



AUG 25 2005

Jonathan W. Emord, Esq.
1800 Alexander Bell Drive
Suite 200
Reston, VA 20191

RE: Health Claim Petition: Chromium Picolinate and 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 (Docket No. 2004Q-0144)

Dear Mr. Emord:

This letter responds to the health claim petition dated December 19, 2003, submitted to the Food and Drug Administration (FDA or the agency), on behalf of Nutrition 21, Inc. pursuant to Section 403(r)(5)(D) of the Federal Food, Drug, and Cosmetic Act (the Act) (21 U.S.C. § 343(r)(5)(D)). The petition requested that the agency authorize a health claim characterizing the relationship between the consumption of chromium picolinate and a reduced 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.

This petition proposed the following as model health claims for dietary supplements, which will be referred to by number in the rest of this letter:

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.

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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.

FDA evaluated the scientific evidence provided with the petition and other evidence related to your requested health claims. The Tufts University Evidence Based Practice Center assisted the FDA by doing an independent scientific review.¹

Based on a preliminary review, FDA determined that the scientific evidence supporting the proposed health claim did not meet the "significant scientific agreement" standard under section 403(r)(3)(B)(i) of the Act (21 U.S.C. § 343(r)(3)(B)(i)). FDA notified you of this decision and you submitted a letter dated March 24, 2004 stating that your client, Nutrition 21, Inc., chose to seek FDA review of the petition as a qualified health claim. Accordingly, FDA filed the petition on April 7, 2004 as a qualified health claim petition and posted the petition on the FDA website for a 60-day comment period, consistent with the agency's guidance for procedure on qualified health claims.² In a letter to FDA dated May 4, 2004, you modified the language for Claim #3 by adding the underlined words to read "Chromium picolinate may reduce the risk of abnormally elevated blood sugar levels." In letters to FDA dated November 12, 2004, March 22, 2005 and August 10, 2005, you submitted articles (see Docket # 2004Q-0144) for consideration in FDA's review of this petition. By mutual agreement, the decision date for this petition was last extended to August 25, 2005.

The agency received a total of six comments on the petition. Comments were from individual consumers (3) and health professionals (3). The comments supported the use of chromium picolinate for improving blood glucose regulation and encouraged providing this information to consumers by way of a qualified health claim. FDA considered the relevant comments in its evaluation of this petition.

This letter sets forth the results of FDA's scientific review of the evidence for the proposed qualified health claims. This letter also sets forth the factors that FDA intends to consider in the exercise of its enforcement discretion for a qualified health claim regarding the consumption of chromium picolinate and a reduced risk of insulin resistance and, therefore, a possible reduced risk of type 2 diabetes. Finally, this letter sets forth the basis for FDA's determination that there is not credible evidence to support a claim with respect to chromium picolinate and a reduction of risk for the other disease or health related conditions requested by the petitioner.

¹ The report submitted by Tufts University Evidence Based Practice Center is included in the docket.

² "Interim Procedures for Qualified Health Claims in the Labeling of Conventional Human Food and Human Dietary Supplements" (July 10, 2003). [<http://www.cfsan.fda.gov/~dms/nuttf-e.html>]

I. Overview of Data and Eligibility for a Qualified Health Claim

A health claim characterizes the relationship between a substance and a disease or health-related condition (21 CFR 101.14(a)(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, is at risk (21 CFR 101.14(b)(1)). Health claims characterize the relationship between the substance and a reduction in risk of contracting a particular disease.³ In a review of a qualified health claim petition, the agency first identifies the substance and disease or health-related condition that are the subject of the proposed claim and the population to which the claim is targeted.⁴ FDA considers the data and information provided in the petition, in addition to other written data and information available to the agency, to determine whether the data and information could support a relationship between the substance and the disease or health-related condition.⁵

The agency then separates individual reports of human studies from other types of data and information. FDA focuses its review on reports of human intervention and observational studies.⁶

In addition to individual reports of human studies, the agency also considers other types of data and information in its review, such as meta-analyses,⁷ review articles,⁸ and animal and *in vitro* studies. These other types of data and information may be useful to assist the agency in understanding the scientific issues about the substance, the disease or health-related condition, or both, but cannot by themselves support a health claim relationship. Reports that discuss a number of different studies, such as meta-analyses and review articles, do not provide sufficient information on the individual studies reviewed for FDA to determine critical elements such as the study population characteristics and the composition of the products used. Similarly, the lack of detailed information on studies summarized in review articles and meta-analyses prevents FDA from determining whether the studies are flawed in critical elements such as design, conduct of studies, and data analysis. FDA must be able to review the critical elements of a study to determine

³ See *Whitaker v. Thompson*, 353 F.3d 947, 950-51 (D.C. Cir 2004) (Reh'g *en banc* denied on March 9, 2004) upholding FDA's interpretation of what constitutes a health claim.

[<http://pacer.cadc.uscourts.gov/docs/common/opinions/200401/03-5020a.pdf>]

⁴ See guidance entitled "Interim Evidence-based Ranking System for Scientific Data," July 10, 2003.

[<http://www.cfsan.fda.gov/~dms/hclmgui4.html>]

⁵ For brevity, "disease" will be used as shorthand for "disease or health-related condition" in the rest of the section.

⁶ In an intervention study, subjects similar to each other are randomly assigned to either receive the intervention or not to receive the intervention, whereas in an observational study, the subjects (or their medical records) are observed for a certain outcome (i.e., disease). Intervention studies provide the strongest evidence for an effect. See Guidance entitled "Significant Scientific Agreement in the Review of Health Claims for Conventional Foods and Dietary Supplements" (December 22, 1999).

[<http://www.cfsan.fda.gov/~dms/ssaguide.html>]

⁷ A meta-analysis is the process of systematically combining and evaluating the results of clinical trials that have been completed or terminated (Spilker, 1991).

⁸ Review articles summarize the findings of individual studies.

whether any scientific conclusions can be drawn from it. Therefore, FDA uses meta-analyses, review articles, and similar publications⁹ to identify reports of additional studies that may be useful to the health claim review and as background about the substance-disease relationship. If additional studies are identified, the agency evaluates them individually.

FDA uses animal and *in vitro* studies as background information regarding mechanisms of action that might be involved in any relationship between the substance and the disease. The physiology of animals is different than that of humans. *In vitro* studies are conducted in an artificial environment and cannot account for a multitude of normal physiological processes such as digestion, absorption, distribution, and metabolism that affect how humans respond to the consumption of foods and dietary substances (IOM, 2005). Animal and *in vitro* studies can be used to generate hypotheses or to explore a mechanism of action but cannot adequately support a relationship between the substance and the disease.

FDA evaluates the individual reports of human studies to determine whether any scientific conclusions can be drawn from each study. The absence of critical factors such as a control group or a statistical analysis means that scientific conclusions cannot be drawn from the study (Spilker, 1991; Federal Judicial Center, 2000). Studies from which FDA cannot draw any scientific conclusions do not support the health claim relationship, and these are eliminated from further review.

Because health claims involve reducing the risk of a disease in people who do not already have the disease that is the subject of the claim, FDA considers evidence from studies in individuals diagnosed with the disease that is the subject of the health claim only if it is scientifically appropriate to extrapolate to individuals who do not have the disease. That is, the available scientific evidence must demonstrate that: (1) the mechanism(s) for the mitigation or treatment effects measured in the diseased populations are the same as the mechanism(s) for risk reduction effects in non-diseased populations; and (2) the substance affects these mechanisms in the same way in both diseased people and healthy people. If such evidence is not available, the agency cannot draw any scientific conclusions about risk reduction from studies that use diseased subjects to evaluate the substance-disease relationship.

