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Fatty alcohol ethoxylates, $C_{16–18}$ and C_{18} unsaturated

MAK Value Documentation – Translation of the German version from 2022

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Keywords

fatty alcohol ethoxylates, $C_{16–18}$ and C_{18}-unsaturated; local effect; inflammation forestomach mucosa; corticomedullary calcinosis; non-ionic surfactant; UVCB substance

Abstract

The German Senate Commission for the Investigation of Health Hazards of Chemical Compounds in the Work Area (MAK Commission) summarized and evaluated the data for fatty alcohol ethoxylates, $C_{16–18}$ and C_{18} unsaturated [68920-66-1] to derive an occupational exposure limit value (maximum concentration at the workplace, MAK value), considering all toxicological end points. Relevant studies were identified from a literature search and also unpublished study reports were used. It is a UVCB substance (substances of Unknown or Variable composition, Complex reaction products or Biological materials). There are no human data or inhalation studies in animals performed with fatty alcohol ethoxylates, $C_{16–18}$ and C_{18} unsaturated to derive a maximum concentration at the workplace (MAK value). A fatty alcohol ethoxylate, $C_{16–18}$ and C_{18} unsaturated with < 2.5 ethoxylate units, is not irritating to skin or eyes of rabbits, but $C_{16–18}$ and C_{18} unsaturated with 10 ethoxylate units is irritating in the forestomach of rats in a 13-week gavage study at 500 mg/kg body weight and day. The systemic NOAEL for this substance is 100 mg/kg body weight and day. Fatty alcohol ethoxylates are non-ionic surfactants, therefore an effect on the pulmonary surfactant can be assumed after inhalation. As no data on inhalation toxicity are available, a MAK value cannot be established. In vitro and in vivo studies with alcohol ethoxylates of similar length and similar grade of unsaturation showed no genotoxic potential. Data with similar fatty alcohol ethoxylates do not point to a carcinogenic potential for fatty alcohol ethoxylates, $C_{16–18}$ and C_{18} unsaturated. Investigations with alcohol ethoxylates of similar length and similar degree of saturation do not show an effect on developmental toxicity. Fatty alcohol ethoxylates, $C_{16–18}$ and C_{18} unsaturated are not sensitizing to the skin; investigations on airway sensitization are lacking. The substance does not penetrate the skin in toxicologically relevant amounts.

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MAK value	**not yet established, see Section II b of the List of MAK and BAT Values**
Peak limitation	–
Absorption through the skin	–
Sensitization	–
Carcinogenicity	–
Prenatal toxicity	–
Germ cell mutagenicity	–
BAT value	–
Synonyms	alcohols, $C_{16–18}$ and C_{18} unsaturated, ethoxylated
Chemical name (IUPAC)	–
CAS number	68920-66-1
Structural formula	$HO–(CH_2–CH_2–O)_n–R_1/R_2$ R_1: $(CH_2)_{15–17}–CH_3$ R_2: $(CH_2)_x–CH=CH–(CH_2)_y–CH_3$; x + y = 15
Molar mass	– $C_{16–18/18unsatd}EO_{<2.5}$: about 300 g/mol
Melting point	$C_{16–18/18unsatd}EO_{<2.5}$: −67 to +18 °C (ECHA 2020)
Boiling point at 1012 hPa	$C_{16–18/18unsatd}EO_{<2.5}$: 369 °C (ECHA 2020)
Density at 20 °C	$C_{16–18/18unsatd}EO_{<2.5}$: 0.8956 g/cm³ (ECHA 2020)
Vapour pressure at 20 °C	$C_{16–18/18unsatd}EO_{<2.5}$: < 5.5×10^{-5} hPa (calculated) (ECHA 2020)
log K_{OW} at 22 °C	$C_{16–18/18unsatd}EO_{<2.5}$: 4.6 (ECHA 2020)
Solubility	$C_{16–18/18unsatd}EO_{<2.5}$: < 4.7 mg/l water at 24 °C (ECHA 2020)
Hydrolytic stability	no data
Stability	no data
Purity	no data
Impurities	no data
Uses	$C_{16–18/18unsatd}EO_{<2.5}$: in lubricants, lubricating agents, detergents and cleaning agents, surfactant for the treatment of metal surfaces, in air fresheners (ECHA 2020) and as solubilizer for essential oils in foam and bath oils (Henkel KGaA 1983)
Concentrations used	1% to 10% in metal-working fluids (Neste 2019)

Fatty alcohol ethoxylates $C_{16–18}$ and C_{18} unsaturated ($C_{16–18/18unsatd}$) have been assigned the CAS number 68920-66-1. They are UVCB substances (Chemical Substances of Unknown or Variable Composition) that are composed of a variable number of ethylene oxide units (EO).

