

ORIGINAL SUBMISSION

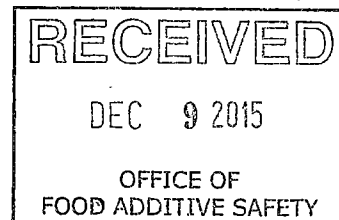
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2614
GRN 000614

December 8, 2015

Paulette M. Gaynor, Ph.D.
Office of Food Additive Safety (HFS-200)
Center for Food Safety and Applied Nutrition
Food And Drug Administration
5100 Paint Branch Parkway
College Park, MD 20740-3835



Subject: GRAS Notification for the Use of Chromium Polynicotinate in Enhanced Water Beverages

Dear Dr. Gaynor:

Pursuant to proposed 21 CFR 170.36 (62 FR 18960; April 17, 1997), Exponent, Inc. hereby provides notice of a claim that the food ingredient described in the enclosed notification document is exempt from the premarket approval requirement of the Federal Food, Drug, and Cosmetic Act because it has been determined to be generally recognized as safe (GRAS), based on scientific procedures, for use as a source of dietary chromium in enhanced water beverages.

Three paper copies of the notification are provided as required; we also have provided a copy of the notification on the enclosed CD-ROM. If you have any questions or require additional information, please do not hesitate to contact me at 202-772-4953, or mmurphy@exponent.com.

(b) (6)
Sincerely,

(b) (6)
Mary M. Murphy, MS, RD
Senior Managing Scientist



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Mary M. Murphy, MS, RD
Senior Managing Scientist

GRAS Determination for the Use of Chromium Polynicotinate in Enhanced Water Beverages

SUBMITTED BY:

Exponent, Inc.
1150 Connecticut Avenue, NW
Suite 1100
Washington, DC 20036

SUBMITTED TO:

U.S. Food and Drug Administration
Center for Food Safety and Applied Nutrition
Office of Food Additive Safety
HFS-200
5100 Paint Branch Parkway
College Park, MD 20740-3835

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December 8, 2015

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List of Exhibits

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List of Acronyms

°C	degree Celsius
ADME	absorption, distribution, metabolism and excretion
AI	adequate intake
ATSDR	Agency for Toxic Substances and Disease Registry
BAM	Bacteriological Analytical Manual
bw	bodyweight
CASRN	Chemical Abstract Service Registry Number
cc	cubic centimeter
CDC	Centers for Disease Control and Prevention
CFR	Code of Federal Regulations
CFU	colony forming units
cGMP	current Good Manufacturing Practice
cm	centimeter
COA	certificate of analysis
Cr	chromium
CrNic	chromium nicotinate
d	day
DHHS	Department of Health and Human Services
DNA	deoxyribonucleic acid
DRI	dietary reference intake
EAR	estimated average requirement
EDI	estimated daily intake
EFSA	European Food Safety Authority
EFSA CONTAM Panel	EFSA Panel on Contaminants in the Food Chain
EPA	U.S. Environmental Protection Agency
FAO	Food and Agricultural Organization of the United Nations
FARE	Foods and Residue Evaluation (software)
FDA	U.S. Food and Drug Administration
g	gram
GLP	Good Laboratory Practice
GRAS	generally recognized as safe
GSE	grape seed extract
h	hour
HDL	high-density lipoprotein
HDT	highest dose tested
HPLC	high performance liquid chromatography
i.p.	intraperitoneal

i.v.	intravenous
IOM	Institute of Medicine
IRI	immunoreactive insulin
JECFA	Joint FAO/WHO Expert Committee on Food Additives
kg	kilogram
L	liter
LD50	lethal dose, 50%
LDL	low-density lipoprotein
LDT	lowest dose tested
LOAEL	lowest-observed-adverse-effect-level
LOEL	lowest-observable-effect-level
M	mole
MCL	maximum contaminant level
mg	milligram
mL	milliliter
mM	millimole
mo	month
MOE	margin of exposure
MPN	most probable number
NBC	niacin-bound chromium (III) complex
NCHS	National Center for Health Statistics
NE	niacin equivalent
ng	nanogram
NHANES	National Health and Nutrition Examination Survey
nmoles	nanomoles
NOAEL	no-observed-adverse-effect-level
NTP	National Toxicology Program
ODT	only dose tested
OECD	Organisation for Economic Co-operation and Development
ppb	parts per billion
ppm	parts per million
RCT	randomized controlled trial
RDA	Recommended Dietary Allowance
RfD	reference dose
SBP	systolic blood pressure
SCF	Scientific Committee on Food
TC	total cholesterol
TDI	tolerable daily intake
TOXNET	Toxicology Data Network
U.S.	United States
UL	tolerable upper intake level

USDA	United States Department of Agriculture
USP	United States Pharmacopeia
WHO	World Health Organization
wk	week
WWEIA	What We Eat in America
y	year
μCi	microcurie
μg	microgram
μL	microliter
μM	micromole

GRAS Exemption Claim

Name and Address of Notifier

Exponent, Inc., hereby notifies the U.S. Food and Drug Administration (FDA) that the use of chromium polynicotinate as described below is exempt from the pre-market approval requirements of the Federal Food, Drug, and Cosmetic Act because Exponent, Inc., has determined that such use is generally recognized as safe (GRAS) through scientific procedures.

(b) (6)



December 8, 2015

Name: Nga L. Tran, DrPH
Title: Principal Scientist
Company: Exponent, Inc.

Date

Name of GRAS Substance

The name of the substance that is the subject of this GRAS determination is chromium polynicotinate.

Intended Use and Consumer Exposure

Chromium polynicotinate is intended for use in enhanced water beverages at a maximum use level of 575 µg/L, equivalent to 575 ppb. The addition of chromium polynicotinate to enhanced water beverages provides a dietary source of chromium.

The estimated daily intake (EDI) of chromium polynicotinate from the proposed use in enhanced water beverages was derived using the What We Eat in America (WWEIA) dietary component of the National Health and Nutrition Examination Surveys (NHANES) 2009-2010 and 2011-2012 (2009-2012).

In the U.S. population 2 years and older, the mean and 90th percentile *per user* EDIs of chromium polynicotinate from the proposed use in enhanced water beverages are 202 and 342 µg/day, respectively, or 3.1 and 5.6 µg/kg bw/day, respectively. On a body weight basis, the 90th percentile *per user* EDI of chromium polynicotinate was lowest among the U.S. population 2 years and older and adults 19 years and older (5.6 µg/kg bw/day in each group) and highest among children ages 2-18 years (6.2 µg/kg bw/day).

Basis for GRAS Determination

Exponent, Inc.'s GRAS determination for the intended use of chromium polynicotinate is based on scientific procedures as described under 21 Code of Federal Regulations (CFR) § 170.30(b).

The intended use of chromium polynicotinate has been determined to be safe, and has also been determined to be GRAS, by demonstrating that safety of intake under the proposed conditions of use is based on knowledge and information that is both publicly available and widely accepted by experts qualified by scientific training and experience to evaluate the safety of substances added to food.

Availability of Information

The data and information that serve as the basis for this GRAS determination, as well as the information that has become available since the GRAS determination, will be sent to the FDA upon request, or are available for the FDA's review and copying at reasonable times from at the office of Mary Murphy at Exponent Inc., 1150 Connecticut Ave, NW, Suite 1100, Washington, DC 20036.

Description of Substance

Common or Usual Name

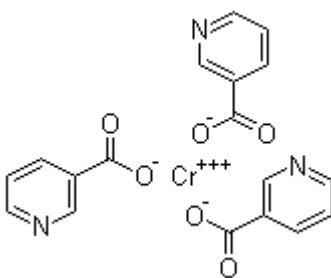
Chromium polynicotinate, also known as chromium nicotinate. It is sold under the trade name ChromeMate® CM-100M.

Synonyms of chromium polynicotinate are O-coordinated chromium (poly)nicotinate, O-coordinated chromium di-nicotinate, O-coordinated chromium nicotinate, O-coordinated chromium di-pyridine-m-carboxylate, tetra aquo-dinicotinato chromium complex, chromium (poly)nicotinate, chromium di-nicotinate, chromium nicotinate, oxygen coordinated niacin bound chromium complex, niacin bound chromium, triaquahydroxybis(3-pyridinecarboxylato-O) chromium (III) (EFSA, 2008).

Identity

Chromium polynicotinate is an oxygen-coordinated, niacin-bound trivalent chromium complex containing 10% elemental chromium in a fine mesh powder. The powder also contains sodium, chloride, and water. Chromium polynicotinate contains a mixture of di- and tri-nicotinate, though tri-nicotinate is the predominant form. The molecular weight of chromium tri-nicotinate is 418.3 g/mol and the Chemical Abstracts Registry Number is CASRN 64452-96-6. The structure of chromium tri-nicotinate is shown in Figure 1.

Figure 1. Structure of chromium tri-nicotinate (polynicotinate)



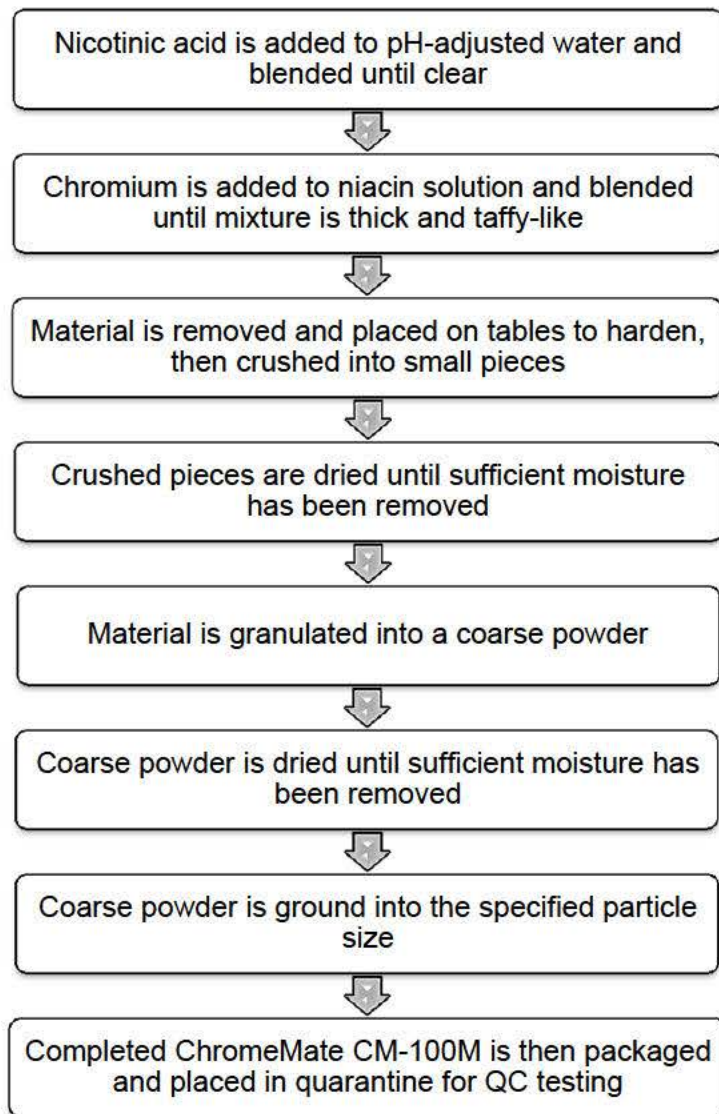
Source: CAS.ChemNet.com

Manufacturing and Production

Chromium polynicotinate is manufactured under current Good Manufacturing Practice (cGMP). The manufacturer also is registered with NSF International and complies with GMP requirements as listed in the NSF/ANSI Standard 173, Section 8, Dietary Supplements.

The production process for ChromeMate® CM-100M™ chromium polynicotinate is detailed in Figure 2 below. Chromium (III) chloride hexahydrate is the starting form of chromium used in the production of chromium polynicotinate. The only processing aid used in the manufacture of chromium polynicotinate is food-grade sodium hydroxide, which is used for pH adjustment. The resulting chromium polynicotinate contains sodium and chloride from materials used in the production process.

Figure 2. Flow diagram of the production process for ChromeMate® CM-100M™ (chromium polynicotinate)



Product Specifications

The chromium polynicotinate that is the subject of this GRAS determination meets product specifications appropriate for a food ingredient with limits for physical and chemical characteristics of the product as well as potential microbiological contaminants (Table 1). Analytical data reported in Certificates of Analysis (COAs) from representative non-consecutive batches of chromium polynicotinate demonstrate that the ingredient consistently meets these product specifications (see Appendix A). As shown in Table 1 below, the specifications establish a minimum level of chromium in the finished product of 100,000 µg/g (i.e., 10% by weight) and a minimum level of niacin of 600,000 µg/g (i.e., 60%).

Table 1. Specifications for chromium polynicotinate

Component	Unit	Specification	Method of Analysis
Physical Characteristics			
Color	-	Lavender	Visual
Identification	-	Matches standard	FT-NIR
Moisture	%	<8	105°C 4 hours
Physical appearance	-	Powder, non-fibrous	Visual
Tap density	g/cc	>0.60	USP 29 <616>
Bulk density	g/cc	>0.45	USP <616>
Wt % through 140 mesh		>85	USP <786>
Chemical Characteristics			
chromium	µg/g	NLT 100,000	AOAC 965.17/968.08, USP <730>
nicotinic acid	µg/g	NLT 600,000	HPLC
pH (1% solution)	-	2.5-3.5	USP 29 <791>
Heavy metals			
Arsenic	ppm	<1	USP <730>
Cadmium	ppm	<0.3	USP <730>
Mercury	ppm	<0.3	USP <730>
Lead	ppm	<0.5	USP <730>
Microbiological contaminants			
Coliform	MPN/g	<3	AOAC 966.24
E. coli	MPN/g	<3	AOAC 966.24
Mold	CFU/g	<100	FDA BAM (7th Ed)
Salmonella	CFU/g	Not detected	AOAC 2004.03
Staphylococcus aureus	CFU/g	<10	AOAC 975.55
Total plate count	CFU/g	<3000	AOAC 966.23
Yeast	CFU/g	<100	FDA BAM (7th Ed)

CFU – colony-forming unit; FDA BAM – Food and Drug Administration Bacteriological Analytical Manual; FT-NIR – Fourier Transform Near-Infrared; HPLC – high performance liquid chromatography; MPN – most probable number; NLT – not less than; USP – United States Pharmacopeia

Regulated Uses and History of Consumption

Chromium polynicotinate is a complex of trivalent chromium and nicotinic acid. The constituents of chromium polynicotinate, chromium and nicotinic acid, are both nutrients for which Dietary Reference Intakes (DRIs) have been established (IOM, 1998; IOM, 2001). The compounds are also consumed as natural constituents in foods and may be added to foods as fortification or enrichment nutrients.

