CHROMIUM PICOLINATE HEALTH CLAIM SUBMISSION

Based on our review of the reliable and credible scientific literature regarding the effects of chromium picolinate supplementation on glucose metabolism, we conclude that there is significant scientific agreement in support of the following health claims:

- Chromium picolinate may reduce the risk of insulin resistance.
- Chromium picolinate may reduce the risk of cardiovascular disease when caused by insulin resistance.
- Chromium picolinate may reduce the risk of abnormally elevated blood sugar levels.
- Chromium picolinate may reduce the risk of cardiovascular disease when caused by abnormally elevated blood sugar levels.
- Chromium picolinate may reduce the risk of type 2 diabetes.
- Chromium picolinate may reduce the risk of cardiovascular disease when caused by type 2 diabetes.
- Chromium picolinate may reduce the risk of retinopathy when caused by abnormally high blood sugar levels.
- Chromium picolinate may reduce the risk of kidney disease when caused by abnormally high blood sugar levels.

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1.0 Background on Diabetes

1.1 Diabetes

Diabetes mellitus is a metabolic disorder affecting about 16 million people, or 6% - 7% of the U.S. population.[1-3] It is projected that there will be 800,000 new cases of diabetes each year, and 23 million affected people within 10 years.[1-3] Diabetes occurs in all populations and age groups, but is especially prevalent among the elderly, the obese, African Americans, Mexican Americans, Puerto Ricans, Cuban Americans and Native Americans.[1-3] Diabetes is the sixth leading cause of death in the United States, directly accounting for more than 193,000 deaths during 1997.[3] Life expectancy for people with diabetes is approximately 15 years less than for those who do not have diabetes.[3] Annually, diabetes directly and indirectly consumes over $105,000,000,000 and is responsible for about 10% of all U.S. health care costs and about 25% of all Medicare expenditures.[4]

The principal clinical symptom of diabetes is abnormally elevated blood or plasma glucose concentrations ("hyperglycemia").[1,3] Hyperglycemia results from inability to remove glucose from the blood following its absorption from the diet or secretion by the liver.[5] The two most common manifestations of diabetes, "type 1 diabetes" and "type 2 diabetes," differ in etiology and pathogenesis.[5] Type 1 diabetes is an autoimmune disease, with typical onset prior to age 20 years, in which the insulin-secreting cells of the pancreas are destroyed. In this disease, insufficient pancreatic secretion of insulin impairs glucose removal from blood. Affected individuals require exogenous insulin in order to prevent life-threatening severe hyperglycemia.

Type 2 diabetes results from loss of responsiveness ("sensitivity") of target tissues to insulin; impaired removal of glucose from the blood produces hyperglycemia even in the presence of elevated concentrations of insulin ("hyperinsulinemia").[5] Impairment of glucose uptake in the presence of insulin ("insulin resistance") is the definitive functional characteristic of type 2 diabetes.[5] In contrast with type 1 diabetes, type 2 diabetes usually is diagnosed in adulthood and is about 10 times more prevalent than type 1 diabetes in the U.S.[3,5] However, advanced type 2 diabetes resembles type 1 diabetes in that many individuals with advanced type 2 diabetes exhibit downregulation of pancreatic insulin secretion and also require exogenous insulin.[5]

1.2 Diagnosis of Diabetes

The American Diabetes Association (ADA) recommends evaluation of the fasting plasma glucose concentration when screening for the presence of diabetes.[6] According to the ADA, diabetes is present when the fasting plasma glucose concentration is greater than 126 mg/dL.[6] However, the presence of type 2 diabetes is more readily identified by measurement of plasma glucose concentration 2 hours after the ingestion of a standardized solution containing 75 g of glucose; if plasma glucose concentration is greater than 199 mg/dL, type 2 diabetes is present.[6]

Type 2 diabetes necessarily is preceded by the precursor condition, "prediabetes."[7-10] According to the ADA, prediabetes is characterized by either "impaired fasting glucose" (fasting plasma glucose concentration between 100 and 125 mg/dL) or "impaired glucose tolerance" (plasma glucose concentration between 140 and 199 mg/dL when measured 2 hours after the ingestion of a standardized solution containing 75 g of glucose).[6] It has been argued persuasively that the measurement of plasma glucose concentration 2 hours after the ingestion of a standardized solution containing 75 g of glucose is the more sensitive and specific functional indicator of ability to maintain normal glucose homeostasis

("normal glucose tolerance") and therefore is more likely to detect individuals with prediabetes.[11] Whichever its manifestation, prediabetes significantly increases the risk for the development of type 2 diabetes.[9,12-19] For example, in a study conducted in Germany, it was estimated that every year about 4% of individuals with normal or slightly elevated fasting plasma glucose concentrations but unimpaired glucose tolerance develop impaired glucose tolerance and between 2% and 3% of individuals with impaired glucose tolerance progress to type 2 diabetes; in addition, each year about 10% of individuals with both elevated fasting plasma glucose concentrations and impaired glucose tolerance develop type 2 diabetes.[20]

Although its use is not recommended by the ADA for the diagnosis of prediabetes or diabetes, measurement of the proportion of circulating hemoglobin that has undergone spontaneous glycation (a nonenzymatic process that occurs at a rate proportional to plasma glucose concentration[21-32]) to form the glycated protein, HbA_{1c}, can be used to monitor the physiologic impact of circulating glucose.[6,24,31,33] Plasma HbA_{1c} percentage is considered to be the best available estimate of the overall average plasma glucose concentration during the preceding 12 to 120 days and is resistant to short-term fluctuations in plasma glucose concentration.[22,32,34-43] Each "1%" of HbA_{1c} corresponds to about 35 mg of glucose per deciliter of plasma.[31] Individuals with normal glucose homeostasis ("normal glucose tolerance") exhibit plasma HbA1c of 2% to 4%; the upper limit reflecting normal glucose tolerance is considered to be between 6% and 7% and a value greater than 7% is considered to reflect excessively high amounts of glucose in the blood capable of causing spontaneous biochemical damage to tissues (such as function-impairing glycation of proteins).[24,31,33] In several studies, plasma HbA_{1c} greater than 7% has been found to predict increased risks for atherosclerotic lesions,[44-46] hypertension,[47] fatal and non-fatal myocardial infarction,[44,48-50] and fatal and non-fatal stroke.[48]

1.3 Pathogenesis of Type 1 Diabetes

Type 1 diabetes (hyperglycemia with hypoinsulinemia) results from autoimmune destruction of pancreatic β-cells.[3,5,6] In the etiology of this disease, various genetic factors (including abnormalities of the major histocompatibility complex) contribute to the production of antibodies targeted at pancreatic islet β-cells.[5] As pancreatic β-cell mass diminishes, affected individuals progress from normal glucose homeostasis to steadily-decreasing insulin secretion in response to hyperglycemia (hypoinsulinemic hyperglycemia) and ultimately to complete lack of ability to secrete insulin and death.[5]

1.4 Pathogenesis of Type 2 Diabetes

In contrast with type 1 diabetes, loss of target tissue responsiveness or sensitivity to insulin ("insulin resistance"), not loss of insulin secretory capacity, is the initiating metabolic defect in the onset of type 2 diabetes.[3,5,7,36,51-65] In the development of type 2 diabetes the amount of insulin locally available to target tissues (predominantly hepatocytes, myocytes and adipocytes) that is required in order to produce a normal rate of tissue uptake of glucose is increased, prolonging episodes of hyperglycemia and stimulating hyperglycemia-induced hypersecretion of insulin by pancreatic β-cells.
In mild loss of insulin sensitivity, pancreatic hypersecretion of insulin successfully maintains normal glucose homeostasis ("compensated hyperinsulinemia"; fasting hyperinsulinemia without fasting hyperglycemia). The resulting fasting hyperinsulinemia is measurable in some individuals many years antecedent to the development of measurable hyperglycemia.

Gradual progression of the severity of insulin resistance, evidenced by the requirement for steadily increasing amounts of insulin to stimulate tissue uptake of glucose, first compromises the ability to

resolve an acute episode of hyperglycemia (uncompensated hyperinsulinemia; impaired glucose tolerance) and eventually produces residual fasting mild hyperglycemia (impaired fasting glucose). In some individuals, the distinctions between compensated hyperinsulinemia, impaired glucose tolerance and impaired fasting glucose are blurred and elements of the pathogenic sequence may overlap. Chronic hypersecretion of insulin and hyperinsulinemia may produce downregulation of pancreatic β-cell function, resulting in inadequate insulin secretory responses to increases in plasma glucose concentration and prolonged episodes of hyperglycemia that progress to severe fasting hyperglycemia and diabetes. In addition, there is evidence that at least some individuals experience downregulation of pancreatic β-cell function early in the pathogenesis of type 2 diabetes[66-69] suggesting that in those individuals, inhibition of insulin clearance (resulting in increased half-life of insulin in the circulation) contributes to hyperinsulinemia.

