

## **Chromium**

---

### ***Function***

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 1999; Environmental Protection Agency 2004). 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 (chromium III) to potentiate the action of insulin and that is carried out by chromium as a part of one or more organic complexes (Nielsen 1999; 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 was more effective to that end than 200 µg per day (Anderson et al. 1997b). This beneficial effect of chromium picolinate administration 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 (Food and Nutrition Board 2001).

### **Safety Evidence**

No credible data or reports have shown adverse effects of chromium III in humans, and animal data also suggest that orally administered chromium is extremely innocuous (Nielsen 1999; Dourson 1994; Hathcock 1996; Food and Nutrition Board 2001; Expert Group on Vitamins and Minerals 2003). Conversely, chromium VI (chromate) is clearly established as the work-related etiologic agent in lung disease, including lung cancer in chromate and stainless steel workers (Gad 1989). This form is not produced from dietary forms by any biological system and thus data on it are not relevant to dietary chromium safety.

One report described chromosome breakage *in vitro* when high concentrations of chromium (as chromium III) picolinate were added directly to cells (Stearns et al. 1995). These data showed that even at the high concentrations used *in vitro*, the only evidence for DNA damage was linked to picolinic acid, not chromium. Overall, the data of Stearns and coworkers do not provide appropriate evidence that chromium in foods or dietary supplements carries any risk of causing DNA damage or cancer. This conclusion is reached by applying EPA’s guidelines for the interpretation of *in vitro* and experimental data (Environmental Protection Agency 1991, 1996).

A recent report of a study with fruit flies suggested that chromium picolinate caused sterility and lethal mutations, an effect possibly initiated by absorption and reactivity of intact chromium picolinate molecules (Hepburn et al. 2003). The authors acknowledged, however, that the effects could have been physiological rather than mutagenic. They also suggested that other published studies with intravenously injected chromium in rodents could indicate an increased risk of cancer in humans. The high dosage and the low absorption efficiency for chromium (2 percent of dose, or less) prevent any meaningful interpretation of such data and raise doubts about any such conclusions.

Studies with vertebrate animals have found evidence for adverse effects of dietary chromium at extreme doses (IRIS 2004; Expert Group on Vitamins and Minerals 2003) but none at more relevant doses (Anderson et al. 1997a). Chromium and chromium picolinate are not mutagenic, carcinogenic, or teratogenic in animals.

Picolinic acid is a metabolite of tryptophan, and total daily exposure is many times higher than the amounts contained in dietary supplements of chromium picolinate. It is naturally present in human breast milk (3  $\mu\text{M}$ ), cow milk (5  $\mu\text{M}$ ), 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 supplement of 200  $\mu\text{g}$  of chromium as  $\text{CrPic}_3$  would include 1.4 mg of picolinate. Assuming total absorption of the picolinate from a 200  $\mu\text{g}$  supplement and no catabolism of the picolinate, the supplement would increase urinary output by 10 percent. Even at a chromium supplement level of 1,000  $\mu\text{g}$ , 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  $\mu\text{g}$  per day (Food and Nutrition Board 2001, 2004). No pattern of adverse effects has been observed in approximately thirty clinical trials. Supplementation with 400  $\mu\text{g}$  of chromium as chromium picolinate produced no evidence of mutagenesis after eight weeks (Kato et al. 1998). The FNB Committee on the Framework for Evaluating the Safety of Dietary Supplements concluded that chromium picolinate is safe at levels up to 200  $\mu\text{g}$  of chromium per day (Food and Nutrition Board 2004).

A number of anecdotal reports have attributed adverse effects to supplements of chromium in general (Food and Nutrition Board 2001; Expert Group on Vitamins and Minerals 2003) and to chromium picolinate in particular (Wasser and Feldman 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 and Feldman 1997). The authors acknowledged that “the only other medications [the patient] received were antihypertensive agents,” but nonetheless definitively attributed the effect to chromium picolinate rather than

From: **Vitamin and Mineral Safety 2<sup>nd</sup>** Edition ~ by John N. Hathcock, Ph.D.  
Council for Responsible Nutrition (CRN) All rights reserved. Republication or redistribution of  
content is expressly prohibited without prior written consent of CRN.

looking into other factors. Specifically, the renal toxicity of antihypertensive agents and pathological effects of poorly controlled hypertension apparently were not considered. Nonetheless, the case continues to be credulously cited (Food and Nutrition Board 2004; Hepburn et al. 2003) failing to mention published letters (Michenfelder et al. 1997; Hathcock 1997) pointing out major flaws in the report's conclusions.