The documentation is based mainly on the REACH registration data for fatty alcohol ethoxylates $C_{16–18}$ and C_{18} unsaturated with < 2.5 ethylene oxide units (abbreviated $C_{16–18/18unsatd}EO_{<2.5}$) publicly available (ECHA 2020). A review of alcohol

ethoxylates with differing chain lengths ($C_{8–18}$) and differing numbers of ethylene oxide units from 2 to 20 ($EO_{2–20}$) (HERA 2009) has been used to fill data gaps. Cited unpublished toxicological studies from companies have been made available to the Commission.

1 Toxic Effects and Mode of Action

After the treatment of Wistar rats with a fatty alcohol ethoxylate ($C_{16–18/18unsatd}EO_{10}$) over a period of 13 weeks by gavage, reduced body weight gains, inflammation in the forestomach and a decreased serum protein level were found at 500 mg/kg body weight and day. In all dose groups, substance-induced corticomedullary calcinosis was observed in the kidneys of females.

The available studies of skin and eye irritation in rabbits, sensitization, reproductive toxicity, genotoxicity and carcinogenicity, some of them with alcohol ethoxylates of similar chain length, did not reveal any substance-related findings.

2 Mechanism of Action

There are no experimental data available.

Fatty alcohol ethoxylates are non-ionic surfactants; therefore, an effect on the pulmonary surfactant can be assumed after inhalation. Studies investigating this possible effect are not available.

Fatty alcohol ethoxylates do not react readily with nucleophilic structures in proteins due to their low electrophilic reactivity. Therefore, a sensitizing effect is not to be expected.

3 Toxicokinetics and Metabolism

No studies with fatty alcohol ethoxylates $C_{16–18/18unsatd}$ are available; thus, experimental data from alcohol ethoxylates of similar chain length are used for the evaluation.

Alcohol ethoxylates of similar chain length are absorbed in the gastrointestinal tract in amounts of more than 75%; after 24 to 48 hours, about 1% are found in the liver and kidneys. A small proportion is cleaved at the ether bond and the alkyl chain is metabolized to CO_2 and water. The majority is excreted in the urine and faeces, depending on the number of ethylene oxide units, and a small amount is exhaled as CO_2. Longer alkyl chains increase the proportion of exhaled CO_2 and lead to a lower amount being excreted with the urine (detection by radioactive labelling) (ECHA 2020).

After Wistar rats were given a single oral dose of 20, 40, 100, 200, 500 or 1000 mg $C_{14–18}EO_{10}$/kg body weight (^{14}C-labelled), absorption and elimination were determined for 72 hours. One animal from each of the dose groups given 40, 200 and 1000 mg/kg body weight was studied in a metabolism cage to monitor $^{14}CO_2$ exhalation, the other animals were kept in a non-closed system. Radioactivity was determined in the gastrointestinal tract, liver, oesophagus, kidneys and blood. The majority of the substance (80%–90%) was absorbed in the intestine, of which about 30% was excreted in bile and 2% was exhaled as $^{14}CO_2$. Within 72 hours, 98% to 99% of the substance was excreted, 90% of it within the first 24 hours. About 40% to 50% of the substance was excreted in the urine and faeces. Very low residual radioactivity (about 1%) was found in the liver and even less in the kidneys. There were no signs of toxicity in the animals (HERA 2009). Oral absorption is thus largely complete.

With the mathematical models of Fiserova-Bergerova et al. (1990) and IH SkinPerm (Tibaldi et al. 2014), fluxes of 16 and 0.25 µg/cm^2 and hour, respectively, are calculated for a saturated aqueous solution (4.7 mg/l), using a log K_{OW} of 4.6 and a mean molar mass of 300 g/mol (which corresponds approximately to $C_{16–18/18unsatd}EO_{<2.5}$). Assuming exposure of

2000 cm^2 of skin for 1 hour, this would correspond to absorbed amounts of 32 and 0.5 mg, respectively. Higher degrees of ethoxylation would reduce the amounts absorbed.

In a study in humans, 2 volunteers were exposed non-occlusively to 100 mg of ^{14}C-labelled $C_{12}EO_6$ (in 1 ml of 50% aqueous ethanol) on a 90 cm^2 area of the forearm for 8 hours. After 144 hours, the application site was washed with ethanol and the radioactivity in the blood, urine, faeces, expired air, adhesive tapes from the exposed skin and the application system was determined. A maximum of 1.82% of the applied amount had been absorbed and excreted in the urine. Data for earlier time points were not reported (Drotman 1980). If it is assumed that 2% was absorbed in 24 hours, a flux of 0.022 mg/cm^2 and a permeability coefficient Kp of 0.0000092 cm/h are calculated. Using the permeability coefficient, exposure of a 2000 cm^2 area of skin to a saturated aqueous solution (4.7 mg/l) for 1 hour would result in the dermal absorption of 0.043 mg fatty alcohol ethoxylates $C_{16-18/18unsatd}$.

