SUMMARY OF DATA FOR CHEMICAL SELECTION

Chromium Picolinate
14639-25-9

BASIS OF NOMINATION TO THE CSWG

The nomination of chromium picolinate is based on the potential for widespread consumer exposure. Marketed as a dietary supplement, chromium picolinate is heavily promoted as a muscle builder and weight-loss agent. Industry claims suggest that several million persons may ingest chromium picolinate tablets; sales of chromium-based supplements are approximately $100 million a year.

Some researchers suggest that chromium picolinate causes a significant increase in lean body mass by altering the rate of internalization of insulin. Other investigators have indicated that recommended doses of chromium picolinate by other than the oral route would cause accumulation of chromium in the liver and kidneys, an unknown risk to the consumer. Scrutiny of the literature on chromium picolinate reveals contentious discussion between researchers and some unexpected stakeholders.

A beneficiary of the Dietary Supplement Health and Education Act of 1994, chromium picolinate can be sold legally without evidence of safety or efficacy.

SELECTION STATUS

ACTION BY CSWG: 4/28/98

Studies requested:

- Subchronic studies of chromium picolinate and picolinic acid
- Carcinogenicity
- Micronucleus assay
- Metabolism and disposition studies
- Reproductive toxicity and teratogenicity studies

Priority: High

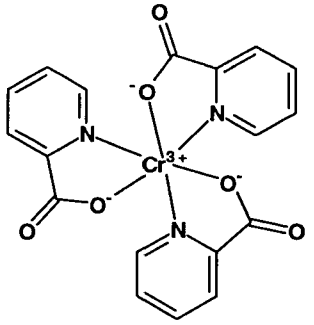
Rationale/Remarks:

- Widespread human exposure from use as a dietary supplement; exposure of young women of childbearing age because of use to promote weight loss.
- Testing should be performed on a well-characterized complex.
- Testing should distinguish toxicity due to chromium from that due to picolinate.
- Reconsider for carcinogenicity after subchronic studies are completed.
- NCI will conduct Ames *Salmonella* and mouse lymphoma assays.
- Since chromium is a required micronutrient, testing should be conducted at some reasonable multiple of human exposure.

CHEMICAL IDENTIFICATION

CAS Registry Number:	14639-25-9
Chemical Abstract Service Name:	Chromium, tris (2-pyridinecarboxylato-N(1), O(2))-(9CI)
Synonyms and Trade Names:	Chromium picolinate; chromium 2-pyridine-carboxylate; chromium tripicolinate; chromium, tris (picolinato)-; picolinic acid, chromium salt; 2-pyridinecarboxylic acid, chromium salt; tris(picolinato)chromium
Structural Class:	Mineral chelate

Structure, Molecular Formula and Molecular Weight:



$C_{18}H_{12}CrN_3O_6$ Mol. wt.: 418.31

Chemical and Physical Properties:

Description:	Red solid; lipophilic (Evans & Pouchnik, 1993; Budavari, 1996)
Solubility:	Solubility in water (pH. 7.0) = 0.6 mM; chloroform = 2.0 mM (Budavari, 1996)

Technical Products and Impurities: Chromium picolinate is available in research quantities from ICN Pharmaceuticals, Inc. (ICN Pharmaceuticals, Inc., 1998). As an over-the-counter dietary

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supplement it is also available at health food stores, supermarkets, pharmacies, and mail order companies. Chromium picolinate formulations are available in capsules, tablets, and chewing gums (Tuchman, 1995; Federal Trade Commission, 1996; Dialog Information Services, 1997a,b). One 1.67 mg capsule of chromium picolinate corresponds to 208 μg of chromium and 1.46 mg of picolinate (Stearns *et al.,* 1995a).

The commercially available chromium picolinate products shown in Table 1 were identified in a survey of two Maryland CVS pharmacies conducted in February and March, 1998.