Next, FDA rates the remaining human intervention and observational studies for methodological quality. This quality rating is based on several criteria related to study design (e.g., use of a placebo control versus a non-placebo controlled group), data collection (e.g., type of dietary assessment method), the quality of the statistical analysis, the type of outcome measured (e.g., disease incidence versus validated surrogate endpoint), and study population characteristics other than relevance to the U.S. population (e.g., selection bias and whether important information about the study subjects--e.g., age, smoker vs. non-smoker--was gathered and reported). For example, if

⁹ Other examples include book chapters, abstracts, letters to the editor, and committee reports.

the scientific study adequately addressed all or most of the above criteria, it would receive a high methodological quality rating. Moderate or low quality ratings would be given based on the extent of the deficiencies or uncertainties in the quality criteria. Studies that are so deficient that scientific conclusions cannot be drawn from them cannot be used to support the health claim relationship, and these are eliminated from further review.

Finally, FDA evaluates the results of the remaining studies. The agency then rates the strength of the total body of publicly available evidence.¹⁰ The agency conducts this rating evaluation by considering the study type (e.g., intervention, prospective cohort, case-control, cross-sectional), the methodological quality rating previously assigned, the quantity of evidence (number of the various types of studies and sample sizes), whether the body of scientific evidence supports a health claim relationship for the U.S. population or target subgroup, whether study results supporting the proposed claim have been replicated¹¹, and the overall consistency¹² of the total body of evidence.¹³ Based on the totality of the scientific evidence, FDA determines whether such evidence is credible to support the substance/disease relationship, and, if so, determines the ranking that reflects the level of comfort among qualified scientists that such a relationship is scientifically valid.

A. Substance

A health claim characterizes the relationship between a substance and a disease or health-related condition (21 CFR 101.14(a)(1)). A substance means a specific food or component of food regardless of whether the food is in conventional form or a dietary supplement (21 CFR 101.14(a)(2)). The petition identified chromium picolinate as the substance that is the subject of the proposed claim. Chromium is widely distributed throughout the food supply (e.g., cereals, meats, poultry, fish, beer, wine, fruits, and vegetables) with content being highly variable depending on preparation and processing (IOM, 2001). Picolinic acid is commonly complexed with chromium.¹⁴ Therefore, the agency concludes that the substance, chromium picolinate, identified in the petition is a

¹⁰ See *supra*, note 4.

¹¹ Replication of scientific findings is important for evaluating the strength of scientific evidence (Wilson, E.B. *An Introduction to Scientific Research*. Dover Publications, 1990; pages 46-48).

¹² Consistency of findings among similar and different study designs is important for evaluating causation and the strength of scientific evidence (Hill A.B. The environment and disease: association or causation? *Proceedings of the Royal Society of Medicine*. 1965;58:295-300); see also Systems to rate the scientific evidence from the Agency for Healthcare Research and Quality, which defines "consistency" as "the extent to which similar findings are reported using similar and different study designs."
[<http://www.ahrq.gov/clinic/epcsums/strengthsum.htm#Contents>]

¹³ See *supra*, note 4.

¹⁴ Although chromium exists in several oxidation states, the trivalent state is found in food and the body. Since chromium is a trivalent cation that occurs as Cr³⁺ positive charge, it has a high affinity for negatively charged ions and will form inorganic salts (e.g., chromium chloride). Organic acids (e.g. picolinic acid) can co-ordinate with Cr (III) cations to form organic acid-metal complexes or chelates (Columbia Electronic Dictionary and American Heritage Dictionary).

component of food and meets the definition of substance in the health claim regulation (21 CFR 101.14(a)(2)).

B. Disease or Health-Related Condition

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 or a state of health leading to such dysfunctioning (21 CFR 101.14(a)(5)). The petition has identified insulin resistance, cardiovascular disease, abnormally elevated blood sugar levels, type 2 diabetes, retinopathy, and kidney disease as the diseases or health related conditions that are the subjects of the proposed claims.

Diabetes is a disorder of metabolism resulting from the body's impaired ability to use blood glucose (sugar) for energy.¹⁵ In type 1 diabetes, the pancreas no longer makes insulin and therefore blood glucose cannot enter the cells to be used for energy. In type 2 diabetes, either the pancreas does not make enough insulin or the body is unable to use insulin effectively (i.e., insulin resistance). A diagnosis of type 2 diabetes can be made after positive results on any one of three tests, with confirmation from a second positive test on a different day: 1) random (taken any time of day) plasma glucose value of 200 mg/dL or more, along with the presence of diabetes symptoms, 2) a plasma glucose value of 126 mg/dL or more after a person has fasted for 8 hours, and 3) an oral glucose tolerance test (OGTT) plasma glucose value of 200 mg/dL or more in a blood sample taken 2 hours after a person has consumed a drink containing 75 grams of glucose dissolved in water. Elevated or abnormally high blood sugar levels (fasting blood sugar of > 100 mg/dL and < 126 mg/dL) and insulin resistance¹⁶ are considered risk factors for type 2 diabetes.^{17,18}

Diabetes generally results from high blood glucose levels, which can damage many parts of the body, such as the heart, blood vessels, eyes, and kidneys.¹⁹ Cardiovascular disease can lead to heart attacks and strokes, the leading causes of death for people with diabetes. Retinopathy is an eye disease caused by damaged blood vessels that leak blood into the vitreous²⁰ of the eye resulting in impaired vision. In kidney disease, the kidneys fail to

¹⁵ National Institute Health (NIH), National Institute of Diabetes & Digestive & Kidney Diseases [<http://diabetes.niddk.nih.gov/dm/pubs/overview/index.htm#what>]

¹⁶ Insulin resistance is a condition in which the cells of the body become resistant to the effects of insulin. As a result, higher levels of insulin are needed for glucose to enter the cells and to achieve normal blood glucose concentration.

¹⁷ NIH, National Diabetes Education Program [<http://ndep.nih.gov/diabetes/WTMD/diabetes.htm>]

¹⁸ NIH, National Diabetes Information Clearinghouse [<http://diabetes.niddk.nih.gov/dm/pubs/insulinresistance/>]

¹⁹ NIH, National Diabetes Information Clearinghouse [<http://diabetes.niddk.nih.gov/complications/index.htm>]

²⁰ Vitreous is a transparent jellylike substance filling the interior of the eyeball behind the lens of the eye (Stedman's Medical Dictionary).

rid the body of waste. Kidney failure is the final stage of a slow deterioration of the kidneys, a process known as nephropathy.

The agency concludes that type 2 diabetes, cardiovascular disease, retinopathy and kidney disease are diseases because in these states, systems of the body have been damaged such that the body is not functioning properly. The agency concludes that elevated or abnormally high blood sugar levels (fasting blood sugar of > 100 mg/dL and < 126 mg/dL) and insulin resistance are states of health leading to disease (type 2 diabetes) and are therefore health-related conditions. Thus, the petitioner has satisfied the requirement in 21 CFR 101.14(a)(5).

C. Safety Review

Under 21 CFR 101.14(b)(3)(ii), if the substance is to be consumed at other than decreased dietary levels, the substance must be a food or a food ingredient or a component of a food ingredient whose use at levels necessary to justify a claim must be demonstrated by the proponent of the claim, to FDA's satisfaction, to be safe and lawful under applicable food safety provisions of the Act.

