 animal died after treatment with distilled bisphenol A diglycidyl ether, but no data for cause of death	Dow Chemical Company 1977; Greim 2003
nuclear anomalies, bone marrow	hamster, Chinese, 6 ♂, 6 ♀	2 days, 0, 825, 1650, 3300 mg/kg body weight and day, gavage, examination: 24 hours after 2nd dose, vehicle: polyethylene glycol 400, test substance: technical grade bisphenol A diglycidyl ether	–	Jolly bodies = micronuclei not increased	Ciba-Geigy 1978 a; Greim 2003

Tab. 3 *(continued)*

Test system		Dose	Result	Comments	References
CA, bone marrow	hamster, Chinese, 4 ♂, 4 ♀	2 days, 0, 825, 1650, 3300 mg/kg body weight and day, gavage, examination: 6 hours after 2nd dose, vehicle: polyethylene glycol 400, test substance: technical grade bisphenol A diglycidyl ether	–		Ciba-Geigy 1982 b; Greim 2003
germ cells					
CA, spermatocytes	mouse, NMRI, 12–18 ♂	5 days, day 0, 2, 3, 5, 9, 0, 1000, 3000 mg/kg body weight and day, gavage, examination: 3 days after last dose, vehicle: polyethylene glycol 400, test substance: technical grade bisphenol A diglycidyl ether	–		Ciba-Geigy 1982 a; Greim 2003
CA, spermatogonia	mouse, Tif.MAGf, 8 ♂	5 days, 0, 375, 750, 1500, 3000 mg/kg body weight and day, gavage, examination: 1 day after last dose, vehicle: polyethylene glycol 400, test substance: technical grade bisphenol A diglycidyl ether	–	no positive control	Ciba-Geigy 1984; Greim 2003
dominant lethal mutations	mouse, Tif.MAGf, 20 ♂	single, mating for 6 weeks, 0, 3333, 10 000 mg/kg body weight, gavage, vehicle: polyethylene glycol 400, test substance: technical grade bisphenol A diglycidyl ether	–		Ciba-Geigy 1982 c; Greim 2003
dominant lethal mutations	mouse, B6D2F1, 10 ♂	3 applications/week, at least 8 weeks, mating for 2 weeks after end of exposure, 0, about 3000 mg/kg body weight and application, dermal, undiluted, test substances: technical grade and distilled bisphenol A diglycidyl ether	–	no data whether open or occlusive application	Dow Chemical Company 1977; Greim 2003

CA: chromosomal aberration test; DMSO: dimethyl sulfoxide; MN: micronucleus test; PCE/NCE: ratio of polychromatic to normochromatic erythrocytes

Pure or technical grade bisphenol A diglycidyl ether did not induce clastogenic or mutagenic effects in the following in vivo genotoxicity tests: 2 host-mediated assays in rats or mice, a test for DNA strand breaks in the liver of Wistar rats, 3 micronucleus tests in the bone marrow of mice or hamsters, tests for chromosomal aberrations in the bone marrow of hamsters and in the spermatocytes and spermatogonia of mice, 2 dominant lethal tests in mice (see Table 3).

DNA adducts

As described in the 1997 documentation, a study was carried out with occlusive dermal application of bisphenol A diglycidyl ether ^{14}C-labelled in the glycidyl side chain in doses of 0.4, 0.8 and 2.0 mg/animal. DNA adducts in the skin were induced in male C3H mice at 0.8 mg/animal and above. No DNA adducts were found at 0.4 mg/animal (Bentley et al. 1989; Greim 2003). The exocyclic glycidaldehyde deoxyadenosine adduct hydroxymethylethenodeoxyadenosine-3′-monophosphate was identified as the DNA adduct (Greim 2003; Steiner et al. 1992). After a single occlusive dermal application of 2 mg bisphenol A diglycidyl ether (333 µg/cm^2) or 2 mg glycidaldehyde to male C3H mice for 24 hours, 166 adducts/10^6 nucleotides on average were observed in the mice treated with glycidaldehyde (2 animals), while after exposure to bisphenol A diglycidyl ether for 48, 96 and 196 hours (5 animals), 0.32 adducts/10^6 nucleotides on average were detected in epidermal DNA (Greim 2003; Steiner et al. 1992). On the basis of these figures, glycidaldehyde was about 518 times more potent than bisphenol A diglycidyl ether. It was not possible to take readings in every case because of problems in sample preparation; therefore, the reported findings were derived from a small number of animals (n = 2–5). As readings were not taken at any other time after exposure, conclusions cannot be drawn about the repair of the DNA adducts.

The DNA adduct 1,N^6-ethenodeoxyadenosine is regarded as promutagenic. It leads to A⟶T, A⟶C and A⟶G base-pair substitutions (Swenberg et al. 2011), which may result in AT⟶GC transitions and AT⟶TA and AT⟶CG transversions (Bartsch 1999). Therefore, it is assumed that the DNA adduct 7-(hydroxymethyl)-1,N^6-ethenodeoxyadenosine that forms in mice treated with bisphenol A diglycidyl ether is likewise promutagenic.

Quantitative data for DNA adduct formation induced by bisphenol A diglycidyl ether: The availability of glycidaldehyde from bisphenol A diglycidyl ether is calculated by comparing the number of DNA adducts that were formed after the treatment of male C3H mice with bisphenol A diglycidyl ether with the number formed after treatment with glycidaldehyde; this procedure was described in the 1997 documentation. Single dermal applications of 2 mg glycidaldehyde induced 166 adducts/10^6 nucleotides on average and single dermal applications of 2 mg bisphenol A diglycidyl ether led to a maximum of 0.8 adducts/10^6 nucleotides. Assuming a linear relationship between the dose and adduct formation, this corresponds to a glycidaldehyde dose of 10 µg. As 2 mg bisphenol A diglycidyl ether contains 0.85 mg of glycidaldehyde equivalents, it can be deduced that at the given dose at most 1.1% of the glycidaldehyde fraction of bisphenol A diglycidyl ether are available for DNA binding (Greim 2003; Steiner et al. 1992).

The dose of 2 mg/animal applied to determine adduct formation was much lower than the nominal dose of about 20 mg/animal applied epicutaneously in the carcinogenicity study 2 to 3 times a week (Greim 2003; Union Carbide 1981). In the carcinogenicity study, the male mice with the highest level of exposure received 100 mg/kg body weight and day on 3 days a week. Based on an average body weight of about 35 g, this corresponds to a dose of 3.5 mg/animal (Dow Chemical Company 1998 b; Greim 2003). Therefore, the doses that led to DNA adducts in mouse skin after a single application did not induce skin tumours in mice in carcinogenicity studies. There are no quantitative data available to estimate the probability of DNA adduct formation in humans after exposure to bisphenol A diglycidyl ether.

5.7 Carcinogenicity

The dermal carcinogenicity studies described in the 1997 documentation and the 2001 supplement are summarized in Table 4 (Greim 2003). Table 5 shows the key data for a new oral carcinogenicity study that has been published since publication of the 2001 supplement.

Tab. 4 Dermal studies that investigated the carcinogenicity of bisphenol A diglycidyl ether: benign and malignant skin tumours

