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

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COMMITTEE FOR VETERINARY MEDICINAL PRODUCTS

IRON DICHLORIDE AND IRON SULPHATE

SUMMARY REPORT

1. Iron dichloride and iron sulphate are normally used as a supplement in iron deficiency anaemia in new-born domestic animals (mostly piglets and calves) and to treat iron deficiency. In veterinary medicine, the recommended doses of iron sulphate used are generally low (i.e. cattle 8 to 15 g/animal, horses 2 to 8 g/animal and sheep and swine 0.5 to 2 g/animal, given orally, each day for 2 weeks or more. Dose levels in horses, cattle, sheep and swine were 0.25 to 0.50 mg/kg bw after intravenous infusion of a 0.01% solution. It is indicated for metabolic disturbances and deficiency states. In human medicine, the usual therapeutic dose of iron is about 200 mg per day (2 to 3 mg/kg bw).

2. Iron ammonium citrate, iron dextran and iron glucoheptonate have already been scientifically assessed by the CVMP and an entry into Annex II of Council Regulation (EEC) 2377/90 has been recommended.

   Iron gluconate (E 579) is a permitted food additive under the European Parliament and Council Directive 95/2/EC.

3. Iron is an essential component of haemoglobin, myoglobin (i.e. in the transport and utilisation of oxygen) and haem enzymes (e.g. cytochromes, catalases, peroxidases). It will correct both physical symptoms and decreased haemoglobin levels secondary to iron deficiency. In man, daily requirements ranging from 13 to 80 µg/kg bw/day, are determined by physiological losses and the needs imposed by growth. Iron deficiency is the most common cause of nutritional anaemia.

   The latest recommended daily intake, e.g. in the Nordic countries, was set at 12 to 18 mg iron per day per person. Dietary sources of iron include cereals, meat and vegetables. In addition, there is a widespread use of food fortification (e.g. flour) with iron. Supplemental iron is also taken by women during pregnancy and lactation.

4. Information on pharmacokinetics of iron was presented. Iron is absorbed through the mucosal barrier as $iron^{2+}$ where it oxidises to $iron^{3+}$. The $iron^{3+}$ is less well absorbed than the $iron^{2+}$. Oral bioavailability of iron is mostly related to the form of iron ingested which is poorly absorbed. Iron absorption occurs mainly in the upper part of the small intestine. Haem iron is fairly well absorbed, while non-haem iron is absorbed at a rate from 5 to 15%. The uptake of iron from the diet is dependent on the iron requirement of the body, i.e. body iron status, iron content and composition of food. The major enhancer of non-haem iron absorption is meat, and various organic acids, particularly ascorbic acid. In contrast, polyphenols including tannins, the dietary fibre complex, may decrease the non-haem iron absorption substantially.

   After absorption into enterocytes, iron is immediately bound to proteins, to form either haemosiderin, ferritin or transferrin, and transported to the bone marrow, where it is incorporated into haemoglobin. Abundant iron is also stored as ferritin and haemosiderin in the hepatocytes and in the macrophages in the spleen and bone marrow. Iron is not readily eliminated; most of it is reused, while only small amounts are eliminated.

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5. Acute toxicity studies were performed in rats and mice. The oral LD_{50} values in rats and mice were in a range of 319 to 680 mg/kg bw for iron sulphate, thus iron was considered as moderately toxic. The subcutaneous LD_{50} values for iron sulphate in mice and rats were 60.3 and 155 mg/kg bw, respectively. The intraperitoneal LD_{50} values for iron sulphate in mice and rats were 289 mg/kg bw.

6. No acceptable repeated dose toxicity studies were carried out.

7. No tolerance studies in target species were supplied.

8. No acceptable reproduction toxicity studies were available.

9. No information on mutagenicity was provided.

10. No specific studies for carcinogenicity have been performed. Subchronic and chronic studies concerning co-carcinogenic activity of dietary administered iron are reported. In these studies, rats were treated with known carcinogens together with iron in doses causing either heavy iron overload or iron deficiency. Iron overload seems to potentiate the effects of treatment with known carcinogens, while iron deficiency diminishes the risk of developing tumors.

11. No specific studies on immunotoxicity were available.

12. Literature on observations in humans was available. In humans, excess iron or iron overload may cause iron poisoning. Severe poisoning in children may occur following ingestion of more than 0.5 g of iron, which corresponds to about 2.5 g iron sulphate. The lethal dose is 80 to 250 mg $iron^{2+}$/kg bw. Severe iron poisoning is characterised by damage to the intestinal epithelial lining, which can cause blood containing diarrhoea and vomiting. Acidosis, liver and/or kidney failure and cardiovascular collapse may follow. Iron in doses of 100 to 400 mg per day can cause symptoms in the gastrointestinal tract.

13. The Joint FAO/WHO Expert Committee on Food Additives (JECFA) established in 1983 a provisional tolerable daily intake of 0.8 mg/kg bw for iron from all sources, with the exception of iron oxides used as colouring agents, supplemental iron taken during pregnancy or lactation and supplemental iron for specific clinical requirements. The Scientific Committee for Food recommended in 1993 a maximum level for iron intake of 30 to 100 mg/person/day.

14. No residue depletion studies in target species after recommended dosages of iron dichloride and iron sulphate were provided.

    The concentrations likely to occur in the edible tissues of food producing animals following recommended use of iron dichloride and iron sulphate will pose no significant risk to the health of the consumer and would be far below the provisional tolerable daily intake established by JECFA.

Conclusions and recommendations

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:

- iron is an essential element and a normal constituent of the diet in man,
- treated animals are unlikely to be sent for slaughter during or immediately after treatment,
- the concentration of iron expected in the edible tissues from the animals treated with iron dichloride and iron sulphate does not constitute any health risk for a consumer;

the Committee considers that there is no need to establish an MRL for iron dichloride and iron sulphate 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
Iron dichloride	All food producing species	
Iron sulphate	All food producing species	