Polyethylene Glycol

Document History
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I. IDENTIFICATION

Chemical Name: Polyethylene glycol (mw >200)
Synonyms: a1pha-hydroxy-omega-h~droxy-poIv (oxy-1, 2-ethyanediyl); PEG; polyoxyethylene; PGE; Carbowax; Polyglycol E; Jeffox
CAS Number: 25322-68-3
Molecular Formula:
H (OCH_2CH_2) nOH, where n = > 4
Chemical Structure: H (OCH_2CH_2) $_n$OH
[A specific polyethylene glycol is usually identified by the numeral in its name, which relates to its average molecular weight (mw).]

II. CHEMICAL AND PHYSICAL PROPERTIES[1–5]

Physical State and Appearance: Clear viscous liquids or white solids. PEGs of average molecular weights below 600 are liquid; those with average molecular weights above 1000 are solid.
Odor Description and Threshold: No data available
Molecular Weight: Average molecular weights range from about 200 to greater than 6000. Chemical and physical properties vary with molecular weight.
Conversion Factors: No data available
Melting Point: PEG 400: 4°–8°C (39°–46°F); PEG 600: 20°–25°C (68°–77°F); PEGJ500: 44°–48°C (111°–118°F); PEG 4000: 54°–58°C (129°–136°F); PEG 6000: 53°–63°C (127°–145°F)
Boiling Point: No data available
Specific Gravity: 1.110–1.128 at 20°–25°C
Vapor Pressure: <0.01 mmHg (at 20°C) (for solid); 8.35E-04 mm Hg (at 25°C) (PEG 200); Vapor pressure decreases in relation to average molecular weight.
Saturated Vapor Concentration: No data available
Flammability Limits: No data available
Flash Point: 199°–238°C (390°–460°F) (C.O.C). [The flash point increases in relation to average molecular weight.]
Autoignition Temperature: 581°C (1078°F) (for solid)
Solubility in Water: Soluble in water and many organic solvents. Readily soluble in aromatic hydrocarbons; only slightly soluble in aliphatic hydrocarbons.
Reactivity and Incompatibilities: PEG does not hydrolyze or deteriorate on storage. Incompatible with strong oxidizing agents.

III. USES[1,2]

Polyethylene glycols are used as water-soluble lubricants for rubber molds, textile fibers, and metal-forming operations. They also are used in food and food packaging; in water paints, paper coatings, and polishes; in the ceramics industry; as a base in ointments and suppositories; and as plasticizers, solvents, binders, dispersing agents, and chemical intermediates.

IV. ANIMAL TOXICITY DATA

A. Acute Toxicity and Irritancy

1. Oral Toxicity

TABLE I

Species	Results	Reference
PEG (unspecified m.w.)		
Rat	LD_{50} = 32 g/kg	(4)
Guinea pig	LD_{50} = 22.5 g/kg	(4)
PEG 200		
Rat	LD_{50} = 28.9 g/kg	(4)
	LD_{50} = 28.25 g/kg (female)	(6)
	LD_{50} = 34 g/kg (male)	(6)
Mouse	LD_{50} = 38.3 g/kg	(4)
	LD_{50} = 33.9 g/kg	(6)
Rabbit	LD_{50} = 19.9 g/kg	(4)
	LD_{50} = 14.1 g/kg	(6)
Guinea pig	LD_{50} = 14.1 g/kg = 16.9 g/kg (female)	(6)
PEG 300		
Rat	LD_{50} = 27.5 g/kg	(4)
	LD_{50} = 29.2 g/kg (female)	(6)
	LD_{50} = 29.9 g/kg (male)	(6)
Rabbit	LD_{50} = 17,300 mg/kg	(4)
	LD_{50} = 21.1 g/kg (female)	(6)

TABLE I (cont.)

Species	Results	Reference
Mouse	LD_{50} = 31 g/kg	(6)
Guinea pig	LD_{50} = 19,600 mg/kg	(4)
	LD_{50} = 21.1 g/kg (male)	(5)
PEG 400		
Mouse	LD_{50} = 28.92 g/kg	(4)
	LD_{50} = 35.6 g/kg	(6)
Rat	LD_{50} = 32.5 g/kg	(4)
	LD_{50} = >10 mL/kg (male, no mortality)	(7)
Rabbit	LD_{50} = 26.8 g/kg	(4)
	LD_{50} = 223 g/kg (male)	(6)
Guinea pig	LD_{50} = 15.7 g/kg	(4)
	LD_{50} = 213 g/kg (female)	(6)
PEG 600		
Rat	LD_{50} = 38.1 g/kg	(4)
	LD_{50} = 30.5 g/kg (female)	(6)
	LD_{50} = 32.6 g/kg (male)	(6)
Mouse	LD_{50} = 47 g/kg	(4)
	LD_{50} = 35.6 g/kg	(6)
Guinea pig	LD_{50} = 28.3 g/kg (female)	(6)
Rabbit	LD_{50} = 18.9 g/kg (male)	(6)
PEG 1000		
Rat	LD_{50} = 32 g/kg	(4)
	LD_{50} = 44.7 g/kg (male)	(6)
Guinea pig	LD_{50} = 22.5 g/kg	(4)
	LD_{50} = 41 g/kg (female)	(6)
Rabbit	LD_{50} = >50 g/kg (female)	(6)
Mouse	LD_{50} = >50 g/kg	(6)
PEG 1500		
Rat	LD_{50} = 44.2 g/kg	(4)
Rabbit	LD_{50} = 28.9 g/kg	(4)
Guinea pig	LD_{50} = 28.9 g/kg	(4)
PEG 4000		
Rat	LD_{50} = 50 g/kg	(4)
	LD_{50} = >50 g/kg	(6)
Rabbit	LD_{50} = 76 g/kg	(4)
	LD_{50} = >50 g/kg (male)	(6)
Guinea pig	LD_{50} = 50.9 g/kg	(4)
	LD_{50} = 46.4 g/kg (female)	(6)
Mouse	LD_{50} = >50 g/kg	(6)
PEG 6000		
Rat	LD_{50} = 50 g/kg	(4)
Guinea pig	LD_{50} = 50 g/kg	(4)
PEG 8000		
Rat	LD_{50} = >50 g/kg	(6)
Rabbit	LD_{50} = >50 g/kg (male)	(6)
Guinea pig	LD_{50} = >50 g/kg (female)	(6)
Mouse	LD_{50} = >50 g/kg	(6)

