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Polyethylene glycols (PEGs) (average molar mass 200–600)

MAK Value Documentation, supplement - Translation of the German version from 2019

A. Hartwig[1,*] MAK Commission[2,*]

1 *Chair of the Permanent Senate Commission for the Investigation of Health Hazards of Chemical Compounds in the Work Area, Deutsche Forschungsgemeinschaft, Institute of Applied Biosciences, Department of Food Chemistry and Toxicology, Karlsruhe Institute of Technology (KIT), Adenauerring 20a, Building 50.41, 76131 Karlsruhe, Germany*

2 *Permanent Senate Commission for the Investigation of Health Hazards of Chemical Compounds in the Work Area, Deutsche Forschungsgemeinschaft, Kennedyallee 40, 53175 Bonn, Germany*

* *E-Mail: A. Hartwig (andrea.hartwig@kit.edu), MAK Commission (arbeitsstoffkommission@dfg.de)*

Keywords

polyethylene glycols, toxicity, maximum workplace concentration, MAK value, sensitization, developmental toxicity, peak limitation

Abstract

The German Commission for the Investigation of Health Hazards of Chemical Compounds in the Work Area has re-evaluated polyethylene glycols (PEGs) (average molar mass 200–600) [25322-68-3] considering all toxicological endpoints. In 13-week studies in rats, the NOAEC for aerosols of PEG 200 and PEG 400 was the highest concentration tested of 1000 mg/m^3. Taking into account the increased respiratory volume at the workplace (see List of MAK and BAT Values, Sections I b and I c), the extrapolation of data in animals to humans and the preferred value approach, the maximum concentration at the workplace (MAK value) has now been lowered to 200 mg/m^3 for the inhalable fraction. PEG 300 is composed of PEG 200 and PEG 400. PEG 600 is composed of 50% PEG 400. Therefore, the MAK value also applies to PEG 300 and PEG 600. In a chronic study at 2000 mg PEG 400/kg body weight and day, the body weight gain in rats was diminished. Therefore, the critical effect of PEGs is expected to be systemic and PEGs are classified in Peak Limitation Category II. As the half-life is between 2 and 4 hours, the excursion factor of 2 is confirmed. Because formation of a mist is possible, exposure should be minimized for reasons of occupational safety and hygiene. Several studies in rats, mice and rabbits with PEG 200 and PEG 400 show that the margins between the NOAECs for developmental toxicity scaled to a concentration at the workplace and the MAK value of 200 mg/m^3 are sufficient. Therefore, damage to the embryo or foetus is unlikely when the MAK value is not exceeded and PEGs remain classified in Pregnancy Risk Group C. PEGs are not genotoxic and are not suspected to be carcinogenic. According to skin absorption models, PEGs are not taken up via the skin in toxicologically relevant amounts. A large number of studies in humans show that PEGs are not skin sensitizers, however, it cannot be excluded that autoxidation products of PEG might induce a low number of positive reactions. There are no data on respiratory sensitization.

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MAK value (2018)	**200 mg/m³ I (inhalable fraction)**
Peak limitation (2002)	**Category II, excursion factor 2**
Absorption through the skin	–
Sensitization	–
Carcinogenicity	–
Prenatal toxicity (1995)	**Pregnancy Risk Group C**
Germ cell mutagenicity	–
BAT value	–
CAS number	25322-68-3
log K_{OW} at 30 °C	−0.958 (ECHA 2017)

Documentation for polyethylene glycols (average molar mass 200–600) (PEGs) was published in 1995 (Greim 1998), followed by a supplement on peak limitation in 2002 (Greim 2002, available in German only). A REACH registration dossier is available for CAS number 25322-68-3 (general CAS number for PEGs), but is valid only for polyethylene glycol 200 (ECHA 2017).

Metal-working fluid concentrates can contain up to 20% PEGs. Irritation of the skin is not to be expected at this concentration, as PEGs do not induce irritation of the skin even in undiluted form.

In 2016, the Commission began using a revised approach for assessing substances with a MAK value based on systemic effects and derived from inhalation studies in animals or studies with volunteers at rest; this new approach takes into account that the respiratory volume at the workplace is higher than under these experimental conditions (see List of MAK and BAT Values, Sections I b and I c). This supplement evaluates whether the MAK value and the pregnancy risk group for PEGs need to be re-assessed as a result of the higher respiratory volume at the workplace.

1 Toxic Effects and Mode of Action

PEGs up to a molar mass of 600 g/mol are viscous and fluid at room temperature. PEGs are completely soluble in water and do not cause irritation. This is probably the reason why accumulation or toxicity is not observed in the lungs of rats even after exposure to PEG 200 and PEG 400 aerosols at the highest concentration tested of 1000 mg/m³. Systemic toxic effects on the body weights and kidneys of rats were observed after medium-term and long-term oral exposure at dose levels of 2000 mg/kg body weight and above. At very high doses of about 20 000 mg/kg body weight, PEG 200 was teratogenic only in mice, but not in rats, rabbits and hamsters. In vivo tests with tetraethylene glycol (equivalent to PEG 200) yielded questionable evidence for a clastogenic potential in mice, but not in rats. A contact sensitizing potential could not be conclusively determined for PEGs on the basis of the findings from the few available clinical observations or from studies with guinea pigs and mice. However, degradation products formed by the autoxidation of PEGs may lead to irritation and in individual cases also to the development of contact allergic reactions.

2 Mechanism of Action

There are no new data available.