Table 1. Survey of chromium picolinate products

Product Name	Manufacturer/ Distributer	Concentration (μg Cr)	Total recommended daily dose (μg Cr)
Natural Performance Chromium Picolinate	Natural Performance	200	200-400
CVS Chromium Picolinate	CVS	200	400
Chromium picolinate	Great American Nutrition	200	200-600
Pyruvate C Weight Loss Program (with pyruvate)	Richardson Lab	100	400
Fat Burners (multi-formula)	Amerifit	25	100
Chroma Slim for men (multi-formula)	Richardson	100	400
Diet System 6 (multi-formula)	Applied Nutrition	50	300 (max.)
Ultra Chroma Slim (multi-formula)	Richardson	67	400
Ultraburn Chromium (multi-formula)	Thompson Medical	50	200
Ultraformula Fat Burner (multi-formula)	Natural Performance	50	200
Chroma-trim gum	Gum Tech International	100	300

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EXPOSURE INFORMATION

Production and Producers: Picolinate is a bidentate chelating ligand which coordinates with chromium through the pyridine nitrogen and the carboxyl oxygen. Mono-, di-, or tri-picolinate complexes can be prepared by dissolving 0.01 mole chromium chloride hexahydrate in 25 ml deionized water followed by 0.01, 0.02, or 0.03 mole picolinic acid, then stirring until a reddish color appears, indicating complex formation (Evans & Pouchnick, 1993).

The synthetic process for metal picolinates was patented by the U.S. Department of Agriculture (USDA) and leased to Nutrition 21. Nutrition 21 holds the exclusive U.S. license on the patent rights to chromium picolinate and sells it to the public through distributors (Coleman, 1997). According to recent chemical catalogs and directories, chromium picolinate is manufactured and/or distributed by American Ingredients, Inc., Ashland Chemical Co., DNP International Co., Inc., ICN Pharmaceuticals, Inc., Pharmline, Inc., and V.L. Clark Chemical Co. (Hunter, 1997; McCoy, 1997; ICN Pharmaceuticals, Inc., 1998).

No data were reported for chromium picolinate by the US International Trade Commission (USITC) in the ten most recent volumes of *Synthetic Organic Chemicals, US Production and Sales*, for the years 1984-1993. This source is no longer published. No quantitative information on annual production was found in the other available literature.

Total retail sales for chromium-based dietary supplements have been estimated at $100 million a year (Federal Trade Commission, 1996).

Chromium picolinate is not listed in the EPA's Toxic Substances Control Act (TSCA) Inventory.

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Use Pattern: Chromium picolinate is a nutritional supplement being marketed heavily through health food stores, supplement suppliers, and weight loss fitness centers (Clarke, 1998). The promoters' claims assert that the supplement will cause significant and long-term weight loss, increase metabolic rate, control appetite, reduce serum cholesterol, regulate blood sugar levels, increase energy and/or stamina, improve body composition by reducing body fat and building muscle, and treat and prevent diabetes. Independent research by the USDA does not support the marketing claims made by the holder of the patent rights to chromium picolinate (Coleman, 1997; Federal Trade Commission, 1996). Patent claims by Dobbins (1990, 1991) cite the use of chromium picolinate in the prevention and treatment of alcoholism.

Chromium (III) is considered an essential trace nutrient. It is a cofactor for insulin action and has a role in the peripheral activities of this hormone by forming a ternary complex with insulin receptors, facilitating the attachment of insulin to these sites. Prolonged use of a diet deficient in chromium may lead to impaired glucose metabolism, and possibly effects on growth and on lipid and protein metabolism (Goyer, 1991). The estimated safe and adequate daily dietary intake of chromium for adults is between 50 and 200 μg (Marcus & Coulston, 1990).

Picolinic acid, a natural derivative of the amino acid tryptophan, is thought to facilitate chromium absorption. The supposed "enhanced bioavailability" of chromium picolinate forms the basis for claims that the supplement increases muscle mass and decreases body fat (Coleman, 1997).

