Evidence Supporting Proposed Food-Related Health Claims For Chromium Picolinate Supplementation

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Tufts-New England Medical Center
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Agency for Healthcare Quality & Research

Ethan Balk, MD MPH
Athina Tatsioni, MD
Mei Chung, MPH
Anastassios Pittas, MD
Alice Lichtenstein, PhD
Joseph Lau, MD

Nutrition 21, Inc petitioned the Food and Drug Administration (FDA) for the following eight food-related health claims for chromium picolinate supplementation:

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

Nutrition 21, Inc. included 34 published articles in their petition to substantiate the health claims.

Through the Agency for Healthcare Research and Quality (AHRQ), the Tufts-New England Medical Center Evidence-based Practice Center (Tufts-NEMC EPC) has been asked to systematically review the evidence regarding the effect of chromium supplementation on the outcomes in the proposed health claims.

METHODS

The methodology for reviewing health claim petitions, including topic evaluation, literature search, study eligibility criteria, and study evaluation, were established by the Tufts-NEMC EPC, the Oregon Health & Science University EPC, AHRQ, and the FDA prior to the evaluation of this health claim petition. The methodology merges elements of processes used by the EPCs, an interim FDA grading system, and the United States Preventive Services Task Force (USPSTF) approach. Revisions to the methodology to fit this particular set of health claims were made by the Tufts-NEMC EPC in consultation with AHRQ and the FDA.

Health Claim Review

The review team included a nutritionist, an endocrinologist, in addition to EPC staff, all of whom have experience in systematic reviews. The EPC worked in consultation with AHRQ and FDA representatives to clarify issues related to the proposed health claims, the populations, conditions, and outcomes of interest, and the relevant study designs needed to assess the health claims.

Table 1a. Definitions of Metabolic Syndrome or Insulin Resistance Syndrome

ATP III 2001{2001 1005 /id} (Metabolic Syndrome)	**WHO 1999{1999 1008 /id}** (Insulin Resistance)	**AACE 2003**{Einhorn, 2003 1007 /id} (Insulin Resistance Syndrome)
3 of: • Abdominal obesity (Waist circumference) o Men: > 40 in (102 cm) o Women: > 35 in (88 cm) • Tg ≥ 150 mg/dL • HDL o Men: < 40 mg/dL (1.0 mmol/L) o Women: < 50 mg/dL (1.3 mmol/L) • BP ≥ 130/85 mm Hg • FBS ≥ 110 mg/dL (6.1 mmol/L)	**1 of:** • Type 2 DM • Impaired fasting glucose • Impaired glucose tolerance • FBS < 110 mg/dL (6.1 mmol/L), **but** glucose uptake < lowest quartile for background population under investigation under hyperinsulinemic, euglycemic conditions **PLUS 2 of:** • BP ≥ 140/90 and/or antihypertensive medication • Tg ≥ 150 mg/dL (1.7 mmol/L) • HDL o Men: < 35 mg/dL (0.9 mmol/L) o Women: < 39 mg/dL (1.0 mmol/L) • BMI and/or Waist:Hip ratio o Men: 30 kg/m^2 and/or > 0.9 o Women: 30 kg/m^2 and/or > 0.85 • Urinary albumin excretion rate ≥ 20 mcg/min or Albumin:Creatinine ratio ≥ 30 mg/g	**2 of:** • Tg ≥ 150 mg/dL (1.69 mmol/L) • HDL: Men: < 40 mg/dL (1.04 mmol/L) Women: < 50 mg/dL (1.29 mmol/L) • BP >= 130/85 mm Hg • 2-hr post-glucose challenge 140-200 mg/dL (7.8-11.1 mmol/L) • FBS 110-125 mg/dL (6.1-6.9 mmol/L) **PLUS other risk factors, including** • Cardiovascular disease • Hypertension • Polycystic ovary syndrome • Non-alcoholic fatty liver disease • Acanthosis nigricans • Family history of: Type 2 DM, Hypertension, or Cardiovascular Disease • History of Gestational Diabetes or Glucose Intolerance • Non-Caucasian • Sedentary lifestyle • BMI > 25.0 kg/m^2 • Waist circumference o Men: > 40 in (102 cm) o Women: > 35 in (88 cm) • Age > 40 years

BMI = body mass index, BP = blood pressure, DM = diabetes mellitus, FBS = fasting blood sugar, HDL = high density lipoprotein, Tg = triglycerides.

Table 1b. Definition of Glucose Intolerance and Diabetes by American Diabetes Association (ADA), 1997/2003{Genuth, 2003 1006 /id}

Glucose Intolerance	Diabetes Mellitus [c]
Impaired Fasting Glucose FBS[a] ≥ 100 mg/dL (5.6 mmol/L) *and* < 125 mg/dL (6.9 mmol/L) **Impaired Glucose Tolerance** 2-hour OGTT[b] Glucose ≥ 140 mg/dL (7.8 mmol/L) *and* < 200 mg/dL (11.1 mmol/L)	• Classical symptoms of diabetes [d] *and* Random glucose (casual plasma glucose)[e] ≥ 200 mg/dL (11.1 mmol/L) ***or*** • FBS[a] ≥ 126 mg/dL (7.0 mmol/L) ***or*** • 2-hour OGTT[b] Glucose ≥ 200 mg/dL (11.1 mmol/L)

1 mmol/L glucose = 18.018 mg/dL (multiply mg/dL by 18.018 or divide mmol/L by 0.0555).

[a] FBS, fasting blood sugar (glucose), is defined as no consumption of food or beverage (other than water) for at least 8 hours.

[b] 2-hour OGTT, oral glucose tolerance test, is 2 hour post-load glucose during a 75-gram OGTT.

[c] Diagnosis of diabetes must be confirmed by repeating any of the tests on a different day.

[d] Classic symptoms of diabetes include: polyuria, polydipsia, and unexplained weight loss.

[e] Random/Casual is defined as anytime of the day without regard to time since last meal.

Glucose Metabolism

Each of the proposed health claims either suggests that chromium improves glucose homeostasis, including insulin sensitivity, or that chromium reduces the risk of organ damage caused by hyperglycemia or insulin resistance. To assist the classification of studies for specific health claims, we sought common definitions of glucose intolerance and insulin resistance in the medical literature. We identified 2 consensus statements regarding definitions of glucose intolerance and diabetes and 3 consensus statements regarding insulin resistance (Tables 1a and 1b):

- Glucose Intolerance, as defined by the American Diabetes Association (ADA) {Genuth, 2003 1006 /id} and the World Health Organization (WHO) 1999 report{1999 1008 /id}
- Diabetes mellitus, as defined by the ADA {Genuth, 2003 1006 /id} and WHO{1999 1008 /id}
- Metabolic syndrome, as defined by the National Cholesterol Education Program's Adult Treatment Panel (ATP) III {2001 1005 /id}
- Insulin resistance, as defined by the World Health Organization (WHO){1999 1008 /id}
- Insulin resistance syndrome, as defined by the American Association of Clinical Endocrinologists (AACE){Einhorn, 2003 1007 /id}

The lack of a uniform definition for the insulin resistance syndrome (metabolic syndrome) highlights the uncertainties regarding the current understanding of the syndrome. All definitions include an abnormal blood glucose component (either fasting or 2 hours after an oral glucose tolerance test [OGTT]), although different thresholds are chosen. Other components used by some consensus groups include various measures of obesity/overweight, triglycerides (Tg), high density lipoprotein (HDL), blood pressure (BP), urinary albumin excretion rate, and other risk factors.

After reviewing the available definitions of glucose intolerance/diabetes and insulin resistance, we established the following definitions. Studies were classified as healthy population, glucose intolerance (impaired fasting glucose or impaired glucose tolerance), insulin resistance, or type 2 diabetes based either on explicit classification by the study authors or by mean values at baseline of diagnostic variables used by any of the consensus definitions. Thus studies whose eligibility criteria included diabetes were classified as studies of subjects with diabetes. Studies that reported that the mean baseline fasting blood glucose was greater than 100 mg/dL but less than 125 mg/dL were classified as impaired fasting glucose. Studies with abnormal mean baseline Tg or HDL were examined to determine whether they could be classified as insulin resistance if they met additional criteria as shown in Table 1a. Studies with subjects with normal mean baseline glucose and other relevant parameters were classified as healthy. Studies of obese subjects with otherwise normal parameters were also classified as healthy.

Literature Search

FDA provided the Tufts-NEMC EPC with articles which had been submitted by the petitioner. To supplement these articles, the EPC performed an independent search of the literature.

We searched both MEDLINE and Commonwealth Agricultural Bureau (CAB) Abstracts for literature on chromium and factors related to glucose metabolism. Table 2 contains the search strategy used. Articles were limited to English (in both databases) and Human studies (in

MEDLINE). Case reports, general reviews, editorials, and other non-primary studies were excluded (in MEDLINE). Additional studies were found in reference lists of reviewed articles and by members of the EPC. All available studies were included – from 1966 in MEDLINE and from 1971 in CAB Abstracts – through the date of the final search, June 24, 2004.

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Table 2. MEDLINE and CAB Abstracts search strategy and results

#	Search History	Results
1	chromium.mp.	24629
2	exp diabetes mellitus	172528
3	diabet$.mp.	231831
4	blood sugar$.tw.	12545
5	exp hyperglycemia	13072
6	glycohemoglobin.mp.	446
7	glucose.mp.	316819
8	(HbA1c or Hb A1c or Hgb A1c).tw.	4735
9	(hemoglobin A1c or hemoglobinA1c).tw.	1159
10	metabolic syndrome.mp.	2315
11	exp insulin resistance	14005
12	homa.tw.	859
13	homeostasis assessment.tw.	29
14	or/2-13	493615
15	1 and 14	1369
16	limit 15 to human [Limit not valid in: CAB Abs; records were retained]	980
17	limit 16 to English language	864
18	limit 17 to (addresses or bibliography or biography or case reports or congresses or consensus development conference or consensus development conference, nih or dictionary or directory or editorial or festschrift or government publications or interview or lectures or legal cases or legislation or news or newspaper article or patient education handout or periodical index or "review" or review, academic or "review literature" or review, multicase or "review of reported cases" or review, tutorial) [MEDLINE only]	124
19	17 not 18 Ovid MEDLINE <1966 to July Week 4 2004> (351) CAB Abstracts <1973 to June 2004> (389)	740
20	remove duplicates from 19 Ovid MEDLINE <1966 to July Week 4 2004> (351) CAB Abstracts <1973 to June 2004> (313)	**664**

Study Selection

All abstracts identified through the literature search were reviewed. At this stage, eligibility criteria were broadly defined to include all English language primary experimental or observational studies that evaluated any source of chromium in at least 5 human subjects, irrespective of the study outcomes or the study eligibility criteria reported in the abstracts.

Articles that passed the abstract screening process were retrieved. The retrieved articles and articles submitted to FDA by Nutrition 21, Inc. were reviewed for eligibility. Articles were rejected during this round based on the following criteria: review articles, non-Human studies, fewer than 5 subjects in the chromium treatment arm(s). Of the remaining articles, only those that met the following eligibility criteria were included:

- Prospective intervention study (retrospective observational studies were excluded);
- Intervention consisted of chromium only (studies of combination supplements with more than one potentially active ingredients were excluded, i.e., if the study did not include a chromium-only arm).

