5 GENERAL TOXICOLOGY

5.1 Toxic mechanisms and *in vitro* studies

The ethylene glycol ether 2–methoxyethanol is teratogenic and has testicular and hematologic effects. The adverse effects have been attributed to the major metabolite methoxyacetic acid (7, 38, 56) or to further metabolism of methoxyacetic acid (46). In parallel with the metabolism of 2–methoxyethanol to yield methoxyacetic acid, ßPGME is metabolized to 2–methoxypropionic acid. It might therefore be suspected that the toxicity of these two glycol ethers would also be similar. Accordingly, ßPGME (and ßPGMEA) would have teratogenic, hematological and testicular effects. This hypothesis gained support in a study by Merkle *et al.*, who found ßPGMEA to be slightly teratogenic in the rat and more so in the rabbit (28).

PGMEA is rapidly hydrolyzed to PGME and acetic acid by carboxylases in the nasal mucosa (53). The liberated acetic acid may be responsible for the damage to the olfactory epithelium observed in laboratory animals exposed to PGMEA (32) (see Section 6.1).

Jäckh *et al.* investigated the cytotoxicity of various glycol ethers and their acid metabolites in Chinese hamster ovary cells without metabolic activation. The ethylene glycol ethers 2–methoxyethanol and 2–ethoxyethanol and the propylene glycol ethers PGME and ßPGME exhibited similar cytotoxicity, with EC_{50} values (defined as the the concentration allowing 50 % of seeded cells to form colonies after 16 hr of incubation with the test substance) ranging from 0.2 to 0.5 mmol/ml. Methoxypropionate (EC_{50} = 0.1 mmol/ml) was more cytotoxic than its parent compound ßPGME (EC_{50} = 0.3 mmol/ml) but less toxic than methoxy–, ethoxy– and butoxyacetate (EC_{50} = 0.04–0.05 mmol/ml), the oxidation products of the ethylene glycol ethers (22).

3–Methoxypropionate, a structural isomer of 2–methoxypropionate, retarded growth and produced abnormalities in post-implantation rat embryo cultures at concentrations of 2 and 5 mM. Methoxyacetate and ethoxyacetate were more potent than 3–methoxypropionate, while the nonteratogenic butoxyacetate was less potent at the same concentrations (37).

5.2 Factors influencing toxicity

As the exposure level of PGME increases from 300 to 3000 ppm, the elimination rate decreases in rats (see also Section 4.5). The decrease seems to be due to saturation of the O–demethylation capacity while conjugation increases in relative terms (35). Due to metabolic saturation, the relationship between ambient air exposure level and blood PGME concentration, and possibly also the toxic effects, will not be linear but curve upwards.

PGME may induce its own metabolism in rats. Following 10 days of exposure at 3000 ppm (6 hr/d) an increased elimination rate was shown by lowered end-of-exposure blood levels (from 1816 to 1002 μg/g), shortened half time (from 15.7 to 9.7 hr) and increased blood clearance (from 0.5 to 0.8 $ml \cdot min^{-1} \cdot kg^{-1}$ body weight) of PGME. Both liver weight and the amount of cytochrome P–450 in the liver increased significantly. In addition, hepatic microsomal aniline hydroxylase and p–nitroanisole–O–demethylase activities doubled or tripled (35). Induction of the metabolism of propylene glycol ethers is a possible explanation of the transient effects on the central nervous system, liver, urine, and blood chemistry (these effects are described in the following section).

Sex differences in the metabolism of PGME have been observed in rats. The end-of-exposure concentration of PGME in blood was about 40 % higher in male rats than in female rats exposed to 3000 ppm for 6 hours. After 24 hr the blood PGME levels were nearly 8 times greater in males than in females. In addition, males had about 30 % longer half time of PGME in blood, and their blood propylene glycol levels were approximately double those of the females (35).

5.3 General effects

The propylene glycol ethers are of low and approximately equal acute toxicity. The LD_{50} ranges from 4 to 14 g/kg body weight for all routes of administration (oral, intraperitoneal and dermal) except the intravenous in the mouse, rat, rabbit and dog (Table 5).

In amounts close to lethal doses in animals the propylene glycol ethers have a depressant action on the central nervous system and the heart and may produce eye, nose and lung irritation. Signs of intoxication included: anxiety, vomiting, diarrhea, dyspnea, ataxia, hypotension, ventricular and auricular arrhythmia, respiratory depression and narcosis (40, 45).