Using the penetration data determined in studies carried out in vivo in rats exposed for 5 minutes to ^{14}C-labelled $C_{12}EO_3$ at a concentration of 0.25% (HERA 2009) as the basis for calculation, 16.8 mg of substance would be absorbed through the skin after exposure of a skin area of 2000 cm^2 to a 0.25% solution for 1 hour. The animal studies have further shown that short-chain alcohol ethoxylates ($C_{8-14}EO_{3-7}$) penetrate the skin better than long-chain alcohol ethoxylates ($C_{>14}EO_{>7}$) (HERA 2009).

4 Effects in Humans

Only skin sensitization studies are available.

In various patch tests with occlusive 24-hour application of the substance according to the test guidelines of COLIPA (European Cosmetic Industry Association) with a 72-hour follow-up period, the only effect was slight redness in individual persons for a short time. The substances tested included $C_{16-18}EO_5$, $C_{16-18}EO_8$ and $C_{16-18}EO_{14}$, but only in 0.1% aqueous formulations. Higher ethoxylated compounds ($C_{16-18}EO_{12}$ and $C_{16-18}EO_{20}$; undiluted and in a 20% formulation) caused in some cases very slight irritant effects (HERA 2009).

In a study, undiluted $C_{16-18}EO_5$ and $C_{16-18}EO_{14}$ alcohol ethoxylates did not cause skin irritation in 27 volunteers after occlusive application for 4 hours. A 20% aqueous formulation of sodium lauryl sulfate, which was included as a positive control, caused skin irritation in 14 of the 27 volunteers. At most 1 of 32 test persons reacted to four other shorter-chain $C_{11}EO_7$ alcohol ethoxylates and $C_{12-15}EO_7$ alcohol ethoxylates (Basketter et al. 2004).

There are only 2 reports of suspected allergic reactions to ethoxylated C_{16-18} fatty alcohols. Only one reports reactions to ceteareth-2 and ceteareth-3 ($C_{16-18}EO_2$ and $C_{16-18}EO_3$, both 20% in petrolatum) in a woman with recurrent itchy dermatitis of the axillary region after using a roll-on deodorant. She produced 1+ and 2+ reactions to both test formulations after 48 and 72 hours, respectively. There were also reactions to cetyl (C_{16}), stearyl (C_{18}) and ceterayl alcohol (C_{16-18}) (each 30% in petrolatum) and to myristyl alcohol (5% in petrolatum). There were no reactions to ceteareth-20, ceteareth-25 and ceteareth-30 (each 20% in petrolatum) (Corazza et al. 2013).

A patient with dermatitis on her face and eyelids suspected make-up removing wet wipes of having induced the reaction. The results of an application test with the product and a ROAT (repeated open application test) were positive. Cetearyl alcohol (20% in petrolatum) and stearyl alcohol (10% in petrolatum) caused a 1+ and a questionable reaction, respectively, in patch tests. Steareth-10 ($C_{18}EO_{10}$), which was subsequently tested as a 5% aqueous formulation, did not produce a 1+ reaction until 4 days later (Aerts et al. 2017).

In addition, several case reports described reactions to the structurally only slightly similar ethoxylated lauryl alcohol (for example, laureth-4 ($C_{12}EO_4$) (Svensson 1988)), especially to the, on average, ninefold ethoxylated lauryl alcohol (laureth-9, polidocanol; $C_{12}EO_9$) also used in topical formulations. Currently, local anaesthetics are tested using a DKG (German Contact Allergy Group) test series, in which $C_{12}EO_9$ is a component tested as a 3% formulation in petrolatum. Previously, a 0.5% formulation in water was used (Frosch and Schulze-Dirks 1989; Uter et al. 2000 b). In the Information Network of Dermatological Clinics (IVDK), the 0.5% (3186 patients) and the 3% formulation (6202 patients) were tested

on a total of 8739 patients. About 1.3% of those tested reacted to the 0.5% formulation and 2.1% to the 3% formulation. Most reactions were 1+ reactions (1.0% and 1.8%, respectively), however, half of them were considered clinically relevant; the weak reactions should therefore probably not, or should not always, be interpreted as "false positives". In 649 patients, both formulations were tested, with only moderate concordance of the results (Cohen's kappa: 0.53, confidence interval (CI): 0.29–0.76) (Uter et al. 2000 b). With these data, also a logistic regression analysis was performed for the parameters of the MOAHLFA index (Male, Occupational dermatitis, Atopic dermatitis, Hand dermatitis, Leg dermatitis, Face dermatitis, Age). The presence of leg dermatitis and an age of over 40 years were found to be significant risk factors for patients sensitized to $C_{12}EO_9$ (odds ratios 2.32 (CI: 1.02–2.35) and 2.91 (CI: 1.74–5.19), respectively). The presence of atopic dermatitis, on the other hand, was not a risk factor, although many atopic patients in Germany were treated with antipruritic formulations containing $C_{12}EO_9$ (Uter et al. 2000 a). It is not possible to draw any conclusions about the skin-sensitizing potential of the fatty alcohol ethoxylates $C_{16–18/18unsatd}$ based on these reactions to the shorter-chain and higher ethoxylated lauryl alcohol because the reactions were obtained in a collective that underwent very selective testing, they were for the most part weak and some of them were of unclear clinical relevance. Furthermore, it is assumed that individual predisposing factors may be involved.