Eligible study populations and outcomes addressed 1 of the 8 proposed health claims, in consultation with FDA and AHRQ:

- Studies of healthy subjects without diabetes were analyzed for health claims 1, 3, and 5.
- Studies of subjects with evidence of glucose intolerance or insulin resistance (but not diabetes) were analyzed for all health claims except 6.
- Studies of subjects with type 2 diabetes were analyzed for health claims 4, 6, 7 and 8.

Table 3a shows how each of the 8 health claims is categorized based on study population and outcomes. Table 3b shows the number of studies that report data relevant for each of the 8 health claims.

In keeping with the regulating statute that food-related health claims are not allowed for disease treatment, we did not include analyses of the effect of chromium on glucose control in patients with type 2 diabetes. We also did not include any studies of patients with type 1 diabetes. We applied the following criteria for outcome measurements to categorize studies for specific health claims:

- Studies with measures of insulin resistance were analyzed for health claim 1. As discussed under *Relevant Measures of Glucose Metabolism and Insulin Resistance*, measures of insulin alone were not considered adequate measures of insulin resistance.
- Studies with measures of glucose metabolism were analyzed for health claims 3 and 5.
- Studies with cardiovascular disease clinical outcomes or cardiovascular risk factors were eligible for health claims 2, 4, and 6. As per the National Institutes of Health, we included only total cholesterol, HDL, low density lipoprotein (LDL), Tg, and blood pressure as cardiovascular risk factors.
- Studies with retinopathy or measures of kidney function were analyzed for health claims 7 and 8, respectively.

Studies were eligible for consideration regarding a given health claim only if the study had both an appropriate population and appropriate outcomes. We accepted controlled and uncontrolled studies, and randomized and non-randomized studies. After consultation with AHRQ and FDA we also accepted published letters that met inclusion criteria; however, we did

not include abstracts or conference proceedings. Studies could be of any duration. Any dose or formulation of chromium was accepted.

Included studies are listed in Appendix 1. In summary and evidence tables, studies are listed by author and year. Refer to Appendix 1 for complete study references.

Table 3a. Health claims 1 to 8 categorized by study population and outcome.

Outcomes	Population		
	Normal	Insulin Resistance	Diabetes
Insulin Resistance	1	1	
Glucose Metabolism	3, 5	3, 5	
CVD & CVD Risk Factors		2, 4	4, 6
Retinopathy		7	7
Kidney Disease		8	8

Table 3b. Health claims, populations, outcomes, and number of studies for each claim.

Health Claim #	Health Claim	Population	Outcome	# of Studies	
				CP	Other*
1	CP may reduce the risk of insulin resistance.	• Normal Glucose Tolerance • Glucose Intolerance	Measures of insulin resistance	2	4
2	CP may reduce the risk of CVD when caused by insulin resistance	• Insulin Resistance (not just elevated glucose [4]**) • Abnormal CVD RF	CVD & CVD risk factors	1	2
3	CP may reduce the risk of abnormally elevated blood sugar levels	• Normal Glucose Tolerance • Glucose Intolerance	Glucose	6	21
4	CP may reduce the risk of CVD when caused by abnormally elevated blood sugar levels	• Elevated Glucose (not specifically insulin resistance [2]** or DM [6]**) • Abnormal CVD RF	CVD & CVD risk factors	0	2
5	CP may reduce the risk of Type 2 DM	• Normal Glucose Tolerance • Glucose Intolerance	Incident Type 2 DM	0	0
6	CP may reduce the risk of CVD when caused by Type 2 DM	• DM 2 • Abnormal CVD RF	CVD & CVD risk factors	4	8
7	CP may reduce the risk of retinopathy when caused by abnormally high blood sugar levels	• Glucose Intolerance • DM 2	Retinopathy	0	0
8	CP may reduce the risk of kidney disease when caused by abnormally high blood sugar levels	• Glucose Intolerance • DM 2	Kidney disease	1	0

CP = chromium picolinate; CVD = cardiovascular disease; DM = diabetes.

* Other = chromium chloride, chromium nicotinate (niacin, glucose tolerance factor), and brewer's yeast.

** Number in brackets refers to health claims.

Relevant Measures of Glucose Metabolism and Insulin Resistance

For the purpose of determining which studies are eligible for inclusion regarding health claims specific to insulin resistance and abnormal glucose levels, both the mean insulin resistance measures or glucose measures at baseline and the author's definitions were considered. Thus, if a study of purportedly healthy individuals had an abnormally high mean fasting blood glucose the study was classified as a study of subjects with elevated glucose. Also, if a study analyzed a subset of subjects reported to have insulin resistance that subset of subjects is included in the analysis of studies of insulin resistance.

To assess eligibility of studies that are relevant to health claims specific to insulin resistance (health claims 1 and 2), we used either a clinical definition of insulin resistance (any of the 3 available definitions shown in Table 1) or a laboratory measurement of insulin resistance, as described below.{Radziuk, 2000 1010 /id} A study that presented data on any one of the following widely accepted laboratory measurements of insulin sensitivity was eligible to enter into our analysis for health claims 1 and 2:

- Hyperinsulinemic Euglycemic or Hyperinsulinemic Hyperglycemic Clamp.
  The clamp is often referred to the gold standard in the measurement of insulin sensitivity. It is conceptually simple but technically difficult.
- Insulin Modified Intravenous Glucose Tolerance Test (IVGTT).
  This test has been validated against the hyperinsulinemic euglycemic clamp. A computer package is used to estimate indices of glucose-insulin dynamics including insulin sensitivity from glucose and insulin measurements..
- Insulin/Glucose Ratio from Fasting Values.
  This is an excellent simple test in patients with normal glucose tolerance or impaired glucose tolerance but is not accurate in patients with diabetes.
- HOmeostasis Model Assessment (HOMA).
  Calculated as

  $$\text{Fasting Insulin} \times \text{Fasting Glucose} \div 22.5$$

  This test has been validated against the hyperinsulinemic euglycemic clamp.{Matthews, 1985 1011 /id}
- QUantitative Insulin sensitivity ChecK Index (QUICKI).
  Calculated as

  $$1/[\log(\text{Insulin}) + \log(\text{Glucose})]$$

  This test has been developed in non-obese, obese and type 2 diabetes patients and validated against the hyperinsulinemic euglycemic clamp.
- Oral Glucose Tolerance Test (OGTT)-Related Measures.
  If an OGTT is done, then additional measurements can be used, most of them are ratios between insulin and glucose levels (or areas under the curve).

Data Extraction Process

The data from each evaluated study was extracted by one reviewer directly into the evidence tables (which are described below, under *Reporting Results*). The data in the evidence tables were checked by at least one other reviewer. All tables were reviewed in conference by all reviewers. The evidence tables are listed alphabetically by first author in Appendix 2. Based on the data in the evidence tables, each article was categorized in conference to one or more of the health claims.

Reporting Results

The data from each study are included in evidence tables that provide detailed study data, summary tables that provide the most pertinent data, summary matrices that provide a succinct overview of the data for each health claim, and descriptively in the text.

Evidence Tables

The evidence tables describe the study characteristics, study design, eligibility criteria, chromium intervention and control, concomitant treatments and comorbidities, the outcomes of interest, and the results. In addition, baseline factors that are used by the various consensus statements to define disorders of glucose and insulin metabolism are reported under "Insulin Resistance Criteria." The population of each study is described, as determined by the eligibility criteria and the Insulin Resistance Criteria. Taking all the factors into consideration, each study is assigned a quality grade, as described below under *Grading Evidence*.

The following results are reported in the evidence tables: mean baseline and final values and 95% confidence intervals (CI), the within-cohort changes between baseline and final values and their associated 95% CIs and *P*-values, and the net changes and their associated 95% CIs and *P*-values. The net change is the difference between the within-cohort change for the chromium cohort and the within-cohort change for the control cohort, or

$$\text{Net change} = [\text{Chromium}_{\text{Final}} - \text{Chromium}_{\text{Base}}] - [\text{Control}_{\text{Final}} - \text{Control}_{\text{Base}}].$$

The 95% CIs were calculated from reported standard deviations (SD) or standard errors (SE), when necessary. The 95% CIs for the within-cohort and net changes are calculated only from reported variances for those values. No estimates of SEs were calculated or used to estimate 95% CIs. All *P*-values are those reported in article tables or text; none was calculated from other data in the articles. The evidence tables maintain the units reported in the articles. When non-standard units were reported (eg, mmol/L) the same value in standard units (eg, mg/dL) are included for the baseline mean values.

Evidence Table Abbreviations

The following are the common abbreviations used across evidence tables:

95% CI = 95% confidence interval; BP = blood pressure; Cr = chromium; DM = diabetes mellitus; FBS = fasting blood sugar (glucose); HDL = high density lipoprotein; LDL = low density lipoprotein; mo = month(s); ND = no data; NS = not statistically significant ($P>0.05$); OGTT = oral glucose tolerance test; P Btw = *P*-value of net change (between cohorts) of mean outcome level; P W/in = *P*-value of within-cohort change from baseline of mean outcome level; SD = standard deviation; SE = standard error; Tg = triglycerides; UAER = urine albumin excretion rate; UI = MEDLINE unique identifier; Waist circ = waist circumference; wk = week(s); yr = years.

Summary Tables

For each health claim, all relevant studies are summarized in Summary Tables. These tables were developed by condensing information from the evidence tables and are designed to facilitate comparisons and synthesis across studies. Summary tables include information regarding study design, study size, intervention and control, study population, outcome measures, results, and methodological quality. Both the within-chromium-cohort and net (between-cohort) changes and their associated *P*-values are reported. All results are reported in standard units. Because the health claims are specific to chromium picolinate but FDA is

interested in the evidence for all chromium products, separate summary tables are presented for chromium picolinate and all other chromium products. Within the summary tables, controlled trials are presented first, followed by non-controlled trials. Within each of these sections, articles are ordered first by study quality from A to C (see below, under *Grading Evidence*), then by total number of subjects taking chromium analyzed from largest to smallest, then alphabetically by first author. Summary tables that include multiple outcomes (eg, glucose metabolism) are an exception in that first they order studies by specific outcome. A study with multiple outcomes may be presented multiple times both across tables and within tables.

Summary Table Abbreviations

The following are the common abbreviations used across summary tables: Base (Cr) = baseline mean value of outcome for the chromium cohort; Br Yeast = brewer's yeast; Cr Nic = chromium nicotinate; $CrCl_3$ = chromium chloride; Gluc Intol = glucose intolerance; *P* (Net Δ) =*P*-value of net change of mean outcome level; Ins Res = insulin resistance; mo = month(s); N = number of subjects; nd = no data; Net Δ = net change of mean outcome level, as described above; NS = not statistically significant (*P*>0.05); *P* (Δ Cr) = *P*-value of within-chromium cohort change of mean outcome level from baseline; Tor Yeast = torula yeast; wk =week(s); Δ (Cr) = within-chromium cohort change of mean outcome level from baseline.