## **Published Official Reviews of Chromium Safety**

An FNB committee reporting on Dietary Reference Intakes (DRI) 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, this FNB committee did not set a UL for chromium (Food and Nutrition Board 2001). The FNB Committee on the Framework for Evaluating the Safety of Dietary Supplements has released a monograph on chromium picolinate; it found no credible evidence of toxicity but concluded that the evidence was convincing only up to a level of 200 µg of chromium (Food and Nutrition Board 2004). The detailed report supplied an excellent summary of the clinical trials that have been done on this ingredient (Food and Nutrition Board 2004).

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

The UK EVM found no credible evidence of adverse effects but identified a GL of 10,000 µg (10 mg) per day, based on extrapolation from animal research on chromium chloride and chromium picolinate (Expert Group on Vitamins and Minerals 2003). In making this decision, UK EVM derived its GL directly from the experiments of Anderson and coworkers, who performed histopathologic examinations of the treated rats and found no adverse effects resulting from chromium chloride (CrCl<sub>3</sub>) or chromium picolinate (CrPic<sub>3</sub>). (The rats were fed 15 mg of chromium per kg of body weight per day.) A composite UF of 100 was applied by UK EVM to the highest level of chromium chloride used, which was identified as the NOAEL. In the Anderson study relied upon by UK EVM, chromium chloride and chromium picolinate were used with the same levels of chromium, and each produced no evidence of toxicity. Inexplicably, UK EVM refused to apply the GL derived from Anderson's data to the picolinate form.

From: **Vitamin and Mineral Safety 2<sup>nd</sup>** Edition ~ by John N. Hathcock, Ph.D.  
Council for Responsible Nutrition (CRN) All rights reserved. Republication or redistribution of  
content is expressly prohibited without prior written consent of CRN.

The EPA set its RfD for chromium (as chromium III) based on animal data related to chromic oxide (Cr<sub>2</sub>O<sub>3</sub>), a form of chromium less soluble and bioavailable than either the chloride or the picolinate. From chromic oxide data with mice, 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, EPA calculated a chromium RfD of 1 mg per kg, which is equivalent to 70,000 µg for a 70 kg man. Thus, chromium III has an extraordinarily wide margin of safety. Even if chromium picolinate were 100 times more bioavailable than chromic oxide, the extrapolated RfD would be 700 µg.

## **CRN ULS for Chromium**

---

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 B1 from the FNB's 2004 monograph and other official reviews of forms of chromium III, CRN sets its ULS for chromium at 1,000 µg per day, including the picolinate form and other forms of chromium III.

### **Comparison of Safety Values for Chromium**

<b>CRN ULS</b>	1,000 µg (any form of chromium III)
<b>US FNB UL</b>	Reviewed but not established (no toxicological basis)
<b>EC SCF UL</b>	Reviewed but not established (no toxicological basis)
<b>EC supplement maximum</b>	Not established (as of May 2004)
<b>UK EVM GL</b>	10 mg (10,000 µg), but not including the picolinate form

### *References*

Anderson RA, Bryden NA, Polansky MM. Lack of toxicity of chromium chloride and chromium picolinate in rats. *J Am Coll Nutr* 1997b; 16:273-279.

Anderson RA, Cheng N, Bryden NA, Polansky MN, Cheng N, Chi J, Feng J. Elevated intakes of supplemental chromium improve glucose and insulin variable in individuals with type 2 diabetes. *Diabetes* 1997a; 46:1786-1791.

Bulbulian R, Pringle DD, Liddy MS. Chromium picolinate supplementation in male and female swimmers. *Med Sci Sports Ex* 1996; 28S:S111.

From: **Vitamin and Mineral Safety 2<sup>nd</sup>** Edition ~ by John N. Hathcock, Ph.D.  
Council for Responsible Nutrition (CRN) All rights reserved. Republication or redistribution of  
content is expressly prohibited without prior written consent of CRN.

Dourson ML. The chromium reference dose. In: Mertz W, Abernathy CO, Olin SS, eds. Risk  
assessment of essential elements. Washington, DC: ILSI Press, 1994; 207-212.

Environmental Protection Agency, 2004. Integrated Risk Information System (IRIS). Chromium:  
Reference Dose for Chronic Oral Exposure (RfD). Available online at <http://www.epa.gov/iris/>.