Author:	Greim 2003; Holland et al. 1979			
Substance:	technical grade bisphenol A diglycidyl ether, 85% bisphenol A diglycidyl ether (monomer); 7% bisphenol A diglycidyl ether dimer; 1% bisphenol A diglycidyl ether trimer, impurities: 1% diol of bisphenol A diglycidyl ether; epichlorohydrin 1476 mg/kg; phenyl glycidyl ether 369 mg/kg; 2,3-dichlorohydrin 180 mg/kg (Union Carbide 1981)			
Species:	mouse, C3Hf/Bd and C57BL/6Bd			
Administration route:	dermal, shaved dorsal skin, non-occlusive application			
Dose:	50 µl 10% (v/v) in acetone: 15 mg/animal and week, about 560 mg/kg body weight and week taking into consideration the reported body weight of 27 g, about 190 mg/kg body weight and day; 50 µl 50% (v/v) in acetone: 75 mg/animal and week, about 2800 mg/kg body weight and week taking into consideration the reported body weight of 25 g, about 930 mg/kg body weight and day; control group: acetone			
Duration:	2 years, 3 times/week			
Toxicity:	C3H mouse: body weights: slight decrease at high dose; mortality: ♂ slight increase at high dose, ♀ no unusual findings; C57BL mouse: body weights: ♂ significant decrease at high dose ($p < 0.05$), ♀ no unusual findings; mortality: ♂ significant increase at high dose ($p < 0.05$), ♀ no unusual findings, application site: sporadic focal dermatitis presumably of allergic aetiology			
impurity: epichlorohydrin		**Dose (mg/kg body weight and day)**		
		0	**about 190**	**about 930**
1476 mg/kg C3Hf/Bd	♂ ♀	0/40 (0%) 1/40 (3%) papilloma, no other details	0/40 (0%) 0/40 (0%)	0/40 (0%) 0/40 (0%)
1476 mg/kg C57BL/6Bd	♂	0/20 (0%)	1/20 (5%) papilloma, no other details	6/20 (30%) 6 × 1 carcinoma/animal, no other details
	♀	0/20 (0%)	0/20 (0%)	2/20 (10%) carcinoma, papilloma, no other details
increased incidences of carcinomas in one strain; impurities may have contributed to their development				
Author:	Greim 2003; Zakova et al. 1985			
Substance:	technical grade bisphenol A diglycidyl ether, epichlorohydrin content 4.3 mg/kg			
Species:	mouse, CF1			
Administration route:	dermal, shaved dorsal skin, non-occlusive application			
Dose:	200 µl 1% (v/v) in acetone: about 2.4 mg/animal and day, about 96 mg/kg body weight and day assuming a body weight of 25 g; 200 µl 10% (v/v) in acetone: about 24 mg/animal and day, about 960 mg/kg body weight assuming a body weight of 25 g; positive control: 200 µl 2% (v/v) β-propiolactone in acetone			
Duration:	2 years, twice/week			
Toxicity:	mortality, body weight gains, symptoms, normal feed consumption, sub-irritant concentrations, application site: minimal or moderate focal acanthosis of the epidermis, mild fibrosis and occasionally focal suppuration in the dermis and ulceration of the epidermis; local effects not induced by the substance attributed to trauma or secondary bacterial infection			
impurity: epichlorohydrin		**Dose (mg/kg body weight and day)**		
		0	**about 96**	**about 960**
4.3 mg/kg	♂	1/50 (2%) subcutaneous fibrosarcoma	0/50 (0%)	0/50 (0%)
	♀	0/50 (0%)	0/50 (0%)	0/49 (0%)

Tab. 4 *(continued)*

Author:	Greim 2003; Peristianis et al. 1988			
Substance:	technical grade bisphenol A diglycidyl ether, epichlorohydrin content < 29 mg/kg or < 3 mg/kg; pure bisphenol A diglycidyl ether			
Species:	mouse, CF1			
Administration route:	dermal, shaved dorsal skin, non-occlusive application			
Dose:	200 µl 1% (v/v) in acetone: about 2.4 mg/animal and day, about 96 mg/kg body weight and day assuming a body weight of 25 g; 200 µl 10% (v/v) in acetone: about 24 mg/animal and day, about 960 mg/kg body weight and day assuming a body weight of 25 g; positive control: 200 µl 2% (v/v) β-propiolactone in acetone			
Duration:	2 years, twice/week			
Toxicity:	mortality in normal range, mild skin irritation with a small increase in the average number of epidermal cell layers			
impurity: epichlorohydrin		**Dose (mg/kg body weight and day)**		
		0	**about 96**	**about 960**
< 29 mg/kg	♂	1/99 (1%)	0/50 (0%)	1/50 (2%) squamous cell carcinoma
	♀	0/100 (0%)	0/50 (0%)	1/50 (2%) subcutis: fibrosarcoma
< 3 mg/kg	♂		3/50 (6%) squamous cell papilloma, basal cell carcinoma, fibroma	2/50 (4%) basal cell carcinoma, sebaceous gland adenoma
	♀		1/50 (2%) haemangioendothelioma	1/50 (2%) basal cell carcinoma
0 mg/kg	♂		0/50 (0%)	3/50 (6%) 2 haemangiosarcomas, subcutis: fibrosarcoma
	♀		1/50 (2%) subcutis: anaplastic sarcoma	0/50 (0%)
		historical control data:		
	♂ ♀	2/199 (1.0%) 2/300 (0.7%) only fibrosarcomas		
slight increase in incidences; inconsistent pattern for different types of tumours and their cellular origin				
Author:	Greim 2003; Union Carbide 1981			
Substance:	technical grade bisphenol A diglycidyl ether: purity: 97%, impurities: 2% diol of bisphenol A diglycidyl ether, epichlorohydrin 4 mg/kg, phenyl glycidyl ether 220 mg/kg; technical grade bisphenol A diglycidyl ether: purity: 89%, impurities: 4% diol of bisphenol A diglycidyl ether; epichlorohydrin 29 mg/kg, 1,3-dichlorohydrin 15 mg/kg; technical grade bisphenol A diglycidyl ether: purity: 89%, impurities: epichlorohydrin 3 mg/kg			
Species:	mouse, C3Hf/Bd			
Administration route:	dermal, shaved dorsal skin, non-occlusive application			
Dose:	50 µl 50% (w/v) in acetone, 75 mg/animal and week, about 2500 mg/kg body weight and week taking into consideration the reported body weight of 30 g, about 830 mg/kg body weight and day; control group: acetone			
Duration:	2 years, 3 times/week			
Toxicity:	body weights in normal range; mortality: ♂ significant increase for all tested substances ($p < 0.01$); ♀ no unusual findings; haematological and clinico-chemical parameters in the normal ranges, application site: mild and transient irritation at 50%			

Tab. 4 *(continued)*

impurity: epichlorohydrin		Dose (mg/kg body weight and day)	
		0	**about 830**
4 mg/kg	♂	0/40 (0%)	0/40 (0%)
	♀	0/40 (0%)	0/40 (0%)
29 mg/kg	♂	0/40 (0%)	0/40 (0%)
	♀	0/40 (0%)	0/40 (0%)
3 mg/kg	♂	0/40 (0%)	0/40 (0%)
	♀	0/40 (0%)	0/40 (0%)

Author:	Dow Chemical Company 1998 a; Greim 2003
Substance:	bisphenol A diglycidyl ether, purity: 99.32% ± 0.11%
Species:	rat, Fischer-344, 70 ♀ per group; interim sacrifice of 20 ♀ per group after 12 months
Administration route:	dermal, shaved dorsal skin, non-occlusive application, about 10% of the body surface area
Dose:	300 µl 0.06%, 6.0%, 60% bisphenol A diglycidyl ether in acetone per application, 0, 1, 100, 1000 mg/kg body weight and day
Duration:	2 years, 5 times/week
Toxicity:	1 mg/kg body weight and day: no toxic effects, 100 mg/kg body weight and day and above: mild chronic dermatitis, 1000 mg/kg body weight and day: reduced body weight gains

		Dose (mg/kg body weight and day)			
		0	**10**	**100**	**1000**
	♀	0/40 (0%)	0/50 (0%)	0/40 (0%)	0/50 (0%)

Author:	Dow Chemical Company 1998 b; Greim 2003
Substance:	bisphenol A diglycidyl ether, purity: 99.32% ± 0.11%
Species:	mouse, B6C3F1, 70 ♂ per group, interim sacrifice of 20 ♂ animals per group after 12 months
Administration route:	dermal, shaved dorsal skin, open application, about 10% of the body surface area
Dose:	50 µl 0.005%, 0.5%, 5.0% bisphenol A diglycidyl ether in acetone per application, 0, 0.1, 10, 100 mg/kg body weight and day
Duration:	2 years, 3 times/week
Toxicity:	0.1 mg/kg body weight and day: no toxic effects, 10 mg/kg body weight and day and above: chronic dermatitis, histological examination revealed epidermal hyperplasia, scab formation and occasional ulceration, MTD (maximum tolerated dose) reached

		Dose (mg/kg body weight and day)			
		0	**0.1**	**10**	**100**
	♂	0/50 (0%)	0/49 (0%)	1/47 (2%) squamous cell carcinoma	0/49 (0%)

In dermal carcinogenicity studies with pure and technical grade bisphenol A diglycidyl ether, which may contain epichlorohydrin and other impurities, local tumours were occasionally observed in mice at the application site. Studies with other types of application were not available at this time (Greim 2003). In animal studies, epichlorohydrin (1-chloro-2,3-epoxypropane) was a directly acting genotoxic carcinogen with mainly local effects (Hartwig 2015).