3 Toxicokinetics and Metabolism

3.1 Absorption, distribution, elimination

PEGs with a molar mass of up to 400 g/mol are absorbed by humans and rats in percentages of about 60% after oral administration. The absorption decreases at higher molar masses (Greim 1998). There are no data for absorption by inhalation and through the skin.

Fluxes of 149, 22.9 and 47.4 µg/cm² and hour, respectively, were calculated for undiluted PEG 200 using the models of Fiserova-Bergerova et al. (1990), Guy and Potts (1993) and Wilschut et al. (1995). Assuming exposure of 2000 cm² of skin for 1 hour, the absorbed amount is calculated to be 298, 45.8 and 94.8 mg, respectively. A similar calculation carried out for PEG 600 resulted in a maximum absorbed amount of 13.4 mg. The data for PEG 200 thus represent the worst-case scenario.

PEG 400 was rapidly eliminated by volunteers after intravenous injection (50% in about 3 hours) and about 30% was eliminated within 3 hours after oral administration (Shaffer et al. 1950). The half-life thus lies between 2 and 4 hours.

3.2 Metabolism

The monoacids and diacids of diethylene and triethylene glycols, which can be components of low molecular PEGs, may form during metabolism (Greim 1998). The polymer homologues of ethylene glycol (n = 1–8) are oxidized by alcohol dehydrogenase. This activity decreases with increasing chain length (Herold et al. 1989).

4 Effects in Humans

The documentation from 1995 (Greim 1998) included data only for repeated dermal and intravenous exposure.

Local effects on skin and mucous membranes

In a study, undiluted PEG 400 did not induce irritation of the skin in 28 volunteers after occlusive application for 4 hours. A 20% aqueous formulation of sodium lauryl sulfate, which was concurrently tested as a reference standard, produced reactions in 12 of the 28 volunteers (Basketter et al. 2004).

Allergenic effects

In spite of the wide-ranging use of PEGs in cosmetics and topical formulations, there are only a few isolated case reports of suspected allergic reactions to PEGs. However, these reports are only of patients who exhibited reactions after topical medications (particularly formulations containing nitrofurazone) were applied to infected areas of skin. Two other case reports concern reactions to diclofenac formulations containing the structurally closely related PEG 350 monomethyl ether (Table 1). Only a low incidence of positive results in patch tests was reported for groups of patients suspected of being sensitized to cosmetics or topically applied formulations and (in most cases) even for ulcus cruris patients (Table 1).

In the case reports, but also in studies with larger patient collectives, PEGs were applied in patch tests both in undiluted form and in some cases in a wide range of test concentrations ranging from 1% to 80% with water or

petrolatum as the vehicle to determine the cause of the allergies. None of the studies can be used to assess which of the formulations was sufficiently sensitive and specific in the patch test. A reaction index (defined as the quotient: (a – d – i)/(a + d + i); with: a = the number of allergic reactions, d = the number of questionable reactions, i = the number of irritant reactions (Brasch and Henseler 1992)) of –0.3 was calculated for the reactions to PEG ointment (mixture (1:1) of PEG 300 and PEG 1500) (Schnuch et al. 1993) because there was a relatively high incidence of questionable reactions and also irritation. Consequently, a number of the weak (+) positive reactions to the PEG ointment should perhaps be interpreted as false positives. A study performed from July 1996 to June 2001 determined a higher incidence of erythematous reactions to ointments containing PEGs in 441 patients who exhibited irritant reactions to 0.5% sodium lauryl sulfate in water than in 641 patients who did not exhibit this type of reaction (0.4% in comparison with 0.1%). The number of reactions that were assessed as allergic was similarly low in both groups (0.5% and 0.4%, respectively). Only 1+ reactions (corresponding to a positivity ratio (defined as the percentage of weak (+) positive reactions among the total number of positive reactions (Geier et al. 2003 b)) of 100%) were observed in patients who exhibited an irritant reaction to sodium lauryl sulfate, while 2+ to 3+ reactions (corresponding to a positivity ratio of about 25%) to ointments containing PEGs were reported for the group that did not react to 0.3% sodium lauryl sulfate. In this study, reaction indices of 0.2 and 0.3, respectively, were determined for the two groups (Geier et al. 2003 c). A reaction index of –0.17 and a positivity ratio of 70.9% were calculated using an unpublished analysis of the data from a total of 120 712 patients collected from 1996 to 2013 by the Information Network of Departments of Dermatology (IVDK) (IVDK 2015; see also Table 1).

Most publications do not provide information about the purity, origin and age of the test substances, which means that the observed reactions may have been induced by impurities (see below). Also, the prevalence of questionable and irritant reactions is rarely reported, making it difficult to classify the vast majority of reactions to highly concentrated or undiluted PEGs. However, as demonstrated by case study reports, strong allergic reactions to PEGs apparently do occur in rare cases. However, these reactions result from the application of PEGs to damaged skin. It remains unclear whether this effect is relevant for conditions at the workplace.

Even though high molecular PEGs may lead to marked, and in some cases anaphylactoid, reactions after oral administration and particularly after parenteral injection (Wenande and Garvey 2016), apparently these types of reactions have not been reported for low molecular PEGs. However, in very rare cases, positive results were induced in prick tests not only by high molecular PEGs, but also by PEG 400 (Badiu et al. 2015). Immediate urticarial reactions were observed only in very rare cases after topical application of low molecular PEGs (Fisher 1977, 1978; see Table 1).

