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December 19, 2003

PETITIONER: Nutrition 21, Inc.

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Burke, VA 22015

SUBJECT: Petition for Health Claims:

1. Chromium picolinate may reduce the risk of insulin resistance.
2. Chromium picolinate may reduce the risk of cardiovascular disease when caused by insulin resistance.
3. Chromium picolinate may reduce abnormally elevated blood sugar levels.
4. Chromium picolinate may reduce the risk of cardiovascular disease when caused by abnormally elevated blood sugar levels.
5. Chromium picolinate may reduce the risk of type 2 diabetes.
6. Chromium picolinate may reduce the risk of cardiovascular disease when caused by type 2 diabetes.
7. Chromium picolinate may reduce the risk of retinopathy when caused by abnormally high blood sugar levels.
8. Chromium picolinate may reduce the risk of kidney disease when caused by abnormally high blood sugar levels.

Food and Drug Administration
Office of Nutritional Products, Labeling, and Dietary Supplements
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I. Introduction and Statement of Purpose

The undersigned, Nutrition 21, Inc. (hereinafter "Petitioner"), submits this petition pursuant to sections 403(r)(5)(D) of the Federal Food, Drug, and Cosmetic Act ("FDCA") (21 U.S.C. § 343(r)(5)(D)) for health claims associating chromium picolinate with reduction in the risk of (1) insulin resistance; (2) cardiovascular disease when caused by insulin resistance; (3) abnormally elevated blood sugar levels; (4) cardiovascular disease when caused by abnormally elevated blood sugar levels; (5) type 2 diabetes; (6) cardiovascular disease when caused by type 2 diabetes; (7) retinopathy when caused by abnormally high blood sugar levels; and (8) kidney

disease when caused by abnormally high blood sugar levels. The proposed claims are contained in section D below. Attached hereto and constituting a part of this petition are exhibits satisfying the requirements as specified in 21 C.F.R. § 101.70(f).

This petition presents a logical and valid evaluation of the scientific studies and clinical trials concerning the relationship between chromium picolinate and insulin resistance; cardiovascular disease when caused by insulin resistance; abnormally elevated blood sugar levels; cardiovascular disease when caused by abnormally elevated blood sugar levels; type 2 diabetes; cardiovascular disease when caused by type 2 diabetes; retinopathy when caused by abnormally high blood sugar levels; and kidney disease when caused by abnormally high blood sugar levels. There is substantial scientific evidence that poor chromium status is a factor contributing to the incidence of impaired glucose tolerance and type 2 diabetes. The attached scientific studies demonstrate that the consumption of chromium picolinate may reduce the risk of the above-mentioned diseases and justify permitting health claims that link consumption of chromium picolinate with reduction in the risks of those diseases. See Scientific Report attached as Exhibit 1.

As explained in detail below and in the attached documents, chromium is an essential nutrient for which the FDA has established a Recommended Daily Intake. Chromium is present in foods consumed daily in the United States. As described in exacting detail in Exhibit 1, chromium picolinate is the absorbable, non-toxic form of chromium shown to have risk reduction effects on the development of type 2 diabetes and associated diseases triggered by insulin resistance and type 2 diabetes. Moreover, chromium picolinate has a history of safe use as a dietary supplement in the United States for more than ten years. Id. at 28-31. Thus, chromium picolinate is a safe and lawful substance and contributes nutritive value. 21 C.F.R. §

101.14(b)(i) and (ii). Similarly, chromium picolinate is a substance within the meaning of 21 C.F.R. § 101.14(a)(2).

As discussed below (and in detail in Exhibit 1), chromium picolinate possesses properties that have a multitude of beneficial effects in the body including having glucose-regulatory activity. Exhibit 1 at 13. Type 2 diabetes is a metabolic disorder characterized by abnormally elevated blood glucose levels and either insufficient levels of insulin or insulin resistance. *Id.* at 4. Abnormally elevated blood glucose levels are also a primary causative factor contributing to retinopathy, kidney disease, and cardiovascular disease. *Id.* at 7-9. Thus, chromium picolinate is associated with the diseases that are the subject of this petition. 21 C.F.R. § 101.14(b)(i). The scientific report (Exhibit 1), the PDR for Nutritional Supplements chapter on chromium picolinate (Exhibit 2), the Institute of Medicine's chapter on chromium picolinate (Attachment 256 to Exhibit 1), and all of the attached scientific articles establish that, based on the totality of publicly available scientific evidence (including evidence from well-designed studies conducted in a manner consistent with generally recognized scientific procedures and principles), there is significant scientific agreement among experts qualified by scientific training and experience to evaluate such claims that chromium picolinate reduces the risk of insulin resistance; cardiovascular disease when caused by insulin resistance; abnormally elevated blood sugar levels; cardiovascular disease when caused by abnormally elevated blood sugar levels; type 2 diabetes; cardiovascular disease when caused by type 2 diabetes; retinopathy when caused by abnormally high blood sugar levels; and kidney disease when caused by abnormally high blood sugar levels.