Quality Grading of Evidence

Studies accepted in evidence reports have been designed, conducted , analyzed, and reported with various degrees of methodological rigor and completeness. Deficiencies in any of these processes may lead to biased results. To assess the quality of the studies, and thus to provide readers with an additional means to interpret the value of the evidence, we have applied a 3-category grading system (A, B, C) to each trial. This scheme defines a generic grading system for study quality that is applicable to each type of study design:

- A — Least bias; results are valid. A study that mostly adheres to the commonly held concepts of high quality, including the following: a formal randomized study; clear description of the population, setting, interventions and comparison groups; appropriate measurement of outcomes; appropriate statistical and analytic methods and reporting; no reporting errors; less than 20% dropout; clear reporting of dropouts; and no obvious bias.
- B — Susceptible to some bias, but not sufficient to invalidate the results. A study that does not meet all the criteria in category A. It has some deficiencies but none likely to cause major bias. Study may be missing information making assessment of the limitations and potential problems difficult.
- C — Significant bias that may invalidate the results. A study with serious errors in design, analysis, or reporting. These studies may have large amounts of missing information or discrepancies in reporting. All non-controlled studies are given this grade.

Summary Matrices

To provide a clear summary of the overall body of evidence regarding each health claim, we created summary matrices, which succinctly present all studies with data for each health claim categorized by chromium supplement type (picolinate vs. other), population (normal, insulin resistant, hyperglycemic, and type 2 DM), and study quality. Because both controlled and non-controlled studies were evaluated, for clarity, quality C controlled studies (C) are separated from quality C non-controlled (NC) studies. The number of subjects taking chromium supplementation and effects are presented. When necessary, separate effects are presented for different specific outcomes (such as CVD events, lipids, and blood pressure).

The effect for each study outcomes is categorized by the following criteria:

- ++ A statistically significant improvement where $P < 0.01$.
- \+ A statistically significant improvement where $P < 0.05$.
- 0 A non-significant effect.
- — A statistically significant worsening where $P < 0.05$.
- ? A difficult-to-interpret result *or* where statistical significance is not reported.

Footnotes are provided when within-chromium-arm changes are statistically significant but no data are provided regarding significance compared to control (for controlled studies).

Assignment of Overall Grade

The topic experts assigned each proposed health claim an overall grade based on the interpretation of the overall quantity of the evidence. The determination was based on magnitude of effect, consistency across studies, number of studies, and total number of subjects. Uncontrolled studies were not considered in assignment of overall grades. The following system was used:

- A High level of comfort with validity of health claim based on high quality studies of relevant population. Significant scientific agreement in high quality studies of relevant population that health claim is valid.
- B Good to moderate level of comfort with validity of health claim based on high quality studies of relevant population.
- C Low level of comfort with validity of health claim based on either moderate quality studies or studies of moderately applicable populations.
- D Extremely low level of comfort with validity of health claim due to either poor quality of studies or limited applicability of study populations.
- F Claim is unlikely to be valid based on at least moderate quality studies in relevant population of *no effect*.
- I Little or no credible evidence for the intended population, insufficient to determine the validity of the claim.

Results

Chromium Trials for Health Claim 1

"Chromium picolinate may reduce the risk of insulin resistance."

Overall assessment and grade

Chromium Picolinate

Two studies with 24 non-diabetic subjects total taking chromium picolinate evaluated insulin resistance. One study found no effect and the other found a significant increase (improvement) in insulin sensitivity with chromium picolinate compared to control.

The evidence was judged to be insufficient to assign an overall grade.

Overall Grade: I

Other Chromium Products

Four poor-quality studies with 49 non-diabetic subjects total taking other chromium products evaluated insulin resistance. Overall, no effect on insulin resistance was found.

The evidence was judged to be insufficient to assign an overall grade.

Overall Grade: I

Summary

Six studies evaluated measures of insulin resistance in subjects without diabetes. Among these, 2 RCTs evaluated chromium picolinate in healthy subjects. Four studies evaluated chromium chloride or brewer's yeast, including 2 RCTs, 1 non-randomized controlled trial, and 1 uncontrolled cohort study. Among these, 1 RCT and the cohort study also evaluated brewer's yeast. Overall, 1 study was of fair quality and 5 were of poor quality (1 of which was non-controlled).

Chromium picolinate trials (Tables 4, 5, & 8)

One of the 2 studies of chromium picolinate was of fair quality, one was of poor quality. Both used Bergman's method for IVGTT to measure insulin sensitivity in subjects with normal glucose metabolism; Amato 2000 also measured glucose effectiveness. Although Cefalu 1999 had a large difference in baseline insulin sensitivity between the chromium and the control subjects (2.5 vs. 3.1 min^{-1} μU^{-1} mL), this difference was not statistically significant. They reported a significant improvement (increase) in insulin sensitivity at both 4 and 8 months among those taking chromium picolinate compared to control. Amato 2000 found no significant change in insulin sensitivity or glucose effectiveness.

Other chromium trials (Tables 6, 7, & 8)

All 4 studies of chromium chloride and brewer's yeast were of poor quality. One of the RCTs did not report data (Offenbacher 1985); the other analyzed only the 14 of 23 subjects who agreed to an OGTT and included 1 subject with NIDDM (Riales 1981). Wang 1989 was not randomized

and Potter 1985 did not include a control group. No study found a significant effect on insulin sensitivity; although Riales 1981 did find an improvement (21% reduction) in the ratio of the sum of insulin values to the sum of glucose values. The apparent net reduction of insulin to glucose ratio in Wang 1989 was due to an increase in the ratio in the control group; the ratio was unchanged in the chromium group. Potter 1985 reported a non-significant worsening (11% reduction) in tissue sensitivity to insulin in a single cohort of subjects taking chromium chloride. Overall, no improvement in insulin resistance was found with chromium supplementation.

Table 4. Trials of Chromium Picolinate on Insulin Sensitivity (Health Claim 1)

Author, Year	Duration	Chromium N	Chromium µg/d	Control N	Control Source	Units Reported	Insulin Sensitivity Base (Cr)	Δ (Cr)	*P* (Δ Cr)	Net Δ	*P* (Net Δ)	Quality	Population
Randomized Controlled Trials													
Amato, 2000	8 wk	9	1000	10	Placebo	min/µU mL ($x10^{-4}$)	3.0	0	NS	-0.3	nd	B	Normal
Cefalu, 1999	32 wk	15	1000	14	Placebo	min^{-1} $µU^{-1}$ mL	2.5 [a]	+1.4	nd	+1.8	<.005	C	Normal (high risk)

[a] Large though statistically non-significant difference in baseline values between Cr and placebo group (3.1 min^{-1} $µU^{-1}$ mL). Results estimated from graph.

Table 5. Trials of Chromium Picolinate on Glucose Effectiveness (Health Claim 1)

Author, Year	Duration	Chromium N	Chromium µg/d	Control N	Control Source	Glucose effectiveness (min^{-1}) Base (Cr)	Δ (Cr)	*P* (Δ Cr)	Net Δ	*P* (Net Δ)	Quality	Population
Randomized Controlled Trials												
Amato, 2000	8 wk	9	1000	10	Placebo	0.02	0	NS	+0.02	nd	B	Normal

Table 6. Trials of Other Chromium Products on Insulin:Glucose Ratio (Health Claim 1)

Author, Year	Outcome	Duration	Chromium Type	Chromium N	Chromium µg/d	Control N	Control Source	Insulin:Glucose Ratio Base (Cr)	Δ (Cr)	*P* (Δ Cr)	Net Δ	*P* (Net Δ)	Quality	Population
Randomized Controlled Trials														
Wang, 1989	Insulin:Glucose	12 wk	$CrCl_3$	10	50	10	Lactose	0.13	0%	NS	-20%	NS	C	Normal
			Br Yeast	10	15			0.16	0%	NS	-20%	NS		
Offenbacher, 1985	Insulin:Glucose	10 wk	$CrCl_3$	8	200	7	Lactose	"After supplementation, the ratio of insulin to glucose was lower in the brewer's yeast and $CrCl_3$ groups, but these differences were not significant."				NS	C	Normal
			Br Yeast	8	5									
Riales, 1981	Sum Insulin: Sum Glucose	12 wk	$CrCl_3$	8	200	6	Water	2.54	-18%	NS	-21%	nd	C	Normal

Table 7. Trials of Other Chromium Products on Tissue Sensitivity to Insulin (Health Claim 1)

Author, Year	Duration	Chromium Type	Chromium N	Chromium µg/d	Control N	Control Source	Tissue sensitivity to insulin (µU/mL) Base (Cr)	Δ (Cr)	*P* (Δ Cr)	Net Δ	*P* (Net Δ)	Quality	Population
Non-Controlled Trials													
Potter, 1985	12 wks	$CrCl_3$	5	200	--	--	5.5	-0.6	NS	--	--	C	Gluc Intol

Table 8. Summary Findings for Health Claim 1 (Effect on insulin resistance)

Quality	Chromium Picolinate						Other Chromium Products					
	Normal			Insulin Resistant			Normal			Insulin Resistant		
	Study	N	Effect	Study	N	Effect	Study	N	Effect	Study	N	Effect
A												
B	Amato, 2000	9	0									
C	Cefalu, 1999	15	++				Wang, 1989 Offenbacher, 1985 Riales, 1981	20 16 8	0 0 0			
NC							Potter, 1985	5	0			

NC = No control group. Rated C in Evidence and Summary Tables.
N = number of subjects taking chromium supplement.

Chromium Trials for Health Claim 2

"Chromium picolinate may reduce the risk of cardiovascular disease when caused by insulin resistance."

Overall assessment and grade

Chromium Picolinate

One non-controlled study with 10 subjects with possible insulin resistance taking chromium picolinate evaluated cardiovascular risk factors and found no effect. No study evaluated cardiovascular disease.

The evidence was judged to be insufficient to assign an overall grade.

Overall Grade: I

Other Chromium Products

Two non-controlled studies of 11 subjects total with possible insulin resistance taking other chromium products evaluated cardiovascular risk factors and found no effect. No study evaluated cardiovascular disease.

The evidence was judged to be insufficient to assign an overall grade.

Overall Grade: I

Summary

Three studies evaluated the effect of chromium supplements on cardiovascular risk factors in subjects with baseline evidence of insulin resistance. All 3 were non-controlled and, therefore, of poor quality. One trial evaluated chromium picolinate; two evaluated other chromium products, including chromium chloride and nicotinate. No study examined the risk of cardiovascular events or incident disease.

Chromium picolinate trials (Tables 9 & 11)

The study of chromium picolinate included obese subjects. According to the baseline data, we determined that Kato 1998 included subjects with insulin resistance. They examined total cholesterol and HDL; The study found no significant changes from baseline.

Other chromium trials (Table 10 & 11)

One non-controlled trial of chromium chloride 200 μg evaluated cardiovascular risk factors in subjects with insulin resistance. Insulin resistance was based on mean baseline data. Potter 1995 found no change in total cholesterol and LDL, but both HDL and triglycerides non-significantly worsened. The second trial tested chromium nicotinate 220 μg. In a sub-analysis of subjects with abnormally elevated fasting insulin, Wilson 1995 found consistent, though non-significant worsening of lipid and triglyceride levels after 90 days.