Experimental studies

In a Human Repeated Insult Patch Test (RIPT) in 216 volunteers, 200 of whom participated until the end of the study, 50% solutions of PEG 200, PEG 400, PEG 1000, PEG 3350 and PEG 8000 (in water), and undiluted PEG 200 and PEG 400 were applied 9 times at 48-hour intervals for a period of 24 hours. The number of volunteers treated for induction ranged from 183 (last treatment) to 205 (first treatment). After the eighth induction treatment, 1 volunteer exhibited a reaction (infiltrated erythema) to both PEG 200 formulations. At the challenge treatment, however, a well-defined reaction to the PEG 200 or to the PEG 400 formulation was not produced in any of the 200 volunteers. A second volunteer exhibited an erythematous reaction to PEG 1000, PEG 3350 and PEG 8000 after the first, but not after the second, challenge treatment (Leung and Ballantyne 1998).

In an earlier, very poorly documented study, about 0.5 ml of a 3% aqueous formulation of a solid soap containing PEG 300 was applied occlusively to the upper arm of 200 volunteers 10 times for 2 to 3 days for a total exposure period of three and a half weeks. After an interval of 2 weeks, the challenge treatment was carried out with the occlusive application of a 1% formulation for 3 days. One volunteer exhibited a marked, scattered reaction that was reproducible to a similar degree in 3 subsequent challenge treatments carried out at intervals of 2 weeks. Tests were then performed with the individual constituents of the soap, which resulted in a strong reaction to 3% PEG 300 in petrolatum. Additional tests carried out with 3% and 1% PEG 600, PEG 1000, PEG 4000 and PEG 6000 (in petrolatum),

respectively, yielded a positive result in each case. However, an open application test performed by applying 3% PEG 300 in petrolatum to the cheek and forearm for 7 days did not produce a reaction (Maibach 1975).

Tab. 1 Reports of reactions to PEGs in patch tests in patients with suspected contact allergy

Tested persons	Substance/test concentration (vehicle)	Result (positive reactions)	Remarks	References
51 patients with sensitization to lanolin alcohols	PEG 200	11.8% (6/51, 4 × 1+, 2 × 2+)	test period: 1/1976 to 6/1980; readings after 24, 48 and 72 hours (no other data); in addition 2, 3, 3 and 2 erythematous and 2, 5, 2 and 5 questionable reactions to PEG 200, PEG 300, PEG 400 and PEG 600, respectively; 1 × 1+ and 1 × 2+ to PEG 1000 and 1 × 1+ to PEG 4000, no reaction to PEG 6000; no data for irritant reactions	Auth 1981; Auth et al. 1984
	PEG 300	3.9% (2/51, 1 × 1+ and 1 × 2+)		
	PEG 400	0%		
	PEG 600/10% in each case (water)	2% (1/51, 1+)		
180 patients (of these 120 patients with suspected sensitization to topical medications)	PEG 400/undiluted	3.9% (7/180)	test period: not specified; in addition, 4 ×, 3 × and 1 × positive reactions to PEG 1500, PEG 3000 and PEG 6000, respectively; in 4 cases, isolated positive reactions to PEG 400, no reactions to other PEGs	Bajaj et al. 1990
467 patients with suspected sensitization to topical medications	PEG 400/undiluted	5.4% (25/467)	positive reaction in 1 patient in each case, also after up to 20, 33 and 49 days	
423 patients with ulcus cruris	PEG 300 and PEG 1540/undiluted	0.7% (3/423) (no other data)	test period: not specified; patients were examined within 58 months	Barbaud et al. 2009
92 patients	PEG 300/10% (water)	4.4% (4/92; no other data)	no data	Braun 1969
40 additional patients with reactions to a formulation containing nitrofurazone		30% (12/40; 2+ or 3+, no other data)	in 5 of the 12 patients, also a positive reaction (no other data) to PEG 400 (10% in water)	
106 metal workers with exposure to metal-working fluids	PEG ointment (mixture (1:1) of PEG 300 and PEG 1500)/undiluted	0%	test period: 1998 to 2001	Geier et al. 2003 a
172 metal workers with exposure to metal-working fluids	PEG ointment (mixture (1:1) of PEG 300 and PEG 1500)/undiluted	0%	test period: 2002 to 2003	Geier et al. 2004
83 metal workers with exposure to metal-working fluids	PEG ointment (mixture (1:1) of PEG 300 and PEG 1500)/undiluted	3.7% (3/83)	test period: 6/2004 to 6/2005	Geier et al. 2006
586 metal workers with exposure to metal-working fluids	PEG ointment (mixture (1:1) of PEG 300 and PEG 1500)/undiluted	0%	test period: 2005 to 2009; 3 × questionable and 3 × irritant reactions	Geier et al. 2013
1566 patients with eczema	PEG 400/undiluted	0.06% (1/1566)	test period: 11/1972 to 11/1973; in addition 4 × irritant reactions	Hannuksela et al. 1975
776 patients	"PEG" (no other data)/4% ("oil")	0.4% (3/776)	test period: 7/1974 to 6/1976; in addition 8 × irritant reactions	Iden and Schroeter 1977