In a Human Repeated Insult Patch Test (HRIPT) with 200 volunteers, no irritant or sensitizing effects were observed in tests using 60% formulations of steareth-2, steareth-10 and steareth-20 ($C_{18}EO_2$, $C_{18}EO_{10}$ and $C_{18}EO_{20}$, respectively). Also shorter-chain alcohols with various degree of ethoxylation ($C_{12}EO_9$, $C_{12–13}EO_{6.5}$, $C_{12–15}EO_7$, $C_{12–15}EO_9$, $C_{12–15}EO_{12}$, $C_{14–15}EO_7$) did not produce sensitization in the HRIPT at concentrations between 2.5% and 25% (HERA 2009).

5 Animal Experiments and in vitro Studies

5.1 Acute toxicity

5.1.1 Inhalation

In a review of alcohol ethoxylates, it is reported that alcohol ethoxylates were not acutely toxic up to their saturated vapour concentrations in air. For aerosols of the undiluted substances, 1-hour or 4-hour inhalation LC_{50} values in rats were in the range from 1500 to 20 700 mg/m^3. In some studies, no mortalities occurred up to 52 000 mg/m^3 (no other details; HERA 2009).

5.1.2 Oral administration

In a study conducted in 1982 following a protocol that was similar to that of OECD Test Guideline 401, 2000 mg/kg body weight of an alcohol ethoxylate (no other details) in carboxymethyl cellulose administered by gavage to 5 male and 5 female Wistar rats did not cause any effects (ECHA 2020).

In a review of alcohol ethoxylates, LD_{50} values in rats (no other details) of > 4000 mg/kg body weight are given for chain lengths of 15 or more C atoms (HERA 2009).

5.1.3 Dermal application

Three studies with occlusive 24-hour application of 2000 mg/kg body weight of an alcohol ethoxylate to the intact skin of Wistar rats did not result in mortality or any local effects. The body weight gains of the males were slightly reduced in the first 7 days; this was reversible after 14 days (ECHA 2020).

In a study carried out in 1990 using a protocol similar to that of OECD Test Guideline 402, 3000 mg/kg body weight of an alcohol ethoxylate ($C_{12–14}$; not further specified) was applied occlusively without a vehicle to the skin of 10 male and 10 female New Zealand White rabbits for 24 hours. Mortality was not observed. The animals displayed decreased grooming, 2 males and 3 females exhibited decreased muscle tone from days 6 to 8 and 3 males and 3 females suffered

dyspnoea. Body weights were slightly reduced on day 7 compared with those on the day of the test, but after another 7 days were again within the range given for the control animals. Necrosis, fissuring of the skin and sloughing occurred at the application site (ECHA 2020).

In New Zealand White rabbits, the LD_{50} was above 2000 mg/kg body weight after the occlusive application of an alcohol ethoxylate (no other details) without a vehicle to abraded skin for 24 hours. The study was conducted in 1982 using a procedure similar to that of OECD Test Guideline 402. There were no local or systemic effects and no mortality (ECHA 2020).

Another study carried out with New Zealand White rabbits in 1987 following a protocol that was similar to that of OECD Test Guideline 402 yielded an LD_{50} of 2000 mg/kg body weight for males and 2216 mg/kg body weight for females after occlusive application of up to 3700 mg/kg body weight of an alcohol ethoxylate (no other details) without a vehicle. At and above 1900 mg/kg body weight, mortality occurred, the body weight gains were transiently reduced and salivation, lethargy, unsteady gait and coma were observed. The animals that died had dark red or dark purple lungs (no other details; ECHA 2020).

In the review of alcohol ethoxylates already mentioned, the dermal effects described in unpublished company studies by the Union Carbide Corporation from 1981 were evaluated. Only at very high doses of 16 000 mg/kg body weight or more did skin irritation, ataxia and lung lesions occur in rabbits, with most substances having a maximum of 15 C atoms (no other details; HERA 2009).

5.2 Subacute, subchronic and chronic toxicity

5.2.1 Inhalation

There are no data available.

5.2.2 Oral administration

In a 28-day preliminary study with fatty alcohol ethoxylate $C_{16–18/18unsatd}EO_{10}$, groups of 10 male and 10 female Wistar rats were given gavage doses of 0 or 500 mg/kg body weight and day in tap water for 5 days per week. By week 4, the body weight gains of the males were significantly reduced, in the females oedematous thickening of the forestomach mucosa was observed, and both males and females had reduced serum protein levels. As this was a range-finding study, a detailed histopathological examination was not performed (Henkel KGaA 1983).