Chromium

Chromium (III) is present in many foods in the food supply. With the exception of select foods such as beef, the mean level of chromium (III) per 100 g in commonly consumed foods is in the range of <1 to approximately 15 µg, though variation in analytical levels tends to be high (Thor et al., 2011). Based on the mean chromium (III) content measured in 22 well-balanced diets, adult women in the United States are estimated to consume approximately 23 to 29 µg/day of chromium (III) from food and adult men are estimated to consume on average 39 to 54 µg/day (IOM, 2001).

Chromium (III) is also used as a dietary supplement, with doses typically ranging from 20 to 200 µg (ODS, 2013). Supplemental forms of chromium (III) mainly include chromium chloride, chromium nicotinate, chromium picolinate, high-chromium yeast, and chromium citrate (ODS, 2013). Based on reported intakes of chromium-containing dietary supplements in the National Health and Nutrition Examination Survey (NHANES) 2009-2012, mean and 90th percentile intakes of chromium from dietary supplements among users of chromium-containing supplements ages 2 years and older were estimated by Exponent at 77 and 120 µg/day, respectively (see next chapter for details on data source).

Niacin

Niacin, which refers to nicotinamide and nicotinic acid as well as derivatives exhibiting the biological activity of nicotinamide, is a water-soluble vitamin. Niacin acts as both a donor and acceptor of a hydride ion in biological reduction-oxidation reactions, including intracellular respiration, the oxidation of fuel molecules, and fatty acid and steroid synthesis (IOM, 1998). Niacin is a GRAS affirmed substance (21 Code of Federal Regulations (CFR) §184.1530) and is added to grains to conform with established standards of identity for enriched products such as flour (21 CFR §137.165).

The mean intake of niacin from food and beverages by Americans aged two years and over is 25.1 mg/day, with mean intake by children ages 2-19 years of 22.1 mg/day and mean intake by adults ages 20 years and older of 26.1 mg/day (USDA, 2014). The total intake of niacin from food and supplements combined by Americans ages two years and over is 32.9 mg/day (USDA, 2014). Estimates of niacin intake in the U.S. do not distinguish between niacin intrinsic to a food and synthetic niacin added as a fortification or enrichment nutrient.

Intended Use and Estimated Daily Intake

Proposed Use and Level

The intended use of chromium polynicotinate is in enhanced water beverages at a maximum use level of 575 µg per liter of beverage (µg/L), equivalent to 575 ppb. The addition of chromium polynicotinate to enhanced water beverages is intended to provide an additional dietary source of chromium.

Estimated Daily Intakes

Dietary Consumption Data

The estimated daily intake (EDI) of chromium polynicotinate from the proposed uses in enhanced water beverages was determined from data in food consumption records collected in the What We Eat in America (WWEIA) component of NHANES conducted in 2009-2010 and 2011-2012 (NHANES 2009-2012). This continuous survey uses a complex multistage probability sample designed to be representative of the civilian U.S. population (CDC, 2012, 2014). The NHANES datasets provide nationally representative nutrition and health data and prevalence estimates for nutrition and health status measures in the United States. The dietary component of the survey is conducted as a partnership between the U.S. Department of Agriculture (USDA) and the U.S. Department of Health and Human Services (DHHS). The DHHS is responsible for the sample design and data collection, and the USDA is responsible for the survey's dietary data collection methodology, maintenance of the databases used to code and process the data, and data review and processing. Statistical weights are provided by the National Center for Health Statistics (NCHS) to adjust for the differential probabilities of selection.

As part of the examination, trained dietary interviewers collected detailed information on all foods and beverages consumed by respondents in the previous 24 hour time period (midnight to midnight). A second dietary recall was administered by telephone three to ten days after the first dietary interview, but not on the same day of the week as the first interview. A total of 14,911 individuals two years and older in the survey period 2009-2012 provided two complete days of dietary recalls.

Supplement Data

Dietary supplement sources of chromium polynicotinate were reviewed in the 30-day dietary supplement use component of NHANES 2009-2012. In the supplement use component of the survey, participants were asked if they had taken a dietary supplement or non-prescription antacid in the past 30 days, how long they had been taking each dietary supplement or non-prescription antacid reported, how many days it was taken in the past 30 days, the amount that was taken on those days and the reason(s) that they are taking the dietary supplement or non-

prescription antacid. Label information such as supplement name, manufacturer and/or distributor, serving size, form of serving size, and ingredients and amounts were recorded by NCHS for each supplement or antacid reported by participants.

Exponent identified the chromium content in chromium- containing supplements in the supplement database (ingredient code 10000093; estimated intakes were reported in the previous chapter). The identified supplements include one supplement ingredient code for chromium polynicotinate (ingredient code 10000908). There were no reported uses of chromium polynicotinate containing supplements during NHANES 2009-2012.

Representative Foods

Food codes corresponding to the enhanced water beverages to which chromium polynicotinate will be added were identified in the WWEIA, NHANES 2009-2012. A total of four food codes were identified for enhanced or fortified water beverages as specified by the so named WWEIA food category. The products in this food category include regular and low calorie beverages; examples of these types of beverages as described in the WWEIA, NHANES food list include Vitamin Water, Propel Water, Glaceau Water, Glaceau Smart water, SoBe Lifewater. The food codes used in the analysis are listed in Appendix B.

Analysis

Estimates of chromium polynicotinate, chromium, and niacin resulting from the proposed uses in enhanced water beverage were derived based on reported intakes of the beverages listed in Appendix B.

Exponent estimated daily intakes on a *per user* basis. In this analysis, a “user” is anyone who reported consuming at least one of the select beverages on either of the survey days; this definition of a “user” is consistent with that of the USDA’s definition. Each individual who reported consuming a beverage on either of the survey days was included in the analysis, and zero consumption days were included in calculating that individual’s two-day average intake. For example, if someone reported consuming 100 grams of an enhanced water drink on day 1 and 0 grams of an enhanced water drink on day 2, his/her 2-day average consumption would be 50 grams ($[100+0]/2$). A two-day average typically overestimates long-term (chronic) daily intake; however, only two nonconsecutive days of food consumption data are available in the most recent NHANES 2009-2012 survey database.

The 2-day average intake of chromium polynicotinate (as well as chromium and niacin) was estimated by multiplying the reported intake of beverages from the 24-hour recall with the chromium polynicotinate use level and the cumulative sum over the two 24-hour recalls was divided by two. The resulting intake of chromium and niacin from enhanced water beverages was also estimated assuming chromium polynicotinate is up to 11% chromium and 67% niacin. These levels of chromium and niacin correspond to typical expected maximum levels based on representative data in COAs (Appendix A).

The two-day average *per user* mean and 90th percentile intakes of chromium polynicotinate, chromium, and niacin from proposed uses were derived for the total population ages 2 years and older and subpopulations of children 2-18 years and adults 19 years and older using Exponent's Foods and Residue Evaluation Program (FARE® 10.206) software. Each individual's intake of chromium polynicotinate was divided by his/her bodyweight to provide the *per user* intakes on a bodyweight basis. All beverages were assumed to contain the maximum proposed use of chromium polynicotinate of 575 ppb as consumed.

Results

EDIs of Enhanced Water Beverages

In the U.S. population ≥ 2 years, the mean and 90th percentile *per user* EDIs of enhanced water beverages are 351 and 595 g/day, respectively, or 5.3 and 9.8 g/kg bw/day, respectively (Table 2). The mean and 90th percentile *per user* EDIs of enhanced water beverages represent intakes of approximately 12 and 20 fluid ounces assuming one fluid ounce weighs 29.6 g. The 90th percentile *per user* EDIs of enhanced water beverages by children and adults are 360 and 624 g/day, respectively.

Table 2. *Per user* two-day average estimated daily intake (EDI) of enhanced water beverages; WWEIA/NHANES 2009-2012

Population	Number of users ^a	% Users	g/day		g/kg bw/day	
			Mean	90th Percentile	Mean	90th Percentile
Children, 2-18 y	85	2.3	262	360	5.7	10.7
Adults, ≥ 19 y	150	1.9	383	624	5.2	9.8
Total, ≥ 2 y	235	2.0	351	595	5.3	9.8

^a Unweighted number of consumers; % user and *per user* estimates based on statistical weights provided by NCHS.

EDIs of Chromium Polynicotinate from the Proposed Use

The *per user* estimated intakes of chromium polynicotinate from the proposed use are presented in Table 3. In the U.S. population ≥ 2 years, the mean and 90th percentile *per user* EDIs of chromium polynicotinate from the proposed use are 202 and 342 $\mu\text{g/day}$, respectively, or 3.1 and 5.6 $\mu\text{g/kg bw/day}$, respectively. On a body weight basis, the 90th percentile *per user* EDI of chromium polynicotinate was lowest among the U.S. population ≥ 2 years and adults ≥ 19 years (5.6 $\mu\text{g/kg bw/day}$) and highest among children ages 2-18 years (6.2 $\mu\text{g/kg bw/day}$).

Table 3. *Per user* two-day average estimated daily intake (EDI) of chromium polynicotinate from the proposed use in enhanced water beverages; WWEIA/NHANES 2009-2012

Population	Number of users ^a	% Users	µg/day		µg/kg bw/day	
			Mean	90th Percentile	Mean	90th Percentile
Children, 2-18 y	85	2.3	151	207	3.3	6.2
Adults, ≥19 y	150	1.9	220	359	3.0	5.6
Total, ≥2 y	235	2.0	202	342	3.1	5.6

^a Unweighted number of consumers; % user and *per user* estimates based on statistical weights provided by NCHS.

EDIs of Chromium and Niacin from the Proposed Use

The *per user* estimated intakes of chromium and niacin from the proposed use are presented in Table 4. In the U.S. population ≥ 2 years, the mean and 90th percentile *per user* EDIs of chromium from the proposed use are 22 and 38 µg/day, respectively, and the mean and 90th percentile *per user* EDIs of niacin from the proposed use are 0.14 and 0.23 mg/day, respectively.

Table 4. *Per user* two-day average estimated daily intake (EDI) of chromium and niacin from the proposed use of chromium polynicotinate in enhanced water beverages; WWEIA/NHANES 2009-2012

Population	Number of users ^a	% Users	Chromium µg/day		Niacin mg/day	
			Mean	90th Percentile	Mean	90th Percentile
Children, 2-18 y	85	2.3	17	23	0.10	0.14
Adults, ≥19 y	150	1.9	24	39	0.15	0.24
Total, ≥2 y	235	2.0	22	38	0.14	0.23

^a Unweighted number of consumers; % user and *per user* estimates based on statistical weights provided by NCHS. Assumed 11% chromium and 67% niacin in chromium polynicotinate based on upper levels in representative samples.

Safety Evaluation

Introduction

Chromium polynicotinate is a complex of trivalent chromium (chromium III) and nicotinic acid. The chromium polynicotinate that is the subject of this GRAS determination is sold under the trade name ChromeMate® CM-100M. Throughout this discussion, the term chromium polynicotinate is used to refer to test substances described as chromium nicotinate or any of the other names for chromium polynicotinate as previously listed in the Description of Substance chapter.

The safe use of chromium polynicotinate as an ingredient in enhanced water beverages was assessed based on a critical review of the safety of the chromium polynicotinate complex. Additionally, the safety of chromium and niacin were also considered. Literature searches were initially conducted in 2014 and recently updated through August 2015. Search terms used included CASRN 64452-96-6, chromium polynicotinate, oxygen-coordinated niacin bound chromium complex, niacin bound chromium, chromium nicotinate. Search engines utilized included the following: Agency for Toxic Substances and Disease Registry (ATSDR); Australia (New Zealand) (to capture governmental agency information, including Australia's National Health and Medical Research Council and New Zealand's Ministry of Health); Centers for Disease Control and Prevention (CDC); European Food Safety Authority (EFSA); Google Scholar; Health Canada; Institute of Medicine (IOM); Joint FAO/WHO Expert Committee on Food Additives (JECFA); National Health and Nutrition Examination Survey (NHANES); National Toxicology Program (NTP); PubMed; Toxicology Data Network (TOXNET); U.S. Department of Agriculture (USDA); U.S. Environmental Protection Agency (EPA); U.S. Food and Drug Administration (FDA); World Health Organization (WHO).

Safety Data on Chromium Polynicotinate

Absorption, Distribution, Metabolism and Excretion (ADME)

Human Studies

The exact mode of absorption and distribution of chromium polynicotinate in humans is unknown. However, the nicotinate complex will be partially broken down into its constituents chromium (III) and nicotinic acid in stomach acid. It is postulated that chromium (III) and nicotinic acid released from the complex would be absorbed by the usual mechanisms, and the remaining chromium polynicotinate would be absorbed as the complex (EFSA, 2008).

In a randomized, blinded, crossover trial conducted by DiSilvestro and Dy (2007), the acute absorption of chromium polynicotinate from a variety of supplements was evaluated based on 24-hour urinary chromium values in twelve young adult, non-overweight females. Doses administered orally delivered 200 µg chromium. Each subject was given each of four different

supplements with at least a 1-week washout period between successive dosing. Two forms of chromium polynicotinate were used, chromium polynicotinate (GTF Chromium; Interhealth) and chromium nicotinate-glycinate (Chelavite; Albion). Subjects provided a 24-hour urine sample prior to the start of supplementation and subjects collected urine for the next 24 hours following supplementation. Subjects were instructed to eat a generally consistent diet for the 24 hours before each supplement ingestion. Subjects were not consumers of chromium-containing supplements at the time of study participation. Chromium levels in the 24-hour urine samples were determined in triplicate. Following supplementation with chromium polynicotinate, the 24-hour urinary chromium values were 339 ± 58 ng, and following supplementation with chromium nicotinate-glycinate, the 24-hour urinary chromium values were 276 ± 78 ng.

Animal Studies

The absorption and retention of three trivalent chromium compounds (chromium chloride, chromium polynicotinate and chromium picolinate) were investigated over a 12-hour period in rats (Olin et al., 1994). Male ($n = 100$) and female ($n = 24$) rats (150 - 170 g) were gavaged with $44 \mu\text{Ci}$ (2.7 nmoles) ^{51}Cr as chromium chloride $\times 6\text{H}_2\text{O}$, chromium polynicotinate or chromium picolinate prepared in a 25% egg white slurry. Urine samples were taken at 6 and 12 hours and assayed for ^{51}Cr . Rats were sacrificed at 1, 3, 6 and 12 hours post-gavage. Cardiac blood was collected and liver, kidneys, pancreas, testes and gastrocnemius were assayed for ^{51}Cr . There were no differences between males and females and therefore these data were combined. On average, 90% of the dose was recovered. The highest retentions for individual tissues were observed in muscle, followed by the blood and liver. For the majority of the time points and tissues, the average percentage of retained ^{51}Cr was higher in rats given chromium polynicotinate than in rats given chromium chloride or chromium picolinate. Tissues collected one hour post-gavage from rats receiving chromium polynicotinate retained 3.2 to 8.4-fold the level of chromium measured in the tissues from chromium picolinate or chromium chloride groups. Three hours post-gavage, the blood, muscle and pancreas from rats administered chromium polynicotinate contained 2.4- to 8-fold the levels of residue measured for chromium picolinate treated rats. By 6 and 12 hours post-gavage, the levels of chromium retained in tissues from rats administered chromium polynicotinate contained 1.8- to 3.8-fold that of the tissues from rats administered chromium picolinate. The percentage of the ^{51}Cr dose retained in body tissues and fluids with respect to the administered dose was less than 1% for all chromium sources at all time points, though the study investigators concluded that there could be significant differences in the bioavailability of different chromium compounds in the rat.