Tab. 1 *(continued)*

Tested persons	Substance/test concentration (vehicle)	Result (positive reactions)	Remarks	References
120 712 patients	PEG ointment (mixture (1:1) of PEG 300 and PEG 1500)/undiluted	0.21% (178 × 1+, 60 × 2+, 13 × 3+)	test period 1996 to 2013; in addition 245 × erythematous, 36 × follicular and 73 × irritant reactions	IVDK 2015
475 patients with stasis dermatitis or leg eczema	PEG ointment (mixture (1:1) of PEG 300 and PEG 1500)/undiluted	1.3% (6/475) (no other data)	test period: 11/1989 to 7/1993; overlap with the collective of Schnuch et al. (1993)	Lange-Ionescu et al. 1996
644 patients	PEG ointment (mixture (1:1) of PEG 300 and PEG 1500)/undiluted	2.5% (16/644)	test period: 1974 to 1980; no data for irritant reactions; 2496 patients in all were examined during the time period	Maak et al. 1983
18 patients with positive reactions to ointment bases and 20 control persons	PEG 400/80% (water)	5.3% (2/18) and 0%	no reactions to PEG 1000 and PEG 4000	
100 patients with ulcus cruris	PEG 400/undiluted	0%	test period: not specified	Marasović and Vuksić 1999
836 patients	PEG 400/undiluted	4.2% (35/836; 13 × 1+, 18 × 2+, 4 × 3+)	test period: 6/1996 to 12/2015; no data for irritant reactions; in 12 cases, reactions occurred only on day 4 or later; in 28 cases, the reactions were attributed to formulations containing nitrofurazone; in 7 cases, a possible cause was not specified	Özkaya and Kılıç 2018
50 patients with contact dermatitis	PEG 200/undiluted	10% (5/50; 1 × 1+, 2 × 2+, 2 × 3+)	test period: not specified; in addition 4 × questionable reactions	Pasricha 1987
423 (random) patients	PEG 300/10% (water)	4.5% (19/423)	test period: 1973 to 1974	Pevny and Uhlich 1975
148 patients	PEG 400/undiluted	0%	no data	Rietschel and Fowler 2008*; p 291*
279 patients	PEG 400/undiluted	0.7% (2/279)	test period: 7/1975 to 6/1976; the test with PEG 400 was part of a test series for preservatives carried out with 279 of a total of 2000 examined patients	Rudner 1977
4948 patients	PEG ointment (mixture (1:1) of PEG 300 and PEG 1500)/undiluted	0.2% (8/4948)	test period: 1987 to 1989; findings from 21 dermatology clinics; only 2+ and 3+ reactions were evaluated as allergic reactions; in addition 9 × questionable reactions	Scheuer et al. 1992
2054 patients	PEG ointment (mixture (1:1) of PEG 300 and PEG 1500)/undiluted	0.34% (7/2054)	test period: 1990/91; in addition 1 × irritant and 12 × questionable reactions; overlap with the collective of Lange-Ionescu et al. (1996)	Schnuch et al. 1993
220 consecutively tested patients	PEG 400/undiluted	2.8% (4/220)	test period: not specified; positive reactions in 4 of 129 men	Sharma et al. 2004
314 patients with suspected dermatitis induced by creams or ointments	PEG 300, PEG 400 and PEG 555/3% (water)	0.32% (1/314)	test period: 1/1988 to 3/1992; no reaction to PEG 1540	Stenveld et al. 1994
50 patients with suspected allergic contact eczema on the hands or feet	PEG 400/undiluted	4% (2/50)	test period: 12/2000 to 5/2001; positive reactions in 2 men; overall, positive reactions to 1 of 30 test substances in 28 (17 ♂, 11 ♀) of 50 (32 ♂, 18 ♀) test persons	Vani et al. 2005

Tab. 1 *(continued)*

Tested persons	Substance/test concentration (vehicle)	Result (positive reactions)	Remarks	References
Case reports				
1 patient with a reaction to a 2% mupirocin formulation in a PEG ointment	PEG 400/5% and 50% (petrolatum)	2+ and 3+, respectively (after 48 and 96 hours)	also 2+ and 3+ reactions to 5% and 50% PEG 3350, respectively, in petrolatum	Daly 1987
2 patients with immediate reactions to topical formulations containing PEGs	open test with PEG 400 (case 1) and PEG 300 (case 2)/undiluted	pruritic erythematous reactions after 15 minutes and urticarial reactions after 20 minutes	in both cases, no reaction in the patch test with undiluted PEG	Fisher 1977, 1978
2 patients with reactions to nitrofurazone formulations containing PEGs	PEG 300 and PEG 400/undiluted	strong reactions in both cases (no other data)		Fisher 1978
1 patient with a reaction to a nitrofurazone formulation containing PEGs	PEG 200 and PEG 300/1% (petrolatum); PEG 300/4% (petrolatum); PEG 400/undiluted; PEG 600/1% (petrolatum)	2+ reactions to 4% PEG 300 and to PEG 400 after 48 and 96 hours		Guijarro et al. 1999
1 patient with a reaction to ear drops containing PEGs	PEG 400/undiluted and PEG 300/0.3% (water)	positive in each case (no other data)	also a positive ROAT with both undiluted PEGs (may have been the same patient as in Hannuksela et al. (1975))	Hannuksela and Salo 1986
1 patient with a reaction to a single application of a diclofenac formulation	PEG 350 monomethylether/1% and 5% (water)	1+ and 2+ (after 96 hours)		Kleyn et al. 2004
2 patients with reactions to nitrofurazone formulations containing PEGs	"PEG" (no other data)/4% (petrolatum)	both 2+ (after 48 hours) and 3+ and "4+", respectively (after 96 hours)	also positive reaction to nitrofurazone	Moreno Escobosa et al. 2009
4 patients with reactions to nitrofurazone formulations containing PEGs	"PEG" (no other data)/4% (petrolatum)	3 of 4 positive (no other data)		Prieto et al. 2006
2 patients with reactions to nitrofurazone formulations containing PEGs	PEG 400/30% (water)	erythematous reaction with infiltration in both cases (after 48 hours)	also reactions to PEG 1500 and PEG 4000 (40% in water) in both patients	Strauss 1950
1 patient with a reaction to a 3% diclofenac formulation	PEG 350 monomethylether/5% and 10% (petrolatum)	2+ (after 96 hours) in both cases	no reaction during testing on back; positive reaction only during follow-up testing on the upper arm	Taibjee et al. 2003