With repeated exposure of animals to sublethal doses of PGME or DPGME, the initial signs of intoxication gradually disappear. Initially, rats and rabbits exposed to PGME at 3000 ppm became sedated and lost weight. These effects disappeared gradually during continued exposure and were completely gone after 14 days (19, 24, 29, 33, 40). Rats repeatedly exposed to DPGME at 300–400 ppm (7 hr/d) were also affected during the first weeks of exposure but appeared normal thereafter (40).

PGME

A number of organs were examined for gross pathological or histopathological changes following inhalation exposure of rats and rabbits to 3000 ppm PGME for 13 weeks (6 hr/d, 5 d/wk). Apart from minor effects in some organs, reported in the following pages, no changes attributed to this treatment were observed (24).

PGMEA

Various organs and tissues from rats and mice of both sexes exposed to 3000 ppm PGMEA for two weeks were investigated microscopically. No adverse effects were observed, except in the nasal epithelium (discussed in Section 6.1) and kidneys (Section 6.4) (32).

DPGME

Various organs from 10 rats and 7 rabbits of each sex were examined for gross pathological or histopathological changes following inhalation exposure to 200 ppm DPGME for 13 weeks (6 hr/d, 5 d/wk). There was no histopathological evidence of damage in any of the examined tissues, and no change in urine ketones was observed (25).

Table 5. Acute toxicity of propylene glycol ethers expressed as LD_{50} values (g/kg body weight).

Species	Number of animals	Route of administration					Reference
		oral	intra-venous	intra-peritoneal	sub-cutaneous	dermal	
				PGME			
mouse	5 females 5 males	10.7	4.9				(50)
rat	170 both sexes	6.1					(40)
rat	10 males	7.5					(49)
rat	5 males	5.2					(48)
rat	5 females 5 males	7.9	3.9	3.9	7.2		(50)
rabbit	4 males					12.9	(48)
rabbit	3 females 3 males	5.2	1.1		4.6		(50)
dog	3 females	~5–6					(50)
dog	3 males		~2–2.5				(50)
				ßPGME			
rat	10 males	5.7					(49)
				PGMEA, ßPGMEA			
				no data			
				DPGME			
rat	169 both sexes	5.1					(40)
rat	5 males	5.4					(48)
rabbit	4 females					9.5	(48)

6 ORGAN EFFECTS

6.1 Skin and mucous membranes

PGME

In a series of experiments Stewart and coworkers investigated the adverse effects of PGME in male volunteers. An unspecified number of subjects detected the odor of PGME vapor in a truck cab at 10 ppm but not at 5 ppm. Exposure to 300 ppm for 5 min produced mild irritation of eyes, nose and throat. At 750 ppm the PGME vapor was judged to be extremely irritating (51).

The effects of PGME in males were further investigated in experimental chamber exposures. The effects studied in these experiments are listed in Table 6. One man exposed to 50 ppm experienced flushing of the cheeks after 7 min in the exposure chamber and was not used in the following experiments. Four of six males stated immediately upon exposure to 95 ppm PGME that the odor was too strong to be tolerated and wished to terminate the experiment. However, odor tolerance developed within 25 min. One of the subjects complained of mild eye irritation after one hour of exposure to 95 ppm, and two complained after two hours. A total of 23 men were exposed to 231–249 ppm PGME for 1–7 hr. After 15 to 30 minutes eight men experienced eye irritation, three had nose irritation, one had a headache and one was nauseated. After 45 to 60 minutes 20 of the 23 males had developed eye irritation and increased blinking, 15 complained of nose irritation, two of throat irritation and one had a headache. Eight of ten men remaining in the chamber after 2 hr complained of eye irritation and five had nasal irritation. Of the four subjects remaining in the chamber for 7 hr, all had eye irritation and lacrimation, but none of them was still able to detect the odor of PGME (51).