Table 9. Trials of Chromium Picolinate on Cardiovascular Disease Risk Factors (Health Claim 2)

Author, Year	Outcome	Duration	Chromium N	Chromium µg/d	Control N	Control Source	Results (mg/dL or %) Base (Cr)	Δ (Cr)	*P* (Δ Cr)	Net Δ	*P* (Net Δ)	Quality	Population
Non-Controlled Trials													
Kato, 1998	HDL	8 wk	10	400	--	--	45	+1	NS	--	--	C	Gluc Intol
	Cholesterol						247	-9	NS				

Chol:HDL = total cholesterol to HDL ratio

Table 10. Trials of Other Chromium Products on Cardiovascular Disease Risk Factors (Health Claim 2)

Author, Year	Outcome	Duration	Chromium Type	Chromium N	Chromium µg/d	Control N	Control Source	Results (mg/dL) Base (Cr)	Δ (Cr)	*P* (Δ Cr)	Net Δ	*P* (Net Δ)	Quality	Population
Non-Controlled Trials														
Potter, 1985	LDL	12 wk	$CrCl_3$	5	200	--	--	147	-7	NS	--	--	C	Gluc Intol
	HDL							51	-5	NS				
	Cholesterol							221	-9	NS				
	Triglycerides							112	+14	NS				
Wilson, 1995	LDL	90 days	Cr Nic	6	220	--	--	112	+23	NS	--	--	C	Ins Res
	HDL							58	-4	NS				
	Cholesterol							189	+19	NS				
	Triglycerides							71	+35	NS				
	Chol:HDL							3.6	+31%	NS				

Table 11. Summary Findings for Health Claim 2 (Effect on CVD caused by insulin resistance)

Quality	Chromium Picolinate Insulin Resistant Study	N	Effect CVD	LDL	HDL	TC	Tg	BP	Other Chromium Products Insulin Resistant Study	N	Effect CVD	LDL	HDL	TC	Tg	BP
A																
B																
C																
NC	Kato, 1998	10			0	0			Potter, 1985	5		0	0	0	0	
									Wilson, 1995	6		0	0	0	0	

NC = No control group. Rated C in Evidence and Summary Tables.
N = number of subjects taking chromium supplement.
CVD = cardiovascular event; LDL = low density lipoprotein; HDL = high density lipoprotein; TC = total cholesterol; Tg = triglycerides; BP = blood pressure.

Chromium Trials for Health Claim 3

"Chromium picolinate may reduce abnormally elevated blood sugar levels."

Overall assessment and grade

Chromium Picolinate

Six studies evaluated the effect of chromium picolinate on glucose measurements in about 95 total non-diabetic subjects. Two fair-quality studies found no effect or a possible worsening of glucose level; however, only 1 of these studies included subjects with elevated baseline blood glucose levels. The remaining 4 studies were of poor quality and also generally found no effect. No dose effect was evident across studies.

The evidence was judged to be insufficient to assign an overall grade.

Overall Grade: I

Other Chromium Products

Eleven small fair-quality studies and 12 poor-quality studies were generally consistent in finding no effect on glucose levels of supplementation with other chromium products in about 349 total non-diabetic subjects. The 4 studies of subjects with baseline abnormal blood glucose levels also generally found no effect of chromium. No dose or source effect was evident across or within studies.

Despite a few small, generally poor-quality studies showing an improvement in glucose with chromium, the preponderance of the evidence indicates that other chromium products have no effect on glucose levels in non-diabetics.

Overall Grade: F

Summary

Twenty-six studies evaluated glucose metabolism in subjects without diabetes. Among these, 6 evaluated chromium picolinate, including 4 RCTs, 1 non-randomized controlled trial, and 1 uncontrolled cohort study. One of the RCTs (Grant 1997) included an intervention (chromium without exercise) that did not have an equivalent control; this was treated as a non-controlled trial. Twenty-one studies evaluated other chromium products (1 study compared chromium picolinate to chromium nicotinate), of which 9 RCTs, 1 non-randomized controlled trial, and 2 uncontrolled cohort studies used chromium chloride; 4 RCTs used chromium nicotinate; 4 RCTs, 2 non-randomized controlled trials (no data on randomization in 1), and 2 cohort studies used brewer's yeast. Overall, 12 studies were of fair quality and 14 studies were of poor quality (4 of which were non-controlled); 1 of the fair quality studies (Wilson 1995) also reported relevant data on a non-controlled subset of insulin resistant subjects.

Chromium picolinate trials (Tables 12, 13, & 16)

Of the 6 studies that evaluated chromium picolinate, 2 were of fair quality and 4 were of poor quality. Three out of the 4 RCTs as well as the non-randomized controlled trial, and the prospective cohort study examined the effect of chromium picolinate on fasting blood sugar (FBS). Their duration ranged from 9 to13 weeks. Sample sizes were generally small and did not exceed 44 participants in controlled trials while the cohort study recruited only 10 subjects. Chromium picolinate dosages

varied from 400 to 1000 μg/day. Only the RCT by Joseph 1999 and the uncontrolled trial (Kato 1998) included subjects who on average had abnormally elevated glucose levels (>100 mg/dL). No study specifically recruited subjects based on abnormal glucose levels. Based on baseline insulin resistance criteria, 2 studies evaluated subjects with either insulin resistance or glucose intolerance. The methodological quality of RCTs was fair or poor (grade B or C).

No study found a significant improvement (reduction) in FBS with chromium picolinate use. While the study by Grant 1997 found a net reduction in FBS of 5 mg/dL in the controlled intervention (chromium with exercise versus placebo with exercise), there was actually no effect within the cohort on chromium picolinate, but an increase in FBS in the control arm. The only statistically significant effect seen was a worsening (increase) in FBS in obese, inactive, non-diabetic subjects with baseline criteria indicating glucose intolerance by Joseph 1999; however, the subjects in the control arm had a similar increase in FBS.

Two RCTs reported results on 2-hour oral glucose tolerance test (OGTT) glucose levels, 2 RCTs reported glucose OGTT area under the curve (AUC) at 2 or 3 hours, and 1 RCT reported a sum of glucose measurements over a 24 hour period. Only the study by Joseph 1999 definitely included subjects with abnormal blood sugar at baseline. None of the results was statistically significant. Joseph 1999 reported a non-significant worsening of 3-hour AUC glucose.

In summary, 5 RCTs and 1 non-controlled trial found no reduction of glucose levels in subjects without diabetes. There is no evidence across studies of a dose effect.

Other chromium trials (Tables 14, 15, & 16)

Of the 21 studies of other chromium products, 10 were of fair quality and 11 were of poor quality (in addition to 1 fair-quality study that reported poor quality data on insulin resistant subjects). Sixteen RCTs, 1 non-randomized controlled trial, and 1 uncontrolled cohort study examined the effect of other chromium products on FBS. Their duration ranged from 5 to12 weeks. Sample sizes did not exceed 61 participants. Chromium dosages varied from 50 to 250 μg/day for chromium chloride, 200 to 800 μg/day for chromium nicotinate, and 5-15 μg/day for brewer's yeast. Urberg 1987 compared 200 μg/day chromium chloride to the same dose of a chromium chloride with nicotinate product. Only 4 of the studies (Abraham 1992, Lefavi 1993, Hermann 1998, Crawford 1999) had subjects taking chromium who on average had abnormally elevated FBS (>100 mg/dL). No study specifically recruited subjects with abnormal glucose metabolism (although Anderson 1991 categorized subjects by 90 minute OGTT glucose into high and low glucose). About two-thirds of the RCTs were of fair quality (grade B); the remainder were of poor quality (grade C).

Only Hermann 1998 reported a significant net improvement in FBS after supplementing 240 μg/day chromium chloride for 8 weeks; however, this finding was restricted to the 5 male subjects. Among all 8 subjects, no significant effect was found. Offenbacher 1980 found a significant 4% within-cohort improvement among 11 subjects who were taking only 10.8 μg/day of chromium from brewer's yeast for 8 weeks. The net change compared to torula yeast control was of the same magnitude and may have been statistically significant; however, this was not reported. The other significant within-cohort changes included worsening in FBS found by Li in 1992 and 1994 were not maintained after comparison to the control arms. A number of other studies reported non-significant improvements in FBS; however, a similar number of studies reported non-significant worsening of FBS. Among the 4 studies that reported

that subjects taking chromium had, on average, abnormally elevated FBS, none reported a significant improvement in FBS with any given dose of chromium. Overall, no beneficial effect of chromium products on FBS was found. No difference in effect due to chromium dose or source across studies or in the studies that directly compared different doses or sources was evident.

Nine RCTs and 1 non-controlled cohort reported results on 1, 1.5, or 2 hour OGTT glucose; 4 RCTs report 1 or 2 hour OGTT glucose AUC; 2 RCTs and 1 non-controlled study report sum of glucose measurements at 1.5 and 4 hours; and 1 non-controlled trial reported change in glycosylated hemoglobin. This latter study from 1984 did not employ the current standard measure of hemoglobin A_{1c}, but instead used the older measure that includes all types of glycosylated hemoglobins.

These studies ranged in duration from 3 days to 6 months; however, most were at least 8 weeks long. The study by Anderson 1983 included 76 subjects, but otherwise the largest study included 28 subjects. The chromium chloride studies were all of 200 μg/day, the chromium nicotinate (or chromium chloride with nicotinate) studies used dosages of 200, 400, or 800 μg/day; and the brewer's yeast studies ranged in dosage from 4 to 218 μg/day, although most used products with less than 15 μg/day and Gill 1981 did not report the dosage.

The standard OGTT glucose measurements at 2 hours (glucose level and AUC) were evaluated by 7 RCTs and 1 uncontrolled study. Of these, only Offenbacher 1980 and Urberg 1987 reported significant improvements in subjects taking chromium where there was no change in the control subjects. Other studies reported non-significant overall effects on 2-hour OGTT glucose. The 2 studies with subjects with glucose intolerance (Anderson 1991 subset and Potter 1985) found no change in 2-hour OGTT glucose measurements with chromium chloride.

Most of the studies that evaluated other glucose metabolism measurements reported either no change with chromium or incongruous results where the glucose measurements were reduced by much greater amounts in the control groups than the treatment groups. The Anderson 1991 study reported significantly lower end-of-study summed 90-minute and 4-hour OGTT glucose measurements with chromium chloride supplementation among subjects categorized as hyperglycemic based on a baseline OGTT (although the 2-hour OGTT glucose was unchanged). In contrast, there was no change in normal subjects. Lefavi 1993 reported a non-significant improvement of –15% in 1-hour OGTT glucose with 200 μg chromium nicotinate.

Although some studies reported a significant improvement in glucose levels with other chromium products, 2 studies reported worsened FBS with chromium chloride and most studies reported no significant change. Most studies reporting a beneficial effect were of poor quality or uncontrolled. Among the few studies with reported statistically significant effects, there was no consistent dose effect of chromium. Lefavi 1993 reported a larger improvement with 200 μg than 800 μg per day of chromium nicotinate, and Offenbacher 1980 reported among the largest improvements with only 10.9 μg per day of chromium from brewer's yeast.