ROAT: repeated open application test; 1+, 2+, 3+, 4+: severity of the skin reaction

The positive reactions observed in earlier RIPTs carried out with PEG 1500 and PEG 4000 (Smyth et al. 1942) and with PEG 200, PEG 300 and PEG 400 (Smyth et al. 1945) were probably caused by impurities, as later RIPTs performed

in groups of 100 female and 100 male volunteers using new batches of PEG 400 and PEG 4000 did not yield positive reactions (Greim 1998; Smyth et al. 1950).

In addition to unconverted ethylene oxide, possible impurities are primarily hydroperoxides formed by (aut)oxidation and the secondary products that are derived from these, which probably include formaldehyde and acetaldehyde.

Hydroperoxides, hydroxylated and ethoxylated aldehydes and formaldehyde have been found to form from ethoxylated alcohols such as laureth-5 (3,6,9,12,15-pentaoxaheptacosan-1-ol) and others (Bergh et al. 1998 a, b; Bodin et al. 2001, 2003); these were investigated for possible sensitizing effects in animal studies. It is therefore possible that PEGs may act as potential pre-haptens and form both irritant oxidation products and reactive electrophilic haptens following activation by autoxidation (for example, as a result of improper storage conditions). However, the reactions initially observed in patients during tests performed with various oxidized ethoxylated alcohols were only reproducible in follow-up tests in 1 of 9 cases and the authors attributed the initial reactions to irritation (Matura et al. 2004).

An earlier study found 1.4 to 9.3 micro-equivalents of peroxide/ml PEG in 3 batches each of PEG 300 and PEG 400. The ethylene oxide content of these batches was not determined exactly and was reported only as being less than 0.01% (McGinty et al. 1975). In a recent study, the high molecular derivates PEG 1450 (50% solution) and PEG 20 000 (25% solution) contained about 720 and 2400 micro-equivalents of peroxide/g PEG, respectively, after storage for 6 days (40 °C; interior lighting, aqueous solution, pH 5.0). The peroxide content approximately doubled after the solution was stored for another 20 days at 25 °C in dark storage conditions (Kumar and Kalonia 2006).

Summary: Neither observations from individual case reports nor the results of tests carried out with larger collectives suggest that PEGs have any noteworthy contact sensitizing potential. However, it is possible that degradation products may be formed during the autoxidation of PEGs (possibly also as a result of improper storage conditions) which may induce irritant reactions, and in individual cases even contact allergic reactions.

5 Animal Experiments and in vitro Studies

5.1 Acute toxicity

The acute toxicity of PEGs is very low irrespective of the route of administration (Greim 1998).

5.2 Subacute, subchronic and chronic toxicity

5.2.1 Inhalation

In studies with whole-body exposure of rats and mice to PEG 200 for 6 or 13 weeks (6 hours/day, 5 days/week), neither histological effects in the lungs, nor impairments of lung function or systemic effects were found, even at the highest concentration tested of 1000 mg/m^3. The same findings were reported in a study with head-nose exposure of rats to PEG 400 at a concentration of 1288 mg/m^3 for 13 weeks (6 hours/day, 5 days/week). Both studies were performed with respirable aerosols (Greim 1998). All studies included an examination of the nasopharynx and the nasal conchae.

5.2.2 Oral administration

Two male and 2 female Cynomolgus monkeys received daily doses of PEG 200 by gavage, initially 4 ml/kg body weight and day. After 3 weeks, the dose was decreased to 2 ml/kg body weight and day (2200 mg/kg body weight and day) because of the toxic effects observed, and exposure continued at this level for another 10 weeks. Oxalate crystals were found in the renal tubules of the animals; the authors did not attribute their development to the

presence of ethylene glycol because it made up less than 1% of the PEG 200 formulation. No adverse effects were observed in 20 male and 20 female rats exposed in a similar way, first to doses of 5 and then to 2.5 ml/kg body weight and day (Prentice and Majeed 1978).

In a study with F344 rats given PEG 400 by gavage at dose levels of 0, 1100, 2800 or 5600 mg/kg body weight and day on 5 days a week for 13 weeks, the NOAEL (no observed adverse effect level) was 1100 mg/kg body weight and day. At the LOAEL (lowest observed adverse effect level) of 2800 mg/kg body weight and day, higher protein and bilirubin concentrations, increased *N*-acetylglucosaminidase activity and a higher number of vascular cells in the urine were found in the males. These are signs of slight kidney toxicity (Hermansky et al. 1995).

A NOAEL of 2% in the feed was derived from a study in which groups of 20 rats per sex and dose were given oral doses of PEG 400 for 2 years. Body weight gains were reduced at 4% (no other details; Greim 1998; Smyth et al. 1955). The scope of this study was limited because the histopathological examination included only 9 organs, only the liver and kidney weights were determined and no clinico-chemical examinations were performed. In all, 90% of the animals died of pneumonia. The study does not comply with the current test guidelines. Converting the data according to EFSA (2012) results in a NOAEL of 1000 mg/kg body weight and day and a LOAEL of 2000 mg/kg body weight and day.