2. Eye Irritation

PEGs cause only mild and transient ocular irritation.[8] Instillation of 0.5 mL of undiluted PEG 200, 300, 400, or 600 into the eyes of rabbit eyes resulted in no perceptible irritation or injury after 24 hours. PEG 400 has been used on human eyes for decontamination after accidents with phenol. A 1:1 solution of PEG 400 in water caused only a slight burning sensation and no injury.[9]

3. Skin Absorption

Results of reported skin toxicity studies have been equivocal. Some reports have indicated no toxicity from repeated topical application to intact skin, while another report documents acute mortality following topical exposure.[10–13]

In a study designed to assess the effect of daily topical application of a PEG-based cream to open wounds for 7 days, the dorsal hair of rabbits was shaved and two paravertebral skin excisions (2.5 cm x 15 cm) were prepared on each animal.[10] Animals were randomly selected to serve as controls or receive topical treatment with PEG. Animals receiving topical PEG had a specified amount of test cream applied to their wounds at each dressing change. Animals serving as controls underwent the same procedures but did not receive any topical cream. The dressings of all animals were changed every 12 hours with or without application of Furacin-soluble dressing or PEG-based cream, using ketamine to prevent any pain associated with the dressing change. One group of four experimental rabbits received 20g of PEG cream (consisting of PEG 300 [63%], PEG 1000 [5%], and

PEG 4000 [32%]), while another group of six control animals that was similarly prepared received no topical treatment. Three of the four PEG-treated animals died, but all six controls survived.

Analysis by gas chromatography-mass spectrometry (GC-MS) of the urine and serum of PEG-treated rabbits showed that PEGs and their metabolites (hydroxyglycolic acids and diglycolic acid homologs) were present, demonstrating that PEG reached systemic circulation and was metabolized. Since PEG metabolites (reactive aldehydes and acids) are toxic to kidney epithelial cells, the authors postulated that skin absorption and systemic metabolism of PEG led to kidney failure and death. However, the study did not include

gross or histopathology of the kidneys of the treated or control rabbits. PEG exposure via damaged or broken/cut skin can lead to serious systemic toxicity.

4. *Skin Irritation*

PEGs were not or very slightly irritating to the skin of rabbits and humans.[8] When tested in accordance with Organization for Economic Cooperation & Development (OECD) Test Guideline 404 (Acute Dermal Irritation/Corrosion), PEG 400 was nonirritating to rabbit skin exposed for 4 hours.[14] No irritation was observed in a 4-hour patch test with undiluted PEG 400, in which 0.2 mL was applied to the skin of the upper outer arms of 30 human volunteers.[15]

5. *Skin Sensitization*

One case of contact sensitization to PEG 300, 600, 1000, 4000, and 6000 was reported in a study of 200 patients exposed to PEG in bar soap.[16] In another study with lower molecular weight PEGs varying from 200 to 700, four patients showed allergic reactions to liquid PEGs in topically applied medications. Two of the four had immediate urticarial reactions to PEG 400, while two others had delayed eczematous reactions to PEG 200 and PEG 300. Cross reactions occurred between PEG 200, 300, and 400, but not between these PEGs and higher mw solid PEGs from 1000 to 6000.[17] PEGs 200–400 may cause allergic contact urticaria and eczema, but the higher mw PEGs are not sensitizers.[18]

CTFA reported that PEG 400 did not induce allergic contact dermatitis in a number of repeat insult patch tests (HRIPT) in humans.[19] HRIPT with PEGs ranging in molecular weight from 200 to 8000 had a very low incidence of responses (0–0.5%) observed, suggesting that PEGs are not human skin sensitizers.[8] In animal tests, pure PEGs were also practically without sensitizing properties(20), indicating that impurities or oxidation products may have been the culprit for the observed effects in earlier studies on humans with certain PEGs.[8]

6. *Inhalation Toxicity*

No data available.

7. *Other Toxicity*

TABLE II

Species	Results	Reference
PEG (unspecified m.w.)		
Rat	LD_{50} = 15.6 (i.p.)	(4)
Mouse	LD_{50} = 2 g/kg (i.p.)	(4)
PEG 200		
Mouse	LD_{50} = 7.5 g/kg (i.p.)	(4)
Mouse	LD_{50} = 11.8 g/kg (i.p.)	(6)
PEG 300		
Rat	LD_{50} = 17 g/kg (i.p.)	(4)
Mouse	LD_{50} = 10.4 g/kg (i.p.)	(6)
PEG 400		
Mouse	LD_{50} = 9.95 g/kg (i.p.)	(4)
	LD_{50} = 12.9 g/kg (i.p.)	(6)
	LD_{50} = 5 g/kg (iv.)	(4)
Rat	LD_{50} = 9.7 g/kg (i.p.)	(4)
	LD_{50} = 7.3 g/kg (iv.)	(4)
PEG 600		
Mouse	LD_{50} = 10.2 g/kg (i.p.)	(6)
PEG 1000		
Rat	LD_{50} = 15.57 g/kg (i.p.)	(4)
Mouse	LD_{50} = 2 g/kg (i.p.)	(4)
	LD_{50} = 3.1 g/kg (i.p.)	(6)
PEG 1500		
Rat	LD_{50} = 17.7 g/kg (i.p.)	(4)
Rabbit	LD_{50} = 8 g/kg (iv.)	(4)
PEG 4000		
Rat	LD_{50} = 11.5 g/kg (i.p.)	(4)
Mouse	LD_{50} = 18 g/kg (s.c.)	(4)
	LD_{50} = 16 g/kg (iv.)	(4)
	LD_{50} = 107 g/kg (i.p.)	(6)
PEG 6000		
Rat	LD_{50} = 6.8 g/kg (i.p.)	(4)

B. Subacute Toxicity

In a 2-week inhalation study, groups of were exposed (whole body) to PEG 3350 mean aerosol concentrations of 0 (control), 109, 567, or 1008 mg/m^3 6 hr/day 5 days/week for a total of 9 exposures during an 11-day period.[21] An extra 10 rats/sex were included in the control and high exposure groups; these were used to evaluate recovery during a 2-week period following the final exposure. The mass median particle diameters for the 109, 567, and 1008 mg/m^3 groups were 6.1, 5, and 3.8 microns, respectively.