In the last experiment two subjects were exposed to a PGME concentration steadily increasing from 1 to 2050 ppm over a 2-hr period. The subjects noted the odor at less than 25 ppm, reported objectionable odor at 50-75 ppm, light-headedness and mild eye irritation at 300-400 ppm, eye, nose and throat irritation at 500 ppm and lacrimation and rhinorrhea at 700 ppm. One of the subjects became incapacitated by eye irritation at 1000 ppm and was removed from the chamber. The second subject stayed in the chamber until 2050 ppm of PGME was reached. He experienced severe lacrimation, blepharospasm and throat irritation and was unwilling to breathe through his nose because of pain. The nose and throat pain disappeared within 15 min following exposure. The eye irritation disappeared in about 1 hr, while nasal congestion was present for 24 hr (51).

In a study of the ability of chemicals to cause injury to the rabbit eye PGME scored 4 in one study and 3 in a later study. The injury was scored from 1 to 10 based on the amount and concentration of chemical needed to cause keratoconus, iritis, corneal opaqueness and corneal necrosis. The scores 3 and 4 indicate that instillation of 0.1 and 0.02 ml, respectively, of undiluted PGME causes severe injury (8, 48).

Table 6. *Clinical and laboratory parameters investigated by Stewart et al. (51) in their studies on acute effects of PGME vapor. Various exposure protocols were used. One man was exposed to 47 ppm for 1 hr, six to 95 ppm for 3.5 hr and 23 men were exposed to 231–249 ppm for 1–7 hr. Two men were exposed to a PGME concentration steadily increasing from 1 to 2050 ppm in 2 hr. One of these men terminated the experiment at 1000 ppm. The effects are further described in Sections 6.1 and 6.8.*

Parameter studied	Effect observed	Parameter studied	Effect observed
Physical examination		***Subjective responses***	
Body temperature	no	Detection of odor	yes
Blood pressure	no	Odor intensity	yes
Pulse rate	no	Headache	yes
Respiratory rate	no	Irritability	yes
Vital capacity	no	Light-headedness	yes
Tidal volume	no	Nausea	yes
Electrocardiogram	no	Eye, nose or throat irritation	yes
		Sleepiness	no
Blood analysis		Speech difficulty	no
Blood cell count	no	Chest discomfort	no
Sedimentation rate	no	Abdominal pain	no
Serum glutamic oxaloacetic transaminase	no	Loss of apetite	no
Serum glutamic puryvic transaminase	no		
Lactic dehydrogenase	no	***Neurological tests***	
Serum alkaline phosphatase	no	Modified Romberg	yes
Blood urea nitrogen	no	Brake reaction-time	no
Serum creatinine	no	Heel-to-toe	no
		Finger-to-nose	no
Urine analysis		Crawford manual dexterity	no
24–hr creatinine excretion	no	Flannagan	no
Urobilinogen	no		
Catecholamines	no		

PGME scored 2 on a 10–step scale with respect to skin injury. The scores 1 and 2 correspond to no irritation and to the least visible capillary injection, respectively. A score of 10 indicates necrosis from a 0.01 % solution (48).

One drop of PGME placed in the rabbit eye for five consecutive days caused a mild transitory irritation of the conjunctiva. There was no cumulative effect and no indication of corneal injury (40). Gross and histological examination of the skin of rabbits exposed daily by dermal application for up to 13 weeks (5 d/wk), with doses between 1 and 10 ml PGME per kg body weight revealed some animals with scaling and erythema. However, there was no significant difference between PGME-treated animals and controls treated with water (40).

PGMEA

Degeneration of the olfactory epithelium was observed in three of five male rats and in one of five female rats exposed to 3000 ppm PGMEA for two weeks (6 hr/d; 5 d first week, 4 d second week). In mice exposed to 300, 1000 or 3000 ppm at the same schedule this degeneration was observed to be dose-related. The authors suggested that the effect was related to acetic acid resulting from hydrolysis of PGMEA in the nasal epithelium (32).

DPGME

The irritating concentration of DPGME in man was reported in a review paper to be 74 ppm (450 mg/m^3), or about twice the odor threshold (44).

Application of 0.04 ml of a 20 % aqueous solution of DPGME to one eye of each of ten human male volunteers caused a minor stinging sensation for 30–45 sec, and was accompanied by slight excess lacrimation and blepharospasm for about 1 min. A mild injection of the conjunctival vessels and a minor increase in intraocular tension were observed during the first hour (6).

