

## Risk Assessment

## Cobalt

### General information

#### Chemistry

Cobalt is a transition metal that exists in oxidation states +2 and +3. Within this risk assessment the word cobalt refers to ionic cobalt except where specific cobalt compounds are mentioned.

#### Natural occurrence

Cobalt is widely distributed in the environment, accounting for 0.001% of the earth's crust. It forms bivalent and trivalent compounds, those of biological interest being bivalent.

#### Occurrence in food, food supplements and medicines

High concentrations of cobalt are found in fish (0.01 mg/kg), nuts (0.09 mg/kg), green leafy vegetables (0.009 mg/kg) and fresh cereals (0.01 mg/kg), and most of the cobalt ingested is inorganic. The mean population intake of cobalt is 0.012 mg/day. There is no evidence of cobalt being used in food supplements. However, cobalt (as the sulphate) is included in some multi-constituent licensed medicines, at a maximum daily dose of 0.25 mg.

#### Other sources of exposure

Atmospheric concentrations of cobalt are usually around 1 ng/m<sup>3</sup>, but levels up to 10 ng/m<sup>3</sup> have been reported in heavily industrialised cities. Occupational exposure to cobalt occurs mainly by inhalation. Uncontaminated samples of fresh water contain concentrations of cobalt ranging from 0.001 to 0.010 mg/L.

#### Recommended amounts

Recommended intakes of cobalt have not been set as the only form of cobalt required by the body is vitamin B<sub>12</sub>, of which cobalt is an integral part. In the UK, COMA has set a RNI value for vitamin B<sub>12</sub> of 1.5 µg/day (equivalent to 0.006 µg cobalt) for adults, including pregnant women (COMA, 1991). This amount is considered adequate not only to reduce the risk of megaloblastic anaemia in normal individuals, but also to provide sufficient stores to withstand a period without intake. During lactation, an increment of 0.5 µg vitamin B<sub>12</sub>/day is recommended. For infants, the RNI for vitamin B<sub>12</sub> is 0.3 µg/day.

#### Analysis of tissue levels and cobalt status

Cobalt can be measured in whole blood, serum and various tissues. There are no recognised markers or indicators of cobalt status.

### **Brief overview of non-nutritional beneficial effects**

No suggested non-nutritional beneficial effects have been identified.

### **Function**

Cobalt is an essential trace element being an integral part of vitamin B<sub>12</sub>, which is essential for folate and fatty acid metabolism.

### **Deficiency**

Although cobalt is an essential trace element, cobalt deficiency has not been reported in humans. A wasting disease in cattle, of which a key feature is anaemia, has been demonstrated to be due to cobalt deficiency in pastures.

### **Interactions**

No compounds that interact with cobalt have been identified.

### **Absorption and bioavailability**

The extent of gastrointestinal absorption of cobalt depends upon the dose, with very low doses being almost completely absorbed, whereas larger doses are less well absorbed. Nutritional factors also influence absorption, for example, absorption is reduced by amino acids, and increased in iron deficiency.

### **Distribution and metabolism**

In human autopsy studies, the liver (the organ where vitamin B<sub>12</sub> is stored) contains the highest concentration of cobalt (approximately 20% of the total body content). In the human body there is no evidence of accumulation of cobalt with age.

### **Excretion**

Cobalt is mainly excreted in the urine but also in the faeces. Independent of the route of exposure, most cobalt is eliminated rapidly, with a small proportion being eliminated slowly and having a half-life of the order of years.

## Toxicity

### Human data

Cardiomyopathy was reported in heavy beer drinkers in the 1960s as a result of the use of cobalt chloride as a foam stabiliser, present in beer at concentrations of 1 – 1.5 ppm. Ethanol and cobalt have an additive effect, reducing blood flow to the heart and thus causing anoxia and damage to the heart muscle. Animal studies indicate that protein (particularly tryptophan, DL-methionine and L-cysteine) deficiency is a risk factor for cobalt toxicity.