FDA evaluates whether a substance is "safe and lawful" under the applicable food safety provisions of the Act. For dietary supplements, the applicable safety provisions require, among other things, that the dietary ingredient not present a significant or unreasonable risk of illness or injury under conditions of use recommended or suggested in labeling or, if no conditions of use are suggested or recommended in the labeling, under ordinary conditions of use (section 402(f)(1)(A) of the Act (21 U.S.C. 342(f)(1)(A))). Further, a dietary supplement must not contain a poisonous or deleterious substance which may render the supplement injurious to health under the conditions of use recommended or suggested in the labeling (section 402(f)(1)(D) of the Act (21 U.S.C. 342(f)(1)(D))).

The petition asserts that 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 literature. The petition acknowledges chromium as an essential mineral. The petition further states that chromium plays an essential role in normal carbohydrate metabolism and that it potentiates the action of insulin *in vivo* and *in vitro*. The petition cites FDA's Reference Daily Intake (RDI) for chromium (120 μg per day) and the Adequate Intake (AI) established by the Institute of Medicine (IOM) for chromium (35 μg /day for men 19-50 years, 25 μg /day for women 19-50 years, 30 μg /day for men 51+ years, and 20 μg /day for women 51+ years). The petition reviews the history of safe use of chromium picolinate in dietary supplements in humans and points out that the clinical studies suggesting safety with the consumption of dietary supplements containing chromium picolinate greatly outnumber the few published case reports of possible adverse events. The petition concludes that daily dietary supplementation with chromium picolinate in amounts providing 200 to 1,000 μg /day of chromium is safe.

To support its conclusion that chromium picolinate is safe for use as a dietary supplement, the petition also provides information about the safety of chromium picolinate in conventional foods. The petition states that chromium in the food supply is typically in the trivalent state as is chromium picolinate. The petition included a self GRAS determination for the use of Chromax® Chromium picolinate as a nutrient supplement in food.

The petition concerns the consumption of chromium picolinate as a dietary supplement. Supplemental chromium complexed with picolinic acid is more efficiently absorbed (2-5%) than dietary chromium (0.5-2%) (Anderson et al., 1996; Olin et al., 1994). FDA has established an RDI for chromium from all sources of 120 µg/day (21 CFR 101.9(8)(iv)). National survey data are not available on the intake of chromium at various percentiles. However, according to data from the Third National Health and Nutrition Examination Survey, the average supplemental intake of chromium for all individuals at the 99th percentile is 200 µg chromium (IOM, 2001).

Recently, the IOM reviewed the available literature on dietary supplementation of chromium picolinate to develop a framework for evaluating safety of dietary supplements, i.e., a prototype monograph (IOM, 2005). The monograph concluded that there is neither consistent evidence of reasonable expectations of harm from chromium picolinate nor sufficient evidence to raise concern regarding the safety or toxicity of chromium picolinate when used in the intended manner for a length of time consistent with the published clinical data (i.e., up to 1.6 mg chromium picolinate per day [200 µg chromium per day] for 3-6 months). Information is lacking on the long-term effect of chronic chromium picolinate consumption and on individual patterns (i.e., how much and how long) of chromium picolinate dietary supplement use (IOM, 2001 and 2005). Furthermore, the IOM (2001) stated that no adverse effects have been convincingly associated with excess intake of chromium from food or supplements, but this does not mean that there is no potential for adverse effects resulting from high intakes. The IOM stated that there is a need for more research to assess the safety of high-dose chromium intake from supplements (IOM, 2001).

Chromium picolinate was nominated to the National Toxicology Program²¹ (NTP) for toxicological studies because of the potential for widespread consumer use as a dietary supplement. Results of those studies are partially completed. Thus far, genetic toxicology studies and a short-term (13 weeks) animal feeding study do not suggest any mutagenic effect. A 2-year rodent bioassay to determine potential toxicity and/or carcinogenicity of prolonged chromium picolinate exposure is underway.

Because there was insufficient evidence to set an Estimated Average Requirement (EAR) for chromium, the IOM set an AI for conventional foods based on estimated mean

²¹National Toxicology Program, Department of Health and Human Services [<http://ntp-server.niehs.nih.gov/index.cfm?objectid=6DE07683-F1F6-975E-7D52259C338BBE34> and <http://ntp.niehs.nih.gov/index.cfm?objectid=0712660D-C915-D0EC-2CF95E4C710EA647>]

intakes. For ages 19-50, the AI is 35 µg/day and 25 µg/day for men and women, respectively, and for ages over 50 the AI is 30 µg/day and 20 µg/day for men and women, respectively (IOM, 2001). There were limited studies on dose-response data and no clear indications of a lowest-observed-adverse-effect level (LOAEL) or no-observed-adverse-effect level (NOAEL). As a result, there were insufficient data to establish a Tolerable Upper Intake Level (UL) for chromium in conventional foods (IOM, 2001).

FDA concludes at this time, under the preliminary requirements of 21 CFR 101.14(b)(3)(ii), that the use of chromium picolinate in dietary supplements as described in the qualified health claims discussed in section IV is safe and lawful under the applicable provisions of the Act.

II. The Agency's Consideration of a Qualified Health Claim

FDA identified the following surrogate endpoints to use in identifying type 2 diabetes risk reduction for purposes of a health claim evaluation: fasting blood sugar level (FBS), OGTT and insulin resistance.²² Insulin resistance is assessed by various measurements of insulin sensitivity,²³ including the glycemic clamp method, homeostasis model assessment, and fasting insulin/glucose ratio. Blood pressure, serum total cholesterol, and low density lipoprotein (LDL) cholesterol levels are considered to be surrogate endpoints for cardiovascular disease.²⁴ Therefore, to evaluate the potential effects of chromium picolinate consumption on type 2 diabetes risk or cardiovascular disease risk, FDA considered these endpoints as indicators or predictors of type 2 diabetes or cardiovascular disease. There are no surrogate endpoints for diabetic microvascular complications, such as kidney disease or retinopathy.

The petition cited a total of 381 publications as evidence to substantiate the relationship for this claim (see Docket # 2004Q-0144). These publications consisted of 65 reviews, 3 meta-analyses, 3 committee reports, 3 book chapters, 22 abstracts, 4 letters, 1 reference citation, 1 survey on supplement use, 9 animal studies, 7 *in vitro* studies, 38 articles on progression, risk factors and diagnosis of diabetes, 104 articles on complications associated with diabetes, 2 articles on the prevalence of diabetes, 10 articles on treatment of diabetes, 21 studies on the metabolism associated with diabetes, 3 articles on nutrient/dietary factors (other than chromium picolinate) that are associated with chronic disease, 1 article on the chromium composition of foods, 1 study on chromium intake, 14 studies on the effect of chromium on body composition, iron status, DNA damage or

²² The NIH has identified FBS (100 to 125 mg/dL), OGTT of greater than 140 to less than 200 mg/dL, and insulin resistance as risk biomarkers for type 2 diabetes (i.e., prediabetes). See *supra*, notes 17 and 18.

²³ Insulin sensitivity is the cell's responsiveness to insulin. The lower the amount of insulin needed to increase glucose uptake by the cells, the more sensitive.