DPGME scored 2 on a 10–step scale with respect to eye injury in the rabbit. This score means that 0.5 ml of undiluted PGME causes severe eye injury. DPGME caused no skin irritation in rabbits (48).

One drop of DPGME placed in the rabbit eye on each of five consecutive days caused a mild transitory irritation of the conjunctiva. There was no cumulative effect and no indication of corneal injury (40).

In a more recent experiment, 0.1 ml of undiluted DPGME instilled into the inferior conjunctival sac caused moderately severe conjunctoblepharitis in all six female rabbits. The effect peaked after about 6 hr and disappeared within a week. A 40 % aqueous solution of DPGME produced mild conjunctival irritation and a 20 % solution was without effects. There was a dose-related increase of intraocular tension and corneal thickness in the exposed rabbit eyes (6).

No studies on ßPGME or ßPGMEA were found.

6.2 Respiratory system

PGME

Rats exposed to 10000 ppm PGME for 6 hr developed microscopic changes revealing slight local irritation and congestion in the lungs (40). The same observation was made in rats exposed to 6000 ppm for 16 weeks and in a small number of monkeys and rabbits exposed to 1500 ppm or more for 5-29 weeks (see Table 10 for details). No effects on the lungs were seen in rabbits or monkeys exposed to 800 ppm (40).

No gross pathological or histopathological effects were seen in the lungs or respiratory tracts of rats and mice of both sexes exposed to 3000 ppm PGME for two weeks (6 hr/d; 5 d first week, 4 d second week) (29). A 13–week study with rats and rabbits of both sexes exposed to 300, 1000 or 3000 ppm (6 hr/d, 5 d/wk) was also negative (24).

PGMEA

No changes in lung weight, gross pathology or histology were observed in rats and mice exposed to 3000 ppm PGMEA for 2 weeks (6 hr per day) (32).

DPGME

Rats, rabbits, guinea pigs and monkeys of both sexes were exposed to 300–400 ppm DPGME for 26–31 weeks (7 hr/d, 5 d/wk). Judging by organ weight and macroscopic and histological examination , there were no effects on the lungs in any of the species studied (40).

Histological examination of lungs and trachea from rats and rabbits of both sexes exposed to up to 200 ppm DPGME for 13 weeks (6 hr/d, 5 d/wk) revealed no exposure-related effects (25).

No studies on ßPGME or ßPGMEA were found.

6.3 Liver

PGME

Stewart *et al.* exposed a total of 32 male volunteers to PGME vapor in various short-term (1–7 hr) inhalation experiments at concentrations ranging from 47 to approximately 1000 ppm (see Section 6.1 and Tables 6 and 7 for details). All subjects had normal values with respect to clinical chemistry (Table 6), and there was no difference between preexposure and postexposure values (51).

Both the absolute and the relative liver weights of male rats and the relative liver weights of female rats and female mice were higher than that of controls after two weeks of exposure (6 hr/d; 5 d first week, 4 d second week) to 3000 ppm PGME. Six weeks after termination of the PGME exposure the liver weights had returned to normal. There were no treatment-related changes in either rats or mice exposed to up to 3000 ppm PGME with respect to liver histology, serum glutamic-pyruvic transaminase activity, urea nitrogen, glucose, total protein, albumin, globulins or total bilirubin. Serum alkaline phosphatase activity was statistically significantly lower than controls ($p<0.05$) in male rats exposed to 3000 ppm and in female rats exposed to 300, 1000 or 3000 ppm (6 hr/d; 5 d first week, 4 d second week). According to the authors, however, these depressions were probably related to the nutritional status of the animals (29).

Rats exposed to 3000 ppm PGME for 13 weeks (6 hr/d, 5 d/wk) exhibited small increases (6 to 8%) in liver weight relative to controls. Hepatocellular swelling without degenerative changes was observed in the female but not in the male rats. In addition, the female rats exhibited slightly increased serum glutamic pyruvic transferase activities. Slightly elevated alkaline phosphatase activities ($p<0.05$) were observed in rabbits exposed to 3000 ppm PGME for 13 weeks (6 hr/d, 5 d/wk). These enzyme acitivities were, however, not higher than values observed in control animals in recent studies in the same laboratory (24).

Miller and coworkers also observed increased liver weights in rats of both sexes and hepatocellular swelling in female but not male rats exposed to 3000 ppm PGME for 13 weeks (6 hr/d, 5 d/wk). Clinical chemistry analyses were not conducted (33).

