Risk Assessment Chromium

General information

Chemistry

Chromium is a metallic element that can exist in a variety of oxidation states; oxidation states other than 0, +2, +3 and +6 are uncommon. Biologically, trivalent (III) and hexavalent (VI) chromium are most important. Within this risk assessment the word chromium refers to ionic chromium except where specific chromium compounds are mentioned.

Natural occurrence

Trivalent chromium is ubiquitous in nature, occurring in air, water, soil and biological materials. Hexavalent chromium compounds are man-made and do not occur naturally in the environment.

Occurrence in foods, food supplements and medicines

Chromium in foods or supplements is in the trivalent form. Processed meats (0.23 mg/kg), whole grain products (bread and miscellaneous cereals 0.13-0.14 mg/kg), pulses and spices are the better sources of chromium, but chromium levels are low in staple foods.

Chromium is not contained in any licensed medicines, but is present (together with other nutrients) in a number of supplements that may only be sold under the supervision of a pharmacist, for use in malabsorptive states, conditions leading to hypoproteinaemia and perioperative nutritional support, at levels up to 0.2 mg. It is also present in a number of multivitamin and mineral food supplements at levels up to 0.6 mg.

Recommended amounts

COMA has set no RNIs but suggested that an adequate level of intake for trivalent chromium lies above 0.025 mg/day for adults and between 0.0001 and 0.001 mg/kg/day for children and adolescents (COMA, 1991). COMA also noted that no adverse effects were observed at intakes of 1000 – 2000 mg/day trivalent chromium. The US National Research Council (NRC) specify an Estimated Safe and Adequate Daily Dietary Intake (ESADDI) of 0.05 – 0.2 mg/day for adults and 0.01 – 0.04 mg/day for infants (0 – 0.5 years).

Analysis of tissue levels and chromium status

Plasma or serum levels reflect trivalent chromium intake, but chromium tissue stores do not rapidly equilibrate with blood chromium, so fasting plasma or serum concentrations may not be an indication of chromium status. Elevated serum chromium may be a good indicator of excessive exposure to chromium.

Brief overview of non-nutritional beneficial effects

Beneficial effects of trivalent chromium on adult-onset type II diabetes mellitus and glucose tolerance have been claimed. Increased lean body mass and decreased total body fat have been attributed to trivalent chromium and chromium compounds have been used to enhance weight loss.

Function

Trivalent chromium has been shown to potentiate insulin action and thereby influences carbohydrate, lipid and protein metabolism.

Deficiency

In humans, deficiency has only been observed in patients on long-term parenteral nutrition. The symptoms observed were impaired glucose tolerance and glucose utilisation, weight loss, neuropathy, elevated plasma fatty acids, depressed respiratory quotient and abnormalities in nitrogen metabolism.

Interactions

Chromium interacts with iron by affecting its binding to transferrin, and has been shown to impair iron metabolism and storage.

Absorption and bioavailability

Intestinal absorption of trivalent chromium is low (0.5 – 2.0%). The mechanism of absorption has not been clearly defined, but it appears to involve processes other than passive diffusion. Chromium picolinate is absorbed more effectively than other forms of trivalent chromium.

Distribution and metabolism

Absorbed trivalent chromium does not enter blood cells, but binds to plasma proteins such as transferrin and is transported to the liver. In contrast, hexavalent chromium does penetrate red blood cells, where it is reduced by glutathione to trivalent chromium, which binds to haemoglobin. Excess hexavalent chromium is taken up into the kidneys, spleen, liver, lungs and bone.

Excretion

Ingested trivalent chromium remains largely unabsorbed and is excreted via the faeces. Absorbed chromium is mainly excreted via urine, with only small amounts being eliminated in perspiration and bile.

Toxicity

Human toxicity

Data on the acute effects of oral exposure to chromium are available from two case reports on accidental or intentional ingestion of chromium at levels of 7.5 mg/kg bw (as hexavalent dichromate) and 4.1 mg/kg bw (as hexavalent chromic acid) respectively. Death was preceded by gastrointestinal haemorrhage and severe kidney and liver damage. Haematological effects have also been reported in individuals consuming sublethal doses. Ingestion of basic chromium sulphate (trivalent) (48 g in 400 mL, equivalent to 800 mg/kg) caused death by cardiogenic and renal shock, pancreatitis, haemorrhage and gut mucosal necrosis.

Chronic exposure to hexavalent chromium is reported to induce renal failure, anaemia, haemolysis and liver failure. Anaemia, haemolysis and liver and renal dysfunction have also been reported in case studies describing chronic exposure to trivalent chromium, but where follow up was reported, these were reversible, and parameters had returned to normal in one year.

Supplementation studies

Trivalent chromium (usually in the form of picolinate) has been investigated in a number of human supplementation studies. The studies have investigated the effects of chromium on a variety of end points ranging from serum chromium to DNA damage. Doses of up to 1 mg/day chromium have been used, for periods up to 64 weeks. No adverse effects were observed, although in many of the studies it is unclear whether such effects were investigated.