The scientific studies described in this petition directly address the important public health issues associated with the above-listed diseases and further national and DHHS policies

by identifying low cost means of reducing the risk of those diseases and disease conditions.

Diabetes and diseases caused by insulin resistance and type 2 diabetes are major public health concerns in the United States, affecting about 16 million people in this country. Id. at 4.

Incidence of type 2 diabetes is on the rise in the general population and it is projected to reach 23 million people within the next 10 years. Id. at 4.

The Petitioner believes that the truthful health information conveyed by its proposed succinct health claims will enable consumers to make prudent and effective dietary choices. Food sources of chromium lack consistency in chromium levels and are not reliable nutrient sources. Chromium levels in foods are affected by processing, handling, manufacturing, packaging, cooking, lot variance, and geochemical source characteristics. In addition chromium is generally poorly absorbed and some forms have toxic effects. Chromium picolinate is nontoxic and has been shown to have beneficial effects, reducing insulin resistance and aiding carbohydrate metabolism. Labeling chromium picolinate dietary supplements with the proposed claims will inform consumers at the point of sale of current scientific evidence concerning means to reduce the risk of insulin resistance; cardiovascular disease when caused by insulin resistance; abnormally elevated blood sugar levels; cardiovascular disease when caused by abnormally elevated blood sugar levels; type 2 diabetes; cardiovascular disease when caused by type 2 diabetes; retinopathy when caused by abnormally high blood sugar levels; and kidney disease when caused by abnormally high blood sugar levels.

In accordance with FDA's July 10, 2003 "Interim Procedures for Qualified Health Claims in the Labeling of Conventional Human Food and Human Dietary Supplements" and consistent with the decisions in Pearson v. Shalala, 164 F.3d. 650 (D.C.Cir. 1999), reh'g denied en banc, 172 F.2d 72 (D.C.Cir. 1999); Pearson v. Shalala, 130 F.Supp.2d 105 (2001), recon.

denied, Pearson v. Thompson, 141 F. Supp. 2d 105 (D.D.C. 2001); and Whitaker v. Thompson, 248 F. Supp. 2d 1 (D.D.C. 2002), the Petitioner respectfully requests that if the agency finds any of the proposed claims not to satisfy its “significant scientific agreement” standard, that the agency authorize under the qualified claims procedures that claim with such succinct and accurate disclaimer as is, or such disclaimers as are, reasonably necessary to avoid a potentially misleading connotation.

A. Preliminary Requirements

1. Chromium picolinate meets the requirements of §101.14(b)

Chromium picolinate meets the relevant eligibility requirements of 21 C.F.R. §

101.14(b). Section 101.14(b) requires:

(b) Eligibility. For a substance to be eligible for a health claim:

- (1) the substance must be associated with a disease or health-related condition for which the general U.S. population, or an identified U.S. population subgroup (e.g., the elderly), is at risk, or, alternatively, the petition submitted by the proponent of the claim otherwise explains the prevalence of the disease or health-related condition in the U.S. population and the relevance of the claim in the context of the total daily diet and satisfies the other requirements of this section.
- (2) If the substance is to be consumed as a component of a conventional food at decreased dietary levels, the substance must be a nutrient listed in 21 U.S.C. 343(q)(1)(C) or (q)(1)(D), or one that the Food and Drug Administration (FDA) has required to be included in the label or labeling under 21 U.S.C. 343(q)(2)(A); or
- (3) If the substance is to be consumed at other than decreased dietary levels:
 - (i) The substance must, regardless of whether the food is a conventional food or a dietary supplement, contribute taste, aroma, or nutritive value, or any other technical effect listed in § 170.3(o) of this chapter, to the food and must retain that attribute when consumed at levels that are necessary to justify a claim; and
 - (ii) The substance must be a food or a food ingredient or a component of a food ingredient whose use at the levels necessary to justify a claim has been demonstrated by the proponent of the claim, to FDA's satisfaction, to be safe and lawful under the applicable food safety provisions of the Federal Food, Drug and Cosmetic Act.