All rats were housed individually. Toxicologically-significant changes in the absolute and relative

weights of the lungs of both sexes were noted at the 567 mg/m^3 and 1008 mg/m^3 exposure concentrations. The absolute lung weights for the high exposure group males and females were 16% and 20% higher than the controls, respectively. Absolute and relative lung weights remained elevated compared with controls following a 2-week recovery period. Histologically, exposure-related lesions were observed in the lung only at the end of the exposure period. These lesions were mild, and consisted of alveoli containing macrophages (alveolar histiocytosis) with foamy vacuolated cytoplasm. There were no exposure-related clinical signs, ophthalmologic changes, or mortalities noted during the study. The authors of the study set the no observable effect level (NOEL) at between 109 mg/m^3 and 567 mg/m^3.

The effects of oral, intravenous or intraperitoneal administration of PEG 400 on gastrointestinal, renal, and liver function in Hannover Wistar rats was studied.[22] Ten rats per sex per dose group were dosed with PEG 400 either orally (10 mL/kg), intravenously (2 mL/kg), or intraperitoneally (10 mL/kg). Urine was collected from half of the animals in each group (5/sex) and blood samples were taken from the other half. Starting at an oral dose of 2000 mg/kg, PEG 400 reduced gastric emptying severely. While no effect on intestinal transit was detected, the contents changed to a watery consistency with liquid accumulation, which occurred at oral doses ≥1000 mg/kg (≥10%). In serum, PEG 400 slightly and transiently changed metabolic parameters including glucose, lactate, triglycerides, free fatty acids, or creatinine as well as electrolytes (Na+, Cl−, Mg2+) and osmolality.

C. Subchronic Toxicity

In a 90-day oral (dietary) toxicity study, groups of five Sherman rats/sex/dose were fed diets containing 2%, 4%, 8%, 16%, or 24% PEG 200, 300, 400, 600, 1000, 1500, 1540, 4000, or 6000.[23] A control group received a regular diet without PEG. The lowest level at which a statistically significant effect was observed was 8%; rats exposed to this dietary concentration of PEG 300, 1500, 1540, and 4000 had a significant decrease in weight gain as compared with the control group. Effects observed at the 16% and 24% dietary levels included decreased weight gain, increased kidney and liver weights, and decreased food consumption, as compared with the control group. The authors indicated that the subchronic oral toxicity of PEGs with mean molecular weights of 200–4000 was essentially the same for all. The NOEL was a 4% dietary concentration (approx. 2 g/kg/day).

In a subchronic (13-week) toxicity study with Fischer 344 rats, diets containing 0, 0.1, 0.5, 1.5, or 3% Polyox N-10 (PEG with an average molecular weight of 100,000 daltons) were fed to groups of 20 rats/sex/dose.[24] Slight increases in food consumption, body weight, and body weight gain and a dose-related increase in liver weight were observed, but these were not associated with any histopathology, and morphometric analysis showed no alteration in the number or size of the hepatocytes. Because of the lack of correlative pathology findings, the liver weight increase was not considered to be deleterious, but rather a secondary response to increased food consumption.

Groups of Fischer-344 rats (10/sexldose) were administered PEG 400 by gavage at doses of 1.1, 2.8, or 5.6 g/kg for 5 days/week for 13 weeks.[25] Control animals received 5 mL/kg water by gavage. An additional 10 rats/sex/dose were added to the control and 5.6 g/kg groups and were kept for 6 weeks after the 13-week dosing period. The primary objective of the study was to examine the potential renal toxicity of PEG 400. Six rats died during the study; however, all of the deaths were attributed to errors in dosing procedure. Mean body weights of the high-dose rats of both sexes were slightly decreased throughout the dosing and recovery phases of the study. There were no treatment-related effects on hematology or clinical chemistry measurements. Urine osmolality and specific gravity were increased in a dose-related manner in male and female rats. Urine NAG activity was significantly elevated in male rats only. Urine pH was significantly decreased at all doses in males, and at the mid- and high-dose levels in female rats. Urinary protein and bilirubin were increased in male rats at all treatments levels, and the incidence of red and white blood cells in the urine were also elevated in the high-dose males.

Following a 6-week recovery period, no biologically significant changes in urinalysis, clinical chemistry or hematology were seen in high-dose rats of either sex. Relative kidney weights of male rats were increased at all PEG 400 dose levels at termination of dosing; however, following a 6-week recovery period, no differences were noted in this parameter. No microscopic changes were observed in the kidneys or urinary bladder. The authors considered the urinalysis data indicative of reversible renal toxicity at 2.8 g/kg (male) and 5.6 g/kg (both sexes). The overall NOEL for the study was 1.1 g/kg.

The colorectal cancer-preventive properties of PEG 8000 were studied in 30 female F344 rats administered one i.p. injection of azoxymethane

(20 mg/kg), and 7 days later randomly allocated to one of two groups: one group (20 rats) fed standard diet and the other (10 rats) fed a diet supplemented with 5% PEG 8000 (3000 mg/kg/day) for 15 weeks.[26] Dietary exposure to PEG 8000 markedly decreased the total number of aberrant crypt foci (ACF) per rat (average of six/rat in the PEG 8000 group and 107/rat in the control group), and the size of ACF in rats fed PEG 8000 diets were 100-fold smaller than in controls. The authors concluded that PEG 8000 has chemopreventive activity and should be should be tested clinically.

In a subchronic inhalation study, groups of Fischer-344 rats(36/sex/level) and B6C3F1 mice (15/sex/level) were exposed (whole body) to aerosol concentrations of 0, 100, or 1000 mg/m^3 PEG 200 for 6 hours/day, 5 days/week, for 13 weeks.[23] There were no lesions or biologically-significant alterations in blood chemistry, hematology, or pulmonary resistance at either exposure concentration in mice or rats.

D. Chronic Toxicity/Carcinogenicity

In a 1-year oral (dietary) toxicity study, groups of four dogs were fed diets wetted with PEG 400, PEG 1540, or PEG 4000 — equivalent to 2% PEG in each diet (approx.600 mg/kg/day).[23] Control groups were fed the same diets wetted with water. After 1 year, no adverse effects were observed in any of the PEG-exposed groups.