²⁴ National Heart, Lung and Blood Institute (NHLBI), Heart and Blood Vessel Diseases [http://www.nhlbi.nih.gov/health/dci/Diseases/Atherosclerosis/Atherosclerosis_WhatIs.html] and the National Cholesterol Education Program's (NCEP) third report of the expert panel entitled, "Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (Adult Treatment Panel III)" (2001, page 3) [http://www.nhlbi.nih.gov/guidelines/cholesterol/atp_iii.htm].

depression, 8 studies on the metabolism, body levels and deficiency symptoms of chromium, 11 studies on the safety of chromium, 1 case report on chromium picolinate, 27 human intervention studies on forms of chromium other than chromium picolinate, and 23 human intervention studies on chromium picolinate.

In addition to the studies in the petition that were considered, one additional intervention study on chromium picolinate was identified from a literature search (Kato, 1998). While reviewing the literature for chromium picolinate, 9 additional studies on other forms of chromium were identified (Crawford et al., 1999; Gill et al., 1981; Hermann et al., 1994; Hermann et al., 1998; Li et al., 1992; Li et al., 1994; Liu et al., 1978; Offenbacher et al., 1985; Vinson et al., 1984).

A. Assessment of Review Articles, Meta-Analyses and Abstracts

Although useful for background information, the review articles, meta-analyses, and abstracts do not contain sufficient information on the individual studies which they reviewed and, therefore, FDA could not draw any scientific conclusions from this information. FDA could not determine factors such as the study population characteristics or the composition of the products used (e.g., conventional food or dietary supplement). Similarly, the lack of detailed information on studies summarized in review articles and meta-analyses prevents FDA from determining whether the studies are flawed in critical elements such as design, conduct of studies, and data analysis. FDA must be able to review the critical elements of a study to determine whether any scientific conclusions can be drawn from it. As a result, the review articles, meta-analyses, and abstracts supplied by the petitioner do not provide information from which scientific conclusions can be drawn regarding the substance-disease relationships claimed by the petitioner.

B. Assessment of Animal and *In Vitro* Studies

FDA uses animal and *in vitro* studies as background information regarding mechanisms of action that might be involved in any relationship between the substance and the disease, and they can also be used to generate hypotheses or to explore a mechanism of action, but they cannot adequately support a relationship between the substance and the disease in humans. FDA did not consider the animal or *in vitro* studies submitted with the petition as providing any supportive information about the substance/disease relationship because such studies cannot mimic the normal human physiology that may be involved in the risk reduction of any type of diabetes or conditions leading to diabetes, nor can the studies mimic the human body's response to the consumption of chromium picolinate. Therefore, FDA cannot draw any scientific conclusions from the animal or *in vitro* studies regarding chromium picolinate and the reduction of risk of disease or health related conditions.

C. Assessment of the Intervention Studies

Chromium picolinate is the substance that is the subject of the proposed claims. In this instance, FDA need not determine whether it would be appropriate to consider studies on other forms of chromium because reliance on such studies would not affect FDA's ultimate conclusion for any requested claim. Nonetheless, FDA summarizes in this letter the human intervention studies using other forms of chromium (e.g., chromium chloride, chromium nicotinate, and chromium in Brewer's yeast).

Of the 24 intervention studies on chromium picolinate reviewed, 8 studies did not address any of the 8 proposed claims. One study examined the effects of chromium picolinate on LDL and total cholesterol in healthy populations (Press et al., 1990). This study did not address any of the petitioner's proposed claims. Seven studies examined the effects of chromium picolinate on cardiovascular disease risk (e.g., total cholesterol levels, LDL cholesterol levels, and/or blood pressure) (Ghosh et al., 2002; Lee and Reasner, 1994; Anderson et al., 1997; Rabinovitz et al., 2004; Vrtovec et al., 2005; Evans, 1989) or blood urea nitrogen (Anderson et al., 1997) in individuals that had type 2 diabetes. These seven studies did not address any of the petitioner's proposed claims.²⁵

Of the 36 intervention studies on other forms of chromium reviewed, 6 studies did not address any of the 8 proposed claims. The 6 studies examined the effects of other forms of chromium on cardiovascular disease (e.g., blood total cholesterol and/or LDL cholesterol levels) in individuals with type 2 diabetes. These six studies did not address any of the petitioner's proposed claims (Trow et al., 2000; Bahiriji et al., 2000; Rabinowitz et al., 1983; Mossop et al., 1983; Uusitupa et al., 1983; Grant et al., 1982).²⁶

Claim 1: Chromium picolinate may reduce the risk of insulin resistance.

There were 5 studies that evaluated the effect of chromium picolinate on the risk of insulin resistance (Morris et al., 2000; Ravina et al., 1995; Gunton et al., 2005; Amato et al., 2000; Cefalu et al., 1999). Two of these studies were conducted in individuals already diagnosed with diabetes (Morris et al., 2000; Ravina et al., 1995). FDA considers evidence from studies in individuals already diagnosed with diabetes only if it is scientifically appropriate to extrapolate to individuals who do not have the disease. That is, the available scientific evidence must demonstrate that: (1) the mechanism(s) for the mitigation or treatment effects measured in the diseased populations are the same as the mechanism(s) for risk reduction effects in non-diseased populations; and (2) the substance affects these mechanisms in the same way in both diseased people and healthy people. Because the mechanism(s) by which chromium may affect glucose metabolism

²⁵ Although one of the petitioned claims is for chromium picolinate and a reduced risk of "cardiovascular disease when caused by type 2 diabetes," the studies on cardiovascular disease risk in type 2 diabetics do not provide information on whether the cardiovascular disease risk was induced by type 2 diabetes, and therefore do not address the proposed claim. For further discussion, see Section II under Claim #6.

²⁶ See *supra*.

and/or insulin response is hypothetical (Vincent, 2000), it is not known whether results from studies on the treatment of diabetes with chromium picolinate can be extrapolated to risk reduction of insulin resistance in individuals without diabetes. Therefore, the agency could not draw any scientific conclusions from these two studies for this claim.

Gunton et al. (2005) and Amato et al. (2000) did not conduct statistical analysis between control and chromium picolinate group. Statistical analysis between the two groups is a critical factor because it provides the comparison between subjects consuming chromium picolinate and those not consuming chromium picolinate, to determine whether there is a reduction in risk of insulin resistance (Spilker, 1991). When statistics are not performed on the specific substance/disease relationship, it can not be determined whether there is a difference between the two groups. As a result, these studies provided no information about how chromium picolinate may reduce the risk of insulin resistance; hence, no scientific conclusions could be drawn from them.

Cefalu et al. (1999) was a double-blind, randomized study of moderate methodological quality in which subjects at high risk for diabetes were provided a placebo or 1,000 µg/day of chromium picolinate for 8 months. Insulin resistance was evaluated by measuring insulin sensitivity.²⁷ Compared to the control group, there was a significant increase in insulin sensitivity for subjects that took the chromium picolinate supplement.

There were five studies that measured the effect of other forms of chromium on risk of insulin resistance (Offenbacher et al., 1985; Riales et al., 1981; Potter et al., 1985; Wang et al., 1989; Elias et al., 1984). One study did not include a control group for evaluating the relative effect of chromium (Potter et al., 1985). Therefore, it cannot be determined whether changes in the endpoint of interest were due to chromium or to unrelated and uncontrolled extraneous factors. Hence, scientific conclusions could not be drawn from this study (Spilker, 1991).