Table 12. Trials of Chromium Picolinate on Fasting Blood Sugar (Health Claim 3)

Author, Year	Duration	Chromium N	Chromium µg/d	Control N	Control Source	Results (mg/dL) Base (Cr)	Δ (Cr)	*P* (Δ Cr)	Net Δ	*P* (Net Δ)	Quality	Population
Randomized Controlled Trials												
Volpe, 2001	12 wk	22	400	22	Placebo	91	-1	NS	-2	NS	B	Normal
Joseph, 1999	12 wk	17	924	15	Placebo	103	+5	<.05	-1	NS	B	Normal + Gluc Intol
Grant, 1997 [a]	9 wk	~11	400 [b]	~11	Placebo[b]	90	0	NS	-5	nd	C	Normal
Boyd, 1998 [c]	13 wk	9 [d]	1000	9 [d]	Placebo	88	-7	NS	+2	NS	C	Normal
Non-Controlled Trials												
Kato, 1998	8 wk	10	400	--	--	112	-4	NS			C	Gluc Intol + Ins Res
Grant, 1997 [a]	9 wk	~11	400 [e]	--	--	90	0	NS			C	Normal

[a] Study included 4 arms: CP with exercise; CP without exercise; chromium nicotinate with exercise; and placebo with exercise. The comparison of CP with exercise vs. placebo with exercise is included in Table 12 under randomized controlled trials. The treatment arm of CP without exercise does not have a corresponding (no exercise) placebo group and is therefore included in Table 12 under non-controlled trials. The comparison of chromium nicotinate with exercise vs. placebo with exercise is included in Table 14 under randomized controlled trials.

[b] With exercise; no data on how many subjects were randomized to each arm; estimates from graph.

[c] Non-randomized controlled trial

[d] Implied

[e] Without exercise

Table 13. Trials of Chromium Picolinate on Other Measures of Glucose Metabolism (Health Claim 3)

Author, Year	Outcome	Duration	Chromium N	Chromium µg/d	Control N	Control Source	Results (mg/dL or mg/dL hr) Base (Cr)	Δ (Cr)	*P* (Δ Cr)	Net Δ	*P* (Net Δ)	Quality	Population
Randomized Controlled Trials													
OGTT Single Time Point Measurement of Glucose													
Volpe, 2001	2 hr	12 wk	22	400	22	Placebo	88	-1	NS	+1	NS	B	Normal
Grant, 1997 [a]	2 hr	9 wk	~11	400[b]	~11	Placebo[b]	104	-9	NS	-11	nd	C	Normal
Area Under the Curve (AUC) of Glucose													
Grant, 1997	2 hr	9 wk	~11 ~11	400[a] 400[b]	~11	Placebo	"No significant difference among treatments" [c]				NS NS	C	Normal
Joseph, 1999	3 hr	12 wk	17	924	15	Placebo	4450	+396	NS	+649	NS	B	Normal + Gluc Intol
Sum of Measurements of Glucose at Different Time Points													
Cefalu, 1999	24 hr profile	32 wk	15	1000	14	Placebo	2625 [d]	+125 [c]	nd	0	NS	C	Normal
Non-Controlled Trials													
OGTT Single Time Point Measurement of Glucose													
Grant, 1997 [a]	2 hr	9 wk	~11	400 [e]	~11	Placebo	117	0	NS	-2	nd	C	Normal

OGTT: oral glucose tolerance test; AUC: area under the curve

[a] Study included 4 arms: CP with exercise; CP without exercise; chromium nicotinate with exercise; and placebo with exercise. The comparison of CP with exercise vs. placebo with exercise is included in Table 12 under randomized controlled trials. The treatment arm of CP without exercise does not have a corresponding (no exercise) placebo group and is therefore included in Table 12 under non-controlled trials. The comparison of chromium nicotinate with exercise vs. placebo with exercise is included in Table 14 under randomized controlled trials.

[b] With exercise; no data on how many subjects were randomized to each arm; estimates from graph.

[c] Across all study arms (see footnote a).

[d] Estimated from graph.

[e] Without exercise

Table 14. Trials of Other Chromium Products on Fasting Blood Sugar (Health Claim 3)

Author, Year	Duration	Chromium			Control		Results (mg/dL)					Quality	Population
		Type	N	µg/d	N	Source	Base (Cr)	Δ (Cr)	*P* (Δ Cr)	Net Δ	*P* (Net Δ)		
Randomized Controlled Trials													
Martinez, 1985	10 wk	$CrCl_3$	13[a]	200	8	Placebo	90	0	NS	-2	nd	B	Normal
		$CrCl_3$	15[b]	200	17	Placebo	89	+2	NS	+1	nd		
Abraham, 1992	11 mo	$CrCl_3$	27	250	24	Placebo	104	-1	NS	+6	NS	B	Gluc Intol
Lefavi, 1993	8 wk	Cr Nic	12	200	11	Placebo	102	-10	nd	-3	NS	B	Normal
		Cr Nic	11	800			98	-6	nd	+1	NS		
Offenbacher 1985	10 wk	Br Yeast	8	5	7	Lactose	95	0	NS	+3	nd	B	Normal
		$CrCl_3$	8	200			94	+6	NS	+9	nd		
Li, 1992	13 wk	Br Yeast	15	7	15	Tor Yeast	88	+11	<.001	-1	nd	B	Normal
Wilson, 1995	90 days	Cr Nic	15	220	11	Placebo	90	-3	nd	-2	NS	B	Normal
Offenbacher 1980	8 wk	Br Yeast	12	10.8	12	Tor Yeast	92	-4	<.05	-4	nd	B	Normal
Li, 1994	12 wk	Br Yeast	11	7	11	Tor Yeast	86	+5	<.01	-2	NS	B	Normal
Anderson, 1991	5 wk	$CrCl_3$	9	200	9	Placebo	88[c]	+2[c]	NS	+4[c]	NS[d]	B	Normal
		$CrCl_3$	8	200	8	Placebo	92[c]	+5[c]	NS	+2[c]	NS[d]		Gluc Intol
Hermann, 1998	8 wk	$CrCl_3$	8[e]	240	8	Lactose	105	-5	nd	-7	NS	B	Normal
		$CrCl_3$	3[f]	240	5	Lactose	126	-13	nd	-14	<.05		
		$CrCl_3$	5[g]	240	3	Lactose	99	-4	nd	-4	NS		
Anderson, 1983	3 mo	$CrCl_3$	76[e]	200	76	Placebo	nd	nd	nd	0	NS	C	Normal
		$CrCl_3$	48[f]	200	48	Placebo	nd	nd	nd	+1	NS		
		$CrCl_3$	28[g]	200	28	Placebo	nd	nd	nd	0	NS		
Wang, 1989[h]	12 wk	$CrCl_3$	10	50	10	Lactose	94	-2	NS	-4	NS	C	Normal
		Br Yeast	10	15			94	-4	NS	-6	NS		
Crawford, 1999	2 mo	Cr Nic	8	600	10	Placebo	102	-16	NS	-15	NS	C	Normal
Riales, 1981	12 wk	$CrCl_3$	8	200	6	Water	100[c]	-10[c]	NS	-6[c]	nd	C	Normal
Urberg, 1987	4 wk	$CrCl_3$	~5-6	200	~5-6	Nicotinic Acid	95	+5	NS	+6	nd	C	Normal
		$CrCl_3$+Nic	~5-6	200			96	-7	<.10	-6	nd		
Hermann, 1994	12 wk	$CrCl_3$	5	150	8	Placebo	92	-11	NS	-4	nd	C	Normal
Non-Controlled Trials													
Grant, 1997	9 wk	Cr Nic	~11[j]	400	--	--	95[c]	-5[c]	NS	--	--	C	Normal
Wilson, 1995	90 days	Cr Nic	6	220	--	--	88	-2	NS	--	--	C	Ins Res

[a] Subjects on no medications that potentially could affect glycemia.
[b] Subjects on medications that potentially could affect glycemia.
[c] Estimated from graph.
[d] Significance of difference between final values.
[e] Total
[f] Men
[g] Women
[h] Non-randomized, controlled trial.
[j] No data on how many subjects randomized to each arm.

Table 15. Trials of Other Chromium Products on Other Measures of Glucose Metabolism (Health Claim 3)

Author, Year	Out-come	Dura-tion	Chromium Type	Chromium N	Chromium µg/d	Control N	Control Source	Results (mg/dL or mg/dL h or %) Base (Cr)	Δ (Cr)	*P* (Δ Cr)	Net Δ	*P* (Net Δ)	Quality	Popu-lation
Randomized Controlled Trials														
OGTT Single Time Point Measurement of Glucose														
Lefavi, 1993	1 hr	8 wk	Cr Nic	12	200	11	Placebo	112	-27	nd	-17	NS	B	Normal
			Cr Nic	11	800			115	-15	nd	-5	NS		
Offenbacher 1985	1 hr	10 wk	Br Yeast	8	5	7	Lactose	127	+2	NS	+28	nd	B	Normal
			$CrCl_3$	8	200			146	+6	NS	+32	nd		
Anderson, 1983	90 min	3 mo	$CrCl_3$	76 [a]	200	76	Placebo	nd	nd	nd	-1	NS	C	Normal
			$CrCl_3$	48 [b]	200	48	Placebo	nd	nd	nd	0	NS		
			$CrCl_3$	28 [c]	200	28	Placebo	nd	nd	nd	-2	NS		
Riales, 1981	90 min	12 wk	$CrCl_3$	8	200	6	Water	124 [d]	-4 [d]	NS	+12 [d]	nd	C	Normal
Martinez, 1985	2 hr	10 wk	$CrCl_3$	13 [e]	200	8	Placebo	83	-1	NS	-20	nd	B	Normal
			$CrCl_3$	15 [f]	200	8	Placebo	82	+5	NS	-2	nd		
Li, 1992	2 hr	13 wk	Br Yeast	15	15	7	Tor Yeast	82	+11	<.001	-1	nd	B	Normal
Li, 1994	2 hr	12 wk	Br Yeast	11	7	11	Tor Yeast	97	-4	NS	0	NS	B	Normal
Anderson, 1991	2 hr	5 wk	$CrCl_3$	9	200	9	Placebo	70 [d]	-2 [d]	NS	+4 [d]	NS[g]	B	Normal
			$CrCl_3$	8	200	8	Placebo	90 [d]	-4 [d]	NS	-4 [d]	NS[g]		Gluc Intol
Grant, 1997	2 hr	9 wk	Cr Nic	~11 [h]	400	~11 [h]	Placebo	106 [d]	-3 [d]	NS	-6 [d]	NS	C	Normal
Area Under the Curve (AUC) of Glucose														
Gill, 1981 [j]	1 hr	3 d	Br Yeast	~5 [h,k]	nd	~5 [h]	Tor Yeast	102	+6	NS	+1	nd	C	Normal
			Br Yeast	~2-3 [h,L]	nd	~2-3 [h]	Tor Yeast	94	+10	NS	+7	nd		Ins Res
Offenbacher, 1980	2 hr	8 wk	Br Yeast	12	10.8	12	Tor Yeast	527 [d]	-59 [d]	<.05	-74 [d]	nd	B	Normal
Grant, 1997	2 hr	9 wk	Cr Nic	~11 [h]	400	~11 [h]	Placebo	"No significant difference among treatments" [m]				NS	C	Normal
Urberg, 1987	2 hr	4 wk	$CrCl_3$	~5-6 [h]	200	~5-6 [h]	Nicotinic Acid	15,589	-304	NS	-648	nd	C	Normal
			$CrCl_3$+Nic	~5-6 [h]	200			16,462	-2,436	<.025	-2,780	nd		
Sum of Measurements of Glucose at Different Time Points														
Anderson, 1991	90 min	5 wk	$CrCl_3$	9	200	9	Placebo	nd	nd	nd	+4 [n]	NS [g]	C	Normal
			$CrCl_3$	8	200	8	Placebo	nd	nd	nd	-64 [n]	<.01 [g]		Gluc Intol
Riales, 1981	90 min	12 wk	$CrCl_3$	8	200	6	Water	535 [d]	-17 [d]	NS	+12 [d]	nd	C	Normal
Anderson, 1991	4 hr	5 wk	$CrCl_3$	9	200	9	Placebo	nd	nd	nd	+9 [n]	NS [g]	C	Normal
			$CrCl_3$	8	200	8	Placebo	nd	nd	nd	-63 [n]	<.05 [g]		Gluc Intol
Non-Controlled Trials														
OGTT Single Time Point Measurement														
Potter, 1985	2 hr	12 wk	$CrCl_3$	6	200	--	--	161	-3	NS	--	--	C	Gluc Intol
Sum of Measurements of Glucose at Different Time Points														
Liu, 1978	3 hr	3 mo	Br Yeast	15	4	--	--	660	-36	NS	--	--	C	Normal
Glycosylated Hemoglobin [o]														
Vinson, 1984	--	6 mo	Br Yeast	6	218	--	--	7.5%	-0.9%	NS	--	--	C	Normal

hr = hours; min = minutes; OGTT = oral glucose tolerance test.