A dermal carcinogenicity study in female F344 rats with 99.32% bisphenol A diglycidyl ether in acetone did not reveal substance-induced increases in tumour incidences up to 1000 mg/kg body weight and day (5 days per week). A squamous cell carcinoma was observed in male B6C3F1 mice given the middle dose of 10 mg/kg body weight and day

on 3 days a week; otherwise, the tumour incidences were not increased after doses of up to 100 mg/kg body weight and day. Chronic dermatitis and histopathologically visible changes to the skin, such as epidermal hyperplasia, scab formation and occasionally ulceration, were observed at the middle dose of 10 mg/kg body weight and day and above (Dow Chemical Company 1998 a, b; Greim 2003).

Considering all available dermal carcinogenicity studies, the following malignant local tumours were observed: 1 squamous cell carcinoma, 3 basal cell carcinomas, 2 haemangiosarcomas, 1 haemangioendothelioma, 2 fibrosarcomas in the subcutis, 1 anaplastic sarcoma in the subcutis (Greim 2003; Peristianis et al. 1988) in mice treated with pure or technical grade bisphenol A diglycidyl ether and 1 squamous cell carcinoma (pure substance; Dow Chemical Company 1998 b; Greim 2003). In another study, 7 carcinomas (not specified further) were found in C57BL mice exposed to bisphenol A diglycidyl ether containing considerable amounts of impurities (Greim 2003; Holland et al. 1979). A total of 1270 mice were treated in the dermal studies (600 (Greim 2003; Peristianis et al. 1988), 240 (Greim 2003; Holland et al. 1979), 200 (Greim 2003; Zakova et al. 1985), 80 (Greim 2003; Union Carbide 1981) and 150 (Dow Chemical Company 1998 b; Greim 2003)). The findings obtained for the types of tumours and their cellular origin were inconsistent.

Since the 2001 supplement, an oral carcinogenicity study was carried out in male and female F344 rats according to OECD Test Guideline 453 (Table 5). In this carcinogenicity study with gavage doses, no substance-induced increases in tumour incidences were found up to the high dose of 100 mg/kg body weight and day. Local effects on the oesophagus, forestomach or stomach were not induced by the substance (Dow Chemical Company 2004; see Section 5.2.2).

Tab. 5 Oral study that investigated the carcinogenicity of bisphenol A diglycidyl ether

Author:		Dow Chemical Company 2004			
Purity:		at least 99.32%			
Species:		rat, F344, 65 ♂, 65 ♀ per group			
Administration route:		gavage, vehicle: aqueous suspension of 0.5% Methocel and 0.1% Tween® 80, OECD Test Guideline 453			
Dose:		0, 2, 15, 100 mg/kg body weight and day			
Duration:		2 years, 7 days/week			
Toxicity:		100 mg/kg body weight and day: toxic effects on the spleen in ♂ (see Section 5.2.2); oesophagus, forestomach, stomach without substance-induced findings; DNA adducts not determined			
		Dose (mg/kg body weight and day)			
		0	2	15	100
surviving animals after 2 years	♂	33/55 (60%)	38/55 (69%)	37/55 (67%)	38/55 (69%)
	♀	42/55 (76%)	40/55 (73%)	40/55 (73%)	42/55 (76%)
tumours					
incidences of tumours not increased by the substance					

The IARC (International Agency for Research on Cancer) listed bisphenol A diglycidyl ether in group 3 ("not classifiable as to its carcinogenicity to humans") (IARC 1989, 1999).

5.8 Other effects

An in vitro study in oligonucleotides showed that the human and mouse alkylpurine-DNA-N-glycosylases, which are responsible for the excision of 1,N^6-ethenoadenine, also recognize and remove 7-(hydroxymethyl)-1,N^6-ethenoadenine. The efficiency of human alkylpurine-DNA-N-glycosylase in removing 7-(hydroxymethyl)-1,N^6-ethenoadenine is about half that of the excision of 1,N^6-ethenoadenine, whereas the efficiency of the murine enzyme in removing the 2 different adducts was about the same (Wang et al. 2006). The efficiency of the alkylpurine-DNA-N-glycosylase in removing 7-(hydroxymethyl)-1,N^6-ethenoadenine in humans and rats cannot be compared on the basis of the published data because different reference parameters were reported.

In an in vitro study, bisphenol A diglycidyl ether induced apoptosis in Jurkat (human T-cell lymphoma) and HCT-116 (human epithelial colorectal carcinoma) cells. The substance promoted the cytotoxic effects of TNF (tumour necrosis factor)-related apoptosis-inducing ligand (TRAIL) and indomethacin. The cytotoxic effects of bisphenol A diglycidyl ether do not require PPAR-γ expression and are mediated by caspase-dependent and caspase-independent pathways (Fehlberg et al. 2002).

In an in vitro study in the CHO-K1 cell line (AR-EcoScreen for androgenic activity and c-luc for the evaluation of cytotoxicity), bisphenol A diglycidyl ether did not cause androgenic or anti-androgenic effects up to 0.1 mM. Likewise, the substance did not induce cytotoxicity at this concentration. However, the chlorohydroxy derivative bisphenol A bis(3-chloro-2-hydroxypropyl)ether induced slight anti-androgenic effects. This derivative also binds to the androgen receptor; therefore, this was regarded as the cause of the anti-androgenic effects (Satoh et al. 2004).

In an in vitro study in breast cancer cells (T47D), the derivatives bisphenol A diglycidyl ether bis-diol and bisphenol A bis(3-chloro-2-hydroxypropyl)ether did not induce oestrogenic effects up to 0.1 mM and did not bind to the oestrogen receptor (Nakazawa et al. 2002).

In an in vitro study in human placental JEG-3 cells, bisphenol A diglycidyl ether and bisphenol A bis(3-chloro-2-hydroxypropyl)ether caused more severe cytotoxicity than bisphenol A diglycidyl ether mono-diol. The latter derivative was the only compound that significantly inhibited the CYP19 activity (IC_{50}: concentration at which 50% inhibition is reached: 49 ± 5 mM). A lipidome analysis revealed that bisphenol A diglycidyl ether led to the accumulation of triacylglycerides and bisphenol A bis(3-chloro-2-hydroxypropyl)ether caused a marked decrease in diacylglycerides and triacylglycerides and several membrane lipids (Marqueño et al. 2019).

6 Manifesto (MAK value/classification)

Sensitizing effects on the skin are the main effects from the point of view of occupational medicine. In addition, they were the critical effects in animal studies together with the effects on the spleen that were observed in rats after administration by gavage.

MAK value and peak limitation. There are no inhalation studies available.

Bisphenol A diglycidyl ether has a very low vapour pressure of below 0.0001 hPa at 25 °C. As pointed out in the 1997 documentation, inhalation exposure is limited to the powdered polymers, which contain only small amounts of the monomer. It was not possible by heating bisphenol A diglycidyl ether to generate a concentration in air that was high enough to carry out an inhalation study at room temperature (Greim 2003). The REACH registration dossier recorded the use of the substance in sprays (ECHA 2019 a). Therefore, exposure to bisphenol A diglycidyl ether aerosol may occur at the workplace.

As studies with oral administration are not suitable for the evaluation of inhalation toxicity (see Section 3.1; ECHA 2019 a), data that can be used to derive a MAK value are not available. Bisphenol A diglycidyl ether is therefore listed in Section IIb of the List of MAK and BAT Values.

Thus, it has not been classified in any of the peak limitation categories.

Prenatal toxicity. In prenatal developmental toxicity studies in rats and rabbits given gavage doses of commercially available, low-molecular bisphenol A diglycidyl ether, no developmental toxicity was observed in the animals up to the highest doses tested of 540 mg/kg body weight and day (rats) or 180 mg/kg body weight and day (rabbits) in spite of slight maternal toxicity (Greim 2003). In another prenatal developmental toxicity study in New Zealand White rabbits with occlusive dermal application of bisphenol A diglycidyl ether, toxic effects on development were not detected up to the high dose of 300 mg/kg body weight and day. Systemic maternal toxicity was not found; only irritation at the application site was observed at 100 mg/kg body weight and day and above (Greim 2003). In a 1-generation study with commercially available bisphenol A diglycidyl ether and a 2-generation study in rats with the pure substance, effects

on postnatal development were not found up the highest doses tested of 540 mg/kg body weight and day (commercial substance) and 750 mg/kg body weight and day (pure substance), respectively (Greim 2003).