In a 2-year oral (dietary) toxicity study, groups of rats were fed diets containing PEG 400, PEG 1540, or PEG 4000.[23] Groups of 35 Sherman rats/sex/dose were fed diets containing 0%, 0.02%, 0.08%, 0.4%, 2%, 4%, or 8% PEG 1540; groups of 20 Wistar rats/sex/dose were fed diets containing 0%, 1%, 2%, 4%, or 8% PEG 400; and groups of 20 Wistar rats/sex/dose were fed diets containing 0%, 0.5%, 1%, 2%, 4%, or 8% PEG 4000. Only minor toxicity was observed, consisting of cloudy swelling of the liver at 8% PEG 1540, decreased weight gain in males at 4% and 8% PEG 400, and decreased weight gain at 8% PEG 4000. The lowest NOEL was for PEG 400, a dietary concentration of 2% (approximately 1 g/kg/day).

In a 2-year oral (drinking water) toxicity study, nine groups of eight Wistar rats/sex/dose were exposed to PEG 1500 at concentrations of 2%, 0.4%, 0.08%, or 0.02% ,and to PEG 4000 at concentrations of 0.08%, 0.02%, 0.005%, or 0.00l25%.[28] A control group was given plain water. The mean dosage levels calculated from water consumption were 1690, 270, 59, and 15 mg/kg/day of PEG 1500, and 62, 17, 3.6, and 0.85 mg/kg/day of PEG 4000. The only significant effects noted in the study were retarded growth at the two highest doses of PEG 1500 and at the highest dose of PEG 4000. Although 40% of the rats older than 1 year had neoplastic processes in the lungs (lymphosarcoma), the incidence was not correlated with dosage and was not considered by the authors to be related to test material administration. The NOELs for PEG 1500 and PEG 4000 in this study were 59 mg/kg/day and 17 mg/kg/day, respectively.

In a chronic (104-week) toxicity study with Fischer 344 rats, diets containing 0, 0.1, 0.5, or 2% Polyox N-10 (PEG with an average molecular weight of 100,000 daltons) were fed to groups of 100 rats/sex/dose.[24] Interim sacrifices were performed on 10 rats/sex/group after 12 and 18 months of dietary exposure. No treatment-related effects on clinical signs, body weights, organ weights, clinical pathology, urinalysis, gross pathology or histology were observed. In conclusion, Polyox N-10 given orally is not absorbed from the gastrointestinal tract, and does not produce chronic toxicity or oncogenic effects.

E. Reproductive/Developmental Toxicity

In a teratology study with PEG 400[29], timed pregnant Sprague-Dawley rats and New Zealand White rabbits were randomly assigned to dose groups (10/group). The animals were dosed between Gestational Days 6–17 (rats) and 6–18 (rabbits) by oral gavage at dose volumes of 1 mL/kg (rats) and 2 mL/kg (rabbits) with PEG 400 or 0.5% methylcellulose (vehicle control). Body weights and food consumption were recorded daily. Cesarean sections were performed on Gestational Days 21 and 28 for the rats and rabbits, respectively. Reproductive parameters, numbers of corpora lutea, implantation sites, and resorptions were recorded and the fetuses were examined for external, visceral and skeletal malformations. In the rabbits, loose stool was noted in the PEG 400 group. There were no treatment-related mortalities. Body weights, food consumption, and reproductive parameters were comparable between the groups. Some differences were noted in the incidences of minor anomalies between groups but none were biologically significant.

Pregnant CD-1 mice were gavaged on Gestation Days 6–17 with 0.5 or 0.7 mL/animal/day (equal to 564 or 789 mg/animal/day, or 22.5 or 31.6 g/kg/day) of undiluted PEG 200.[30] No signs of maternal toxicity were noted, but one dam at the highest dose died on the day of sacrifice (it was unclear if this death was related to treatment).

All dams were sacrificed on Gestation Day 18 and all fetuses were examined. Teratogenic effects, consisting of malformations of the skull, paws, and thoracic skeleton were observed at the high dose and, to a lesser extent, at the low dose. Fetal loss was increased and means fetal bodyweight was decreased in the treated groups as compared with the control group. In this study, PEG 200 was teratogenic and fetotoxic at doses that were non-toxic to the dams.

In the same study, Sprague-Dawley rats were gavaged on Gestation Days 6–14 or 11–16 with 1.5–5 mL/animal/day (equal to 1.69–5.64 g/animal/day) of undiluted PEG 200.[30] Some maternal deaths occurred at all doses tested. No embryo-fetal or developmental toxicity was reported.

In another rat teratology study, rats were dosed orally with 1 or 10 g/kg/day PEG 200 from Gestation Day 6–15.[31] No teratogenic effects were observed. However, fetotoxicity and maternal toxicity were not described.

PEG 200 was tested on cultured 10-day-old rat embryos at concentrations ranging from O.25%–2% (v/v), with or without S-9 mix from the mouse, rat, hamster, rabbit, or man as a metabolic activation system.[32] PEG 200 exposure at 0.25% and 0.5% with mouse S-9 mix produced abnormalities in brain development (hypoplasia of the prosencephalon, fore- and mid-brain opened). At 0.5% or 0.75% with S-9 mix from the rat, hamster, rabbit, or human, PEG 200 was embryo-lethal. At 1% with any S-9 mix, PEG 200 also was embryo-lethal.

3-generation fertility study was conducted with a group of 16 female rats fed diets containing 4% PEG 1540.[33] The criteria measured in each of three generations continuously exposed to PEG 1540 were mean numbers of pups/litter; live pups/litter; dead pups/litter; pups weaned/litter; and pup weight at weaning. None of these parameters differed significantly from the control group.

F. Genotoxicity

When tested in the Ames Salmonella assay, PEG 200 and PEG 400 were negative.[34,35] PEG (m.w. un-specified) was also negative in an *in vitro* assay in *Escherichia coli*, with or without metabolic activation.[36] PEG 6000 was positive in the mouse lymphoma L5178Y assay without metabolic activation at a concentration of 150 g/L. A small increase in the mutation frequency (2.3-fold) was observed at a cytotoxic concentration (about 20 mM), exceeding current recommended practices. This test was only performed in the absence of a metabolic activation system.[37]

The clastogenicity of PEG 200 and PEG 400 was evaluated in cultured Chinese hamster epithelial cells (CHEL) and Chinese hamster ovary (CHO) cells, with or without metabolic activation.[38] PEG 200 induced statistically-significant and dose-related increases in chromosomal aberrations in CHEL cells. In contrast, PEG 400 did not show any clastogenic activity in CHEL cells up to the highest test concentration (7 mM). PEG 400 was also assayed with CHO cells in the presence or absence of S9 and significant increases in aberration frequency were only observed with metabolic activation and at concentrations exceeding the upper limit for cytotoxic effects (10 mM).

