COMMITTEE FOR VETERINARY MEDICINAL PRODUCTS

PROPYLENE GLYCOL

SUMMARY REPORT

1. Propylene glycol ((+)-propane-1,2-diol) is employed as a humectant and carbohydrate substitute in semi-moist pet foods. In the pharmaceutical industry it is used as a solvent and as a stabilising agent for vitamin preparations. It is listed as E490 in Council Directive 91/248/EEC (which amended Council Directive 70/524/EEC) for addition to the feed of cattle for fattening, calves, lambs, kids, pigs and poultry at a concentration not exceeding 36000 mg per kg of complete feed, and to the feed of dairy cows at a concentration not exceeding 12000 mg per kg of complete feed. Council Directive 95/2/EC concerning food additives authorises the use of propylene glycol as a carrier solvent for colours, emulsifiers and enzymes at a maximum concentration of 1 g propylene glycol in 1 kg of the foodstuff.

2. In veterinary medicine propylene glycol is used for the treatment of acetonemia and ketosis. It is administered orally, at doses of up to 200 ml, twice a day for 4 days to cattle, and 100 ml/day, for up to 5 days for sheep. It is also used as an excipient in a large number of parenteral and topical medicinal products, as a solvent or vehicle, particularly for drugs which are unstable or insoluble in water.

3. Propylene glycol can provide a source of energy for animals; this has been attributed to its metabolism via lactate to pyruvate and then to the tricarboxylic acid cycle and/or the gluconeogenic pathway to glycogenesis.

4. Secondary pharmacodynamic effects are rare after oral administration but more common after parenteral administration and include central nervous system depression and ataxia. Haemolytic effects have been observed after intravenous administration of high doses to several species.

5. In humans, propylene glycol is readily absorbed from the gastrointestinal tract and rapidly metabolised and excreted. The terminal elimination half-life was about 4 hours with an average total body clearance of 0.1 l/kg and volume of distribution of 0.5 l/kg. 20-50% of an oral dose was excreted unchanged in the urine within 24 hours of administration, the rest of the dose was metabolised by the liver.

6. In dogs, peak plasma concentrations were achieved 0.5-4 hours after an oral dose of approximately 8-12 mg/kg bw. 24 hours after dosing, propylene glycol was no longer detectable in the blood. Around 12-36% of the administered dose was excreted unchanged in urine. In rats, peak plasma concentrations were found 10 minutes after an oral dose of 370 mg/kg bw and 90 minutes after dosing with 5900 mg/kg bw. Following intravenous administration to rabbits, the half-life for elimination in blood was around 10 minutes. It was not bound to plasma proteins. It was metabolised by the liver to substances of low toxicity.

7. In rats, propylene glycol caused skeletal muscle damage and creatinine kinase release following intramuscular administration and took 3-5 days to be absorbed following subcutaneous administration. Injection site reactions (including dermal necrosis) following subcutaneous injection of a proprietary product to guinea pigs were attributed to the inclusion of propylene glycol in the formulation. In humans, propylene glycol enhanced the rate of percutaneous absorption of a number of topically-administered drugs.
8. Propylene glycol was of low acute toxicity. The acute oral LD$_{50}$ values were 21-32 g/kg bw in the rat, 22-24 g/kg bw in the mouse, 19 g/kg bw in the rabbit and 18-19 g/kg bw in the guinea pig. The subcutaneous LD$_{50}$ was reported to be 25-28 g/kg bw in the rat and 19 g/kg bw in the mouse. Intravenous LD$_{50}$ values of 5-8 g/kg bw and 4-6 g/kg bw were reported in the mouse and rabbit respectively.

9. As part of the combined chronic toxicity/carcinogenicity study summarised in paragraph 12, a 15-week study was carried out in which rats were fed diets containing 0 or 50000 ppm propylene glycol. There were no substance-related effects on haematology, clinical chemistry or urinalysis values. No substance-related effects were found at necropsy. The NOEL was 50000 ppm, equivalent to approximately 1700/2100 mg/kg bw per day in males/females respectively.

10. Cats were fed diets containing the equivalent of 1600 or 8000 mg/kg bw per day for 5 weeks. There was a dose-related increase in Heinz body formation and a dose-related decrease in erythrocyte half-life. In cats fed the 8000 mg/kg bw diet, there was a decrease in PCV accompanied by punctate reticulocytosis and bone marrow erythroid hyperplasia. A dose-related increase in iron pigment was found in the liver and spleen of all cats. No NOEL was established.