A series of inhalation experiments (7 hr/d, 5 d/wk) was conducted by Rowe and colleagues with PGME. Increased liver weights were observed in monkeys and rabbits after exposure to 1500 ppm and higher for 26-29 weeks, in guinea pigs after exposure to 6000 ppm for 16 weeks and in rats after exposure to 3000 ppm and higher for 17 weeks. Microscopic examination revealed slight (unspecified) changes in the livers from female rabbits exposed to 1500 ppm or higher for 13-26 weeks and guinea pigs of both sexes exposed to 6000 ppm for 16 weeks. Only 3 of 10 female and 6 of 10 male rats survived exposure 6000 ppm for 17 weeks. Increased liver weights were observed in the surviving animals. Increased liver weights and unspecified microscopic changes in the liver were also observed in male rats after exposure to 6000 ppm for 4 days (40).

PGMEA

In rats and mice of both sexes exposed to 0, 300, 1000 or 3000 ppm PGMEA 6 hr/d for two weeks (5 d first week, 4 d second week), liver weights were unaffected, except in female rats in the highest exposure group; these had a significantly higher mean relative liver weight compared to controls. However, the weight change was not accompanied by any other gross or histopathological finding. Further, clinical chemistry analyses — serum glutamic-pyruvic transaminase and alkaline phosphatase activities, urea nitrogen, glucose, total bilirubin, total protein, albumin and globulins — revealed no adverse effects (32).

DPGME

Female guinea pigs and rabbits and monkeys of both sexes exposed to 300–400 ppm DPGME for 26–31 weeks (7 hr/d, 5 d/wk) exhibited slight but definite changes of granulation in the cytoplasm and numerous vacuoles in the liver cells. These changes were not seen in rats of either sex (40).

There were no statistically significant hepatic effects in rats and rabbits of both sexes exposed to up to 200 ppm DPGME for 13 weeks (6 hr/d, 5 d/wk). The parameters investigated were liver weight and histology, alkaline phosphatase and serum glutamic pyruvic transaminase activities, serum proteins (total protein, albumin and globulin) and urobilinogen (25).

6.4 Kidneys

PGME

Kidneys with a normal appearance by gross examination and normal blood urea levels were observed in male rabbits that survived 13 weeks of daily (5 d/wk) dermal doses of 2 ml (5 of 6 survived), 4 ml (5 of 7 survived) or 7 ml (1 of 9 survived) PGME per kg body weight. Interstitial nephritis and tubular necroses were observed in 3 of 19 male rabbits that died during 13 weeks of exposure to 7 or 10 $ml \cdot kg^{-1} \cdot d^{-1}$ (40). Other rabbits that died exhibited only a slight granular degeneration in the tubules.

Rats of both sexes exposed to 10000 ppm PGME (17 weeks, 2 hr/d, 5 d/wk; or a single 6–hr exposure) and male rats and guinea pigs of both sexes exposed to 6000 ppm (16 weeks; 7 hr/d, 5 d/wk) had increased kidney weights but normal blood urea levels, and the histological appearance of the kidneys was normal (40).

There were no effects on absolute or relative weight, gross pathology or histology in the kidneys of rats and mice exposed to 300, 1000 or 3000 ppm PGME for two weeks (6 hr/d; 5 d first week, 4 d second week). At the highest exposure level of 3000 PGME urine pH was increased and there was a tendency to a decrease in specific gravity. The effects gradually regressed and had disappeared 6 weeks after exposure (29). In a 13–week study exposure of rats and rabbits to 100, 300 and 3000 ppm (6 hr/d, 5 d/wk) had no effect. However elevated urine pH was observed in male rats after 4 weeks, but not after 12 weeks, of exposure to 3000 ppm (24).

PGMEA

All five male and two of five female rats exposed to 3000 ppm PGMEA for two weeks (6 hr/d) had slightly reticulated (pale, honeycombed) kidneys and a slight increase in the eosinophilic granularity of the proximal convoluted tubules of the kidneys. The effect was not seen in any sex of mice after similar exposure. Other renal parameters, kidney weight and blood urea, were within normal limits (32).