a. Chromium picolinate is associated with a disease affecting the general U.S. population

A "disease or health-related condition" means "damage to an organ, part, structure, or system of the body such that it does not function properly (e.g., cardiovascular disease), or a state of health leading to such dysfunctioning (e.g., hypertension); except that diseases resulting from essential nutrient deficiencies (e.g., scurvy, pellagra) are not included in this definition (claims pertaining to such diseases are thereby not subject to §.101.13 or § 101.70)." 21 C.F.R. § 101.14(a)(5).

Type 2 diabetes is a metabolic disease for which the general U.S. population is at risk. Exhibit 1 at 4. Diabetes (both types 1 and 2) currently affect about 16 million people in the U.S. and is projected to affect 23 million within 10 years. Id. Type 2 diabetes is about ten times more prevalent than type 1 diabetes in the U.S. Id. Type 2 diabetes results from the loss of the responsiveness of target tissues to insulin. Id. Insulin is necessary for the transport of glucose from the bloodstream into surrounding tissues. Glucose is required by all tissues in the body in order for the tissues to function. In type 2 diabetes the impaired removal of glucose from the blood produces hyperglycemia (elevated levels of glucose) even in the presence of elevated concentrations of insulin (“hyperinsulinemia”). Id. The impairment of glucose uptake in the presence of insulin (“insulin resistance”) is the definitive functional characteristic of type 2 diabetes. Id.

Health complications from diabetes are significant and include kidney disease, heart disease, stroke, blindness, and limb amputation. Id. at 7-9. Diabetic retinopathy is the leading cause of blindness in adults aged 20 through 74 years. Id. Diabetic kidney disease is the cause of 40% of all new cases of end-stage renal disease and is the leading cause for limb amputation in the U.S. Id. Heart disease and stroke occur two to four times more frequently in adults with diabetes than in non-diabetic populations. Id.

Insulin resistance and abnormally elevated blood sugar levels are precursors to type 2 diabetes and to retinopathy, kidney disease, and cardiovascular disease induced by abnormally high blood sugar levels (or insulin resistance or type 2 diabetes in the case of cardiovascular disease). Exhibit 1 at 5-10, 32-33. Chromium potentiates the action of insulin. Id. at 13. When the body suffers from chromium insufficiency, glucose utilization is impaired and insulin requirements are raised. Exhibit 1 at 13; Exhibit 2 at 96; Attachment 256 at 201. As discussed

further below, in Exhibit 1, and in the attached scientific articles, supplementation with chromium picolinate has been shown to have beneficial effects on reducing the risk of diabetes type 2 and diseases caused by insulin resistance.

Thus, each disease condition referenced in the eight claims are diseases within the meaning of 21 C.F.R. § 101.14(a)(5) that affect the general US population.

b. Chromium picolinate contributes nutritive value at the levels present in supplements

In accordance with section 101.14(b)(3)(i), chromium picolinate contributes nutritive value. FDA has established a Recommended Daily Intake (RDI) for chromium at 120 mcg. 21 CFR § 101.9(b)(8)(iv). The Institute of Medicine established the Adequate Intake (AI) for chromium to be 35 micrograms (mcg) per day for men 19-50 years of age and 25 mcg for women 19-50 years of age; 30 mcg/day for men 51 and older and 20 mcg/day for women 51 and older. Attachment 256 at 208-209; Exhibit 1 at 10.

Chromium is an essential trace mineral. Exhibit 1 at 10; Exhibit 2 at 96. It appears to play an essential role in normal carbohydrate metabolism. Exhibit 1 at 13; Exhibit 2 at 96. It appears to be necessary for the maintenance of normal glucose tolerance. Id. The IOM states that chromium potentiates the action of insulin *in vivo* and *in vitro*. Attachment 256 at 197. The IOM also states that chromium deficiency, seen in total parenteral nutrition patients, impairs glucose utilization and raises insulin requirements. Id. at 201. The scientific evidence shows that chromium facilitates the interaction of insulin with its receptor and plays an essential role in supporting efficient insulin function and blood glucose control. Thus, chromium contributes nutritive value.

