

CHROMIUM

This monograph is intended to serve as a guide to industry for the preparation of Product Licence Applications (PLA) and labels for natural health product market authorization. It is not intended to be a comprehensive review of the medicinal ingredient. It is a referenced document to be used as a labelling standard.

Note: Text in parentheses is additional optional information which can be included on the PLA and product labels at the applicants' discretion. The solidus (/) indicates that the terms are synonyms or that the statements are synonymous. Either term or statement may be selected by the applicant.

Date: December 9, 2009

Proper name(s): Chromium (O'Neil et al. 2009; Sweetman 2007)

Common name(s): Chromium (O'Neil et al. 2009; Sweetman 2007)

Source material(s):

- ▶ Chromium (III) bisglycinate/Chromic bisglycinate (Albion 2000)
- ▶ Chromium (III) chloride/Chromic chloride (O'Neil et al. 2009)
- ▶ Chromium (III) chloride hexahydrate/Chromic chloride hexahydrate (O'Neil et al. 2009)
- ▶ Chromium (III) citrate/Chromic citrate (HC 2007)
- ▶ Chromium (III) dinicotinate/Chromic dinicotinate (Evans and Pouchnik 1993)
- ▶ Chromium (III)-enriched yeast/Chromic-enriched yeast (HC 2007)
- ▶ Chromium (III) fumarate/Chromic fumarate (HC 2007)
- ▶ Chromium (III) glutarate/Chromic glutarate (HC 2007)
- ▶ Chromium (III) hydrolyzed animal protein (HAP) chelate/Chromic HAP chelate (Albion 1995; Albion 1993)
- ▶ Chromium (III) hydrolyzed vegetable protein (HVP) chelate/Chromic HVP chelate

- (Albion 1995; Albion 1993)
- ▶ Chromium (III) malate/Chromic malate (HC 2007)
 - ▶ Chromium (III) nicotinate/Chromic nicotinate (Grant et al. 1997; Evans and Pouchnik 1993)
 - ▶ Chromium (III) picolinate/Chromic picolinate (EFSA 2009)
 - ▶ Chromium (III) pidolate/Chromic pidolate (Anderson et al. 2001)
 - ▶ Chromium (III) polynicotinate/Chromic polynicotinate (Murray 1996)
 - ▶ Chromium (III) potassium sulfate dodecahydrate/Chromic potassium sulfate dodecahydrate (ANZFA 2004)
 - ▶ Chromium (III) succinate/Chromic succinate (HC 2007)
 - ▶ Chromium (III) sulfate /Chromic sulfate (ANZFA 2004; ANZFA 2002)

Route(s) of administration: Oral

Dosage form(s): The acceptable pharmaceutical dosage forms include, but are not limited to, chewables (e.g. gummies, tablets), caplets, capsules, strips, lozenges, powders or liquids where the dose is measured in drops, teaspoons or tablespoons. This monograph is not intended to include foods or food-like dosage forms such as bars, chewing gums or beverages.

Use(s) or Purpose(s): Statement(s) to the effect of:

General: A factor in the maintenance of good health (IOM 2006)

Specific:

- ▶ Provides support for healthy glucose metabolism (IOM 2006; Shils et al. 2006; IOM 2001; Groff and Gropper 2000).
- ▶ Helps the body to metabolize carbohydrates and fats (IOM 2006; Shils et al. 2006; IOM 2001; Groff and Gropper 2000).

Dose-specific: For products providing daily doses of chromium at or above the Adequate Intake (AI) (adjusted for the life stage groups), the following use or purpose is acceptable:
Helps to prevent chromium deficiency (IOM 2006; Shils et al. 2006; IOM 2001; Groff and Gropper 2000).

[Note: Chromium deficiency is rare in North America (IOM 2006; Shils et al. 2006)]

See Appendix 1 for definitions and Table 2 in Appendix 2 for AI values.

Dose(s):

Note:

- When chromium picolinate is used as source material for elemental chromium, the product should be indicated for adult subpopulation only (EFSA 2009; EVM 2003; SCF 2003).
- When chromium HAP chelate or chromium HVP chelate is used as source material, the product should be indicated for an adult subpopulation only.

Table 1: Dose information for chromium presented as dose per day

Life stage group	Chromium III (µg/day)		
	Minimum ¹	Maximum ²	
Adults ³	≥ 19 y	2.2	500

¹Based on approximately 5% of the highest AI (IOM 2006). See Appendix 1 for definitions and Table 2 in Appendix 2 for AI values.

²Maximum dose supported by the following references: Kleefsta et al. 2006; Campbell et al. 2002; Anderson et al. 2001; Campbell et al. 1999; Crawford et al. 1999; Anderson et al. 1997; Campbell et al. 1997; Roebach et al. 1991; Mossop et al. 1983.

³Includes pregnant and breastfeeding women, except for use of chromium picolinate (EFSA 2009; Manygoats et al. 2002; IOM 2001; Sugden et al. 1992).