In another study, absorption of radioactive chromium polynicotinate, chromium tripicolinic acid, chromium dinicotinic acid glycine cysteine glutamic acid, and chromium chloride was determined in 6-week old male Wistar rats (Polansky et al., 1993 as cited in EFSA, 2008). Weanling rats were fed a cornstarch-based diet containing less than 30 ng chromium/g for 3 weeks and then subsequently administered 2 μg of radiolabeled chromium by gavage. The rats were sacrificed after 4 and 24 hours, the gastrointestinal tract was removed and the body, minus head and gastrointestinal tract, was counted for radioactivity levels indicative of chromium distribution to those tissues. In all cases, rates of absorption were less than 1% and there were no significant differences between the groups.

In a study by Anderson et al. (1996), the tissue concentrations of chromium from oral administration of nine different chromium compounds including chromium polynicotinate were investigated in weanling (6-weeks of age) rats. Eleven-day-old CD Sprague-Dawley rat pups and their mothers were obtained and raised for an additional 10 days on a low chromium diet containing 30 ± 5 ng chromium/g diet. Each treatment group contained 5 male rats. Control animals received the low chromium diet as well as one group that was raised on the control diet but in stainless steel cages with stainless steel food cups. Treatment groups were administered 5,000 ng chromium per g of diet. Chromium compounds included chromic chloride, chromium acetate, chromic potassium sulfate, chromium dinicotinic acid-diglycine-cysteine-glutamic acid complex, chromium-dinicotinic acid-dihistidine, chromium trihistidine, chromium triglycine, chromium tripicolinic acid, and chromium polynicotinate. After 3 weeks on the diet, rats were fasted for 18 hours and sacrificed. The lowest quarter of the largest lobe of the liver, the left kidney and gastrocnemius muscle from the left side, heart, spleen and lungs were analyzed for chromium content. Serum glucose, cholesterol and triglycerides were measured from blood taken at necropsy. Tissues were rinsed with deionized water and stored frozen. Chromium concentrations were determined by graphite furnace atomic absorption spectrometry using pyrolytically coated tubes. Kidney chromium concentrations following supplementation with chromium polynicotinate were significantly greater than concentrations in the control group. The authors concluded that increases in chromium concentration in the liver, spleen, lung, gastrocnemius muscle, and heart in animals consuming 5,000 ng chromium/g diet as chromium polynicotinate were not statistically significant. Increases in kidney chromium levels in the animals consuming the chromium polynicotinate supplemented diets were more than 10-fold those observed in any of the other tissues.

Anderson and colleagues (1996) investigated the absorption and retention of chromium in six week old male rats gavaged with $0.15 \mu\text{g}$ chromium containing $0.318 \mu\text{g}$ radioactive ^{51}Cr . The radioactive chromium was administered as various chromium salts, including chromium polynicotinate synthesized using radioactive chromium. Five rats were assigned to each chromium salt type ($n = 5$) and only a single dose level was tested. Based on the number of counts in the animals after removal of the gastrointestinal tract divided by the total number of counts measured in the animals 10 minutes after chromium administration, the study authors calculated the absorption and retention of chromium polynicotinate as the percent of dose in the whole body. The apparent absorption of chromium from chromium polynicotinate as a percent of the administered dose was $1.3 \pm 0.3\%$ after 4 hours and $1.0 \pm 0.5\%$ after 24 hours. The amount of labelled chromium in the blood after 4 hours for chromium polynicotinate was $0.05 \pm 0.005\%$ and after 24 hours was $0.019 \pm 0.004\%$, which was significantly lower than the level at 4 hours. The absorption and retention of chromium polynicotinate was not significantly different from the control. Incorporation of labelled chromium in the animals and tissues were not significantly different from control and were similar after 4 and 24 hours.

In the study by Lachinsky et al. (2012), pharmacokinetic parameters of chromium (III) compounds were studied in rats after oral and parenteral administration. In this study, female Wistar rats (200-300 g) were fasted for 4-6 hours before and 1 hour after the respective administration of labelled ^{51}Cr -compounds (chromium picolinate, chromium polynicotinate, chromium phenylalaninate, chromium propionate, or chromium chloride. Aqueous solutions were administered by gastric intubation, intraperitoneal (i.p.) or intravenous (i.v.) (tail vein)

injections. After administration, rats were housed in cages of 3-4 rats/cage except in some experiments in which some rats were housed in individual metabolic cages over 2 days for quantitative collection of urine and feces. The rats were sacrificed and radioactivity in excrement and tissues was measured. The authors concluded that the rather ionic and water soluble compounds such as chromium phenylalaninate and chromium chloride were significantly better absorbed and retained than the more organic, poorly soluble complexes including chromium tripicolinate, chromium polynicotinate, and chromium propionate. The authors also stated that the true intestinal chromium absorption of most chromium compounds was remarkably different from the retention values due to substantial and rapid urinary excretion of recently absorbed ^{51}Cr . The amount of absorbed ^{51}Cr was very low from all compounds under study, and the authors stated that the precise long-term measurements of retained ^{51}Cr was only possible after i.p. or i.v. injection. Following the ^{51}Cr -whole-body-retention for up to 7 weeks, retention curves were similar for all chromium compounds under study, except for chromium tripicolinate due to excretion of the compound by the kidneys. The whole body retention of $^{51}\text{Cr(III)}$ from chromium picolinate, chromium polynicotinate, chromium phenylalaninate, chromium propionate, or chromium chloride was generally low (0.04-0.24%) in rats with slightly higher values for chromium chloride and chromium phenylalaninate.

Altogether, studies in animals reveal very low bioavailability for chromium (approximately 0.5-2%) regardless of the identity of the particular chromium complex, including chromium nicotinate (Olin et al, 1994; EFSA, 2008; Anderson et al., 1996; Lachinsky et al., 2012).

Pre-Clinical Data

Acute Oral Toxicity

In the acute oral toxicity study by Shara et al. (2005), Sprague-Dawley rats (3/sex/dose, age 10-11 weeks) were administered a single dose of chromium polynicotinate at 5,000 mg/kg bw in demineralized water by gavage. On the day of dosing, all the animals were observed for mortality and signs of intoxication at 30 minutes, and 1, 2, 4, and 6 hours following dosing. Thereafter, they were observed twice daily for 14 days. Body weights of rats were individually recorded before dosing, and at weekly intervals thereafter. Group mean body weights were calculated. All animals were sacrificed at the end of the observation period and subjected to a necropsy. Chromium polynicotinate did not cause any mortality and did not induce any signs of toxicity in the treated male and female rats following dosing and during the observation period. The body weight gain of treated rats was not found to be adversely affected. No gross pathological alterations were evident at terminal necropsy in any of the rats. Based on these results and under the conditions of this study, the oral lethal dose, 50% (LD_{50}) was $> 5,000$ mg/kg bw. This study was conducted in accordance with Organisation for Economic Cooperation and Development (OECD) guideline 425 and under Good Laboratory Practice (GLP).

Short-Term Toxicity

A study of the short-term toxicity of chromium polynicotinate was reported in a patent filed for the chromium polynicotinate complex (U.S. Patent 5,194,615; Jensen, 1993); this study was cited by EFSA in a review of chromium safety (EFSA, 2008). In this study, 15 male albino rats (180 to 200 g) were placed on a synthetic rat diet for 2 weeks. The rats were then divided into three groups of five. Group 1 was maintained on the synthetic diet (control group). Group 2 was fed the diet with 10 mg/kg chromium polynicotinate added to the drinking water, which was reported to be equivalent to approximately 1.5 mg/kg bw/day assuming 200 g bw and consumption of 30 ml drinking water/day. Group 3 was fed the diet with 10 mg/kg chromium chloride added to the drinking water, which was reported to be equivalent to approximately 1.5 mg/kg bw/day assuming 200 g bw and consumption of 30 ml drinking water/day. This diet regime was maintained for six weeks. Each animal was weighed every two weeks. At the end of six weeks of treatment, all animals were euthanized and subjected to necropsy and the organs were assayed for chromium content. Blood was collected from each rat and serum was assayed for glucose, triglycerides and cholesterol. As reported in the patent, the authors concluded that the growth rates of the rats from each group demonstrated that the diet supplemented with chromium polynicotinate had a marked effect on the total body weight (supporting data on the % total body weight change were not available in the patent). The growth rates of rats from groups 1 and 3 were almost parallel until the toxicity of chromium chloride caused a decrease in the weight of the animals in group 3. The results of the serum analysis indicated that compared to the control group, serum glucose levels were 2.6-fold lower in the chromium polynicotinate group and 2.2-fold lower in the chromium chloride group. In the patent, the authors also concluded that chromium polynicotinate had a marked effect on the total fat content in the rats. Cholesterol levels were similar across the control, chromium polynicotinate, and chromium chloride groups (53, 48, and 52 mg/dL, respectively). The serum triglyceride level in the control group was 86 mg/dL while levels in the chromium polynicotinate and chromium chloride groups were lower at 49 and 64 mg/dL, respectively. Statistical significance was not reported. There were no reports of gross effects on the body organs examined. Results showed that chromium contents in the heart, liver, spleen, kidney and muscle of rats receiving chromium polynicotinate or chromium chloride were maximally 2.75-fold higher for the chromium polynicotinate treated animals and 6.2-fold higher for chromium chloride treated animals compared to those in the control group. In the control and chromium polynicotinate groups, chromium was found primarily in the liver. In the chromium chloride group, the level of chromium in the liver was comparable to levels in rats in the other treatment groups (control, chromium polynicotinate), though chromium was most concentrated in the kidney. The concentration of chromium in heart, liver, spleen, kidney and muscle tissue of rats supplemented with chromium polynicotinate were 84, 69, 146, 39 and 75% of the values for the chromium chloride group, respectively. This unpublished study was not of conventional toxicological design.

Anderson et al. (1996), conducted a short-term 6-week feeding study reporting ADME parameters as well as some indicators of the safety of various forms of chromium including chromium picolinate. The detailed study design is described above under the section on ADME. For the safety parameters measured, the authors reported that the different forms of chromium at 5000 ng chromium/kg diet did not significantly alter body weight after three weeks of treatment. All forms of chromium tested resulted in decreased epididymal fat pad weight, lower testes

weight and lower liver weights. Kidney, heart and spleen weights were not significantly altered by dietary chromium. No changes were reported in serum triglycerides or cholesterol; glucose levels were only significantly lower than the controls for the chromium dinicotinic acid-diglycine-cysteine-glutamic acid complex. This study was not of conventional toxicological design.

Subchronic Toxicity

Shara et al. (2005) reported a 30, 60 and 90-day subchronic toxicity study in rats with chromium polynicotinate. In this study, Sprague-Dawley rats (6/sex/dose/time point, age 5-6 weeks) were given either 0 ppm, 5 ppm, 50 ppm, or 125 ppm of chromium polynicotinate per day for up to 90 consecutive days in the diet. Food and water consumption were measured twice or thrice weekly. Mortality and morbidity were evaluated once daily on weekdays, weekends and holidays. Clinical signs were evaluated once- to- twice daily. Body weights and ocular health observations were recorded on day one, weekly thereafter, and before necropsy. Selected organ weights as percentages of body and brain weight, hematology, clinical chemistry, hepatic lipid peroxidation and deoxyribonucleic acid (DNA) fragmentation were assessed following 30, 60 or 90 days of treatment. Organs including adrenal glands, brain, epididymides, esophagus, eyes, heart, intestine, kidney, liver, lymph nodes, lungs, mammary glands, ovaries or testes, pancreas, pituitary, prostate, salivary glands, seminal vesicles, skin, and spleen were weighed and either processed immediately or appropriately preserved and stored.

No differences in body weight, food consumption or water consumption were reported for treated animals compared with control groups following 30, 60 or 90 days of exposure. No significant differences were observed in organ weights (absolute, relative to body weight or relative to brain weight) for treated animals compared with control groups following 90 days of exposure. Chromium polynicotinate treatment had no effect on hepatic DNA fragmentation in male and female rats in any of the treatment groups. No significant differences were reported for hematology or clinical chemistry parameters (white blood cells, red blood cells, hemoglobin, hematocrit, mean corpuscular volume, mean corpuscular hemoglobin, mean corpuscular concentration, platelet count, reticulocyte count, segmented neutrophils, absolute banded neutrophils, lymphocyte, monocyte, eosinophils, basophils, total serum protein, total albumin, globulin, alkaline phosphatase, blood urea nitrogen, creatinine, aspartate aminotransferase, cholesterol, total bilirubin, glucose, calcium, chloride, phosphorus, sodium, potassium, iron, total iron binding capacity and iron/total iron binding). No histopathological changes were attributed to treatment with chromium polynicotinate.

The NOAEL in this study was 125 ppm chromium polynicotinate, the highest dose tested. A lowest-observed-adverse-effect-level (LOAEL) was not established. Based on the method by Derelanko and Auletta (2014), the NOAEL conversion of 125 ppm chromium polynicotinate is equivalent to 6.25 mg chromium polynicotinate/kg bw/day (males and females, combined).

Reproductive Toxicity

U.S. Patent 5,194,615: Jensen, 1993 includes a study of placental transfer of chromium; this study was cited by EFSA in a review of chromium safety (EFSA, 2008). In this placental transfer study, fifteen timed-pregnant albino rats were used. From the study description available, it is unclear on which gestation days treatment commenced and ceased. After an equilibration period of one week, animals were then divided into three groups of five animals each. Group 1 was maintained on the semi-purified rat diet (control group). Group 2 was fed synthetic diet with 10 mg/kg chromium polynicotinate added to the drinking water, calculated to amount to 1.5 mg/kg bw/day assuming 200 g bw and consumption of 30 ml drinking water/day. Group 3 was fed synthetic diet with 10 mg/kg chromium chloride added to the drinking water, calculated to amount to 1.5 mg/kg bw/day assuming 200 g bw and consumption of 30 ml drinking water/day. This diet regime was maintained for one week, after which the animals were weighed and sacrificed, and the organs and fetuses analyzed for chromium content. Blood was collected from each rat and the serum assayed for glucose, triglycerides and cholesterol. Jensen (1993) reported that the fetal tissue chromium concentration in the chromium polynicotinate group achieved a 30% increase compared to the control group and a 21% increase compared to the chromium chloride group.