The definitive point at which secretion of insulin by pancreatic β-cells reflects dysregulation of glucose homeostasis is not known; among adults with apparently normal glucose tolerance, the plasma insulin concentration required to produce a fixed rate of tissue glucose uptake varies at least 3-fold.[70,71] Nonetheless, among adults with type 2 diabetes, the mean rate of tissue glucose uptake in the presence of a fixed concentration of insulin was observed to be only 10% the rate in individuals with normal glucose tolerance.[72]

Insulin resistance appears to result from several defects in the relationships among insulin, its receptor, and the genome. Those defects affect insulin binding to its receptor, postbinding physiology and biochemistry of the insulin-receptor complex, the physiology of the major insulin effector proteins, p85-α phosphatidylinositol 3-kinase and peroxisome proliferator activated receptor-γ, trafficking of the insulin-responsive glucose transporter and protein kinase C (PKC) physiology and possibly produce inappropriate downregulation of insulin receptors.[3,5,73-78] There also is evidence that the glycation of insulin is a feature of defective pancreatic β-cell function in fully-developed type 2 diabetes; the secretion of glycated insulin would reduce the secretion of metabolically active insulin (impaired insulin secretion), interfere with the binding of unglycated insulin to its receptor (decreased sensitivity to circulating insulin; insulin resistance) and attenuate the clearance of circulating total insulin (increased half-life in the circulation; hyperinsulinemia).[79]

1.5 Loss of Normal Glucose Tolerance Increases the Risk for Other Diseases

So-called microvascular diseases (retinopathy, nephropathy, and neuropathy) caused by diabetes impose an enormous social and economic burden in the U.S.[3,80] The mechanisms of hyperglycemia-induced microvascular pathology include interference with the structural integrity of the vascular endothelium, increased resistance to blood flow, interference with nerve signal transmission, and stimulation of intracellular conversion of glucose to sorbitol, an intracellular metabolic toxin.[3,5]

Diabetic retinopathy is the leading cause of blindness in adults aged 20 through 74 years, afflicting 12,000 to 24,000 new individuals annually.[3,80] In retinopathy, damage to the small blood vessels that nourish the retina reduces blood flow and nutrient supply, weakens vessel walls and stimulates the growth of new endothelial cells and blood vessels that impede photoreception. Edema into the central macula also can block vision. In addition, diabetes increases the risks for cataract formation and macular degeneration.[3]

Diabetic kidney disease (nephropathy) accounts for 40% of all new cases of end-stage renal disease[81] and accounts for approximately $4,000,000,000 in direct medical costs yearly.[3] Evidence of impaired kidney function is evident in as few as 5 years after the appearance of type 2 diabetes[3] and 10% of adults with diabetes eventually will develop end-stage renal disease.[82] Every year, about 0.5% to 0.7% of adults with both diabetes and end-stage renal disease will suffer myocardial infarction, 2% to 2.5% will require surgical revascularization and 8% to 10% will be afflicted with a stroke or transient ischemic attack.[82]

Over 60% of individuals with diabetes eventually experience degenerative damage to the peripheral nerves (causing both pain and loss of sensation) and the autonomic nerves (which regulate heart rate, gastric motility, bladder function and sexual responsiveness).[3] Loss of peripheral nerve function is associated with increased risk for limb infections, ulcerations (causing over 200,000 foot ulcers annually[3])and amputations (diabetic neuropathy is the leading cause for amputation of limbs in the U.S.,[4] causing over 80,000 limb amputations annually[3]). Autonomic neuropathy can result in cardiac arrhythmias, hypertension, digestive disorders (heartburn, decreased gastric motility, constipation) and impotence (a dysfunction affecting about 50% of males with diabetes[3]).

Approximately 65% of all deaths in individuals with diabetes are not caused by diabetes *per se* but are attributed to hypertension, cerebrovascular disease, cardiovascular disease, and coronary artery disease.[83,84] In several studies diabetes has been found to significantly increase the risks for a number of other diseases, including hypertension, cerebrovascular disease (including stroke), cardiovascular disease, and coronary artery disease.[85-110] Similarly, impaired glucose tolerance (prediabetes) has been associated with significantly increased thickness of carotid artery walls (atherosclerosis)[105,111-113] and significantly increased risks for coronary artery disease[46,92,103,105-107,111,114-134] and mortality from cardiovascular disease.[129,135-146]

Numerous consequences of hyperglycemia may contribute to the increased risks for hypertension, cerebrovascular disease, cardiovascular disease, and coronary artery disease associated with loss of normal glucose tolerance. For example, hyperglycemia stimulates the irreversible glycation of collagen and other endothelial wall proteins,[147] producing increased thickening of blood vessel walls,[119] and attenuates endothelium-dependent vasodilation.[148,149] Similarly, hyperglycemia stimulates the irreversible glycation of both low-density lipoproteins and high-density lipoproteins[147,150-153] as well as the oxidation of low-density lipoprotein cholesterol.[154-156] In addition, hyperglycemia been found to significantly increase the risks for hypercholesterolemia and hypertriglyceridemia,[88,90,97,107] themselves well-recognized risk factors for cardiovascular disease. Indeed, the risk for cardiovascular disease appears to be directly proportional to the fasting and postprandial glucose concentration, even among individuals with normal glucose tolerance.[119,135,136]

Hyperinsulinemia also increases the risk for diabetes as well as diseases other than diabetes. Postprandial hyperinsulinemia increases the risks for impaired glucose tolerance,[157] type 2 diabetes,[20,65,158-163] coronary artery disease,[103,164,165] stroke[91,103,166] and hypertension.[10,103,167-174] Similarly, fasting hyperinsulinemia also significantly increased the risks for type 2 diabetes,[65,140,159,163,175-178] hypertension,[90,140,179-187] hypertriglyceridemia,[179-181,183,185] obesity,[169,188] thrombosis,[189-196] increased atherogenicity of low-density lipoprotein particles,[197,198] acceleration of vascular plaque formation,[156,178,199-205] impaired fibrinolysis,[191,192,195,203,206-214] fragility of arterial plaques[215] and coronary artery disease.[90,132,138,164,165,178,200,212,216-226]

In one cross-sectional study of men and women 26 to 82 years old without diabetes or apparent cardiovascular disease, fasting hyperinsulinemia significantly increased the risks for impaired glucose tolerance, impaired fasting glucose, hypertriglyceridemia, low serum high-density lipoprotein concentration, hypertension and obesity, even when risks were adjusted for body mass index and serum lipid concentrations.[226] In addition, fasting plasma insulin concentration was significantly directly proportional to plasma concentrations of plasminogen activator inhibitor 1 (PAI-1), tissue-type plasminogen activator (tPA), clotting factor VII, fibrinogen, and von Willebrand factor. Elevated plasma concentrations of PAI-1, tPA, clotting factor VII, fibrinogen, and von Willebrand factor reflect impaired fibrinolysis and accelerated formation of acellular thin-walled vascular plaques prone to acute rupture and hypercoagulability[226-229] (risk factors for coronary artery disease[106,230,231]). In addition, elevated plasma PAI-1 concentration increases the risk for type 2 diabetes[232] while elevated plasma tPA concentration increases the risk for stroke.[233]

It should be noted that, in contrast to the vast majority of published epidemiologic studies, two such studies have failed to observed a significant relationships between hyperinsulinemia and risk for cardiovascular or cerebrovascular disease.[234,235]

Resistance to the actions of insulin secondary to the effects of sex steroids produces transient diabetes mellitus in 2% to 5% of pregnancies.[3] Gestational diabetes mellitus affects about 100,000 pregnant women annually in the U.S.[3] Although most affected women recover normal glucose tolerance postparturiently, about half will develop type 2 diabetes later in life.[3] However, women with untreated gestational diabetes experience a 5-fold increase in the incidence of major congenital malformations; even with effective treatment, the risk for fetal or neonatal death is doubled.[3] In addition, infants born to mothers with either type 1, type 2 or gestational diabetes are at significantly increased risks for macrosomia, hypoglycemia, hypocalcemia, respiratory distress syndrome, polycythemia, hyperbilirubinemia, renal vein thrombosis, persistence of fetal circulation, cardiomyopathy, congenital heart disease, and caudal regression syndrome.[5]

Diabetes can cause many other health problems. Ketoacidosis and hyperosmolar coma secondary to diabetes may become life threatening.[3] Individuals with diabetes are predisposed to develop periodontal disease, oral mucosal infections, salivary gland dysfunction and the "burning mouth" syndrome.[3] Peripheral insulin resistance, hyperinsulinemia and insulin-induced thecal androgen hypersecretion and interference with the synchrony of follicular development are common in women with polycystic ovary syndrome, suggesting a primary etiologic role for abnormal glucose homeostasis in the pathogenesis of this disease.[236]

1.6 Interruption of the Pathogenesis of Type 2 Diabetes Decreases the Risk for the Development of Type 2 Diabetes

The development of diabetes follows a pathogenic sequence from health through a continuum of increasingly disrupted glucose homeostasis to disease.[3,5,7,51-63,65] An abnormality in insulin physiology produces initial insulin resistance (decreased sensitivity of peripheral target tissues to insulin stimulation of glucose uptake) with compensatory increased pancreatic secretion of insulin (compensated hyperinsulinemia without hyperglycemia). Progression of the severity of insulin resistance impairs glucose tolerance and produces transient postprandial hyperglycemia and hyperinsulinemia (uncompensated hyperinsulinemia with hyperglycemia). Continued progressive loss of glucose

homeostatic ability may produce residual fasting hyperglycemia and type 2 diabetes. Eventual downregulation of pancreatic β-cell function may contribute to fasting hyperglycemia and increase the severity of type 2 diabetes.