In the main study with fatty alcohol ethoxylate $C_{16–18/18unsatd}EO_{10}$, groups of 10 male and 10 female Wistar rats were given gavage doses of 0, 20, 100 or 500 mg/kg body weight and day in tap water on 5 days per week for 13 weeks. At 500 mg/kg body weight and day, decreased body weight gains were observed in the males (significant) and females (not significant) and inflammation of the forestomach occurred in male and female rats, which was attributed to an irritant effect of the substance. Furthermore, an increase in the relative adrenal, heart and liver weights and a decreased serum protein level were found. Slight signs of inflammation in the forestomach were observed at 100 mg/kg body weight and day, but these were much weaker. Such effects did not occur in feeding studies; therefore, they are attributable to gavage administration. In all dose groups, substance-related, but not dose-dependent, corticomedullary calcinosis occurred in the kidneys of the female animals; even during a 3-month follow-up period this was not reversible (Henkel KGaA 1983). Since absolute organ weights are not affected, the increase in relative organ weights is probably the result of the reduced body weight gains. Corticomedullary calcification is a common finding exclusively in female rats of various strains. This lesion can be triggered by imbalances in the magnesium, calcium and phosphorus levels in the diet, especially by a low ratio of calcium to phosphorus (Rao 2002). In this study, the substance possibly led to a shift in the calcium/phosphorus balance in the body. Since the effect is diet-dependent and sex-specific, did not show any dose dependency and no other renal findings occurred, it is of questionable human relevance. Furthermore, in the carcinogenicity studies with Charles River rats up to 320 mg/kg body weight and day or with Sprague Dawley rats up to 500 mg/kg body weight and day,

no histopathological findings occurred in the kidneys (Section 5.7). The systemic NOAEL (no observed adverse effect level) is therefore 100 mg/kg body weight and day.

In another 90-day feeding study in rats (no other details) from 1981 with 20, 100 or 500 mg $C_{16–18}EO_{10}$/kg body weight and day, the levels of several liver enzymes in the blood, of ammonia in the kidneys, and of creatinine were monitored. None of the parameters yielded unusual findings. Detailed information on the design and scope of this investigation was, however, not available (no other details; HERA 2009).

In a carcinogenicity study with dietary administration of $C_{14–15}EO_7$ in Sprague Dawley rats, the NOAEL was 50 mg/kg body weight and day. Doses of 0, 50, 250 or 500 mg/kg body weight and day were administered. At 250 and 500 mg/kg body weight and day, food intake and body weight gains were decreased and, in the females, increased relative liver, kidney and brain weights were observed. There were no histopathological findings in these organs (no other details; HERA 2009). Since the absolute organ weights were not affected, the increase in relative organ weights is probably the result of the reduced body weight gains.

A carcinogenicity study with administration of $C_{14–15}EO_7$ in the diet at concentrations of 0, 0.1%, 0.5% and 1% (corresponding to doses of 0, 33, 160, 320 mg/kg body weight and day) to Charles River rats for 1 to 2 years yielded a NOAEL of 160 mg/kg body weight and day (no other details; HERA 2009).

5.2.3 Dermal application

There are no data available.

5.3 Local effects on skin and mucous membranes

5.3.1 Skin

In a study from 1997 carried out according to OECD Test Guideline 404, semi-occlusive application of 0.5 ml of fatty alcohol ethoxylate $C_{16–18/18unsatd}EO_{<2.5}$ (no vehicle) for 4 hours to the shaved dorsal skin of 3 Russian rabbits resulted in mild irritation. The erythema score was 2.3 of a maximum of 4 for all 3 rabbits at 24, 48 and 72 hours and was completely reversible by the end of the observation period of 21 days. Oedema, which was observed in all 3 rabbits with a score of 1.4 of a maximum of 4 after 24, 48 and 72 hours, was likewise reversible within this period (ECHA 2020).

An analogous study carried out in 2008 according to OECD Test Guideline 404 resulted in a score of 1.4 of a maximum of 4 for erythema and 0.33 of a maximum of 4 for oedema at 24, 48 and 72 hours in 3 New Zealand White rabbits, and was reversible by the end of the observation period (ECHA 2020). In this test, the substance caused slight irritation.

5.3.2 Eyes

In a study from 2008 carried out according to OECD Test Guideline 405, 0.1 ml of fatty alcohol ethoxylate $C_{16–18/18unsatd}EO_{<2.5}$ (no vehicle) instilled into one eye of each of 3 New Zealand White rabbits was not found to cause irritation after 72 hours. For the conjunctiva, the maximum score was 0.4 of a maximum of 3 and was completely reversible. There were no findings at any time in the cornea, iris or for chemosis, the corresponding values being 0 in each case. The substance is non-irritant to the eye of rabbits (ECHA 2020).

5.4 Allergenic effects

5.4.1 Sensitizing effects on the skin

In a study from 1995 carried out according to OECD Test Guideline 406, a Buehler test was performed in female Dunkin Hartley guinea pigs with occlusive epicutaneous induction and challenge treatment with undiluted $C_{16–18}EO_1$. No reaction occurred 24 and 48 hours after the challenge treatment (ECHA 2015).