PEG 400 was tested for mutagenic activity with the CHO mutation test.[19] CHO cells were incubated with PEG 400 at concentrations ranging from 0.01%–0.0625% (by volume) for 5 hours both with and without S9 metabolic activation. Cell survival was determined after 24 hours, and the mutant fraction was determined after 7 days. Dimethylnitrosamine (DMN) and ethylmethane sulfonate (EMS) were used as positive controls both with and without metabolic activation. These agents had highly statistically significant mutation frequencies that were within the normally expected range of values observed in historical controls. The mutation frequencies for the solvent, dimethylsulfoxide (DMSO) and negative controls both with and without metabolic activation were in an acceptable and low range based upon historical control values. PEG 400 was relatively non-toxic at all concentrations tested, and there was no dose-related increase in the frequency of mutants, either with or without metabolic activation.

A sister-chromatid exchange (SCE) test was also conducted with PEG 400.[19] CHO cells were incubated with PEG 400 at concentrations ranging from 1.0% to 0.0625% (by volume) for 5 hours without metabolic activation, or for 2 hours using S9 metabolic activation. EMS was used as a positive control in this study. In the absence of metabolic activation, no statistically significant increases occurred in the SCE frequency at any of the tested PEG 400 concentrations. In the presence of a metabolic activation system, the only SCE value that was statistically significant from the solvent control group occurred at the 0.5% dose level. However, there was no indication of a correlation between PEG 400 concentration and SCE induction.

PEG 400 was also tested in the unscheduled DNA synthesis (UDS) assay.[19] Rat hepatocytes were treated with PEG 400 prepared in DMSO at concentrations ranging from 100×10−3% to

0.1×10−3%(by volume) for 2 hours in a culture medium containing [3H]thymidine and hydroxyurea. UDS activity was determined by analyzing radioactive incorporation into isolated hepatocyte nuclei or in precipitated DNA. The positive controls used were DMN and 4-nitroquinoline oxide. At concentrations of 3 × 10−3% and 100 × 10−3%, PEG 400 induced elevated levels of UDS measured in the nuclei and DNA of the hepatocytes. The only statistically significant increase in radioactive thymidine incorporation was measured in the DNA of the cells treated with the high dose. However, for concentrations between 3×10−3%and 100×10−3%, there was no significant elevation of UDS levels measured in either the nuclei or DNA and the authors concluded that these results did not indicate a dose-response relationship

PEG 200 was evaluated in an *in vivo* bone marrow chromosome aberration assay used to evaluate its clastogenic potential.[19] Sprague-Dawley rats were given a single 10 mL/kg oral dose of 0, 1250, 2500, or 5000 mg/kg PEG 200 (n = 5/sex/group) diluted in water. The dose levels were selected based on a preliminary test in which PEG 200 was nontoxic up to 5000 mg/kg. A positive-control group received an intraperitoneal (i.p.) injection of 30 mg/kg cyclophosphamide to demonstrate the responsiveness of the animals to a recognized clastogenic agent. Animals were killed at 12, 24, or 48 hours after dosing. Bone marrow tissue from the femur of each rat was isolated and prepared for staining of the chromosomes of mitotic cells on slides. Cells were evaluated for chromosome number, specific type of chromosome- or chromatid-type aberrations, and further classified for deletions and exchanges. None of the three dose levels of PEG 200 tested produced statistically significant or dose-related increases in relative numbers of chromosome aberrations compared to negative-control values. Simple chromatid breaks and fragments were observed, but the frequencies were within the range of spontaneous incidence for the test system. The positive control (cyclophosphamide) group exhibited significant increases in the numbers and types of chromosomal damage in both male and female rats.

An ambiguous result was obtained in a micronucleus test with Swiss–Webster mice after single intraperitoneal injection of PEG 200. 30 hours after administration (but not at 24 or 72 hours), a slight increase of micronuclei was observed in high dose males (5000 mg/kg bw). However, when the number of scored erythrocytes was doubled, an increase in micronuclei was also observed in the low-dose group. According to the authors the effect may have been due to testing artifacts.[8]

A dominant lethal assay was also performed with PEG 200.[19] Male Fischer 344 rats (20 per group) were exposed to 0, 5000, 25,000, or 50,000 ppm PEG-4 in drinking water for 5 consecutive days. The respective daily consumption levels of the three doses of PEG 200 were 425 ± 45, 2441 ± 328, and 5699 ± 1341 mg/kg. At the end of the 5-day dosing period, the PEG 200 drinking water was replaced with regular water. Beginning 24 hours after the last PEG 200 exposure, the males were mated with two naive (nontreated) virgin females. When those females showed evidence of copulation, they were replaced with two more females, until each male had mated with 10 females or until 10 weeks had passed. At the end of the 10th week after PEG 200 exposure, males were killed for necropsy. The females were observed and killed on Gestation Day 15, at which time corpora lutea and implantation sites (resorptions and live embryos) were counted. Reproductive parameters, including number of fertile males and number of gravid females with viable implants, were not affected by PEG 200 treatment. There were no significant preimplantation losses or dominant lethal effects observed. A concurrent positive control group of males receiving an i.p. injection of 0.5 mg/kg triethylenemelamine (TEM) were bred with naïve females in a similar manner. The TEM group showed increased pre- and postimplantation loss, increased early resorptions and significant dominant lethal effects. In summary, almost all of the *in vitro* and all of the *in vivo* genotoxicity assays with PEG 200 or 400 were negative. The weight of evidence suggests that PEG 200 and 400 are not genotoxic.