Duration(s) of use: Statement(s) to the effect of:

For products using chromium picolinate as source material:

Consult a health care practitioner for use beyond 6 months (Anton et al. 2008; Campbell et al. 2002; Campbell et al. 1999; Cefalu et al. 1999; Kato et al. 1998; Pasman et al. 1997; Anderson et al. 1997; Lee and Reasner 1994).

Risk information: Statement(s) to the effect of:

Caution(s) and warning(s):

For products providing 200 - 500 µg/day of elemental chromium from chromium picolinate:

Consult a health care practitioner prior to use if you have a kidney disorder (Wani et al. 2006; Cupp and Tracy 2003; Cerulli et al. 1998; McCarty 1997; Wasser et al. 1997) and/or diabetes (Bunner and McGinnis 1998).

Contraindication(s):

For products using chromium picolinate as source material:

Do not use if you are pregnant or breastfeeding (EFSA 2009; Manygoats et al. 2002; IOM 2001; Sugden et al. 1992).

Known adverse reaction(s): No statement required.

Non-medicinal ingredients: Must be chosen from the current NHPD *Natural Health Products Ingredients Database* and must meet the limitations outlined in that database.

Specifications: The finished product must comply with the minimum specifications outlined in the current NHPD *Compendium of Monographs*.

References cited:

Albion 2000: Implications of the “other half” of a mineral compound. Albion Research Notes 2000;9(3) [Accessed 2009 December 04]. Available from:

http://www.news.albionminerals.com/human-nutrition/research-notes-pdf/doc_view/738-implications-of-the-qother-halfq-of-a-mineral-compound?tmpl=component&format=raw

Albion 1995: Chromium...has the public been misled?. Albion Research Notes 1995;4(3) [Accessed 2009 December 4]. Available from:

http://www.news.albionminerals.com/human-nutrition/research-notes-pdf/doc_view/722-chromium-has-the-public-been-misled?tmpl=component&format=raw

Albion 1993: Chromium—an often controversial, but very essential trace mineral. Albion Research Notes 1993;2(5) [Accessed 2009 December 4]. Available from:

http://www.news.albionminerals.com/human-nutrition/research-notes-pdf/doc_view/382-chromiun-an-often-controversial-but-very-essential-trace-mineral?tmpl=component&format=raw

Anderson RA, Roussel AM, Zouari N, Mahjoub S, Matheau JM, Kerkeni A. 2001. Potential antioxidant effects of zinc and chromium supplementation in people with type 2 diabetes mellitus. *Journal of the American College of Nutrition* 20(3):212-218.

Anderson RA, Cheng N, Bryden NA, Polansky MM, Cheng N, Chi J, Feug J. 1997. Elevated intakes of supplemental chromium improve glucose and insulin variables in individuals with type 2 diabetes. *Diabetes* 46(11):1786-1791.

Anton SD, Morrison CD, Cefalu WT, Martin CK, Coulon S, Geiselman P, Hongmei H, White CL, Williamson DA. 2008. *Diabetes Technology & Therapeutics* 10:405-412.

ANZFA 2004: Australia New Zealand Food Authority: Proposal P242 - Food for Special Medical Purposes: Preliminary Final Assessment Report. Canberra (AU): Department of Health and Ageing, Commonwealth of Australia. 4 August 2004. [Accessed 2009 December 4] Available from: http://www.foodstandards.gov.au/_srcfiles/P242_FSMP_PFAR.pdf

ANZFA 2002: Australia New Zealand Food Authority: Proposal P93 - Review of Infant Formula. Supplement Final Assessment (Inquiry - s.24) Report. Canberra (AU): Department of Health and Ageing, Commonwealth of Australia. 13 March 2002. [Accessed 2009 December 4] Available from: [http://www.foodstandards.gov.au/_srcfiles/P93_completeFinalAssRep\(supplement\).pdf](http://www.foodstandards.gov.au/_srcfiles/P93_completeFinalAssRep(supplement).pdf)

Bunner SP, McGinnis R. 1998. Chromium-induced hypoglycemia. *Psychosomatics* 39(3):298-299.

Campbell WW, Beard JL, Joseph LJ, Davey SL, Evans WJ. 1997. Chromium picolinate supplementation and resistive training by older men: effects on iron-status and hematologic indexes. *The American Journal of Clinical Nutrition* 66(4):944-949.

Campbell WW, Joseph LJO, Davey SL, Cyr-Campbell D, Anderson RA, Evans WJ. 1999. Effects of resistance training and chromium picolinate on body composition and skeletal muscle in older men. *Journal of Applied Physiology* 86(1):29-39.

Campbell WW, Joseph LJO, Anderson RA, Davey SL, Hinton J, Evans WJ. 2002. Effects of resistive training and chromium picolinate on body composition and skeletal muscle size in older women. *International Journal of Sport Nutrition and Exercise Metabolism* 12(2):125-135.