Chromium exists in several valence states. Most chromium in the food supply is in the trivalent state. Chromium picolinate is an organic, trivalent form. Exhibit 1 at 14. The efficiency of absorption of chromium from inorganic compounds is very low. Exhibit 1 at 12; Exhibit 2 at 97. Evidence from both animal and human studies show that chromium picolinate is more absorbable than inorganic forms and other organic forms of chromium. Exhibit 1 at 12. Moreover, clinical trials with chromium picolinate have consistently shown beneficial effects on the pathogenesis of type 2 diabetes, but clinical trials on other forms of chromium have not shown those beneficial effects or have yielded only marginal and inconsistent results. *Id.* at 15-28. Thus, chromium picolinate is a form that contributes nutritive value.

Chromium picolinate has been sold as a dietary supplement in the United States for more than ten years. Exhibit 1 at 28. The Petitioner sells chromium picolinate in capsules at 400 mcg per capsule (333% of the chromium DRI of 120 mcg). As discussed in further detail in Exhibit 1, chromium picolinate is the most widely used chromium supplement and is the most widely recommend form when recommended by health professionals. *Id.* at 28. Chromium picolinate thus contributes nutritive value at levels present in supplements.

c. **Chromium picolinate is safe and lawful under the FDCA**

“For each such ingredient listed, the petitioner should state how the ingredient complies with the requirements of § 101.14(b)(3)(ii), e.g., that its use is generally recognized as safe (GRAS), listed as a food additive, or authorized by a prior sanction issued by the agency, and what the basis is for the GRAS claim, the food additive status, or prior sanctioned status.” 21 C.F.R. § 101.70(f)(A).

Chromium picolinate is safe and lawful as evidenced by its continued sale as a dietary supplement in the U.S. for more than ten years without report of serious or recurring adverse

effects and the lack of serious adverse effects reported in the chromium picolinate studies on normal and diabetic subjects. Exhibit 1 at 28-31; see, Exhibit 2 at 99 and Attachment 256 at 213-216.

Chromium is found in many sources in the U.S. food supply, typically in very small amounts (1 to 2 micrograms per serving). Exhibit 1 at 10; Exhibit 2 at 96; Attachment 256 at 211. Whole grains, cereals, black pepper, thyme, mushrooms, brown sugar, coffee, tea, beer, wine, meat products, and brewer's yeast are good food sources of chromium. Exhibit 2 at 96. Chromium in the food supply is typically in the trivalent state as is chromium picolinate. Id.

In April 2000 a panel of independent experts, qualified by scientific training and experience to evaluate the safety of substances added to food, found Petitioner's chromium picolinate, Chromax®, GRAS. A copy of that report is attached as Attachment A to Exhibit 1.¹ See also Exhibit 1 at 28. The GRAS determination was amended in April 2003 to include the safety and toxicity information that became available after that April 2000 determination. Exhibit 1 at 28.

Thus, chromium picolinate is safe and lawful under the FDCA as a dietary supplement and as a substance to be added to foods. In summary, since chromium picolinate meets the requirements of 21 C.F.R. § 101.14(b), the preliminary requirements of 21 C.F.R. § 101.70 are fully satisfied.

¹ Petitioner's confidential and proprietary information has been redacted from Attachment A to Exhibit 1.

B. Summary of Scientific Data

1. Significant scientific agreement exists to support the proposed claims

There is significant scientific agreement among experts who study the effect of chromium picolinate on insulin resistance; abnormally elevated blood sugar levels; cardiovascular disease when caused by abnormally elevated blood sugar levels; type 2 diabetes; cardiovascular disease when caused by type 2 diabetes; retinopathy when caused by abnormally high blood sugar levels; and kidney disease when caused by abnormally high blood sugar levels that chromium picolinate is an effective modifier (reducer) of the risk of those diseases. See, Exhibit 1 at 32-35. The scientific literature makes it clear that chromium picolinate has glucose regulatory activity in healthy and diseased populations. See e.g., Exhibit 1 throughout; Exhibit 2 at 96; Attachment 256 at 198-201. The scientific literature shows that poor chromium status is a factor contributing to the incidence of: abnormally elevated blood sugar levels; type II diabetes; and retinopathy, kidney disease, and cardiovascular disease when caused by abnormally elevated or high blood sugar levels. See id.