5.2.3 Dermal application

Occlusive application of PEG 200, PEG 300 or PEG 400 to the skin of male and female rabbits at dose levels of up to 2500 mg/kg body weight and day for 90 days did not cause systemic effects (Greim 1998).

5.3 Local effects on skin and mucous membranes

5.3.1 Skin

PEGs do not cause irritation of the skin (Greim 1998).

5.3.2 Eyes

PEGs do not cause irritation of the eyes (Greim 1998).

5.4 Allergenic effects

5.4.1 Sensitizing effects on the skin

Maximization tests performed to determine the contact sensitizing potential of PEG 200, PEG 400 and PEG 1000, PEG 3350 and PEG 8000 yielded negative results. However, no information was provided on the concentrations and vehicles used for intradermal induction treatment. It is likely that the substances used for topical induction treatment were applied in undiluted form; in the case of PEG 200, PEG 400 and PEG 1000, treatment was preceded by the application of 10% sodium lauryl sulfate in petrolatum. For the challenge treatment, the substances were applied in undiluted form (PEG 200 and PEG 400), as a 75% solution (PEG 1000), or a 25% solution (PEG 3350 and PEG 8000). After the challenge treatment with PEG 200, positive reactions (at least slight well-defined confluent erythema) were produced in only 2 of 20 animals. In the control groups consisting of 10 animals each and in the other groups treated with PEGs, at the most very slight (barely discernible) non-confluent erythema was observed (Leung and Ballantyne 1998).

In an optimization test with intradermal induction treatment (0.1% or 2%; vehicle probably water), two tests carried out with PEG 400 in groups of 20 Pirbright-White guinea pigs yielded negative results. The same formulations were used for both the induction treatments and the intradermal challenge treatments; undiluted PEG 400 was

applied for the topical challenge treatments. The 0.1% formulation provoked a response in 1 of 20 animals after intradermal challenge treatment, but no reactions were produced either in the second group treated with the higher concentration or in both groups by topical challenge treatment (Maurer 1985).

Also in a maximization test and a Buehler test with α-hexylcinnamaldehyde, sensitization to PEG 400 was not observed; both tests used PEG 400 as the vehicle (control) (Stropp 2000).

PEG 200 and PEG 300 were not sensitizing in a modified Draize test with groups of 13 to 16 guinea pigs. PEG 400 produced weak reactions with oedematous lesions smaller than 1 mm in diameter in 62% of the animals. PEG 1500 and PEG 4000 induced reactions with necrotic lesions smaller than 1 mm in diameter in 77% and 74% of the animals, respectively (Greim 1998; Smyth et al. 1950). Under the same experimental conditions (intradermal injection of 0.05 ml followed by intradermal injection of 0.1 ml three times a week, 8 doses in total for induction; 3 weeks later, intradermal injection of 0.05 ml for the challenge treatment), a 0.1% solution of PEG 4000 did not provoke positive reactions in 20 guinea pigs (Carpenter et al. 1971; Greim 1998). It is therefore possible that, at least in the case of high molecular PEGs, impurities were responsible for the positive results obtained in the study of Smyth et al. (1950).

Summary: The findings of recent studies in guinea pigs and mice do not provide evidence that PEGs have contact sensitizing potential. Positive results obtained by earlier, incompletely documented studies may have been caused by impurities (see also Section 4); these, however, have not been characterized in detail.

5.4.2 Sensitizing effects on the airways

There are no data available.

5.5 Reproductive and developmental toxicity

5.5.1 Fertility

There are no data available.

5.5.2 Developmental toxicity

Developmental toxicity was not induced in rats given PEG 200 at a dose level of 10 g/kg body weight and day from gestation days 6 to 15 (no other details; Fruijtier-Pölloth 2005).

The following study findings were discussed in the 1995 documentation (Greim 1998):

PEG 200 given to pregnant CD-1 mice on gestation days 6 to 17 at maternally non-toxic, oral doses of 0.5 and 0.7 ml/animal (Vannier et al. 1989) or 0.6 ml/animal (route and length of administration not specified; Vannier et al. 1992) induced malformations in the offspring (skull, paws, thoracic skeleton). The doses given are equivalent to 17 and 23 g/kg body weight and 20 g/kg body weight, calculated on the basis of the corrected relationship given in Vannier et al. (1992) (the unit published in the study as "mg/kg body weight" should be "g/kg body weight").

No effects were induced in the offspring of Sprague Dawley rats given maternally toxic doses of up to 5 ml/animal (Vannier et al. 1989) or 4 ml/animal (route and length of administration not specified; Vannier et al. 1992) on gestation days 6 to 14 and 11 to 16, respectively. The doses are equivalent to 7.5 to 25 g/kg body weight or 20 g/kg body weight, calculated on the basis of the corrected relationship given in Vannier et al. (1992) (the unit published in the study as "mg/kg body weight" should be "g/kg body weight").