DPGME

Kidneys with a normal appearance by gross examination, and normal blood urea levels were observed in all rabbits surviving 13 weeks of daily (5 d/wk) dermal doses of 1 ml (all 5 males survived), 3 ml (9 of 11 males survived), 5 ml (6 of 11 males survived) or 10 ml (1 of 7 males survived) DPGME per kilogram of body weight (40).

Rats and rabbits of both sexes exposed to up to 200 ppm DPGME for 13 weeks (6 hr/d, 5 d/wk) showed no statistically significant effects compared to controls with respect to kidney weight and histology, urea nitrogen and urine specific gravity, but female rabbits exposed to 200 ppm had 14 % higher relative kidney weight. However, both the relative and absolute kidney weights of the DPGME-treated animals were within the range of historical controls. As there were no signs of nephrotoxicity, the increased kidney weights were thought to be unrelated to the exposure to DPGME (25).

No studies on ßPGME or ßPGMEA are reported.

6.5 Gastrointestinal tract

Apart from signs of irritation on the gastric epithelium following high oral doses of PGME or DPGME (40) no adverse effects on the gastrointestinal tract have been observed after exposure to PGME, PGMEA or DPGME.

No studies on ßPGME or ßPGMEA are reported.

6.6 Circulatory system

PGME or DPGME (≥ 0.3 ml/kg body weight) intravenously administered to anesthetized dogs induced transitory changes in the electrocardiogram, accompanied by hypotension. Ventricular asystole and auricular fibrillation occurred at higher doses (0.8 ml/kg body weight). This effect persisted for as long as five minutes (45). No reports mention any effects on the heart or blood circulation at lower exposure levels.

No studies on PGMEA, ßPGME or ßPGMEA are reported.

6.7 Hematological system

PGME

There were no treatment-related changes in packed cell volume, erythrocyte count, hemoglobin or total leukocyte count in rats of both sexes exposed to PGME at up to 3000 ppm for a total of 9 days (6 hr/d). The mean platelet counts were elevated, but this change was considered to be of uncertain toxicologic significance in view of the variability of this parameter in the control animals. There were no statistically significant changes in the animals in the recovery group, including platelet counts, when sacrificed 6 weeks after termination of exposure. No hematological effects were observed in either male or female mice (29).

White cell counts in female rats exposed to 300 ppm PGME for 13 weeks (6 hr/d, 5 d/wk) were reported to be higher than in controls. On the other hand, the white cell counts were reduced in the female rats exposed to 3000 ppm in the same experiment. The significance of these findings is difficult to evaluate since neither the number of animals or the levels of significance are given. The investigators consider the deviations in white cell count to be sporadic occurrences unrelated to exposure. No other hematologic effects were found in either rats or rabbits (33).

Rats and rabbits of both sexes were exposed to 300, 1000 and 3000 ppm PGME for 13 weeks (6 hr/d, 5 d/wk). No hematological effects (bone marrow, thymus and lymph node histology, packed cell volume, erythrocyte count, hemoglobin, total and differential leukocyte count) were observed in either species (24).

PGMEA

There were no effects on thymus and spleen weights, histology of bone marrow or thymus or hematology parameters (not specified) in mice and rats of both sexes exposed to 300, 1000 or 3000 ppm PGMEA for two weeks (6 hr/d; 5 d first week, 4 d second week) (32).

ßPGMEA

A 4–week inhalation study with ßPGMEA in male Wistar rats showed no bone marrow effects. The highest exposure level was 2800 ppm (internal report by Klimisch *et al.* 1984, cited by Merkle *et al.* 1987 (28)).

DPGME

DPGME has been suggested as one possible cause of bone marrow injury observed in seven lithographers working with multicolor offset and ultraviolet curing printing. Personal and area samples revealed air levels of 0.6–6.4 ppm DPGME. Neither benzene nor ethylene glycol monomethyl ether, known inducers of bone marrow injury, were found in the products used. Gloves were used only intermittently and frequent and prolonged skin contact with wash solutions occurred during clean-up. The products used contained a number of other organic solvents,

including ethylene glycol monoethyl ether, methyl ethyl ketone, and aromatic and halogenated hydrocarbons (9). Thus, exposure to ethylene glycol monoethyl ether cannot be excluded as a cause of bone marrow injury. In view of the negative findings in animal experiments, it seems highly unlikely that DPGME could cause the bone marrow injury observed in the lithographers.