The mechanism of action of chromium in glucose regulation is discussed in Exhibit 1 at 13. As discussed in that exhibit chromium appears to increase insulin sensitivity by accelerating the clearance of glucose from plasma in the presence of a fixed amount of insulin. Id. It also inhibits an enzyme that dephosphorylates (deactivates) the phosphorylated insulin receptor. Id. As discussed in the attached exhibits, those beneficial effects of chromium's mechanism of action are also seen in animal studies. Id. at 15. Dietary supplementation with chromium picolinate in animals with impaired glucose tolerance and in animals with diabetes increased insulin sensitivity and glucose uptake. Id. Relevant human clinical trials and other evidence are discussed in detail in Exhibit 1 and are summarized in the following section.

2. Scientific evidence demonstrates the public health benefits of chromium picolinate

As discussed in Exhibit 1 insulin resistance occurs in the prediabetic state, years before diagnosable diabetes. Exhibit 1 at 5-7. Insulin resistance precedes the diagnosis of type 2 diabetes. Id. Diabetes prevention requires increasing insulin sensitivity, i.e., increasing the body's reaction to insulin already present (without increasing insulin secretion) in order to lower elevated blood glucose levels. Id. As discussed in detail in Exhibit 1, insulin resistance and poor glucose metabolism precede diabetes. Treatments that improve impaired glucose tolerance and insulin sensitivity can prevent or delay the onset of diabetes. Exhibit 1 at 9-10.

Human studies on chromium picolinate supplementation on pre-diabetic, diabetic, and normoglycemic populations are discussed in detail in Exhibit 1 at 15-24. The human studies are numerous and varied. They are fully vetted in the attached scientific report. See id. Overall, the studies show that daily chromium picolinate supplementation at amounts of 200 mcg of chromium or greater has a glucose regulatory effect that reduces the risk of insulin resistance; abnormally elevated blood sugar levels; cardiovascular disease when caused by abnormally elevated blood sugar levels; type 2 diabetes; cardiovascular disease when caused by type 2 diabetes; retinopathy when caused by abnormally high blood sugar levels; and kidney disease when caused by abnormally high blood sugar levels. See id.

Among the studies is one on obese middle-aged human subjects with a family history of diabetes, who were not diabetic, showing a significant increase in insulin sensitivity compared to placebo. Id. at 15-16. Also included are studies on normoglycemic individuals showing reduction in blood glucose levels in individuals with elevated baseline insulin and/or glucose levels with no reports of hypoglycemia. Id. at 26-27. Numerous other clinical studies fully vetted in Exhibit 1 at 15-24 (including case controlled, randomized trials) on diabetic populations

show that daily supplementation with chromium picolinate has positive results on glucose metabolism and insulin sensitivity based on metabolic changes that also occur in healthy individuals. See id. Thus, the attached reports, scientific articles, and exhibits demonstrate significant scientific agreement that chromium picolinate reduces the risk of insulin resistance; abnormally elevated blood sugar levels; cardiovascular disease when caused by abnormally elevated blood sugar levels; type 2 diabetes; cardiovascular disease when caused by type 2 diabetes; retinopathy when caused by abnormally high blood sugar levels; and kidney disease when caused by abnormally high blood sugar levels. Id. at 28, 32-35.

3. Scientific Summary Issues

1. **Is there an optimum level of the particular substance to be consumed beyond which no benefit would be expected?**

Clinical trials have tested daily doses up to 1000 mcg (or 1 mg) of chromium as chromium picolinate in adults for up to eight months. Exhibit 1 at 29. While no optimum level beyond which no benefit would be expected has been established, those clinical trials have revealed a lack of significant adverse effects caused by chromium picolinate supplementation at that dose and duration. Id. Moreover benefit was observed at that upper level. See id.

2. **Is there any level at which an adverse effect from the substance or from foods containing the substance occurs for any segment of the population?**

According to the Institute of Medicine (IOM), the studies on the side effects of trivalent chromium do not provide dose-response information or clear indications of a lowest-observed-adverse-effect level (LOAEL). Attachment 257 at 215. The IOM states that no adverse effects have been convincingly associated with excess intake of chromium from food or supplements, although IOM cautions that the fact of no adverse effects does not mean that there is no potential for adverse effects resulting from high intakes. Id. at 216. The IOM states that trivalent

chromium (which includes chromium picolinate) has a low level of toxicity and several studies have demonstrated the safety of large doses of it. Id. at 213.