Cefalu WT, Bell-Farrow AD, Stegner J, Wang ZQ, King T, Morgan T, Terry JG. 1999. Effect of chromium picolinate on insulin sensitivity in vivo. *The Journal of Trace Elements in Experimental Medicine* 12(2):71-83.

Cerulli J, Grabe DW, Gauthier I, Malone M, McGoldrick MD. 1998. Chromium picolinate toxicity. *The Annals of Pharmacotherapy* 32(4):428-431.

Crawford V, Scheckenbach R, Preuss HG. 1999. Effects of niacin-bound chromium supplementation on body composition in overweight African-American women. *Diabetes, Obesity and Metabolism* 1:331-337.

Cupp MJ, Tracy TS. 2003. *Dietary Supplements: Toxicology and Clinical Pharmacology*. Chapter 3 Chromium Picolinate. Totowa (NJ): Humana Press Inc.

EFSA 2009. European Food Safety Authority. The EFSA Journal: Scientific Opinion Chromium picolinate, zinc picolinate and zinc picolinate dehydrate added for nutritional purposes in food supplements. *The EFSA Journal* 1113: 1-41. Adopted 4 June 2009.

Evans GW, Pouchnik DJ. 1993. Composition and biological activity of chromium-pyridine

carboxylate complexes. *Journal of Inorganic Biochemistry* 49(3):177-187.

EVM 2003: Expert Group on Vitamins and Minerals of the Food Standards Agency (FSA). Part 3: Trace Elements- Chromium and Zinc. In *Safe Upper Levels for Vitamins and Minerals; Report of the Expert Group on Vitamins and Minerals*. London, England. 1-31, 171-179, 253-262.

Grant KE, Chandler RM, Castle AL, Ivy JL. 1997. Chromium and exercise training: effect on obese women. *Medicine and Science in Sports and Exercise* 28(8):992-998.

Groff J, Gropper S. 2000. *Advanced Nutrition and Human Metabolism*, 3rd edition. Belmont (CA): Wadsworth/Thomson Learning.

HC 2007: Health Canada. Online Drug Product Database. Ottawa (ON): Health Canada. [Accessed 2009 December 4]. Available from: <http://webprod.hc-sc.gc.ca/dpd-bdpp/index-eng.jsp>

IOM 2006: Institute of Medicine. Otten JJ, Pitz Hellwig J, Meyers LD, editors. 2006. *Institute of Medicine. Dietary Reference Intakes: The Essential Guide to Nutrient Requirements*. Washington (DC): National Academies Press.

IOM 2001: Institute of Medicine. Panel on Micronutrients, Subcommittees on Upper Reference Levels of Nutrients and Interpretation and Uses of Dietary Reference Intakes, and the Standing Committee on the Scientific Evaluation of Dietary Reference Intakes, Food and Nutrition Board, Institute of Medicine. 2001. *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.

Kato I, Vogelmann JH, Dilman V, Karkoszka J, Frenkel K, Durr NP, Orentreich N, Toniolo P. 1998. Effect of supplementation with chromium picolinate on antibody titers to 5-hydroxymethyl uracil. *European Journal of Epidemiology* 14(6):621-626.

Kleefstra N, Houweling ST, Jansman FGA, Groenier KH, Gans ROB, Meyboom-de Jong B, Bakker SJL, Bilo HJG. 2006. Chromium treatment has no effect in patients with poorly controlled, insulin-treated type 2 diabetes in an obese western population: a randomized, double-blind, placebo-controlled trial. *Diabetes Care* 29(3):521-525.

Lee NA, Reasner CA. 1994. Beneficial effect of chromium supplementation on serum triglyceride levels in NIDDM. *Diabetes Care* 17(12):1449-1452.

Manygoats KR, Yazzie M, Stearns DM. 2002. Ultrastructural damage in chromium picolinate-treated cells: a TEM study. *Journal of Biological Inorganic Chemistry* 7(7-8):791-798.

McCarty MF. 1997. Over the counter chromium and renal failure [letter]. *Annals of Internal Medicine* 127:654-5

Mossop RT. 1983. Effects of chromium III on fasting blood glucose, cholesterol and cholesterol HDL levels in diabetics. *The Central African Journal of Medicine* 29:80-82.

Murray MT. 1996. *Encyclopedia of Nutritional Supplements: The Essential Guide for Improving Your Health Naturally*. Rocklin (CA): Prima Health.

O'Neil MJ, Smith A, Heckelman PE, Budavari S, editors. 2009. *Merck Index: An Encyclopedia of Chemicals, Drugs, & Biologicals*, 13th edition. Whitehouse Station (NJ): Merck & Co., Inc.; Electronic version. [Accessed 2009 December 4]. Available from: www.medicinescomplete.com

Pasman WJ, Westerterp-Plantenga MS, Saris WHM. 1997. The effectiveness of long-term supplementation of carbohydrate, chromium, fibre and caffeine on weight maintenance. *International Journal of Obesity and Related Metabolic Disorders*. 21(12):1143-1151.

