

Chromium

Introduction

The biological effects of chromium strongly depend on its specific chemical form. Nutritive effects are exclusively related to chromium III (valence 3+), and all major toxic effects are associated with chromium VI (valence 6+) (Nielsen 1994; Environmental Protection Agency [EPA] 1998). The first recognized nutritional effects of chromium were its actions as a “glucose tolerance factor,” a function that relies on the ability of trivalent chromium (III) to potentiate the action of insulin with chromium as a part of one or more organic complexes (Nielsen 1994; Stoecker 1999). Some researchers have reported that chromium may influence body composition in animals (Page et al. 1993) and humans (Bulbulian et al. 1996), but other research did not find such effects (Lukaski et al. 1996). Recent studies have found that chromium supplementation, in the form of chromium picolinate, decreased symptoms in type II diabetes patients and that 1,000 µg per day of chromium in this form were more effective to that end than 200 µg per day in other forms (Anderson, Bryden, et al. 1997). This beneficial effect of chromium picolinate has been attributed to increased insulin action rather than to increased secretion (Ghosh et al. 2002). The usual dietary intakes of chromium are 25 to 45 µg (Institute of Medicine [IOM] 2001, 2006).

Safety Considerations

Chromium VI (chromate, valence 6+) is clearly established as the work-related etiological agent in lung disease, including lung cancer, in chromate and stainless steel workers (Gad 1989). However, this form (chromium VI) is not produced from dietary forms by any biological system and thus data on it are not relevant to dietary chromium safety.

Regarding chromium III (valence 3+), no credible data or reports have shown adverse effects in humans from its consumption, and animal data also suggest that orally administered chromium is extremely innocuous (Dourson 1994; Nielsen 1994; Hathcock 1996; IOM 2001; Expert Group on Vitamins and Minerals [EVM] 2003; European Food Safety Authority [EFSA] 2010).

The potential genotoxicity of chromium III has been assessed in several experiments. Results of in vitro assays are conflicting, with some evidence indicating that certain chromium III compounds may cause chromosomal damage in vitro at high concentrations (EFSA 2010); however, chromium III compounds do not have genotoxic activity in vivo (EFSA 2010). Moreover, ingestion of various chromium III compounds did not produce carcinogenicity in mice and rats in long-term studies (Schroeder et al. 1964, 1965; Ivankovic and Preussman 1975). The National Toxicology Program (NTP) of the U.S. Department of Health and Human Services (DHHS) performed carcinogenicity studies on chromium picolinate monohydrate and concluded that there was no evidence of carcinogenic activity due to the tested substance in female rats or in male or female mice (DHHS 2008; Stout et al. 2009). Although the NTP stated that there was equivocal evidence of carcinogenic activity in male rats (based on an increase in the incidence of preputial gland adenomas), the absence of a dose-response effect, as well as the lack of such effects across sexes or species, indicates that chromium picolinate is not carcinogenic.

The available data from studies in mice provide evidence of a lack of developmental toxicity associated with chromium III ingestion. In a limited number of animal studies, inconsistent findings with respect to reproductive toxicity have been reported, with no effects on reproduction parameters observed in some studies but some effects noted in others (EFSA 2010). The LOAEL values from the latter studies are several orders of magnitude higher than the intake of chromium III from food and supplements, indicating a large margin of safety.

Picolinic acid is a metabolite of tryptophan, and total daily exposure via this route is many times higher than the amounts contained in chromium picolinate dietary supplements. It is naturally present in human breast milk (3 μM), cow milk (5 μM), and other foods such as broccoli, beans, and potatoes (Robello et al. 1982). The estimated urinary output of picolinate by adults is 14 mg per day (Evans 1993). A chromium picolinate-containing dietary supplement (CrPic_3) with 200 μg chromium would include 1.4 mg of picolinate. Assuming total absorption of the picolinate from this strength supplement and no catabolism of the picolinate, the supplement would increase urinary output by 10 percent. Even with a chromium-containing supplement level of 1,000 μg , the daily picolinate exposure of adults would be increased by only 50 percent.

Human clinical trials have provided strong support for the safety of chromium supplements in chromium picolinate form at levels of up to 1,000 µg per day (IOM 2001, 2006; Broadhurst and Domenico 2006). No pattern of adverse effects has been observed in these trials.

A number of anecdotal reports have attributed adverse effects to supplements of chromium in general (IOM 2001; EVM 2003) and to chromium picolinate in particular (Wasser et al. 1997). One report, concerning a single case of renal failure in a person who was taking chromium picolinate, attributed the disease to the chromium supplement (Wasser et al. 1997). The authors acknowledged that the patient also received “antihypertensive agents,” but nonetheless attributed the effect solely to chromium picolinate; the renal toxicity of antihypertensive agents and pathological effects of poorly controlled hypertension apparently were not considered. Critical letters were published in response to the report (Michenfelder et al. 1997; Hathcock 1997), pointing out the flaws in the conclusion. Despite these methodological issues and the critical response, the case is often cited without caveat (Hepburn et al. 2003; IOM 2006).