The ECHA registration database also lists 3 negative results in maximization tests for "alcohols, $C_{12–18}$, ethoxylated" with shorter-chain fatty alcohol ethoxylates, namely $C_{12–13}EO_2$ (intradermal induction at 0.1%, topical induction at 100%; challenge at 50%), $C_{12–14}EO_2$ (1%, 100%; 25% and 50%) and $C_{12–15}EO_3$ (0.05%, 50%; 25%) (ECHA 2015).

A modified Cumulative Contact Enhancement Test (CCET) carried out with $C_{12}EO_5$ (laureth-5) in 15 female Dunkin Hartley guinea pigs without the use of an adjuvant yielded negative results. Induction was performed at the start of the study and on days 2, 7 and 9 by occlusive application of a 10% aqueous formulation. After the occlusive challenge treatment on day 21, a maximum of 2 animals reacted to 5%, 1% or 0.1% aqueous formulations at different readings after 48, 72 and 96 hours in both the treated group and the control group (Bergh et al. 1998 a).

In other studies, positive results were obtained with autoxidized $C_{12}EO_5$ (10 weeks, indirect daylight) in a CCET (induction with 20%, challenge with 9% in water) (Karlberg et al. 2003). The sensitization was attributed to the hydroxyaldehydes, ethoxylated aldehydes or hydroperoxides formed during autoxidation, some of which were also studied separately in the CCET (Bergh et al. 1998 a, b; Bodin et al. 2001, 2003). Since it is questionable to what extent these results can be transferred to the fatty alcohol ethoxylates $C_{16–18/18unsatd}$ and since their significance for the clinically observed reactions is unclear, the findings are not presented in more detail and are not included in the evaluation.

A HERA review of alcohol ethoxylates lists unpublished company studies describing maximization tests. Of 25 studies with different alcohol ethoxylates with 9–21 C atoms and 2–21 EO units, only one study with a higher ethoxylated, short-chain fatty alcohol ($C_{7–9}EO_6$) yielded positive results. Also in 13 studies with the Buehler test, there were no positive results for alcohol ethoxylates with 9–15 C atoms and 3–13 EO units (no other details; HERA 2009).

5.4.2 Sensitizing effects on the airways

There are no studies available.

5.5 Reproductive and developmental toxicity

5.5.1 Fertility

A 2-generation study from 1977 with CD rats was carried out with $C_{14–15}EO_7$. Groups of 25 male and 25 female animals were given daily doses of 0, 25, 50 or 250 mg/kg body weight (group A) with the diet. In another 25 animals per sex and dose group, only the females were given the substance from days 6 to 15 of gestation (group B). Substance-related findings in the females of group A given the high dose were slightly reduced body weight gains in the parents and slightly reduced body weights in the pups on day 21 of life. No effects were observed in any group on fertility, litter size, the number of male and female pups, neonatal and juvenile survival, and weight development of juveniles up to the end of lactation. Similarly, the external appearance and behaviour of all parent and juvenile animals were not altered. There were no substance-related histopathological findings in the organs of either parent animals or pups. The NOAEL for fertility in the parents and pups is considered to be 250 mg/kg body weight and day, the NOAEL for systemic toxicity is considered to be 50 mg/kg body weight and day (HERA 2009).

A feeding study conducted in 1977 according to the same protocol and with the same dose of $C_{12}EO_6$ in CD rats likewise resulted in slightly reduced body weight gains in the dams and reduced body weights of the pups on day 21 of life at 250 mg/kg body weight and day. These were the only effects. This dose is considered to be the NOAEL for fertility and LOAEL (lowest observed adverse effect level) for systemic toxicity (HERA 2009).

In a 2-generation study conducted in 1985 with a protocol similar to OECD Test Guideline 416, male and female weanling F344 rats were dermally exposed to $C_{9–11}EO_6$ in water in doses of 0, 10, 100 or 250 mg/kg body weight and day 3 times a week except during the mating periods (concentration of the solution not specified). The oestrus cycle and sperm parameters were not investigated, or only in some animals. Parental animals received the substance for 119 days, F1 animals for 133 days. At the high dose, the body weights of the parents and pups were sporadically decreased, and not always with statistical significance, and the weights of the liver, lungs, kidneys and heart were "changed" in the

F1 generation (no other details), without a histopathological correlate in each case. There were no effects on mating, fertility indices and mean gestation length. The systemic NOAEL for fertility and developmental toxicity is given as 250 mg/kg body weight and day (no other details; ECHA 2020). There were no effects on testis weights, sperm count and the lactate dehydrogenase isoenzyme X in F0 and F1 male adults. Thus, the NOAEL for fertility for both parents and pups is considered to be 250 mg/kg body weight and day (HERA 2009).

5.5.2 Developmental toxicity

In a developmental toxicity study, groups of 25 rabbits were orally given 0, 20, 100 or 200 mg $C_{12}EO_6$/kg body weight and day from gestation days 2 to 16. Caesarean section was carried out on gestation day 28. At and above 100 mg/kg body weight and day, ataxia and slightly reduced body weights occurred in the dams. Nine control and 31 treated animals died during the study. In 7 treated and 2 control rabbits, the pups were born early. The surviving animals in the high dose group had a slight loss of body weight. The NOAEL is given as 50 mg/kg body weight and day (no other details), although many study details are not available (HERA 2009).