The PDR for Nutritional Medicines states that there is a report of a 24-year-old developing rhabdomyolysis² after ingesting 1200 mcg of chromium picolinate. Exhibit 2 at 99. However, the IOM states that reports of chromium-induced rhabdomyolysis failed to account for other potential etiologic factors including strenuous exercise, weight lifting, trauma, seizure, sepsis, and alcohol and drug abuse. Attachment 257 at 215.

The IOM states that while chronic interstitial nephritis in humans has been attributed to chromium picolinate ingesting in two case reports, there is no evidence of kidney damage in experimental animals for up to two years of oral chromium consumption, including chromium picolinate. Id. at 213. IOM also reports that trivalent chromium has tested negative for genotoxicity and that studies with positive results were flawed. Id. at 214. Trivalent chromium has shown no significant evidence of carcinogenicity in human or animals. Id. Finally, IOM reports that there are no studies in humans to suggest that trivalent chromium is a reproductive or developmental toxicant. Id.

Exhibit 1 addresses in further detail the seven individual case reports of possible adverse reaction. Id. at 28-29. In light of the estimated 10 million people that consume dietary supplements containing chromium picolinate annually, chromium picolinate has an excellent safety profile. Id.

3. Are there certain populations that must receive special consideration?

Animal and human studies have shown that chromium picolinate supplementation does not have a negative impact on glucose metabolism in healthy populations. Exhibit 1 at 15, 26-

² Rhabdomyolysis is characterized by skeletal muscle injury and release of muscle cell contents into the plasma. Attachment 257 at 215.

27; 28-31. There were no reports of hypoglycemia in studies on normoglycemic individuals. Id. at 27.

The PDR cautions that pregnant women and nursing mothers should avoid doses of chromium above those recommended by the ESADDI.³ Exhibit 2 at 99. It also states that persons with a history of hypoglycemia should exercise caution in the use of chromium supplements. Id. However, in clinical trials with over 1000 subjects with impaired glucose tolerance or type 2 diabetes given doses up to 1000 mcg (1mg) chromium as chromium picolinate, no incidence of hypoglycemia was observed. Exhibit 1 at 16-24.

The PDR reports that in one study persons on beta-blockers who took 600 mcg daily of chromium in high-chromium yeast had modestly elevated HDL-cholesterol levels after two months of chromium use. Id.

The IOM states that individuals with preexisting renal and liver disease may be susceptible to adverse effects from excess chromium intake. Attachment 257 at 215.

4. What other nutritional or health factors (both positive and negative) are important to consider when consuming the substance?

There is some indication that concomitant intake of ascorbate and chromium may increase the absorption of chromium. Exhibit 2 at 99. Conversely, concomitant intake of chromium with foods rich in phytic acid (such as unleavened bread, raw beans, seeds, nuts, grains, and soy isolates) may decrease the absorption of chromium. Id.

A number of studies have reported increased absorption of chromium with aerobic exercise (evidenced by increased urinary excretion of chromium).

Attachment 257 at 199. IOM states that further studies are needed to clarify how much of the

³ The Estimated Safe and Adequate Daily Dietary Intake (ESADDI) for chromium is 50 to 200 micrograms daily. Exhibit 2 at 99. The ESADDI is a recommendation of the National Research Council, National Academy of Sciences' Food and Nutrition Board.

observed beneficial effects of exercise on glucose and insulin metabolism may be due to improved chromium absorption. Id.

IOM also reports that consumption of diets high in simple sugars (35 percent of total kcal) increased urinary chromium excretion in adults. Id. at 204. Urinary chromium excretion was found to be related to the insulinogenic properties of carbohydrates. Id.

Finally, IOM states that animal studies indicate that the habitual consumption of certain medications that alter stomach acidity or gastrointestinal prostaglandins may affect chromium absorption and retention. Id. at 204. Animals dosed with chromium (chromium chloride) and prostaglandin inhibitors such as aspirin showed markedly increased levels of chromium in blood, tissues, and urine. Id. Conversely medications such as antacids or dimethylprostaglandin E₂ reduced chromium absorption and retention in rats. Id.

4. Potential effect of the use of the proposed claims on food consumption, including significant alterations in eating habits and corresponding changes in nutrient intakes.