Animal data

The available data are limited, but oral exposure to trivalent chromium and hexavalent chromium compounds has resulted in adverse gastrointestinal, hepatic, renal, immunological, neurological, developmental and reproductive effects.

Trivalent chromium compounds are less toxic than hexavalent chromium compounds, with chronic intakes of up to 750 mg/kg bw/day not being associated with adverse effects. Doses of 14 mg/kg bw/day hexavalent chromium for 3 weeks resulted in decreased body weights.

Both forms of chromium have been reported to reduce fertility, foetal weight, and crown length and increase post-implantation losses in mice.

Carcinogenicity and genotoxicity

There is no clear evidence of carcinogenicity where chromium has been tested in rats via the oral route. No data are available relating to the mutagenicity *in vivo* of oral exposure to trivalent chromium.

In general, *in vitro* mutagenicity tests have yielded positive results for hexavalent chromium, and negative results for trivalent. However, two studies in mammalian cells have shown that chromium picolinate (a form of trivalent chromium) may cause DNA damage. The authors of one study proposed that the picolonate moiety was responsible for the activity. However, the authors of another study

proposed a mechanism involving reduction to chromium II and production of hydroxyl radicals. Chromium nicotinate and chromium III chloride were also investigated in one of these studies and did not damage DNA. The significance of these observations is unclear and no *in vivo* genotoxicity data are available.

Mechanism of toxicity

Chromium (VI) induces oxidative stress *in vivo*.

Dose-response characterisation

No data have been identified.

Vulnerable groups

No vulnerable groups have been identified.

Genetic variations

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

Wasser and Feldman, 1997

This was a clinical report of renal failure in a patient taking supplements of 0.6 mg chromium picolinate (trivalent) daily for six weeks to aid weight loss. It is reported that tests had shown normal renal function 2 years previously. Findings from a renal biopsy supported a diagnosis of nephrotoxicity, which the authors attributed to ingestion of chromium.

Cerulli et al., 1998

This was a clinical report of observation of a single patient after ingestion of 1.2 – 2.4 mg/day chromium picolinate for 4 – 5 months. She presented with weight loss, anaemia, haemolysis, liver dysfunction and renal failure. In addition to her intake of over-the-counter chromium supplements, the patient was receiving medication for schizophrenia and depression, but this medication was not believed to be related to the symptoms presented.

Jeejeebhoy, 1999

This was a review paper describing the results of 19 randomised controlled human supplementation trials, in which individuals received between 0.175 and 1 mg trivalent chromium/day for durations of between 6 and 64 weeks. No evidence of toxic effects was identified. Studies considered in the review include:

Anderson et al., 1985

In a double-blind crossover study, 76 adult subjects were given 0.2 mg/day chromic chloride (trivalent) or placebo for three months. Mean basal serum chromium increased significantly from 0.13 ± 0.02 (SE) ng/mL to 0.38 ± 0.02 (SE) ng/mL. This was primarily a study of efficacy and did not report any adverse effects.

Roeback et al., 1991

In a randomised, double blind, placebo-controlled trial, 63 male patients, prescribed beta-blockers for the treatment of hypertension, were given 0.6 mg/day trivalent chromium or placebo for 8 weeks. A low number of side effects were reported, including mild gastrointestinal symptoms and decreased appetite; however, these were of similar low frequency in both treated and control groups.

Abraham et al., 1992

In a randomised clinical trial, 76 patients with atherosclerotic disease were given 0.15 mg/day chromium chloride or placebo for a period of 7 to 16 months. Mean serum chromium levels were significantly increased from 2.69 nmol/L to 12.12 nmol/L. Clinical chemistry indicated no adverse effects on liver or renal function and there were no haematological abnormalities. The authors reported that both placebo and chromium supplement were well tolerated and that patients reported no adverse effects.

Campbell et al., 1999

In a randomised, double-blind study, 23 men aged 50-75 years were given 0.924 mg/day chromium (as picolinate) or placebo for a period of 12 weeks, during which time the subjects participated in a resistance training programme. Five subjects did not complete the study due to reasons unrelated to chromium or placebo treatment (injury, aggravation of injuries, family commitments). The authors did not report any treatment- or placebo-related effects, but this was primarily a study of efficacy.

Animal data

Ivankovic & Preussman, 1975

This was a chronic toxicity/carcinogenicity study, in which trivalent chromium (as chromic oxide) was incorporated into diet at 0, 1, 2, or 5 % (equivalent to 150, 300 or 750 mg chromium/kg bw/day). The compound was baked into bread and fed to rats 5 out of 7 days per week for 840 days (a total of 600 feeds). At the weekends a control diet and a vegetable supplement were given. No adverse effects were observed at any dose level. In a preliminary 90-day study using the same dosing regime, a decrease in organ weights was apparent at the top dose. No statistical analysis was given and the findings were not followed up. Although samples were taken for histological analysis in the main study, the results are not reported. On the basis of this study, it can be concluded that chromic oxide is not carcinogenic, or overtly toxic.