G. Metabolism /Pharmacokinetics

PEGs seem to be slow-acting parasympathomimetic-like compounds. When given intravenously, they tend to produce an increase in blood clotting, and if given rapidly they may cause clumping of cells, leading to death from embolism.[39] A recent study in rabbits demonstrated that following application of PEG to broken skin the parent material and metabolites (hydroxyglycolic acids and diglycolic acid homologs) were present in both the urine and serum of the exposed animals. The authors attributed kidney failure in the exposed rabbits to the presence of the PEG metabolites.[10]

Pharmacokinetic and mass balance evaluations were conducted in parallel with a chronic oral (dietary) toxicity study with Polyox N-10 (PEG with average mw of 100,000) in F344 rats.[24] This study showed essentially complete recoveries (99% in males, 104% in females) from the excreta,

with nearly all the radiolabel being eliminated in the feces (98% in males, 101% in females) in rats given an oral dose of ^{14}C-labelled Polyox N-10. Recoveries from the urine, expired air, blood, and other tissues were negligible (<1%).

Higher molecular weight PEGs (4000–6000) were not absorbed from the rat gut during a 5-hour period, while lower mw PEGs (1000–1540) were absorbed to a slight extent. Approximately 24% of PEG 400, 3.2% of PEG 900 and 1.7% of PEG 4000 was bioavailable in the rat(.40) Rats and humans appear to absorb similar percentages of the administered dose of PEGs, while PEGs are more bioavailable in the dog than in either rats or humans. When intravenous doses of 1 g PEG 6000 or PEG 1000 were injected in human subjects, 96% and 85% of the administered dose (respectively) was excreted in the urine within 12 hours. When 10 g oral doses of PEG 6000 and PEG 1000 were administered to five human subjects, no PEG 6000 and only 8% of the PEG 1000 was detected in the urine within 24 hours. Following i.v. administration of a 1 g dose of PEG 400 to human subjects, 77% was recovered in the urine in 12 hours. Oral administration of 5–10 g doses of PEG 400 resulted in 40%–50% recovery of the administered dose in the urine.[39]

V. HUMAN USE AND EXPERIENCE

Most industrial exposures to PEGs occur via topical contact. Inhalation exposures would be expected only when mists are formed by spraying, violent agitation, or when the material is heated.

Anaphylaxis related to PEG has been reported in three case reports: the first related to ingestion of a multiple vitamin tablet containing PEG 8000 and PEG 20000; the second involving ingestion of a throat lozenge containing PEG 8000; the third involving ingestion of a polyethylene glycol electrolyte lavage solution.[41–43] In the first case, PEG solutions at concentrations of 1 mg/L elicited positive results in skin prick tests in a patient who had suffered 5 previous unexplained episodes of anaphylaxis for a period of 5 years, the most recent culminating in hypotension, unconsciousness, and a grand mal seizure.[41] In the second case, the patient was prick-tested against all of the ingredients in the throat lozenge and responded only with PEG 8000 (massive local reaction with wheal formation over entire body). However, no specific antibodies against PEG 8000 were demonstrated against either PEG 8000 or other PEGs. The pathologic mechanism of the anaphylaxis in this patient was unresolved. In the third case, a 70-year old male patient developed an anaphylactic reaction following oral ingestion of a polyethylene glycol electrolyte lavage solution (Golyte1y).[43]

In an *in vivo* human study, the influence of skin damage by sodium lauryl sulphate (SLS) on percutaneous penetration of polyethylene glycols (PEGs) of different molecular weights was studied.[44] Percutaneous penetration of PEGs was determined using tape stripping of the stratum corneum. The forearm skin of volunteers was pretreated with 5% w/w SLS for 4 hours, and 24 hours later patches with PEGs were applied for 6 hours. The penetration parameters were deduced by data regression to Fick's law for unsteady-state diffusion. The trans-epidermal water loss increased after SLS treatment from 6.3 ± 2.1 to 17.9 ± 8.7 g/m^2/hour. The diffusion coefficient for all PEGs was increased in the SLS-damaged skin. The increase was smaller for higher molecular weight PEGs. In addition, the partition coefficient of PEGs between stratum corneum and water was larger in the SLS-compromised skin, and showed a tendency to increase with molecular weight. The permeability coefficient decreased gradually with increasing PEG molecular weight in both control and SLS-compromised skin. SLS caused a threefold increase in the permeability coefficient for all molecular weights. The results of this study show the deleterious effect of SLS on the skin barrier for hydrophilic PEGs.

There are no reports of human injuries or adverse effects from industrial use of PEGs.[6,39,45,46]

VI. RATIONALE

Toxicity is unlikely following oral exposures to small amounts of PEG, or as a result of contact with undamaged skin; however, repeated topical contact with cut, broken, or damaged skin has been shown to produce systemic toxicity and death in laboratory animals.

Human repeat insult patch tests with PEGs ranging in molecular weight from 200 to 8000 had a very low incidence of responses (0–0.5%) observed, suggesting that PEGs are not human skin sensitizers. In animal tests, pure PEGs were also practically without sensitizing properties, indicating that impurities or oxidation products may have been the culprit for the observed effects in earlier studies. The available data do not support a DSENS notation. Two cases of anaphylaxis have been reported for PEG 8000.

In teratology studies in the rat and rabbit, PEG 400 produced no adverse effects on reproductive performance or fetal development. PEG 200 produced no adverse developmental or reproductive effects in the rat, however developmental and fetotoxic effects at non-maternally toxic doses were observed in the mouse in one study. No adverse effects on reproduction or fetal/pup development was reported in a three-generation reproduction study in which rats were fed diets containing 4% PEG 1540. The overall weight of evidence suggests that occupational exposure to PEGs is unlikely to present a developmental or reproductive hazard.

Almost all of the *in vitro* and all of the *in vivo* genotoxicity assays with PEG 200 or 400 were negative. The weight of evidence suggests that low molecular weight PEGs are not genotoxic.

PEGs have been studied in subchronic and chronic toxicity studies via the oral, dermal, and inhalation routes. The lowest oral dose at which an effect attributable to treatment (retarded growth) was observed was 62 mg/kg/day (0.08%) PEG 4000 in a 2-year chronic oral (drinking water) study in the rat. The lowest aerosol concentration producing toxicologically significant effects was 567 mg/m^3 PEG 3350 in a 2-week inhalation study in the rat. Exposure of rats and mice to aerosol concentrations of up to 1000 mg/m^3 PEG 200 for 13 weeks resulted in no lesions or biologically significant alterations in blood chemistry, hematology, or pulmonary resistance.[27] The available data on the subacute/subchronic inhalation toxicity of PEGs suggest that lower m.w. PEGs are less toxic via the inhalation route than the higher mw PEGs.