Daily chromium picolinate consumption meets or exceeds the RDI (120 mcg daily) only in a small fraction of the population. Exhibit 1 at 10-11. Self-selected diet studies suggest that typical chromium intake in the U.S. ranges from 22 to 48 mcg per day for men and 13 to 36 mcg per day for women. Exhibit 1 at 10-22; see also, Attachment 256 at 212. Recent data, based on the Continuing Survey of Food Intakes by Individuals conducted from 1994 to 1996, estimated chromium daily intake at less than 20 mcg per day. Exhibit 1 at 11. Not only are those levels below the RDI, they are far below the 200 mcg or greater levels found to have glucose-regulatory effects in the scientific research cited herein.

Nutrient intakes of chromium vary due to food handling, preparation, packaging, lot variability, and even geochemical source characteristics. Attachment 256 at 211. Thus, dietary

supplements are the best source for consistent nutrient intakes of chromium. Petitioner conducted a survey of dietary supplement users and found that 80% stated that they were aware of chromium picolinate whereas only 8% knew of other forms of chromium.⁴ Exhibit 1 at 28. In a 2001 survey of diabetes educators attending the American Association of Diabetes Educators 30% of respondents stated that they recommended chromium supplementation to their patients. Id. Of those respondents who recommended chromium supplementation, 96% recommended chromium picolinate.⁵ Id. Similarly, in a survey of pharmacists, chromium picolinate was one of the top five recommended nutritional supplements. Id.

The proposed claims may increase use of chromium picolinate dietary supplements among the general population, including populations at risk of type 2 diabetes and retinopathy, kidney disease, and cardiovascular disease (when caused by abnormally elevated blood sugar levels). The Petitioner does not anticipate substantial dietary changes in the general population but does expect there to be some increase in consumer preferences for chromium picolinate-containing dietary supplements and foods. The effect on such people is expected to be beneficial, reducing the risk of insulin resistance; cardiovascular disease when caused by insulin resistance; abnormally elevated blood sugar levels; cardiovascular disease when caused by abnormally elevated blood sugar levels; type 2 diabetes; cardiovascular disease when caused by type 2 diabetes; retinopathy when caused by abnormally high blood sugar levels; and kidney disease when caused by abnormally high blood sugar levels.

5. Prevalence of the disease or health-related condition in the U.S. population and the relevance of the claims in the context of the total daily diet.

Diabetes occurs in all populations and age groups but its prevalence is increasing in blacks, Hispanics, Native Americans, and Asians. Id. It is estimated that there will be 800,000

⁴ The survey of dietary supplement users is unpublished and on file with Nutrition 21.

⁵ The survey of diabetes educators is unpublished and on file with Nutrition 21.

new cases of diabetes each year, and that there will be - within 10 years - 23 million people with the disease in the United States. Id. The death rate due to diabetes and its complications has increased by about 30% in the past 12 years. Id. Life expectancy among diabetics is approximately 15 years less than for non-diabetics. Diabetes is the sixth leading cause of death in the U.S. Id. Type 2 diabetes makes up 90% of all diabetes and is usually diagnosed in adults. Id. Its prevalence has been increasing and is attributed to the increasing number of aging, overweight, and obese individuals. Id. Moreover, diabetes is estimated to cost the public \$105 billion annually and involves 10% of U.S. healthcare costs and 25% of Medicare costs. Id.

The eight proposed health claims are directly relevant to the daily diet of the U.S. general population. As discussed above, the intake of chromium in the U.S. daily diet is estimated to be far below the minimum levels (200 mcg) at which chromium has disease prevention and glucose-regulatory effects. Moreover, because of the variability of nutrient levels in foods and the poor absorbability of some forms of chromium, food is unlikely to be, if not incapable of being, an adequate source of chromium to provide those beneficial effects. Thus, the claims appearing on chromium picolinate dietary supplements would educate consumers about the importance of this nutrient, in this form, in preventing or reducing the risk of insulin resistance; cardiovascular disease when caused by insulin resistance; abnormally elevated blood sugar levels; cardiovascular disease when caused by abnormally elevated blood sugar levels; type 2 diabetes; cardiovascular disease when caused by type 2 diabetes; retinopathy when caused by abnormally high blood sugar levels; and kidney disease when caused by abnormally high blood sugar levels.