Few other data on human toxicity are available where exposure is by ingestion. The majority of the available papers refer to reports from case studies. For example, Carson *et al.* (1986) reported cases of acute effects following ingestion of excess amounts of cobalt salts (30 mg/day) for the treatment of anaemias, including gastrointestinal upset, skin rashes and hot flushes. Features of chronic toxicity include effects on the heart, thyroid and possibly the kidney (Carson *et al.*, 1986). Patients receiving 0.17 – 3.9 mg cobalt/kg bw/day (equivalent to 10 – 234 mg in a 60 kg adult) for 6 days to 8 months, usually to treat anaemia, showed a 20 – 90 % depression in iodine uptake, resulting in goitre and classic signs of hypothyroidism.

### Animal data

Animal studies have shown that cobalt accumulates in the myocardium and causes myocytolysis. Detrimental effects on sperm production and fertility have been observed in rats.

### Carcinogenicity and genotoxicity

No carcinogenicity data are available following exposure by the oral route. Mixed results were obtained with cobalt compounds in a range of *in vitro* and *in vivo* genotoxicity tests.

### Mechanisms of toxicity

No relevant data have been identified.

### Dose response characterisation

There are insufficient data to establish a dose response relationship.

### Vulnerable groups

No vulnerable groups have been identified.

### Genetic variation

No genetic variations have been identified

## Studies of particular importance in the risk assessment

(For full review see <http://www.food.gov.uk/science/ouradvisors/vitandmin/evmpapers> or the enclosed CD)

### Human data

*Seghizzi et al., 1994*

A review of the literature from the 1960s described endemics of cardiomyopathy with mortality rates of up to 50 % in heavy consumers of cobalt-fortified beer (containing cobalt concentrations of 1 – 1.5 ppm). The intake of cobalt in such consumers was estimated to be 6 – 8 mg daily. Dietary protein deficiency may be an important factor in cobalt induced cardiomyopathy, and zinc and magnesium deficiency may also play a part.

### Animal data

*Pedigo et al., 1988*

Cobalt chloride was administered to groups of 10 mice in drinking water providing 23, 42 or 72 mg cobalt/kg bw/day for up to 13 weeks. The highest dose level resulted in a dose- and time-dependent decrease in testicular weight and decreased epididymal sperm concentration, along with decreases in both motility and percent motile forms of sperm. Fertility was decreased at week 13. There was a dose-dependent decrease in testicular weights (as a ratio to body weight), whilst serum testosterone levels were increased 5 to 7 fold at all dose levels.

*Paternain et al., 1988*

Cobalt chloride (25, 50 or 100 mg cobalt/kg bw/day) was administered to mice on days 6 to 15 of gestation by oral gavage. An increase in stunted foetus/litter rates was observed at 50 and 100 mg cobalt/kg bw/day, although this was not statistically significant. The number of corpora lutea, implants, resorptions, live and dead foetuses and sex distribution were unaffected by treatment. Maternal toxicity (decreased weight gain and food consumption) was seen at all dose levels. An erythropoietic effect was apparent in the top dose group.

*Anderson et al., 1992*

Cobalt chloride administered to groups of 10 mice in drinking water providing 72 mg cobalt/kg bw/day for a thirteen week period, resulted in seminiferous tubule degeneration. Groups of mice were evaluated at 7, 9, 11 and 13 weeks treatment. Initial changes involved vacuolation of Sertoli cells and formation of abnormal spermatid nuclei, followed by the presence of multi-nucleated cells and the sloughing off of cells. Continued degeneration resulted in shrinkage of tubules and the accumulation of some calcified necrotic debris. Groups of mice were allowed to recover for 20 weeks after the treatment period. Repopulation of the tubules was observed in a few animals only.

*Cardiovascular effects*

In addition to the above papers, consideration was given to the studies of Morvai *et al.* and Sandusky *et al.* which provided evidence of cardiovascular effects of cobalt from animal models, substantiating the observations that have been made in humans.

*Sandusky et al., 1981*

Groups of dogs were maintained on normal diet or protein and thiamine deficient diet and received 500 mg of cobalt chloride twice weekly by intravenous infusion. Dyspnoea and exercise intolerance was observed in all the dosed animals and tachycardia in those maintained on protein and thiamine deficient diet.

