The European Agency for the Evaluation of Medicinal Products

EMEA/MRL/031/95

COMMITTEE FOR VETERINARY MEDICINAL PRODUCTS

PROPANE, N-BUTANE, ISOBUTANE

SUMMARY REPORT

1. Propane, n-butane, and isobutane are low molecular weight alkanes with 3 and 4 single bonded carbon atoms. They are gases at room temperature, stable substances and chemically quite inert.

2. In veterinary medicine but also in cosmetic industry n-butane, isobutane and propane are used as propellants. In the veterinary product concerned by the assessment a mixture of all three substances is used as propellant in a foam aerosol for intramammary mastitis treatment in cows. Possible other routes of administration are topical use on skin or mucous membranes or intrauterine instillation.

3. Acute inhalation of propane, n-butane and isobutane sensitised the myocardium of laboratory animals to adrenaline induced arrhythmia. In mice propane, which is considered a simple asphyxiant, concentrations of 10-12% caused respiratory depression and bronchospasm. Isobutane resulted in increased pulmonary resistance and depressed respiratory minute volume in monkeys at concentrations of 5-10% (arrhythmia, myocardial depression, tachycardia, decrease in aortic blood pressure and increase in left atrial pressure were reported for another study), in dogs at up to 20% in respiratory depression, bronchospasm, and decreased pulmonary compliance, and in rats in decreased respiration rate to apnoea, reduced tidal volume and electrocardiographic silence. Not propane but n -butane and isobutane had anaesthetic activity in mice at a concentration of 22% in 1 min (n-butane) or a concentration of 35% in 25 min (isobutane). In dogs isobutane was not fully anaesthetic, n-butane not at all. In humans 1% propane in the air for 10 min remained without effect, concentrations up to 10% for 2 min caused vertigo and 1% n-butane for 10 min produced drowsiness. Corresponding plasma concentration for the observed effects have not been reported.

4. The 2 h LC_{50} of inhaled isobutane in mice was 52%. For n-butane a 2 h LC_{50} of 680 mg/l (29%) was found in mice and a 4 h LC_{50} of 658 mg/l (28%) in rats. Lethal concentrations in the air for dogs were 20-25% n-butane or 55% isobutane. 90 day inhalative exposure to isobutane up to 400 ppm or propane up to 750 ppm caused no toxic effects in monkeys. Isobutane and propane-isobutane mixtures were mild to moderate irritants to rabbit skin but a propane-isobutane mixtures was not irritating to humans. Up to 10% propane caused no irritation in eye, nose or respiratory tract. n-Butane, isobutane and propane were found not to be mutagenic in the Salmonella/microsome test with and without metabolic activation..

5. No data on oral or dermal absorption or absorption from other application sites were presented. Following exposure in the air the major route of absorption for propane, n-butane and isobutane is absorption in the lungs with little or no dermal absorption. In rats and mice absorbed n-butane is recovered in highest concentrations in perinephric fat, brain, spleen, liver and kidney following exposure to lethal concentrations. The n-butane concentration in the nervous tissue correlate with the degree of observed central nervous depression. A similar distribution is to be expected for propane and isobutane. After systemic absorption propane is mainly eliminated in expired air. N-butane is the lowest molecular weight alkane to bind to cytochrome P-450. The main metabolites recovered in vitro from rat liver microsomes is the hydroxylation product 2-butanol which could be excreted in urine as a glucuronic acid conjugate or be oxidised to a ketone and exhaled in the air. Further metabolism was not investigated. As seen for propane elimination of unchanged n-butane by exhalation is to be expected. Following inhalation exposure isobutane was detected in

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human blood. The only metabolite detected in vitro was *tert.*-butanol (2-methyl-2-propanol), which can be oxidised to a ketone and exhaled either unchanged or be excreted as glucuronide in urine.

6. The maximum amounts administered to a cow by intramammary instillation assuming treatment of 4 udder quarters with the recommended dose of 1 injector/quarter on two consecutive days would be 5.12 g of each propane and isobutane and 15.36 g n-butane. The actual amounts of gas remaining in the udder will be lower, as some gas will escape due to the resulting high pressure. Allowing for 100% absorption from the application site, the substances will be distributed in the body of the animal and, disregarding elimination, any resulting residue levels will be even lower.

   Based on these considerations treatment of food-producing animals with products containing propane, n-butane and isobutane does not pose a risk to consumers.

CONCLUSION AND RECOMMENDATION

Considering the low toxicity of propane, n-butane and isobutane, their rapid metabolism to non-toxic metabolites, and their use as propellants, the Committee for Veterinary Medicinal Products recommends the inclusion of propane, n-butane and isobutane in Annex II of Council Regulation (EEC) No 2377/90 as indicated in the following table:

Pharmacollogically active substance	Animal species	Other provisions
Propane, n-butane, isobutane	All food producing species	