The European Agency for the Evaluation of Medicinal Products
Veterinary Medicines and Inspections

EMEA/MRL/049/95-CORRIGENDUM[1]

COMMITTEE FOR VETERINARY MEDICINAL PRODUCTS

DIMETHYL and DIETHYL PHTHALATES

SUMMARY REPORT

1. Dimethyl and diethyl phthalates are the esters derived from o-phthalic acid and methanol and ethanol respectively. They are used in veterinary medicines as plasticizers in film coating, at levels of 0.1% or below. Dimethyl phthalate is also used as an insect repellent in some topical formulations, again at levels of 0.1% or less. Both esters are used in some topical products as co-solvents at levels of up to 5%, while dimethyl phthalate is used in some oral or bolus products at levels of up to 5%.

2. Absorption of the shorter chain dialkyl phthalates (up to dibutyl) is high (up to 90%) in rodents after oral administration. Up to 50% of topically applied doses of dimethyl or diethyl phthalates were absorbed in the rat. The shorter chain dialkyl phthalates are rapidly hydrolysed to the monoester and the corresponding alcohols. Following absorption, the phthalate esters are detected in the blood and elimination half-lives are of the order of 1 to 3 hours. They are rapidly excreted with the majority of an oral dose (up to 90%) being recovered in the urine and faeces 24 hours after administration, with up to 50% being recovered within 8 hours.

3. The dimethyl and diethyl phthalates are of low acute toxicity to rodents. For example, the acute oral LD_{50} values in rats were in the range of 2 to 6 g/kg b.w.

4. The shorter chain dialkyl phthalates were of low toxicity when given to rodents in short term studies. For example, when rats were given dietary diethyl phthalate at levels of up to 5% for 16 weeks, the main sign of toxicity was a reduction in the rate of weight gain; the NOEL was 0.2% in the diet equivalent to approximately 100 mg/kg bw/day.

5. There are no teratology studies with dimethyl or diethyl phthalate following oral administration. However, no evidence of teratogenic effects were seen when rats were given intraperitoneal doses of up to 1.34 g/kg bw/day dimethyl phthalate or up to 1.89 g/kg bw/day diethyl phthalate on days 5, 10 and 15 of gestation. When rats were given intraperitoneal doses of up to 2.4 g/kg bw/day dimethyl phthalate on days 3, 6 and 9 of gestation, there was no evidence of a teratogenic effect.

6. The longer chain dialkyl phthalates have been reported to reduce the fertility of male rodents. For example, reduced testicular weights and severe testicular atrophy have been noted in rats given repeated oral doses of dipentyl and di-2-ethylhexyl phthalate. However, repeated daily dosing of rats with dimethyl phthalate (up to 2.8 g/kg bw/day) for up to 10 days, or diethyl phthalate (up to 1.6 g/kg bw/day) for up to 10 days, had no effects on testicular weights and testicular histology. The dialkyl phthalates have not been shown to affect female reproductive parameters when tested in multigeneration studies.

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7. Dimethyl and diethyl phthalates, and a range of other dialkyl phthalates gave negative results in the Ames test. Similarly, the metabolites monomethyl and monoethyl phthalates also gave negative results, both in the Ames test and in a reversion assay with *Escherichia coli*. In *in vitro* cytogenetic assays, dimethyl phthalate (using human lymphocytes) and diethyl phthalate (using human lymphocytes and Chinese hamster fibroblasts) gave negative results. Dimethyl and diethyl phthalates were tested in a number of *in vivo* cytogenetic assays in mice and negative results were obtained.

8. Diethyl phthalate has not been tested in a carcinogenicity study. Dimethyl phthalate has been tested in a carcinogenicity study but this was not conducted to modern standards. It was tested in a 2 year study in which rats where given up to 8% in the diet and no evidence of carcinogenicity was seen. The longer chain phthalate esters di-2-ethylhexyl phthalate and a branched dinonyl phthalate have been shown to be hepato-carcinogenic in rodents. These higher, branched chain esters of o-phthalic acid induce hepatic peroxisome proliferation in rodent liver with concomitant increases in associated hepatic enzymes such as catalase. Peroxisome proliferators as a group are recognised hepatocarcinogens in rodents. Dimethyl phthalate and diethyl phthalate did not induce hepatic peroxisome proliferation in the livers of rats administered the compounds.

   In view of the negative mutagenicity studies with both compounds, and their failure to induce hepatic peroxisome proliferation in rodents, taken together with the negative results in the rat 2-year dietary study with dimethyl phthalate, it was concluded that dimethyl and diethyl phthalates were not carcinogenic.

9. There are no data in humans following exposure to dimethyl or diethyl phthalates.

10. There are no residues studies with dimethyl or diethyl phthalates.

Conclusions and recommendation

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

- dimethyl and diethyl phthalates have low toxicity;
- dimethyl and diethyl phthalates are rapidly metabolised and excreted.

The Committee for Veterinary Medicinal Products considers that there is no need to establish MRLs for dimethyl and diethyl phthalates and recommends their inclusion into Annex II of Council Regulation (EEC) No 2377/90 in accordance with the following table:

Pharmacologically active substance(s)	Animal species	Other provisions
Dimethyl phthalate	All food producing species	
Diethyl phthalate	All food producing species	