Human Exposure: The primary exposure of humans to chromium picolinate occurs through its use as a nutritional supplement. One manufacturer estimated that "several million Americans" take chromium picolinate (Gorman & Herrington, 1997).

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No listing was found for chromium picolinate in the National Occupational Exposure Survey (NOES), which was conducted by the National Institute for Occupational Safety and Health (NIOSH) between 1981 and 1983.

Environmental Occurrence: No information on the environmental occurrence of chromium picolinate was identified in the available literature.

Regulatory Status: No standards or guidelines have been set by NIOSH or OSHA for occupational exposure to or workplace allowable levels of chromium picolinate. Chromium picolinate was not on the American Conference of Governmental Industrial Hygienists (ACGIH) list of compounds for which recommendations for a threshold limit value (TLV) or biological exposure index (BEI) are made.

Since 1994, dietary supplements have been regulated under the Dietary Supplement Health and Education Act (DSHEA). For dietary supplements on the market prior to October 15, 1994, the DSHEA requires no proof of safety in order for them to remain on the market. The labeling requirements for supplements allow warnings and dosage recommendations as well as substantiated "structure or function" claims. All claims must prominently note that they have not been evaluated by the FDA, and they must bear the statement "This product is not intended to diagnose, treat, cure, or prevent any disease" (Croom & Walker, 1995).

In November 1996, the Federal Trade Commission (FTC) announced settlements with Nutrition 21 and two other companies charged with making unsupported claims about weight loss and health benefits for chromium picolinate. The FTC also maintained that: the companies failed to substantiate their claim that 90 percent of American adults do not consume enough chromium in their diets to support normal insulin function; that the companies falsely claimed chromium picolinate's benefits are proven by scientific studies;

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and that some of the companies made unsubstantiated claims that the testimonials used in their ads reflected the typical experiences of consumers who used chromium picolinate products. Under the proposed consent agreements to settle the allegations, the respondents would be prohibited from making any of the challenged claims for chromium picolinate in the future unless they had competent and reliable scientific evidence to support them (Federal Trade Commission, 1996).

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EVIDENCE FOR POSSIBLE CARCINOGENIC ACTIVITY

Human Data: No epidemiological studies or case reports investigating the association of exposure to chromium picolinate and cancer risk in humans were identified in the available literature.

Between January 1995 and April 1996, the Georgia Poison Center received 33 calls involving chromium picolinate (29 humans and 4 animals). Amounts ingested ranged from 100 to 6000 μg. While many of the adverse drug reactions (ADR) could be attributed to ingredients such as niacin and ephedra in combination type chromium picolinate products, chromium picolinate alone also had some moderate side effects in humans including chest pain, erythema/flushing, dehydration, agitation, dizziness, and headache (Gorman & Herrington, 1997).

Wasser and coworkers (1997) reported a case of chronic renal failure in a female patient who had used 600 μg of chromium picolinate daily for 6 weeks 5 months earlier. They felt that the renal biopsy supported a diagnosis of chromium-induced nephrotoxicity in that the findings were consistent with chronic interstitial nephritis from heavy metal exposure.

A male patient who took chromium picolinate on three separate occasions (200, 400, and 400 μg) experienced three progressively worse episodes of cognitive, perceptual, and motor changes. The symptoms ("feeling funny", disrupted thinking, and difficulty in driving) subsided within 2 hours (Huszonek, 1993).

Animal Data: No 2-year carcinogenicity studies of chromium picolinate in animals were identified in the available literature.

The toxicity of chromium picolinate was evaluated in Sprague-Dawley rats (8 animals per

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group; sex not specified). Chromium was added to the diet as picolinate at levels of 0, 5, 25, 50, or 100 mg/kg for 20 weeks. There were no statistically significant differences in body weight, organ weights, or blood variables among all the groups tested at 11, 17, and 24 weeks of age. Blood variables measured included glucose, cholesterol, triglycerides, blood urea nitrogen, lactic acid dehydrogenase, transaminases, total protein, and creatinine. Liver and kidney chromium concentrations increased linearly for the chromium picolinate fed animals. Histological evaluations were done on one kidney and on one third of the largest liver lobe of each animal in the 100 mg group; no detectable differences were found (Anderson *et al.*, 1997).