Change in body weight was calculated based on weights after parturition and before dissection. Reductions in mean body weight were reported as 2.1% in the control group, 10.3% in the chromium polynicotinate treated group and 4.3% in the chromium chloride treated group (Jensen, 1993). The results of the serum analysis indicated that compared to the control group, serum glucose levels were 3.8-fold lower in the chromium polynicotinate group and 4.4-fold lower in the chromium chloride group. Cholesterol levels in the control, chromium polynicotinate, and chromium chloride groups were 80, 61, and 93 mg/dl, respectively. The serum triglyceride level in the control group was 69 mg/dL while levels in the chromium polynicotinate and chromium chloride groups were 76 and 104 mg/dl, respectively. Statistical significance was not reported for chromium content, body weight change or serum analysis. No adverse effects were reported. Jensen (1993) concluded that the data demonstrated that chromium from both chromium salts is transported across the placenta; Jensen (1993) also concluded that chromium polynicotinate “does exhibit biological activity”, though it is not concentrated in tissues and toxicity is very low. This unpublished study was not of conventional toxicological design, and the conclusions made by Jensen have not been peer-reviewed.

In the patent, Jensen (1993) reported an additional study on timed-pregnant albino rats in which the body weight and organ analysis for chromium content was assessed after exposure for 10 days rather than 7 days as described in the study above. The average chromium content in the fetus of rats in the chromium polynicotinate group was 1.665 versus 1.269 µg per fetus in the control group; the chromium content of the fetus in the chromium chloride group averaged 1.142 µg per fetus. Statistical significance was not reported. As opposed to the study above, in this study the body weights were determined before dissection but not before parturition, which did not account for the weight of the fetuses or fluid retention in the study. However, in the patent Jensen reported that the weight change was found to be approximately the same for Group 1 and Group 2, and both Groups 1 and 2 were less than Group 3. Reduction in body weight was reported as 9.1% for the control group, 9.3% in the chromium polynicotinate group and 14.7% in

the chromium chloride group. Jensen (1993) stated that the data from the second study of placental transfer verified the improved transport of the chromium polynicotinate complex over chromium chloride and reconfirmed the lack of toxicity of chromium polynicotinate in contrast to the toxicity of chromium chloride in the kidney. This study was not of conventional toxicological design and was not peer-reviewed.

Deshmukh et al. (2009a) evaluated the effects of chromium polynicotinate in a two-generation reproduction study in Sprague-Dawley rats. The study was based upon the United States Food and Drug Administration (FDA) Redbook Guidelines for Reproduction Studies IV.C.9.a and Guidelines for Developmental Toxicity Studies IV.C.9.b., Food Additive Safety and was GLP compliant by OECD standards. The chromium polynicotinate tested in the study was a patented oxygen-coordinated niacin-bound chromium (III) complex commercially known as ChromeMate® CM-100 M (powder) (U.S. Patents 4,923,855, 4,954,492 and 5,194,615). Chromium polynicotinate [Lot#306013] was provided by the study sponsor InterHealth Nutraceuticals, Benicia, CA, USA. Rats (7-9 weeks of age, 30/sex/dose) were maintained on feed containing chromium polynicotinate at 0, 4, 15, or 60 ppm for 10 weeks prior to mating, during mating, and, for females through gestation and lactation, across two generations. Since chromium polynicotinate may be consumed by human beings up to a maximum dose of 4 mg of chromium polynicotinate/day, the highest dose level for this study was selected so as not to exceed 100 times the maximum recommended human dose, which was calculated as a dietary equivalent concentration of 60 ppm. Test material intake was determined to be 0, 0.38, 1.48 and 5.88 mg/kg bw/day for F₀ males, 0, 0.49, 1.94 and 8.24 mg/kg bw/day for F₀ females, 0, 0.43, 2.47 and 9.71 mg/kg bw/day for F₁ males and 0, 0.66, 2.53 and 9.83 mg/kg bw/day for F₁ females. For the parents (F₀ and F₁) and the offspring (F₁ and F_{2a}), reproductive parameters such as fertility and mating, gestation, parturition, litters, lactation, sexual maturity and development of offspring were assessed.

Deshmukh et al. (2009a) did not observe effects on food consumption for treated rats when compared to the respective control groups. There were no remarkable incidences of mortality or clinical signs; all deaths and abnormal clinical signs observed in the rats during F₀ and F₁ generations, such as transient/reversible spells of emaciation, abdominal breathing, respiratory rales, hypoactivity, circling disorder and lacrimation, were considered by the authors to be incidental and not treatment-related. No effects on body weight or body weight gain were reported for parental F₀ and F₁ generations or in F₁ and F_{2a} offspring when compared to the respective control groups. Exposure of male and female rats, from both the F₀ and F₁ generations, to chromium polynicotinate at levels of up to 60 ppm in the diet during premating and mating periods and the gestation period in females did not reveal any treatment-related adverse effects on reproductive performance in terms of fertility and mating, gestation, parturition and the litters born. Similarly, the unaltered length and normalization of estrous cycles in treated females, mating performance as evidenced from unaltered indices of male fertility and female fertility were evidence of a lack of reproductive toxicity. Maintenance of normal gestation was evident from unaltered gestation length and gestation indices. Furthermore, the pups born alive did not exhibit signs of toxicity or developmental effects and live birth indices were within normal range. The values of male fertility indices for treatment groups in F₀ and F₁ generations did not differ significantly from those of the controls, and were comparable with the historical control data for the test facility. The values of male fertility

indices for the F₀ generation in control, 4, 15 and 60 ppm groups were 90%, 100%, 80% and 92.2%, respectively. Similarly, these values for treatment groups in F₁ generation were 96%, 103%, 100% and 100%, respectively. For both the F₀ and F₁ generations exposed to chromium polynicotinate at up to 60 ppm in the diet, evaluations of sperm parameters for male rats during the premating and mating period, and the period thereafter up to their termination, did not reveal any changes that could be attributed to the test article. No changes were reported in organ weight group mean values of absolute and relative weight (% of body weight and % of brain weight) of liver, kidneys, brain, spleen, adrenals, pituitary, testes, seminal vesicles (with Cowper's glands), prostate, epididymides, ovaries and uterus when compared to respective control groups. The group mean values of absolute and relative weights (% of body weights and % of brain weights) of the brain, spleen and thymus from pups of the F₁ and F_{2a} generation were not significantly different between the control and treatment groups. No gross pathology or histopathology effects were reported in parental F₀ and F₁ generation animals or in the F₁ and F_{1a} generation offspring. Comparison of the offspring data with respective control groups and also across the F₁ and F_{2a} generations did not reveal any adverse effects on litter size, sex ratio, live birth indices or viability indices for days 4, 7, 14 and 21 of lactation for all dietary levels of chromium polynicotinate evaluated. Sexual maturation was only measured for the F_{2a} generation, and reported as age of balano-preputial separation in males and vaginal opening in females. There was no effect on the age of sexual maturity for the F_{2a} generation. For the F₁ and F_{2a} generations compared to controls, there was no effect on landmarks of physical development including days required for unfolding of ear pinna, hair growth on the body, time (days) for eruption of teeth, and opening of eyes and ears. The NOAEL for all effects measured was 60 ppm dietary, the highest level tested in the study. For the purpose of this review, the most conservative NOAEL on a mg/kg bw/day at the 60 ppm dietary level translates to 5.88 mg/kg bw/day, for F₀ males, though NOAELs for other groups were higher. NOAELs for parental toxicity, reproductive toxicity and offspring toxicity were as follows:

- F₀ males: 5.88 mg/kg bw/day
- F₀ females: 8.24 mg/kg bw/day
- F₁ males: 9.71 mg/kg bw/day
- F₁ females: 9.83 mg/kg bw/day

Developmental Toxicity and Teratogenicity

The study by Deshmukh et al. (2009b) evaluated the developmental toxicity of chromium polynicotinate in Sprague-Dawley rats. The study was based upon the United States FDA Redbook Guidelines for Reproduction Studies IV.C.9.a and Guidelines for Developmental Toxicity Studies IV.C.9.b., Food Additive Safety and the OECD principles of GLP. Test articles were the same as those utilized in the two-generation reproductive study by Deshmukh et al. (2009a) and rats were obtained from the F_{2b} generation of that study. Rats (30/sex/dose) were 10-12 weeks of age before mating. The male and female animals from the treatment groups were subjected to indirect exposure to chromium polynicotinate during lactation and to direct exposure of chromium polynicotinate by dietary admixture, from the time they were weaned (i.e., from the 4th week of life) up to sacrifice (including growth phase, mating period and gestation). Chromium polynicotinate dietary exposure levels of 4, 15, or 60 ppm in this study were the same as those employed for the two-generation reproductive toxicity study. Mean test

material intake was calculated by the authors to be 0.49, 1.57, or 5.86 mg/kg bw/day, respectively. Following mating at maturity, the pregnant rats were observed daily for clinical signs of adverse effects and body weight and feed consumption were recorded. On day 20 of gestation, animals were subjected to a necropsy and caesarean section to examine the uterus, ovaries and fetuses for assessment of different parameters of pregnancy and embryo-fetal defects.

No changes were reported in sperm positive females (mating behavior), maternal deaths during pregnancy, number of pregnant/nonpregnant females, pregnancy rate (%), and females with resorptions between the control group rats and niacin-bound chromium (III) complex (NBC) groups. Chromium polynicotinate feeding at dietary levels of 0, 4, 15, or 60 ppm did not affect maternal body weight on days 0, 7, 14, and 20 of gestation. No treatment-related clinical abnormalities were observed in any of the groups. At terminal necropsy on day 20 of gestation, no remarkable gross pathological changes were noted in dams of control or any of the chromium polynicotinate-treated groups. Observations made on the gravid uteri of females euthanized on day 20 of gestation did not reveal any remarkable alterations indicative of adverse effects of chromium polynicotinate on absolute and relative uterus weight, number of corpora lutea, number of implantations, number of live and dead implants, number of early and late resorptions, and pre- and post-implantation losses (%). No effects on the alterations in litter size, number of fetuses, sex ratios of the fetuses, and fetal weights were reported in the study. There were no treatment-related adverse fetal external, visceral or skeletal observations reported in the study. Based on the study findings, the study investigators reported NOAELs for chromium polynicotinate as follows:

- NOAEL for maternal toxicity: 60 ppm chromium polynicotinate (highest dose tested), 5.86 mg/kg bw/day
- NOAEL for developmental toxicity: 60 ppm chromium polynicotinate (highest dose tested), 5.86 mg/kg bw/day

Neurotoxicology

No neurotoxicity data for chromium polynicotinate were identified.

Immunotoxicity

No immunotoxicity data for chromium polynicotinate were identified.

Genotoxicity

Ames Assay

The *Salmonella typhimurium* reverse mutation test was conducted to determine the ability of chromium polynicotinate to induce mutation in DNA. The plate incorporation method was utilized with strains TA 1535, TA 97a, TA 98, TA 100 and TA 102 in the presence and absence of a metabolic activation system (S9). This study was conducted under OECD guideline 471 and

GLP. Under the conditions of this study, chromium polynicotinate was not mutagenic (Shara et al., 2005).

In Vitro Mammalian Cell Mutation

Shara et al. (2005) investigated the mutagenic potential of chromium polynicotinate (identified as niacin-bound chromium (III) complex) in an L5178Y TK (+/-) mouse lymphoma assay. The assay was performed with and without metabolic activation. The solvent, diluent and negative control used in this assay was dimethyl sulfoxide. Concentrations of 1, 2.5, 5, 10, 25, 50, 100 and 200 µg/ml of chromium polynicotinate were tested in comparison to negative (vehicle) controls without the metabolic activation system. In the confirmatory 24-hour treatment, the same concentrations of chromium polynicotinate were tested. Relative total growth, the plating efficiencies and mutant frequencies observed in the negative and positive controls were critically reviewed. Each trial consisted of duplicate cultures of the negative (vehicle) and positive controls, and single cultures treated at each of the eight dosage levels of chromium polynicotinate. Following a 2-day expression period, cultures were assessed for viability and cloning efficiency. The mutant frequency was expressed as the number of mutant colonies per million surviving cells at the time of mutant selection. Chromium polynicotinate-associated toxicity, as evidenced by relative total growth, was not observed in this study. There was evidence of substance-related precipitate at concentration levels of 50 (without activation only), 100 and 200 µg/ml. The plating efficiencies and mutant frequencies observed in the negative and positive controls were within the acceptable range in this study. This study was conducted under GLP. Under the conditions of this study, no evidence of mutagenic activity was detected and chromium polynicotinate was concluded to be negative for the induction of mutagenicity in this assay.

In Vitro Chromosome Aberration

Stearns et al. (1995) investigated the chromosome damaging ability of chromium (III) complexes in Chinese hamster ovary cells. Chinese hamster ovary AA8 cells were treated for 24 hours with stock solutions of aqueous chromium polynicotinate or stock suspensions of particulate chromium polynicotinate in acetone. Stock solutions were diluted with 0.28 mM NaOH to give 0.10 M chromium polynicotinate for cell treatment. Controls consisted of untreated cells and cells treated with 200 µL of acetone alone. Cytotoxicity was measured as a reduction in plating efficiency of treated groups relative to controls (untreated or acetone). Colcemid was added at the last 30-40 minutes of treatment. Experiments were carried out in triplicate or quadruplicate, with 100 metaphases analyzed for each experiment. Acetone treatment (200 µL) produced no reduction in colony formation. Soluble chromium polynicotinate treatment was nontoxic, and ≥93% survival was observed up to the 2.0 mM dose. Soluble chromium polynicotinate was nontoxic at all doses tested, producing $97 \pm 3\%$ survival from 10 µM to 2.0 mM. Particulate chromium polynicotinate treatment produced ≥89% survival up to the 8.0 µg/cm² dose only, which would correspond to 0.10 mM chromium polynicotinate if completely dissolved. However, the particulate chromium polynicotinate may be relatively insoluble, and the difference in toxicities may be due to two different uptake mechanisms for soluble and particulate chromium polynicotinate. Chromium polynicotinate was not clastogenic at doses equivalent to 50 µM to 1.0 mM for soluble chromium polynicotinate and up to 40 µg/cm² for

particulate chromium polynicotinate. Clastogenic effects in Chinese hamster ovary cells occurred upon exposure to high concentrations of chromium picolinate added to the medium. Clastogenicity was not exhibited by chromium chloride, chromium polynicotinate, or nicotinic acid. Chromium polynicotinate achieved 18-fold greater cell concentrations than chromium picolinate and did not produce chromosomal aberrations compared to chromium picolinate (Stearns et al., 1995; EFSA, 2008).

Oxidative Stress/DNA Fragmentation

Comparative induction of oxidative stress in cultured murine macrophage cells (J774A.1) by chromium picolinate and chromium polynicotinate were evaluated by Bagchi et al. (2002). The macrophage cells were treated with a range of concentrations (0, 10, 30 and 50 µg/ml) of the two salts for 0 and 24 hours at 37°C. Small dose-dependent increases in lipid peroxidation, superoxide anion and hydroxyl radical production and DNA fragmentation were observed with both chromium salts. Greater increases in superoxide anion production and DNA fragmentation were observed with chromium picolinate in comparison to chromium polynicotinate. Approximately 1.0-, 1.1- and 1.5-fold increases in cytochrome c reduction were observed following incubation of these cells with 10, 30 and 50 mg/ml concentrations of chromium (III) picolinate, respectively, as compared with the control untreated cells. Under the same experimental conditions, approximately 1.0-, 1.0- and 1.2-fold increases in cytochrome c reduction were observed following treatment with the same concentrations of chromium polynicotinate. Neither chromium salt resulted in a significant decrease in cell viability in comparison to the control, but it was concluded that both of these chromium salts induce low levels of oxidative stress in cultured macrophage cells (Bagchi et al., 2002; EFSA, 2008).