Roeback JR Jr, Hla KM, Chambless LE, Fletcher RH. 1991. Effects of chromium supplementation on serum high-density lipoprotein cholesterol levels in men taking beta-blockers: a randomized, controlled trial. *Annals of Internal Medicine* 155(12):917-924.

SCF 2003. Scientific Committee on Food. Opinion of the Scientific Committee on Food on the tolerable upper intake level of chromium (expressed on 4 April 2003). European Commission, Health and Consumer Protection Directorate-General, Directorate C - Scientific Opinions, C2 - Management of scientific committees; scientific co-operation and networks.

Shils ME, Olson JA, Shike M, Ross AC, editors. 2006. *Modern Nutrition in Health and Disease*, 10th edition. Philadelphia (PA): Lippincott Williams and Wilkins.

Sugden KD, Geer RD, Rogers SJ. 1992. Oxygen radical-mediated DNA damage by redox-active Cr(III) complexes. *Biochemistry* 31(46):11626-11631.

Sweetman SC, editor. 2007. *Martindale: The Complete Drug Reference*, 35th edition. London (GB): Pharmaceutical Press.

Wani S, Weskamp C, Marple J, Spry L. 2006. Acute tubular necrosis associated with chromium picolinate-containing dietary supplement. *The Annals of Pharmacotherapy* 40(3):563-566.

Wasser WG, Feldman NS, D'Agati VD. 1997. Chronic renal failure after ingestion of over-the-counter chromium picolinate. *Annals of Internal Medicine* 126(5):410.

References reviewed:

Anderson MA, Petersson Grawé KV, Karlsson OM, Abramsson-Zetterberg LAG, Hellman BE. 2007. Evaluation of the potential genotoxicity of chromium picolinate in mammalian cells in vivo and in vitro. *Food and Chemical Toxicology* 45:1097-1106.

Anderson RA. 1998. Chromium, Glucose Intolerance and Diabetes. Review Article. *Journal of*

the American College of Nutrition 17(6): 548-555.

Anderson RA, Bryden NA, Polansky MM. 1997. Lack of toxicity of chromium chloride and chromium picolinate in rats. *Journal of the American College of Nutrition* 16(3):273-279.

Anderson RA, Bryden NA, Polansky MM, Gautschi K. 1996. Dietary chromium effects on tissue chromium concentrations and chromium absorption in rats. *The Journal of Trace Elements in Experimental Medicine* 9(1):11-25.

Anderson RA, Polansky MM, Bryden NA, Patterson KY, Veillon C, Glinsmann WH. 1983. Effects of chromium supplementation on urinary Cr excretion of human subjects and correlation of Cr excretion with selected clinical parameters. *The Journal of Nutrition* 113(2):276-281.

ATSDR 2008: Agency for Toxic Substances and Disease Registry. 2008. Draft Toxicological Profile for Chromium. U.S Department of Health and Human Services. [Accessed 2009 December 4]. Available from: <http://www.atsdr.cdc.gov/toxprofiles/tp7.html>

Bagchi D, Bagchi M, Balmoori J, Ye X, Stohs SJ. 1997. Comparative induction of oxidative stress in cultured J774A.1 macrophage cells by chromium picolinate and chromium nicotinate. *Research Communications in Molecular Pathology and Pharmacology* 97(3):335-346.

Bailey MM, Boohaker JG, Jernigan PL, Townsend MB, Sturdivant J, Rasco JF, Vincent JB, Hood RD. 2008. Effects of Pre- and Postnatal Exposure to Chromium Picolinate or Picolinic Acid on Neurological Development in CD-1 Mice. *Biological Trace Element Research* 124:70-82.

Bailey MM, Boohaker JG, Sawyer RD, Behling JE, Rasco JF, Jernigan JJ, Hood RD, Vincent JB. 2006. Exposure of pregnant mice to chromium picolinate results in skeletal defects in their offspring. *Birth Defects Research. Part B. Developmental and Reproductive Toxicology* 77(3):244-249.

Bailey MM, Sturdivant J, Jernigan PL, Townsend MB, Bushman J, Ankareddi I, Rasco JF, Hood RD, Vincent JB. 2008. Original Article: Comparison of the Potential for Developmental Toxicity of Prenatal Exposure to Two Dietary Chromium Supplements, Chromium Picolinate and $[Cr_3O(O_2CCH_2CH_3)_6(H_2O)_3]$ in Mice. *Birth Defects Research (Part B)* 83:27-31.

Berner TO, Murphy MM, Slesinki R. 2004. Determining the safety of chromium tripicolinate. The ENVIRON Health Sciences Institute, Arlington. *Food and Chemical Toxicology* 42:1029-1042.