[a] Total

[b] Men

[c] Women

[d] Estimated from graph.

[e] Subjects on no medications that potentially could affect glycemia.

[f] Subjects on medications that potentially could affect glycemia.

[g] Significance of difference between final values.
[h] No data on how many subjects randomized to each arm.
[j] Non-randomized, controlled trial
[k] Low-insulin subgroup.
[L] High-insulin subgroup.
[m] Across all study arms (see Table 13, footnote a).
[n] Difference between final values.
[o] Normal range for glycosylated Hgb = 5.5-9.0%.

Table 16. Summary Findings for Health Claim 3 (Effect on blood sugar levels)

Quality	Chromium Picolinate								Other Chromium Products							
	Normal		Effect		Insulin Resistant [a]		Effect		Normal		Effect		Insulin Resistant [a]		Effect	
	Study	N	FBS	OGTT	Study	N	FBS	OGTT	Study	N	FBS	OGTT	Study	N	FBS	OGTT
A																
B	Volpe, 2001	22	0	0	Joseph, 1999	17	0	0	Martinez, 1985	28	0	0	Abraham, 1992	27	0	
									Lefavi, 1993	23	0	0				
									Offenbacher 1985	16	0	0				
									Li, 1992	15	0[b]	0[b]				
									Wilson, 1995[c]	15	0					
									Offenbacher 1980	12	+[d]	+[d]				
									Li, 1994	11	0[b]	0				
									Anderson, 1991	9	0	0	Anderson, 1991	8	0	0/+/++[e]
									Hermann, 1998	8	0					
C	Grant, 1997 [f]	11	0	0					Anderson, 1983	76	0	0				
	Boyd, 1998	9	0						Wang, 1989	20	0					
									Grant, 1997 [f]	11	0	0				
	Cefalu, 1999	15		0					Crawford, 1999	8	0					
									Riales, 1981	8	0	0				
									Urberg, 1987	6	0	0/+[g]				
									Hermann, 1994	5	0					
									Gill, 1981[h]	5		0				
NC	Grant, 1997 [f]	11	0	0	Kato, 1998	10	0		Liu, 1978	15		0	Wilson, 1995[c]	6	0	
									Vinson, 1984	6		0[j]	Potter, 1985	5		0

NC = No control group. Rated C in Evidence and Summary Tables. N = number of subjects taking chromium supplement.
FBS = fasting blood sugar; OGTT = oral glucose tolerance tests.
[a] Includes populations with insulin resistance, glucose intolerance, or combination populations of normal and glucose intolerance.
[b] Both chromium and control arms had significant worsening of similar magnitude. No data on significance compared to control.
[c] Same study.
[d] Reduction in glucose and glucose area under the curve both significant compared to baseline. No data on significance compared to control.
[e] 0 for 2-hour OGTT glucose; + for sum of OGTT glucose measurements to 4 hours; ++ for sum of OGTT glucose measurements to 90 minutes.
[f] Same study.
[g] 0 for $CrCl_3$; + for $CrCl_3$ & nicotinic acid compared to baseline. However, no data on significance compared to control.
[h] The cohort of insulin resistant subjects from Gill 1981 are omitted here because N<5.
[j] Glycosylated hemoglobin.

Chromium Trials for Health Claim 4

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

Overall assessment and grade

Chromium Picolinate

No study evaluated cardiovascular risk factors or cardiovascular disease in non-diabetic subjects with abnormally elevated blood sugar levels taking chromium picolinate.

The evidence was judged to be insufficient to assign an overall grade.

Overall Grade: I

Other Chromium Products

One fair-quality RCT and 1 non-controlled trial found no significant effect in 45 total non-diabetic subjects with abnormally elevated blood sugar levels taking other chromium products on cardiovascular risk factors. No study evaluated cardiovascular disease.

The evidence was judged to be insufficient to assign an overall grade.

Overall Grade: I

Summary

Two studies evaluated the effect of chromium supplements on cardiovascular risk factors in subjects with baseline evidence of abnormal blood sugar. One fair-quality RCT and 1 non-controlled trial (poor quality) each evaluated chromium chloride. No study examined the risk of cardiovascular events or incident disease.

Chromium picolinate trials

There were no chromium picolinate trials.

Other chromium trials (Tables 17 & 18)

The RCT of 250 µg chromium chloride reported a significant improvement in triglyceride levels of –12% and a non-significant improvement in HDL of +14%. No change was found in total cholesterol or LDL. The non-controlled trial of chromium chloride 200 µg found no change in total cholesterol and LDL, but both HDL and triglycerides worsened.

Table 17. Trials of Other Chromium Products on Cardiovascular Disease Risk Factors (Health Claim 4)

Author, Year	Outcome	Duration	Chromium			Control		Results (mg/dL)					Quality	Population
			Type	N	µg/d	N	Source	Base (Cr)	Δ (Cr)	*P* (Δ Cr)	Net Δ	*P* (Net Δ)		
Randomized-Controlled Trials														
Abraham, 1992	LDL	12 wks	$CrCl_3$	40	250	36	Placebo	167	+6	NS	-2	NS	B	Hyperglycemia [a]
	HDL							36	+8	<.005	+5	NS		
	Cholesterol							240	+12	NS	-6	NS		
	Triglycerides							163	-14	NS	-19	<.02		
Non-Controlled Trials														
Potter, 1985	LDL	12 wks	$CrCl_3$	5	200	--	--	147	-7	NS	--	--	C	Gluc Intol
	HDL							51	-5	NS				
	Cholesterol							221	-9	NS				
	Triglycerides							112	+14	NS				

[a] Both diabetics and non diabetics included in each comparison group.

Table 18. Summary Findings for Health Claim 4 (Effect on CVD caused by abnormally elevated blood sugars)

Quality	Chromium Picolinate								Other Chromium Products							
	Hyperglycemia		Effect						Hyperglycemia		Effect					
	Study	N	CVD	LDL	HDL	TC	Tg	BP	Study	N	CVD	LDL	HDL	TC	Tg	BP
A																
B									Abraham, 1992	40		0	0	0	+	
C																
NC									Potter, 1985	5		0	0	0	0	

NC = No control group. Rated C in Evidence and Summary Tables.
N = number of subjects taking chromium supplement.
CVD = cardiovascular event; LDL = low density lipoprotein; HDL = high density lipoprotein; TC = total cholesterol; Tg = triglycerides; BP = blood pressure.

Chromium Trials for Health Claim 5

"Chromium picolinate may reduce the risk of type 2 diabetes."

No study reported data on the effect of chromium on the likelihood of developing type 2 diabetes.

As described in sections on other health claims, there is insufficient evidence or evidence of no effect regarding the effect of chromium on risk factors for developing type 2 diabetes. There is insufficient evidence that chromium may reduce the risk of insulin resistance (Health Claim 1). There is insufficient evidence that chromium picolinate may reduce abnormally elevated blood sugar levels, but there is evidence that other chromium products have no effect on reducing abnormally elevated blood sugar levels (Health Claim 3).

Overall assessment and grade

Chromium Picolinate
Overall Grade: I

Other Chromium Products
Overall Grade: I

Chromium Trials for Health Claim 6

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

Overall assessment and grade

Chromium Picolinate

Two fair-quality studies and 2 poor-quality studies with 187 diabetic subjects total taking chromium picolinate evaluated cardiovascular risk factors; however, no study explicitly included subjects who had elevated risk of cardiovascular disease from dyslipidemia or hypertension. One study of poor quality found significant improvements in LDL and total cholesterol from baseline, but no data were reported regarding the significance between chromium and control. One study of fair quality found non-significant improvements also in LDL and total cholesterol. Another study of fair quality study found significantly lower total cholesterol in subjects taking high dose, but not lower dose, chromium picolinate than subjects taking placebo. The fourth study, of poor quality, reported that triglycerides were significantly improved, although limited data were reported. Overall, one study each reported significant improvement in LDL, total cholesterol, and triglycerides, but insufficient data were reported to assess the data completely. The studies reported no effects on HDL or blood pressure. Importantly, no study examined the risk of cardiovascular events or incident disease.

The evidence was judged to be insufficient to assign an overall grade for overall risk of cardiovascular disease.

Overall Grade: I

Other Chromium Products

Eight studies with 291 diabetic subjects total taking other chromium products evaluated cardiovascular risk factors; of these, 1 was of good quality, 2 of fair quality, and 5 of poor quality. The studies reported no significant effect on LDL, generally significant improvements in HDL, no significant effect on total cholesterol, and mixed, generally non-significant, effects on triglycerides. The only good-quality study found no effect on cholesterol levels and a non-significant worsening of triglycerides. Across a wide range of doses (1.28 to 600 μg) and comparing chromium chloride to brewer's yeast, the effect of chromium on HDL was similar both across studies and within 1 specific study (Bahijiri 2000). The effect on HDL appears to be similar across studies regardless of mean baseline HDL. Importantly, no study examined the risk of cardiovascular events or incident disease.

The evidence was judged to be insufficient to assign an overall grade for overall risk of cardiovascular disease. The possible effect on HDL, which was not consistent with the lack of effect reported for chromium picolinate, was not judged to be sufficient to make a health claim on the overall risk of cardiovascular disease.

Overall Grade: I

Summary

Twelve studies evaluated the effects of chromium on cardiovascular disease risk factors in subjects with type 2 diabetes. Among these, 4 RCTs evaluated chromium picolinate, 3 RCTs evaluated chromium chloride, and 3 RCTs and 2 non-controlled studies evaluated brewer's yeast.

No study examined the risk of cardiovascular events or incident disease. Overall, there was 1 good-quality study, 4 fair-quality studies (2 of which reported some data poorly), and 7 poor-quality studies, of which 2 were non-controlled trials.

Chromium picolinate trials (Tables 19-22 & 28)

Of the 4 RCTs of chromium picolinate, 3 each reported results on LDL, HDL, total cholesterol, and triglycerides. One study also examined blood pressure. Two studies were of fair quality, but reported some data poorly; the other 2 were of poor quality.