Carcinogenicity and Chronic Toxicity

Preuss et al. (2001) found that rats fed large amounts of chromium polynicotinate for over a year exhibited no evidence of toxicity. One hundred and four hybrid (Brown Norway/Fischer 344) rats were equally divided after a weaning and an acclimatization period of 5 weeks into two groups for treatment (52/dose). The sex of the rats was not reported by the authors; it is inferred that only male rats were tested based on the inclusion of epididymal fat pad weight. Group 1 received standard diet and Group 2 received standard diet supplemented with chromium polynicotinate (ChromeMate, InterHealth Nutraceuticals, Inc., Benicia, CA, USA) at 5 mg/kg diet, zinc monomethionine and 200 mg grape seed extracts (GSE)/day. At the end of the study, blood chemistry values were measured. Additionally, randomly selected rats were used from each group for evaluation of lipid peroxidation/free radical formation (hepatic thiobarbituric acid reactive species (TBARS) formation). Systolic blood pressure (SBP) measurements were made twice a week. Body weight gains were virtually the same between the two groups over the one-year dietary study period. The weights of hearts, kidneys and livers were not significantly different among groups. However, the weight of epididymal fat pad was significantly less at 12 months in Group 2. Almost from the initiation of the treatment, the SBP figures of Group 2 were significantly lower compared to Group 1 (control). Hepatic TBARS formation, an estimate of lipid peroxidation, was significantly lower after 1 year in Group 2 and HbA1C, a marker of longer term blood glucose levels, was also significantly lower in Group 2. It was concluded that prolonged supplementation with a combination of agents including GSE in addition to chromium

polynicotinate can markedly lower SBP in normotensive rats, lessen oxidative damage to fats, and lower HbA1C without showing signs of toxicity. This study was not of conventional toxicological design and the significance of some of the endpoints measured is unclear.

In a study by Perricone et al. (2010), Sprague-Dawley rats (10/sex/dose) were administered chromium polynicotinate in a high sucrose diet for 150 days. Concentrations of chromium polynicotinate in the diet were 0, 2.8, 8.7, and 28 ppm, which are roughly equivalent to human doses of 1000 (1X), 3000 (3X), and 10,000 (10X) µg/day, respectively. During the first phase of the study (Days 0-150) animals (male and female) received chromium polynicotinate and basal diet. During days 151-312 (Phase 2), chromium polynicotinate was administered via the diet as in Phase 1, but for two satellite groups provided 8.7 and 28 ppm dietary levels, chromium treatment was removed. Phase 3 of the study included males only (Days 313-460). During this phase, males received treatment at the same levels as in Phases 1 and 2, but two satellite groups at the 8.7 and 28 ppm dietary levels also received a supplement formula containing antioxidants and other factors. Blood pressure, nitric oxide, insulin systems and inflammatory parameters were examined. No differences were detected between males and females. Blood pressure effects related to potential positive health outcomes were reported though these effects did not indicate toxic potential. No signs of toxicity were observed. This study was not of conventional toxicological design.

Shara et al. (2007) investigated the long-term effects of chromium polynicotinate in male and female Sprague-Dawley rats. The chromium polynicotinate utilized in the study was an oxygen-coordinated niacin-bound complex, which is the commercial product ChromeMate CM-100M (powder) (U.S. Patents 4,923,855, 4,954,492 and 5,194,615). Chromium polynicotinate [Lot # 0410013] was obtained from InterHealth Nutraceuticals, Benicia, CA, USA. In this study, rats 5-6 weeks of age were administered chromium polynicotinate at doses of 0 or 25 ppm in the feed for up to 52 weeks. Test material intake was calculated to be 1.7 mg/kg bw/day for males and 2.2 mg/kg bw/day for females as determined by EFSA (2014). Six male and female rats were used per each group and time point, and groups of animals were sacrificed at 26, 39, and 52 weeks of treatment. Food and water consumption were measured twice or thrice weekly. Mortality/morbidity was evaluated once daily on week days, weekends and holidays. Clinical signs were evaluated once to twice daily. Body weights and ocular health observations were recorded on day one, weekly thereafter, and before necropsy. Selected organ weights as such and as percentages of body and brain weight, hematology, clinical chemistry, hepatic lipid peroxidation and DNA fragmentation were evaluated at 26, 39, and 52 weeks of treatment. White blood cells, red blood cells, hemoglobin, hematocrit, mean corpuscular volume, mean corpuscular hemoglobin, mean corpuscular concentration, platelet count, reticulocyte count, segmented neutrophils, absolute banded neutrophils, lymphocyte, monocyte, eosinophils, basophils, total serum protein, total albumin, globulin, alkaline phosphatase, blood urea nitrogen, creatinine, aspartate aminotransferase, cholesterol, total bilirubin, glucose, calcium, chloride, phosphorus, sodium, potassium, iron, total iron binding capacity and iron/total iron binding capacity parameters were determined in each sample. Organs including adrenal glands, brain, epididymides, esophagus, eyes, heart, intestine, kidney, liver, lymph nodes, lungs, mammary glands, ovaries or testes, pancreas, pituitary, prostate, salivary glands, seminal vesicles, skin, spleen, stomach, thymus, thyroid glands, trachea and urinary bladder, were collected and

weighed at necropsy on 26, 39 and 52 weeks of treatment. Histopathological evaluations were performed.

Routine observations did not reveal any physical or ocular treatment-related effects at any time during the study period. At 26, 39, or 52 weeks of treatment, body weight gain was significantly reduced by 7.7%, 8.1% and 14.9% in male rats, and 5.5%, 11.4% and 9.6% in female rats, respectively, in the chromium polynicotinate treatment groups. There was no statistical difference in the mean body weights at any time point. There were no statistically significant differences in the food or water consumption patterns of chromium polynicotinate-supplemented animals relative to their corresponding controls. No significant differences in absolute or relative organ weights were observed in any of the treatment groups as compared to the control groups. A slight reduction in hepatic lipid peroxidation was observed in all chromium polynicotinate-treated samples as compared to the control samples. No significant differences were observed in clinical chemistry or hematology in any of the treatment groups as compared to the control groups. No treatment-related histologic findings were reported. This study was not of conventional toxicological design due to the inclusion of only one treatment level which limits the ability to appropriately evaluate dose-response.

Since there was no statistically significant reduction in mean body weight of the groups, the body weight gain reduction of 5.5-14.9% is of limited biological relevance and not considered to be adverse. Table 5 below presents the mean body weight and body weight gain data as provided by the study investigators (Shara et al., 2007). The EFSA CONTAM Panel (EFSA Panel on Contaminants in the Food Chain) did not consider the statistically significant decreases in body weight gain in this study to be adverse (EFSA, 2014). A NOAEL of 1.7 mg/kg bw/day for males and 2.2 mg/kg bw/day for females was assigned by EFSA (2014) based on the absence of adverse effects at the 25 ppm dietary level.

Table 5. Mean body weight and body weight gain in chronic study of chromium polynicotinate by Shara et al. (2007)

Week	Males – Control	Males – 25 ppm Chromium Polynicotinate		Female - Control	Females – 25 ppm Chromium Polynicotinate	
	Mean BW (g)	Mean BW (g)	% BW gain	Mean BW (g)	Mean BW (g)	% BW gain
26	518.78±28.27	481.11±38.66	-7.7*	298.5±25.41	283.05±21.70	-5.5*
39	574.7±41.78	532±51.44	-8.1*	332.17±49.45	298.25±18.93	-11.4*
52	637.4±50.31	554.6±52.67	-14.9*	323.0±28.63	294.67±14.09	-9.6*

* BW (body weight) gain was reported as statistically significant ($p < 0.05$) from control values.

Human Studies

Clinical studies of the effects of chromium polynicotinate in adults, including healthy adults and adults with chronic conditions such as obesity, hypercholesterolemia, or cardiovascular disease have been conducted and reported. Chromium polynicotinate was consumed daily for periods ranging from 8 to 9 weeks in five studies, and from 13 to 16 weeks in three studies (Table 6). Assuming that chromium accounts for approximately 10% by weight of the chromium polynicotinate complex, daily intake of chromium polynicotinate ranged from approximately 400 to 8000 µg/day while daily intake of chromium was approximately 40 to 800 µg/day.

In general, these studies were focused on possible beneficial effects of chromium polynicotinate intake, studying effects on body weight, routine blood chemistry, fat and non-fat body mass, insulin response to an oral glucose load, plasma insulin, glucose, total cholesterol, triglycerides, HDL-cholesterol, LDL-cholesterol and 1-hour post-challenge insulin and glucose values and antidepressant therapy of dysthymic disorder (Aghdassi et al., 2010; Crawford et al., 1999; Grant et al., 1997; Guimarães et al., 2013; Lefavi et al., 1993; Preuss et al., 2000; Thomas and Gropper, 1996; Wilson and Gondy, 1995). These studies were not designed to study the safety of chromium polynicotinate, though no adverse effects were reported other than mild, primarily transient gastrointestinal disturbances. The clinical studies of chromium polynicotinate supplementation at levels of intake ranging from 400 to 8000 µg/day provide no evidence of untoward effects under these conditions of use.

Table 6. Repeat-intake clinical studies of chromium polynicotinate

Reference	Study Design	Intervention	Test Dose as Chromium Polynicotinate (µg/day) and Duration ^a	Test Dose as Chromium (III) (µg/day) ^a	Endpoints	Safety Results of Test Group
Aghdassi et al., 2010	RCT 46 adults HIV+ with elevated glucose, lipids, or evidence of body fat redistribution, with insulin-resistance Mean age 48 y	Test: -400 µg (200 µg pills, twice per day) of chromium polynicotinate (n=23) Control: -Placebo of di-calcium phosphate (n=23) Source: by Interhealth Nutraceuticals Inc., Benicia, California	0 or 400 Duration: 16 wk	0 or 40	Fasting blood insulin, glucose, lipid profile and body composition were measured before and after intervention.	Chromium was tolerated without side effects; chromium improved insulin resistance, metabolic abnormalities, and body composition in HIV+ patients.
Crawford et al., 1999	RCT, crossover 18 overweight African American women Age not specified	Test: -600 µg chromium polynicotinate (provided 3x/day as 200 µg/day) (n=8, 10) Control: -placebo (provided 3x/day) (n=10, 8) Source: ChromeMate ® Interhealth Nutraceuticals Inc., Benicia, California	0 or 600 Duration: 2 mo	0 or 60	Blood chemistries measured by routine clinical methods. Fat and nonfat body masses estimated using bioelectrical impedance.	Significant loss of fat and sparing of muscle compared to placebo. Once chromium polynicotinate was given at these levels, there was a 'carry-over' effect. Blood chemistries revealed no significant adverse effects from ingestion of chromium polynicotinate.
Grant et al, 1997.	RCT, parallel 43 healthy, sedentary, obese women Mean age 24.4 y, range 18-35y	Test: -400 µg chromium polynicotinate twice a day (provided in 2 doses of 200 µg/day) with exercise (n not specified) -400 µg chromium picolinate (provided in 2 doses of 200 µg/day) without exercise (n not specified) -400 µg chromium picolinate (provided in 2 doses of 200 µg/day)	0 or 400 Duration : 9 wk	0 or 40	Body weight and body composition, basal plasma hormone and substrate levels, and determination of glucose and insulin response to an oral glucose load.	Exercise training combined with chromium polynicotinate supplementation resulted in significant weight loss compared to baseline and lowered the insulin response to an oral glucose load; no changes in control group.

Reference	Study Design	Intervention	Test Dose as Chromium Polynicotinate (µg/day) and Duration ^a	Test Dose as Chromium (III) (µg/day) ^a	Endpoints	Safety Results of Test Group
		with exercise (n not specified) Control: -Placebo with /exercise (n not specified) Source: Shaklee, Inc., USA (San Francisco, CA)				
Guimarães et al., 2013	RCT, parallel 56 adults with type 2 diabetes Mean age 50.90 ± 0.93 y	Test: -50 µg and 200 µg of chromium (III) as chromium polynicotinate (n=13, n=16) Control: -Placebo capsule (n=13) Source: Supleforma (Goiania, Goiás, Brazil)	0, 500, 2000 Duration: 90 d	0, 50, or 200	Chromium status, sensitivity to insulin, glycemic control, and lipid profile	Supplementation at 50 and 200 µg of chromium as chromium polynicotinate did not promote glycemic control, increase insulin sensitivity, or change the lipid profile of subjects with diabetes.
Lefavi et al., 1993	RCT, parallel 34 college-age male bodybuilders Age range 18-28y	Test: -200 µg chromium (III) bound to 1.8 mg nicotinic acid (n=12) -800 µg chromium (III) bound to 7.2 mg nicotinic acid (n=11) Control: -Placebo (n=11) Source: ChromeMate Interhealth Inc., Concord, CA	0, 2000, 8000 Duration: 8 wk	0, 200, or 800	12-hour fasting insulin, glucose, total cholesterol (TC), triglyceride, HDL-cholesterol, TC:HDL, LDL-cholesterol, and 1-hour post-challenge insulin and glucose values were determined at pre- and post-supplementation periods.	Mean TC in the placebo group increased from 139.9 to 153.4 mg/dl, yet decreased from 147.9 to 126.8 mg/dl and 159.2 to 131.3 mg/dl in the 200 and 800 µg groups, respectively (p<0.03). Mean TC:HDL increased from 3.02 to 3.73 in the placebo group and decreased from 3.62 to 3.37 and 3.43 to 3.27 in 200 and 800 µg groups, respectively (p<0.04). Differences in insulin concentration and glucose tolerance, markers of insulin function, were not significant between groups.

Reference	Study Design	Intervention	Test Dose as Chromium Polynicotinate (µg/day) and Duration ^a	Test Dose as Chromium (III) (µg/day) ^a	Endpoints	Safety Results of Test Group
						The authors concluded that the data support independent effects of chromium polynicotinate on glucose and lipid metabolism.
Preuss et al., 2000	RCT, parallel 38 adults with hypercholesterolemia Age not specified	Test: -400 µg chromium polynicotinate (taken in 2 doses of 200 µg) (n=10) -200 mg grape seed extract (taken in 2 doses of 100 mg) (n=10) -400 µg chromium polynicotinate + 200 mg grape seed extract (taken in 2 doses of 200 µg and 100 mg each) (n=9) Control: -Placebo (n=9) Source: ChromeMate, Interhealth Inc., Benicia, CA	0 or 400 with or without grape seed extract Duration: 2 mo	0 or 40	Blood lipids including total cholesterol, LDL cholesterol, HDL cholesterol, and triglycerides; blood pressure.	Low overall incidence of predominantly gastrointestinal-related adverse events (3 in the chromium group, 1 in the combination group, 4 in the placebo group). All reported adverse events were mild and resolved. No significant changes in blood lipids or blood pressure in the chromium group. Total cholesterol decreased significantly in the combination group.
Thomas and Gropper, 1996	RCT, crossover 14 healthy adults + 5 diabetic adults Mean age: 44.8 y	Test: -200 µg chromium (III) bound to 1.8 mg nicotinic acid in a base of 540 mg lactose powder (n=19) Control: -Placebo containing 1.8 mg nicotinic acid in a base of 540 mg lactose powder (n=19) Source: Interhealth, Inc., Concord, CA	0 or ~2000 Duration: 8 wk	0 or ~200	Plasma glucose and lipids, including total cholesterol, HDL cholesterol, LDL cholesterol, and triglycerides.	No statistically significant effects of chromium polynicotinate on plasma insulin, glucose, or lipid concentrations, although chromium polynicotinate supplementation slightly lowered fasting plasma total and LDL cholesterol, triglycerides, and glucose concentrations, and 90-min postprandial glucose concentrations in individuals with diabetes.