There were no statistically significant hematologic effects in rats and rabbits of both sexes exposed to up to 200 ppm DPGME for 13 weeks (6 hr/d, 5 d/wk). The parameters investigated were bone marrow, thymus and lymph node histology, packed cell volume, hemoglobin, erythrocyte count, total and differential leukocyte count and platelet count (25).

6.8 Central nervous system

PGME

In a series of experiments Stewart and coworkers investigated acute effects of PGME vapor on male volunteers (see Section 6.1 and Tables 6 and 7 for details). There was no deterioration in vision, coordination, neurological responses or brake reaction time during 3.5 hr of exposure at 100 ppm and 7 hr of exposure at 250 ppm. Two subjects were exposed to a PGME concentration rising steadily from 1 to 2050 ppm over a 2–hr interval. At 300–400 ppm both subjects reported that they felt slightly light-headed. After one hour, when the concentration had reached 1000 ppm, one of the subjects was unable to perform a normal modified Romberg test (*i.e.* to balance on one foot with his eyes closed and both arms at his sides). He was then severely affected by eye, nose and throat irritation and was removed from the exposure chamber (irritant properties are described in Section 6.1). After an additional hour in the chamber, when the concentration had reached 2050 ppm, the second subject completed the tests with normal pre-exposure scores (51).

PGME vapor produced a transient nonspecific depression of behavior in female rats exposed at 5000 or 10000 ppm, but not at 2500 ppm (4 hr/d for 10 days). The substance was judged to be ineffective with regard to the conditioned avoidance-escape behavior of the rats (14). In a number of rat experiments a transient sedative effect of PGME has been noted during exposure at 3000 ppm. The effect disappeared after 1–2 weeks. Less pronounced sedation has been noted in mice, guinea pigs and rabbits (19, 24, 29, 33).

No weight changes or histopathological deviations were observed in the brains of rats and rabbits of both sexes exposed to 3000 ppm PGME for 13 weeks (6 hr/d, 5 d/wk) (24).

DPGME

No adverse effects (weight change and histology) were observed in the brains of rats and rabbits of both sexes exposed to 200 ppm DPGME for 13 weeks (6 hr/d, 5 d/wk) (25).

6.9 Peripheral nervous system

There are no reports on any effects on the peripheral nervous system.

7 IMMUNOTOXICITY AND ALLERGY

DPGME

Undiluted DPGME was applied to the backs of 200 subjects (100 men and 100 women) and allowed to remain in contact with the skin for five days. Three weeks later the compound was applied again to the backs of the same subjects and allowed to remain for 48 hr. In a second experiment, DPGME was tested in 50 subjects (25 men and 25 women). This time the material was applied to the backs of the subjects and allowed to remain for 4–8 hr every other day until 10 applications had been made. After three weeks DPGME was reapplied for 24–48 hr. None of the subjects exhibited any evidence of irritation or sensitization at any time (40). Although these experiments were not conducted in accordance with modern test protocols, the results seem to indicate that DPGME is not a skin sensitizer.

There are no studies on the other propylene glycol ethers.

8 MUTAGENICITY, GENOTOXICITY

PGME

The genetic toxicology of the glycol ethers was reviewed by McGregor in 1984. PGME was negative in a bacterial mutation test with *S. typhimurium*, with and without metabolic activation. Furthermore, PGME did not increase unscheduled DNA synthesis in hepatocytes, nor the number of chromosomal aberrations in Chinese hamster ovary cells (unpublished report cited by McGregor (27)).

There is no information about the other propylene glycol ethers.

Most studies have been conducted with 2–methoxyethanol and 2–ethoxyethanol. Although a few tests have yielded positive responses the available evidence is sufficient to conclude that, in general, the glycol ethers are not strongly genotoxic (27).

9 CARCINOGENICITY

No studies on the carcinogenicity of propylene glycol ethers are available.

10 REPRODUCTIVE TOXICITY

PGME

There were no changes in testis weight or histology in rats or mice exposed to PGME containing 4 % beta isomer at levels up to 3000 ppm for two weeks (6 hr/d; 5 d first week, 4 d second week) (29). A second study, extended to 13 weeks of exposure at levels up to 3000 ppm PGME containing 1.8 % ßPGME, and including rabbits, was also negative (24).

