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Polyethylene glycol*

Classification/MAK value:		**PEGs with average molecular weight of 200–600: 1000 mg/m^3** **Peak limitation category IV** **Pregnancy risk group C** **PEGs with average molecular weight > 600: see Section IIb of the List of MAK and BAT Values**
Classification dates from:		**1995**
Synonyms:		polyethylene oxide polyglycol polyoxyethylene
Trade name:		Carbowax®
Chemical name (CAS):		α-hydro-ω-hydroxypoly(oxy-1,2-ethanediyl)
CAS number:		25322-68-3
Structural formula:		$HO–(CH_2–CH_2–O)_x–H$, $x \geq 4$
Molecular formula:		$(C_2H_4O)_x.H_2O$, $x \geq 4$
Molecular weight:		200–4000000
Physical state:	PEG200–PEG600	liquid
	PEGs >600	waxy to solid

	PEG 200	PEG 300	PEG 400	PEG 600	PEG 1000	PEG 4000	PEG 10000	PEG 35000
Density at 20°C (g/cm^3):	1.12	1.13	1.13	1.13	1.2	1.2	1.2	1.2
Melting point (°C):	*c* –50	–15– –10	4–8	17–22	35–40	53–58	55–60	*c* 60
Vapour pressure at 20°C:	< 0.1	< 0.1	< 0.01	< 0.01	< 0.001	< 0.001	< 0.001	< 0.001
Solubility in water (g/100 g):	∞	∞	∞	∞	75	55	53	50

* In the present documentation the abbreviation PEG is used for polyethylene glycol. The commercially available PEGs are distinguished by writing the average molecular weight after the abbreviation, e.g., PEG200. The toxicological studies which have been carried out with tetraethylene glycol (≈ PEG200) are also described.

Solubility in organic solvents: PEGs are readily soluble in polar and non-polar solvents and insoluble in aliphatic hydrocarbons (Hoechst 1992b).

Volatility and stability to heat: PEGs are practically involatile. Prolonged heating at 150°C causes weight losses which are ascribed to the escape of volatile decomposition products. Which breakdown products are formed depends on the air supply; in addition to water, carbon dioxide and aldehydes, simple alcohols, acids and glycol esters can be formed (Hoechst 1992b).

Production: PEGs are synthesized by polymerization of ethylene oxide in the presence of water or ethylene glycol and alkaline catalysts (Rowe and Wolf 1982). Fractional distillation as used to fractionate simple glycols cannot be applied with the poorly volatile PEGs (Hoechst 1992b).

Purity: In PEG300 and PEG400 (McGinty *et al.* 1975) and in PEG1540 and PEG4000 (Hamburger *et al.* 1975) peroxides have been detected; they are formed by autoxidation during ageing. Reports from the 1960s indicate that autoxidation can be prevented by addition of 0.01 % to 0.5 % olefin oxides, e.g., ethylene oxide (Fiedler 1989). There are no more recent reports of the levels of dioxane and ethylene oxide from the synthesis or of the use of ethylene oxide as an additive.

Uses: PEGs are used, for example,

- in the pharmaceutical and cosmetic industries, e.g., as ointment bases, in creams, lotions, face lotions, lipsticks and toothpastes
- in the textile and leather industries, e.g., as plasticizers, antistatic agents, emulsifying agents
- in the rubber industry, e.g., as lubricants, mould-release agents, vulcanization accelerators
- in the ceramic industry, e.g., as plasticizers and binding agents
- in the paper industry, e.g. as moisturizers for paper and cardboard

– in the foodstuffs industry, e.g., as carriers for aromatic substances
– as antifoaming agents in the production of polyurethanes
– PEG200 to PEG600 are used as components of metal-working fluids (Hoechst 1992a)

1 Toxic Effects and Modes of Action

Polyethylene glycols (PEGs) up to a molecular weight of 400 are readily absorbed after ingestion. When the molecular weight is above 400, less than 10 % of the dose is absorbed. Excretion of the ingested PEG which is not absorbed takes place largely as the unchanged substance in the faeces. After parenteral administration the substance is mainly excreted in the urine. PEGs are not readily absorbed through intact skin. Through large areas of damaged skin, low molecular weight PEGs can be absorbed and metabolized to low molecular weight oligomers and their hydroxy acids and diacids or to the monomer, ethylene glycol. This can result in metabolic acidosis, increases in serum osmolality and total calcium level, in reduced levels of ionic calcium in the serum and in acute renal failure. In experimental animals single doses of PEG are practically non-toxic. When lethal doses are administered they cause narcosis and death from respiratory paralysis. The oral toxicity decreases with increasing molecular weight. Only after very high PEG doses does long-term oral administration of those PEGs which have been studied lead to adverse effects on kidney and liver, body weights and survival. In a 13-week inhalation study, very high concentrations of PEG200 aerosols proved to be practically non-toxic.

PEGs do not cause irritation of the skin, mucous membranes or eyes. Even prolonged skin contact does not cause damage. Slight sensitizing effects have been reported in persons with dermatitis or eczema. On test persons with healthy skin, no allergenic effects were observed.

PEG200 in very high doses is teratogenic in the mouse but not in rats, rabbits or hamsters. Studies with PEG400 administered to rats and rabbits yielded no evidence of reproductive toxicity even after high doses.

PEG200 and PEG400 do not exhibit genotoxic potential in the *Salmonella* mutagenicity test or in tests for DNA repair and mutation in mammalian cells. *In vivo* tests with tetraethylene glycol (≈ PEG200) yielded questionable evidence for a clastogenic potential in the mouse but not in the rat.

2 Mechanism of Action

Monoacids and diacids of diethylene and triethylene glycols which are formed during metabolism are considered to be responsible for the symptoms observed after application of low molecular weight PEGs to the damaged skin of rabbits and man (acidosis, hypercalcaemia, renal failure). The diacids form stable, soluble complexes with calcium (Herold *et al.* 1982).

3 Toxicokinetics

After oral administration of 5 and 10 g doses of PEG400 to three persons (Shaffer *et al.* 1950) the amount absorbed was estimated to be 52 % to 65 % of the dose, which is similar to the proportion of a PEG400 dose absorbed from the intestines of rats.

Within 5 hours after oral administration of a 25 % solution of PEG400 (dose not specified), rats had absorbed 62 % of the dose through the gastrointestinal tract; the absorption coefficient was 680 mg/hour/kg body weight (Shaffer *et al.* 1950). With 25 % solutions of PEG1000 and PEG1540, less than 2 % of the dose was absorbed within 5 hours; PEG4000 and PEG6000 were not absorbed at all (Shaffer and Critchfield 1947).