The progressive development of type 2 diabetes suggests the availability of several opportunities to delay or prevent disease outcome.[7,59] Indeed, the American Diabetes Association has concluded that, "There is now substantial evidence that type 2 diabetes can be prevented or delayed."[229] Both rational thought and the available evidence indicate that the interruption of the pathogenic sequence of type 2 diabetes can reduce the risk for the outcome of the uninterrupted sequence (i.e., the development of type 2 diabetes). For example, lifestyle modifications relying upon weight loss and maintenance programs and exercise regimens have been shown to delay or prevent the progression of the required precursor condition, prediabetes (in these studies, expressed as impaired glucose tolerance) to type 2 diabetes.[237-240] In further proof of principle, three different classes of pharmacological agents, the biguanides, the α-glucosidase inhibitors, and the thiazolidinediones, have been shown to be effective in preventing or delaying the progression of prediabetes to type 2 diabetes[237,241] and in preventing or delaying the conversion of gestational diabetes to type 2 diabetes.[242] All of the available evidence clearly indicates that any means, including nutritional, of preventing, reducing, ameliorating or reversing the required precursor condition, prediabetes, can prevent the progression of that required precursor condition to type 2 diabetes and, therefore, can prevent the development of type 2 diabetes.[237-242]

1.7 Interruption of the Pathogenesis of Type 2 Diabetes Decreases the Risks for the Development of Other Diseases for which Individuals with Type 2 Diabetes are at Increased Risk

Individuals with type 2 diabetes are at significantly increased risks for retinopathy, nephropathy, neuropathy, hypertension, atherosclerosis, cerebrovascular disease, cardiovascular disease, coronary artery disease and stroke.[3,4,46,80,81,83-85,85-105,107-146,216-218,220,222-225,243] However, several observational and controlled clinical studies have demonstrated that the prevention or delay of the progression of prediabetes to diabetes also delays the onset of, slows the progression of and decreases the risks for diabetes-induced retinopathy, nephropathy, neuropathy,[44,241,242,244,245] hypercholesterolemia (a risk factor for coronary artery disease),[242] and cardiovascular disease.[55,86,246-248] It should be noted that interruption of the pathogenesis of type 2 diabetes by the prevention or delay of the progression of prediabetes to diabetes has not always been observed to reduce the subsequent incidence of diseases caused by diabetes (or to which diabetes is a major etiologic contributor).[249-252] The failure to observe an effect or statistically significant association in epidemiologic studies can result from differences in study design, study populations, methods of modeling epidemiologic data, etc.; importantly, the results of all of the relevant controlled clinical trials consistently have demonstrated that interruption of the pathogenesis of type 2 diabetes by the prevention or delay of the progression of prediabetes to diabetes has reduced the subsequent incidence of diseases caused by diabetes (or to which diabetes is a major etiologic contributor).[55,86,241,242,244-248]

2.0 Background on Chromium

2.1 Chromium in U.S. Diets

Chromium [as Cr(III)] is an essential trace mineral found in foods and supplements in the oxidized form, Cr(III) (the most stable form of chromium).[253] Chromium is present in small amounts in many foods commonly consumed in the U.S.[254] and is considered one of the least toxic nutrients.[255,256] A significant

portion of the chromium present in foods is believed to originate from the soil and from external sources during growing, processing, preparation, fortification and handling.[254] Currently the Institute of Medicine recommends that adult men aged 14 to 50 years consume 35 mcg of chromium daily and adult women aged 14 to 50 years consume 25 mcg of chromium daily.[256] Those recommendations are reduced by 5 mcg daily for individuals over the age of 50 years.[256]

The United States Department of Agriculture (USDA) nutrient composition database does not include data on the chromium content of foods, and consequently no estimates of chromium intake for the U.S. population based on national food consumption survey data have been published. In the absence of nutrient composition data for chromium, results from chromium analyses of self-selected diets have been used to provide estimates of typical chromium intake in the U.S.[254,257,258] Anderson and Kozlovsky[257] estimated that the 7-day average chromium intake by 10 adult males was 33 ± 3 mcg (range 22 to 48 mcg per day), and the estimated intake by 22 adult females was 25 ± 1 mcg (range 13 to 36 mcg per day). Those estimates correspond with approximately 14 mcg and 16 mcg of chromium per 1000 kcal of dietary energy intake for males and females, respectively.

In another study of the chromium content of self-selected diets, in which the chromium contents of foods was directly measured, the average chromium concentration of diets selected by 8 adult males was 18.6 mcg per 1000 kcals, and the average chromium concentration in diets selected by 11 adult females was 12.5 mcg per 1000 kcals.[254] The self-selected daily chromium intake was determined to be 38.8 ± 6.5 mcg per day for the males and 23.1 ± 2.9 mcg per day for the females.[258] When corrected for self-selected energy intake, self-selected daily chromium intake was determined to be 54.1 ± 7.2 mcg per day by males and 28.7 ± 3.1 mcg per day for females.[258]

Those estimates of dietary chromium intake are lower than the estimated daily intake of 60 mcg from food reported by the Agency for Toxic Substances and Disease Registry (ATSDR)[259] and the 25 to 224 mcg per day earlier reported by Kumpulainen *et al.*[260] It has been suggested that improved instrumentation and optimization of chromium analyses have produced more accurate estimates of dietary chromium intakes than were available previously and that, therefore, the more recent estimates (published by Anderson *et al.*)[254,257,258] may be more representative of true chromium intakes from dietary sources.[261]

More recently, Juturu *et al.*[262] reported estimates of the intake of chromium based on food servings consumed by free-living male and female adults and children as reported in the Continuing Survey of Food Intakes by Individuals (CSFII) conducted from 1994 to 1996. In that study, the consumption of chromium from food sources averaged less than 20 mcg per day based on data from the Food Data Bank of Nutritionist V.[262] However, it is not possible to determine dietary chromium intake with precision from food consumption data alone because the content of chromium in food is variable among different food lots and may be influenced by processing and cooking at high temperatures, increasing the inaccuracy of existing food composition databanks.

2.2 Absorption and Bioavailability of Chromium

Trivalent chromium (Cr(III)) is present in many foods and is ingested as a normal part of the daily diet. However, only about 0.4 to 2.0% of dietary trivalent chromium is absorbed by laboratory animals and humans, predominantly in the small intestine,[263] whether from food[257,264,265] or from dietary supplements containing chromium.[264,266] The efficiency of intestinal absorption of dietary trivalent chromium may or

may not be inversely related to trivalent chromium dietary intake. In one study, the efficiency of absorption of 10 mcg of chromium daily averaged 2.0% while the efficiency of absorption of 40 mcg of chromium daily averaged 0.5%, resulting in a relatively constant daily influx of dietary trivalent chromium into the bloodstream.[257] However, in another study, the apparent absorption (estimated from urinary excretion rates) of chromium averaged 0.4% when either 60 mcg or 260 mcg were consumed daily, resulting in a greater than 3-fold difference in the amount of bioavailable chromium.[264]

Within the small low range of absorption efficiencies, the absorption of trivalent chromium following ingestion is strongly influenced by the chemical complex in which the trivalent chromium is administered. Ingestion of trivalent chromium in the form of inorganic salts that are insoluble in water, such as chromic oxide, results in little or no absorption in rats[263] or healthy humans.[266] By contrast, chromium chloride and trivalent chromium in association with a chelating agent, such as picolinate or nicotinate, are relatively more water soluble and are more efficiently absorbed in the gastrointestinal tracts of rats[267] and humans.[266] However, chromium chloride and chromium nicotinate are relatively unstable in the presence of starch and may be very poorly absorbed from starch-containing foods, diets or dietary supplements.[268]

The absorption of trivalent chromium from chromium picolinate has been reported to be greater than that from other forms of chromium.[269] For example, the chromium contents of the kidneys and livers of rats fed either chromium picolinate or chromium chloride in amounts up to 100 mg of chromium per kg of diet for 140 days increased linearly with increasing chromium intake, with approximately 2- to 6-fold greater chromium contents in the organs of the rats fed supplemental chromium picolinate.[267] In a comparative study, using urinary chromium excretion as a surrogate marker for dietary chromium absorption,[264,265,270-274] adults with type 2 diabetes absorbed chromium from chromium picolinate significantly more efficiently than from chromium chloride or chromium nicotinate.[275] In healthy humans, the absorption of 400 mcg of chromium as chromium picolinate daily averaged 2.8%, with a range of 1.5% to 5.2%.[270] In older men, the efficiency of absorption of chromium from the foods in 2 diets averaged 0.3% ± 0.3% or 0.6% ± 0.6%, while the efficiency of absorption of chromium from 924 mcg daily of chromium picolinate plus the foods in the same 2 diets was significantly increased in both situations and averaged 1.1% ± 0.5% or 0.9% ± 0.5%, respectively.[265]

In humans, chromium is excreted mainly in urine, although small amounts are lost in hair, perspiration and bile.[264,276] The 24-hour urinary excretion rates for normal human subjects consuming 60 mcg of chromium daily in food were reported to average about 0.2 to 0.3 mcg in unsupplemented males and females and were similar to estimates of the amount of chromium that was absorbed daily.[264] However, when chromium intake was increased via dietary supplementation with chromium chloride[264] or chromium picolinate,[265] 24-hour urinary excretion rates increased in direct proportion to total intakes.[264]

2.3 Chromium Status and Aging

Statistically significant age-related decreases in serum chromium concentrations were observed in 40,872 patients referred by their physicians to an independent medical research clinic and laboratory.[276] This effect of aging was observed in both males and females and suggests that dietary chromium requirements increase with age in adults.

2.4 Chromium Potentiates the Biological Actions of Insulin

Cr(III) is required by the human body for normal carbohydrate and lipid metabolism,[277,278] acting as an "insulin-sensitizing agent" (substance that accelerates the clearance of glucose from plasma in the presence of a fixed amount of insulin[59,76]). Evidence of chromium's role was first suggested in 1957 when a "glucose tolerance factor" (GTF), found in brewer's yeast, prevented an age-related decline of glucose tolerance in rats. Cr(III) was identified shortly thereafter as the active ingredient of GTF.[279] In rats, in the absence of chromium, hypersecretion of insulin is required in order to maintain normal glucose tolerance.[280] In humans fed parenterally, chromium-free nutrient solutions produce insulin-unresponsive impairment of glucose tolerance which is reversible upon the addition of chromium to the infusate.[281,282] Even chronic low intakes of chromium impair glucose tolerance.[283] Two cross-sectional observational studies have found significantly lower plasma chromium concentrations in individuals with type 2 diabetes than in individuals with normal glucose homeostasis,[284,285] although another, older study, did not.[286]

A sequence of reactions implement the "insulin-sensitizing" effects of Cr(III) on the physiologic actions of insulin.[256,269,277,287-289] Insulin in the extracellular fluid reversibly binds to its receptor within the plasma membrane of a target cell, triggering movement of vesicle-bound transferrin receptor to the target cell plasma membrane. Cr(III)-bound transferrin, the predominant plasma carrier of Cr(III), binds to the transferrin receptor and is internalized by endocytosis into the cytoplasm of the target cell. Within the cytoplasm, Cr(III) is released from transferrin and binds with apochromodulin, a low molecular weight chromium binding substance, forming the activated messenger, holochromodulin. Activated holochromodulin interacts with the insulin-receptor complex, autoamplifying the occupied receptor's insulin-stimulated tyrosine kinase activity and further increasing tyrosine kinase phosphorylation of the β-subunits of insulin receptors whose α-subunits are occupied by insulin. Phosphorylation of the β-subunit stimulates the transmission of the insulin signal to the cytoplasm with consequent transmembrane glucose transport, increasing intracellular glucose content at the expense of plasma glucose concentration.

