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COMMITTEE FOR VETERINARY MEDICINAL PRODUCTS

MINERAL HYDROCARBONS

SUMMARY REPORT

1. Mineral hydrocarbons are a heterogeneous group of substances consisting of mixtures of different-sized hydrocarbon molecules, which may include saturated and/or unsaturated hydrocarbons, which may be linear, branched or cyclic. The relative proportions of these different hydrocarbon molecules varies widely between different mineral hydrocarbon materials and varies to a lesser extent from batch to batch of the same material. Different commercially-available mineral hydrocarbons are defined on the basis of their physical characteristics, such as viscosity and density, rather than on the basis of their precise chemical identity. The mineral hydrocarbons used in veterinary medicinal products include paraffins (alkanes), branched paraffins (branched alkanes) and alicyclic compounds. However, aromatic compounds such as benzene, napthalene and polycyclic hydrocarbons and their derivatives are not used.

2. Mineral hydrocarbons are used in veterinary medicinal products as adjuvants in vaccines, bases for ointments, anti-dusting agents in medicated feeds, vehicles in antimastitic intramammary infusions, emollients in teat dips, ingredients in antiparasiticides, and vehicles in some subcutaneously-applied depot products.

   Examples include;

   · slow release devices; microcrystalline waxes
   · intramammary preparations; light mineral oils (liquid paraffin)
   · sheep dips; very light mineral hydrocarbons (also used as solvents in other products) vaccines; mineral oils as adjuvants (liquid paraffin).

   They are also used in human medicines, pesticides, food contact materials, food processing aids, chewing gum bases and in human foods as food additives. Humans also eat biogenic hydrocarbons as natural components of foods from animal and plant sources. Intakes of biogenic hydrocarbons are normally within the range of 10-100 mg/person/day (0.17-1.7 mg/kg bw/day), and the intake of hydrocarbons from all sources has been estimated to be normally about 240 mg/person/day (4 mg/kg bw/day). In human medicinal use of liquid paraffin, people have been exposed to oral doses of up to 100 ml/person/day (approximately 1500 mg/kg bw/day) over several days or even longer without any evidence of major adverse effects. The characteristics of the mineral oils in relation to molecular weights, viscosity and chemical structure are poorly defined. They can be approximately classified as follows :

   · high viscocity ; C30, viscosity at 100 degrees; not less than 11cSt, molecular weight, not less than 500;
   · medium and low viscosity; C10-C25, viscosity at 100 degrees, 3-8.5 cSt, molecular weights, 300-500;
   · microcrystalline waxes; C20-C60, viscosity at 100 degrees, 10-30 cSt, molecular weight, 300-750+

3. The rate of absorption from the gut of linear alkanes (n-alkanes) and branched alkanes has been shown to become lower as the carbon number is increased. n-alkanes of carbon numbers >C29 are not significantly absorbed. The absorption of ingested cyclic alkanes has not been extensively studied, but it is clear that the smallest of these molecules are readily taken up from the gut. Dermally-applied mineral hydrocarbons extensively permeate the stratum corneum, but molecules of $\geq$C10 do not appear to cross the full thickness of the skin to enter the blood-stream. Absorbed hydrocarbons are initially distributed via the lymphatics to lymph nodes and the liver, but later the hydrocarbons are further distributed to adipose tissue. Hydrocarbons of medium carbon numbers

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(C20 - C32) are the main substances which accumulate in both animal and human tissues, following oral exposure, as larger molecules are not readily absorbed and smaller molecules are more readily mobilised for metabolism. Release of medium-sized hydrocarbons from fatty stores is very slow, but, once mobilised, hydrocarbons can be converted by the liver to fatty acids. These can then be further metabolised to normal components of the body or beta-oxidized to carbon dioxide.

4. Very early oral repeat-dosing studies of mineral hydrocarbons are of limited use for safety assessment because of incomplete reporting of the types of oil and doses used. More recent (1960s and 70s) non-GLP rat and dog sub-chronic studies of paraffinic oils showed no histological evidence of foreign body reactions or other toxicological effects at doses up to 120 mg/kg bw/day in rats and up to 50 mg/kg bw/day in dogs, although vacuoles were seen in mesenteric lymph nodes of rats given 5000 mg/kg bw/day.

5. The toxicities of 14 mineral hydrocarbons have been evaluated in modern GLP-compliant 90-day repeat-dose oral studies using dietary concentrations ranging from 0.002% (20 mg/kg) to 2% (20 g/kg) fed to F344 rats. The mineral hydrocarbons tested were nine white oils [P100(H), P70(H), HTWO, N70(A), N70(H), OTWO, P15(H), N15(H) and N10(A)], two paraffin waxes (IMPW and LMPW), two microcrystalline waxes (HMPW and HSW) and one blended microcrystalline/paraffin wax (BLEND). The two materials with the highest molecular weights, the high melting point wax (HMPW) and the high sulphur wax (HSW), did not accumulate in tissues and did not cause any toxicity at any of the doses tested: NOEL = 2% (equivalent to approximately 2000 mg/kg bw/day). Other hydrocarbons accumulated in tissues and caused a range of inflammatory lesions at various degrees of severity. Effects included haematological effects (increased neutrophil and monocyte counts and decreased rbc-related parameters), increased weights of liver and lymph nodes, histiocytosis of lymph nodes, and granulomata in the liver. For some of the hydrocarbons materials tested (OTWO, HTWO, N15(H), LMPW, IMPW, and BLEND), adverse effects were seen at the lowest dose tested, and thus NOELs for these materials could not be established. Animals dosed with low melting point wax (LMPW), or intermediate melting point wax (IMPW) also developed an inflammatory lesion at the base of the heart mitral valve, characterised by increased cellularity and destruction of the fibrous core of the valve. For some other materials, only the lowest dose (0.002%) was without effect, giving NOELs of approximately 2 mg/kg bw/day for N10(A), P15(H), P70(H), N70(A), and N70(H). Paraffinic white oil P100(H) did not produce any toxicity at any dose, but there was accumulation of hydrocarbon material only in the liver at the highest dose level : NOEL = 2% (equivalent to approximately 2000 mg/kg bw/day). Females were more susceptible than males. Some studies incorporated withdrawal periods of 28 or 85 days, but lesions were still present at the end of these periods. Some additional studies comparing the effects of some of these hydrocarbons in female F344 rats with the effects in female Sprague-Dawley rats showed that similar effects were seen in both strains, but that F344 was the most sensitive.