No dermal absorption could be demonstrated after occlusive application of PEG400 and PEG4000 (each 4 times 10g) for 48 hours to the intact and scarified skin of horses (Principe 1968).

After epicutaneous application of PEG1500 and PEG4000 (PEG4000 as a 50 % aqueous solution) to rabbits in doses of 10 g/kg body weight on 5 days per week for 13 weeks, only little absorption through the skin took place (no other details, Smyth *et al.* 1942).

The distribution of these substances in the organism has not been described.

No metabolism of PEG400 to ethylene glycol after oral administration to dogs and man could be demonstrated (determination of oxidizable substances in the plasma, Shaffer *et al.* 1950). After application of large doses of an ointment containing 63 % PEG300 (≈ hexaethylene glycol, ethylene glycol content 0.01 %) to damaged skin of man and rabbits, monoacids and diacids of diethylene and triethylene glycol were detected in the serum and urine by mass spectroscopy (no other details). The presence of oxalate was not mentioned but in the patients (see Section 4.2) ethylene glycol was detected in the serum (Bruns *et al.* 1982; Herold *et al.* 1982). Because details of doses were not given, it cannot be determined whether this ethylene glycol was present in the ointment or whether it was produced in the metabolism of PEG300. In addition, it must be remembered that PEG300 is a mixture which can contain low levels of diethylene and triethylene glycol. Metabolism to low molecular weight PEGs can, however, not be excluded.

After intravenous, intramuscular and subcutaneous administration, PEGs of all molecular weight classes are excreted almost completely within 24 hours, mainly in the urine. After oral administration, the excretion of PEG400 also takes place via the urine

whereas higher molecular weight PEGs (which are not absorbed) are mainly eliminated via the faeces.

Studies of PEG excretion are presented in Table 1.

Table 1. Studies of the excretion of PEG after oral, intravenous, intramuscular and subcutaneous administration

PEG	Species	Dose, form	Study period	Recovery (%) urine	faeces	References
oral						
400	man	*c* 70–140 mg/kg body weight	24 h	40–49	n.d.	Shaffer *et al.* 1950
	rabbit	8.5 g/animal	72 h	32–44	18	Shaffer *et al.* 1950
810	man	*c* 140 mg/kg body weight	6–8 h	< 1	n.d.	Kärber 1951
	rat	n.s.	24 h	< 1	n.d.	Kärber 1951
			48 h	n.d.	62	
1000	man	140 mg/kg body weight	24 h	8	n.d.	Shaffer and Critchfield 1947
4000	rat	70 mg/kg body weight	7 days	4	86	Carpenter *et al.* 1971
	horse	4.26 g/animal	3 days	1	n.d.	Principe 1968
6000	man	*c* 140 mg/kg body weight	24 h	0	n.d.	Shaffer and Critchfield 1947
4000000	rat[a]	67 mg/kg body weight, gavage	4 days	1	n.d.	Smyth *et al.* 1970
3	dog[a]	465 mg/kg body weight, in the diet	4 days	1	91	Smyth *et al.* 1970
intravenous						
400	man	*c* 14 mg/kg body weight	12 h	76–79	n.d.	Shaffer *et al.* 1950
	rabbit	0.4–0.75 g/animal	24–48 h	47–66	n.d.	Shaffer *et al.* 1950
	dog	n.s., 5% solution	n.s.	75–88	n.d.	Shaffer *et al.* 1950
	horse	5 g/animal	24 h	97–99	n.d.	Principe 1968
1000	man	*c* 14 mg/kg body weight	12 h	85	n.d.	Shaffer and Critchfield 1947
4000	rat	70 mg/kg body weight	7 days	61	20	Carpenter *et al.* 1971
6000	man	*c* 14 mg/kg body weight	12 h	96	n.d.	Shaffer and Critchfield 1947
intramuscular/subcutaneous						
300	dog	2 ml/kg body weight, i.m. and s.c.	48 h	93–97	n.d.	Carpenter and Shaffer 1952
400	dog	2 ml/kg body weight, i.m. and s.c.	24 h	85–87	n.d.	Carpenter and Shaffer 1952
810	rat	n.s., s.c.	3 days	[b]	n.d.	Kärber 1951
4000	horse	1.2 g/animal, i.m.	22 h	98	n.d.	Principe 1968
		0.9 g/animal, s.c.	34 h	> 99		

n.s.: not specified, n.d.: not determined, i.m.: intramuscular, s.c.: subcutaneous

[a]after administration of radioactive substance no radioactivity was detectable in body tissues, gastrointestinal tract or exhaled air;

[b]excretion mainly in the urine (no other details)

4 Effects in Man

4.1 Single exposures

There are no reports available on adverse effects of PEGs after short-term exposure during industrial use of these substances (AIHA 1980).

4.2 Repeated exposure

Three patients with burns affecting up to 56 % of their skin were treated with an antimicrobial ointment containing 63 % PEG300, 5 % PEG1000 and 32 % PEG4000 (application frequency not stated; usual would be twice daily; amount not stated). The total PEG content was given as 99.8 % and that of ethylene glycol as 0.01 %. The patients died of acute renal failure 12 to 27 days after the accident. The serum ethylene glycol levels were given as 1.3 mmole/l (about 80 mg/l; the time at which the blood sample was taken was not specified), the serum osmolality and the total serum calcium levels were increased. In whole blood the levels of calcium ions and the pH value were decreased. In addition, in serum and urine the monoacids and diacids of diethylene and triethylene glycol were detected by mass spectroscopy (no other details). The symptoms are like those of ethylene glycol poisoning. The authors suggested that the intoxication was a result of absorption of PEG through the damaged skin and its metabolism to the diacids and ethylene glycol (Bruns *et al.* 1982, see Section 5.2.3).

Another publication described 7 cases of renal failure after repeated intravenous injection of PEG300 into patients with chronic pyelonephritis (no other details, McCabe *et al.* 1959).

There are no reports available on adverse effects of PEG after long-term exposure during industrial use of these substances (AIHA 1980).

4.3 Effects on skin and mucous membranes

In patch tests carried out on 200 healthy volunteers no skin reactions to PEG400 or PEG4000 were seen (no other details, Smyth *et al.* 1950). Undiluted PEG200 and PEG600 applied once for 24 hours or applied repeatedly (14 days, every second day for 24 hours) did not cause skin irritation (Meyer and Stürmer 1952).

