The European Agency for the Evaluation of Medicinal Products
Veterinary Medicines Evaluation Unit

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COMMITTEE FOR VETERINARY MEDICINAL PRODUCTS

MANGANESE COMPOUNDS

SUMMARY REPORT

1. Manganese is used in mono-preparations and combination products to treat manganese deficiency. Manganese containing compounds used in veterinary and human medicines are the carbonate, chloride, gluconate, glycerophosphate, pidolate, ribonucleate, sulphate and oxides of manganese. In veterinary medicine these compounds are used to prevent skeletal abnormalities in calves and perosis in poultry. In cattle the recommended dose of manganese sulphate is 0.2-0.6 g for a 500 kg weighing animal. Treatment duration of 9 weeks has been recommended for dietary supplements for cattle. Target animals, dosage schedules and routes of administration were not specified.

   Manganese sulphate (monohydrate and tetrahydrate), manganese oxides (MnO and Mn_2O_3), manganese carbonate, manganese chloride (tetrahydrate) and manganese hydrogen phosphate (trihydrate) are authorised in the EU as feed additives with a maximum dose of 250 mg Mn/kg feed. Information available indicates that cattle diet should contain at least 40 mg/kg feed manganese to prevent deficiency. To prevent skeletal deformities in calves 200 mg/kg feed has been mentioned to be sufficient, recommended dietary intake for pigs is 40 mg/kg feed (or 24-57 mg manganese/45 kg bw) and for poultry feed a level of at least 55 mg/kg feed has been recommended.

   The normal daily human intake is about 2-9 mg. In human medicine manganese compounds are used as general stimulating agents or as adjunct treatment for allergic and neurological disorders. In humans recommended daily intake is 0.5 (infants) to 5.0 (adults) mg/day. In case of manganese deficiency in humans doses up to 10 mg /day have been mentioned.

2. Manganese is an essential element for animals. Birds require more than mammals. Manganese is indispensable for the action of glycosyltransferase. This enzyme plays a role in the formation of the mucopolysaccharide chondroitin sulphate, which is a component of cartilage and due to its action on the formation of cartilage it also is important for bone formation. Dietary deficiency of manganese causes infertility (reported in cattle, pigs and sheep), skeletal deformities both congenitally and after birth (perosis in birds, limb deformities in calves and pigs) and effects on blood biochemistry and blood clotting and may cause mortality. Although manganese is also part of pyruvic carboxylase and several other enzymes, other divalent cations may serve as alternatives for its role in the activity of these enzymes.

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3. Absorption from the gastrointestinal tract is claimed to be low under normal conditions and is dependent on the form of the manganese. The absorption of manganese is increased by iron deficiency and decreased by excess dietary calcium or phosphorus. Manganese chloride and sulphate have similar bioavailability, while manganese methionine and proteinate have somewhat higher bioavailability. Manganese oxide, precipitated manganese carbonate and manganese dioxide, in descending order, are less well utilised than manganese sulphate in poultry and sheep. Absorbed manganese is transported to the liver and excreted with bile into the intestine, after which there is enterohepatic recirculation. Absorption from injection sites is slow. Soluble chelates are rapidly absorbed. Trivalent manganese (may be formed in the intestinal tract from divalent manganese) is transported in the blood by transferrin. The turnover of manganese in mammalian tissues is rapid. Absorbed manganese is initially retained by mitochondria in liver, pancreas and kidneys. About 40% of total body manganese content are retained in the bone marrow. Erythrocytes retain manganese in a porphyrin complex. Liver, pancreas, adrenals and intestine play a role in the predominantly faecal excretion of manganese. Small amounts may be excreted in urine.

4. Oral LD_{50} in rats was 380 mg/kg bw for potassium permanganate and 837 mg/kg bw for manganese acetate (these and all other doses in this paragraph were expressed as Mn^{2+}). Intraperitoneal LD_{50} of manganese perchlorate in rats, manganese sulphate in mice was in the range 44-62 mg/kg bw. Intravenous LD_{50} values were 6.19 mg/kg bw for manganese acetate in mice and 56 mg/kg bw for manganese chloride in dogs. Minimum oral lethal dose of manganese fluoride in Guinea pigs was 118 mg/kg bw.