Trivalent Cr(III) ions also inhibit phosphotyrosine phosphatase, an enzyme that dephosphorylates (deactivates) the phosphorylated insulin receptor. Concurrent stimulation of β-subunit phosphorylation and inhibition of its dephosphorylation result in an increased proportion of activated insulin-responsive receptors. Consequently, the greater the proportion of activated insulin receptors responsive to circulating insulin, and the greater the amplification of the insulin signal, the more rapid the resultant decline in plasma glucose concentration and the shorter the duration of pancreatic insulin secretion. When extracellular fluid insulin concentrations subside, insulin releases from its receptor. The unbound receptor has very low affinity for holochromodulin and, in the absence of insulin, releases holochromodulin with Cr(III) into the extracellular fluid (presumably with subsequent diffusion into the plasma).

3.0 Description Of Chromium Picolinate

Chromium picolinate is a stable complex of trivalent chromium (Cr (III)) and picolinic acid. Alternate chemical names for this substance are tris(2-pyridinecarboxylato-N_1, O_2)chromium and chromium(III) trispicolinate.[290]

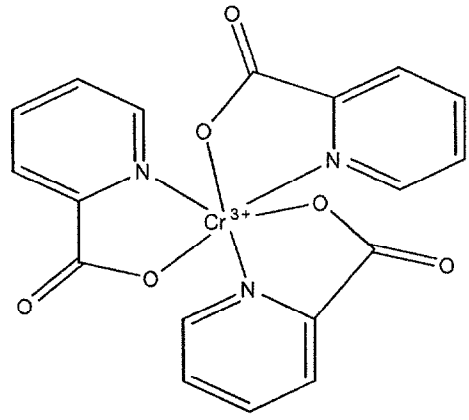
3.1 Physical and Chemical Properties of Chromium Picolinate

The physical and chemical properties of chromium picolinate include:

Composition: C - 51.68%, O - 22.95%, Cr -12.43%, N - 10.05%, H - 2.89%
Molecular Weight: 418.31 Daltons
Solubility (in water): Soluble in water at pH 7 (>100 mcg/ml)
Solubility (in chloroform): Soluble in chloroform (2.0 mM)

The Chemical Abstracts Service ("CAS") Registry Number for chromium picolinate is 14639-25-9. The empirical formula for chromium picolinate is $C_{18}H_{12}CrN_3O_6$. The structural formula for this compound is shown in Figure 1.[290]

Figure 1. Structural Formula for Chromium Picolinate



4.0 Chromium studies

4.1 *In Vitro* Studies Evaluating the Effects of Chromium Picolinate on Insulin Sensitivity and Glucose Metabolism

Chromium has been shown to enhance target cell sensitivity to insulin by increasing the binding of insulin to its receptor sites, initial receptor site activation and post-receptor transmission of intracellular signalling.[256,269,277,287-289] Chromium picolinate has been shown to enter target cells and to bind to apochromodulin intact (i.e., as chromium picolinate)[291] and enhance intracellular signaling by serving as an "autoamplifier" for intracellular insulin signals, such as insulin receptor mediated tyrosine kinase activities.[292,293]

In cultured human skeletal muscle cells, chromium picolinate significantly potentiated insulin-stimulated glucose uptake and glycogen synthesis.[292,293] In addition, the intracellular activity of insulin receptor substrate-1 (IRS-1) associated phosphotidylinositol 3-kinase (PI3K) activity (a downstream member of the insulin signaling cascade[269]) was significantly increased by chromium picolinate in a concentration-dependent manner.[292,293] Those findings indicate that chromium picolinate acted to increase the sensitivity of human skeletal muscle cells to fixed amounts of insulin.

Chromium picolinate also may enhance insulin-receptor interactions. In cultured rat skeletal muscle cells, in a concentration at which chromium chloride and chromium nicotinate had no effect, chromium picolinate significantly increased insulin-receptor binding and the subsequent uptakes of glucose and leucine.[289] In addition, the presence of chromium picolinate also significantly increased the fluidity of skeletal muscle cell membranes, which may have further facilitated insulin-receptor binding.[289]

4.2 Preclinical Studies Evaluating the Effects of Chromium Picolinate Supplementation

Dietary supplementation with chromium picolinate has been shown to increase insulin sensitivity and glucose uptake in animals with impaired glucose tolerance. For example, the addition of chromium picolinate to the drinking water of a genetic strain of rat prone to obesity and the insulin resistance syndrome (JCR-LA corpulent) for 12 weeks, providing approximately 80 mcg of chromium as chromium picolinate daily per kg of bodyweight, significantly increased insulin-stimulated membrane translocation of the myocyte GLUT4 glucose transporter and the rate of glucose clearance from the blood but significantly decreased fasting plasma insulin concentration, compared to the effects of unsupplemented water.[294] Interestingly, such relatively short-term supplementation with chromium picolinate had no effects on lean rats with normal glucose tolerance; rather than being refractory to chromium picolinate supplementation, rats with normal glucose tolerance may have limited capacity to further stimulate GLUT4 kinetics or glucose uptake in the presence of adequate amounts of insulin.

Similarly, dietary supplementation with chromium picolinate has increased insulin sensitivity and glucose uptake in animals with diabetes. For example, in rats treated with dexamethasone in order to produce glucocorticoid-induced diabetes, concurrent dietary supplementation with chromium picolinate (30 mg/kg/day) prevented the postchallenge hyperinsulinemia and loss of glucose tolerance exhibited by unsupplemented dexamethasone-treated rats.[295]

4.3 Clinical Studies Evaluating the Effects of Chromium Picolinate Supplementation in Individuals with Pre-Diabetes

Cefalu *et al.*[53] studied the impact of dietary supplementation with chromium picolinate on 29 obese middle-aged human subjects with mild fasting hyperinsulinemia but without hyperglycemia. After both 4 and 8 months of daily dietary supplementation with either 1000 mcg of chromium (in the form of chromium picolinate) or placebo, subjects receiving daily dietary supplementation with chromium picolinate exhibited significantly greater (compared to the response to placebo) increases in insulin sensitivity, although (as expected in normoglycemic individuals) plasma glucose concentrations were unaffected. Similarly, young adults with fasting hyperinsulinemia without hyperglycemia experienced significantly greater (compared to the response to placebo) decreases in fasting plasma insulin concentrations after 90 days of daily dietary supplementation with 200 mcg of chromium (as chromium picolinate).[278] Those results demonstrate that supplementation of the diet with chromium picolinate can reduce the likelihood of later development of insulin resistance (and therefore of diabetes) in currently healthy individuals at elevated risk of losing glucose tolerance. Furthermore, in a subset of an uncontrolled 5 week trial of daily dietary supplementation with 200 mcg of chromium (as chromium picolinate), adults with impaired glucose tolerance experienced significantly improved glucose tolerance and significantly decreased fasting insulin concentrations.[283]

4.4 Clinical Studies Evaluating the Effects of Chromium Supplementation on Individuals with Diabetes

Human clinical studies evaluating the effects of chromium picolinate supplementation in subjects with diabetes are listed in Table 1. The results of these studies demonstrate that daily dietary supplementation with 200 mcg to 1000 mcg of chromium (as chromium picolinate) consistently improved hyperglycemia and measures of insulin sensitivity.[53,296-307] One trial of subjects with severe diabetes and daily dietary supplementation with only 200 mcg of chromium (as chromium picolinate) failed to observe these effects.[308] Nonetheless, it is clear from these studies that daily dietary supplementation with chromium (as chromium picolinate) significantly improves glucose homeostasis and, in so doing, reduces the risks for the development of diseases for which type 2 diabetes is a causative or contributory etiologic factor.

Other chromium complexes also have been evaluated in human clinical studies (Tables 2 and 3).[278,283,309-330] Overall, dietary supplementation with chromium chloride, yeast containing chromium or chromium nicotinate has produced either no effects or inconsistent effects on glucose homeostasis, suggesting that those chromium complexes differ functionally from chromium picolinate.

Table 1. Clinical Studies of the Effects of Dietary Supplementation with Chromium Picolinate on Glucose Homeostasis

Author	Year	Subject Characteristics	Number of Subjects	Cr (mcg/day)
Randomized controlled clinical trials published in peer-reviewed journals				
Ghosh[301]	2002	Type 2 Diabetes Mellitus	50	400
Anderson[296]	1997	Type 2 Diabetes Mellitus	180	1000
Lee[308]	1994	Type 2 Diabetes Mellitus	30	200
Evans[299]	1989	Type 2 Diabetes Mellitus	11	200
Jovanovic[303]	1999	Gestational Diabetes Mellitus	20	300 - 800
Randomized controlled clinical trials not published in peer-reviewed journals				
Houweling[302]	2003	Type 2 Diabetes Mellitus	52	500, 1000
Feng[300]	2002	Type 2 Diabetes Mellitus	136	500
Uncontrolled ("open label") clinical trials published in peer-reviewed journals				
Morris[304]	2000	Type 2 Diabetes Mellitus	5	400
Cheng[298]	1999	Type 2 Diabetes Mellitus	833	500
Ravina[306]	1995	Type 1 Diabetes Mellitus; Type 2 Diabetes Mellitus	162	200
Ravina[307]	1999	Steroid-Induced Diabetes Mellitus	44	300 – 600
Uncontrolled ("open label") clinical trials not published in peer-reviewed journals				
Rabinovitz[305]	2000	Type 2 Diabetes Mellitus	39	400
Bahadori[297]	1999	Type 2 Diabetes Mellitus	16	1000