Exposure of pregnant Wistar rats to PGME (content of ßPGME not specified) at 200 and 600 ppm for 6 hr per day from day 6 through 17 of gestation had no effect on litter size, pup weight, viability or external appearance. Male rats exposed for 10 days at the same levels showed no reduction in testes weight or atrophy of the seminiferous tubules, an effect seen after exposure to 2–methoxyethanol (11).

Pregnant rats and rabbits were exposed (6 hr/d) to 500, 1500 and 3000 ppm PGME containing 1.32 % ßPGME during organogenesis (days 6 through 15 and 6 through 18, respectively). There were mild signs of maternal toxicity, lethargy and decreased weight gain in both species and fetal toxicity and delayed sternal ossification in rats at 3000 ppm, but no signs of teratogenic effects at any exposure level (19).

ßPGME

Miller and coworkers state that no testicular effects were seen in rats and mice after a 2–week exposure to a PGME mixture containing up to 18 % beta isomer. The highest exposure concentration was 3000 ppm. No further details of these unpublished experiments were given (34).

Results from an unpublished pilot study with ßPGME demonstrated the same embryotoxic profile in the rat as ßPGMEA (see below). The details of the pilot study are not given (28).

3– Methoxypropionic acid, a structural isomer of 2–methoxypropionic acid, the common metabolite of ßPGME and ßPGMEA, retarded growth and caused abnormalities in post-implantation rat embryo cultures (see Section 5.1 for details).

ßPGMEA

Pregnant Wistar rats exposed to 110, 550 or 2700 ppm ßPGMEA for 6 hr/d on gestation days 6–15 exhibited maternal toxicity at the 550 ppm level and maternal and fetal toxicity at the 2700 ppm level. The effects reported include slight sedation, pulsative respiration, decreased body weight gain ($p=0.01$), reduced uterus weight ($p=0.05$ at 2700 ppm), reduced number of live fetuses at 2700 ppm ($p=0.05$), weights of female and male fetuses at 2700 ppm ($p=0.01$), increased percentage of dead implantations at 2700 ppm ($p=0.05$) and increased percentage of fetuses with anomalies at 2700 ppm (not significant). At the highest exposure level

of 2700 ppm ßPGMEA a few fetuses had skeletal anomalies of the thoracic vertebrae—dumbbell-shaped or bipartite notches of the cartilage. At 550 ppm one fetus had bipartite notches. These anomalies were not seen in the control group and at the lowest exposure level and were interpreted as signs of a slight teratogenic effect (28).

The teratogenicity was more pronounced in Himalayan rabbits. These were exposed to 0, 36, 145 or 550 ppm (6 hr/d) ßPGMEA from gestation days 6 through 18. There were no signs of maternal toxicity except a slight decrease in body weight gain at day 18 of gestation ($p=0.05$) which had disappeared by day 29. Fetal toxicity was manifested as increased percentage of dead implantations at 550 ppm ($p=0.05$), reduced female fetuses weight at 145 ppm ($p=0.05$) and reduced female and male fetuses weight at 550 ppm ($p=0.01$). No anomalous fetuses were seen at 0 and 145 ppm. At 36 ppm 3 anomalies (diaphragmatic hernia, absent gall bladder and scoliosis) were observed in 65 fetuses. At 550 ppm all 62 fetuses from 13 litters had anomalies. These anomalies included: anarsacra (1 fetus), cleft palate (3 fetuses), hernia umbilicalis (2 fetuses), digit anomalies (17 fetuses), internal hydrocephalus (1 fetus), heart defects (4 fetuses), hydroureter (2 fetuses) and sternal anomalies (53 fetuses) (28).

Dermal exposure of rabbits to 1000 and 2000 mg/kg ßPGMEA from gestation days 6 through 18 did not produce any maternal or fetal effects (28).

A 4–week inhalation study with ßPGMEA in male Wistar rats showed no testicular effects even at the highest dose level of 2800 ppm. The details of the experiment have not been published (28).

DPGME

There were no changes in testes weight or testicular histology in rats or rabbits exposed to 15, 50 or 200 ppm DPGME for 13 weeks (6 hr/d, 5 d/wk) (25).

There are no reports of teratogenic effects of DPGME.