Beskid M, Jachimowicz J, Taraszewska A, Kukulska D. 1995. Histological and ultrastructural changes in the rat brain following systemic administration of picolinic acid. *Experimental and Toxicologic Pathology* 47(1):25-30.

Bosco MC, Rapisarda A, Massazza S, Melillo G, Young H, Varesio L. 2000. The tryptophan catabolite picolinic acid selectively induces the chemokines macrophage inflammatory protein-

1 α and -1 β in macrophages. *The Journal of Immunology* 164(6):3283-3291.

COM 2004: Committee on Mutagenicity of Chemicals in Food, Consumer Products and the Environment. Statement on the Mutagenicity of Trivalent Chromium and Chromium Picolinate. December 2004. Department of Health. United Kingdom. [Accessed 2009 December 4]. Available from: <http://www.advisorybodies.doh.gov.uk/Com/chromium.htm>

CRN 2003: Council for Responsible Nutrition. Chromium Picolinate: Safe at a Wide Range of Intakes. [Accessed 2009 December 4]. Available from: <http://www.crnusa.org/pdfs/CRNChromPicBG.pdf>

Coryell V, Stearns D. 2006. Molecular analysis of hprt mutations induced by chromium picolinate in CHO AA8 cells. *Mutation Research* 610:114-123.

Dillon CT, Lay PA, Bonin AM, Cholewa M, Legge GJF. 2000. Permeability, cytotoxicity, and genotoxicity of Cr(III) complexes and some Cr(V) analogues in V79 Chinese hamster lung cells. *Chemical Research in Toxicology* 13(8):742-748.

EFSA 2009: European Food Safety Authority. Summary of Opinion: Scientific Opinion Chromium picolinate, zinc picolinate and zinc picolinate dehydrate added for nutritional purposes in food supplements. Adopted 4 June 2009.

ENVIRON 2002: ENVIRON International Corporation. 2002. Generally Recognized as Safe (GRAS) Determination for the User of Chromax Chromium Picolinate as a Nutrient Supplement in Food. Arlington(VA).

EPA 1998: U.S. Environmental Protection Agency. 1998. Toxicological Review of Trivalent Chromium: In support of summary information on the Integrated Risk Information System (IRIS). Washington (DC).

Evans GW, Bowman TD. 1992. Chromium picolinate increases membrane fluidity and rate of insulin internalization. *Journal of Inorganic Biochemistry* 46(4):243-250.

Evans GW, Johnson PE. 1980. Characterization and quantitation of a zinc-binding ligand in human milk. *Pediatric Research* 14(7):876-880.

Fernandez-Pol JA. 1978. Morphological changes induced by picolinic acid in cultured mammalian cells. *Experimental and Molecular Pathology* 29(3):348-357.

Fowler JF. 2000. Systemic contact dermatitis caused by oral chromium picolinate. *Cutis* 65(2):116.

FSA 2004: Food Standards Agency. United Kingdom. Agency revises chromium picolinate advice Monday 13 December 2004. [Accessed 2009 December 4]. Available from: <http://www.food.gov.uk/news/newsarchive/2004/dec/chromiumupdate>

Gammelgaard B, Jensen K, Steffansen B. 1999. In vitro metabolism and permeation studies in rat jejunum: organic chromium compared to inorganic chromium. *Journal of Trace Elements in Medicine and Biology* 13(1-2):82-88.

Gargas ML, Norton RL, Paustenbach DJ, Finley BL. 1994. Urinary excretion of chromium by humans following ingestion of chromium picolinate: implications for biomonitoring. *Drug Metabolism and Disposition* 22(4):522-529.

Goda K, Kishimoto R, Shimizu S, Hamane Y, Ueda M. 1996. Quinolinic acid and active oxygens: possible contribution of active oxygens during cell death in the brain. *Advances in Experimental Medicine and Biology* 398:247-254.

Goodwin FK, Sack RL. 1974. Behavioral effects of new dopamine- β -hydroxylase inhibitor (fusaric acid) in man. *Journal of Psychiatric Research* 11:211-217.

Greenberg D, Komorowski JR, Loveday K. 1999. Rat chromosomes are unharmed by orally administered chromium picolinate. *Journal of the American College of Nutrition*.18:527.

Guidi R, Rao M. 2004. In vitro Mammalian Chromosome Aberration Test. Bioreliance Report no AA85MC.331.BTL

Gudi R, Slesinski RS, Clarke JJ, San RHC. 2005. Chromium picolinate does not produce chromosome damage in CHO cells. *Mutation Research* 587(1-2):140-146.

HC 1996: Health Canada. Drugs Directorate Labelling Standard: Mineral Supplements. Ottawa (ON): Health Canada.