In hamsters given maternally non-toxic, oral doses of PEG 200 of up to 5 g/kg body weight (the unit published in the study as "mg/kg body weight" should be "g/kg body weight" because the authors reported that the dose of 10 mg/kg body weight was lethal for the dams, which is implausible in view of the low acute toxicity) on gestation days 6 to 14, neither teratogenicity nor embryotoxicity were observed. In the offspring of rabbits treated orally

with PEG 200 at the maternally toxic dose of 1.12 g/kg body weight (the unit "mg/kg body weight" given in the study report is implausible, see above) on gestation days 6 to 18, neither embryotoxicity nor teratogenicity were found (Vannier et al. 1992).

No signs of maternal toxicity were determined in 16 rabbits given PEG 400 at dose levels of 0.2, 0.4 or 0.8 g/kg body weight and day by intravenous injection from gestation days 7 to 19. Embryotoxic or teratogenic effects were also not detected (Hoffmann-La Roche 1979 a in Greim 1998). Likewise, in 30 rats given the same intravenous doses from days 7 to 16 after conception, there was no evidence of maternal toxicity, embryotoxicity or teratogenic effects (Hoffmann-La Roche 1979 b in Greim 1998).

After gavage administration of PEG 400 doses of 11 g/kg body weight or daily application of 1.1 g/animal to the shaved skin of the back and flanks of groups of 20 Wistar rats from days 7 to 16 after conception or daily application of 1.7 g/animal to the shaved skin of the flanks of 10 rabbits from gestation days 7 to 19, no signs of maternal toxicity, embryotoxicity or teratogenic effects were found (Hoechst 1979 in Greim 1998).

Summary: The NOAELs for developmental toxicity after gavage administration in rats were 25 000 mg/kg body weight for PEG 200 and 11 000 mg/kg body weight for PEG 400. After intravenous injection in rabbits, the NOAEL for the developmental toxicity of PEG 400 was 800 mg/kg body weight, the highest dose tested.

5.6 Genotoxicity

5.6.1 In vitro

In the Salmonella mutagenicity test, PEG 200 and PEG 400 at concentrations up to 10 mg/plate were not mutagenic either with or without the addition of metabolic activation. Tetraethylene glycol (equivalent to PEG 200) was not mutagenic in the Salmonella mutagenicity test. PEG 400 did not induce sister chromatid exchange in Chinese hamster ovary (CHO) cells. Slight, but not dose-dependent, increases in the incidences of sister chromatid exchange and chromosomal damage in CHO cells were reported for tetraethylene glycol in the presence and absence of a metabolic activation system. PEG 400 (no other details of the test method) and tetraethylene glycol (hypoxanthine guanine phosphoribosyl transferase (HPRT) test) were not mutagenic in CHO cells (Greim 1998).

In a Chinese hamster epithelial liver cell line (CHEL) with sufficient metabolic capacity, PEG 200 and tetraethylene glycol, but not PEG 400, were clastogenic at concentrations of 2.5 mM and above. PEG 400 was tested only at a concentration of 7 mM. In CHO cells, the number of chromosomal aberrations was increased only after exposure to tetraethylene glycol at concentrations of 1.1 mM and above with metabolic activation. At concentrations of 20 mM and above, chromosomal aberrations were induced by PEG 400 and tetraethylene glycol also without metabolic activation; however, this was attributed to the high concentration. The clastogenic effects induced by tetraethylene glycol after activation were attributed to possible oxidative metabolites that may have formed (Biondi et al. 2002). In an HPRT test carried out according to OECD Test Guideline 476, PEG 200 was not mutagenic in CHO cells at concentrations of up to 5 mM (ECHA 2017).

5.6.2 In vivo

After administration of tetraethylene glycol (equivalent to PEG 200) at dose levels of up to 5000 mg/kg body weight, no chromosomal aberrations in rats and questionable increases in the incidence of micronuclei in mice were observed. According to a study that lacks sufficient documentation and can therefore not be validated, tetraethylene glycol induced dominant lethal mutations in rats (Greim 1998). No data are available for other PEGs.

5.7 Carcinogenicity

Limited earlier 2-year studies did not reveal carcinogenic effects in rats given up to 4% tetraethylene glycol and PEG 200 in the feed (Fruijtier-Pölloth 2005). No valid carcinogenicity studies are available for PEG 400 (Greim 1998). There are no data available for PEG 600.

6 Manifesto (MAK value/classification)

No adverse effects were observed in rats after inhalation exposure to PEG 200 or PEG 400 for 13 weeks at the highest concentration tested of 1000 mg/m³. Reduced body weight gains were determined after chronic administration of PEG 400 via the feed at dose levels of 2000 mg/kg body weight and day and above. Gavage administration of PEG 400 for 13 weeks induced slight toxic effects in the kidneys at a dose of 2800 mg/kg body weight and day.

MAK value. A NOAEL of 1100 mg/kg body weight and day was derived after gavage administration of PEG 400 for 13 weeks. A NOAEL of 1000 mg/kg body weight and day was determined in rats fed a diet containing PEG 400 for 2 years. Reduced body weight gains were observed at 2000 mg/kg body weight and day (no other details). However, the scope of this study was limited in comparison with today's standards (see Section 5.2.2). The following toxicokinetic data are taken into consideration for the extrapolation of the NOAEL of 1000 mg/kg body weight and day to a concentration in workplace air: the daily exposure of the animals in comparison with the 5 days per week exposure at the workplace (7:5), the corresponding species-specific correction value for the rat (1:4), the oral absorption of 60% determined in experimental studies, the body weight (70 kg) and respiratory volume (10 m³) of the person and the assumed 100% absorption by inhalation. A concentration of 1470 mg/m³ is calculated from this. Taking into consideration the extrapolation of the data from animal studies to humans (1:2) and the preferred value approach, a MAK value of 500 mg/m³ could be derived for the inhalable fraction.