Workers who handled PEG reported no or only very little irritation of the skin or eyes. Acute exposure of the eyes to PEG caused conjunctival oedema (no other details, AIHA 1980).

4.4 Allergenic effects

In patch tests with PEG1500 and PEG4000 (PEG4000 as a 50 % aqueous solution) applied to 97 to 109 healthy male test persons (7 days induction, 10 days later provocation for 2 days), skin irritation was observed in 3 % and sensitization in 3 % and 4 % of cases, respectively. The skin reactions were milder than those produced by the plaster used in the test (Smyth *et al.* 1942).

In a patch test carried out as above on 23 healthy male test persons, PEG200 produced positive results in 22 % of the persons, PEG300 in 9 % and PEG400 in 4 % (Smyth *et al.* 1945).

In a later study, however, it was reported that with PEG400 and PEG4000 batches from a new production series, no reactions were observed on 100 healthy male and 100 healthy female test persons (Smyth *et al.* 1950). It is therefore likely that the reactions seen in the earlier studies were produced by impurities (e.g. ethylene oxide) which were no longer present in later batches.

In allergological tests, sensitization to PEG300 was seen in 4.5 % of 423 patients with skin disorders (Pevny and Uhlich 1975) and in 4 % of 92 such patients (Braun 1969). These results may be ascribed either to the presence of impurities or stabilizers in the tested substance or to methods which were inadequate with respect to the times of recording the reactions (unspecified in the publication); if the reactions are recorded only once it is not possible to distinguish reliably between toxic and allergic reactions. The sensitization frequency was considered to be low in the light of the extensive use of the substances. In contrast to the above are the results obtained with 1566 patients with eczema, among whom one allergic reaction (0.06 %) and 4 toxic reactions to undiluted PEG400 were observed (Hannuksela *et al.* 1975).

In tests with an undiluted polyethylene glycol ointment applied to 2065 patients with eczema, positive results were obtained in 0.34 % of cases (Schnuch *et al.* 1993).

In patch tests carried out during a period of 2 years on 180 patients of whom 120 had a suspected allergy to medicines, reactions to PEG400 were observed in 7 persons, to PEG1500 in 4, to PEG3000 in 3 and to PEG6000 in 1 person. Cross reactions between PEG400 and PEG15000 were seen in 3 cases and between PEG400 and PEG3000 in 2 cases. One patient produced reactions to PEG1500, PEG3000 and PEG6000. Reactions only to PEG400 were seen in 4 persons. Of the 180 persons tested, 8 (4.4 %) produced positive results. With 467 persons tested during a period of 5 years because of suspected allergy to topically applied medicaments, reactions to PEG400 were seen in 25 cases (5.3 %) (Baja *et al.* 1990).

In patch tests carried out on 314 patients with suspected contact dermatitis after use of ointments and creams, only one patient produced a reaction with PEG; the patient produced a reaction to PEG300, PEG400 and PEG555 but not to PEG1540. The authors considered that the risk of sensitization to PEGs, especially to those with high molecular weights, is low (Stenveld *et al.* 1994).

In general pure PEG does not have sensitizing effects on persons with healthy skin.

5 Animal Experiments and *in vitro* Studies

5.1 Acute toxicity

5.1.1 Inhalation

Groups of 6 male and 6 female F344 rats and B6C3F$_1$ mice were exposed for 6 hours to a PEG200 concentration of 2516 mg/m^3. Survival, blood counts, haematological parameters, respiratory physiology and histopathology were not different from the control values (no other details, Crook *et al.* 1980a).

5.1.2 Ingestion

The oral LD_{50} values for the rat, mouse, guinea pig and rabbit for PEGs with molecular weights up to 2000 were in the range between 14 and 50 g/kg body weight. For higher molecular weight PEGs the LD_{50} is said to be greater than 50 g/kg body weight. The LD_{50} for PEG4000000 is more than 4 g/kg body weight. The toxicity of PEGs decreases as the molecular weight increases (Rowe and Wolf 1982). Thus orally administered PEGs are practically non-toxic. The symptoms seen after administration of lethal doses were narcosis and death from respiratory failure (Meyer and Stürmer 1952).

Autopsy of rats given PEG doses of 50 g/kg body weight revealed cloudy swelling of the kidneys and liver and congestion in the gastrointestinal tract (Smyth *et al.* 1942, 1945, 1950).

5.1.3 Dermal, intraperitoneal, intravenous, intramuscular and subcutaneous application

Applied dermally, PEGs are practically non-toxic (Smyth *et al.* 1950). One of 6 rabbits died after being treated with a PEG200 dose of 20 ml/kg body weight (22.4 g/kg body weight). The same doses of PEG300 and PEG400 were tolerated without deaths (Smyth *et al.* 1945).

The LD_{50} values determined after intraperitoneal, intravenous and subcutaneous application of PEG are shown in Table 2.

After administration of PEG by these routes too, the LD_{50} values for mouse, rat and rabbit were mostly larger than 5 g/kg body weight.

After infusion of PEG200, PEG300, PEG400, PEG1000, PEG1500, PEG1540, PEG4000 and PEG6000, each in doses up to 10 g/kg body weight (2.5 ml of a 5 % solution infused per minute) into the ear veins of 2 male rabbits, microscopic examination revealed cloudy swelling of the epithelium of the kidney tubules only with PEG4000 and PEG6000; this could have been a result of the large volume of solution infused (500 ml) (Smyth *et al.* 1950).