Low Density Lipoprotein (LDL, Table 19)

Among the 3 studies of LDL, 2 studies found net decreases in LDL of 15 mg/dL. The within-chromium effect was statistically significant in the smaller cross-over study (Evans 1989), but no data on significance were reported on the net change. The decrease in Ghosh 2002 was non-significant. The third study (Lee 1994) reported no change in final LDL values with chromium. In neither of the studies that reported baseline LDL, was baseline level abnormal. There was no clear association between chromium dose and effect.

High Density Lipoprotein (HDL, Table 20)

The 3 studies of HDL reported no change with chromium picolinate supplementation. Only Ghosh 2002 reported mean baseline HDL level, which was normal.

Total Cholesterol (Table 21)

Each of the 3 studies of total cholesterol reported net improvements of <10% in total cholesterol. Anderson 1997, in a fair-quality study, reported no change with 200 µg chromium picolinate, but significantly lower total cholesterol after 4 months of treatment with 1000 µg chromium picolinate than after treatment with control. Ghosh 2000 reported a non-significant improvement of –7.5% in total cholesterol with 400 µg chromium picolinate for 12 weeks in a fair-quality study. In a poor-quality study, Evans 1989 found an improvement of –8% in total cholesterol with 200 µg chromium picolinate, which was statistically significant compared to baseline, but no data were reported regarding the significance of the net effect. While Anderson 1997 did find a differential effect based on dose, the other 2 studies found similar effects at lower doses to what Anderson 1997 reported at high dose. Only Evans 1989 included subjects who on average had substantially elevated total cholesterol levels (for type 2 diabetics).

Triglycerides (Table 22)

Ghosh 2002 and Anderson 1997 found no change in triglyceride levels with chromium picolinate in fair- and poor-quality studies, respectively. Lee 1994, on the other hand, in a poorly reported study, found a significant reduction in triglyceride levels from an unreported baseline level. No study reported that subjects had abnormally elevated triglyceride levels at baseline. There was no clear dose effect.

Blood Pressure

Ghosh 2002 was the only study to report the effect of chromium picolinate on blood pressure. It was reported that both diastolic and systolic blood pressures "showed a reduction in both study arms thus negating a significant influence of chromium on blood pressure." Data were not shown.

Other chromium trials (Tables 23-28)

Eight studies evaluated the effect of other chromium supplements on cardiovascular risk factors in subjects with type 2 diabetes. Four studies evaluated LDL, 6 HDL, all 8 total cholesterol, 6 triglycerides, and 1 total cholesterol:HDL ratio. One study was of good quality, 2 fair quality, and 5 poor quality.

Low Density Lipoprotein (LDL, Table 23)

No trial reported a significant effect of chromium supplements on LDL. The good-quality trial of 200 µg chromium chloride and the fair-quality trials of 250 µg chromium chloride both found no change in LDL level with chromium supplementation. Trow 2000, in a non-controlled study of brewer's yeast with 100 µg chromium also found no change in LDL. Vinson 1984 reported varying results of brewer's yeast with 218 µg chromium in a non-controlled study, depending on what diabetes treatments subjects were receiving. Diabetics on no treatment had a non-significant improvement in LDL (31% reduction); those taking insulin had non-significant worsening (6% increase) in LDL; while those on oral medication had no change. There was no clear association between effect and either chromium dose or baseline LDL level across studies.

High Density Lipoprotein (HDL, Table 24))

The 1 good-quality RCT showed no change in HDL with chromium chloride or brewer's yeast supplementation, while the 2 fair-quality trials found net improvements ranging from +14% to +21%, and the 2 poor-quality controlled studies found net improvements of +29% and +51% in HDL. Among the 5 controlled trials, 3 reported that the changes were statistically significant either compared to baseline or compared to the change in the placebo group; one study did not report statistical significance. However, the significant improvement in HDL with chromium chloride reported by Abraham 1992 was not significant compared to control. One of the non-controlled studies reported a non-significant improvement of +10% in HDL with brewer's yeast, while the other non-controlled study reported a significant increase in HDL among diabetics not taking medication of +34%, a non-significant improvement among those on insulin of +13%, and no change in those on oral medication. There was no clear dose effect of chromium, ranging from 1.28 µg to 600 µg. The studies with abnormally low baseline HDL (< 40 mg/dL) generally had the smallest effects.

Total Cholesterol (Table 25)

None of the 5 RCTs, 1 non-randomized controlled trial, or 2 non-controlled studies reported a significant effect of chromium supplementation on total cholesterol. Overall, the effects were similar in studies with abnormally elevated baseline total cholesterol as those with lower levels. The non-randomized trial by Mossop 1983 was the only controlled study to find a net improvement (reduction) of more than 10 mg/dL in total cholesterol, with 600 µg chromium chloride. Vinson 1984 also found a non-significant improvement (–17%) in a non-controlled study. Rabinowitz 1983 reported a range of effects compared to control depending on chromium source/dose and sub-group (–15% to +10%); all were non-significant. Other studies found no change in total cholesterol with brewer's yeast or chromium chloride.

Triglycerides (Table 26)

The effect of brewer's yeast or chromium chloride supplementation varied across the 5 RCTs and 1 non-controlled study. The single good-quality study reported a non-significant change (+9%) in triglycerides with 200 µg chromium chloride. Bahiriji 2000 and Abraham 1992, both

fair-quality studies, found significant improvements (–12% to –23%) in triglyceride levels with chromium chloride 200 µg or 250 µg, or brewer's yeast with 23 µg chromium. Rabinowitz 1983, a poor-quality study, found a wide range of effects (–27% to +13%) that were non-significant and did not follow any obvious pattern. The other poor-quality controlled study found no change. The non-controlled study by Trow 2000 reported a non-significant worsening (+25%) in triglyceride levels. Effect size was not clearly related to chromium dose or size or baseline triglyceride levels either within or across studies.

Total cholesterol to HDL ratio (Table 27)

Vinson 1984, a poor-quality non-controlled study, reported the effect of high-chromium dose brewer's yeast (218 µg chromium) on total cholesterol:HDL ratio. Results were not consistent. A significant improvement (39% reduction) was found among subjects with type 2 diabetes who were not taking medication; a non-significant 6% reduction in the ratio occurred in subjects who took insulin; but a non-significant worsening (+5%) in the ratio occurred in those on oral diabetes medication.

Table 19. Trials of Chromium Picolinate on Low Density Lipoprotein (LDL) (Health Claim 6)

Author, Year	Duration	Chromium N	Chromium µg/d	Control N	Control	LDL (mg/dL)	Δ (Cr)	*P* (Δ Cr)	Net Δ	*P* (Net Δ)	Quality	Population
Randomized Controlled Trials												
Ghosh, 2002	12 wk	43	400	43	Placebo	127	-19	nd	-15	NS	B	Type 2 DM
Evans, 1989	6 wk	6 [a]	200	11	$CaPO_4$	148	-8	.05	-15 [a]	nd	C	Type 2 DM
		5 [a]				142	-8					
Lee, 1994	2 mo	28	200	28	Placebo	nd	nd	nd	0 [b]	NS	C	Type 2 DM

[a] Each arm in cross-over study reported separately. Net Δ is weighted mean of the net Δs from each arm.
[b] Difference between final values (not net Δ)

Table 20. Trials of Chromium Picolinate on High Density Lipoprotein (HDL) (Health Claim 6)

Author, Year	Duration	Chromium N	Chromium µg/d	Control N	Control	HDL (mg/dL)	Δ (Cr)	*P* (Δ Cr)	Net Δ	*P* (Net Δ)	Quality	Population
Randomized Controlled Trials												
Ghosh, 2002	12 wk	43	400	43	Placebo	50	-8	nd	0	NS	B	Type 2 DM
Anderson, 1997	4 mo	53	200	50	Placebo	There were no significant effects of supplemental chromium				NS	C	Type 2 DM
		52	1000							NS		
Lee, 1994	2 mo	28	200	28	Placebo	nd	nd	nd	0 [a]	NS	C	Type 2 DM

[a] Difference between final values (not net Δ)

Table 21. Trials of Chromium Picolinate on Total Cholesterol (Health Claim 6)

Author, Year	Duration	Chromium N	Chromium µg/d	Control N	Control	Total Cholesterol (mg/dL)	Δ (Cr)	*P* (Δ Cr)	Net Δ	*P* (Net Δ)	Quality	Population
Randomized Controlled Trials												
Anderson, 1997	4 mo	53	200	50	Placebo	201 [a]	0 [a]	nd	-4 [a]	nd	B	Type 2 DM
		52	1000			197 [a]	-14 [a]	nd	-18 [a]	nd [b]		
Ghosh, 2002	12 wk	43	400	43	Placebo	201	-27	nd	-15	NS	B	Type 2 DM
Evans, 1989	6 wk	6 [b]	200	11	$CaPO_4$	218	-10	.044	-18 [c]	nd	C	Type 2 DM
		5 [b]				216	-26					

[a] Values were estimated from figure.
[b] $P<0.05$ for difference between final total cholesterol in chromium 1000 µg and placebo cohorts.
[c] Each arm in cross-over study reported separately. Net Δ is weighted mean of the net Δs from each arm.

Table 22. Trials of Chromium Picolinate on Triglycerides (Tg) (Health Claim 6)

Author, Year	Duration	Chromium N	Chromium µg/d	Control N	Control	Tg (mg/dL)	Δ (Cr)	*P* (Δ Cr)	Net Δ	*P* (Net Δ)	Quality	Population
Randomized Controlled Trials												
Ghosh, 2002	12 wk	43	400	43	Placebo	133	+18	nd	-9	NS	B	Type 2 DM
Anderson, 1997	4 mo	53	200	50	Placebo	There were no significant effects of supplemental chromium				NS	C	Type 2 DM
		52	1000							NS		
Lee, 1994	2 mo	28	200	28	Placebo	nd	nd	nd	-28 [a]	<.05	C	Type 2 DM

[a] Difference between final values (not net Δ)

Table 23. Trials of Other Chromium Products on Low Density Lipoprotein (LDL) (Health Claim 6)

Author, Year	Duration	Chromium Type	Chromium N	Chromium µg/d	Control	LDL (mg/dL) Base (Cr)	Δ (Cr)	*P* (Δ Cr)	Net Δ	*P* (Net Δ)	Quality	Population
Randomized Controlled Trials												
Uusitupa, 1983	6 wk	$CrCl_3$	10	200	10 0.02 M HCl	161	-2	NS	-10	NS	A	Type 2 DM
Abraham, 1992	12 wks	$CrCl_3$	40	250	36 Placebo	167	+6	NS	-2	NS	B	Hyperglycemic[a]
Non-Controlled Trials												
Trow, 2000	8 wk	Br Yeast	12	100	-- --	120	+1	NS	--	--	C	Type 2 DM
Vinson, 1984	4 mo	Br Yeast	5	218	-- --	151	-47	<0.10	--	--	C	Type 2 DM (no medication)
	6 mo		7	218		163	+9	NS	--	--		Type 2 DM (on insulin)
	4 mo		5	218		152	-4	NS	--	--		Type 2 DM (on oral drugs)

[a] Both diabetics and non diabetics included in each comparison group.