Anderson et al., 1997

Trivalent chromium was given to rats in the diet. A lack of toxicity was demonstrated at levels up to 100 mg chromium per kg of diet as chromium chloride or picolinate for 24 weeks. Assuming a dietary intake of 15 g and a 100 g rat, the intake in the 100 g chromium per kg diet would be 1.5 mg/day or 15 mg/kg bw/day. The animals receiving chromium picolinate had significantly higher renal and hepatic chromium, indicating higher absorption of this compound. There were no histological changes in the liver and kidneys but other organs were not examined histologically.

Reproductive toxicity

Elbetieha & Al-Hamood, 1997

Reproductive toxicity was assessed after exposure of sexually mature male and female mice to trivalent (and hexavalent) chromium in drinking water for 12 weeks. Females received approximately 500 or 1250 mg/kg bw/day and the males, approximately 250 or 1250 mg/kg bw/day trivalent chromium (as chromium chloride). Reduced fertility (assessed by number of pregnant females, viable foetuses and resorptions) was apparent in male mice at the highest dose. In females, exposure to trivalent chromium resulted in a decreased number of implantation sites and viable foetuses at both doses. A parallel study was used to assess organ weights at doses of 500 and 1250 mg/kg bw/day trivalent chromium. In males, bodyweights were significantly reduced and testes weights increased at both doses. Seminal vesicle weights were decreased at the top dose. Female mice were tested only at 120 mg/kg bw/day, which resulted in increased ovarian weight and decreased uterine weight.

Exposure assessment

Total exposure/intake:

Food	Mean: 0.10 mg/day 97.5th percentile: 0.17 mg/day (1997 TDS)
Water	up to 0.002 mg/day (estimated intake from 2 litres of water containing < 0.001 mg/L)
Supplements	up to 0.6 mg/day (Annex 4)
Maximum estimated intake:	0.17 + 0.002 + 0.6 = 0.77 mg/day

No potential high intake groups have been identified.

Risk assessment

The data on oral chromium toxicity are limited. However, it is apparent that the toxicity of chromium varies depending on the valency state, with hexavalent (VI) chromium, being generally more toxic than trivalent (III) chromium. This risk assessment concentrates on the evaluation of trivalent chromium as this is the form found in food and dietary supplements.

Ingested trivalent chromium has a low level of toxicity, due partly to its poor absorption. Chromic acid at chronic doses of up to 750 mg chromium/kg bw/day given in food to adult animals for periods of up to 24 weeks was not associated with adverse effects. Absorption was not demonstrated in this study. Chromium picolinate and chromium chloride were not associated with adverse effects at doses of 15 mg chromium/kg bw/day. Increased levels of tissue chromium indicated that absorption had occurred. Higher doses of chromium (approximately 100 mg/kg bw/day) are associated with reproductive and developmental effects, although these may be secondary to parental toxicity.

In general, hexavalent chromium has given positive results in *in vitro* mutagenicity tests, whereas trivalent chromium compounds have been negative. However, chromium picolinate, a synthetic chromium compound with a higher solubility and lipophilicity than other trivalent chromium compounds, has caused DNA damage in mammalian cells. The significance of these observations is unclear and no *in vivo* genotoxicity data are available.

Limited data from human supplementation studies have indicated that doses up to 1 mg/day of trivalent chromium compounds in general were not associated with adverse effects, although it is unclear what adverse effects were evaluated. The human studies were conducted in a variety of small groups and investigated a range of different endpoints, so limited conclusions may be drawn from these. Two case reports associating chromium picolinate with renal failure exist but the significance of these is uncertain.

ESTABLISHMENT OF GUIDANCE LEVEL

Overall, there are insufficient data from human or animal studies to derive a Safe Upper Level for chromium, although the oral toxicity of poorly absorbed trivalent chromium appears to be low.

There are few available data on chromium (III) toxicity in humans by the oral route. Acute chromium toxicity is associated with vomiting, diarrhoea, haemorrhage and blood loss into the gastrointestinal tract resulting in cardiovascular shock. The available animal data are also limited but adverse gastrointestinal, hepatic, renal, immunological, neurological, developmental and reproductive effects have been reported.

The study by Anderson *et al*. (1997) indicated that 15 mg/kg bw/day chromium (as chromium chloride) was not associated with adverse effects in the rat. Based on this study, and allowing uncertainty factors of 10 for inter-species variation and 10 for inter-individual variation, a total daily intake of about 0.15 mg/kg bw/day (or 10 mg/person) would be expected to be without adverse health effects. This value can be used for guidance purposes and applies to trivalent chromium only. Chromium picolinate is also excluded from this guidance. Unlike other forms of trivalent chromium, chromium picolinate was shown to cause DNA damage in mammalian cells *in vitro*. Additionally, two case reports have associated renal failure with the use of chromium picolinate supplements. The significance of such results is unclear but may be due to the higher solubility and lipophilicity of chromium picolinate than other trivalent chromium compounds, which enable it to be readily absorbed and able to pass through

membranes and enter cells. Further research is therefore needed to investigate the safety of this compound.

References

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