Table 2. LD_{50} values for PEG administered by various routes

Species	PEG	LD_{50} (g/kg body weight)	References
intraperitoneal			
mouse	400	14.5	Bartsch *et al.* 1976
mouse	400	9.2	Shideman and Procita 1951
mouse	1000	2.0	Shideman and Procita 1951
mouse	4000	8.0	Shideman and Procita 1951
rat	200	8–9	Quadbeck 1950
rat	300	16–18	Quadbeck 1950
rat	300	17	Smyth *et al.* 1950
rat	400	14.7	Bartsch *et al.* 1976
rat	400	12.3	Rowe and Wolf 1982
rat	600	14.1	Rowe and Wolf 1982
rat	1000	15.6	Smyth *et al.* 1950
rat	1500	17.7	Smyth *et al.* 1950
rat	1540	15.4	Smyth *et al.* 1950
rat	4000	11.6–13	Smyth *et al.* 1950
rat	4000	9.7	Rowe and Wolf 1982
rat	6000	6.8	Smyth *et al.* 1950
rat	10000	12.6	Smyth *et al.* 1950
intravenous			
mouse	400	8.6	Bartsch *et al.* 1976
rat	300	8	Carpenter and Shaffer 1952
rat	300	7.1	Rowe and Wolf 1982
rat	400	4.7	Rowe and Wolf 1982
rat	600	7.7	Pfordte 1971
rat	810	13	Kärber 1951
rat	1500	8.5	Rowe and Wolf 1982
rat	4000	7.5	Rowe and Wolf 1982
rat	4000000	> 10	Smyth *et al.* 1970
rabbit	200	> 10	Smyth *et al.* 1950
rabbit	300	> 10	Smyth *et al.* 1950
rabbit	400	> 10	Smyth *et al.* 1950
rabbit	1000	> 10	Smyth *et al.* 1950
rabbit	1540	> 10	Smyth *et al.* 1950
rabbit	4000	> 10	Smyth *et al.* 1950
rabbit	6000	> 10	Smyth *et al.* 1950
subcutaneous			
rat	810	16	Kärber 1951

PEG200 (diluted 1:2 with physiological saline) infused in lethal amounts into anaesthetized rats caused increased blood pressure and reduced heart rate with arrhythmia. Doses of 6 ml per hour and more caused convulsions, and 12 ml per hour (21 ml/kg is the lethal volume) haematuria (Weifenbach 1973).

Extremely high intravenous doses of PEG400, PEG1000 and PEG4000 (> 3 g/kg body weight) caused reductions in blood pressure and intermittent apnoea in six anaesthetized dogs. Histological examination revealed moderate to severe pulmonary oedema and multiple focal infarctions in the lungs; there was no macroscopically visible

damage of the heart or kidneys. Intraperitoneal injection of lethal doses into mice caused progressive respiratory depression (Shideman and Procita 1951).

Intramuscular injection of undiluted PEG300 in doses of 0.5 and 2.0 ml/kg body weight (0.56 and 2.24 g/kg body weight) and subcutaneous injection of 2.5, 5 and 10 ml/kg body weight (2.8, 5.6 and 11.2 g/kg body weight) into Sherman rats caused local reactions such as inflammation and scab formation at the injection site which regressed within 14 days (Carpenter and Shaffer 1952).

After subcutaneous injection of lethal doses (17.5 g/kg body weight) of PEG810 into male and female rats, adverse effects on motility, appetite and respiration were observed with narcotic effects and lack of reflexes as symptoms of CNS depression. Histopathological examination yielded no evidence of changes in the liver and kidneys (Kärber 1951).

5.2 Subacute, subchronic and chronic toxicity

The toxicity observed in early studies after oral administration of PEG may be ascribed to the presence of impurities because in studies carried out since 1950 the toxicity was lower and the purity of the PEG batches used probably higher. Therefore the results of more recent studies are considered more reliable (Smyth *et al.* 1950).

5.2.1 Inhalation

Groups of 36 male and 36 female F344 rats and 15 male and 15 female B6C3F$_1$ mice were exposed to PEG200 aerosol concentrations of 122 and 1001 mg/m^3, 6 hours daily, 5 days per week for 6 and 13 weeks in whole animal exposure chambers and then observed for another 4 weeks. The average particle size in the aerosols was 0.8 and 0.71 µm, respectively, for the two exposure concentrations. After each exposure, the fur of the animals exposed to the higher concentration was oily. In the rats, no treatment-related effects on temperature, ECG, heart rate, blood pressure, activity, reflexes or respiratory parameters (respiration rate, volume, flow, airway resistance) were found. In neither species were there effects on body or organ weights, haematological parameters or histopathology of 20 organs (Crook *et al.* 1980b).

In a 13-week inhalation study, groups of 10 male and 10 female rats were exposed by head-only exposure to a mixture of PEG400 and ethanol (1:1) for 6 hours daily on 5 days per week. No changes relative to control animals exposed to air were found (Bayer 1995). The concentration of PEG400 was determined analytically as 1288 mg/m^3; the average aerodynamic diameter of the aerosol particles was 1.09 ± 0.03 µm. Clinical chemical parameters, lung function, body weight development, food and water consumption, weights of 11 organs and histopathology of about 50 organs and tissues were determined (Bayer 1989).

Groups of 10 male and 10 female F344 rats were exposed to aerosols of PEG3350 (20 % w/w in water) in concentrations of 109, 567 and 1008 mg/m^3, 6 hours daily, 5 days per week for 2 weeks. No exposure-related effects on clinical or opthalmological

parameters, clinical chemistry, urine analysis or results of autopsy were found. The average aerodynamic diameters of the PEG aerosol particles were 6.1, 5.8 and 3.8 µm for the three exposure concentrations. An increase in the neutrophil count in males exposed to 1008 mg/m^3, reduced body weight gain in males at 567 and 1008 mg/m^3 and an increase in absolute lung weights in males at 567 mg/m^3 and females at 1008 mg/m^3 were seen as effects of exposure which were partially or fully reversible by the end of the 2-week recovery period. The only dose-dependent histological change seen in all exposure groups was a slight increase in the number of alveolar macrophages with foamy cytoplasm (no other details). This effect was reversible within the 2-week recovery period except in the highest dose group. Necrosis was not seen in the lung tissue (Klonne *et al.* 1989). A NOAEL (no observed adverse effect level) cannot be derived from the results of this study because it was not determined whether inflammation mediators were released by the macrophages. In addition, it is unclear whether the effects observed at high concentrations (increased lung weights, body weight reductions) can also occur at 100 mg/m^3 if the exposure period is longer than 2 weeks.

In a 28-day inhalation study (4 hours/day, 5 days/week) with a PEG of unspecified molecular weight (Lutrol 9) in a concentration of about 1000 mg/m^3, groups of 9 male and 9 female Sprague-Dawley rats exhibited no exposure-related effects apart from peribronchial lymphocyte aggregation. The study did not include a control group (BASF 1979).

5.2.2 Ingestion

The results obtained after repeated oral administration of PEG are shown in Table 3.

In 90-day studies in which the substances were administered to rats in the drinking water or the diet, no observed adverse effect levels between 1.5 and 5 g/kg body weight and day were found for all PEGs investigated. Higher doses caused kidney or liver damage and reduced body weight gains.

The testis degeneration observed in rats given PEG4000 doses of 0.23 g/kg body weight and day in one study (Smyth *et al.* 1942) may be ascribed to the presence of impurities because, in later studies, feeding of PEG4000 doses of 1.6 g/kg body weight and day for 90 days did not have any effects (Smyth *et al.* 1950).