In the 2-generation feeding study from 1977 described in Section 5.5.1 with oral administration of $C_{14–15}EO_7$ doses of 0, 25, 50 or 250 mg/kg body weight and day to rats, necropsy of pregnant females was performed on gestation day 13 in some animals and on gestation day 21 in the others. The findings were reduced body weight gains of the dams, slightly reduced body weights of the offspring and slightly increased mean liver weights of the F1 and F2 animals in the 250 mg/kg group after continuous administration with the diet. Therefore, the NOAEL for maternal and developmental toxicity was considered to be 50 mg/kg body weight and day (HERA 2009).

In the 2-generation study from 1977 described in Section 5.5.1 with CD rats given $C_{12}EO_6$ with the diet, the pregnant females were likewise killed on either day 13 or 21 of gestation. Continuous administration of 250 mg/kg body weight and day resulted in reduced body weight gains in the dams and offspring, increased embryo lethality and soft tissue abnormalities. Therefore, the NOAEL for maternal and developmental toxicity was considered to be 50 mg/kg body weight and day (HERA 2009).

For the 2-generation study described in Section 5.5.1 with dermal application of $C_{9–11}EO_6$ to rats 3 times a week, the highest dose tested of 250 mg/kg body weight and day is given as the NOAEL for the parents and offspring (HERA 2009).

5.6 Genotoxicity

In the REACH registration dossier on fatty alcohol ethoxylates $C_{16–18/18unsatd}EO_{<2.5}$ (ECHA 2020), analogous substances are referred to without a specific substance description being given in most cases.

5.6.1 In vitro

In a study from 1997 carried out according to OECD Test Guideline 471, the substance (not further specified) in concentrations up to 5000 µg/plate did not cause mutations in the Salmonella strains TA98, TA100, TA1535 and TA1537 in the presence and absence of a metabolic activation system. The highest concentrations were cytotoxic; the positive controls produced the expected results, indicating a functioning test system. The strains TA102 or Escherichia coli WP2 were not tested (ECHA 2020).

In a chromosomal aberration study from 1995 carried out in CHO cells (a cell line from Chinese hamster ovary) according to OECD Test Guideline 473, the substance (not further specified) was tested in 1% ethanol at concentrations of 313 to 5000 µg/ml in the presence, and at concentrations of 1.25 to 78 µg/ml in the absence of a metabolic activation system. The test results were negative. The positive controls used were methyl methanesulfonate and cyclophosphamide; data for cytotoxicity were not given (ECHA 2020).

In a gene mutation assay in CHO cells from 1995 carried out according to OECD Test Guideline 476, the substance (not further specified) did not lead to an increased incidence of mutations in the HPRT locus test. Concentrations of 1.8 to 100 µg/ml were used in the presence and absence of a metabolic activation system, with the highest concentration

representing the limit of solubility of the substance and leading to cytotoxicity. Ethyl methanesulfonate and 3-methylcholanthrene were used as positive controls (ECHA 2020).

In a review of alcohol ethoxylates, all tested substances were not mutagenic in Salmonella typhimurium and Escherichia coli, not genotoxic in the $TK^{+/-}$ mutation assay in mouse lymphoma cells, and did not induce gene conversions in Saccharomyces cerevisiae or chromosomal aberrations in Chinese hamster V79 or CHO cells in the presence or absence of a metabolic activation system (HERA 2009).

5.6.2 In vivo

In a micronucleus test in polychromatic and normochromatic erythrocytes from the bone marrow of 5 male and 5 female Swiss-Webster mice carried out according to OECD Test Guideline 474 in 2001, intraperitoneal administration of up to 640 mg diethylene glycol monohexyl ether (C_6EO_2)/kg body weight (substance not further specified) yielded a negative result. The mice were examined after 30, 48 and 72 hours and exhibited signs of toxicity (no other details), although it is not possible to say whether the substance reached the bone marrow. The positive control used was triethylene melamine (ECHA 2020).

In the review of alcohol ethoxylates, all tested substances yielded negative results in the chromosomal aberration test in Chinese hamster bone marrow cells in 2 different studies after single oral doses of up to 1700 mg $C_{13–15}EO_7$/kg body weight as a 20% aqueous solution and doses of up to 2500 mg $C_{12–14}EO_7$/kg body weight as a 10% aqueous solution, respectively. There were also no clastogenic effects in the bone marrow of Wistar rats after single oral doses of up to 1000 mg $C_{14–15}EO_7$/kg body weight, nor micronuclei or chromosomal abnormalities in the bone marrow of CD-1 mice after single intraperitoneal doses of up to 100 mg $C_{12–14}EO_9$ or $C_{12–15}EO_3$/kg body weight (no other details) (HERA 2009).