One study used diabetic patients (Elias et al., 1984). FDA considers evidence from studies in individuals already diagnosed with diabetes only if it is scientifically appropriate to extrapolate to individuals who do not have the disease. That is, the available scientific evidence must demonstrate that: (1) the mechanism(s) for the mitigation or treatment effects measured in the diseased populations are the same as the mechanism(s) for risk reduction effects in non-diseased populations; and (2) the substance affects these mechanisms in the same way in both diseased people and healthy people. Because the mechanism(s) by which chromium may affect glucose metabolism and/or insulin response is hypothetical (Vincent, 2000), it is not known whether results from studies on the treatment of diabetes with chromium picolinate can be extrapolated to risk reduction of insulin resistance in individuals without diabetes. Therefore, the agency could not draw any scientific conclusions from this study for this claim.

²⁷ See *supra*, note 23.

Two studies did not conduct statistical analysis between the control and chromium group (Riales et al., 1981; Offenbacher et al., 1985). Statistical analysis between the two groups is a critical factor because it provides the comparison between subjects consuming chromium and those not consuming chromium, to determine whether there is a reduction in risk of insulin resistance. When statistics are not performed on the specific substance/disease relationship, it cannot be determined whether there is a difference between the two groups (Spilker, 1991). As a result, these studies provided no information about how chromium may reduce the risk of insulin resistance; hence, no scientific conclusions could be drawn from them.

One study was identified in which chromium chloride was provided to healthy subjects to evaluate its effectiveness on reducing the risk of insulin resistance (Wang et al., 1989). This study was of moderate methodological quality. This study did not show a statistically significant beneficial effect of chromium chloride supplementation on measures of insulin resistance.

Claim 2: Chromium picolinate may reduce the risk of cardiovascular disease when caused by insulin resistance.

Cardiovascular disease can be a complication of diabetes. There is no scientific evidence to support the literal meaning of the proposed claim because if cardiovascular disease has been *caused* by insulin resistance, then it is not possible to reduce the risk of cardiovascular disease because it already exists. If the claim is interpreted to mean that insulin resistance increases *the risk* of cardiovascular disease, and such risk is reduced with the consumption of chromium picolinate, then individual studies are required to show both that 1) insulin resistance increased the risk of cardiovascular disease *and* 2) chromium picolinate reduced the insulin resistance-induced risk.²⁸ There were no studies available that evaluated both of these effects in the same study.

Claim 3: Chromium picolinate may reduce the risk of abnormally elevated blood sugar levels.

Of the 13 studies that evaluated the effect of chromium picolinate on blood sugar levels, 8 studies were not further reviewed because scientific conclusions could not be drawn from them (Walker et al., 1998; Ravina et al., 1999; Jovanovic et al., 1999; Cheng et al., 1999; Grant et al., 1997; Kato et al., 1998; Pasman et al., 1997; Gunton et al., 2005).

Walker et al. (1998) did not provide the data within the report; therefore, the agency was not able to evaluate the reliability of the data or the statistical interpretation of the data.

²⁸ Conclusions can not be drawn collectively from studies that measured one of the two relationships because different study populations were used for each relationship and there are numerous risk factors of cardiovascular disease (e.g., age, race, body weight and lifestyle) that need to be simultaneously accounted for in evaluating the relationship between chromium picolinate/cardiovascular disease and insulin resistance/cardiovascular disease.

For three of the studies, the subjects were already diagnosed with diabetes (Ravina et al., 1999; Jovanovic et al., 1999; Cheng et al., 1999). FDA considers evidence from studies in individuals already diagnosed with diabetes only if it is scientifically appropriate to extrapolate to individuals who do not have the disease. That is, the available scientific evidence must demonstrate that: (1) the mechanism(s) for the mitigation or treatment effects measured in the diseased populations are the same as the mechanism(s) for risk reduction effects in non-diseased populations; and (2) the substance affects these mechanisms in the same way in both diseased people and healthy people. Because the mechanism(s) by which chromium may affect glucose metabolism and/or insulin response is hypothetical (Vincent, 2000), it is not known whether results from studies on the treatment of diabetes with chromium picolinate could be extrapolated to risk reduction of abnormally elevated blood sugar levels in individuals without diabetes. Therefore, the agency could not draw any scientific conclusions from these three studies for this claim.

Two studies did not include a control group (Kato et al., 1998; Grant et al., 1997). Therefore, it could not be determined whether changes in the endpoint of interest were due to chromium picolinate or to unrelated and uncontrolled extraneous factors. Hence, scientific conclusions could not be drawn from these studies (Spilker, 1991).

Statistical analyses were not conducted between the chromium picolinate and control group in 2 studies (Passman et al., 1997; Gunton et al., 2005). Conducting statistical analysis between the two groups is a critical factor because it provides the comparison between subjects consuming chromium picolinate and those not consuming chromium picolinate, to determine whether there is a reduction in diabetes risk. When statistics are not performed on the specific substance/disease relationship, it cannot be determined whether there is a difference between the two groups (Spilker, 1991). As a result, these studies provided no information about how chromium picolinate may reduce the risk of abnormally elevated blood sugar levels; hence, no scientific conclusions could be drawn from these studies.

Volpe et al. (2001) conducted a 12 week randomized study that provided obese U.S. women ($n=22$ per group) 400 $\mu\text{g/day}$ of chromium as chromium picolinate. This study was determined to be of moderate methodological quality. There was no statistically significant difference in FBS or OGTT between the chromium picolinate and placebo group.

Boyd et al. (1998) was a 13 week nonrandomized study in which healthy U.S. men and women ($n=9$ per group) were given either a placebo or 1 g/day chromium picolinate. This study was determined to be of moderate methodological quality. There was no statistically significant beneficial effect of chromium picolinate on FBS or OGTT compared to the placebo control group.

A 12 week randomized study by Joseph et al. (1999) was conducted on U.S. men and women who were healthy or had glucose intolerance.²⁹ This study was of moderate methodological quality. Subjects ($n=15$ or 17 per group) received either a placebo or $924 \mu\text{g/day}$ of chromium as chromium picolinate and underwent resistance training twice weekly. There was no statistically significant beneficial effect of chromium picolinate on FBS compared to the control group.

Frauchiger et al. (2004) was a single-dose, cross-over design study in which young Swiss men ($n = 13$ per group) were provided a placebo, 400 or $800 \mu\text{g}$ of chromium as chromium picolinate 30 minutes prior to the consumption of a test meal. This study was of moderate methodological quality. There was no statistically significant beneficial effect ($P < 0.05$) in OGTT when either 400 or $800 \mu\text{g}$ of chromium picolinate was consumed.³⁰

Cefalu et al. (1999) was a double-blind, randomized study in which subjects at high risk for diabetes were provided a placebo or $1,000 \mu\text{g/day}$ of chromium picolinate for 8 months. There was no statistically beneficial effect of chromium picolinate on OGTT compared to the control group.

There were a total of 29 studies reviewed that evaluated the effect of other forms of chromium on blood sugar levels. Four of these studies did not include a control group for comparing the relative effect of chromium (Liu et al., 1978; Vinson et al., 1984; Potter et al., 1985; Glinsmann and Mertz, 1966). Therefore, it could not be determined whether changes in the endpoint of interest were due to chromium or to unrelated and uncontrolled extraneous factors. Hence, scientific conclusions could not be drawn from these studies (Spilker, 1991).

Nine studies did not conduct statistical analyses between the control and chromium group (Offenbacher et al., 1985; Martinez et al., 1985; Li et al., 1992; Offenbacher et al. 1980; Riales et al., 1981; Urberg et al., 1987; Gill et al., 1981; Sherman et al., 1968; Crawford et al., 1999). Statistical analysis between the two groups is a critical factor because it provides the comparison between subjects consuming chromium and those not consuming chromium, to determine whether there is a reduction in risk of abnormally elevated blood sugar levels. When statistics are not performed on the specific substance/disease relationship, it cannot be determined whether there is a difference between the two groups (Spilker, 1991). As a result, these studies provided no

²⁹ Glucose intolerance is indicated by higher than normal blood sugar levels, but not so high as to warrant a diagnosis of diabetes.