Treatment of dogs for one year with PEG400, PEG1540 or PEG4000, each in a concentration of 2 % in the diet (about 0.5 to 1 g/kg body weight and day) did not have adverse effects on the animals (Smyth *et al.* 1955).

In a 2-year feeding study with rats, no observed effect levels for PEG400, PEG1500, PEG1540, PEG4000 and PEG4000000 between 1.5 and 3 g/kg body weight and day were found (Table 3).

Table 3. Effects of PEG after repeated oral administration

PEG	Species, number, sex	Dose; administration form; duration	Dose (g/kg body weight and day): effects	References
200	rat 5 ♂	4.8, 10.9 g/kg body weight and day; drinking water; 90 days	**4.8:** NOAEL 10.9: 66% mortality, decreased body weight gain	Smyth *et al.* 1945
	rat 5 ♂, 5 ♀	20, 40, 80, 160, 240 g/kg diet (*c* 1.5, 3, 6, 12, 18 g/kg body weight and day); 90 days	**6:** NOAEL **12:** liver weights increased **18:** liver and kidney weights increased	Smyth *et al.* 1955
300	rat 5 ♂	5.4, 20.5 g/kg body weight and day; drinking water; 90 days	**5.4:** NOAEL **20.5:** 66% mortality, decreased body weight gain, liver and kidney changes	Smyth *et al*. 1945
	rat 5 ♂, 5 ♀	20, 40, 80, 160, 240 g/kg diet (*c* 1.5, 3, 6, 12, 18 g/kg body weight and day); 90 days	**3:** NOAEL **6:** decreased body weight gain **12:** liver and kidney weights increased **18:** decreased body weight gain, liver weights increased	Smyth *et al.* 1955
400	rat 5 ♀	11 g/kg body weight and day; administration form n.s.; 14 days	**11:** NOAEL	Hoffmann-La Roche 1978a
	rat 5 ♂	4.8, 16.4 g/kg body weight and day; drinking water; 90 days	**4.8:** NOAEL **16.4:** 66% mortality, decreased body weight gain	Smyth *et al.* 1945
	rat 5 ♂, 5 ♀	20, 40, 80, 160, 240 g/kg diet (*c* 1.5, 3, 6, 12, 18 g/kg body weight and day); 90 days	**6:** NOAEL **12:** decreased body weight gain **18:** liver and kidney weights increased	Smyth *et al.* 1955
	rat 20 ♂, 20 ♀	10, 20, 40, 80 g/kg diet (*c* 0.75, 1.5, 3, 6 g/kg body weight and day); 2 years	**1.5:** NOAEL from 3: ♂: decreased body weight gain	Smyth *et al.* 1955
	dog 3 ♂, 1 ♀	20 g/kg diet (*c* 0.5 g/kg body weight and day); 1 year	**0.5:** NOAEL	Smyth *et al.* 1955
600	rat 5 ♂, 5 ♀	20, 40, 80, 160, 240 g/kg diet (*c* 1.5, 3, 6, 12, 18 g/kg body weight and day); 90 days	**6:** NOAEL from 12: decreased body weight gain, increased kidney weights	Smyth *et al.* 1955
1000	rat 5 ♂, 5 ♀	20, 40, 80, 160, 240 g/kg diet (*c* 1.5, 3, 6, 12, 18 g/kg body weight and day); 90 days	**6:** NOAEL from 12: decreased body weight gain	Smyth *et al.* 1955

Table 3. continued

PEG	Species, number, sex	Dose; administration form; duration	Dose (g/kg body weight and day): effects	References
1500	rat 5 n.s.	0.88, 2, 4.05, 8.1, 22.9 g/kg body weight and day; drinking water; 90 days	**2:** NOAEL from 4.05: kidney damage	Smyth *et al.* 1942
	rat 5 ♂, 5 ♀	20, 40, 80, 160, 240 g/kg diet (*c* 1.5, 3, 6, 12, 18 g/kg body weight and day); 90 days	**3:** NOAEL from 6: decreased body weight gain **18:** increased kidney weights	Smyth *et al.* 1955
	rat 8 ♂, 8 ♀	0.2, 0.8, 4, 20 g/l drinking water (*c* 0.015, 0.059, 0.27, 1.69 g/kg body weight and day); 2 years	**1.69:** no effects on fertility, survival, haematology or histopathology	Smyth *et al.* 1947, 1950
1540	rat 5 ♂, 5 ♀	20, 40, 80, 160, 240 g/kg diet (*c* 1.5, 3, 6, 12, 18 g/kg body weight and day); 90 days	**3:** NOAEL from 6: decreased body weight gain **18:** increased kidney weights	Smyth *et al.* 1955
	rat n.s.	1.6 g/kg body weight and day; diet; 90 days	**1.6:** no effects on food consumption, weight gain, liver or kidneys, NOAEL	Smyth *et al.* 1950
	rat 35 ♂, 35 ♀	0.2, 0.8, 4, 20, 40, 80 g/kg diet (*c* 0.015, 0.06, 0.3, 1.5, 3, 6 g/kg body weight and day); 2 years	**3:** NOAEL **6:** cloudy swelling in the liver	Smyth *et al.* 1955
	dog 4	20 g/kg diet (*c* 0.5 g/kg body weight and day); 1 year	**0.5:** NOAEL	Smyth *et al.* 1955
4000	rat 5 ♂	0.04–19 g/kg body weight and day; drinking water; 90 days	**0.08:** NOAEL **0.23:** degeneration of the testis tubules, degenerated sperm from 7: decreased body weight gain **19:** kidney damage	Smyth *et al.* 1942
	rat 5 ♂, 5 ♀	20, 40, 80, 160, 240 g/kg diet (*c* 1.5, 3, 6, 12, 18 g/kg body weight and day); 90 days	**3:** NOAEL from 6: decreased body weight gain from 12: increased kidney weights	Smyth *et al.* 1955