6. Chromium picolinate conforms to the definition of the term “substance” in 21 C.F.R. §101.14(a)(2).

“Substance means a specific food or component of food, regardless of whether the food is in conventional food form or a dietary supplement that includes vitamins, minerals, herbs, or

other similar nutritional substances.” 21 C.F.R. §101.14(a). Chromium picolinate is a substance within the meaning of 21 C.F.R. § 101.14(a).

Chromium is found in many sources in the food supply, typically in very small amounts (1 to 2 micrograms per serving). Exhibit 1 at 10; Exhibit 2 at 96; Attachment 256 at 211. Good food sources of chromium are whole grains, cereals, black pepper, thyme, mushrooms, brown sugar, coffee, tea, beer, wine, meat products, and brewer’s yeast. Exhibit 2 at 96. Chromium content in foods may increase or decrease with processing. Attachment 256 at 211. When grains and sugars are refined they are reported to lose chromium. Id. However, when acidic foods are prepared and processed they accumulate chromium, particularly when heated in stainless steel containers. Id. Further complicating determining chromium levels in foods and daily diets is the fact that chromium is quite variable among lots of foods and may be influenced by geochemical factors. Id. at 211. Thus, supplementation with chromium (either as a dietary supplement or supplemented in foods) is the best means to ensure intake of beneficial amounts of chromium on a daily basis.

Chromium picolinate is a dietary supplement and a substance within the meaning of Section 101.14(a). Chromium picolinate is a stable complex of trivalent chromium and picolinic acid. Exhibit 1 at 14. As discussed in detail above, chromium picolinate has greater absorbability and lower toxicity than other forms of chromium. Thus, as a nutritional substance chromium picolinate is the most preferable source of chromium. In conclusion, chromium picolinate is a substance within Section 101.14(a).

C. Analytical Data

The amount of chromium picolinate contained in dietary supplements that bear the Petitioner's health claims may be ascertained by the methodology in the U.S. Pharmacopeia official monograph for Chromium Picolinate and the attached assay method developed by Petitioner. Both documents are attached as Exhibit 3.

D. Model Health Claims

Petitioner proposes the following model claims for chromium picolinate:

- **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 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.**

As discussed above, multiple studies have shown that supplementation of the daily diet with chromium picolinate significantly reduces the risk of the above diseases. Exhibit 1 at 28.

Moreover, clinical trials and the long history of daily use have proven the safety of chromium picolinate for the general population. Exhibit 1 at 28-31.

E. Attachments

Attached are copies of the scientific studies (Exhibit 1) and other information referenced in, and constituting the basis for, this petition. To the best of Petitioner's knowledge, all non-clinical studies relied upon were conducted in compliance with the good laboratory practices regulations in 21 C.F.R. Part 58, and all clinical or other human investigations relied upon were either conducted in accordance with the requirements for institutional review in 21 C.F.R. Part 56 or were not subject to such requirements in accordance with 21 C.F.R. § 56.104 or 56.105, and were conducted in conformance with the requirements for informed consent in 21 C.F.R. § 50 et seq. See generally, 21 C.F.R. § 101.7 (c)-(d).

F. Exclusion from Environmental Assessment

The requested health claim approvals sought in this petition are categorically excluded from the environmental impact statement requirements under 21 C.F.R. § 25.24.

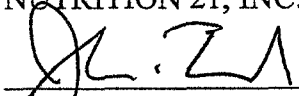
G. Conclusion and Certification

For the foregoing reasons, the Petitioner requests that FDA approve the proposed health claims. The Petitioner looks forward to working with FDA in promulgating a regulation authorizing the use of health claims on dietary supplements containing chromium picolinate concerning the association of chromium picolinate with insulin resistance; cardiovascular disease when caused by insulin resistance; abnormally elevated blood sugar levels; cardiovascular disease when caused by abnormally elevated blood sugar levels; type 2 diabetes; cardiovascular disease when caused by type 2 diabetes; retinopathy when caused by abnormally high blood sugar levels; and kidney disease when caused by abnormally high blood sugar levels.

Any questions concerning this petition may be directed to Jonathan W. Emord, Esq., Emord & Associates, P.C. See below for his contact information. The undersigned certify on behalf of the Petitioner that, to the best of the Petitioner's knowledge, this petition is a representative and balanced submission that includes unfavorable information as well as favorable information known to it to be pertinent to the evaluation of the proposed health claims.

Respectfully submitted,

NUTRITION 21, INC.,


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