The subacute inhalation study with PEG 3350[21] is considered pivotal for the assessment of the WEEL guide for high mw PEGs (>400) because exposure was via the inhalation route and it was conducted and reported in accordance with current testing standards. The NOEL established in this study was 109–567 mg/rn^3. An OEL of 10 mg/m^3 is considered appropriate for high mw PEGs because the study was of short duration, involved daily exposures of 6 hours, and produced effects on absolute and relative lung weights that remained significant following a 2-week recovery period.

The subchronic (13-week) inhalation study with PEG 200[27] is considered pivotal for the assessment of the OEL for low mw PEGs (<400). The absence of any significant adverse effect at exposure concentra-tions up to 1000 mg/m^3 for 13 weeks suggests that an OEL of 10 mg/m^3 is appropriate for low mw PEGs.

VII. RECOMMENDED OEL

8-hr time-weighted average: 10 mg/m^3, as a particulate

VIII. REFERENCES

1 **Budavari, S. (ed):** "Polyethylene Glycol," in *The Merck Index*, 11th ed. Rahway, NJ: Merck & Co., Inc., 1989. pp. 1204.

2. **Hazardous Substances Database (HSDB):** *Polyethylene Glycol* (Record Number 5159). Bethesda, MD: National Library of Medicine, 1993.

3. **Lenga, R.E. and K.L. Votoupal:** *The Sigma-Aldrich Library of Regulatory and Safety Data*, Vol.2. St. Louis, MO: Sigma-Aldrich Corporation, 1993. pp. 3155–3158.

4. **Lewis, RJ., Sr. (ed.):** *Sax's Dangerous Properties of Industrial Materials*, 8th Ed., Volume Ill. New York: VanNostrand Reinhold, 1992. pp. 2837–2839.

5. **Griffin, K.A.:** *Vapor Pressure of Polyethylene Glycol E-200 Dow Chemical Company R&D Report* [Unpublished Data]. Midland, MI: Dow Chemical Company, 1993.

6. **Dow Chemical Company:** *Polyethylene Glycols Handbook.* Midland, MI: Dow Chemical Company, 1978.

7. **McMullin, T. and R. Golden:** *Telone II: Acute Oral Toxicity Study in CRL: CD (SD) Rats Following a Split-Dose Regime* [Unpublished Data]. Midland, MI: Dow AgroSciences LLC, 2006.

8. **Fruijtier-Polloth, C.:** Safety Assessment on Polyethylene Glycols (PEGs) and their Derivatives as Used in Cosmetic Products. *Tox. 214*:1–38 (2005).

9. **Grant, W.M. and J.S. Schuman:** *Toxicology of the Eye*, 4th Ed. Springfield, IL: Charles C. Thomas, 1993. pp. 1183–1184.

10. **Herold, D.A., G.T. Rodeheaver, W.T. Bellamy, L.A. Fitton, D.E. Bruns, and R.F. Edlich:** Toxicity of Topical Polyethylene Glycol. *Toxicol. Appl. Pharmacol. 65*:329–335 (1982).

11. **Luduena, F.P., J.K. Fellows, G.L. Laqueur, and RI. Driver:** Toxicity of Polyethylene Glycols by Repeated Epidermal Application. *J. Ind. Hyg. Toxicol. 29*:390–392 (1947).

12. **Smyth, H.F., Jr., C.P. Carpenter, C.B. Shaffer, J. Seaton, and L. Fischer:** Some Pharmacological Properties of Polyethylene Glycols of High Molecular Weight ("Carbowax" Compounds). *J. Ind. Hyg. Toxicol. 24*:281–284 (1942).

13. **Tusing, T.W., J.R. Elsea, and A.B. Sauveur:** The Chronic Dermal Toxicity of a Series of Polyethylene Glycols. *Am. Pharm. Assoc. 43*:489–490 (1954).

14. **Jacobs, G.A.:** Skin Irritation Tests on Various Mixtures of Tetradecanol and Polyethylene Glycol (Part B—Acute Toxicity Data). *J. Am. Coll. Toxicol. 1(3)*:189–190 (1992).

15. **Basketter, D., M. Chamberlain, H. Griffiths, M. Rowson, E. Whittle, and M. York:** The Classification of Skin Irritants by Human Patch Test. *Food Cosm. Tox. 35*:845–852 (1997).

16. **Maibach, H.I.:** Polyethylene Glycol: Allergic Contact Dermatitis Potential. *Contact Derm. (4)*:247 (1975).

17. **Fisher, A.A.:** Immediate and Delayed Allergic Contact Reactions to Polyethylene Glycol. *Contact Derm. 4*:135–138 (1978).

18. **Fisher, A.A.:** Polyethylene Glycol. *Contact Derm. 3*:253–254 (1986).

19. **Anonymous:** Final Report on the Safety Assessment of Triethylene Glycol and PEG-4. *Int. J. Tox. 25(2)*:121–138 (2006).