Table 3. continued

PEG	Species, number, sex	Dose; administration form; duration	Dose (g/kg body weight and day): effects	References
	rat n.a.	1.6 g/kg body weight and day; diet; 90 days	**1.6:** no effects on food consumption, body weight gain, liver or kidneys, NOAEL	Smyth *et al.* 1950
	rat 8 ♂, 8 ♀	0.00085, 0.0036, 0.017, 0.062 g/kg body weight and day; drinking water; 2 years	**0.062:** no effects on fertility, survival, haematology or histopathology; NOAEL	Smyth *et al.* 1947, 1950
	rat 20 ♂, 20 ♀	0.375, 0.75, 1.5, 3, 6 g/kg body weight and day; diet; 2 years	**3:** NOAEL **6:** decreased body weight gain	Smyth *et al.* 1955
	rabbit 5	5, 10 and 20 g/kg body weight and day; gavage; 6 days/week, 5 weeks	**from 5:** decreased body weight gain, decreased glycogen storage **20:** decreased body weights	Smyth *et al.* 1942
	dog 4	20 g/kg diet (*c* 0.5 g/kg body weight and day); 1 year	**0.5:** NOAEL	Smyth *et al.* 1955
6000	rat 5 ♂, 5 ♀	20, 40, 80, 160, 240 g/kg diet (*c* 1.5, 3, 6, 12, 18 g/kg body weight and day); 90 days	**12:** NOAEL **18:** kidney weights increased, decreased body weight gain	Smyth *et al.* 1955
10000	rat n.s.	1.6 g/kg body weight and day; diet; 90 days	**1.6:** no effects on food consumption, body weight gain, liver or kidneys, NOAEL	Smyth *et al.* 1950
4000000	rat 10 ♂, 10 ♀	8.0, 18.4 g/kg body weight and day; diet; 90 days	**from 8:** cloudy swelling in the renal tubules **18.4:** decreased body weight gain, ♂: decreased relative liver weights	Smyth *et al.* 1970
	rat 36 ♂, 36 ♀	up to 2.76 g/kg body weight and day; diet; 2 years	**2.76:** NOAEL	Smyth *et al.* 1970
	dog 4 ♂, 2 ♀	up to 0.56 g/kg body weight and day; diet; 2 years	**0.56:** NOAEL	Smyth *et al.* 1970

n.s.: not specified, NOAEL: no observed adverse effect level

5.2.3 Dermal absorption

Occlusive dermal application of doses of PEG200, PEG300 or PEG400 up to 2.5 g/kg body weight and of PEG1000, PEG1500, PEG2000, PEG4000, PEG6000 or PEG9000 of 10 g/kg body weight for 90 days to male and female rabbits did not produce systemic effects. No deviation from the control values was seen for blood urea nitrogen, liver or kidney function parameters or results of the histological examination (Smyth *et al.* 1942, 1945, Tusing *et al.* 1954).

Application of 20 g of a mixture containing 63 % PEG300, 5 % PEG1000 and 32 % PEG4000 twice daily to an area of 90 cm^2 of wounded skin of 4 rabbits resulted in the death of 3 animals after 7 days. In the serum of the animals which died, osmolality and total calcium levels were increased. In whole blood the levels of calcium ions and the pH values were decreased. Increased creatinine and blood urea nitrogen levels were indicative of renal failure. In serum and urine, PEG and the homologous diglycolic and hydroxyglycolic acids were detected. The authors suggested that the low molecular weight glycols (monomers, dimers and trimers) present in PEG300 had been absorbed and metabolized to the corresponding aldehydes and acids which form complexes with calcium and have nephrotoxic effects (Herold *et al.* 1982; see Section 4.2).

5.2.4 Intravenous absorption

Daily treatment of groups of 3 male and 3 female baboons with PEG400 doses of 100, 350 or 1000 mg/kg body weight for 29 days produced no substance-induced symptoms apart from weight loss in one female in the highest dose group (Hoffmann-La Roche 1979c). Administered to groups of 12 male and 12 female rats, 7 days per week for 4 weeks, PEG400 doses of 250, 1250 and 2500 mg/kg body weight and day caused an increased respiration rate for 2 to 3 minutes and an increase in the reticulocyte count in the females of the highest dose group. Animals which developed swelling and necrosis at the injection site after two weeks were treated for the second two weeks with intraperitoneal injections (Hoffmann-La Roche 1980a).

Administration of PEG200, PEG300, PEG400, PEG1000, PEG1500, PEG1540, PEG4000 and PEG6000, each in a dose of 350 mg/kg body weight and day, into the ear veins of groups of 5 rabbits for a period of 5 weeks resulted in the death of one animal in each of the groups treated with PEG400, PEG4000 and PEG6000 with increased blood urea nitrogen levels. The only histopathological changes induced by the treatment were cloudy swelling in the renal tubule epithelia and the liver parenchyma in 9 of 45 animals, distributed evenly among the treatment groups (Smyth *et al.* 1950).

Application of doses of PEG200, PEG300, PEG400, PEG1000, PEG1500, PEG1540, and PEG6000 of 1 g/kg body weight and day and of PEG4000 doses of 0.8 g/kg body weight and day to rabbits for 30 days produced mild liver and kidney changes only with PEG200, PEG400 and PEG1000 (no other details, Rowe and Wolf 1982).

In 9 male and female beagle dogs treated with PEG4000 doses of 10, 30 or 90 mg/kg body weight and day for 12 months, no adverse effects on body or organ weights, haematological or biochemical parameters and no histopathological changes were induced by the substance (Carpenter *et al.* 1971).

5.2.5 Intraperitoneal and intramuscular absorption

After intraperitoneal injection of PEG400 doses of 0.6, 1.1, 2.2, 4.4, 8.8 or 17.6 g/kg body weight and day for 10 days to groups of 10 male and 10 female rats and mice, in the highest dose group 20 % of the rats and 80 % of the mice died. The gross pathological and histological examinations revealed neither nephrotoxic nor hepatotoxic effects but only local reactions (Hoffmann-La Roche 1978b, 1980b).

Intramuscular injection of a PEG6000 dose of 1.6 g/kg body weight every five days or three times weekly for 3 weeks did not produce any effects on rats (Rowe and Wolf 1982).

5.3 Effects on skin and mucous membranes

5.3.1 Skin

After dermal application of undiluted PEG200, PEG300 or PEG400 in doses up to 20 ml/kg body weight for 4 hours (not specified whether occlusive) to groups of 6 rabbits (observation for 14 days), neither during contact with the substances nor 24 hours later were any signs of irritation detected (Smyth *et al.* 1945).

Non-occlusive application of doses of 0.05 ml PEG300 or PEG600, 3 times weekly for 8 weeks to mice did not cause any skin changes (Schmid 1970).

Likewise, after semi-occlusive application of 3 g undiluted PEG1500 or of 6 ml of a 50 % solution (3.6 g) to the shaved abdominal skin of each of 10 guinea pigs for 4 days, no skin reactions were observed (Smyth *et al.* 1942).