Environmental Protection Agency. Pesticide assessment guidelines: Subdivision F, hazard  
evaluation, human and domestic animals. Series 84, Mutagenicity, Addendum 9. Office of  
Pesticide Programs, Washington, D.C.: 1991; PB91-158394, 540/09-91-122.

Environmental Protection Agency. Proposed guidelines for carcinogen risk assessment.  
Washington, DC: Office of Research and Development: 1996; EPA/600/P-92/003C.

Evans GW. Chromium picolinate in an efficacious and safe supplement. *Int J Sport Nutr* 1993;  
3:117-122.

Expert Group on Vitamins and Minerals. Safe upper levels for vitamins and minerals, Food  
Standards Agency, United Kingdom, 2003.

Food and Nutrition Board. Dietary reference intakes for vitamin A, vitamin K, arsenic, boron,  
chromium, copper, iodine, iron, manganese, molybdenum, nickel, silicon, vanadium, and zinc.  
Washington, DC: National Academy Press, 2001.

Food and Nutrition Board, 2004. Safety Review: Prototype Monograph on Chromium Picolinate.  
Available at <http://www.iom.edu/fnb>

Gad SC. Acute and chronic systemic chromium toxicity. *Sci Total Environ* 1989; 86:149-157.

Ghosh D, Bhattacharya B, Mikhherjee B, Manna B, Sinha M, Chowdhury J, Chowdhury S. Role of  
chromium supplementation in Indians with type 2 diabetes mellitus. *J Nutr Biochem* 2002;  
13:690-697.

Hathcock JN. Over-the-counter chromium and renal failure. *Ann Intern Med* [letter] 1997;  
127:655.

Hathcock JN. Safety limits for nutrients. *J Nutr* 1996; 126:2386S-2389S.

Hepburn D, Xiao J, Bindom S, Vincent J, O'Donnell J. Nutritional supplement chromium  
picolinate causes sterility and lethal mutations in *Drosophila melanogaster*. *Proc Natl Acad Sci*  
2003; 100:3766-3771.

Kato I, Vogelmann JH, Dilman V, Karkoszka J, Frenkel K, Durr NP, Orentreich N, Toniolo P.  
Effect of supplementation with chromium picolinate on antibody titers to 5-hydroxyuracil.  
*European Journal of Epidemiology* 1998; 14:621-626.

Lukaski HC, Bolonchuk WW, Siders WA, Milne DB. Chromium supplementation and resistance  
training: Effects on body composition, strength, and trace element status of men. *Am J Clin Nutr*  
1996; 63:954-965.

Michenfelder HJ, Tompson J Shepherd M. Over-the-counter chromium and renal failure. *Ann Int  
Med* 1997; 127:655.

From: **Vitamin and Mineral Safety 2<sup>nd</sup>** Edition ~ by John N. Hathcock, Ph.D.  
Council for Responsible Nutrition (CRN) All rights reserved. Republication or redistribution of  
content is expressly prohibited without prior written consent of CRN.

Nielsen FW. Chromium. In: Shils ME, Olson JA, Shike M, Ross AC, eds. *Modern nutrition in health and disease*, 9th ed. Philadelphia: Williams & Wilkins, 1999; 264-268.

Page TG, Southerm LL, Ward TL, Thompson DL Jr. Effect of chromium picolinate on growth and serum and carcass traits of growing-finishing pigs. *J Anim Sci* 1993; 71:656-662.

Robello T, Lonnderdal B, Hurley L. Picolinic acid in milk, pancreatic juice and intestine: Inadequate for role in zinc absorption. *Am J Clin Nutr* 1982; 35:1-5.

Scientific Committee on Food. Opinion of the Scientific Committee on Food on the Tolerable Upper Intake Level of Trivalent Chromium. European Commission, SCF/CS/NUT/UPPLEV/67 Final, Brussels, 2003.

Stearns DM, Wise JP Sr., Patierno SR, Wetterhahn KE. Chromium (III) picolinate produces chromosome damage in Chinese hamster ovary cells. *FASEB J* 1995; 9:1643-1648.

Stoecker BJ. Chromium. In: Shils M, Olson J, Shike M, eds. *Modern nutrition in health and disease*, 9th ed. Baltimore: Williams & Wilkins, 1999; 277-282.

Wasser WG, Feldman NS. Chronic renal failure after ingestion of over-the-counter chromium picolinate. *Ann Intern Med* 1997; 126:410.