As no MAK value was derived, bisphenol A diglycidyl ether has not been classified in any of the pregnancy risk groups.

Carcinogenicity. A large number of dermal carcinogenicity studies in which a total of 1270 mice of various strains were treated reported occasional findings of benign and malignant local tumours (Dow Chemical Company 1998 b; Greim 2003; Holland et al. 1979; Peristianis et al. 1988; Union Carbide 1981; Zakova et al. 1985). The findings obtained for the types of tumours and their cellular origin were inconsistent. Compared with tumours caused by known skin carcinogens, their incidence was very low and there was no consistency within the species. Therefore, the Commission considers the sporadic tumours to be of spontaneous origin. In a new oral carcinogenicity study with bolus gavage doses given to male and female F344 rats as specified in OECD Test Guideline 453, bisphenol A diglycidyl ether was not carcinogenic up to the highest dose tested of 100 mg/kg body weight and day (Dow Chemical Company 2004).

This evaluation is supported by the fact that other skin carcinogens, such as the alkylating compound N-methyl-N′-nitro-N-nitrosoguanidine, caused benign and malignant tumours in the oesophagus, forestomach or stomach in mice, rats, hamsters, rabbits and dogs after oral administration (IARC 1987), whereas bisphenol A diglycidyl ether did not induce any unusual findings in these organs in the 2 gavage studies with 14-week or 2-year administration in F344 rats (Dow Chemical Company 2001, 2004).

After dermal epicutaneous application to mice, bisphenol A diglycidyl ether induced the exocyclic DNA adduct 7-(hydroxymethyl)-1,N^6-ethenoadenosine (Bentley et al. 1989; Greim 2003; Steiner et al. 1992), which is regarded as promutagenic. Bisphenol A diglycidyl ether is directly alkylating (Greim 2003), has a high mutagenic potency (base-pair substitutions) in bacteria and is clastogenic in mammalian cells. However, in a large number of in vivo genotoxicity tests, bisphenol A diglycidyl ether did not cause systemic genotoxicity. The suspected carcinogenic potential deduced from the in vitro data was not confirmed by the findings of the dermal and oral carcinogenicity studies or those of the study with bolus administration carried out according to valid guidelines (see above).

A quantitative aspect seems to be involved here because bisphenol A diglycidyl ether was not carcinogenic in spite of the DNA adducts that were induced in mouse skin. It is assumed that the effects are too slight, which is probably because of sufficient detoxification of bisphenol A diglycidyl ether in vivo. It is well documented that epoxide hydrolase has a higher detoxification capacity in human skin than in mouse skin (Greim 2003; Oesch et al. 1978).

On the basis of these data, classification of bisphenol A diglycidyl ether in Carcinogen Category 3 A is no longer required.

Germ cell mutagenicity. Bisphenol A diglycidyl ether has a high mutagenic potency in bacteria (base-pair substitutions) and is clastogenic in mammalian cells. Bisphenol A diglycidyl ether did not induce either clastogenic or mutagenic effects in a large number of in vivo genotoxicity tests: 2 host-mediated assays in rats or mice, a test for DNA strand breaks in the liver of Wistar rats, 3 micronucleus tests in the bone marrow of mice or hamsters, tests for chromosomal aberrations in the bone marrow of hamsters and in the spermatocytes and spermatogonia of mice and in 2 dominant lethal tests in mice. Therefore, bisphenol A diglycidyl ether is not regarded as causing systemic genotoxicity in vivo. The substance is not classified in any of the categories for germ cell mutagens.

Absorption through the skin. In vivo data from a study in mice and data from a comparative in vitro study with human, rat and mouse skin are available for the absorption of bisphenol A diglycidyl ether through the skin. Both studies suggested that the substance is only slowly absorbed through the skin. When the species were compared directly, the permeability of bisphenol A diglycidyl ether through human skin in vitro was at least around 10 times lower than that through rodent skin. In all skin samples, the starting substance was almost completely inactivated by hydrolysis after passage through the skin. In vitro studies indicate that for bisphenol A diglycidyl ether a higher detoxification capacity can be expected in human skin than, for example, in mouse skin. Therefore, humans probably have a higher tolerance against the formation of the DNA adducts observed in the skin of mice under saturation

conditions. In addition, it is assumed that a specific repair capacity for DNA adducts exists because carcinogenic effects were not observed in dermal carcinogenicity studies with rodents even at doses that were markedly above the threshold for DNA adduct formation in the skin. Therefore, after reviewing the currently available data, it is not very likely that bisphenol A diglycidyl ether will cause carcinogenic effects after limited, short-term dermal contact (1 hour; 2000 cm^2). A total absorbed amount of 0.198 mg, which corresponds to 0.0028 mg/kg body weight, can be estimated from the in vitro data for this type of dermal exposure. A NOAEL of 15 mg/kg body weight was obtained from a 2-year study in rats for potential chronic toxicity caused by bisphenol A diglycidyl ether after oral administration. The following toxicokinetic data are used to extrapolate this dose as the systemic NOAEL to humans: the corresponding toxicokinetic 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) and the extrapolation of data from animal studies to humans (1:2). This results in a dose of 2.6 mg/kg body weight. Even if the calculation were made based on the level of oral absorption derived from the relative AUC in plasma, that is, only 17% instead of 100% (0.44 mg/kg body weight), dermal absorption would remain distinctly below this dose. Therefore, the substance is not designated with an "H" (for substances which can be absorbed through the skin in toxicologically relevant amounts).

Sensitization. Bisphenol A diglycidyl ether was found to have a potential for skin sensitization on the basis of clinical observations and the findings of animal studies and recent in vitro studies. In view of the widespread use of epoxy resins based on bisphenol A diglycidyl ether, only a few case reports are available to assess the sensitizing effects of bisphenol A diglycidyl ether on the airways. Their findings may suggest that bisphenol A diglycidyl ether has the potential to cause sensitization of the airways. However, the resins responsible for the reactions at the workplace have not been characterized precisely and, in most cases, control tests were not performed. Furthermore, the conjugates used in the prick test and for the IgE determinations were not completely characterized. Thus, the findings do not provide sufficient evidence to establish whether bisphenol A diglycidyl ether causes airway sensitization. On this basis, bisphenol A diglycidyl ether is designated with "Sh" (for substances which cause sensitization of the skin), but not with "Sa" (for substances which cause sensitization of the airways). Likewise, epoxy resins containing a corresponding fraction of (monomeric) bisphenol A diglycidyl ether are regarded as contact allergens.

Notes

Competing interests

The established rules and measures of the Commission to avoid conflicts of interest (www.dfg.de/mak/conflicts_interest) ensure that the content and conclusions of the publication are strictly science-based.

References

Aalto-Korte K, Jungewelter S, Henriks-Eckerman M-L, Kuuliala O, Jolanki R (2009) Contact allergy to epoxy (meth)acrylates. Contact Dermatitis 61(1): 9–21. https://doi.org/10.1111/j.1600-0536.2009.01574.x

Aalto-Korte K, Pesonen M, Suuronen K (2015) Occupational allergic contact dermatitis caused by epoxy chemicals: occupations, sensitizing products, and diagnosis. Contact Dermatitis 73(6): 336–342. https://doi.org/10.1111/cod.12445

Authried G, Al-Asadi H, Møller U, Sherson DL (2013) Astmatisk senreaktion efter kontakt med epoxy [Delayed asthma bronchiale due to epoxy resin]. Ugeskr Laeger 175(44): 2643–2644

Bangsgaard N, Thyssen JP, Menné T, Andersen KE, Mortz CG, Paulsen E, Sommerlund M, Veien NK, Laurberg G, Kaaber K, Thormann J, Andersen BL, Danielsen A, Avnstorp C, Kristensen B, Kristensen O, Vissing S, Nielsen NH, Johansen JD (2012) Contact allergy to epoxy resin: risk occupations and consequences. Contact Dermatitis 67(2): 73–77. https://doi.org/10.1111/j.1600-0536.2012.02072.x

Bartsch H (1999) Keynote address: exocyclic adducts as new risk markers for DNA damage in man. In: Singer R, Bartsch H, editors. Exocyclic DNA adducts in mutagenesis and carcinogenesis. IARC Scientific Publication, No. 150. Lyon: IARC. p. 1–16