HC 2007: Health Canada. Monograph- Chromium. [Accessed 2009-December 4]. Available from: http://www.hc-sc.gc.ca/dhp-mps/alt_formats/hpfb-dgpsa/pdf/prodnatur/mono_chromium-chrome-eng.pdf

HC 2007: Health Canada. Monograph- Multi-vitamin/mineral Supplement. [Accessed 2009 December 4]. Available from: http://www.hc-sc.gc.ca/dhp-mps/alt_formats/hpfb-dgpsa/pdf/prodnatur/multivit_min_mono-eng.pdf

HC 2009: Health Canada. Drug Product Database. [Accessed 2009 December 4]. Available from: <http://www.hc-sc.gc.ca/dhp-mps/prodpharma/databasdon/index-eng.php>

HC 2009: Health Canada. Licensed Natural Health Products Database. [Accessed 2009 December 4]. Available from: <http://webprod.hc-sc.gc.ca/lnhpd-bdpsnh/start-debuter.do?lang=eng>

Hepburn DD, Burney JM, Woski S, Vincent JB. 2003. The Nutritional Supplement Chromium Picolinate Generates Oxidative DNA Damage and Peroxidised Lipids In Vivo. *Polyhedron* 22:455-463.

Hepburn DDD, Vincent JB. 2002. In vivo distribution of chromium from chromium picolinate in rats and implications for the safety of the dietary supplement. *Chemical Research in Toxicology* 15(2):93-100.

Hepburn DD, Xiao J, Bindom S, Vincent JB, O'Donnell J. 2003. Nutritional Supplement Chromium Picolinate Causes Sterility and Lethal Mutations in *Drosophila melanogaster*. *PNAS* 100:3766-3771.

Hininger I, Benaraba R, Osman M, Faure H, Roussel AM, Anderson RA. 2007. Safety of trivalent chromium complexes: No evidence for DNA damage in human HaCaT keratinocytes. *Free Radical Biology & Medicine* 42:1759-1765.

Huszonek J. 1993. Over-the-counter chromium picolinate. *The American Journal of Psychiatry*. 150(10):1560-1561.

IRIS 2008: Integrated Risk Information System. Chromium. Washington(DC): U.S. Environmental Protection Agency. [Accessed 2009 December 4]. Available from: <http://www.epa.gov/iris/subst/index.html>.

IRIS 1998: Integrated Risk Information System. Toxicological Review of Trivalent Chromium. In Support of Summary Information on the Integrated Risk Information System. [Accessed 2009 December 4]. Available from: <http://www.epa.gov/ncea/iris/toxreviews/0028-tr.pdf>

Ivankovic S, Preussmann R. 1975. Absence of toxic and carcinogenic effects after administration of high doses of chromic oxide pigment in subacute and long term feeding experiments in rats. *Food and Cosmetic Toxicology* 13:347-351.

Jovanovic L, Gutierrez M, Peterson CM. 1999. Chromium supplementation for women with gestational diabetes mellitus. *The Journal of Trace Elements in Experimental Medicine* 12(2):91-97.

Kerger BD, Paustenbach DJ, Corbett GE, Finley BL. 1996. Absorption and elimination of trivalent and hexavalent chromium in humans following ingestion of a bolus dose of drinking water. *Toxicology and Applied Pharmacology* 141(1):145-158.

Lawrence ME, Kirby DF. 2002. Nutrition and sports supplements: fact or fiction. *Journal of Clinical Gastroenterology* 35(4):299-306.

Lindemann MD, Carter SD, Chiba LI, Dove CR, Lemieux FM, Southern LI. 2004. A regional evaluation of chromium tripicolinate supplementation of diets fed to reproducing sows. *Journal of Animal Science* 82:2972-2977.

Mackenzie RD, Byerrum RU, Decker CF, Hoppert CA, Langham RF. 1958. Chronic toxicity studies II. Hexavalent and trivalent chromium administered in drinking water to rats. *American Medical Association Archives of Industrial Health* 18:232-234.