³⁰ Statistical significance was observed when the subjects were divided into a responder or non-responder group. Responders were defined as subjects who showed a lower rise in blood sugar after consumption of the test meals for both chromium trials compared with the placebo trial. This type of data analysis based on the study findings, however, would obviously yield statistical significance. Therefore, no scientific conclusions about chromium picolinate's effect on blood sugar levels could be drawn from these results.

information about how other forms of chromium may reduce the risk of abnormally elevated blood sugar levels; hence, no scientific conclusions could be drawn from them.

One study was conducted on hypoglycemic patients to determine if chromium chloride had an effect on blood glucose levels (Anderson et al., 1987). The purpose of this study, however, was to determine if chromium chloride would *increase* low blood glucose to normal levels, and therefore the study did not address the proposed claim for a reduction in risk of elevated blood glucose levels.

Three studies on other forms of chromium were conducted in malnourished children in Jordan, Turkey and Egypt (Gurson and Saner, 1971; Carter et al., 1968; Hopkins et al., 1968). Nutrient status and metabolism can be severely altered when an individual is malnourished. For instance, malnutrition can result in lower blood glucose and insulin levels (Torun and Chew, 1994). Therefore, the effect of a nutrient, such as chromium, on blood sugar levels can be very different than the effect of the same nutrient on healthy, well-nourished individuals. Thus, scientific conclusions about chromium's effect on blood sugar levels in the general U.S. population could not be drawn from these studies.

There were 11 studies on healthy subjects (Lefavi et al., 1993; Li et al., 1994; Anderson et al., 1991; Hermann et al., 1998; Anderson et al., 1983; Wang et al., 1989; Hermann et al., 1994; Thomas and Gropper, 1997; Uusitupa et al., 1992; Wilson et al., 1995; Grant et al., 1997), one study on individuals with glucose intolerance (Abraham et al., 1992) and one study on both healthy subjects and those with hyperglycemia (Anderson et al., 1991) that evaluated the effect of other forms of chromium on blood sugar levels. These other forms of chromium were chromium chloride and chromium nicotinate. These studies were of moderate to high methodological quality. None of the 12 studies in healthy subjects showed a significant beneficial effect of chromium supplementation on FBS and/or OGTT. The 2 studies in individuals with glucose intolerance showed no significant beneficial effect of chromium supplementation on FBS (Abraham et al., 1992; Anderson et al., 1991). One of the 2 studies showed a statistically significant benefit for OGTT over a 4 hour period in hyperglycemic individuals (Anderson et al., 1991).³¹

Claim 4: Chromium picolinate may reduce the risk of cardiovascular disease when caused by abnormally elevated blood sugar levels.

Cardiovascular disease can be a complication of abnormally high blood sugar levels and diabetes. There is no scientific evidence to support the literal meaning of the proposed claim because if cardiovascular disease has been *caused* by abnormally elevated blood sugar levels, then it is not possible to reduce the risk of cardiovascular disease because it already exists. If the claim is interpreted to mean that abnormally elevated blood glucose levels increases *the risk* of cardiovascular disease, and such risk is reduced with the consumption of chromium picolinate, then individual studies are required to show both

³¹ The hyperglycemics in this study had higher than normal blood sugar levels, but not so high as to result in a diagnosis of diabetes.

that 1) abnormally elevated blood sugar levels increased the risk of cardiovascular disease *and* 2) chromium picolinate reduced the elevated blood sugar-induced risk.³² There were no studies available that evaluated both of these effects in the same study.

Claim 5: Chromium picolinate may reduce the risk of type 2 diabetes.

No studies were identified that evaluated the effect of chromium picolinate on the incidence of type 2 diabetes.

As discussed under Claim #1, there was one study that showed a beneficial effect of chromium picolinate on the risk of insulin resistance (Cefalu et al., 1999). Another study that evaluated the effectiveness of chromium chloride in reducing the risk of insulin resistance (Wang et al., 1989) did not show a statistically significant beneficial effect of chromium chloride on measures of insulin resistance.

As discussed under Claim #3, the 5 studies from which scientific conclusions could be drawn did not show a statistically significant beneficial effect of chromium picolinate compared to a placebo control on blood sugar levels (Volpe et al., 2001; Boyd et al., 1998; Joseph et al., 1999; Frauchiger et al., 2004; Cefalu et al., 1999).

As discussed under Claim #3, none of the 11 studies in healthy subjects showed a significant beneficial effect of other forms of chromium on FBS and/or OGTT (Lefavi et al., 1993; Li et al., 1994; Anderson et al., 1991; Hermann et al., 1998; Anderson et al., 1983; Wang et al., 1989; Hermann et al., 1994; Thomas and Gropper, 1996; Uusitupa et al., 1992; Wilson et al., 1995; Grant et al., 1997). The 2 studies in individuals with glucose intolerance showed no significant beneficial effect of chromium supplementation on FBS (Abraham et al., 1992; Anderson et al., 1991). One of the 2 studies showed a statistically significant benefit for OGTT over a 4 hour period in hyperglycemic individuals with chromium chloride (Anderson et al., 1991).

Claim 6: Chromium picolinate may reduce the risk of cardiovascular disease when caused by type 2 diabetes.

Cardiovascular disease can be a complication of type 2 diabetes. There is no scientific evidence to support the literal meaning of the proposed claim because if cardiovascular disease has been *caused* by type 2 diabetes, then it is not possible to reduce the risk of cardiovascular disease because it already exists. If the claim is interpreted to mean that type 2 diabetes increases *the risk* of cardiovascular disease, and such risk is reduced with the consumption of chromium picolinate, then individual studies are required to show

³² Conclusions cannot be drawn collectively from studies that measured one of the two relationships because different study populations were used for each relationship and there are numerous risk factors of cardiovascular disease (e.g., age, race, body weight and lifestyle) that need to be simultaneously accounted for in evaluating the relationship between chromium picolinate/cardiovascular disease and abnormally elevated blood sugar levels/cardiovascular disease.

both that 1) type 2 diabetes increased the risk of cardiovascular disease *and* 2) chromium picolinate reduced the type 2 diabetes-induced risk.³³ There were no studies available that evaluated both of these effects in the same study.

Claim 7: Chromium picolinate may reduce the risk of retinopathy when caused by abnormally high blood sugar levels.

Retinopathy can be a complication of abnormally high blood sugar levels and diabetes. There is no scientific evidence to support the literal meaning of the proposed claim because if retinopathy has been *caused* by abnormally high blood sugar levels, then it is not possible to reduce the risk of retinopathy because it already exists. If the claim is interpreted to mean that abnormally high blood sugar levels increases *the risk* of retinopathy, and such risk is reduced with the consumption of chromium picolinate, then individual studies are required to show both that 1) abnormally high blood sugar levels increased the risk of retinopathy *and* 2) chromium picolinate reduced the high blood sugar-induced risk.³⁴ There were no studies available that evaluated both of these effects in the same study.

Claim 8: Chromium picolinate may reduce the risk of kidney disease caused by abnormally high blood sugar levels.