Reference	Study Design	Intervention	Test Dose as Chromium Polynicotinate (µg/day) and Duration ^a	Test Dose as Chromium (III) (µg/day) ^a	Endpoints	Safety Results of Test Group
Wilson and Gony, 1995	RCT, parallel 24 healthy adults Mean age: 36 y	Test: -220 µg of chromium (III) daily in gelatin capsules containing chromium (III) polynicotinate (n=15) Control: -Placebo group received gelatin capsules filled with an inert substance (n=11) Source: Nutrition 21, San Diego, CA	0 or ~2200 Duration: 90 d	0 or ~220	Fasting levels of glucose, immunoreactive insulin (IRI), and lipids (total cholesterol, HDL cholesterol, LDL cholesterol, triglycerides).	No statistically significant differences in fasting glucose, IRI or lipids between the chromium and placebo groups after supplementation, though individuals within the chromium group with initial fasting IRI levels greater than 35 pmol/l had a significant decrease in IRI level after supplementation ($P < 0.03$) despite no significant changes in serum lipids.

Abbreviations: mo - month; RCT- randomized controlled trial

^a When chromium (III) and chromium polynicotinate levels were not both specified, conversion of chromium polynicotinate to chromium (III) was based on assumption that chromium is 10% by weight in chromium polynicotinate.

Summary of Chromium Polynicotinate Safety Data

The average bioavailability of chromium from the U.S. food supply has been estimated at 0.5-2% (Anderson and Kozlovsky, 1985). Studies in humans and animals support the low bioavailability of chromium when administered orally as chromium polynicotinate (Olin et al., 1994; EFSA, 2008; DiSilvestro and Dy, 2007; Anderson et al., 1996; Lachinsky et al., 2012).

The potential toxicity of chromium polynicotinate has been investigated in a series of pre-clinical studies. Chromium polynicotinate was not acutely toxic as the oral lethal dose, 50% (LD₅₀), is > 5,000 mg/kg bw (Shara et al., 2005). Chromium polynicotinate was not mutagenic in the bacterial reverse mutation assay and the L5178Y TK (+/-) mouse lymphoma assay (Shara et al., 2005), and was not genotoxic in a chromosome aberration study (Stearns et al., 1995). Four pre-clinical safety studies of chromium polynicotinate were identified in the peer-reviewed literature (Shara et al., 2005; Shara et al., 2007; Deshmukh et al., 2009a; and Deshmukh et al., 2009b); the information provided in these studies provided a basis for assessing the safety of chromium polynicotinate. Other studies and reports including short-term, chronic duration, and placental transfer studies were identified, though the studies were not of conventional toxicological design and several were not peer-reviewed and not adequately reported for use in a safety assessment (Anderson et al., 1996; Jensen 1993; Preuss et al., 2001; Perricone et al., 2010).

In subchronic (up to 90 days) oral toxicity testing in rats, chromium polynicotinate did not result in adverse effects at the highest dose level tested, 125 ppm (equivalent to 6.25 mg/kg bw/day) (Shara et al., 2005). A two generation-reproductive toxicity study in rats conducted under GLP and in accordance with the United States FDA Redbook Guidelines for Reproduction Studies IV.C.9.a and Guidelines for Developmental Toxicity Studies IV.C.9.b., Food Additive Safety, did not report treatment-related parental toxicity, reproductive effects or offspring effects at the highest dose tested, 60 ppm, equivalent to 5.88 mg/kg bw/day (Deshmukh et al., 2009a). While chromium polynicotinate has been experimentally demonstrated to cross the placenta in rats in a study appearing as part of a patent which was not peer-reviewed (Jensen, 1993), no treatment-related developmental toxicity was reported by Deshmukh et al. (2009a,b). Furthermore, in the study by Deshmukh et al. (2009b) which was conducted under GLP and in accordance with the United States FDA Redbook Guidelines for Reproduction Studies IV.C.9.a and Guidelines for Developmental Toxicity Studies IV.C.9.b., Food Additive Safety, no treatment-related maternal or developmental toxicity was reported at dose levels up to 5.86 mg/kg bw/day of chromium polynicotinate.

The toxicity of chromium polynicotinate was also assessed in a long-term (up to 52 weeks) study (Shara et al., 2007). Dietary chromium polynicotinate intake was reported by EFSA (2014) as 1.7 mg/kg bw/day for males and 2.2 mg/kg bw/day for females. This was the only dose tested in addition to controls. Body weight gain was significantly reduced at 26, 39, and 52 weeks by 7.7%, 8.1% and 14.9% in male rats, respectively, and by 5.5%, 11.4% and 9.6% in female rats, respectively. The authors reported no changes in the mean absolute body weights of the treated groups when compared to control groups at 26, 39, and 52 weeks. No other effects were reported in this study. Although reductions in body weight gain were reported in the study, the reductions were not considered to be biologically or toxicologically relevant and were therefore

not considered to be adverse effects. Furthermore, the effect on body weight gain is not supported by the results in the available subchronic, reproductive and developmental toxicity studies, with the same strain of rats (Sprague-Dawley) at higher dietary doses of 60 to 125 ppm, respectively (Shara et al., 2005; Deshmukh et al., 2009 a, b). Other studies of similar duration (26-52 weeks) did not report measurement of body weight gain (Preuss et al., 2001; Perricone et al., 2010). The European Food Safety Authority (EFSA, 2014) reviewed Shara et al. (2007) and concluded that the reductions in body weight gain were non-adverse and subsequently identified 25 ppm as the no-observed-adverse-effect-level (NOAEL). Therefore, in this safety review the effects on body weight gain in the chronic study were considered to be non-adverse and the highest dose tested (25 ppm, 1.7 mg/kg bw/day for males and 2.2 mg/kg bw/day for females) was interpreted as the NOAEL.

In summary, subchronic (up to 90 days) oral toxicity testing in rats with chromium polynicotinate did not result in adverse effects at the highest dose tested, 125 ppm (equivalent to 6.25 mg/kg bw/day) (Shara et al., 2005). A two generation-reproductive toxicity study in rats did not result in treatment-related parental toxicity, reproductive effects or offspring effects at the highest dose tested, 60 ppm, equivalent to 5.88 mg/kg bw/day (Deshmukh et al., 2009a). Additionally, the developmental toxicity studies with chromium polynicotinate did not report treatment-related toxicity at doses up to 60 ppm (highest dose tested, equivalent to 5.86 mg/kg bw/day) (Deshmukh et al., 2009b). Therefore, NOAELs based on the sub-chronic, 2-generation reproduction, and developmental toxicity studies for chromium polynicotinate in the range of 5.86 – 6.25 mg/kg bw/day can be relied upon for assessing the safety of chromium polynicotinate. Table 7 summarizes the key repeated dose oral toxicity studies for chromium polynicotinate.

Table 7. Summary of key toxicity studies with chromium polynicotinate

Study	Route of Administration	Species	N	NOAEL (mg/kg bw/day)	Reference
2 Generation Reproduction	Dietary (0, 4, 15 or 60 ppm)	Sprague-Dawley	30/sex	5.88 (60 ppm) HDT ^a	Deshmukh et al., 2009a
Developmental Toxicity (20 days treatment)	Dietary (0, 4, 15 or 60 ppm)	Sprague-Dawley	30/sex	5.86 (60 ppm) HDT ^b	Deshmukh et al., 2009b
30, 60, 90 days	Dietary (0, 5, 50, 125 ppm)	Sprague-Dawley	6/sex	6.25 (125 ppm) HDT	Shara et al., 2005
26, 39, 52 weeks	Dietary (0, 25 ppm)	Sprague-Dawley	6/sex	1.7 ^c (25 ppm) ODT	Shara et al., 2007

Abbreviations: HDT – highest dose tested; ODT – only dose tested

^a Reported NOAEL was the lowest NOAEL in the study, based on F₀ males. NOAELs in the study ranged from 5.88 to 9.83 mg/kg bw/day for F₀ and F₁ males and females.

^b Reported NOAEL was the lowest NOAEL in the study estimated from all groups.

^c NOAEL calculated by EFSA 2014

EFSA Review of Chromium Polynicotinate Safety Data

EFSA (2008) provided a scientific opinion on the safety of chromium polynicotinate added for nutritional purposes as a source of chromium in food supplements and in foods intended for particular nutritional uses and on the bioavailability of chromium from this source. EFSA was provided a dossier on chromium polynicotinate (ChromeMate® submitted by Inter Health Nutraceuticals, Inc.). The EFSA Panel noted that the simultaneous use of polynicotinate as a source of chromium (III) in both foods intended for particular nutritional uses and in food supplements, both at use levels up to 200 µg chromium/day, could amount to use levels of 400 µg chromium/day. This would be equivalent to 4 mg chromium polynicotinate daily, providing 2.2 mg polynicotinate/day. This amount of chromium would be above the level of 250 µg chromium/day considered by the WHO as a value for supplementation that should not be exceeded. Although the amount of polynicotinate that would be consumed as a result of these proposed uses would be safe, the EFSA Panel could not conclude that these uses of chromium (III) polynicotinate are of no safety concern.

However, in the EFSA (2010) evaluation of chromium (III) as a nutrient, EFSA determined that the maximum upper intake level established by the WHO of 250 µg chromium/day for supplemental intake would be the same order of magnitude as that which would result from normal dietary intake. EFSA (2010) noted that both the limit of 1 mg of chromium/day proposed by the Scientific Committee on Food (SCF) and of 250 µg chromium/day for supplementation proposed by WHO were based on studies that were not designed to test the safety of chromium and that the genotoxicity testing of chromium (III) compounds indicated that there is not DNA damage *in vivo* and chromium (III) is not carcinogenic. EFSA (2010) also stated that there is a large margin of safety of 4-5 orders of magnitude between a daily intake of 250 µg/day (amounting to 4.1 µg/kg bw/day for a 60 kg person) and the NOAELs derived from the long-term NTP studies of chromium picolinate, which although distinctly different than chromium polynicotinate, would provide the same trivalent chromium (chromium III) as chromium polynicotinate. The NOAEL for chromium picolinate was equivalent to 727 mg chromium (III)/kg bw/day in mice and 300 mg chromium (III)/kg bw/day in rats. EFSA (2010) concluded that chromium (III) as a food supplement is not a concern provided that the intake of chromium (III) does not exceed 250 µg chromium/day.

Safety Data on Chromium

Introduction

Chromium occurs most commonly in valence states of +3 (III) and +6 (VI) (IOM, 2001). Chromium polynicotinate that is the subject of this GRAS determination is a complex of trivalent chromium (chromium (III)) and nicotinic acid. Chromium III is the most stable form of chromium (IOM, 2001), therefore chromium (III) from chromium polynicotinate does not, under standard conditions, convert to chromium (VI), and the possible presence or formation of chromium (VI) from the chromium (III) contained in chromium polynicotinate is not a safety concern.

The toxicity of chromium differs widely depending on the valence state with chromium (VI) compounds being more toxic than chromium (III) compounds (ATSDR, 2012). Based on results of chronic-duration oral studies in animals, chromium (III) compounds (chromium acetate, chromium chloride, chromium polynicotinate, chromium oxide) do not appear to produce reproductive, developmental, gastrointestinal, hematological, hepatic, renal, cardiovascular, endocrine, genotoxic or carcinogenic or musculoskeletal effects. Chromium (III) is considered an essential element for humans (IOM, 2001; ATSDR, 2012) that potentiates insulin action in peripheral tissue and is essential for lipid, protein, and fat metabolism in animals and human beings (EPA IRIS, 1998b; Anderson et al., 1993).

In contrast to chromium (III), chromium (VI) compounds, which produce effects in the gastrointestinal, immunological, hematological, reproductive, developmental, hepatic and renal systems, are considered to be genotoxic and carcinogenic by inhalation (EPA IRIS, 1998a; ATSDR, 2012). The toxicity of chromium (VI) is associated with its reduction within the cell to chromium (III); chromium (VI) is reduced stepwise to chromium (III), giving rise to reactive intermediates as well as DNA and protein adducts (IARC, 2012). Chromium (VI) is readily converted to chromium (III) *in vivo*, but there is no evidence that chromium (III) is oxidized to chromium (VI) *in vivo* (EPA IRIS, 1998a; EFSA, 2014).

Chromium (III) Toxicity

Chromium (III) is much less absorbed from the gastrointestinal tract than is chromium (VI). Oxidation of chromium (III) to chromium (VI) is not favored in food or in the body (EPA IRIS, 1998a; EFSA, 2014). Chromium (VI), but not chromium (III) compounds, have been shown to exert genotoxicity both *in vivo* and *in vitro*. Based on results of chronic-duration oral studies in animals, chromium (III) compounds (chromium acetate, chromium chloride, chromium polynicotinate, chromium oxide, chromium picolinate) do not appear to produce reproductive, developmental, gastrointestinal, hematological, hepatic, renal, cardiovascular, endocrine, carcinogenic or musculoskeletal effects. EPA IRIS (1998b) identified an oral reference dose (RfD) for chromium (III) (insoluble compounds) as 1.5 mg/kg bw/day.

Genotoxicity of Chromium (III) Compounds

The mutagenic potential of chromium (III) compounds has been studied extensively and recently reviewed (EFSA, 2014). Although study results vary depending on the test system, experimental conditions and type of chromium (III) compounds tested, the majority of the assay systems used provide evidence of lack of genotoxicity of chromium (III) compounds both *in vitro* and *in vivo* (EFSA, 2014). However, it should be noted that the ultimate mutagen that binds DNA is the trivalent form produced intracellularly from chromium (VI) and therefore the apparent lack of activity of chromium (III) is solely due to its poor cellular uptake (EFSA, 2014).