- Martin WR, Fuller RE. 1998. Suspected chromium picolinate-induced rhabdomyolysis. *Pharmacotherapy* 18(4):860-862.
- McLeod MN, Gaynes BN, Golden RN. 1999. Chromium potentiation of antidepressant pharmacotherapy for dysthymic disorder in 5 patients. *The Journal of Clinical Psychiatry* 60(4):237-240.
- Mehler AH. 1956. Formation of picolinic and quinolinic acids following enzymatic oxidation of 3-hydroxyanthranilic acid. *The Journal of Biological Chemistry* 218(1):241-254.
- Melillo G, Bosco MC, Musso T, Varesio L. 1996. Immunobiology of picolinic acid. *Advances in Experimental Medicine and Biology* 398:135-141.
- Mita Y, Ishihara K, Yoshiko F, Fukuya Y, Yasumoto K. 2004. Supplementation with Chromium Picolinate Recovers Renal Cr Concentration and Improves Carbohydrate Metabolism and Renal Function in Type 2 Diabetic Mice. *Biological Trace Element Research* 105:229-248.
- Morris GS, Guidry KA, Hegsted M, Hasten DL. 1995. Effects of dietary chromium supplementation on cardiac mass, metabolic enzymes, and contractile proteins. *Nutrition Research* 15(7):1045-1052.
- NIH 2005: National Institute of Health. Office of Dietary Supplements. 2005. Dietary Supplement Fact Sheet Chromium. [Accessed 2009 December 4]. Available from: http://ods.od.nih.gov/factsheets/chromium_pf.asp#h2
- NTP 1998: National Toxicology Program. 1998. Executive Summary Chromium Picolinate. [Accessed 2009 December 4]. Available from: <http://ntp.niehs.nih.gov/go/15342>
- NTP 2009: National Toxicology Program. Database Search Application. 2009. Studies with Chromium Picolinate and Chromium Picolinate Monohydrate. [Accessed 2009 December 4]. Available from: http://ntp-apps.niehs.nih.gov/ntp_tox/index.cfm?fuseaction=ntpsearch.searchresults&searchterm=chromium%20picolinate&crumbspot=1
- NTP 2009: National Toxicology Program. 2009. Testing Status of Agents at NTP. Chromium picolinate monohydrate. [Accessed on 2009 December 4]. Available from: <http://ntp.niehs.nih.gov/?objectid=BD466797-123F-7908-7B4627379E1CE3E6>
- NTP 2009: National Toxicology Program. 2009. Testing Status of Agents at NTP. Chromium picolinate. [Accessed on 2009 December 4]. Available from: <http://ntp.niehs.nih.gov/index.cfm?objectid=BDC7BBDC-123F-7908-7BD2C6D0172F0FB1>
- Press R, Geller J, Evan G. 1990. The Effect of Chromium Picolinate on Serum Cholesterol and Apolipoprotein Fractions in Human Studies. *The Western Journal of Medicine*.152:41-45.
- Reading SA, Wecker L. 1996. Chromium picolinate. *The Journal of the Florida Medical*

Association 83(1):29-31.

Rhodes MC, Hébert CD, Herbert RA, Morinello EJ, Roycroft JH, Travlos GS, Abdo KM. 2005. Absence of toxic effects in F344/N rats and B6C3F1 mice following subchronic administration of chronic administration of chromium picolinate monohydrate. *Food and Chemical Toxicology* 43:21-29.

Roth P, Kirchgessner M. 1985. Utilization of Zinc from Picolinic or Citric Acid Complexes in Relation to Dietary Protein Source in Rats. *Journal of Nutrition* 115:1641-1649.

San RH, Clarke JJ. 2004a. In vitro Mammalian Cell Gene Mutation (CHO/HGPRT) Test with an Independent Repeat Assay. Bioreliance Report no AA85MC.782001.BTL.

San RH, Clarke JJ. 2004. In vitro Mammalian Cell Gene Mutation (CHO/HGPRT) Test with 48-hour exposure. Bioreliance Report no AA85MC.782048.BTL

SCF/EFSA 2006: Scientific Committee on Food/ European Food Safety Authority. 2006. Tolerable Upper Intake Levels for Vitamins and Minerals by the Scientific Panel on Dietetic products, Nutrition and Allergies (NDA) and Scientific Committee on Food (SCF). Edited by EFSA, Parma, February 2006.

Schroeder HA, Balassa JJ, Vinton Jr WH. 1965. Chromium cadmium and lead in rats: effects on lifespan, tumors and tissue levels. *Journal of Nutrition* 86:51-66.

Slesinski RS, Clarke JJ, San RHC, Gudi R. 2005. Lack of mutagenicity of chromium picolinate in the hypoxanthine phosphoribosyltransferase gene mutation assay in Chinese hamster ovary cells. *Mutation Research* 585(1-2):86-95.

Speetjens JK, Collins RA, Vincent JB, Woski SA. 1999. The nutritional supplement chromium(III) tris(picollinate) cleaves DNA. *Chemical Research in Toxicology* 12(6):483-487.

Speetjens JK, Parand A, Crowder MW, Vincent JB, Woski SA. 1999. Low-molecular-weight chromium-binding substance and biomimetic $[\text{Cr}_3\text{O}(\text{O}_2\text{CCH}_2\text{CH}_3)_6(\text{H}_2\text{O})_3]^+$ do not cleave DNA under physiologically-relevant conditions. *Polyhedron* 18(20):2617-2624.

Stearns DM, Belbruno JJ, Wetterhahn KE. 1995. A prediction of chromium(III) accumulation in humans from chromium dietary supplements. *The FASEB Journal* 9(15):1650-1657.

Stearns DM, Wise JP, Patierno SR, Wetterhahn KE. 1995. Chromium(III) picollinate produces chromosome damage in Chinese hamster ovary cells. *The FASEB Journal* 9(15):1643-1649.

Stearns DM, Silveira SM, Wolf KK, Luke AM. 2002. Chromium(III) tris(picollinate) is mutagenic at the hypoxanthine (guanine) phosphoribosyltransferase locus in Chinese hamster ovary cells. *Mutation Research* 513(1-2):135-142.