Bentley P, Bieri F, Kuster H, Muakkassah-Kelly S, Sagelsdorff P, Stäubli W, Waechter F (1989) Hydrolysis of bisphenol A diglycidylether by epoxide hydrolases in cytosolic and microsomal fractions of mouse liver and skin: inhibition by bis epoxycyclopentylether and the effects upon the covalent binding to mouse skin DNA. Carcinogenesis 10(2): 321–327. https://doi.org/10.1093/carcin/10.2.321

Berglind IA, Lind M-L, Lidén C (2012) Epoxy pipe relining – an emerging contact allergy risk for workers. Contact Dermatitis 67(2): 59–65. https://doi.org/10.1111/j.1600-0536.2011.02028.x

Bock M, Schmidt A, Bruckner T, Diepgen TL (2003) Occupational skin disease in the construction industry. Br J Dermatol 149(6): 1165–1171. https://doi.org/10.1111/j.1365-2133.2003.05748.x

Boogaard PJ, Denneman MA, van Sittert NJ (2000 a) Dermal penetration and metabolism of five glycidyl ethers in human, rat and mouse skin. Xenobiotica 30(5): 469–483. https://doi.org/10.1080/004982500237488

Boogaard PJ, de Kloe KP, Bierau J, Kuiken G, Borkulo PED, Watson WP, van Sittert NJ (2000 b) Metabolic inactivation of five glycidyl ethers in lung and liver of humans, rats and mice in vitro. Xenobiotica 30(5): 485–502. https://doi.org/10.1080/004982500237497

Brasch J, Henseler T (1992) The reaction index: a parameter to assess the quality of patch test preparations. Contact Dermatitis 27(3): 203–204. https://doi.org/10.1111/j.1600-0536.1992.tb05267.x

Breuer K, Uter W, Geier J (2015) Epidemiological data on airborne contact dermatitis – results of the IVDK. Contact Dermatitis 73(4): 239–247. https://doi.org/10.1111/cod.12455

Canelas MM, Gonçalo M, Figueiredo A (2010) Contact allergy to epoxy resins – a 10-year study. Contact Dermatitis 62(1): 55. https://doi.org/10.1111/j.1600-0536.2009.01652.x

Ciba-Geigy (1978 a) Nucleus anomaly test in somatic interphase nuclei, Chinese hamster. Study No 78-3011, 16 Aug 1978, Basel: Ciba-Geigy, unpublished

Ciba-Geigy (1978 b) Point mutation assay with mouse lymphoma cells. I In vitro test. II Host-mediated assay. Study No 7823-18, 04 Sep 1978, Basel: Ciba-Geigy, unpublished

Ciba-Geigy (1982 a) Chromosome studies in male germinal epithelium, mouse. Study No 782932, 20 Sep 1982, Basel: Ciba-Geigy, unpublished

Ciba-Geigy (1982 b) Chromosome studies in somatic cells, Chinese hamster. Study No 78-3110, 02 Nov 1982, Basel: Ciba-Geigy, unpublished

Ciba-Geigy (1982 c) Dominant lethal study, mouse. Study No. 790529, 17 Dec 1982, Basel: Ciba-Geigy, unpublished

Ciba-Geigy (1984) Chromosome studies on male germinal epithelium of mouse spermatogonia. Study No 830336, 10 Jan 1984, Basel: Ciba-Geigy, unpublished

Climie IJG, Hutson DH, Stoydin G (1981 a) Metabolism of the epoxy resin component 2,2-bis[4-(2,3]epoxypropoxy)phenyl]propane, the diglycidyl ether of bisphenol A (DGEBPA) in the mouse. Part I. A comparison of the fate of a single dermal application and of a single oral dose of 14C-DGEBPA. Xenobiotica 11(6): 391–399. https://doi.org/10.3109/00498258109045850

Climie IJG, Hutson DH, Stoydin G (1981 b) Metabolism of the epoxy resin component 2,2-bis[4-(2,3-epoxypropoxy)phenyl]propane, the diglycidyl ether of bisphenol A (DGEBPA) in the mouse. Part II. Identification of metabolites in urine and faeces following a single oral dose of 14C-DGEBPA. Xenobiotica 11(6): 401–424. https://doi.org/10.3109/00498258109045851

Condé-Salazar L, Gonzalez de Domingo MA, Guimaraens D (1994) Sensitization to epoxy resin systems in special flooring workers. Contact Dermatitis 31(3): 157–160. https://doi.org/10.1111/j.1600-0536.1994.tb01956.x

Delaine T, Niklasson IB, Emter R, Luthman K, Karlberg A-T, Natsch A (2011) Structure–activity relationship between the in vivo skin sensitizing potency of analogues of phenyl glycidyl ether and the induction of Nrf2-dependent luciferase activity in the KeratinoSens in vitro assay. Chem Res Toxicol 24(8): 1312–1318. https://doi.org/10.1021/tx200196s

Dow Chemical Company (1977) Integrated mutagenicity testing program on several epoxy compounds. 1977, Midland, MI: Dow Chemical Company, unpublished

Dow Chemical Company (1998 a) DGEBPA: two-year dermal chronic toxicity/oncogenicity study in female Fischer 344 rats. Study No 960005, 22 Sep 1998, Midland, MI: Dow Chemical Company, unpublished

Dow Chemical Company (1998 b) DGEBPA: two-year dermal chronic toxicity/oncogenicity study in the male D6C3F1 mouse. Study No 960003, 26 Aug 1998, Midland, MI: Dow Chemical Company, unpublished

Dow Chemical Company (2001) Bisphenol A diglycidyl ether (bisphenol-A-diglycidylether): subchronic oral gavage toxicity study in Fischer 344 rats. Study No 001159, 16 Oct 2001, Midland, MI: Dow Chemical Company, unpublished

Dow Chemical Company (2004) Bisphenol A diglycidyl ether (bisphenol-A-diglycidylether): two-year gavage chronic toxicity/oncogenicity study in Fischer 344 rats. Study No 011134, 28 Jan 2004, Midland, MI: Dow Chemical Company, unpublished

ECHA (European Chemicals Agency) (2019 a) 2,2′-[(1-Methylethylidene)bis(4,1-phenyleneoxymethylene)]bisoxirane (CAS Number 1675-54-3). Registration dossier. Joint submission, first publication 13 Mar 2018, last modification 24 Sep 2018. https://echa.europa.eu/de/registration-dossier/-/registered-dossier/22590, accessed 20 Feb 2019

ECHA (European Chemicals Agency) (2019 b) 4,4′-Isopropylidenediphenol, oligomeric reaction products with 1-chloro-2,3-epoxypropane (CAS Number 25068-38-6). Registration dossier. Joint submission, first publication 01 Apr 2011, last modification 26 Feb 2019. https://echa.europa.eu/de/registration-dossier/-/registered-dossier/15816, accessed 14 Mar 2019

ESSCA Writing Group (2008) The European Surveillance System of Contact Allergies (ESSCA): results of patch testing the standard series, 2004. J Eur Acad Dermatol Venereol 22(2): 174–181. https://doi.org/10.1111/j.1468-3083.2007.02359.x

Fehlberg S, Trautwein S, Göke A, Göke R (2002) Bisphenol A diglycidyl ether induces apoptosis in tumour cells independently of peroxisome proliferator-activated receptor-gamma, in caspase-dependent and -independent manners. Biochem J 362(Pt 3): 573–578. https://doi.org/10.1042/0264-6021:3620573

Forreryd A, Norinder U, Lindberg T, Lindstedt M (2018) Predicting skin sensitizers with confidence – Using conformal prediction to determine applicability domain of GARD. Toxicol In Vitro 48: 179–187. https://doi.org/10.1016/j.tiv.2018.01.021

Gamer AO, Nies E, Vohr H-W (2008) Local lymph node assay (LLNA): comparison of different protocols by testing skin-sensitizing epoxy resin system components. Regul Toxicol Pharmacol 52(3): 290–298. https://doi.org/10.1016/j.yrtph.2008.08.018

Geier J (2010) Kontaktallergie gegen Epoxidharze aus der Perspektive des Informationsverbundes Dermatologischer Kliniken (IVDK) und der Deutschen Kontaktallergie-Gruppe (DKG). Gefahrst Reinhalt Luft 70: 7–9