Table 2. Clinical Studies of the Effects of Dietary Supplementation with Chromium Chloride on Glucose Homeostasis

Author	Year	Subject Characteristics	Number of Subjects	Cr (mcg/day)
Randomized controlled clinical trials published in peer-reviewed journals				
Chromium Chloride:				
Abraham[309]	1992	Type 2 Diabetes Mellitus; Normal Glucose Tolerance	25 51	250
Mossop[313]	1983	Type 2 Diabetes Mellitus	26	600
Uusitupa[316]	1983	Type 2 Diabetes Mellitus	10	200
Anderson[310]	1983	Impaired Glucose Tolerance; Normal Glucose Tolerance	41 35	200
Martinez[327]	1985	Impaired Glucose Tolerance Normal Glucose Tolerance	17 28	200
Riales[323]	1981	Normal Glucose Tolerance	23	200
Urberg[322]	1987	Normal Glucose Tolerance	16	200
Non-randomized controlled clinical trials published in peer-reviewed journals				
Chromium Chloride:				
Sherman[315]	1968	Type 1 Diabetes Mellitus, Type 2 Diabetes Mellitus or Normal Glucose Tolerance	3 7 4	50
Anderson[283]	1991	Impaired Glucose Tolerance Normal Glucose Tolerance	8 9	200
Potter[328]	1985	Impaired Glucose Tolerance, Elderly Subjects	5	200
Levine[329]	1968	Impaired Glucose Tolerance, Elderly Subjects	10	150
Carter[330]	1968	Children with kwashiorkor	9	250
Uncontrolled ("open label") clinical trials published in peer-reviewed journals				
Chromuim Chloride:				
Glinsmann[312]	1966	Type 2 Diabetes Mellitus; Normal Glucose Tolerance	14 10	150 to 1000
Hopkins[324]	1968	Malnourished Infants	12	250
Gurson[325]	1971	Malnourished Children	15	50

Table 3. Clinical Studies of the Effects of Dietary Supplementation with Other Chromium Complexes on Glucose Homeostasis

Author	Year	Subject Characteristics	Number of Subjects	Cr (mcg/day)
Randomized controlled clinical trials published in peer-reviewed journals				
Yeast containing Chromium:				
Elias[317]	1984	Type 2 Diabetes Mellitus	6	20
Offenbacher[318]	1980	Type 2 Diabetes Mellitus; Normal Glucose Tolerance	4 8	10.8
Uusitupa[321]	1992	Impaired Glucose Tolerance; Elderly subjects	26	160
Chromium Nicotinate:				
Juang[326]	2000	Impaired Glucose Tolerance	15	800
Thomas[319]	1996	Type 2 Diabetes Mellitus; Normal Glucose Tolerance	5 14	200
Wilson[278]	1995	Normal Glucose Tolerance	26	220
Lefavi[331]	1983	Normal Glucose Tolerance	34	200 or 800
Non-randomized controlled clinical trials published in peer-reviewed journals				
Combination of Chromium Chloride and Yeast containing Chromium:				
Rabinowitz[314]	1983	Type 2 Diabetes Mellitus; Normal Glucose Tolerance	43 20	150 or 18
Wang[332]	1989	Normal Glucose Tolerance	30	15 or 50
Randomized controlled clinical trials not published in peer-reviewed journals				
Combination of Chromium Chloride and Yeast containing Chromium:				
Bahijiri[311]	2000	Type 2 Diabetes Mellitus	78	223
Uncontrolled ("open label") clinical trials published in peer-reviewed journals				
Yeast containing Chromium:				
Trow[320]	2000	Type 2 Diabetes Mellitus	23	100

4.41 Clinical Studies Evaluating Chromium Picolinate Supplementation in Individuals with Diabetes

4.411 Randomized controlled clinical trials published in peer-reviewed journals

The most recent randomized controlled clinical trial published in a peer-reviewed journal was the randomized controlled cross-over study of Ghosh *et al.*,[301] who compared the effects of daily dietary supplementation with 400 mcg chromium (as chromium picolinate) to the effects of placebo in 50 subjects with type 2 diabetes. Each treatment arm lasted 12 weeks with an intervening 4-week "washout" period during which all subjects consumed the placebo. Daily dietary supplementation with chromium picolinate produced significantly different changes in mean fasting and post-glucose-challenge plasma glucose concentrations, fasting plasma insulin concentrations, and plasma HbA_{1c} percentages. During placebo consumption, mean fasting plasma glucose concentration increased 6%, mean fasting plasma insulin concentration increased 30%, mean post-glucose-challenge plasma glucose concentration was unchanged and mean plasma HbA_{1c} percentage increased 10%. In contrast, during chromium picolinate supplementation, the subjects experienced a 7% decrease in mean fasting plasma glucose concentration, a 20% decrease in mean fasting plasma insulin concentration and a 16% decrease in mean post-glucose-challenge plasma glucose concentration, although mean plasma HbA_{1c} percentage was unchanged. The findings of that study support the conclusion that supplemental chromium picolinate sensitizes target tissues to insulin.

In a parallel randomized controlled clinical trial, Anderson *et al.*[296] compared the effects of placebo to the effects of daily dietary supplementation with either 200 mcg or 1000 mcg of chromium (as chromium picolinate) in 180 subjects with type 2 diabetes. Most of the study subjects were receiving oral medications, predominantly sulfonylureas. After 4 months, compared to the effects on the subjects consuming placebo or 200 mcg of chromium daily, the subjects supplemented with 1000 mcg of chromium daily exhibited significantly greater reductions in mean fasting plasma glucose concentration (mean reduction, placebo: 10%, 200 mcg Cr: 15%, 1000 mcg Cr: 28%) and improvements in oral glucose tolerance (expressed as mean post-glucose-challenge plasma glucose concentration; mean reduction, placebo: 17%, 200 mcg Cr: 24%, 1000 mcg Cr: 30%). Mean fasting insulin concentrations were significantly reduced in both supplemented groups (mean reduction, placebo: 16%, 200 mcg Cr: 31%, 1000 mcg Cr: 33%) as were mean plasma HbA_{1c} percentages (mean reduction, placebo: 7%, 200 mcg Cr: 20%, 1000 mcg Cr: 30%). The reductions in plasma HbA_{1c} percentages were sufficiently large in the subjects supplemented with 1000 mcg of chromium daily that most of those subjects could be considered to have achieved target plasma HbA_{1c} percentages. However, all subjects continued to exhibit some (albeit lesser) degree of fasting hyperglycemia. Nonetheless, the findings of that study support the conclusion that supplemental chromium picolinate sensitizes target tissues to insulin and prevents hyperglycemic glycation of hemoglobin.

Evans *et al.*[299] compared the effects of daily dietary supplementation with 200 mcg of chromium (as chromium picolinate) to the effects of placebo in 11 subjects with type 2 diabetes in a randomized, double-blinded, placebo controlled crossover study, with two 42-day treatment periods and an intervening 14-day "washout" period. In the first arm of the study, placebo produced a 17% increase in mean fasting plasma glucose concentration and a 6% increase in mean plasma HbA_{1c} percentage, while chromium picolinate supplementation produced a 21% decrease in mean fasting plasma glucose concentration and a 3% decrease in mean plasma HbA_{1c} percentage. In the second arm of the study, placebo produced a 5% decrease in mean fasting plasma glucose concentration and an 11% increase in

mean plasma HbA_{1c} percentage, while chromium picolinate supplementation produced a 13% decrease in mean fasting plasma glucose concentration and a 17% decrease in mean plasma HbA_{1c} percentage. The changes in mean fasting plasma glucose concentration and HbA_{1c} percentage in the subjects consuming supplemental chromium picolinate were statistically significantly different from the changes that were observed during placebo consumption during both arms of the study. The findings of that study support the conclusion that supplemental chromium picolinate sensitizes target tissues to insulin and prevents hyperglycemic glycation of hemoglobin.

In contrast, when Lee and Reasner[308] compared the effects of placebo to the effects of daily dietary supplementation with 200 mcg of chromium (as chromium picolinate) in 30 subjects also receiving combination therapies for type 2 diabetes in a 2-month randomized, double-blinded, placebo controlled parallel study, they did not detect significantly different changes in mean fasting plasma glucose concentration or plasma HbA_{1c} percentage.

Jovanovic *et al.*[303] compared the effects of placebo to the effects of daily dietary supplementation with chromium picolinate (4 or 8 mcg of chromium per kg of bodyweight) in 30 women with gestational diabetes. 8 weeks of dietary supplementation with chromium picolinate had no effect on mean fasting plasma glucose concentrations or mean plasma HbA_{1c} percentages but produced significantly greater decreases in fasting and post-glucose challenge plasma insulin concentrations in both groups consuming chromium picolinate. Compared to a 61% increase in the subjects consuming placebo, mean fasting plasma insulin concentration decreased 13% in the subjects supplemented with 4 mcg of chromium per kg of bodyweight and decreased 6% in the subjects supplemented with 8 mcg of chromium per kg of bodyweight. Similarly, compared to a 20% increase in the subjects consuming placebo, mean post-glucose challenge plasma insulin concentration decreased 1% in the subjects supplemented with 4 mcg of chromium per kg of bodyweight and 8% in the subjects supplemented with 8 mcg of chromium per kg of bodyweight. Those findings suggest that dietary supplementation with chromium picolinate may increase maternal tissue insulin sensitivity during gestational diabetes and may reduce the risk of conversion of gestational diabetes to type 2 diabetes.

4.412 Randomized controlled clinical trials not published in peer-reviewed journals

Houweling *et al.*[302] compared the effects of placebo to the effects of daily dietary supplementation with 500 or 1000 mcg of chromium (as chromium picolinate) in 52 subjects with type 2 diabetes and plasma HbA_{1c} percentages > 8% despite daily concomitant administration of oral hypoglycemic agents and >50 U of insulin. After 6 months of chromium picolinate supplementation, a significant reduction of 0.5 percentage points in mean plasma HbA_{1c} percentage was observed in the subjects supplemented with 1000 mcg of chromium daily, but no reduction occurred in the subjects supplemented with 500 mcg of chromium daily or in those consuming placebo. The findings of that study support the conclusion that dietary supplementation with chromium picolinate decreases hyperglycemic glycation of hemoglobin.