Short-Term Tests: McCarty (1996) reported that chromium picolinate was negative in the Ames assay (strains and doses not reported). After reviewing this unpublished study, Stearns and Wetterhahn (1996) noted that the methodology was ambiguous and that the experiment was not properly controlled.

Chromium picolinate did not induce chromosomal aberrations in a rat *in vivo* assay. Male and female Sprague-Dawley rats were dosed once with 0, 33, 250, or 2000 mg/kg of chromium picolinate and were sacrificed 18 or 42 hours later (Esber & Moreno, 1997).

In an *in vitro* assay with Chinese hamster ovary cells, soluble chromium picolinate at doses of 0.05 to 1 mM produced chromosomal aberrations which were 3- to 18- fold above control levels. Particulate chromium picolinate at doses of 8 and 40 $\mu g/cm^2$ produced aberrations 4- and 16- fold above controls, respectively. Picolinic acid at doses of 1 to 2 mM was also clastogenic in this assay. Chromium (III) nicotinate, nicotinic acid, and chromium (III) chloride hexahydrate were not clastogenic, causing the authors to infer that the damage was caused by the picolinate ligand (Stearns *et al.*, 1995b).

At doses of 50 to 500 μg, picolinic acid was not mutagenic in *Salmonella typhimurium*

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strains TA98, TA100, TA1535, TA1537, and TA1538 both with and without metabolic activation; it was also inactive as a comutagen with 2-aminoanthracene in strain TA1538 (Bowden *et al.*, 1976).

Picolinic acid, at a concentration of 2 mM, did not stimulate unscheduled DNA synthesis in UV-irradiated human lymphocytes (Sims *et al.*, 1982).

Metabolism:

Human Data: After oral administration of chromium picolinate supplements at 400 μg Cr/day for 3 days to male and female volunteers, the mean percentage of Cr (III) absorbed was 2.80% with a range of 1.50-5.2%. Absorption estimates were based on urinary excretion levels and pharmacokinetic modeling (Gargas *et al.*, 1994). Using data from the Gargas study, Stearns and coworkers (1995a) estimated that, based on 5.01 mg of chromium picolinate daily for 5 years and absorption of 2.8%, half of the retained dose (1.0 mg of Cr) in a liver of average mass (1.5 kg) would be equivalent to 0.70 μg Cr/g tissue. The researchers also noted that Cr (III) is slowly excreted from cells and tissues and therefore, increased absorption of Cr (III) due to dietary supplementation may lead to accumulation of chromium, with poorly understood consequences.

Animal Data: Chromium picolinate fed to weanling Sprague-Dawley rats at 5000 ng of Cr/g of diet for 3 weeks resulted in significant increases in chromium incorporation into the kidney, liver, spleen, heart, and lung when compared to controls fed basal diet containing 30 ng Cr/g of diet or to the chromic chloride group fed 5000 ng of chromium. Chromium concentrations were greatest in the kidney at 368 ng/g dry weight; chromium concentration in the liver was 50 ng/g (Anderson *et al.*, 1996).

Chromium (III) compounds are essential to normal glucose, protein, and fat metabolism. The biologically active chromium (III) molecule often referred to as glucose tolerance

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factor (GTF) appears to be a dinicotinato-chromium (III) glutathione-like complex. This complex functions by facilitating interaction of insulin with its receptor site, thus influencing glucose, protein, and lipid metabolism. Humans and animals are capable of converting inactive chromium compounds to biologically active forms (ATSDR, 1993).

