COMMITTEE FOR VETERINARY MEDICINAL PRODUCTS

COBALT CARBONATE, COBALT DICHLORIDE, COBALT GLUCONATE, COBALT OXIDE, COBALT SULPHATE AND COBALT TRIOXIDE

SUMMARY REPORT

1. Cobalt (Co) is a trace element essential for animal life. It forms two main oxides, cobalt oxide (CoO) and cobalt trioxide (Co$_3$O$_4$) and the corresponding series of salts. However, the salts of the cobalt$^{3+}$-ion are unstable and reduced to the corresponding cobalt oxides salts. The oxides, and the sulphate (as monohydrate or heptahydrate), gluconate, chloride and carbonate salts of the cobalt oxide ion are those used in the formulations administered to animals. In veterinary medicine, the above cobalt compounds are used in the prevention and treatment of cobalt deficiency diseases in all food producing species.

2. Cobalt is a normal constituent of the diet of animals and humans and occurs in soil pasture and animal tissues. It is a component of vitamin B$_{12}$. In ruminants and horses, cobalt administered via the diet is finally incorporated into vitamin B$_{12}$ by the microorganisms of rumen and caecum. Other animal species require cobalt as pre-formed vitamin B$_{12}$. Little is known of the forms, other than vitamin B$_{12}$, in which cobalt exists in animal tissues.

Routes of cobalt administration include intramuscular or intravenous injections, top-dressing on pasture, salt licks, drinking water, reticular pellets and drench. Different formulations containing cobalt and, sometimes, other minerals often associated with anthelmintics or other drugs are available.

In 1980, the Agricultural Research Council of the U.K. recommended an intake for ruminants of 0.11 mg cobalt/kg dry feed, however young growing animals have higher requirements. Approximately an intake of 0.1 to 2.0 mg/day is generally considered adequate (i.e. a 200 kg steer, eating approximately 5.8 kg dry matter per day, would require 0.64 mg cobalt/day).

Cobalt included in anthelmintic and other products supplies from 0.1 to 1.5 mg/kg bw as a single dose. In salt licks, drinking water and top dressed pasture the approximate intake per day is 1 to 3 mg.

The efficiency by which dietary cobalt is converted to vitamin B$_{12}$ is inversely proportional to its intake. When levels of cobalt are above the requirements, vitamin B$_{12}$ is stored in the liver.

3. Cobalt which is not incorporated into vitamin B$_{12}$ or into its biologically inactive analogues, is not readily absorbed by ruminants and the most part is excreted in the faeces (e.g. in sheep 93% of the administered dose of cobalt underwent faecal excretion within five days). In contrast, man and rodents can absorb 20 to 95% of the dietary cobalt from the intestine. Cobalt absorption shares a common intestinal mucosal pathway with iron.

In all species including poultry, cobalt is distributed to all tissues of the body but mainly to liver and kidneys although little accumulation occurs in any part of the body. The cobalt content of milk is low. Young suckling pre-ruminants are unable to utilise cobalt until they have developed a functional ruminal microbial population.
After absorption cobalt is excreted mainly in urine but also in faeces, sweat, hair and milk. The concentration of cobalt has been reported to be very low in cows’ milk (0.4 to 1.1 µg/l) and 4 to 10 times higher in colostrum. Cobalt supplementation does slightly increase the cobalt content of milk.

4. The amount of cobalt retained in liver increases after oral supplementation in sheep; however even during continuous administration of more than 1.8 g/day of cobalt by rumen boluses (approximately 1000 times higher than common supplementation) concentrations of only 21 to 81 µg/kg of cobalt were found in the liver. In untreated sheep average contents of cobalt was from 150 to 340 µg/kg in liver and approximately 250 µg/kg in kidney. Similar values have been reported for cattle and man.

5. After feeding or drenching calves with toxic doses of cobalt of up to 2 g/day for 20 weeks, a tenfold increase of the cobalt content of bovine liver (from 2100 to 15400 µg/kg dry weight) and kidney (from 1900 to 5400 µg/kg dry weight) was achieved. Control values were 440 to 850 µg/kg in liver (dry weight) and 260 to 410 µg/kg in kidneys (dry weight).