Feng *et al.*[300] examined the effects of daily dietary supplementation with chromium picolinate in subjects with type 2 diabetes on insulin therapy. A total of 104 patients consumed 500 mcg of chromium (as chromium picolinate) daily in addition to receiving insulin therapy; 32 patients were treated with insulin alone. After 3 months, daily dietary supplementation with chromium picolinate appeared to significantly potentiate insulin-induced reductions in fasting and post-glucose-challenge plasma glucose concentrations, reducing mean fasting plasma glucose concentration by another 8% and

mean 2 hr post-glucose-challenge plasma glucose concentrations by another 21%. In addition, the daily insulin dose required to maintain relatively good glucose homeostasis decreased in 81% of the supplemented patients, with an average 19.4% reduction in insulin dose. There were no negative effects of supplemental chromium. In contrast, the 32 patients not supplemented with chromium picolinate exhibited no changes in glucose tolerance or required insulin dosage. The findings of that study support the conclusion that supplemental chromium picolinate sensitizes target tissues to insulin.

4.413 Uncontrolled ("open label") clinical trials published in peer-reviewed journals

Morris *et al.*[304] evaluated the effects of daily dietary supplementation with 400 mcg chromium (as chromium picolinate) in 5 subjects with newly-diagnosed type 2 diabetes. After 12 weeks of supplementation, insulin responsiveness, as assessed by the slope of the glucose disappearance curve during insulin tolerance tests, had significantly increased (by an average of 60%). Mathematical modeling of fasting plasma glucose and insulin concentrations (the HOMA method) indicated that the changes in the slopes of the glucose disappearance curves during insulin tolerance tests were accompanied by a significant decrease in insulin resistance. However, neither mean fasting plasma glucose concentration or mean plasma HbA_{1c} percentage were affected by chromium picolinate supplementation. Both insulin responsiveness and insulin resistance returned to prestudy conditions within 4 weeks of withdrawal of dietary chromium supplementation. The findings of that study support the conclusion that supplemental chromium picolinate sensitizes target tissues to insulin.

Cheng *et al.*[298] evaluated the effects of daily dietary supplementation with 500 mcg chromium (as chromium picolinate) in 833 subjects with type 2 diabetes concurrently treated with oral hypoglycemic medications and/or insulin. A significant 20% decrease in mean fasting plasma glucose concentration and a significant 18% decrease in mean post-glucose-challenge plasma glucose concentration were observed after 1 month of supplementation; these decreases were sustained during 9 additional months of chromium picolinate supplementation. Interestingly, the incidence of symptoms of diabetes (fatigue, extreme thirst, frequent micturition) decreased by about 90% during chromium picolinate supplementation.

Ravina *et al.*[306] evaluated the benefits of daily dietary supplementation with 200 mcg of chromium (as chromium picolinate) in 48 subjects with type 1 diabetes and 114 subjects with type 2 diabetes. Upon commencing supplementation, patients were asked to reduce their usual medication by 50% in order to minimize the potential for hypoglycemic reactions. Before the study began and after 10 days of supplementation the patients underwent intravenous insulin tolerance tests. Patients were considered to be "responders" to supplementation when the calculated rate of glucose fall during the test increased (compared to the prestudy rate) by 0.1 mg/min or more after supplementation with chromium picolinate. Seventy-one percent (71%) of the patients with type 1 diabetes and 73% of those with type 2 diabetes were determined to be responders by this criterion. The researchers noted that a high proportion of those considered to be responsive to chromium picolinate supplementation could maintain their reduced medication schedule with no degradation of glucose tolerance. Subjects with type 1 diabetes who responded to chromium supplementation were able to reduce their insulin dose by an average of 30%; this reduction in exogenous insulin was accompanied by decreased frequency and magnitude of hypoglycemic episodes. Subjects with type 2 diabetes who responded to chromium supplementation and were being treated with oral medications were able to reduce their medication doses by 50%, and those being treated with exogenous insulin were able to reduce or eliminate insulin therapy. Those

findings support the conclusion that dietary supplementation with chromium picolinate sensitizes target tissues to insulin and prevents or decreases hyperglycemic glycation of hemoglobin.

In the same study, Ravina *et al.*[306] further evaluated a subset of 55 subjects who were determined to be 'responders' to supplementation with chromium picolinate. Forty-four of these subjects experienced a decrease in plasma HbA_{1c} percentage that was attributed to chromium picolinate supplementation. Among these 44 subjects, mean plasma HbA_{1c} percentage decreased significantly (by 16%) during the study. However, 4 'responders' exhibited increased plasma HbA_{1c} percentages as a result of supplementation with chromium picolinate. Among the 7 'nonresponders,' plasma HbA_{1c} percentages were unrelated to the rate of decrease in plasma glucose concentration following an intravenous injection of insulin. As a whole, the findings of that study support the conclusion that supplemental chromium picolinate prevents or decreases hyperglycemic glycation of hemoglobin.

In a subsequent study, Ravina *et al.*[307] evaluated the effects of daily dietary supplementation with 300 to 600 mcg of chromium (as chromium picolinate) in a case series of 44 subjects with steroid-induced insulin-resistant diabetes. Initially, daily supplementation with chromium picolinate produced rapid and substantial reductions in fasting hyperglycemia in 2 patients whose glucose tolerance had deteriorated while being treated with glucocorticoids. In a third patient, dexamethasone-induced fasting hyperglycemia was completely resolved by chromium picolinate supplementation. Subsequently, 200 mcg Cr as chromium picolinate was consumed three times daily by 41 similar subjects; 38 experienced amelioration of steroid-induced diabetes that was attributable to chromium picolinate supplementation. The findings of that study support the conclusion that supplemental chromium picolinate sensitizes target tissues to insulin, even in the presence of diabetes-inducing amounts of glucocorticoids.

4.414 Uncontrolled ("open label") clinical trials not published in peer-reviewed journals

Rabinovitz *et al.*[305] evaluated the effects of daily dietary supplementation with 400 mcg of chromium (as chromium picolinate) added to a low-sugar diet in 39 subjects with type 2 diabetes. After 3 weeks, significant decreases were observed in mean fasting plasma glucose concentration (21%) and in mean plasma HbA_{1c} percentage (7%). Those findings support the conclusion that dietary supplementation with chromium picolinate sensitizes target tissues to insulin and prevents or decreases hyperglycemic glycation of hemoglobin.

Bahadori *et al.*[297] evaluated the effects of daily dietary supplementation with 1000 mcg of chromium (as chromium picolinate) in 16 obese subjects with type 2 diabetes. After 4 months of chromium picolinate supplementation, mean fasting plasma insulin concentration was significantly decreased (by 38%). However, insulin resistance (assessed by an insulin suppression test), fasting plasma glucose concentration and plasma HbA_{1c} percentage were not affected. Those data suggest that an increase in insulin clearance – presumably by the liver – and not an increase in target tissue insulin sensitivity contributed to the observed decline in fasting plasma insulin concentrations in this study of obese diabetics. Nonetheless, a reduction in fasting hyperinsulinemia is consistent with the conclusion that daily dietary supplementation with chromium (as chromium picolinate) may reduce the risks for the consequences of loss of glucose tolerance.

4.42 Clinical Studies Evaluating the Effects of Dietary Supplementation with Chromium Chloride, Yeast Containing Chromium, or Chromium Nicotinate on Glucose Homeostasis

The possibility that chromium chloride, yeast containing chromium and chromium nicotinate also may contribute to the maintenance of normal glucose tolerance has been evaluated in human clinical studies (Tables 2 and 3).[278,283,309-332] Overall, dietary supplementation with chromium chloride, yeast containing chromium or chromium nicotinate has produced either no effects or inconsistent effects on glucose homeostasis, suggesting that those chromium complexes differ functionally from chromium picolinate.

4.421 Clinical Studies Evaluating Supplementation with Trivalent Chromium Chloride

There have been 18 published clinical trials testing the effects of trivalent chromium chloride ($CrCl_3$) supplementation on measures of glucose homeostasis.[283,309-316,322-325,327-330,332] Sixteen of these studies failed to observe any effect of $CrCl_3$ supplementation on any measures of glucose homeostasis,[283,309,312-316,322,323,327-329,332] while two studies observed improvement in glucose homeostasis.[310,311]

Out of the 18 published clinical trials, the effects of dietary supplementation with $CrCl_3$ on glucose homeostasis have been examined in 7 randomized placebo-controlled clinical trials.[309,310,313,316,322,323,327] Fasting plasma glucose concentrations were unaffected by 7 to 16 months of daily supplementation with 250 mcg of chromium (as $CrCl_3$) in 76 patients with established atherosclerotic disease,[309] 2 to 4 months of daily supplementation with 600 mcg of chromium (as $CrCl_3$) in 26 patients with established diabetes,[313] 6 weeks of daily supplementation with 200 mcg of chromium (as $CrCl_3$) in 10 patients with established diabetes (the results of oral glucose tolerance tests also were unaffected),[316] 10 weeks of daily supplementation with 200 mcg of chromium (as $CrCl_3$) in 85 older women,[327] 12 weeks of daily supplementation with 200 mcg of chromium (as $CrCl_3$) in 23 men with normal glucose tolerance (the results of oral glucose tolerance tests also were unaffected),[323] and 28 days of daily supplementation with 200 mcg of chromium (as $CrCl_3$) in 16 healthy elderly subjects with normal glucose tolerance (the results of oral glucose tolerance tests also were unaffected).[322] In contrast, in a study of 41 subjects with impaired glucose tolerance (but not diabetes) and 35 subjects with normal glucose tolerance, 3 months of daily supplementation with 200 mcg of chromium (as $CrCl_3$) produced significantly decreased postprandial plasma glucose concentrations.[310]

Out of the 18 published clinical trials, the effects of dietary supplementation with $CrCl_3$ on glucose homeostasis also have been examined in 5 non-randomized placebo-controlled clinical trials.[283,315,328-330] Sherman *et al.*[315] supplemented the diets of 10 individuals with diabetes and 4 individuals with normal glucose tolerance with either placebo or 50 mcg/day of chromium (as $CrCl_3$) during two 16-week crossover periods. Dietary supplementation with $CrCl_3$ did not affect fasting plasma glucose concentrations or the results of postprandial glucose tolerance tests. Similarly, $CrCl_3$ supplementation of subjects with either impaired or normal glucose tolerance who previously had been consuming controlled low-chromium diets produced no change in indicators of glucose tolerance.[283] Potter *et al.*[328] administered $CrCl_3$ (providing 200 mcg of chromium daily) orally for 12 weeks to five elderly subjects with glucose intolerance without effect. Similarly, 10 elderly subjects with abnormal oral glucose tolerance failed to respond to 12 to 16 weeks of dietary supplementation with 150 mcg of chromium (as $CrCl_3$).[329] Carter *et al.*[330] reported that daily dietary supplementation with 250 mcg of chromium (as $CrCl_3$) for 1 to 3 days in nine children with kwashiorkor disease had no effect on plasma glucose concentrations.