Geier J, Uter W, Lessmann H, Schnuch A (2002) Forschungsvorhaben "Frühzeitige Erkennung allergener Stoffe bei beruflicher und nicht-beruflicher Exposition" (FaSt). Abschlussbericht des IVDK. Sankt Augustin: Hauptverband der Gewerblichen Berufsgenossenschaften

Geier J, Uter W, Lessmann H, Hillen U, Goergens U, Kersting K, Fuchs T, Schnuch A (2003 a) Kontaktallergien gegen Epoxidharze – ein unterdiagnostiziertes Problem. Allergo J 12(5): 323–328. https://doi.org/10.1007/BF03361213

Geier J, Uter W, Lessmann H, Schnuch A (2003 b) The positivity ratio – another parameter to assess the diagnostic quality of a patch test preparation. Contact Dermatitis 48(5): 280–282. https://doi.org/10.1034/j.1600-0536.2003.00033.x

Geier J, Lessmann H, Hillen U, Jappe U, Dickel H, Koch P, Frosch PJ, Schnuch A, Uter W (2004) An attempt to improve diagnostics of contact allergy due to epoxy resin systems. First results of the multicentre study EPOX 2002. Contact Dermatitis 51(5–6): 263–272. https://doi.org/10.1111/j.0105-1873.2004.00465.x

Geier J, Krautheim A, Uter W, Lessmann H, Schnuch A (2011 a) Occupational contact allergy in the building trade in Germany: influence of preventive measures and changing exposure. Int Arch Occup Environ Health 84(4): 403–411. https://doi.org/10.1007/s00420-010-0581-8

Geier J, Uter W, Krautheim A, Lessmann H, Schnuch A (2011 b) Die häufigsten Kontaktallergene der Jahre 2007–2009. Aktuelle Daten aus dem Informationsverbund Dermatologischer Kliniken (IVDK). Allergo J 20(2): 93–101. https://doi.org/10.1007/bf03362433

Geier J, Uter W, Lessmann H, Schnuch A (2011 c) Aktuelle Kontaktallergene. Hautarzt 62(10): 751–756. https://doi.org/10.1007/s00105-011-2180-3

Geier J, Lessmann H, Hillen U, Skudlik C, Jappe U (2016) Sensitization to reactive diluents and hardeners in epoxy resin systems. IVDK data 2002–2011. Part I: reaction frequencies. Contact Dermatitis 74(2): 83–93. https://doi.org/10.1111/cod.12491

Girao Popolizio I, Frías Jiménez M, Martínez Arcediano A, Fernández Ibáñez E, Audicana Berasategui MF (2016) Asma ocupacional por doble agente causal [Occupational asthma caused by two different agents]. Arch Prev Riesgos Labor 19(4): 231–233

Göring HD (2001) Allergisches Kontaktekzem durch Epoxidharze und Härter in einem Betrieb für faserverstärkte Kunststoffe. Dermatol Beruf Umwelt 49: 19

Greim H, editor (2001) Bisphenol-A-diglycidyl-methacrylat. MAK Value Documentation in German language. In: Gesundheitsschädliche Arbeitsstoffe, Toxikologisch-arbeitsmedizinische Begründung von MAK-Werten. 32nd issue. Weinheim: Wiley-VCH. Also available from https://doi.org/10.1002/3527600418.mb156594d0032

Greim H, editor (2003) Bisphenol A diglycidyl ether. MAK Value Documentation, 1997 and 2001. In: Occupational Toxicants. Volume 19. Weinheim: Wiley-VCH. p. 43–78. Also available from https://doi.org/10.1002/3527600418.mb167554e0019

Hackett JP (1999) Allergic contact dermatitis in American aircraft manufacture. Am J Contact Dermat 10(3): 157–166. https://doi.org/10.1016/s1046-199x(99)90059-3

Hagvall L, Niklasson IB, Rudbäck J, O'Boyle NM, Niklasson E, Luthman K, Karlberg A-T (2016) Assessment of cross-reactivity of new less sensitizing epoxy resin monomers in epoxy resin-allergic individuals. Contact Dermatitis 75(3): 144–150. https://doi.org/10.1111/cod.12624

Hannu T, Frilander H, Kauppi P, Kuuliala O, Alanko K (2009) IgE-mediated occupational asthma from epoxy resin. Int Arch Allergy Immunol 148(1): 41–44. https://doi.org/10.1159/000151504

Hartwig A, editor (2013) Bisphenol-F-diglycidylether. MAK Value Documentation in German language. In: Gesundheitsschädliche Arbeitsstoffe, Toxikologisch-arbeitsmedizinische Begründung von MAK-Werten. 54th issue. Weinheim: Wiley-VCH. Also available from https://doi.org/10.1002/3527600418.mb209503ismd0054

Hartwig A, editor (2015) Epichlorhydrin. MAK Value Documentation, 2003. In: The MAK Collection for Occupational Health and Safety. Part I: MAK Value Documentations. Weinheim: Wiley-VCH. https://doi.org/10.1002/3527600418.mb10689e3614

Helaskoski E, Suojalehto H, Kuuliala O, Aalto-Korte K (2015) Prick testing with chemicals in the diagnosis of occupational contact urticaria and respiratory diseases. Contact Dermatitis 72(1): 20–32. https://doi.org/10.1111/cod.12308

Hillen U, Jappe U, Frosch PJ, Becker D, Brasch J, Lilie M, Fuchs T, Kreft B, Pirker C, Geier J (2006) Late reactions to the patch-test preparations para-phenylenediamine and epoxy resin: a prospective multicentre investigation of the German Contact Dermatitis Research Group. Br J Dermatol 154(4): 665–670. https://doi.org/10.1111/j.1365-2133.2006.07159.x

Hillen U, Lessmann H, Grabbe S, Geier J (2007) Kontaktsensibilisierungen gegen Bestandteile von Klebstoffen unter Berücksichtigung beruflicher Kontaktsensibilisierungen. Dermatol Beruf Umwelt 55(1): 10–19. https://doi.org/10.5414/DBP55010

Holland JM, Gosslee DG, Williams NJ (1979) Epidermal carcinogenicity of bis(2,3-epoxycyclopentyl)ether, 2,2-bis(p-glycidyloxyphenyl)propane, and m-phenylenediamine in male and female C3H and C57BL/6 mice. Cancer Res 39(5): 1718–1725

Hyoung U-J, Yang Y-J, Kwon S-K, Yoo J-H, Myoung S-C, Kim S-C, Hong Y-P (2007) Developmental toxicity by exposure to bisphenol A diglycidyl ether during gestation and lactation period in Sprague-Dawley male rats. J Prev Med Public Health 40(2): 155–161

IARC (International Agency for Research on Cancer) (1987) N-Methyl-N′-nitro-N-nitrosoguanidine. In: Overall evaluations of carcinogenicity: an updating of IARC monographs volumes 1 to 42. IARC monographs on the evaluation of the carcinogenic risk of chemicals to humans, Suppl 7. Lyon: IARC. p. 248–250. https://publications.iarc.fr/_publications/media/download/3283/b2fe295e10e63fd88e772d2ab60ae9a1e3ddd446.pdf, accessed 08 Aug 2018

IARC (International Agency for Research on Cancer) (1989) Some gylcidyl ethers. In: Some organic solvents, resin monomers and related compounds, pigments and occupational exposures in paint manufacture and painting. IARC monographs on the evaluation of the carcinogenic risk of chemicals to humans. Volume 47. Lyon: IARC. p. 237–262. https://publications.iarc.fr/_publications/media/download/1679/99c031474795027a4681b66e486124ae4cd190af.pdf, accessed 08 Aug 2018

IARC (International Agency for Research on Cancer) (1999) Bisphenol A diglycidyl ether. In: Re-evaluation of some organic chemicals, hydrazine and hydrogen peroxide. IARC monographs on the evaluation of the carcinogenic risk of chemicals to humans. Volume 71. Lyon: IARC. p. 1285–1289. https://publications.iarc.fr/_publications/media/download/2279/d7e4bcce9c42cec078b965c33b0298cf0a3aff3d.pdf, accessed 29 Nov 2018

Irvine C, Pugh CE, Hansen EJ, Rycroft RJG (1994) Cement dermatitis in underground workers during construction of the Channel Tunnel. Occup Med 44(1): 17–23. https://doi.org/10.1093/occmed/44.1.17