20. **Leung, H.W. and R. Ballantyne:** Skin Sensitization Potential of Polyethylene Glycols Evaluated in the Guinea Pig Maximization Test and the Human Repeat Insult Patch Test. *J. Toxicol. Cut. Ocular Toxicol. 17*:81–88 (1998).
21 **Klonne, D.R., D.E. Dodd, P.E. Losco, C.M. Troup, and T.R. Tyler:** Two-Week Aerosol Inhalation Study on Polyethylene Glycol (PEG) 3350 in F-344 Rats. *Drug Chem. Tox. 12(1)*:39–48 (1989).
22. **Pestel, S., H-J. Martin, G-M. Maier and B. Guth:** Effect of Commonly Used Vehicles on Gastrointestinal, Renal and Liver Function in Rats. *J. Pharm. Tox. Methods 54*:200–214 (2006).
23. **Smyth, H.F., Jr., C.P. Carpenter, and C.S. Weil:** The Chronic Oral Toxicity of the Polyethylene Glycols. *J. Am. Pharm. Assoc. 44(1)*:27–30 (1955).
24. **Leung, H.W., B. Ballantyne, S. Hermansky, and S. Frantz:** Peroral Subchronic, Chronic Toxicity, and Pharmacokinetic Studies of a 100-kilodalton Polymer of Ethylene Oxide (Polyox N-10) in the Fischer 344 rat. *Int. J. Toxicol. 19*:305–312 (2000).
25. **Hermansky, S.J., D.A. Neptun, K...A. Loughran, and H.W. Leung:** Effects of Polyethylene Glycol 400 (PEG 400) Following 13 Weeks of Gavage Treatment in Fischer-344 Rats. *Fd. Chem. Toxic. 33 (2)*:139–149 (1995).
26. **Corpet, D. and G. Parnaud:** Polyethylene-Glycol, a Potent Suppressor of Azoxymethane-Induced Colonic Aberrant Crypt Foci in Rats. *Carcino. 20(5)*:915–918 (1999).
27. **Crook, J.W., P.D. Hott, A.E. Cooper, E.G. Cummings, S.A. Thomson, et al.:** *The Subchronic Inhalation Toxicity of Polyethylene Glycol 200 in the Rat and Mouse* (Report No. ARCSL-TR-8 1051). Aberdeen Proving Ground, MD: U.S. Department of Defense. 1981.
28. **Smyth, H.F., Jr., C.P. Carpenter, and C. Boyd Shaffer:** The Toxicity of High Molecular Weight Polyethylene Glycols; Chronic Oral and Parenteral Administration. *J. Am. Pharm. Assoc. 36*:157–160 (1947).
29. **Gupta, U., J. Beaulieu, J. Chapin Hopper, A. Hagler, and P. Hills-Perry:** Teratogenic Evaluation of Alternative Vehicles: PEG-400, Cremophor, Carboxy-methylcellulose; Comparisons with Methylcellulose. *Teratol. 53*:111 (1996). (poster abstract).
30. **Vannier, B., R. Bremaud, M. Benicourt, and P. Julien:** Teratogenic Effects of Polyethylene Glycol 200 in the Mouse but Not in the Rat. *Teratol. 40(3)*:302A (1989).
31. **Starke, W.C., and R.J. Pellerin:** *Oral Toxicity and Teratogenicity of PEG200 and N- Butyl Mercaptan in Rats* (Report No. ARCSL-TR-8 1029). Aberdeen Proving Ground, MD: U.S. Department of Defense, 1981. [Abstract.]
32. **Spezia, F., P. Julien, R. Fournex and B. Vannier:** In Vitro Dysmorphogenic Effects of PEG 200 on Rat Whole-Embryo Cultures in Relation to the Species Origin of the Metabolic Activating System Used. *Teratol. 46(3)*:28A (1992).
33. **Anonymous:** *Three Generation Fertility Study of 4% "Carbowax" 1540* (Special Report Rats Fed 15—23). Pittsburgh: Mellon Institute of Industrial Research, 1952.
34. **Mortelmans, K., S. Haworth, T. Lawlor, W. Speck, B. Trainer and E. Zeiger:** Salmonella Mutagenicity Tests: II. Results from the Testing of 270 Chemicals. *Environ. Mutagen. 8(7)*:l–119 (1986).
35. **Miyauchi, T., et al.:** Mutagenciity Test of Procaterol, a beta2-Anrenergic Stimulant Studies on the Mutagenic Potential of Procaterol in the Bacterial Test Systems. *Oyo Yakuri (Parmacometrics) 17*:432–430 (1979).
36. **Flack, E.R, L.A. Poirier and H.W. Ruelius:** Evaluation of a DNA polymerase- Deficient Mutant of E. Coli for the Rapid Detection of Carcinogens. *Chem.-Biol. Interactions 15*:219–231 (1976).
37. **Wangenheim, J., and G. Bolcsfoldi:** Mouse Lymphoma L5178Y Thymidine Kinase Locus Assay of 50 Compounds. *Mutagenesis 3(3)*:193–205 (1988).
38. **Biondi, O., S. Motta and P. Mossesso:** Low Molecular Weight Polyethylene Glycol Induces Chromosome Aberrations in Chinese Hamster Cells Cultures *in vitro. Mutag. 17(3)*:261–264 (2002).
39. **Rowe, V.K., and M.A. Wolf:** "Polyethylene Glycols," in *Patty's Industrial Hygiene and Toxicology,* 3rd Rev. Ed., Vol. 2C. Clayton, G.D. and F.E. Clayton (Eds.). New York: John Wiley & Sons, Inc., 1982. pp. 3844–3852.
40. **Nitschke, K.D.:** *Polyethylene Glycol: Review of Absorption and Excretion Studies.* (Dow Chemical Company R&D Report HET DR-0112-0269-002). [Unpublished Data.] Midland, MI: Dow Chemical Company, 2005.
41. **Kwee, Y.N., and J. Dolovich:** Anaphylaxis to Polyethylene Glycol (PEG) in a Multivitamin Tablet. *J. Allergy Cl/n. Immunol. 69*:138 (1982).
42. **Hesselbach, C., W. Bohuing, and R. Wetteugel:** Anaphylactic Shock after Sucking a Throat Lozenge. *Dtsch. Med. Wschr. 115*:1397–1399 (1990).
43. **Schuman, E. and P.E. Balsam:** Probable Anaphylactic Reaction to Polyethylene Glycol Electrolyte Lavage Solution. *Gastrointest. Endosc. 37(3)*:411 (1991). [Letter to the editor.]
44. **Jakasa, I, M. Verberk, A. Bunge, J. Kruse, and S. Kezic:** Increased Permeability for Polyethylene Glycols through Skin Compromised by Sodium Lauryl Sulphate. *Exper. Derm. 15*:801–807 (2006).

45. **Krause, L.A.:** "Information on Polyglycols" (Letter to R.R. Langner, Dow Chemical U.S.A., Midland, Mich.) Jan. 19, 1978. [Personal communication to the AIHA WEEL Committee.] New Haven, CT: Olin Corporation, 1978.

46. **Kirsch, H.A.:** "Workplace Exposures in the Manufacture of Polyglycols" (Letter to R.R. Langner, Dow Chemical U.S.A., Midland, Mich.) Jan. 5, 1978. [Personal communication to the AIHA WEEL Committee.] Bellaire, TX: Texaco Inc., 1978.