Out of the 18 published clinical trials, the effects of dietary supplementation with $CrCl_3$ on glucose homeostasis also have been examined in 3 "open label" uncontrolled clinical trials.[312,324,325] Glinsmann and Mertz[312] administered a daily intake of 180 to 1000 mcg of chromium (as $CrCl_3$) for up to 140 days to 6 subjects with type 2 diabetes as an adjunct to hypoglycemic medication, without effect on the results of postsupplementation postprandial glucose tolerance tests. Gurson et al.[325] provided 50 mcg of chromium (as $CrCl_3$) daily to 15 malnourished children without effect on the results of postprandial glucose tolerance tests. Similarly, 12 malnourished Jordanian and Nigerian infants with hypoglycemia and impaired glucose tolerances failed to respond to short-term (1 to 12 days) dietary supplementation with 250 mcg of chromium with significant improvements in glucose tolerance.[324]

Out of the 18 published clinical trials, the effects of dietary supplementation with $CrCl_3$ in combination with yeast containing chromium on glucose homeostasis also have been examined in a randomized placebo-controlled clinical trial[311] and in two non-randomized placebo-controlled clinical trials.[314,332] In a study of 78 subjects with type 2 diabetes, compared to the effects of placebo, dietary supplementation with either $CrCl_3$ (providing 200 mcg of chromium) or brewers yeast (providing 23.2 mcg of chromium daily) significantly reduced both fasting and postprandial plasma glucose concentrations.[311] In contrast, daily dietary supplementation of men with type 1 diabetes, type 2 diabetes or normal glucose tolerance with either 150 mcg of chromium (as $CrCl_3$) or 18 mcg of chromium (as yeast) failed to affect fasting or postprandial plasma glucose concentrations.[314] Similarly, 30 adults with normal glucose tolerance exhibited no responses to daily dietary supplementation with either 50 mcg of chromium (as $CrCl_3$) or 15 mcg of chromium (as yeast).[332]

4.422 Clinical Studies Evaluating Supplementation with Yeast Containing Chromium

There have been 3 randomized placebo-controlled clinical trials[317,318,321] and one open-label uncontrolled study[320] that have evaluated the effects of dietary supplementation with yeast containing chromium on glucose homeostasis. Of those studies, the results of two suggested that daily dietary supplementation with yeast containing chromium may improve or maintain glucose homeostasis,[317,318] while the results of the other two studies suggested that daily dietary supplementation with yeast containing chromium had no effect on glucose homeostasis.[320, 321]

4.423 Clinical Studies Evaluating Supplementation with Chromium Nicotinate

Four randomized placebo-controlled clinical trials have examined the effect of dietary supplementation with chromium tri-nicotinate on glucose homeostasis.[278,319,326,331] Chromium, as chromium tri-nicotinate, at doses of 200,[319,331] 220,[278] or 800[326,331] mcg daily did not affect glucose homeostasis in adults with normal glucose tolerance,[278,319,331] impaired glucose tolerance[326] or type 2 diabetes.[319]

4.43 Summary of Studies Evaluating the Effects of Chromium Supplementation in Individuals with Normal Glucose Tolerance, Prediabetes or Diabetes

Daily dietary supplementation with 200 mcg to 1000 mcg of chromium (as chromium picolinate) has consistently improved hyperglycemia and measures of insulin sensitivity.[53,296-307] It is clear from the available published scientific literature that daily dietary supplementation with chromium (as chromium picolinate) significantly improves glucose homeostasis and, in so doing, reduces the risks for the development of both type 2 diabetes and for diseases for which type 2 diabetes is a causative or contributory etiologic factor.

Dietary supplementation with chromium chloride, chromium nicotinate or yeast containing chromium has produced either no effects or inconsistent trivial effects on glucose homeostasis,[309] suggesting that these chromium complexes differ functionally from chromium picolinate and may not contribute to reduction in risk for abnormalities in glucose homeostasis.

4.5 Clinical Studies on the Effects of Dietary Supplementation with Chromium Picolinate on Body Composition – Data Concerning Glucose Homeostasis

Although much of the clinical research with chromium picolinate in normoglycemic and healthy subjects has focused on the putative impact of this supplement on body composition, some of these studies also examined carbohydrate metabolism. Such studies have examined elderly men and women,[333] obese women participating in aerobic exercise or resistance training,[334] obese adults participating in a study of dietary modification,[335] college students participating in a program of aerobic exercise,[336] overweight but nondiabetic older men and women participating in a resistance training program,[337] middle-aged women participating in a combined weight training and walking program,[338] sedentary young adults[283] and collegiate wrestlers in training.[271]

None of those studies have reported statistically significant changes in plasma glucose concentrations after chromium picolinate supplementation in individuals who already had normal plasma glucose concentrations and apparently normal glucose tolerance. Only individuals who had elevated prestudy plasma insulin or glucose concentrations were reported to respond to dietary supplementation with chromium picolinate with changes in glucose homeostasis. In addition, the effects of dietary supplementation with chromium picolinate on plasma HbA_{1c} percentages were not measured in those studies. However, in one study, the combination of aerobic exercise and daily dietary supplementation with 1000 mcg of chromium (as chromium picolinate) produced significantly greater decreases in mean post-exercise plasma insulin concentration than did the combination of placebo and exercise, suggesting that the insulin-sensitizing effects of exercise and chromium picolinate may be additive.[336]

There have been no reports of degradation of glucose tolerance attributable to chromium picolinate supplementation in normoglycemic individuals or of chromium picolinate-induced hypoglycemic episodes.[271,283,333-338]

4.6 Published Reviews of the Benefits of Dietary Supplementation with Chromium Picolinate

Reviewers evaluating the benefits of dietary supplementation with chromium picolinate have agreed that dietary supplementation with chromium picolinate may improve glucose homeostasis in individuals with abnormalities in glucose homeostasis while not interfering with glucose homeostasis in individuals with normal glucose tolerance. A systematic review concluded that dietary supplementation with chromium may be effective in reducing plasma glucose concentrations in hyperglycemic ("prediabetic") individuals but does not appear to reduce plasma glucose concentrations in euglycemic individuals.[339] Those reviewers also concluded that up to 6 months of daily dietary consumption of up to 1000 mcg of supplemental chromium was safe. Another set of reviewers concluded that the "benefits of chromium supplementation in type 2 diabetes generally become apparent within 6-12 weeks" and that the "best" form of supplemental chromium was as chromium picolinate.[340] Another reviewer concluded that at least 200 mcg of supplemental chromium daily was required in order to elicit a beneficial effect on glucose homeostasis.[269] A meta-analysis concluded that daily dietary supplementation with chromium

was safe and did not reduce fasting plasma glucose concentrations in individuals with normal fasting plasma glucose concentrations, normal glucose tolerance and no evidence of insulin resistance.[341]

5.0 Daily Intake of Supplemental Chromium Picolinate that is Effective in Reducing the Risk of Diabetes

The reliable and credible scientific literature indicates that daily dietary supplementation with 200 mcg to 1000 mcg of chromium (as chromium picolinate) is effective in reducing the risk of developing insulin resistance, prediabetes, type 2 diabetes, certain diseases caused by diabetes and certain diseases caused by insulin resistance and in preventing or delaying the progression of prediabetes to diabetes.[53,283,295-308,333-336,336-341]

6.0 Safety of Supplemental Chromium Picolinate

The safety of chromium picolinate has been extensively reviewed by an independent panel of experts, concluding that chromium picolinate is safe at current or anticipated future levels of intake. The safety review was used to determine that chromium picolinate is Generally Recognized as Safe (GRAS) for addition to specified categories of foods. A copy of the GRAS monograph and a more recent update of this document are included in Appendix A.