Treatment of the shaved abdominal skin of rabbits (not specified whether occlusive) once weekly for 13 weeks with 20 g PEG1500 or 40 ml of a 50 % solution of PEG4000 (24 g) did not produce irritation (Smyth *et al.* 1942).

Dermal occlusive application of PEG300 and PEG400 doses of 2.0 ml/kg body weight and day or of PEG1000, PEG2000, PEG4000, PEG6000 and PEG9000 doses of 10 g/kg body weight and day to male and female rabbits for 90 days did not cause irritation (Tusing *et al.* 1954).

In 4 rabbits treated occlusively for 24 hours with 20 ml/kg body weight of a 5 % aqueous solution of PEG4000000 (1.0 g/kg body weight) on the shaved skin, no signs of irritation were seen (Smyth *et al.* 1970).

5.3.2 Eyes

The application of 0.1 ml PEG200 to the rabbit eye for 24 hours did not cause any irritation (Hoechst 1985).

Signs of diffuse necrosis of the cornea were produced in one to two of five rabbits with undiluted PEG200, PEG300 and PEG400 but not with the 15 % solutions; the effects were described as rapidly reversible (Smyth *et al.* 1945).

In the rabbit eye, 0.5 ml doses of undiluted PEG200, PEG300, PEG400, PEG600, PEG1500 and PEG4000 did not produce irritation during the 18 to 24 hours after application (Carpenter and Smyth 1946).

5.3.3 Mucous membranes

No signs of local intolerance were seen in 6 male rats and 2 female dogs (Swiss hounds) after application of PEG400 doses of 1.0 ml/kg body weight and day for 5 days by gavage (Hoffmann-La Roche 1982).

5.4 Allergenic effects

In the modified Draize test with groups of 13 to 16 guinea pigs, PEG200 and PEG300 were not sensitizing. PEG400 produced weak sensitization reactions with oedematous lesions smaller than 1 mm in diameter in 62 % of the animals. PEG1500 and PEG4000 induced sensitization reactions with necrotic lesions smaller than 1 mm in diameter in 77 % and 74 % of the animals, respectively (Smyth *et al.* 1950). Under the same experimental conditions (0.05 ml injected intradermally, then 0.1 ml injected intradermally three times weekly to a total of 8 doses, 3 weeks later 0.05 ml intradermally) with a 0.1 % solution of PEG4000 tested on 20 guinea pigs no reactions were detected (Carpenter *et al.* 1971); thus it is conceivable that impurities were responsible for the positive results in the study of Smyth *et al.* (1950).

5.5 Reproductive and developmental toxicity

In a study in which oral tetraethylene glycol (≈ PEG200) doses of 1/5000 to 1/50 of the LD_{50} (LD_{50} not specified) were administered daily for 2 to 6 months to rats, testis damage and sperm anomalies were described after doses of about 2500 mg/kg body weight. For female rats given daily doses of 1/1000 to 1/300 of the LD_{50} for 30 days, reduced cycle length was reported (Byshovets *et al.* 1987). Because these results are inadequately documented, the study cannot be used for the present evaluation of PEG.

After administration of tetraethylene glycol doses of 1/500, 1/50 and 1/5 of the LD_{50} to groups of 10 rats on days 1 to 19 of gestation increases in preimplantation and postimplantation losses and malformations in the progeny of the medium and high dose

groups were described. The malformations were only summarized as totals without details of the individual cases; maternal toxicity was not mentioned (Barilyak 1989).

A positive result in a dominant lethal test was described for tetraethylene glycol (Section 5.6.2).

Oral administration of PEG200 on days 6 to 17 of gestation in doses which were not toxic for the dams, 17 and 23 g/kg body weight (Vannier *et al.* 1989) or 20 g/kg (administration route and duration not specified, Vannier *et al.* 1992) produced malformations (no other details) in the progeny of pregnant CD-1 mice. In Sprague-Dawley rats, exposure on days 6 to 14 or days 11 to 16 of gestation to maternally toxic PEG200 doses of 7.5 to 25 g/kg body weight (Vannier *et al.* 1989) or 20 g/kg body weight (administration route and duration not specified, Vannier *et al.* 1992) had no effects on the progeny. For hamsters given maternally toxic oral doses of up to 5 g/kg body weight on days 6 to 14 of gestation, neither teratogenicity nor embryotoxicity was detected. Likewise in the progeny of rabbits treated with the maternally toxic oral dose of 1.12 g/kg body weight on days 6 to 18 of gestation, neither embryotoxicity nor teratogenicity could be demonstrated (quoted from abstract, Vannier *et al.* 1992).

After administration of PEG400 doses of 0.2, 0.4 or 0.8 g/kg body weight and day by intravenous injection to groups of 16 rabbits from day 7 to day 19 of gestation, there were no signs of maternal toxicity. Embryotoxic or teratogenic effects were also not detected (Hoffmann-La Roche 1979a). Similarly in 30 rats given the same intravenous doses from day 7 to day 16 *post conceptionem*, there was no evidence of maternal toxicity, embryotoxicity or teratogenic effects (Hoffmann-La Roche 1979b).

After administration of PEG400 doses of 11 g/kg body weight by gavage or application of 1.1 g/animal to the shaved skin of the back and flanks of groups of 20 Wistar rats, daily from day 7 to day 16 *post conceptionem,* and after application of 1.7 g per animal to the shaved flank skin of 10 rabbits daily from day 7 to 19 of gestation, there were also no signs of maternal toxicity, embryotoxicity or teratogenic effects (Hoechst 1979).

5.6 Genotoxicity

5.6.1 *In vitro*

In the *Salmonella* mutagenicity test in the *S. typhimurium* strains TA98, TA100, TA1535 and TA1537, in the concentration range from 0.1 to 10 mg/plate, PEG200 was not mutagenic in the presence or the absence of a metabolic activation system (S9 fraction from rat and hamster liver) (Mortelmans *et al.* 1986).

Tetraethylene glycol (≈ PEG200) yielded negative results in the *Salmonella* mutagenicity test and in the HPRT (hypoxanthine guanine phosphoribosyl transferase) test in CHO cells (a cell line derived from Chinese hamster ovary cells) in the presence and absence of a metabolic activation system (S9 fraction from the livers of rats pretreated with Aroclor 1254). Increases in SCE (sister chromatid exchange) and chromosomal damage in CHO cells with and without S9 mix have been described; they were, however, not dose-dependent (quoted from abstract, Slesinkski *et al.* 1989).