Official Reviews

World Health Organization (WHO 1996). The WHO reviewed the safety of chromium supplementation and considered that supplementation with chromium should not exceed 250 µg per day. It was noted, however, that research suggests that the upper limit of the safe range of population mean intakes of chromium could be above this level.

EPA (1998). From chromic oxide data with mice, the EPA identified 1.47 g of chromium per kg of body weight as the NOAEL in animals but could not identify a LOAEL. By rounding down to 1 g per kg and applying a composite UF of 1,000, the EPA calculated a chromium maximum of 1 mg per kg, which is equivalent to 70,000 µg for a 70-kg person. Thus, chromium III has an extraordinarily wide margin of safety.

IOM (2001). The IOM could not identify a mean requirement, but set its AI at 25 µg for young adult women and 35 µg for young adult men. The adequacy of intakes in this range is supported

by normal dietary chromium consumption in healthy persons, but it is not clear that such intakes lower the risk of type II diabetes in middle age. The IOM considered the evidence related to chronic renal failure, genotoxicity, carcinogenicity, hepatotoxicity, reproductive toxicity, and other possible effects and could not identify a hazard or dose-response relationship for soluble salts of dietary chromium (that is, chromium III). Thus, the IOM did not set a UL. The organization has released a draft monograph on the safety of chromium picolinate, but no risk assessment conclusion was reached for this form of chromium (IOM 2006). The draft report did, however, supply an excellent summary of the clinical trials that have been done on this ingredient.

European Commission, Scientific Committee on Food (EC SCF 2003). The EC SCF reviewed chromium toxicity and reached conclusions that were, as a whole, the same as those reached by the IOM. The animal data of Anderson, Cheng, et al. (1997) were considered, but, given the absence of adverse effects, the EC SCF decided not to set an UL for chromium.

EVM (2003). The UK's EVM found no credible evidence of adverse effects but identified a guidance level of 10,000 µg (10 mg) per day, based on extrapolation from animal research on chromium chloride and chromium picolinate. In making this decision, the EVM derived its guidance level directly from the experiments of Anderson and coworkers, who performed histopathological examinations of the treated rats and found no adverse effects resulting from chromium chloride (CrCl₃) or chromium picolinate (CrPic₃) (the rats were fed 15 mg of chromium per kg of body weight per day) (Anderson, Cheng, et al. 1997). A composite UF of 100 was applied by the EVM to the highest level of chromium chloride used, which was identified as the NOAEL. In the Anderson study relied upon by the EVM, chromium chloride and chromium picolinate were used with the same levels of chromium, and each produced no evidence of toxicity. The EVM refused to apply the guidance level derived from Anderson's data to the picolinate form based on findings of DNA damage caused by chromium picolinate to mammalian cells in vitro. Subsequently, the Committee on Mutagenicity reviewed further data and concluded that the balance of the evidence suggested that chromium picolinate was not genotoxic. Accordingly, the UK Food Standards Agency (FSA) stated in 2004 that there is no need to avoid chromium picolinate (FSA 2004).

EFSA (2010). The EFSA evaluated the safety of chromium III as a nutrient added to food for particular nutritional uses and foods intended for the general population (including supplements), with a focus on the potential genotoxicity of chromium III. The EFSA concluded that the safety of chromium III as a nutrient added to food is not of concern, provided that the ingestion of chromium III from the food is not greater than 250 µg per day (which the WHO considered as the level of chromium supplementation that should not be exceeded). The EFSA's conclusion was based on the following: (1) the maximum intake levels for supplemental intake established by the WHO would be in the same order of magnitude as normal dietary intake of chromium in the EU; (2) chromium picolinate (and other sources of chromium III) might cause DNA damage at high concentrations in vitro; (3) the DNA damage that may occur in vitro has not been reported in in vivo genotoxicity assays; (4) chromium III is not carcinogenic; and (5) there is a large margin of safety between an intake of 250 µg per day (4.1 µg per kg per day in a 60-kg adult) and the NOAEL of 6,100 mg chromium picolinate monohydrate per kg per day (727 mg chromium III per kg per day) for mice and of 2,400 mg chromium picolinate monohydrate per kg per day (300 mg chromium III per kg per day) for rats in the long-term studies conducted by the NTP.

CRN Recommendations

The CRN concludes that the available clinical trial data are sufficient to indicate safety for chromium supplements at levels of up to 1,000 µg per day for adults. On the basis of both the large number of clinical trials summarized in Table B-1 from the IOM's 2006 draft monograph and other official reviews of forms of chromium III, CRN sets its UL for chromium supplements at 1,000 µg per day, including the picolinate form and other forms of chromium III.

Quantitative Summary for Chromium

CRN UL, supplemental intake	1,000 µg/day (any chemical form of chromium III)
IOM UL, total intake	Not determined
EC SCF UL, total intake	Not determined
EFSA, maximum added to foods (including food supplements)	250 µg/day
EC supplement maximum	Not determined
EVM, guidance level, total intake	10 mg (10,000 µg)/day

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