Table 24. Trials of Other Chromium Products on High Density Lipoprotein (HDL) (Health Claim 6)

Author, Year	Duration	Chromium			Control		HDL (mg/dL)					Quality	Population
		Type	N	µg/d	N	Source	Base (Cr)	Δ (Cr)	*P* (Δ Cr)	Net Δ	*P* (Net Δ)		
Randomized Controlled Trials													
Uusitupa, 1983	6 wk	$CrCl_3$	10	200	10	0.02 M HCl	37	+2	NS	0	NS	A	Type 2 DM
Bahijiri, 2000	16 wk	$CrCl_3$	78/67[a]	200	78/69	Tor Yeast	38	+8	.007	+7	nd	B	Type 2 DM
		Br Yeast	78/74[a]	23.2				+9	.005	+8	nd		
Abraham, 1992	12 wk	$CrCl_3$	40	250	36	Placebo	36	+8	<.005	+5	NS	B	Hyperglycemic[b]
Grant, 1982	7 wk	Br Yeast	26	1.28	26	Cellulose	42	+15	NS	+12	<.05	C	Type 2 DM
Mossop, 1983[c]	2-4 mo	$CrCl_3$	13	600	13	No treatment	45	+17	nd	+23	nd	C	Type 2 DM
Non-Controlled Trials													
Trow, 2000	8 wk	Br Yeast	12	100	--	--	52	+5	NS	--	--	C	Type 2 DM
Vinson, 1984	6 mo	Br Yeast	5	218	--	--	50	+17	<0.01	--	--	C	Type 2 DM (no medication)
	6 mo		7	218			52	+7	NS	--	--		Type 2 DM (on insulin)
	4 mo		5	218			47	+1	NS	--	--		Type 2 DM (on oral drugs)

[a] Number of subjects at the beginning/end of study
[b] Both diabetics and non diabetics included in each comparison group.
[c] Non-randomized, controlled trial.

Table 25. Trials of Other Chromium Products on Total Cholesterol (Health Claim 6)

Author, Year	Duration	Chromium			Control		Total Cholesterol (mg/dL)					Quality	Population
		Type	N	µg/d	N	Source	Base (Cr)	Δ (Cr)	*P* (Δ Cr)	Net Δ	*P* (Net Δ)		
Randomized Controlled Trials													
Uusitupa, 1983	6 wk	$CrCl_3$	10	200	10	0.02 M HCl	244	0	NS	-3	NS	A	Type 2 DM
Bahijiri, 2000	16 wk	$CrCl_3$	78/67[a]	200	78/69	Tor Yeast	199	-7	NS	+3	nd	B	Type 2 DM
		Br Yeast	78/74[a]	23.2				-13	.07	-4	nd		
Abraham, 1992	12 wks	$CrCl_3$	40	250	36	Placebo	240	+12	NS	-6	NS	B	Hyperglycemic[b]
Rabinowitz, 1983	4 mo	$CrCl_3$	21/15[a]	150	21/16	Placebo	221	+5	NS	+3	nd	C	Type 2 DM (ketosis-prone, on insulin)
		Br Yeast w/o GTF	21/13[a]	18				+5	NS	+3	nd		
		Br Yeast w/ GTF	21/16[a]	6				0	NS	-2	nd		
		$CrCl_3$	7/4[a]	150	7/3	Placebo	178	+18	NS	+2	nd		Type 2 DM (ketosis-resistant, not obese)
		Br Yeast w/o GTF	7/5[a]	18				+19	NS	+3	nd		
		Br Yeast w/ GTF	7/6[a]	6				-10	NS	-26	nd		
		$CrCl_3$	15/9[a]	150	15/9	Placebo	215	+12	NS	+9	nd		Type 2 DM (ketosis-resistant, obese)
		Br Yeast w/o GTF	15/10[a]	18				+25	NS	+22	nd		
		Br Yeast w/ GTF	15/8[a]	6				+10	NS	+7	nd		
Grant, 1982	7 wk	Br Yeast	26	1.28	26	Cellulose	220	0	NS	-4	NS	C	Type 2 DM
Mossop, 1983[c]	2-4 mo	$CrCl_3$	13	600	13	No treatment	nd	-8	nd	-14	NS	C	Type 2 DM
Non-Controlled Trials													
Trow, 2000	8 wk	Br Yeast	12	100	--	--	212	+7	NS	--	--	C	Type 2 DM
Vinson, 1984	6 mo	Br Yeast	5	218	--	--	224	-38	NS	--	--	C	Type 2 DM (no medication)

GTF = glucose tolerance factor; HCl = hydrochloric acid; w/ = with; w/o = without.

[a] Number of subjects at the beginning/end of study

[b] Both diabetics and non diabetics included in each comparison group.

[c] Non-randomized, controlled trial.

Table 26. Trials of Other Chromium Products on Triglycerides (Tg) (Health Claim 6)

Author, Year	Dur-ation	Chromium			Control		Tg (mg/dL)					Quality	Population
		Type	N	µg/d	N	Source	Base (Cr)	Δ (Cr)	*P* (Δ Cr)	Net Δ	*P* (Net Δ)		
Randomized Controlled Trials													
Uusitupa, 1983	6 wk	$CrCl_3$	10	200	10	0.02 M HCl	207	+13	NS	+19	NS	A	Type 2 DM
Bahijiri, 2000	16 wk	$CrCl_3$	78/67[a]	200	78/69	Tor Yeast	174	-38	.009	-35	nd	B	Type 2 DM
		Br Yeast	78/74[a]	23.2				-42	.009	-40	nd		
Abraham, 1992	12 wks	$CrCl_3$	40	250	36	Placebo	163	-14	NS	-19	<.02	B	Hyperglycemia[b]
Rabinowitz, 1983	4 mo	$CrCl_3$	21/15[a]	150	21/16	Placebo	230	-2	NS	+11	nd	C	Type 2 DM (ketosis-prone, on insulin)
		Br Yeast w/o GTF	21/13[a]	18				-57	NS	-44	nd		
		Br Yeast w/ GTF	21/16[a]	6				+6	NS	+19	nd		
		$CrCl_3$	7/4[a]	150	7/3	Placebo	179	+7	NS	+3	nd		Type 2 DM (ketosis-resistant, not obese)
		Br Yeast w/o GTF	7/5[a]	18				+9	NS	+5	nd		
		Br Yeast w/ GTF	7/6[a]	6				-45	NS	-49	nd		
		$CrCl_3$	15/9[a]	150	15/9	Placebo	269	+78	NS	+35	nd		Type 2 DM (ketosis-resistant, obese)
		Br Yeast w/o GTF	15/10[a]	18				-17	NS	-60	nd		
		Br Yeast w/ GTF	15/8[a]	6				+85	NS	+42	nd		
Grant, 1982	7 wk	Br Yeast	26	1.28	26	Cellulose	124	+9	NS	-9	NS	C	Type 2 DM
Non-Controlled Trials													
Trow, 2000	8 wk	Br Yeast	12	100	--	--	162	+41	NS	--	--	C	Type 2 DM

[a] Number of subjects at the beginning/end of study

[b] Both diabetics and non diabetics included in each comparison group.

Table 27. Trials of Other Chromium Products on Total Cholesterol:HDL Ratio (Health Claim 6)

Author, Year	Duration	Chromium Type	Chromium N	Chromium µg/d	Control N	Control Source	Tg (mg/dL) Base (Cr)	Tg (mg/dL) Δ (Cr)	Tg (mg/dL) *P* (Δ Cr)	Tg (mg/dL) Net Δ	Tg (mg/dL) *P* (Net Δ)	Quality	Population
Non-Controlled Trials													
Vinson, 1984	4 mo	Br Yeast	5	218	--	--	4.6	-39%	<0.01	--	--	C	Type 2 DM (no medication)
	6 mo		7	218			5.2	-6%	NS	--	--		Type 2 DM (on insulin)
	4 mo		5	218			6.1	+5%	NS	--	--		Type 2 DM (on oral drugs)

Table 28. Summary Findings for Health Claim 6 (Effect on CVD caused by type 2 diabetes)

Quality	Chromium Picolinate Type 2 DM Study	N	Effect CVD	LDL	HDL	TC	Tg	BP	Other Chromium Products Type 2 DM Study	N	Effect CVD	LDL	HDL	TC	Tg	BP
A									Uusitupa, 1983	10		0	0	0	0	
B	Anderson, 1997 [a]	105				0/+[b]			Bahijiri, 2000	141			++[c]	0	++[c]	
	Ghosh, 2002 [a]	43		0	0	0	0		Abraham, 1992	40		0	0	0	+	
C	Anderson, 1997 [a]	105			0		0		Rabinowitz, 1983	43				0	0	
	Ghosh, 2002 [a]	43						0	Grant, 1982	26			+	0	0	
	Lee, 1994	28		0	0		+		Mossop, 1983	13			?[d]	0		
	Evans, 1989	11		+[c]		+[c]										
NC									Trow, 2000	12		0	0	0	0	
									Vinson, 1984	5		0	0/++[e]	0		

NC = No control group. Rated C in Evidence and Summary Tables.
DM = diabetes; N = number of subjects taking chromium supplement.
CVD = cardiovascular event; LDL = low density lipoprotein; HDL = high density lipoprotein; TC = total cholesterol; Tg = triglycerides; BP = blood pressure.
[a] For Anderson and Ghosh: Quality B for some results, C for others.
[b] 0 for 200 µg/day; + for 1000 µg/day
[c] Significant compared to baseline; however, no data on significance compared to control.
[d] No data on statistical significance.
[e] ++ for diabetics not taking medication; 0 for diabetics on insulin or oral drugs.

Chromium Trials for Health Claim 7

"Chromium picolinate may reduce the risk of retinopathy caused by abnormally high blood sugar levels."

No study reported data on the effect of any chromium product on the risk of developing retinopathy.

Overall assessment and grade

Chromium Picolinate
Overall Grade: I

Other Chromium Products
Overall Grade: I

Chromium Trials for Health Claim 8

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

Overall assessment and grade

No adequate study reported data on the effect of any chromium product on the risk of kidney disease.

Chromium Picolinate
Overall Grade: I

Other Chromium Products
Overall Grade: I

Summary

Only 1 study reported any data related to kidney function. Anderson 1997, in a 3-arm RCT compared chromium picolinate 200 μg and 1000 μg to placebo in otherwise healthy subjects with type 2 diabetes. The study lasted 4 months. The authors report only that "there were no significant effects of supplemental chromium" on blood urea nitrogen levels. Blood urea nitrogen is not a well-accepted measure of kidney function. No study evaluated the risk of developing kidney disease. Although this study was considered to be of fair quality overall, because of the incomplete reporting on blood urea nitrogen, it received a grade of C (poor quality) for this outcome.

Overall Assessment of Health Claims

There is insufficient evidence to support any of the proposed health claims. For health claim 3, there are a large number of studies that were mostly consistent in showing little or no effect of chromium supplementation on reducing blood sugar levels in non-diabetic people, particularly among the better quality studies. However, there was insufficient evidence regarding chromium picolinate specifically.

The lack of sufficient evidence was due primarily to the generally poor quality and small sample sizes of the studies examining the effects of chromium on outcomes pertinent to the proposed health claims. In addition, while there are a fair number of studies relevant to health claim 6, the effects found on cardiovascular risk factors were inconsistent across studies and no study evaluated the risk of cardiovascular disease. Therefore the evidence was deemed to be insufficient to determine the validity of the claim.

Table 29. Overall assessment of health claims

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