Kidney disease can be a complication of abnormally high blood sugar levels and diabetes. There is no scientific evidence to support the literal meaning of the proposed claim because if kidney disease has been *caused* by abnormally high blood sugar levels, then it is not possible to reduce the risk of kidney disease because it already exists. If the claim is interpreted to mean that abnormally elevated blood sugar levels increase *the risk* of kidney disease, and such risk is reduced with the consumption of chromium picolinate, then individual studies are required to show both that 1) abnormally high blood sugar levels increased the risk of kidney disease *and* 2) chromium picolinate reduced the high blood sugar level-induced risk.³⁵ There were no studies available that evaluated both of these effects in the same study.

³³ Conclusions cannot be drawn collectively from studies that measured one of the two relationships because different study populations were used for each relationship and there are numerous risk factors of cardiovascular disease (e.g., age, race, body weight and lifestyle) that need to be simultaneously accounted for in evaluating the relationship between chromium picolinate/cardiovascular disease and type 2 diabetes/cardiovascular disease.

³⁴ Conclusions cannot be drawn collectively from studies that measured one of the two relationships because different study populations were used for each relationship and there are various risk factors of retinopathy (e.g., race, duration of elevated blood sugar levels, and blood pressure) that need to be simultaneously accounted for in evaluating the relationship between chromium picolinate/retinopathy and abnormally high blood sugar levels/retinopathy.

³⁵ Conclusions cannot be drawn collectively from studies that measured one of the two relationships because different study populations were used for each relationship and there are various risk factors of kidney disease (e.g., race, blood pressure, and family history) that need to be simultaneously accounted for in evaluating the relationship between chromium picolinate/kidney disease and abnormally high blood sugar levels/kidney disease.

D. Assessment of the Relevant Observational Studies

There were no observational studies available to the agency that evaluated the effect of chromium picolinate or other forms of chromium on reduced risk of any of the proposed diseases or health-related conditions.

III. Strength of the Scientific Evidence

Below, the agency rates the strength of the total body of publicly available evidence. The agency conducts this rating evaluation by considering the study type (e.g., intervention, prospective cohort, case-control, cross-sectional), the methodological quality rating previously assigned, the quantity of evidence (number of the various types of studies and sample sizes), whether the body of scientific evidence supports a health claim relationship for the U.S. population or target subgroup, whether study results supporting the proposed claim have been replicated³⁶, and the overall consistency³⁷ of the total body of evidence. Based on the totality of the scientific evidence, FDA determines whether such evidence is credible to support the substance/disease relationship, and, if so, determines the ranking that reflects the level of comfort among qualified scientists that such a relationship is scientifically valid.

Claim 1: Chromium picolinate may reduce the risk of insulin resistance.

As discussed in Section II, there was one study (Cefalu et al., 1999) that showed a benefit for chromium picolinate and insulin resistance.³⁸ Insulin resistance is a surrogate endpoint for type 2 diabetes, and therefore may predict the development of type 2 diabetes. FDA finds that there is very limited credible evidence for a qualified health claim specifically for chromium picolinate and a reduced risk of insulin resistance, and therefore possibly a reduced risk of type 2 diabetes. However, the reported findings of Cefalu et al., 1999 have not been replicated, and replication of scientific findings is important in order to substantiate results.³⁹ Because there is only one small study in support of the claim, there is very little data from which to conclude whether such a relationship actually exists.

Based on the review of the strength of the total body of publicly available scientific evidence, FDA ranks this evidence as the lowest level for a qualified health claim. For the reasons given above, FDA concludes that the existence of a relationship between chromium picolinate and reduced risk of either insulin resistance or type 2 diabetes is highly uncertain.

³⁶ See *supra*, note 11.

³⁷ See *supra*, note 12.

³⁸ The one study on another form of chromium on reduction of the risk of insulin resistance did not show an effect.

³⁹ See *supra*, note 11.

Claim 2: Chromium picolinate may reduce the risk of cardiovascular disease when caused by insulin resistance.

As discussed in Section II, there was no scientific evidence to support the proposed claim nor was there scientific evidence to demonstrate that an *increased risk* of cardiovascular disease due to insulin resistance is reduced with the consumption of chromium picolinate. Based on the review of the scientific evidence, FDA concludes that there is no credible scientific evidence to support the proposed claim.

Claim 3: Chromium picolinate may reduce the risk of abnormally elevated blood sugar levels.

As discussed in Section II, there were five studies that evaluated the effect of chromium picolinate supplementation on measures of blood sugar levels. None of these studies showed a statistically significant beneficial effect of chromium picolinate on FBS and/or OGTT (Volpe et al., 2001; Boyd et al., 1998; Joseph et al., 1999; Frauchiger et al., 2004; Cefalu et al., 1999).⁴⁰

Based on the review of the strength of the total body of publicly available scientific evidence, FDA concludes that there is no credible scientific evidence for the proposed claim.

Claim 4: Chromium picolinate may reduce the risk of cardiovascular disease when caused by abnormally elevated blood sugar levels.

As discussed in Section II, there is no scientific evidence to support the proposed claim nor is there scientific evidence to demonstrate that an *increased risk* of cardiovascular disease due to abnormally elevated blood sugar levels is reduced with the consumption of chromium picolinate. Based on the review of the total body of publicly available scientific evidence, FDA concludes that there is no credible evidence for the proposed claim.

Claim 5: Chromium picolinate may reduce the risk of type 2 diabetes.

As discussed in Section II, there were no studies that evaluated the effect of chromium picolinate on the incidence of type 2 diabetes. As discussed above for Claim #1, there was one study (Cefalu et al., 1999) that showed a benefit for chromium picolinate and

⁴⁰ None of the 11 studies on other forms of chromium showed a significant beneficial effect of other forms of chromium on FBS and/or OGTT on healthy subjects. One of the 2 studies using hyperglycemic individuals showed a statistically significant benefit for OGTT over a 4 hour period with another form of chromium. However, even if FDA were to consider this study as part of its review of the relationship between chromium picolinate and the risk of abnormally elevated blood sugar levels, the agency would not find credible evidence in support of the claim because of the large body of evidence (17 studies) on all forms of chromium that did not show a benefit.

insulin resistance, a surrogate endpoint for type 2 diabetes. As discussed for Claim #3, there were five studies (Volpe et al., 2001; Boyd et al., 1998; Joseph et al., 1999; Frauchiger et al., 2004; Cefalu et al., 1999) that showed no benefit for chromium picolinate and abnormally elevated blood sugar levels, also a surrogate endpoint for type 2 diabetes.⁴¹

FDA finds that there is very limited credible evidence for a qualified health claim specifically for chromium picolinate and a reduced risk of insulin resistance, and therefore possibly a reduced risk of type 2 diabetes. However, the reported findings of Cefalu et al., 1999 have not been replicated, and replication of scientific findings is important in order to substantiate results.⁴² Because there is only one small study in support of the claim, there is very little data from which to conclude whether such a relationship actually exists. Moreover, there are five studies that did not show a benefit for another surrogate endpoint of type 2 diabetes, blood glucose levels. Consistency of findings among similar and different study designs is important for evaluating the strength of the scientific evidence.⁴³

Based on the review of the strength of the total body of publicly available scientific evidence, FDA ranks this evidence as the lowest level for a qualified health claim. FDA concludes that the existence of a relationship between chromium picolinate and reduced risk of either insulin resistance or type 2 diabetes is highly uncertain. Because the only studies in support of the claim were on insulin resistance, FDA intends to consider the exercise of its enforcement discretion for a claim on type 2 diabetes insofar as the claim expresses that the only evidence in support of a relationship is on insulin resistance.