Stout MD, Nyska A, Collins BJ, Witt KL, Kissling GE, Malarkey DE, Hooth MJ. 2009. Chronic

toxicity and carcinogenicity studies of chromium picolinate monohydrate administered in feed to F344/N rats and B6C351 mice for 2 years. National Toxicology Program. Food and Chemical Toxicology 47: 729-733.

Tan GY, Zheng SS, Zhang MH, Feng JH, Xie P, Bi JM. 2008. Study of Oxidative Damage in Growing-Finishing Pigs with Continuous Excess Dietary Chromium Picolinate Intake. Biological Trace Element Research 126(1-3):129-40.

TGA 2003: Therapeutic Goods Administration. 2003. CMEC Meeting 41 Complementary Medicines Evaluation Committee: Extracted ratified minutes forty-first meeting. Symonston (AU): Commonwealth Department of Health and Ageing, Therapeutic Goods Administration. [Accessed 2009 December 4]. Available from: <http://www.tga.gov.au/docs/pdf/cmec/cmecmi41.pdf>.

TGA 1990: Therapeutic Goods Administration. 1990. Therapeutic Goods Regulations. Canberra (AU): Office of Legislative Drafting and Publishing, Attorney-General's Department, SR 1990 No. 394. [Accessed 2009 December 4]. Available from: <http://www.comlaw.gov.au/ComLaw/Legislation/LegislativeInstrumentCompilation1.nsf/frame1odgmentattachments/1D614DC409BA903BCA2575F4000F1E38>

Vincent JB. 2000. The biochemistry of chromium. The Journal of Nutrition 130(4):715-718.

Wagner JC. 1989. Use of chromium and cobamamide by athletes. Clinical Pharmacy 8:832,834.

Whittaker P, San RHC, Clarke JJ, Seifried HE, Dunkel VC. 2005. Mutagenicity of chromium picolinate and its components in Salmonella typhimurium and L5178Y mouse lymphoma cells. Food and Chemical Toxicology 43(11):1619-1625.

WHO 1996: World Health Organization. 1996. Trace elements in human nutrition and health (A report of a re-evaluation of the role of trace elements in human health and nutrition). Geneva (CH): World Health Organization.

WHO 1997: World Health Organization. 1997. International Agency for Research on Cancer (IARC), Volume 49: Chromium, nickel and Welding. [online]. Geneva (CH): IARC Monographs on the Evaluation of Carcinogenic Risk of Chemicals to Humans, World Health Organization. [Accessed 2009 December 4]. Available from: <http://monographs.iarc.fr/ENG/Monographs/vol49/volume49.pdf>

WHO 2009: World Health Organization. 2009. Concise International Chemical Assessment Document 76. Inorganic Chromium (III) Compounds. Geneva (CH): World Health Organization.

Witmer C, Faria E, Park H, Sadrieh N, Yurkow E, O'Connell S, Sirak A, Schleyer H. 1994. In vivo effects of chromium. Environmental Health Perspectives 102(Supplement 3):169-176.

Yoshikawa Y, Ueda E, Kawabe K, Miyake H, Takino T, Sakurai H, Kojima Y. 2002. Development of new insulinomimetic zinc(II) picolinate complexes with a Zn(N2O2)

coordination mode: structure characterization, in vitro, and in vivo studies, *Journal of Biological Inorganic Chemistry* 7:68-73.

Young PC, Turiansky GW, Bonner MW, Benson PM. 1999. Acute generalized exanthematous pustulosis induced by chromium picolinate. *Journal of the American Academy of Dermatology* 41(5 Part 2):820-823.

Appendix 1: Definitions

Adequate Intake (AI): The recommended average daily intake level based on observed or experimentally determined approximations or estimates of nutrient intake by a group (or groups) of apparently healthy people that are assumed to be adequate. An AI is used when a Recommended Dietary Allowance (RDA) cannot be determined (IOM 2006).

Recommended Dietary Allowances (RDA): The average daily dietary nutrient intake level sufficient to meet the nutrient requirements of nearly all (97-98 %) healthy individuals in a particular life stage and gender group (IOM 2006).

Appendix 2: Adequate intake (AI) values

AI values for chromium are provided below. For the purpose of this monograph, these values are intended to:

- ▶ provide target values for setting appropriate supplement dosage levels;
- ▶ provide the minimum dose for the use of the dose-specific use or purpose: “Helps to prevent chromium deficiency”;
- ▶ facilitate the optional labelling of % AI values.

Table 2: Adequate Intake values for chromium based on life stage group (IOM 2006)

Life stage group		Chromium (µg/day)
Adult males	19-50 y	35
	≥ 51 y	30
Adult females	19-50 y	25
	≥ 51 y	20
Pregnancy	19-50 y	30
Breastfeeding	19-50 y	45