Jacobsen I, Christensen B, Baelum J, Bjerring N, Moeller U, Sherson D (2015) Epoxy and delayed asthma. Eur Respir J 46(Suppl 59): PA1149. https://doi.org/10.1183/13993003.congress-2015.PA1149

Jolanki R (1991) Occupational skin diseases from epoxy compounds. Epoxy resin compounds, epoxy acrylates and 2,3-epoxypropyl trimethyl ammonium chloride. Acta Derm Venereol Suppl (Stockh) 159: 1–80

Jolanki R, Tarvainen K, Tatar T, Estlander T, Henriks-Eckerman M-L, Mustakallio KK, Kanerva L (1996) Occupational dermatoses from exposure to epoxy resin compounds in a ski factory. Contact Dermatitis 34(6): 390–396. https://doi.org/10.1111/j.1600-0536.1996.tb02239.x

Kanerva L, Jolanki R, Tupasela O, Halmepuro L, Keskinen H, Estlander T, Sysilampi ML (1991) Immediate and delayed allergy from epoxy resins based on diglycidyl ether of bisphenol A. Scand J Work Environ Health 17(3): 208–215. https://doi.org/10.5271/sjweh.1718

Kanerva L, Estlander T, Keskinen H, Jolanki R (2000) Occupational allergic airbone contact dermatitis and delayed bronchial asthma from epoxy resin revealed by bronchial provocation test. Eur J Dermatol 10(6): 475–477

Kanerva L, Pelttari M, Jolanki R, Alanko K, Estlander T, Suhonen R (2002) Occupational contact urticaria from diglycidyl ether of bisphenol A epoxy resin. Allergy 57(12): 1205–1207. https://doi.org/10.1034/j.1398-9995.2002.13118.x

Laskowski J, Heise H (2000) Kasuistik über gehäufte Hauterscheinungen in einem Betrieb zum Windflügelbau. Dermatol Beruf Umwelt 48: 151

Lazarov A (2006) European Standard Series patch test results from a contact dermatitis clinic in Israel during the 7-year period from 1998 to 2004. Contact Dermatitis 55(2): 73–76. https://doi.org/10.1111/j.0105-1873.2006.00875.x

Lee HN, Pokorny CD, Law S, Pratt M, Sasseville D, Storrs FJ (2002) Cross-reactivity among epoxy acrylates and bisphenol F epoxy resins in patients with bisphenol A epoxy resin sensitivity. Am J Contact Dermat 13(3): 108–115

Marqueño A, Pérez-Albaladejo E, Flores C, Moyano E, Porte C (2019) Toxic effects of bisphenol A diglycidyl ether and derivatives in human placental cells. Environ Pollut 244: 513–521. https://doi.org/10.1016/j.envpol.2018.10.045

Miyamoto T, Okamura M (1998) [Occupational contact urticaria due to epoxy resin]. Environ Dermatol 5: 53–57

Moulin P, Magnan A, Lehucher-Michel M-P (2009) Occupational allergic contact dermatitis and asthma due to a single low molecular weight agent. J Occup Health 51(1): 91–96. https://doi.org/10.1539/joh.l7110

Moura C, Dias M, Vale T (1994) Contact dermatitis in painters, polishers and varnishers. Contact Dermatitis 31(1): 51–53. https://doi.org/10.1111/j.1600-0536.1994.tb01910.x

Nakazawa H, Yamaguchi A, Inoue K, Yamazaki T, Kato K, Yoshimura Y, Makino T (2002) In vitro assay of hydrolysis and chlorohydroxy derivatives of bisphenol A diglycidyl ether for estrogenic activity. Food Chem Toxicol 40(12): 1827–1832. https://doi.org/10.1016/s0278-6915(02)00165-5

Natsch A, Ryan CA, Foertsch L, Emter R, Jaworska J, Gerberick F, Kern P (2013) A dataset on 145 chemicals tested in alternative assays for skin sensitization undergoing prevalidation. J Appl Toxicol 33(11): 1337–1352. https://doi.org/10.1002/jat.2868

O'Boyle NM, Niklasson IB, Tehrani-Bagha AR, Delaine T, Holmberg K, Luthman K, Karlberg A-T (2014) Epoxy resin monomers with reduced skin sensitizing potency. Chem Res Toxicol 27(6): 1002–1010. https://doi.org/10.1021/tx5000624

Oesch F, Schmassmann H, Bentley P (1978) Specificity of human, rat and mouse skin epoxide hydratase towards K-region epoxides of polycyclic hydrocarbons. Biochem Pharmacol 27(1): 17–20. https://doi.org/10.1016/0006-2952(78)90251-4

Peristianis GC, Doak SMA, Cole PN, Hend RW (1988) Two-year carcinogenicity study on three aromatic epoxy resins applied cutaneously to CF1 mice. Food Chem Toxicol 26(7): 611–624. https://doi.org/10.1016/0278-6915(88)90232-3

Pontén A, Bruze M (1999) Occupational allergic contact dermatitis from epoxy resins based on bisphenol F. Contact Dermatitis 41(4): 235. https://doi.org/10.1111/j.1600-0536.1999.tb06149.x

Pontén A, Bruze M (2001) Contact allergy to epoxy resin based on diglycidyl ether of bisphenol F. Contact Dermatitis 44(2): 98–99. https://doi.org/10.1034/j.1600-0536.2001.4402092.x

Pontén A, Zimerson E, Sörensen O, Bruze M (2002) Sensitizing capacity and cross-reaction pattern of the isomers of diglycidyl ether of bisphenol F in the guinea pig. Contact Dermatitis 47(5): 293–298. https://doi.org/10.1034/j.1600-0536.2002.470507.x

Pontén A, Carstensen O, Rasmussen K, Gruvberger B, Isaksson M, Bruze M (2004 a) Epoxy-based production of wind turbine rotor blades: occupational contact allergies. Dermatitis 15(1): 33–40. https://doi.org/10.2310/6620.2004.20433

Pontén A, Carstensen O, Rasmussen K, Gruvberger B, Isaksson M, Bruze M (2004 b) Epoxy-based production of wind turbine rotor blades: occupational dermatoses. Contact Dermatitis 50(6): 329–338. https://doi.org/10.1111/j.0105-1873.2004.00346.x

Pontén A, Zimerson E, Bruze M (2008) Can simultaneous contact allergies to phenyl glycidyl ether and epoxy resins of the bisphenol A/F-types be explained by contamination of the epoxy resins? Contact Dermatitis 59(5): 273–279. https://doi.org/10.1111/j.1600-0536.2008.01420.x

Pontén A, Zimerson E, Bruze M (2009) Sensitizing capacity and cross-reactivity of phenyl glycidyl ether studied in the guinea-pig maximization test. Contact Dermatitis 60(2): 79–84. https://doi.org/10.1111/j.1600-0536.2008.01475.x

Pratt MD, Belsito DV, DeLeo VA, Fowler JF Jr, Fransway AF, Maibach HI, Marks JG, Mathias CGT, Rietschel RL, Sasseville D, Sherertz EF, Storrs FJ, Taylor JS, Zug K (2004) North American Contact Dermatitis Group patch-test results, 2001–2002 study period. Dermatitis 15(4): 176–183

Prival MJ, Zeiger E (1998) Chemicals mutagenic in Salmonella typhimurium strain TA1535 but not in TA100. Mutat Res 412(3): 251–260. https://doi.org/10.1016/s1383-5718(97)00196-4

van Putten PB, Coenraads PJ, Nater JP (1984) Hand dermatoses and contact allergic reactions in construction workers exposed to epoxy resins. Contact Dermatitis 10(3): 146–150. https://doi.org/10.1111/j.1600-0536.1984.tb00020.x

Rasmussen K, Carstensen O, Pontén A, Gruvberger B, Isaksson M, Bruze M (2005) Risk of contact allergy and dermatitis at a wind turbine plant using epoxy resin-based plastics. Int Arch Occup Environ Health 78(3): 211–217. https://doi.org/10.1007/s00420-004-0575-5

Rast H (2001) Berufliche Hautkrankheiten bei Bauarbeitern in der Schweiz: Ursachen, Bedeutung und Prävention. Dermatol Beruf Umwelt 49: 20–21

Rømyhr O, Nyfors A, Leira HL, Smedbold HT (2006) Allergic contact dermatitis caused by epoxy resin systems in industrial painters. Contact Dermatitis 55(3): 167–172. https://doi.org/10.1111/j.1600-0536.2006.00894.x