6.1 History of Safe Use in Humans

In a survey of dietary supplement users, 80% stated that they were aware of chromium picolinate, whereas only 8% knew of other forms of chromium (*unpublished data on file*). In a 2001 survey of diabetes educators attending a conference hosted by the American Association of Diabetes Educators, 30% stated that they recommend chromium supplementation to their patients. Of the educators who recommended chromium supplementation, 96% specifically recommended chromium picolinate (*unpublished data on file*). In a published survey of pharmacists, chromium picolinate was one of the top five most-recommended supplements.[243]

Chromium picolinate has been available commercially for over ten years. *The Nutrition Business Journal* estimated that 10 million people consume dietary supplements containing chromium picolinate annually (*unpublished data on file*). In light of this extensive consumption, chromium picolinate has an excellent safety profile with only seven published individual case reports and one published case series of possible adverse reactions.[3,7,342-344,344-346,346,347,347,348,348,349]

The seven individual case reports include two case reports of chromium-induced nephrotoxicity,[343,348] one report of rhabdomyolysis,[347] one report of acute generalized exanthematous pustulosis,[349] one report of systemic contact dermatitis,[344] one report of cognitive, perceptual and motor changes[346] and one report of sporadic hypoglycemia.[342] In the latter case, daily dietary supplementation with 1000 mcg of chromium (as chromium picolinate) was effective in minimizing the hyperglycemia of a young man with diabetes in the absence of medications or exogenous insulin; however, 1000 mcg of chromium (as chromium picolinate) appeared to be an excessive level of supplementation. In another case report, a young woman with type 1 diabetes successfully reduced her plasma HbA_{1c} percentage from 11.3% to 7.9% with a 3-month course of chromium picolinate supplementation (providing 600 mcg of chromium daily) without hypoglycemic episodes.[350] In a series of cases reported to the Georgia Poison Center, nine individuals experienced adverse reactions (chest pain, flushing, dehydration, agitation, dizziness or

headache) that could be attributed to the ingestion of 100 to 6000 mcg of chromium (as chromium picolinate).[345] All of these cases resolved spontaneously.

In over 40 human clinical trials in which healthy adults, bodybuilders, overweight individuals, obese individuals, elderly individuals, individuals with hypercholesterolemia, individuals with diabetes and women with gestational diabetes have participated, amounts of chromium picolinate supplying between 200 mcg and 1000 mcg of chromium have been consumed daily for as long as 8 months without adverse reactions.[53,265,272-274,283,295-308,333-341,351-363]

Clinical studies evaluating complete blood counts, liver function, renal function, and electrolyte levels have not detected any abnormal changes after chromium picolinate supplementation in people consuming up to 1000 mcg chromium (as chromium picolinate) for up to 8 months.[53,364] In another clinical trial, 10 obese participants consumed 400 mcg of chromium (as chromium picolinate) daily for 8 weeks without evidence of oxidative DNA damage, suggesting that the intakes typically used for dietary supplementation with chromium picolinate are safe.[365]

6.2 Animal Studies of Safety

Studies of chromium picolinate in animals demonstrate a very low toxicity for the compound. Chromium picolinate has been tested in over 30 studies involving over 50,000 animals. These studies are described and discussed in detail in the GRAS monograph and update included in Appendix A and have demonstrated that chromium picolinate is safe in a wide range of daily intakes. No toxicity has been observed in males, females, pregnant females or their offspring. The safety of chromium picolinate has been tested in cats, chickens, cows, dogs, horses, lambs, pigs, mice and rats.

For example, chromium picolinate administration to rats in daily amounts providing up to 15 mg of chromium per kg of body weight for 24 weeks (equivalent to about 5,000 times the human dose of 200 mcg of chromium a day for approximately 20 years) produced no apparent adverse effects.[267] There were no negative effects on body weight, organ weights, plasma or serum concentrations of glucose, cholesterol, triglycerides, or protein, blood urea nitrogen concentration, plasma lactate dehydrogenase activity or serum enzyme activities. Furthermore, no abnormal changes were observed in the liver or kidneys.

The potential effects of chromium picolinate on reproductive physiology and fertility were examined in swine (metabolically similar to humans). In several studies, daily dietary supplementation of the diets of sows with 200 ppb to 1000 ppb of chromium (as chromium picolinate) produced no negative effects and resulted in significantly greater litter size, higher birth weights, and better piglet and sow health compared to the growth rates and fertility of unsupplemented animals.[366-369]

Several studies in rats have examined the potential mutagenicity and carcinogenicity of chromium picolinate. Rats intubated with a single bolus of chromium picolinate providing 4,000 to 250,000 mcg of chromium per kg of bodyweight exhibited no increases in chromosome damage.[370] Similarly, a study that examined the effects of chromium picolinate supplementation on the bone marrow cells of rats found no indication of chromium-picolinate-induced chromosomal damage.[371] The only animal study to suggest that chromium picolinate could produce oxidative DNA damage administered daily intravenous injections of chromium picolinate for 2 months in amounts about 20-fold greater than the typical amounts consumed by humans supplementing their diets.[372] Because such intravenous injection of

chromium picolinate results in circulating chromium concentrations several orders of magnitude greater than those resulting from oral ingestion of chromium picolinate, that study is of little relevance to the evaluation of the safety of dietary supplementation with chromium picolinate.

6.3 *In Vitro* Studies of Safety

Under certain non-physiologic conditions in *in vitro* studies, chromium picolinate has been reported to cause toxicity. These studies have used extremely high concentrations of chromium picolinate or did not use preparations that were manufactured under Good Manufacturing Practices (GMPs) and contained toxic impurities.

One study observed that the consumption of chromium picolinate in amounts providing chromium in amounts approximately equivalent to the dietary intake of unsupplemented humans produced significantly increased rates of lethal mutations and female sterility in *Drosophilae melanogaster* (fruit flies).[373] In another study, adding chromium picolinate to the culture medium triggered chromosomal changes in Chinese hamster ovary cells.[374] However, the lowest concentration of chromium picolinate found to cause damage in the cell cultures was 3,000 times the concentration measured in the blood of humans after consuming 200 mcg of chromium (as chromium picolinate) daily for 2 months.[305] In contrast, exposure of human macrophages in cell culture to supraphysiologic concentrations of chromium picolinate produced only modest increases (considered by the investigators to be inconsequential) in indices of oxidative stress and DNA fragmentation.[375]

6.4 Chromium Picolinate GRAS Determination

In April 2000, a panel of experts qualified by scientific training and experience to evaluate the safety of substances added to food released their review of the totality of the available data concerning the safety of chromium picolinate (a copy of this report is attached). These data included the results of laboratory, animal, and human studies as well as case reports of possible adverse reactions that might be attributable to chromium picolinate. The panel concluded that the weight of the evidence clearly demonstrates the safety of chromium picolinate and that Chromax® chromium picolinate (Nutrition 21's branded form of chromium picolinate) is Generally Recognized as Safe (GRAS) for addition to a number of food categories for human consumption. That review was updated in April 2003 to include the more recent safety and toxicity studies (a copy of the update is attached).

7.0 Conclusions

- Chromium is an essential mineral required for normal carbohydrate metabolism.
- Chromium facilitates the interaction of insulin with its receptor and plays an essential role in supporting efficient insulin function and blood glucose control.
- Insulin resistance and impaired ability to maintain glucose homeostasis (prediabetes) precede diabetes and are required in order for deviations from normoglycemia and disruptions in insulin physiology to progress to diabetes.
- Nutritional strategies that improve impaired glucose tolerance and restore insulin sensitivity can prevent or delay the progression of prediabetes to diabetes.
- Prevention or delay of the progression of prediabetes reduces the risk of diabetes.
- Diabetes is a causative or contributory etiologic factor for a number of diseases.
- Reduction of the risk of diabetes reduces the risk of diseases for which diabetes is a causative or contributory etiologic factor.
- Prediabetes is a causative or contributory etiologic factor for a number of diseases.
- Prevention or delay of the progression of prediabetes reduces the risk of diseases for which prediabetes is a causative or contributory etiologic factor.
- Dietary supplementation with chromium picolinate in amounts providing 200 mcg to 1000 mcg of chromium daily can improve impaired glucose tolerance and restore insulin sensitivity.
- Dietary supplementation with chromium picolinate in amounts providing 200 mcg to 1000 mcg of chromium daily is effective in improving glucose tolerance and improving insulin sensitivity in people with prediabetes or diabetes.
- By improving glucose tolerance and improving insulin sensitivity, dietary supplementation with chromium picolinate is effective in preventing or delaying the progression of prediabetes to diabetes.
- By preventing or delaying the progression of prediabetes to diabetes, dietary supplementation with chromium picolinate is effective in reducing the risk of diabetes.
- By reducing the risk of diabetes, dietary supplementation with chromium picolinate is effective in reducing the risk of diseases for which diabetes is a causative or contributory etiologic factor.
- By preventing or delaying the progression of prediabetes, dietary supplementation with chromium picolinate is effective in reducing the risk of diseases for which prediabetes is a causative or contributory etiologic factor.

- Chromium picolinate is more stable, better absorbed, and more bioavailable than other supplemental chromium complexes.
- Chromium picolinate (in the form of Chromax® chromium picolinate) was determined to be GRAS (Generally Recognized as Safe) by an independent panel of experts.
- Daily dietary supplementation with chromium picolinate in amounts providing 200 mcg to 1000 mcg of chromium is safe.

8.0 Summary Conclusions

In conclusion, there is significant scientific agreement in support of the following health claims:

- Chromium picolinate may reduce the risk of insulin resistance.
- Chromium picolinate may reduce the risk of cardiovascular disease when caused by insulin resistance.
- Chromium picolinate may reduce the risk of abnormally elevated blood sugar levels.
- Chromium picolinate may reduce the risk of cardiovascular disease when caused by abnormally elevated blood sugar levels.
- Chromium picolinate may reduce the risk of type 2 diabetes.
- Chromium picolinate may reduce the risk of cardiovascular disease when caused by type 2 diabetes.
- Chromium picolinate may reduce the risk of retinopathy when caused by abnormally high blood sugar levels.
- Chromium picolinate may reduce the risk of kidney disease when caused by abnormally high blood sugar levels.

/s/[1] _____ 12/18/03

Name: Vijaya Juturu, Ph.D. Date

/s/_____ 12/18/03

Name: James Komorowski, M.S. Date

/s/_____ 12/18/03

Name: Danielle Greenberg, Ph.D., F.A.C.N. Date

1. The original signature pages are on file with Emord & Associates, P.C., counsel to Petitioner. The scientists requested that the pages not be submitted to FDA to avoid having them posted on the internet.

/s/_____ 12/18/03

Name: Michael J. Glade, Ph.D., F.A.C.N., C.N.S., L.D.N. Date

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