Picolinic acid is an endogenous metabolite of tryptophan, synthesized by the kynurenine pathway, like quinolinic and nicotinic acids (Beskid *et al.*, 1995). No information on the metabolism of picolinic acid was found in the available literature.

Other Biological Effects: Intramuscular injections of picolinic acid significantly slowed the growth of tumors induced by implantation of Ehrlich ascites tumor cells into the flanks of female CBA/J mice. Five daily doses of 1 or 2.5 mg of picolinic acid reduced the diameters of tumor-bearing legs by 29 and 40 percent, respectively. Increases in the daily picolinic acid doses caused little further reduction in the size of tumor-bearing legs. Maximum survival was significantly increased from 70 to 112 days in the group receiving 5 doses of 2.5 mg picolinic acid and from 70 to 89 days in the group receiving 10 daily doses of 2.5 mg (Leuthauser *et al.*, 1982).

Picolinic acid inhibits the growth of numerous cultured normal and transformed mammalian cells. Short-term treatment with picolinic acid arrests normal cells in G_1 (G_0) while transformed cells are blocked in different phases of the cell cycle. With longer exposure to picolinic acid, cytotoxicity and cell death were observed in all transformed cells while most normal cells showed no toxic effects. It has been proposed that this differential response may involve NAD+ metabolism, cyclic AMP interference, or the differences in iron or other trace metal ion requirements of normal and transformed cells (Fernandez-Pol & Johnson, 1977; Leuthauser *et al.*, 1982; Fernandez-Pol *et al.*, 1993).

Structure Activity Relationships: The following structure activity information on chromium is

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from the IARC (1990) review of chromium and chromium compounds.

IARC classified chromium (VI) compounds as "carcinogenic to humans" (Group 1); metallic chromium and chromium (III) compounds were found "not classifiable as to their carcinogenicity to humans" (Group 3).

Chromates (Cr (VI)) enter cells more readily than chromium (III) compounds and are reduced ultimately to chromium (III). The reduction process and the subsequent intracellular activity of reduced chromium species are important for the mechanism of toxicity and carcinogenicity of chromium (VI).

Carcinogenicity. Chromic acetate and chromic chloride hexahydrate, two representative chromium (III) compounds, were not carcinogenic in animal studies reviewed by IARC. Details of the oral, intrapleural, and intrabronchial assays are shown in Table 2. A review of the more recent literature did not identify any additional studies.

Table 2. Carcinogenicity data for chromium (III) compounds

Chemical [CAS RN]	Route	Species	Dose	Tumor Incidence (Treated *vs* control)
Chromic acetate [1066-30-4]	Oral	Mouse	5 mg/l in drinking water for life	Male: 6/39 *vs* 11/44 Female: 9/29 *vs* 22/60
	Oral	Rat	5 mg/l in drinking water for life	Male: 16/39 *vs* 9/35 Female: 18/35 *vs* 15/35
	Intrapleural	Rat	not specified	1/34 *vs* 0/34
	Intrapleural	Rat	25 mg (8 implants over 13 mo)	0/42 (local tumor) *vs* (no control data)
Chromic chloride hexahydrate [10060-12-5]	Oral	Rat	600 mg/l for 25 wk	0/15 *vs* (no control data) (did not promote NEHEA-induced renal tumors)
	Intrabronchial	Rat	2 mg	0/100 *vs* (no control data)

NEHEA = N-nitrosoethylhydroxyethylamine

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Mutagenicity. The chromium (III) compounds reviewed by IARC generally did not produce DNA damage, gene mutation, sister chromatid exchange, or cell transformation in cultured animal and human cells. Chromosomal aberrations were often observed with high concentrations of chromium (III) compounds. Weak effects on gene mutation and mitotic gene conversion were observed in fungi. Negative results were obtained in the large majority of tests for DNA damage and gene mutation in bacteria. Certain complexes of chromium (III) with organic ligands, which favor the penetration of chromium (III) into cells, were reported to induce DNA damage and gene mutation in bacteria and cultured mammalian cells.

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