Sasseville D (1998) Contact urticaria from epoxy resin and reactive diluents. Contact Dermatitis 38(1): 57–58. https://doi.org/10.1111/j.1600-0536.1998.tb05651.x

Satoh K, Ohyama K, Aoki N, Iida M, Nagai F (2004) Study on anti-androgenic effects of bisphenol A diglycidyl ether (BADGE), bisphenol F diglycidyl ether (BFDGE) and their derivatives using cells stably transfected with human androgen receptor, AR-EcoScreen. Food Chem Toxicol 42(6): 983–993. https://doi.org/10.1016/j.fct.2004.02.011

Schubert H-J, Butz M, Reymann M, Schumacher U, Heise H, Nimmrich K, Weiß G (2004) Aktuelles zur Epoxidharzallergie. Aktuelle Derm 30(5): 143–148. https://doi.org/10.1055/s-2004-814510

Shell (1981) Studies on the effect of diglycidyl ether of bisphenol A, on the integrity of rat liver DNA in vivo. Study No TLGR.80.152., Dec 1981, Sittingbourne: Shell, unpublished

Solano E, Fitzgerald B, Cannon J, Cullinan P, Feary J (2016) Late asthmatic response to epoxy resins: a case report. 71(Suppl 3): A259–A260. https://doi.org/10.1136/thoraxjnl-2016-209333.446

Steiner S, Hönger G, Sagelsdorff P (1992) Molecular dosimetry of DNA adducts in C3H mice treated with bisphenol A diglycidylether. Carcinogenesis 13(6): 969–972. https://doi.org/10.1093/carcin/13.6.969

Stutz N, Hertl M, Löffler H (2008) Anaphylaxis caused by contact urticaria because of epoxy resins: an extraordinary emergency. Contact Dermatitis 58(5): 307–309. https://doi.org/10.1111/j.1600-0536.2006.01140.x

Suárez S, Sueiro RA, Garrido J (2000) Genotoxicity of the coating lacquer on food cans, bisphenol A diglycidyl ether (BADGE), its hydrolysis products and a chlorohydrin of BADGE. Mutat Res 470(2): 221–228. https://doi.org/10.1016/s1383-5718(00)00109-1

Sueiro RA, Araujo M, Suárez S, Garrido MJ (2001) Mutagenic potential of bisphenol A diglycidyl ether (BADGE) and its hydrolysis-derived products in the Ames Salmonella assay. Mutagenesis 16(4): 303–307. https://doi.org/10.1093/mutage/16.4.303

Suhonen R (1983) Epoxy-dermatitis in a ski-stick factory. Contact Dermatitis 9(2): 131–133. https://doi.org/10.1111/j.1600-0536.1983.tb04319.x

Suojalehto H, Sastre J, Merimaa E, Lindström I, Suuronen K (2019) Occupational asthma from epoxy compounds. J Allergy Clin Immunol Pract 7(1): 191–198. https://doi.org/10.1016/j.jaip.2018.07.023

Swenberg JA, Lu K, Moeller BC, Gao L, Upton PB, Nakamura J, Starr TB (2011) Endogenous versus exogenous DNA adducts: their role in carcinogenesis, epidemiology, and risk assessment. Toxicol Sci 120(Suppl 1): S130–S145. https://doi.org/10.1093/toxsci/kfq371

Takenouchi O, Fukui S, Okamoto K, Kurotani S, Imai N, Fujishiro M, Kyotani D, Kato Y, Kasahara T, Fujita M, Toyoda A, Sekiya D, Watanabe S, Seto H, Hirota M, Ashikaga T, Miyazawa M (2015) Test battery with the human cell line activation test, direct peptide reactivity assay and DEREK based on a 139 chemical data set for predicting skin sensitizing potential and potency of chemicals. J Appl Toxicol 35(11): 1318–1332. https://doi.org/10.1002/jat.3127

Union Carbide (1981) Chronic dermal toxicity of epoxy resins. I Skin carcinogenic potency and general toxicity (draft) with cover letter dated 04/13/81. NTIS/OTS0204933, new Doc ID 88-8100262. Alexandria, VA: NTIS. https://ntrl.ntis.gov/NTRL/dashboard/searchResults/titleDetail/OTS0204933.xhtml, accessed 19 Sep 2018

Uter W, Gefeller O, Geier J, Lessmann H, Pfahlberg A, Schnuch A (2002) Untersuchungen zur Abhängigkeit der Sensibilisierung gegen wichtige Allergene von arbeitsbedingten sowie individuellen Faktoren. Schriftenreihe der Bundesanstalt für Arbeitsschutz und Arbeitsmedizin. Volume Fb 949. Bremerhaven: Wissenschaftsverlag NW Wirtschaftsverlag NW Verlag für neue Wissenschaft

Uter W, Rühl R, Pfahlberg A, Geier J, Schnuch A, Gefeller O (2004) Contact allergy in construction workers: results of a multifactorial analysis. Ann Occup Hyg 48(1): 21–27. https://doi.org/10.1093/annhyg/meg080

Uter W, Amario-Hita JC, Balato A, Ballmer-Weber B, Bauer A, Belloni Fortina A, Bircher A, Chowdhury MMU, Cooper SM, Czarnecka-Operacz M, Dugonik A, Gallo R, Giménez-Arnau A, Johansen JD, John SM, Kieć-Świerczyńska M, Kmecl T, Kręcisz B, Larese Filon F, Mahler V, Pesonen M, Rustemeyer T, Sadowska-Przytocka A, Sánchez-Pérez J, Schliemann S, Schuttelaar ML, Simon D, Spiewak R, Valiukevičienė S, Weisshaar E, White IR, Wilkinson SM (2017) European Surveillance System on Contact Allergies (ESSCA): results with the European baseline series, 2013/14. J Eur Acad Dermatol Venereol 31(9): 1516–1525. https://doi.org/10.1111/jdv.14423

Wang P, Guliaev AB, Elder RH, Hang B (2006) Alkylpurine-DNA-N-glycosylase excision of 7-(hydroxymethyl)-1,N6-ethenoadenine, a glycidaldehyde-derived DNA adduct. DNA Repair (Amst) 5(1): 23–31. https://doi.org/10.1016/j.dnarep.2005.07.013

Wang L, Wu Y, Zhang W, Kannan K (2012) Widespread occurrence and distribution of bisphenol A diglycidyl ether (BADGE) and its derivatives in human urine from the United States and China. Environ Sci Technol 46(23): 12968–12976. https://doi.org/10.1021/es304050f

Wang L, Xue J, Kannan K (2015) Widespread occurrence and accumulation of bisphenol A diglycidyl ether (BADGE), bisphenol F diglycidyl ether (BFDGE) and their derivatives in human blood and adipose fat. Environ Sci Technol 49(5): 3150–3157. https://doi.org/10.1021/acs.est.5b00096

Warbrick EV, Dearman RJ, Ashby J, Schmezer P, Kimber I (2001) Preliminary assessment of the skin sensitizing activity of selected rodent carcinogens using the local lymph node assay. Toxicology 163(1): 63–69. https://doi.org/10.1016/s0300-483x(01)00380-8

Yang Y-J, Lee S-Y, Kim K-Y, Hong Y-P (2010) Acute testis toxicity of bisphenol A diglycidyl ether in Sprague-Dawley rats. J Prev Med Public Health 43(2): 131–137

Zakova N, Zak F, Froehlich E, Hess R (1985) Evaluation of skin carcinogenicity of technical 2,2-bis-(p-glycidyloxyphenyl)-propane in CF1 mice. Food Chem Toxicol 23(12): 1081–1089. https://doi.org/10.1016/0278-6915(85)90056-0

Zeller KS, Forreryd A, Lindberg T, Gradin R, Chawade A, Lindstedt M (2017) The GARD platform for potency assessment of skin sensitizing chemicals. ALTEX 34(4): 539–559. https://doi.org/10.14573/altex.1701101

Zug KA, Warshaw EM, Fowler JF, Maibach HI, Belsito DL, Pratt MD, Sasseville D, Storrs FJ, Taylor JS, Mathias CGT, Deleo VA, Rietschel RL, Marks J (2009) Patch-test results of the North American Contact Dermatitis Group 2005–2006. Dermatitis 20(3): 149–160