Claim 6: Chromium picolinate may reduce the risk of cardiovascular disease when caused by type 2 diabetes.

As discussed in Section II, there is no scientific evidence to support the proposed claim nor is there scientific evidence to demonstrate that an *increased risk* of cardiovascular disease due to type 2 diabetes is reduced with the consumption of chromium picolinate. Based on the review of the total body of publicly available scientific evidence, FDA concludes that there is no credible evidence for the proposed claim.

Claim 7: Chromium picolinate may reduce the risk of retinopathy when caused by abnormally high blood sugar levels.

⁴¹ The one study on other forms of chromium from which scientific conclusions could be drawn did not show a benefit of chromium chloride on the risk of insulin resistance. One study conducted in individuals with glucose intolerance showed a statistically significant benefit for OGTT over a 4 hour period with another form of chromium. However, as explained in footnote 40, even if FDA were to consider this study as part of its review of the relationship between chromium picolinate and the risk of abnormally elevated blood sugar levels, this would not affect the agency's conclusion on this claim due to the large body of evidence (17 studies) that did not show a benefit.

⁴² See *supra*, note 11.

⁴³ See *supra*, note 12.

As discussed in Section II, there is no scientific evidence to support the proposed claim nor is there evidence to demonstrate that an *increased risk* of retinopathy due to high blood sugar levels is reduced with the consumption of chromium picolinate. Based on the review of the total body of publicly available scientific evidence, FDA concludes that there is no credible evidence to support the proposed claim.

Claim 8: Chromium picolinate may reduce the risk of kidney disease when caused by abnormally high blood sugar levels.

As discussed in Section II, there is no scientific evidence to support the proposed claim nor is there evidence to demonstrate that an *increased risk* of kidney disease due to abnormally high blood sugar levels is reduced with the consumption of chromium picolinate. Based on the review of the total body of publicly available scientific evidence, FDA concludes that there is no credible evidence to support the proposed claim.

IV. Other Enforcement Discretion Factors

A qualified health claim on the label or in the labeling of chromium picolinate is required to meet all applicable statutory and regulatory requirements under the Federal Food, Drug, and Cosmetic Act, with the exception of the requirement that a health claim meet the significant scientific agreement standard and the requirement that the claim be made in accordance with an authorizing regulation.

Qualifying level of chromium in dietary supplements

The general requirements for health claims provide that, if the claim is about the effects of consuming the substance at other than decreased dietary levels, the level of the substance must be sufficiently high and in an appropriate form to justify the claim. Where no definition for “high” has been established, the claim must specify the daily dietary intake necessary to achieve the claimed effect (see 21 CFR 101.14(d)(2)(vii)).

Since a “high” definition is established for chromium, FDA intends to exercise enforcement discretion for dietary supplements bearing a qualified health claim about chromium picolinate and a reduced risk of insulin resistance, and therefore possibly a reduced risk of type 2 diabetes, when the dietary supplement contains chromium at a level that meets or exceeds the requirement for a “high” level of chromium as defined in 21 CFR 101.54(b) (i.e., 24 µg or more per RACC under the current regulation). The RACC for dietary supplements is the maximum amount recommended, as appropriate, on the label for consumption per eating occasion, or in the absence of recommendations, one unit, e.g., one tablet, capsule, packet, teaspoonfuls (21 CFR 101.12(b), Table 2, under “Miscellaneous Category”).

V. Agency's Consideration of Disclaimers or Qualifying Language

We considered but rejected use of a disclaimer or qualifying language to accompany the proposed claims for which there was no credible evidence to support the claim. We concluded that neither a disclaimer nor qualifying language would suffice to prevent consumer deception here, where there is no credible evidence to support any of these claims. Adding a disclaimer or incorporating qualifying language that effectively characterizes the claim as baseless is not a viable regulatory alternative because neither the disclaimer nor the qualifying language can rectify the false message conveyed by the unsubstantiated claim. *See, e.g., In re Warner-Lambert Co.*, 86 F.T.C. 1398, 1414 (1975), *aff'd*, 562 F.2d 749 (D.C. Cir. 1977) (pro forma statements of no absolute prevention followed by promises of fewer colds did not cure or correct the false message that Listerine will prevent colds); *Novartis Consumer Health, Inc. v. Johnson & Johnson-Merck Consumer Pharms. Co.*, 290 F.3d 578, 598 (3d Cir. 2002) ("We do not believe that a disclaimer can rectify a product name that necessarily conveys a false message to the consumer."). In such a situation, adding a disclaimer or qualifying language does not provide additional information to help consumer understanding but merely contradicts the claim. *Resort Car Rental System, Inc. v. FTC*, 518 F.2d 962, 964 (9th Cir.) (per curiam) (upholding FTC order to excise "Dollar a Day" trade name as deceptive because "by its nature [it] has decisive connotation for which qualifying language would result in contradiction in terms."), *cert denied*, 423 U.S. 827 (1975); *Continental Wax Corp. v. FTC*, 330 F.2d 475, 480 (2d Cir. 1964) (same); *Pasadena Research Labs v. United States*, 169 F.2d 375 (9th Cir. 1948) (discussing "self-contradictory labels"). In the FDA context, courts have repeatedly found such disclaimers ineffective. *See, e.g., United States v. Millpax, Inc.*, 313 F.2d 152, 154 & n.1 (7th Cir. 1963) (disclaimer stating that "no claim is made that the product cures anything, either by the writer or the manufacturer" was ineffective where testimonials in a magazine article promoted the product as a cancer cure); *United States v. Kasz Enters., Inc.*, 855 F. Supp. 534, 543 (D.R.I.) ("The intent and effect of the FDCA in protecting consumers from . . . claims that have not been supported by competent scientific proof cannot be circumvented by linguistic game-playing."), *judgment amended on other grounds*, 862 F. Supp. 717 (1994).

VI. Conclusions

Based on FDA's consideration of the scientific evidence, information submitted with your petition, and other pertinent scientific evidence and information, FDA concludes that there is no credible evidence to support qualified health claims for chromium picolinate and reduced risk of: cardiovascular disease when caused by insulin resistance, abnormally elevated blood sugar levels, cardiovascular disease when caused by abnormally elevated blood sugar levels, cardiovascular disease when caused by type 2 diabetes, retinopathy when caused by abnormally high blood sugar levels, or kidney disease when caused by abnormally high blood sugar levels. Thus, FDA is denying these claims. However, FDA concludes that there is very limited credible evidence for

qualified health claims for chromium picolinate and a reduced risk of insulin resistance, and therefore a reduced risk of type 2 diabetes, provided that the qualified claim is appropriately worded so as not to mislead consumers. Thus, FDA intends to consider the exercise of its enforcement discretion for the following qualified health claim:

“One small study suggests that chromium picolinate may reduce the risk of insulin resistance, and therefore possibly may reduce the risk of type 2 diabetes. FDA concludes, however, that the existence of such a relationship between chromium picolinate and either insulin resistance or type 2 diabetes is highly uncertain.”

Please note that scientific information is subject to change, as are consumer consumption patterns. FDA intends to evaluate new information that becomes available to determine whether it necessitates a change in this decision. For example, scientific evidence may become available that will support the use of additional qualified health claims or that will support significant scientific agreement.

Sincerely,



Barbara O. Schneeman, Ph.D.
Director
Office of Nutritional Products, Labeling
and Dietary Supplements
Center for Food Safety
and Applied Nutrition

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