5.7 Carcinogenicity

In a carcinogenicity study from 2002 with dietary administration of $C_{14–15}EO_7$ in Sprague Dawley rats, the NOAEL was 50 mg/kg body weight and day. Doses of 0, 50, 250 or 500 mg/kg body weight and day were administered for 2 years. At the middle dose level, food intake and body weight gains were decreased in females, and, at the high dose level, in females and males. Increased relative weights of the liver, kidneys and brain were found in the females of the middle and high dose group. There were no histopathological findings in these organs (no other details; HERA 2009). Since the absolute organ weights were not affected, the increase in relative organ weights is probably the result of the reduced body weight gains.

In another 2-year carcinogenicity study from 1979 with dietary administration of $C_{14–15}EO_7$ in Charles River rats, concentrations of 0, 0.1%, 0.5% and 1% were administered in the diet (0, 33, 160 and 320 mg/kg body weight and day). The NOAEL was 160 mg/kg body weight and day. Body weight gains were decreased in the high dose group. It is unclear whether a histopathological examination was performed (no other details; HERA 2009).

6 Manifesto (MAK value/classification)

Data in humans are only available for sensitization and these do not reveal a specific effect. Oral administration in rats led mainly to reduced body weight gains and, after gavage administration, to inflammation in the forestomach, which indicates a local effect on the mucous membranes.

MAK value and peak limitation. There are no inhalation studies or human data from which to derive a MAK value. Chronic studies with fatty alcohol ethoxylates (Section 5.2.2) yielded NOAELs in the range of 50 to 160 mg/kg body weight and day. Gavage administration of fatty alcohol ethoxylates $C_{16–18/18unsatd}EO_{10}$ to rats for 13 weeks caused inflammation in the forestomach and a statistically significant decrease in body weight gains at 500 mg/kg body weight

and day. The systemic NOAEL was 100 mg/kg body weight and day (Henkel KGaA 1983). At this dose, there was still slight local inflammation in the forestomach, which is attributed to the gavage administration.

The following toxicokinetic data are taken into consideration for the extrapolation of the NOAEL of 100 mg/kg body weight and day to a concentration in workplace air: the species-specific correction value for the rat (1:4), the assumed oral absorption (100%), the body weight (70 kg) and the respiratory volume (10 m^3) of the person, the assumed 100% absorption by inhalation, the extrapolation to chronic exposure (1:2) and the extrapolation of the data from experimental studies with animals to humans (1:2). The concentration calculated from this is 44 mg/m^3 air.

However, the inflammation in the forestomach in the oral 13-week study is evidence of a local irritant effect on the gastric mucosa. In addition, the fatty alcohol ethoxylates $C_{16–18/18unsatd}$ are non-ionic surfactants, which suggests an effect on the pulmonary surfactant when inhaled. Since no inhalation studies are available from which this effect could be estimated, no MAK value can be derived for fatty alcohol ethoxylates $C_{16–18/18unsatd}$. Assignment to a peak limitation category is therefore not applicable.

Prenatal toxicity. The available studies do not fully meet today's requirements, but do not indicate or suggest any developmental toxicity. Since a MAK value cannot be derived, assignment to a pregnancy risk group is not applicable.

Carcinogenicity and germ cell mutagenicity. Two 2-year studies with a similar fatty alcohol ethoxylate ($C_{14–15}EO_7$) provide no evidence of a carcinogenic effect. Alcohol ethoxylates of similar chain length were not mutagenic or clastogenic in vitro and in vivo. No such effect is to be expected due to the structure, either. Therefore, fatty alcohol ethoxylates $C_{16–18/18unsatd}$ are not classified in one of the categories for germ cell mutagens or carcinogens.

Absorption through the skin. There are no data available for the dermal absorption of fatty alcohol ethoxylates $C_{16–18/18unsatd}$ (ECHA 2020). The acute toxicity of similar fatty alcohol ethoxylates after dermal application was low. The model calculations for dermal absorption (Section 3) suggest the maximum amount absorbed under standard conditions to be 32 mg.

From the systemic NOAEL extrapolated above to a concentration in air of 44 mg/m^3, a systemically tolerable amount of 440 mg for a respiratory volume of 10 m^3 is obtained. The calculated amount absorbed through the skin, as well as the absorption estimated by analogy, is thus less than 25% of the systemically tolerable amount. Fatty alcohol ethoxylates $C_{16–18/18unsatd}$ are therefore not designated with an "H" (for substances which can be absorbed through the skin in toxicologically relevant amounts).

Sensitization. Despite their frequent use, there are very few clinical reports of contact allergic reactions to fatty alcohol ethoxylates $C_{16–18}$. The experimental studies in guinea pigs with these and several similar fatty alcohol ethoxylates do not indicate any contact sensitizing potential. Findings on allergic reactions in the respiratory tract are not available, so that fatty alcohol ethoxylates $C_{16–18/18unsatd}$ are not designated with "Sh" or "Sa" (for substances which cause sensitization of the skin or airways).

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.

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