*Morvai et al., 1993*

Administration of cobalt chloride (50 mg cobalt/kg bw/day) by oral gavage to rats for 3 weeks, caused incipient multifocal myocytolysis and a significant decrease in blood pressure and the blood flow to the heart. Alcohol accentuated the effect of cobalt on blood flow.

## Exposure assessment

Total exposure/intake:

|                           |  |
|---------------------------|--|
| Food                      | Mean: 0.012 mg/day (1994 TDS)<br>97.5th percentile: 0.019 mg/day                                     |
| Water                     | 0.02 mg/day (Estimated from IARC 1991 – range in water 0.001 – 0.01 mg/L and consumption of 2 L/day) |
| Supplements               | 0 (present only as B <sub>12</sub> ) (Annex 4)   |
| Estimated maximum intake: | 0.019 + 0.02 = 0.039 mg/day  |

No potential high intake groups have been identified.

## Risk assessment

Cardiomyopathy was reported in heavy beer drinkers in the 1960s as a result of the use of cobalt chloride as a foam stabiliser. Cobalt without alcohol caused damage to the heart muscle, whilst both alcohol and cobalt reduced blood flow (cobalt significantly so), the combination having an additive effect. It has been suggested that the anoxia caused by the combination of alcohol and cobalt exacerbates the cardiotoxic effects of cobalt. Protein deficiency also appears to be a risk factor. Since cobalt chloride is no longer used as an additive in beer, no further cases have been reported. Although this condition was related to oral cobalt, a combination of exposures is necessary.

Few other human data are available. Case reports suggest that acute intakes of >30 mg/day cobalt may cause gastrointestinal upset, skin rashes and hot flushes. Chronic cobalt intakes of 0.17 – 0.39 mg/kg (10.2 – 23.4 mg total in a 60 kg adult) may depress iodine uptake.

The cardiotoxic effects of cobalt can also be reproduced in animals. Other adverse effects related to cobalt include degeneration of the seminiferous tubules and subsequently decreased fertility. There are no data available to establish whether this effect also occurs in humans. It is therefore prudent to assume that it could.

### ESTABLISHMENT OF GUIDANCE LEVEL

There are insufficient data to set a Safe Upper Level for cobalt. There is no evidence of cobalt being used in food supplements, however, cobalt (as the sulphate) may be included in some multi-constituent licensed medicines, at a maximum daily dose of 0.25 mg.

In case reports cobalt is described to cause decreased iodine uptake in man (. 10 mg) or acute effects such as gastrointestinal upset and skin rashes in man (reported with intakes of 30 mg/day).

Cobalt is known to have adverse effects on the heart in both animals and man. In man, cardiomyopathy occurred in heavy consumers of beer containing cobalt chloride as an additive providing a cobalt intake of 6.8 mg/day. The combined effect of alcohol and cobalt and possibly protein deficiency was probably necessary to cause this condition. Cobalt chloride is no longer used for this purpose.

In laboratory animals, cobalt is associated with adverse effects on spermatogenesis and, ultimately, fertility. Doses of 23 mg cobalt/kg bw/day caused minor testicular effects, the severity of the effect then increasing in a dose related manner. This is the lowest dose at which toxic effects have been observed in animals. It is not known whether the effects on spermatogenesis and fertility also occur in humans exposed to cobalt but it would be prudent to assume that they do. If the conventional uncertainty factors were to be applied (10 for LOAEL to NOAEL extrapolation x 10 for inter-species variation x 10 for inter-individual variation = 1000) for guidance purposes only, an intake of 0.023 mg/kg total cobalt would not be expected to result in any adverse effects. This is equivalent to 1.4 mg/day in a 60 kg adult. This level is lower than the doses causing decreased iodine uptake or acute effects in humans, and below the level associated with cardiomyopathy in beer drinkers (see above). It is also substantially higher than the present daily intake of cobalt in the UK (estimated to be approximately 0.030 mg from food and water).

## References

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