6. White oils have been used extensively as solvent controls in teratogenicity studies, causing no teratogenic effects.

7. Few commercially-available mineral hydrocarbon materials have been fully tested for mutagenicity. However, there are no structural alerts in hydrocarbon molecules. A naphthenic oleum-refined white oil (Primol 185) and some unspecified base oils were negative in a modified Ames test, a mouse lymphoma assay, and a mouse micronucleus test. Some poorly refined mineral hydrocarbon materials are known to contain PAHs, and some of these have been shown to be positive in the Ames test and/or to be carcinogenic in animals. There is no evidence to suggest that oral doses of pure mineral hydrocarbons are mutagenic or carcinogenic.

8. Most of the limited human data on oral exposure relates to the use of liquid paraffin, which has been in extensive use in human medicine since the beginning of the twentieth century, with oral doses of up to 30 ml, whenever required, being recommended. Case reports of exposed individuals and autopsies of the general population provide evidence that mineral oil accumulates in the lymph nodes, liver and spleen, and some (but not all) studies associate these accumulations with inflammatory lesions and granulomata similar to those seen in animal studies. There is no epidemiological evidence to suggest that use of liquid paraffin as a human medicine is associated with any cancer. Repeated skin exposure can cause defatting of skin, erythema, dermatitis, oil acne, and some industrial mineral oils are suspected of causing skin cancers. The oils with this carcinogenic potential usually contain polycyclic aromatic hydrocarbons (PAHs), but the specifications for grades of mineral hydrocarbons used in foods and medicines require these

materials to be almost entirely free of PAHs. Inhalation of mineral oil mists is an occupational hazard, causing respiratory irritation, with chronic exposure being associated with lipoid pneumonia. Epidemiological studies have shown no increased risk of lung cancer in workers exposed to oil mists. Epidemiological studies of people given mineral oil adjuvanted vaccines have shown no increased cancer risk over periods of up to 35 years.

9. The microcrystalline waxes and high viscosity mineral hydrocarbons are unlikely to pose a consumer risk as these are of low toxicity and are poorly absorbed from the gastrointestinal tract. Similarly, the very light mineral hydrocarbons are unlikely to pose a consumer risk as these are rapidly metabolised to simple products such as carbon dioxide and water. ADIs had been set by JECFA for several groups of compounds including the microcrystalline waxes, the high viscosity oils, the low viscosity oils and the medium/low viscosity oils; the ADIs for the waxes and high viscosity oils were full but the others were temporary. The Scientific Committee for Food (SCF) had established a tADI for the waxes. Many of these ADIs or tADIs were of a similar order (0-20mg/kg bw) except for the medium viscosity oils (0-1 mg/kg bw) and the low to medium viscosity oils (0-0.01 mg/kg bw).

10. The total intake from all veterinary sources (assuming that all of the animal produce in the diet came from animals given mineral hydrocarbons) was calculated to be about 40 mg/person/day (0.7 mg/kg bw/day), but this was then arbitrarily divided by ten to estimate a more normal intake of consumers: 0.07 mg/kg bw/day. The estimations show that intake of mineral hydrocarbons from their use in veterinary medicine will contribute only a minor part of the normal total dietary intake of hydrocarbons from all sources (approximately 4 mg/kg bw/day) and is minuscule compared with the intakes of liquid paraffin which may occur as a result of use in human medicine (up to 1500 mg/kg bw/day). The constituents of any mineral hydrocarbon vary from batch to batch depending on the source of raw material and, for similar reasons they vary from supplier to supplier. Each is an heterogeneous mixture of related hydrocarbons and for all these reasons it would be impossible to develop a regulatory method for residues surveillance. Moreover, it would be impossible to distinguish between compounds of biogenic origin and those derived from veterinary medicinal products. For all these reasons it is impossible to establish MRLs for the mineral hydrocarbons.

Conclusions and recommandation

The estimate of total intake of mineral oils from all veterinary sources is sufficiently below the upper limit of the ADIs for mineral hydrocarbons to give assurance that the health consumers will not be affected by any residues resulting from veterinary use of these materials. It is acknowledged that residues resulting from their use in veterinary medicine will contribute little to the normal intake of mineral and biogenic hydrocarbons from all sources. Furthermore, it is not possible to distinguish between veterinary and other sources of hydrocarbons in food. It is recommended that the mineral hydrocarbons are placed into Annex II of Council Regulation (EEC) No 2377/90 as indicated in the following table :

Pharmacologically active substance	Animal species	Other provisions
Mineral hydrocarbons, low to high viscosity including microcrystalline waxes, approximately C10-C60; aliphatic, branched aliphatic and alicyclic compounds	All food producing species	Excludes aromatic and unsaturated compounds