6. The cobalt present in the injectable (intravenous and intramuscular) preparation for horses is low (approximately dose of 0.0017 mg/kg bw). A 250 kg horse would receive 0.425 mg of cobalt in a volume of 5 ml, ensuring that residues, even at the site of intramuscular injection, would be negligible.

7. Due to lack of absorption from the intestine, cobalt toxicity is extremely unlikely to occur in ruminants and its therapeutic index is high (greater than 300). Daily intravenous injection of more than 40 mg of cobalt per animal (individual weight of 454 kg, dose of approximately 0.088 mg/kg bw) was required to produce an adverse effects in dairy calves, whereas single doses of 1.5 mg/kg have been tolerated by 200 kg steers. In sheep, which are even more tolerant, daily administration of cobalt at doses of 160 mg/kg bw for 8 weeks did not cause any adverse effects. However, a dose of cobalt of 300 mg/kg bw as a soluble salt has been estimated as lethal for sheep. Intake of 10 mg/kg in the diet is considered safe.

8. The toxic effects of cobalt are mainly due to competitive inhibition of iron absorption which result in anaemia. Calves may show anorexia, salivation, dyspnoea and muscle incoordination as well as anaemia. In non-ruminants and pre-ruminant calves, cobalt at very high doses (200 to 250 mg/kg feed) blocks the cellular respiratory enzyme systems and can cause polycythaemia due to intracellular hypoxia.

9. In humans, in contrast to the polycythaemia observed in animals, large amounts of cobaltous chloride can depress erythrocyte production. It has also been suggested that daily intake of 8 mg of cobalt sulphate with beer resulted in cobalt toxicity (cardiac myopathy).

10. In humans, cobalt is utilisable only when incorporated as part of the vitamin B_{12} molecule. Methodological errors have contributed to wide variation (from 0.018 to 4.3 µg/100 ml) reported in the concentrations of cobalt in the blood.

11. Variations in the cobalt content of diets and hence in daily intake have been reported in different countries. Intake of cobalt of 0.01 mg/day in Japan, 0.031 mg per day in the former Soviet Union, 0.3 mg to 1.7 mg/day in children in the United States have been reported. Of the dietary constituents, leafy vegetables contain up to 600 µg/kg, organ meats 250 µg/kg, muscle 120 µg/kg, cereals, sugar and dairy products 30 µg/kg.

12. Apart from one early experiment where extremely high doses were administered to calves by drench for periods of weeks, a recent study has indicated that residues of cobalt never exceed the above listed values in all tissues from treated animals.
Conclusions and recommendations

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

- cobalt is a component of vitamin $\text{B}_{12}$, essential in humans and animals,
- cobalt salts are poorly absorbed after oral administration,
- cobalt is not accumulated in mammalian tissues,
- cobalt salts are of low toxicity,
- administration of cobalt by the diet or by parenteral formulations results in residues in tissues which are within the range found in the normal foodstuffs,
- the animals are unlikely to be sent to slaughter during or immediately after treatment,
- cobalt supplements at their recommended rate of administration will not pose any risk to man as far as residues is concerned;

the Committee considers that there is no need to establish an MRL for cobalt sulphate, cobalt carbonate, cobalt oxide, cobalt trioxide, cobalt dichloride and cobalt gluconate and recommends their inclusion into Annex II to Council Regulation (EEC) No 2377/90 in accordance with the following table:

<table>
<thead>
<tr>
<th>Pharmacologically active substance(s)</th>
<th>Animal species</th>
<th>Other provisions</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cobalt carbonate</td>
<td>All food producing species</td>
<td></td>
</tr>
<tr>
<td>Cobalt dichloride</td>
<td>All food producing species</td>
<td></td>
</tr>
<tr>
<td>Cobalt gluconate</td>
<td>All food producing species</td>
<td></td>
</tr>
<tr>
<td>Cobalt oxide</td>
<td>All food producing species</td>
<td></td>
</tr>
<tr>
<td>Cobalt sulphate</td>
<td>All food producing species</td>
<td></td>
</tr>
<tr>
<td>Cobalt trioxide</td>
<td>All food producing species</td>
<td></td>
</tr>
</tbody>
</table>