Chromium picolinate has resulted in positive genotoxic results *in vitro* but not *in vivo* (EFSA, 2014). Based on the results from Stearns et al. (1995), the clastogenicity of chromium picolinate *in vitro* is attributable to the picolinic acid and not attributable to chromium (III). In the Stearns et al. (1995) publication, chromium polynicotinate, chromium picolinate, chromium (III)

chloride hexahydrate, picolinic acid and nicotinic acid were all tested in a chromosome aberration study in Chinese Hamster Ovary cells. The results of the study indicate that both chromium picolinate and picolinic acid are clastogenic *in vitro*. The data indicate that picolinic acid rather than chromium (III) is responsible for the clastogenicity because chromium (III) chloride hexahydrate, chromium polynicotinate and nicotinic were negative for genotoxicity, even though they demonstrated higher levels of cellular-associated chromium (III). Furthermore, the possibility that trace chromium (IV) levels were responsible for the clastogenicity was ruled out because all chromium (III) complexes and stock solutions were prepared from the same source of chromium (III) chloride hexahydrate and picolinic acid alone was determined to be clastogenic.

Existing Exposure Limits for Chromium (III)

In the IOM's review of chromium, there was not sufficient evidence to set an Estimated Average Requirement (EAR) for the nutrient. Therefore, an Adequate Intake (AI) was set based on estimated mean intakes. The AI is 35 µg/day and 25 µg/day for young men and women, respectively. Few serious adverse effects have been associated with excess intake of chromium from food. Therefore, a Tolerable Upper Intake Level (UL) was not established in previous evaluations (IOM, 2001; NHMRC, 2006). EFSA (2010) concluded that the safety of chromium (III) as an added nutrient intended for the general population (including food supplements) is not of concern, provided that the intake of chromium (III) from these sources does not exceed 250 µg/day.

Previously the risk characterization reported in the Opinion of the Scientific Committee on Food on the Tolerable Upper Intake Level of Chromium (EC, 2003) was that the limited data from studies on subchronic, chronic, and reproductive toxicity on soluble trivalent chromium salts and the available human data do not provide clear information on the dose response relationship. Therefore, a tolerable upper intake level cannot be derived. However, EC (2003) does state that in a number of limited human studies there was no evidence of adverse effects associated with supplementary intake of chromium up to a dose of 1 mg chromium/day (does not include chromium picolinate) and that the dietary intake of chromium (III) in European countries is well below these doses.

WHO (1996) addressed the safe range of population intake means for supplements containing chromium and noted: "The relatively non-toxic nature of chromium as found in food indicates that the tolerable limit for chromium is quite high. Findings that supplements of 125-200 µg of chromium/day, in addition to the usual dietary intake, can in some cases reverse hypoglycemia and impaired glucose tolerance, and improve both circulating insulin levels and the lipid profile, suggest that the upper limit of the safe range of population mean intakes could be above 250 µg/day. However, until more is known about chromium, it seems appropriate that supplementation of this element should not exceed this amount."

EFSA (2014) derived a Tolerable Daily Intake (TDI) of 300 µg chromium (III)/kg bw/day from the relevant NOAEL of 286 mg/kg bw/day identified in a long-term rat study, applying the default uncertainty factor of 100 to account for species differences and human variability, and an

additional uncertainty factor 10 to account for the absence of adequate data on reproductive and developmental toxicity. EFSA (2014) concluded that the current dietary exposure to chromium (III) does not raise concerns from a public health point of view. The limits of chromium intake reported by EFSA in 2014 and in other authoritative reviews (EFSA 2010; WHO 1996) are not directly comparable as EFSA considered chromium intake from food, supplements and water and the other reviews considered only supplemental chromium intake. However, the recent review by EFSA (2014) suggests that safe levels of chromium intake may be higher than previously estimated. Table 8 contains a summary of the exposure limits for chromium (III).

Table 8. Exposure limits for chromium (III)

Exposure	Limit	Reference
Tolerable Daily Intake (from food, water and supplements)	300 µg/kg bw/day	EFSA, 2014
Max Intake for Supplements	250 µg/day	EFSA, 2010
Upper Limit for Safe Intake	250 µg/day	WHO, 1996
Oral Reference Dose	1.5 mg/kg bw/day	EPA IRIS, 1998b

Safety Data on Niacin

Introduction

Niacin, which refers to nicotinamide, nicotinic acid, and derivatives exhibiting the biological activity of nicotinamide, is a water-soluble vitamin. Niacin acts as both a donor or acceptor of a hydride ion in biological reduction-oxidation reactions, including intracellular respiration, the oxidation of fuel molecules, and fatty acid and steroid synthesis (IOM 1998).

IOM 1998 Review

The Recommended Daily Allowance (RDA) for niacin was set to 2–12 mg/day for children, 14 mg/day for adolescent girls and women, 16 mg/day for adolescent boys and men, and 18 mg/day and 17 mg/day for pregnant or breast-feeding women (IOM, 1998). The DRIs are expressed in terms of niacin equivalents (NEs) to allow for some conversion of the amino acid tryptophan to niacin. One mg NE is equivalent to 1 mg niacin or 60 mg tryptophan.

The UL for niacin is based on skin flushing, the most prominent side effect of niacin and an effect that is observed at lower doses than other effects attributed to niacin such as hepatotoxicity, non-specific gastro-intestinal effects, glucose intolerance and ocular effects (IOM, 1998). Adverse effects associated with niacin consumption from food have not been reported (IOM, 1998). The UL for niacin applies to all synthetic forms of the nutrient (nicotinic acid and niacinamide) obtained from supplements, fortified foods or a combination of the two. However, in the 1998 review, the IOM notes that nicotinamide does not appear to be associated with flushing effects; the UL based on flushing for nicotinic acid therefore is considered

protective against potential adverse effects of nicotinamide. As shown in Table 9, the ULs for niacin are 10-30 mg/day for children ages 1 to 18 years and 35 mg/day for men and women ages 19 and older (IOM, 1998).

Safety Data Post IOM Review

Dietary reference intakes including tolerable upper intake levels for niacin have been reviewed by several authoritative bodies since the 1998 review by the Institute of Medicine (Australian National Health and Medical Research Council (NHMRC) and the New Zealand Ministry of Health (MoH) 2006); European Commission Scientific Committee on Food (EC SCF), 2002; United Kingdom, Expert Group on Vitamins and Minerals (UK EVM), 2003). Tolerable upper intake levels for niacin established by these regulatory bodies, which include separate limits for nicotinic acid and niacinamide forms of the vitamin, also are summarized in Table 9. These limits also are based on the adverse effect of flushing.

Table 9. Upper limit reference levels for niacin

Age	Form	Limit (mg)	Reference Level	Reference
1-18 y	All synthetic forms (nicotinic acid and niacinamide)	10-30	Tolerable Upper Intake Level (UL)	IOM, 1998
19+ y		35		
Adult	Nicotinic acid	17	Guidance level for supplements ^a	UK EVM, 2003
Adult	Niacinamide	500		
1-18 y	Nicotinic acid	10-30	Upper Limit	NHMRC/ MoH, 2006
19+ y		35		
1-18 y	Niacinamide	150-750		
19+ y		900		
1-17 y	Nicotinic acid	2-8	Upper Limit	EC SCF, 2002
18+ y		10		
1-17 y	Niacinamide	150-700		
18+ y		900		

^a No UL established

Since the establishment of the niacin DRIs by the IOM, reports of its toxicity have been reported though these were associated with pharmacologic doses of niacin. Cases of acute liver failure secondary to niacin toxicity have been reported resulting from attempts to obscure an upcoming urine drug test (Daul and Beuhler, 2011; Ellsworth et al., 2014; Mittal et al., 2007). Clinical trials comparing immediate-release and sustained-release niacin for efficacy and toxicity in hypercholesterolemic patients reported hepatic and gastrointestinal effects (McKenney et al., 1994). Each form of niacin was administered sequentially at 500, 1000, 1500, 2000, and 3000 mg/day, each for six weeks. Vasodilatory symptoms, fatigue, and skin hyperpigmentation were

observed in persons who consumed 1000 mg/day of immediate-release niacin. Gastrointestinal and hepatic effects were observed in persons who consumed 2000 mg/day and 1000 mg/day of sustained-release niacin, respectively. Clinical studies of extended-release niacin reported the most common adverse reactions (incidence >5% and greater than placebo) were flushing, diarrhea, nausea, vomiting, increased cough, and pruritus (FDA, 2013). These reports of adverse effects resulted from pharmacological doses of niacin and therefore the UL does not apply.

Safety Study Summary

Chromium polynicotinate is a complex of trivalent chromium and nicotinic acid. The complex contains a mixture of di- and tri-nicotinate, though tri-nicotinate is the predominant form. Chromium (III) and nicotinic acid, the active constituents of chromium polynicotinate, are both nutrients for which DRIs have been established by the IOM. The compounds are consumed as natural constituents in foods and may be added to foods as fortification or enrichment nutrients.

The exact mode of absorption and distribution of chromium polynicotinate in humans is unknown. However, the nicotinate complex will be partially broken down into its constituents chromium (III) and nicotinic acid in stomach acid. It is postulated that chromium (III) and nicotinic acid released from the complex would be absorbed by the usual mechanisms, and the remaining chromium polynicotinate would be absorbed as the complex (EFSA, 2008).

Chromium polynicotinate is not acutely toxic as the oral LD₅₀ is > 5,000 mg/kg bw (Shara et al., 2005). Chromium polynicotinate was not mutagenic in the bacterial reverse mutation assay and the L5178Y TK (+/-) mouse lymphoma assay (Shara et al., 2005) and was not genotoxic in a chromosome aberration study (Stearns et al., 1995).

Four pre-clinical safety studies of chromium polynicotinate were identified in the peer-reviewed literature (Shara et al., 2005; Shara et al., 2007; Deshmukh et al., 2009a; Deshmukh et al., 2009b); the information provided in these studies provided a basis for assessing the safety of chromium polynicotinate. Other studies and reports including short-term, chronic duration, and placental transfer studies were identified, though the studies were not of conventional toxicological design and some were not peer-reviewed and not adequately reported for use in a safety assessment (Anderson et al., 1996; Jensen 1993; Perricone et al., 2010; Preuss et al., 2001).

Subchronic (up to 90 days) oral toxicity testing in rats with chromium polynicotinate did not result in adverse effects at the highest dose tested, 125 ppm (equivalent to 6.25 mg/kg bw/day) (Shara et al., 2005). A two generation-reproductive toxicity study in rats did not result in treatment-related parental toxicity, reproductive effects or offspring effects at the highest dose tested, 60 ppm, equivalent to 5.88 mg/kg bw/day (Deshmukh et al., 2009a). Additionally, the developmental toxicity studies with chromium polynicotinate did not report treatment-related toxicity at doses up to 60 ppm (highest dose tested, equivalent to 5.86 mg/kg bw/day) (Deshmukh et al., 2009b). The NOAELs based on the sub-chronic, 2-generation reproduction, and developmental toxicity studies for chromium polynicotinate are in the range of 5.86 – 6.25 mg/kg bw/day.

Chromium polynicotinate is intended for use in enhanced water beverages at a maximum use level of 575 µg/L. In the U.S. population ≥ 2 years, the mean and 90th percentile *per user* EDIs of chromium polynicotinate from the proposed use in enhanced water beverages are 202 and 342 µg/day, respectively, or 3.1 and 5.6 µg/kg bw/day, respectively. On a body weight basis, the 90th percentile *per user* EDI of chromium polynicotinate was lowest among the U.S. population ≥ 2 years and adults ≥ 19 years (5.6 µg/kg bw/day) and highest among children ages 2-18 years (6.2 µg/kg bw/day).

The margin of exposure (MOE) between the chromium polynicotinate NOAELs and the per user 90th percentile EDIs of the complex range from 945 to 1116 (Table 10). A MOE of 1000 provides a conservative margin to assure safety for human consumption. Given that the MOE is approximately 1000, the proposed use can be concluded to be safe.

Table 10. Margin of exposure (MOE) between chromium polynicotinate NOAELs and per user 90th percentile EDIs

Population	EDI of Chromium polynicotinate (ug/kg bw/day)	Margin of Exposure (MOE)		
		NOAEL: 5.88 mg/kg bw/day	NOAEL: 5.86 mg/kg bw/day	NOAEL: 6.25 mg/kg bw/day
Children, 2-18 y	6.2	948	945	1008
Adults, ≥ 19 y	5.6	1050	1046	1116
Total, ≥ 2 y	5.6	1050	1046	1116

The conclusion of safety for the intended use based on the MOE is supported by clinical data. Clinical studies of chromium polynicotinate supplementation at levels of intake ranging from 400 to 8000 µg/day provide no evidence of untoward effects under these conditions of use. The *per user* 90th percentile EDIs of chromium polynicotinate for the U.S. population and subpopulations from the proposed uses in enhanced water beverages range from 207 µg/day (children 2-18 years) to 359 µg/day (adults 19 years and older), which are below levels examined in the clinical studies that presented no safety concerns.

The conclusion of safety of consumption of the proposed use of chromium polynicotinate based on the MOE between the chromium polynicotinate NOAELs and the *per user* 90th percentile EDIs is further supported by evaluation of EDIs of chromium and niacin from the proposed use and comparison of cumulative intakes to established upper levels of intakes for each nutrient.

In the U.S. population ≥ 2 years, the mean and 90th percentile *per user* EDIs of chromium from the proposed use are 22 and 38 µg/day, respectively. Based on the mean chromium content measured in 22 well-balanced diets, adult women in the United States are estimated to consume about 23 to 29 µg/day of chromium (III) from food and adult men are estimated to consume on average 39 to 54 µg/day; intakes by children and adolescents were estimated by extrapolation and are lower or comparable to intakes by adults (IOM 2001). Cumulative chromium intakes

from food sources and the 90th percentile proposed use in enhanced water beverages are therefore estimated at up to 77 to 92 µg of chromium (III) based on dietary chromium intakes for men (39 to 54 µg/day), which represent the highest intakes across the U.S. population, and are assuming all individuals are 90th percentile consumers of the enhanced water beverages (providing 38 µg chromium/day). Assuming enhanced water consumers are also 90th percentile consumers of a chromium-containing dietary supplements (providing 120 µg chromium/day), total chromium intakes are estimated at up to 212 µg/day. The IOM did not establish a UL from chromium as data on adverse effects were limited. The EFSA, however, concluded that chromium (III) as a food supplement is not a safety concern provided that the intake of chromium (III) does not exceed 250 µg chromium/day (2010). Given that the conservatively high cumulative estimate of chromium intake of 212 µg/day is below the 250 µg chromium/day recognized as an upper level of intake, the proposed use can be concluded to be safe.

The mean and 90th percentile *per user* EDIs of niacin from the proposed use in enhanced water beverages are 0.14 and 0.23 mg/day, respectively. The mean intake of niacin from food and beverages for Americans aged two years and over is 25.1 mg/day and the estimate total intake of niacin from food and supplements combined for Americans ages two years and over is 32.9 mg/day (USDA, 2014). The proposed use of chromium polynicotinate therefore results in a negligible increase in niacin for the U.S. population. The UL for niacin, which applies only to synthetic forms of nicotinic acid and niacinamide, is between 10 and 30 mg/day for children and adolescents and 35 mg/day for adults. The estimated intakes of niacin for the U.S. population do not distinguish between synthetic and intrinsic forms though the IOM noted that only a small percentage of the U.S. population is likely to exceed the UL for niacin. Given the negligible amount of niacin provided by the proposed use in enhanced water beverages, the proposed use can be concluded to be safe.