5. Manganese toxicity in rats (1.75% of dry feed weight of Mn^{2+}) consisted of retarded growth, poor absorption of calcium, negative phosphorous balance and severe rickets. Excessive dietary Mn^{2+} interferes with iron uptake and metabolism. After parenteral administration of manganese dichloride in rats neuronal degeneration in the cerebral and cerebellar cortex was observed. Experimental "manganism" was induced in monkeys by intraperitoneal injection of manganese dichloride for 18 months. The symptoms resembled those of poisoning in humans (see paragraph 10 on effects in humans).

6. The effects of four different manganese compounds (mentioned were manganese dioxide, carbonate, acetate) fed to mice in the diet for 12 months (doses were not mentioned) on a number of selected parameters were examined. The manganese treatment reduced weight gain. In some brain parts the manganese content was higher after feeding the insoluble salts than after feeding the soluble salts. The manganese concentrations in liver and spleen were increased after feeding manganese carbonate. Manganese dioxide lowered dopamine and increased homovanilic acid, which could be related to its oxidising properties. Manganese acetate resulted in lowered hypothalamic dopamine and the accumulation of manganese in the brain correlated with decreased motor activity.

7. According to abstracts of published papers potassium permanganate, manganese sulphate and manganese chloride were mutagenic in the Ames test, manganese chloride also induced DNA damage in human lymphocytes as determined by the single-cell gel assay technique. Manganese sulphate was mutagenic in *Saccharomyces cerevisiae*. In the wing spot test with orally treated *Drosophila melanogaster*, manganese chloride was also mutagenic. On the other hand, manganese can reduce the mutagenic potential of some compounds (e.g. nickel ions). The mechanism of mutagenesis in bacteria has been indicated to be concentration dependent and may be related to interactions with DNA and/or DNA polymerase.

8. Chronic parenteral injection of manganese chloride induced an increased frequency of lymphosarcomas in female mice. Leukaemia and mammary adenosarcomas were also noted. However, there were also reports suggesting that manganese may have anticarcinogenic properties.

9. Chronic toxicity in humans following chronic exposure (inhalation, ingestion, parenteral administration between a half year and two years) causes "manganism", a central nervous system disease with psychic and neurological disorders (slapping gait, cramps or tremors of body and extremities, slurred speech, hallucinations, insomnia and mental confusion). Some symptoms resemble those of Parkinson's disease. Other symptoms of manganism are nephritis, liver cirrhosis, anorexia, muscular fatigue, sexual impotence, leukopenia, anaemia and monocytosis.

10. According to an abstract of a published paper, blood of normal cattle contains about 190 µg Mn/l**,** but lower levels have also been found. Livers of normal cattle contain 12000 µg/kg and livers of new-born calves 8000 µg/kg.

Conclusions and recommendation

In spite of the deficiencies in the data provided, nevertheless, 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:

- manganese is an essential element;
- manganese is a normal component of the diet in humans;
- the use of manganese in veterinary medicinal products will add negligible amounts to the manganese intake from its use as feed additive.

the Committee concludes that there is no need to establish an MRL for the manganese compounds listed below and recommends their inclusion in Annex II of Council Regulation (EEC) No 2377/90 in accordance with the following table:

Pharmacologically active substance(s)	Animal species	Other provisions
Manganese carbonate	All food producing animals	For oral use only
Manganese chloride	All food producing animals	For oral use only
Manganese gluconate	All food producing animals	For oral use only
Manganese glycerophosphate	All food producing animals	For oral use only
Manganese pidolate	All food producing animals	For oral use only
Manganese ribonucleate	All food producing animals	For oral use only
Manganese sulphate	All food producing animals	For oral use only
Manganese oxide	All food producing animals	For oral use only
Dimanganese trioxide	All food producing animals	For oral use only