In a study with head-nose exposure of rats and mice to both PEG 200 and PEG 400 for 13 weeks, no local and systemic effects were observed even at the highest concentration tested of 1000 mg/m³. The NOAEC (no observed adverse effect concentration) for PEG 200 was 1000 mg/m³ after inhalation exposure for both 6 and 13 weeks. Therefore, an intensification of the effects with increasing exposure duration is not to be assumed. A concentration of 250 mg/m³ is calculated taking into consideration the increased respiratory volume at the workplace in comparison with the respiration of the exposed animals at rest (1:2) and the extrapolation of the data from animal studies to humans (1:2). In accordance with the preferred value approach, a MAK value of 200 mg/m³ I is derived. It is pointed out that the actual NOAEC for these non-toxic substances may be even higher than 1000 mg/m³. Therefore, the previous MAK value still provides sufficient protection against adverse health effects even if the extrapolation from animal studies and the increased respiratory volume at the workplace are taken into consideration. The difference in values should not have any impact on practice, as it is assumed that there is a sufficient margin even between the lowered MAK value and the concentrations that actually occur at the workplace. However, extremely high concentrations of aerosols lead to conditions at the workplace that interfere with work activities (the formation of mist). Therefore, exposure should be minimized for reasons of workplace hygiene and occupational safety.

As PEG 300 is made up of the same constituents as PEG 200 and PEG 400 and PEG 600 is composed of about 50% PEG 400, the MAK value of 200 mg/m³ I applies provisionally also to PEG 300 and PEG 600.

With respect to the use of PEGs in metal-working fluids, they are not expected to induce adverse health effects as long as today's standard of 10 mg/m³ I for the aerosols of metal-working fluids is not exceeded.

Peak limitation. Classification in Peak Limitation Category II has been retained because systemic effects were observed in the oral 2-year study and in the 13-week study. The elimination half-life is 2 to 4 hours; correspondingly, an excursion factor of 2 has been established (Hartwig and MAK Commission 2017). PEGs do not cause irritation and the admissible peak concentration of 400 mg/m³ is below the NOAEC for local effects derived in the 13-week inhalation study.

Prenatal toxicity. No developmental toxicity was observed up to the respective highest dose tested. The NOAELs for developmental toxicity after gavage administration in rats were 25 000 mg/kg body weight for PEG 200 and 11 000 mg/kg body weight for PEG 400. The NOAEL for developmental toxicity after intravenous injection of PEG 400 in rabbits was 800 mg/kg body weight. The workplace concentrations calculated on the basis of these data (extrapolation as described above without 7:5 conversion, species-specific correction values for the rat: 1:4, rabbit: 1:2.4, intravenous absorption 100%) were 26 250 mg/m^3, 11 550 mg/m^3 and 2333 mg/m^3, respectively. The 131-fold, 58-fold and 12-fold margins between the calculated NOAECs for developmental toxicity and the MAK value of 200 mg/m^3 I are sufficiently large. Classification in Pregnancy Risk Group C has therefore been retained.

Carcinogenicity. No valid tests are available for PEGs. Tetraethylene glycol and PEG 200 were not carcinogenic in limited studies in rats. On account of their structure, the other PEGs not tested are not expected to induce carcinogenic effects. For this reason, PEGs continue not to be classified in a category for carcinogens.

Germ cell mutagenicity. A weak clastogenic potential was observed for tetraethylene glycol in vitro. A questionable positive result was observed also in vivo at a dose of 5000 mg/kg body weight in a micronucleus test in mice, but not, however, at the same dose in a chromosomal aberration test in rats. Data for germ cells and for other PEGs are not available. In all, the genotoxic potential of PEGs is estimated to be very low and they have not been classified in a category for germ cell mutagens.

Absorption through the skin. Systemically, PEGs are hardly toxic. PEG 200, PEG 300 and PEG 400 applied occlusively to the skin of rabbits at a dose level of 2500 mg/kg body weight and day for 90 days did not induce any effects. On the basis of a model calculation (Section 3.1), a maximum dermal absorption of 298 mg is estimated for humans after exposure to undiluted PEG 200 under standard conditions (2000 cm^2 of skin, one-hour exposure). The absorbed amount is lower for high molecular PEGs. A tolerable concentration for humans of 250 mg/m^3 was calculated from studies in rats with inhalation exposure to PEG 200 and PEG 400 (see above). At 100% absorption by inhalation and a respiratory volume of 10 m^3, the systemically tolerable intake level is 2500 mg. Therefore, absorption via the skin is less than 25% of the systemically tolerable amount and PEGs continue not to be designated with an "H" (for substances which can be absorbed through the skin in toxicologically relevant amounts).

Sensitization. Contact allergies induced by PEGs were only rarely reported in spite of their wide-ranging use, and are almost always associated with application to previously damaged skin. Degradation products may be formed by the autoxidation of PEGs (in some cases also as a result of improper storage conditions) which may lead to irritation and in individual cases also to the development of contact allergic reactions. However, a contact sensitizing potential could not be conclusively determined for PEGs on the basis of the findings from the few available clinical observations or from studies with guinea pigs and mice; PEGs continue not to be designated with "Sh" (for substances which cause sensitization of the skin). There is no evidence that allergic reactions are induced in the airways and PEGs continue not to be designated with "Sa" (for substances which cause sensitization of the airways).

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