11. In a 2-year toxicity study, groups of 5 male and 5 female Beagle dogs, 10-14 months old at the start, were fed diets intended to provide 2000 or 5000 mg/kg bw per day of propylene glycol. Further groups were fed diets containing dextrose. The dogs given 5000 mg/kg bw per day gained more weight than the untreated dogs; this was attributed to the calorific value of propylene glycol. Haematology, clinical chemistry and urinalysis values were monitored throughout the study. The dogs given 5000 mg/kg bw consumed less water, their urine output was increased and the specific gravity of the urine was reduced. Haemoglobin, haematocrit and erythrocyte counts were reduced and reticulocytes were increased in this group. Bilirubin concentrations were increased in both sexes given 5000 mg/kg bw. There were no pathological changes attributable to treatment. At 2000 mg/kg bw per day, no adverse effects were observed on any of the parameters studied. The NOEL was 2000 mg/kg bw per day.

12. Propylene glycol was not teratogenic in a study in the rabbit using intravenous administration. The related substance, propylene glycol monomethylether was not teratogenic in the rat, mouse or rabbit; these studies were carried out using both oral and subcutaneous administration. There was no evidence of teratogenicity or foetotoxicity in an inhalational study in Wistar rats using atmospheric concentrations of 200 or 600 ppm propylene glycol monomethylether, 6 hours per day, from days 6-17 of gestation. Exposure of male rats to 200 or 600 ppm propylene glycol monomethylether, 6 hours per day for 10 days did not affect testicular pathology. No link with adverse reproductive effects was found following exposure of 84,000 female workers during annual production of 100,000 tonnes propylene glycol in the USA.

13. Propylene glycol was not mutagenic in an in vitro microbial assay for gene mutation using S. typhimurium TA92, TA1535, TA100, TA1537, TA94 and TA98 and dose levels of up to 10,000 µg/plate. A significant increase in structural aberrations (mainly breaks) was observed at the top dose level of 32 mg/ml (420.6nM) in an in vitro chromosomal aberration assay with Chinese hamster fibroblasts; lower doses gave negative results and negative results were obtained in the presence of S-9 metabolic activation. It was shown that osmotic pressure was significantly elevated at 32 mg/ml suggesting that the cells may have been affected by osmotic pressure changes in the culture medium. Negative results were reported in an in vivo micronucleus test. No dominant lethal effect was observed in a study in which mice were given intraperitoneal doses of 10 mg/kg bw propylene glycol. It was concluded that propylene glycol was not mutagenic.
14. Groups of 30/sex Charles River CD rats were fed diets containing 0, 6250, 12500, 25000 or 50000 ppm (equivalent to 0, 200/300, 400/500, 900/1000 or 1700/2100 mg/kg bw per day in males/females respectively) of propylene glycol for 104 weeks. There were no overt signs of toxicity and no substance-related effects on mortality, food consumption or bodyweight gain. There were no substance-related effects on haematology, clinical chemistry or urinalysis values. There were no gross- or histopathological findings attributable to treatment. The top dose level (1700/2100 mg/kg bw) was a NOEL. There was no evidence of carcinogenicity. However the groups sizes used in this study were too low for an adequate assessment of carcinogenicity.

15. Propylene glycol is used in a number of human medicinal preparations, including some intended for intravenous administration, at concentrations of up to 40%. Systemic toxicity is uncommon. However there have been reports of hypersensitivity reactions, lactic acidosis and central nervous system depression. In humans, propylene glycol is readily absorbed from the gastrointestinal tract and rapidly metabolised to substances of low toxicity (ultimately lactic acid and glucose) and rapidly excreted. The half-life for elimination of propylene glycol was 4 hours.

16. The Joint FAO/WHO Expert Committee on Food Additives (JECFA) calculated an ADI of 0-25 mg/kg bw per day, equivalent to 1500 mg/day for a 60 kg adult. The US Food and Drug Administration has classified propylene glycol as a compound that is "generally regarded as safe".

17. There were no residue depletion studies with propylene glycol. Because of its rapid metabolism and excretion, toxicologically-significant residues of propylene glycol are unlikely to be found in meat, milk, etc.

Conclusions and recommendation

Having considered the criteria laid down by the Committee for the inclusion of substances in Annex II of Council Regulation (EEC) No 2377/90 and in particular that:

- propylene glycol is of low toxicity,
- the substance was rapidly metabolised and excreted;

the Committee considers that there is no need to establish an MRL for propylene glycol and recommends its inclusion in Annex II of Council Regulation (EEC) No 2377/90 in accordance with the following table:

<table>
<thead>
<tr>
<th>Pharmacologically active substance(s)</th>
<th>Animal species</th>
<th>Other provisions</th>
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<tbody>
<tr>
<td>Propylene glycol</td>
<td>All food-producing species</td>
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