



COMMITTEE FOR VETERINARY MEDICINAL PRODUCTS

PHLOROGLUCINOL TRIMETHYLPHLOROGLUCINOL

SUMMARY REPORT

1. Phloroglucinol (1,3,5-trihydroxybenzene) is a non atropinic antispasmodic agent which is preferentially used by intramuscular or intravenous injection in veterinary medicine for its spasmolytic properties against the urinary tract. One of its ethers, the trimethylphloroglucinol, is also used. The usual recommended dose by injection is close to 0.5 mg/kg bw.
2. Phloroglucinol inhibits the action of Catechol-O-Methyl Transferase (COMT) inducing in that case a relaxation of the experimental smooth muscular spasms (decrease of the spasms intensity).
3. The levels of ³H-phloroglucinol radioactivity in the blood and in the tissues were studied in the rat after an intravenous injection of 50 mg/kg bw (130 µCi/mg).

The highest concentrations at 15 min after administration were localized in the kidney (5.9 µg/g), liver (6.0 µg/g) and intestine (4.6 µg/g). After 48 hours, the concentrations were 2.3 µg/g and 1.1 µg/g in the liver and in the muscle, respectively.

Phloroglucinol is excreted in urine as parent drug, sulfo- and glucurono-conjugates, and hydroxylated metabolites, such as dimethoxy-1,3 hydroxy-5 benzene or trimethoxybenzene. These metabolites result from O-methylation in the liver.

In cattle, it was demonstrated that 8 strains of rumen bacteria were capable of degrading phloroglucinol under anaerobic conditions, leading to increased metabolic rate in ruminants.

4. In cattle, phloroglucinol may be formed in the rumen during the degradation of more complex molecules present in feed such as flavonoids, anthocyanins, catechins.

So, phloroglucinol can be considered as a naturally occurring substance in ruminants.

5. The LD50 values in mice and rats by oral, subcutaneous and intraperitoneal administrations were closed to 4000 mg/kg bw. Intravenous injections of 250 mg/kg bw were not lethal in the dogs.
6. Four groups of 8 dogs have been treated with a mixture of equal parts of phloroglucinol and trimethylphloroglucinol at the dose levels of 0, 20, 80 and 125 mg/kg bw for 6 months. Animals were sacrificed after 6 and 9 months. No toxicological effects were observed at the clinical examinations in any of the treated groups. No alteration in haematology, blood biochemistry or urine biochemistry parameters were attributable to the treatment. The NOEL 125 mg/kg bw.
7. Phloroglucinol was administered in a three generation study in male and female rats. Four groups of 20 rats have been treated at the dose levels of 0.15%, 0.31% or 0.62% of phloroglucinol (no information about the corresponded dose of phloroglucinol expressed in mg/kg bw) in feed for 221 days (first generation), 105 days (second generation) and 115 days (third generation). Phloroglucinol induced no macroscopic lesions or histologic alteration of organs or endocrine glands. The anatomopathological examinations of foetuses revealed no alteration.

8. Four groups of 20 pregnant female rats were treated between day 7 and day 15 of gestation with phloroglucinol/trimethylphloroglucinol (1/1) at the dose levels of 0, 200, 300 and 400 mg/kg bw. The macroscopic and microscopic examinations revealed no deleterious effect on rat offspring. Phloroglucinol was not teratogenic (NOEL: 400 mg/kg bw).

Four groups of 15 pregnant female rabbits were treated between day 6 and day 14 of gestation with phloroglucinol/trimethylphloroglucinol (1/1) at the dose levels of 0, 400, 600 and 800 mg/kg bw. Phloroglucinol had no adverse effects on rabbit foetuses (NOEL: 800 mg/kg bw).

9. Polyphenols having two meta-hydroxyl groups in the benzene ring, such as phloroglucinol, did not produce a significant amount of hydrogen peroxide and superoxide anion radicals and they were devoid of mutagenicity in the Ames test (strains TA 97, TA 98 and TA 100).

In chromosome aberrations on CHO cells Phloroglucinol was negative after metabolism.

10. Phloroglucinol is used in man as an antispasmodic at doses of 480 mg/day by oral route, 450 mg/day by rectal route or 120 mg/day by intravenous or intramuscular injection.

11. A NOEL of 125 mg/kg bw could be retained from the six month oral toxicity study performed in dogs. With a safety factor of 100, the following ADI of 1.25 mg/kg bw i.e. 75 mg/person could be established.

Conclusion and recommendation

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

the toxicity of phloroglucinol and trimethylphloroglucinol is low,
phloroglucinol is recommended in a small number of individual animals and for infrequent and non-regular treatment,
phloroglucinol is formed naturally in the rumen,
phloroglucinol is rapidly excreted,

The Committee considers that there is no need to establish an MRL for Phloroglucinol and for Trimethylphloroglucinol and recommends their inclusion into Annex II of Council Regulation (EEC) No 2377/90 for all food producing species in accordance with the following table:

Pharmacological active substance	Animal species	Other provisions
Phloroglucinol Trimethylphloroglucinol	All food producing species	