Likewise, no mutagenic effects were detected with PEG400 in the *Salmonella* mutagenicity test in the strains TA98, TA100, TA1535 and TA1537 in concentrations between 0.004 and 10 µl/plate (0.004 10 mg/plate) in the presence or absence of a mutagenic activation system (S9 fraction from the livers of rats pretreated with Aroclor 1254) (Hoechst 1978).

In the concentration range from about 0.6 to 10 mg/ml, PEG400 was not mutagenic in CHO cells either in the presence or absence of S9 mix (no other details) and did not induce SCE (Cosmetic Ingredient Review 1993).

In rat hepatocytes incubated with PEG400 concentrations between 0.001 and 1 mg/ml, significant unscheduled DNA synthesis (UDS) could be detected only at the highest concentration (Cosmetic Ingredient Review 1993).

5.6.2 *In vivo*

Rats were given single oral tetraethylene glycol doses of 1/50 and 1/5 of the LD_{50} (no other details); chromosomal aberrations (especially acentric fragments and deletions) were detected in the bone marrow cells of the high dose group animals 48 hours later. About 15 animals per dose group were probably used; exact numbers are not given. From each animal 50 to 60 cells were analysed. Gaps were not included in the evaluation. The incidence in the controls (1500 cells analysed) was given as 0 %; historical control data were not given (Barilyak *et al.* 1987). It is unusual that the control incidence is 0 %. A third dose group would be required to determine whether the effect is really dose-dependent. The inadequate documentation also makes it impossible to use these results in the present evaluation.

Tetraethylene glycol was administered by intraperitoneal injection to groups of 5 male and 5 female Swiss-Webster mice in single doses of 2500, 4000 and 5000 mg/kg body weight; 30, 48 and 72 hours later the animals were examined for micronucleus formation in the polychromatic erythrocytes in peripheral blood. Only in the 30 hour samples in male animals from the group given 5000 mg/kg body weight was the incidence of micronuclei slightly increased. When the number of erythrocytes evaluated was doubled a significant increase was also detected in the lowest dose group (Union Carbide 1987).

In bone marrow cells of rats given single oral tetraethylene glycol doses of up to 5000 mg/kg body weight, the incidence of chromosomal aberrations 12, 24 and 48 hours after dosing was not increased relative to the control values (Union Carbide 1988).

Because the effects seen in the Union Carbide study (1987) were not dose-dependent and occurred only at very high doses and because negative results were obtained at comparable doses in the study of chromosomal aberrations, it must be considered questionable whether tetraethylene glycol has clastogenic effects *in vivo*.

Tetraethylene glycol was administered to male rats in single doses of 1/500 and 1/50 of the LD_{50} (no other details) and the rats were then mated with females during a period of 2 weeks. In the high dose group the postimplantation losses were increased significantly relative to the control value, a sign of dominant lethal mutations (Barilyak *et al.* 1987). It is unusual that no higher doses were tested and that dominant lethal mutations

should develop at a dose as low as 1/50 of the LD_{50}. These results must be considered to be of questionable validity.

5.7 Carcinogenicity

In a carcinogenicity study in which various substances were investigated, PEG1000 was used as a solvent; 25 % of the female mice in the vehicle control group developed vaginal or cervical carcinomas after intravaginal application of 0.1 ml PEG1000 twice weekly for 18 months (Boyland *et al.* 1961). Information as to the purity of the PEG used is not available.

In other carcinogenicity studies, the results of which cannot be considered to be valid because the application periods were too short, no tumours were observed after oral administration of PEG400 to C3H mice for 30 weeks (Berenblum and Haran 1955), after intraperitoneal injection to CB rats for 26 weeks (Boyland *et al.* 1968) or after subcutaneous injection into SD rats for 20 weeks (Carter 1969).

6 Manifesto (MAK value, classification)

PEGs are hardly absorbed through the intact skin or from the gastrointestinal tract and are not toxic either after short-term or long-term administration.

PEGs are not irritating for skin and mucous membranes. Observations of persons with healthy skin have yielded no evidence of a sensitizing potential of PEGs.

PEG200 and PEG400 were not mutagenic in the *Salmonella* mutagenicity test. PEG400 was not mutagenic in CHO cells and did not induce DNA damage. For tetraethylene glycol (≈ PEG200) slightly but not dose-dependently increased incidences of SCE and chromosomal aberrations in CHO cells with and without S9 mix were reported. *In vivo* after administration of doses up to 5000 mg/kg body weight, a questionable clastogenic potential was detected in mice and no clastogenic potential in rats. According to results from one study which cannot be validated, tetraethylene glycol induced dominant lethal mutations in rats. There are no adequate carcinogenicity studies. The vaginal and cervical tumours which developed in mice after intravaginal application of PEG1000 cannot be assessed because information about the purity of the substance used is not available.

In a 13-week inhalation study of PEG200 and PEG400 the highest concentration tested, 1000 mg/m^3, was shown to be the NOEL (no observed effect level) for rats and mice. Therefore for both substances the MAK value is established at 1000 mg/m^3. Since the components of PEG300 are also found in PEG200 and PEG400 and since PEG600 consists to about 50 % of PEG400 (BASF 1995, Hoechst 1992b), the MAK value applies provisionally also for PEG300 and PEG600. However, it must be pointed out that such extremely high aerosol concentrations are a source of annoyance at the workplace (mist formation). Exposure should therefore be kept to a minimum for reasons of occupational

hygiene and safety at work. Since these substances have only very weak effects, they are classified in Category IV for the limitation of exposure peaks.

In a 2-week inhalation study with rats, PEG3350 caused reversible infiltration of macrophages into the alveoli even at the lowest concentration tested, 100 mg/m^3. Because the exposure period was too short, a MAK value for PEG3350 cannot be deduced from this study.

The remaining PEG cannot be evaluated because the data base is inadequate. They are included in Section IIb of the "List of MAK and BAT Values".

Orally administered PEG200 is readily absorbed and, when administered in the very high doses of 20 g/kg body weight, causes malformations in the progeny of mice but not of rats, hamsters or rabbits. PEG400 did not cause reproductive toxicity in two species after intravenous administration of doses up to 0.8 g/kg body weight. Even if one assumes complete absorption of the inhaled substance, the concentrations at which reproductive toxic effects have been observed are very much higher than the MAK value; therefore PEG200 and PEG400 are classified in Pregnancy risk group C. For the reasons given above, PEG300 and PEG600 are also classified in Pregnancy risk group C.

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