Safety Conclusion

The intended use of chromium polynicotinate is in enhanced water beverages at a maximum use level of 575 µg/L of beverage, equivalent to 575 ppb. The addition of chromium polynicotinate to enhanced water beverages provides a dietary source of chromium.

Based on the maximum proposed use level of chromium polynicotinate in enhanced water beverages, the *per user* total estimated daily intake of chromium polynicotinate from the proposed use by the U.S. population 2 years and older is 342 µg/day and 5.6 µg/kg bw/day at the 90th percentile. Children age 2-18 years are estimated to have the highest intake of chromium polynicotinate on a body weight basis from the use in enhanced water beverages, with *per user* estimated daily intakes of 6.2 µg/kg bw/day at the 90th percentile. The MOE between the chromium polynicotinate NOAEL and the *per user* 90th percentile EDIs provides a conservative margin to assure safety for human consumption. This conclusion of safety is supported by the absence of untoward effects observed in clinical studies providing supplemental chromium polynicotinate at levels above the *per user* 90th percentile EDIs of chromium polynicotinate from the proposed use in enhanced water beverages. Therefore, it can be concluded that the proposed use of chromium polynicotinate in foods is safe within the meaning of the FD&C Act, i.e., meets the standard of reasonable certainty of no harm.

Discussion of Information Inconsistent with GRAS Determination

No information has been identified that would be inconsistent with a finding that the proposed use of chromium polynicotinate, meeting appropriate specifications specified herein and used according to Good Manufacturing Practice (GMP), is GRAS.

Basis for Conclusion that there is Consensus Regarding Safety

The intended use of chromium polynicotinate has been determined to be safe through scientific procedures as set forth in 21 CFR§170.30(b), thus satisfying the so-called “technical” element of the GRAS determination. Because this safety evaluation was based on generally available and widely accepted data and information, it also satisfies the so-called “common knowledge” element of a GRAS determination. Determination of the safety and GRAS status of chromium polynicotinate for addition to foods under its intended conditions of use has been made through the deliberations of an Expert Panel of individuals qualified by scientific training and experience to evaluate the safety of substances intended to be added to food. They have critically reviewed and evaluated the publicly available information summarized in this document and have individually and collectively concluded that chromium polynicotinate, produced consistent with Good Manufacturing Practice and meeting the specifications described herein, is safe under its intended conditions of use. The Panel further unanimously concludes that this use of chromium polynicotinate are GRAS based on scientific procedures, and that other experts qualified to assess the safety of foods and food ingredients would concur with these conclusions. The Panel’s GRAS opinion is included as Exhibit 1 to this document.

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Appendices

Appendix A. Certificates of Analysis for ChomeMate® CM-100



Certificate of Analysis

CHROMEMATE CM-100M

ChromeMate® CM-100M is a unique oxygen-coordinated, niacin-bound chromium complex containing 10% elemental chromium in a fine-mesh powder for use in dietary supplements.

LotNo: [REDACTED]

Date of Report: 8/11/2014

Product Code: [REDACTED]

Country of Origin: USA

Date of Manufacture: June 2014

Research Code: [REDACTED]

Shelf Life : 4 years when stored in tightly closed containers free of excessive heat, moisture, light and air.

TEST RESULTS

No.	Tests	Specification	Results	Test ID - Methodology
PHYSICAL				
1.	Color	Lavender	Complies	Organoleptic
2.	Identification	Matches Standard	Complies	FT-NIR
3.	Moisture (%)	Less than 8	5.0	USP 921
4.	Physical Appearance	Powder, Non Fibrous	Complies	Organoleptic
5.	Tap Density (g/cc)	>0.60	0.73	USP <616>
<i>Ingredients</i>				
6.	Bulk Density (g/cc)	>0.45	0.47	USP <616>
<i>Particle Size</i>				
7.	Wt % through 140 Mesh	>85	91.4	USP <786>
CHEMICAL				
8.	Chromium (mcg/g)	No less than 100,000	102496	AOAC 965.17/968.08
9.	Nicotinic Acid (mg/g)	Not Less Than 600	645	IH 391
10.	pH (1% Solution)	2.5 – 3.5	3.3	USP <791>
<i>Heavy Metals</i>				
11.	As (ppm)	Less than 1	0.055	USP <730>
12.	Cd (ppm)	Less than 0.3	<0.008	USP <730>
13.	Hg (ppm)	Less than 0.3	0.025	USP <730>
14.	Pb (ppm)	Less than 0.5	0.024	USP <730>
MICROBIOLOGICAL				
15.	Coliform (MPN/g)	Less than 3	<3	AOAC 966.24
16.	E. Coli (MPN/g)	Less than 3	<3	AOAC 966.24
17.	Mold (CFU/g)	Less than 100	<10	FDA BAM (7th Ed)
18.	Salmonella (CFU/g)	Not Detected	Not Detected	AOAC 2004.03
19.	Staphylococcus aureus (CFU/g)	Less than 10	<10	AOAC 975.55
20.	Total Plate Count (CFU/g)	Less than 3000	<10	AOAC 966.23
21.	Yeast (CFU/g)	Less than 100	<10	FDA BAM (7th Ed)

Confirmation that specification data from independent laboratory is accurately disclosed on this Certification of Analysis.

By: Navpreet Singh VP, Operations

Approval Date: 8/4/2014

5451 Industrial Way * Benicia, CA 94510 * (707) 751-2800 * FAX (707) 751-2801 * www.InterHealthUSA.com



Certificate of Analysis

CHROMEMATE CM-100M

ChromeMate® CM-100M is a unique oxygen-coordinated, niacin-bound chromium complex containing 10% elemental chromium in a fine-mesh powder for use in dietary supplements.

LotNo: [REDACTED]
Date of Report: 2/19/2014
Product Code: [REDACTED]

Country of Origin: USA
Date of Manufacture: December 2013
Research Code: [REDACTED]

Shelf Life : 64 months when stored in tightly closed containers free of excessive heat, moisture, light and air.

TEST RESULTS

No.	Tests	Specification	Results	Test ID - Methodology
PHYSICAL				
1.	Color	Lavender	Complies	IH106 - Visual
2.	Identification	FTNIR	Matches Standard	IH158 - FT-NIR
3.	Moisture (%)	Less than 8	4.3	IH149 - 105°C 4 hours
4.	Physical Appearance	Powder, Non Fibrous	Complies	IH112 - Visual
5.	Tap Density (g/cc)	>0.60	0.64	IH116 - USP 29 <616>
<i>Ingredients</i>				
6.	Bulk Density (g/cc)	>0.45	0.49	IH101 - USP <616>
<i>Particle Size</i>				
7.	Wt % through 140 Mesh	>85	92.4	IH131 - USP <786>
CHEMICAL				
8.	Chromium (mcg/g)	No less than 100,000	105,000	IH318 - USP <730>
9.	Nicotinic Acid (mg/g)	Not Less Than 600	618	IH391 - HPLC
10.	pH (1% Solution)	2.5 – 3.5	2.9	IH355 - USP 29 <791>
<i>Heavy Metals</i>				
11.	As (ppm)	Less than 1	<0.077	IH305 - USP <730>
12.	Cd (ppm)	Less than 0.3	<0.016	IH308 - USP <730>
13.	Hg (ppm)	Less than 0.3	<0.027	IH350 - USP <730>
14.	Pb (ppm)	Less than 0.5	<0.021	IH345 - USP <730>
MICROBIOLOGICAL				
15.	Coliform (MPN/g)	Less than 3	<3	IH509 - AOAC 966.24
16.	E. Coli (MPN/g)	Less than 3	<3	IH502 - AOAC 966.24
17.	Mold (CFU/g)	Less than 100	<10	IH503 - FDA BAM (18)
18.	Salmonella (ND/25g)	Not Detected	Not Detected	IH504 - AOAC 2004.03
19.	Staphylococcus aureus (CFU/g)	Less than 10	<10	IH505 - AOAC 975.55
20.	Total Plate Count (CFU/g)	Less than 3000	<10	IH507 - AOAC 966.23
21.	Yeast (CFU/g)	Less than 100	<10	IH508 - FDA BAM (18)

Confirmation that specification data from independent laboratory is accurately disclosed on this Certification of Analysis.

By: Fredrick A. Zilz

Approval Date: 2/18/2014

5451 Industrial Way * Benicia, CA 94510 * (707) 751-2800 * FAX (707) 751-2801 * www.InterHealthUSA.com



Certificate of Analysis

CHROMEMATE CM-100M

ChromeMate® CM-100M is a unique oxygen-coordinated, niacin-bound chromium complex containing 10% elemental chromium in a fine-mesh powder for use in dietary supplements.

LotNo: [REDACTED] Country of Origin: USA
Date of Report: 3/25/2014 Date of Manufacture: March 2014
Product Code: [REDACTED] Research Code: [REDACTED]

Shelf Life : 3 years when stored in tightly closed containers free of excessive (4) moisture, light and air.

TEST RESULTS

No.	Tests	Specification	Results	Test ID - Methodology
PHYSICAL				
1.	Color	Lavender	Complies	IH106 - Visual
2.	Identification	FTNIR	Matches Standard	IH158 - FT-NIR
3.	Moisture (%)	Less than 8	4.2	IH149 - 105°C 4 hours
4.	Physical Appearance	Powder, Non Fibrous	Complies	IH112 - Visual
5.	Tap Density (g/cc)	>0.60	0.65	IH116 - USP <616>
<i>Ingredients</i>				
6.	Bulk Density (g/cc)	>0.45	0.47	IH101 - USP <616>
<i>Particle Size</i>				
7.	Wt % through 140 Mesh	>85	92.2	IH131 - USP <786>
CHEMICAL				
8.	Chromium (mcg/g)	No less than 100,000	104000	IH318 - USP <730>
9.	Nicotinic Acid (mg/g)	Not Less Than 600	632	IH391 - HPLC
10.	pH (1% Solution)	2.5 – 3.5	3.1	IH355 - USP 29 <791>
<i>Heavy Metals</i>				
11.	As (ppm)	Less than 1	<0.03	IH305 - USP<730>
12.	Cd (ppm)	Less than 0.3	<0.01	IH308 - USP<730>
13.	Hg (ppm)	Less than 0.3	<0.01	IH350 - USP <730>
14.	Pb (ppm)	Less than 0.5	0.01	IH345 - USP <730>
MICROBIOLOGICAL				
15.	Coliform (MPN/g)	Less than 3	<3	IH509 - AOAC 966.24
16.	E. Coli (MPN/g)	Less than 3	<3	IH502 - AOAC 966.24
17.	Mold (CFU/g)	Less than 100	<10	IH503 - FDA BAM (18)
18.	Salmonella (ND/25g)	Not Detected	Negative	IH504 - AOAC 2004.03
19.	Staphylococcus aureus (CFU/g)	Less than 10	<10	IH505 - AOAC 975.55
20.	Total Plate Count (CFU/g)	Less than 3000	<10	IH507 - AOAC 966.23
21.	Yeast (CFU/g)	Less than 100	<10	IH508 - FDA BAM (18)

Confirmation that specification data from independent laboratory is accurately disclosed on this Certification of Analysis.



By: Fredrick A. Zilz VP, IT

Approval Date: 3/25/2014

5451 Industrial Way * Benicia, CA 94510 * (707) 751-2800 * FAX (707) 751-2801 * www.InterHealthUSA.com



Certificate of Analysis

CHROMEMATE CM-100M

ChromeMate® CM-100M is a unique oxygen-coordinated, niacin-bound chromium complex containing 10% elemental chromium in a fine-mesh powder for use in dietary supplements.

LotNo: [REDACTED]

Date of Report: 6/24/2014

Product Code: [REDACTED]

Country of Origin: USA

Date of Manufacture: April 2014

Research Code: [REDACTED]

Shelf Life : 3 years when stored in tightly closed containers free of excessive (4) moisture, light and air.

TEST RESULTS

No.	Tests	Specification	Results	Test ID - Methodology
PHYSICAL				
1.	Color	Lavender	Complies	IH106 - Visual
2.	Identification	FTNIR	Matches Standard	IH158 - FT-NIR
3.	Moisture (%)	Less than 8	4.4	IH149 - 105°C 4 hours
4.	Physical Appearance	Powder, Non Fibrous	Complies	IH112 - Visual
5.	Tap Density (g/cc)	>0.60	0.668	IH116 - USP <616>
<i>Ingredients</i>				
6.	Bulk Density (g/cc)	>0.45	0.498	IH101 - USP <616>
<i>Particle Size</i>				
7.	Wt % through 140 Mesh	>85	94.4	IH131 - USP <786>
CHEMICAL				
8.	Chromium (mcg/g)	No less than 100,000	108000	IH318 - USP <730>
9.	Nicotinic Acid (mg/g)	Not Less Than 600	674	IH391 - HPLC
10.	pH (1% Solution)	2.5 – 3.5	3.0	IH355 - USP 29 <791>
<i>Heavy Metals</i>				
11.	As (ppm)	Less than 1	0.069	IH305 - USP <730>
12.	Cd (ppm)	Less than 0.3	<0.005	IH308 - USP <730>
13.	Hg (ppm)	Less than 0.3	<0.009	IH350 - USP <730>
14.	Pb (ppm)	Less than 0.5	<0.007	IH345 - USP <730>
MICROBIOLOGICAL				
15.	Coliform (MPN/g)	Less than 3	<3	IH509 - AOAC 966.24
16.	E. Coli (MPN/g)	Less than 3	<3	IH502 - AOAC 966.24
17.	Mold (CFU/g)	Less than 100	<10	IH503 - FDA BAM (18)
18.	Salmonella (ND/25g)	Not Detected	Not Detected	IH504 - AOAC 2004.03
19.	Staphylococcus aureus (CFU/g)	Less than 10	<10	IH505 - AOAC 975.55
20.	Total Plate Count (CFU/g)	Less than 3000	<10	IH507 - AOAC 966.23
21.	Yeast (CFU/g)	Less than 100	<10	IH508 - FDA BAM (18)

Confirmation that specification data from independent laboratory is accurately disclosed on this Certification of Analysis.

By: Fredrick A. Zilz VP, IT

Approval Date: 6/23/2014

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Certificate of Analysis

CHROMEMATE CM-100M

ChromeMate® CM-100M is a unique oxygen-coordinated, niacin-bound chromium complex containing 10% elemental chromium in a fine-mesh powder for use in dietary supplements.

LotNo: [REDACTED]
Date of Report: 4/7/2014
Product Code: [REDACTED]

Country of Origin: USA
Date of Manufacture: October 2013
Research Code: [REDACTED]

Shelf Life: 3 years when stored in tightly closed containers free of excessive heat, moisture, light and air.

TEST RESULTS

No.	Tests	Specification	Results	Test ID - Methodology
PHYSICAL				
1.	Color	Lavender	Complies	IH106 - Visual
2.	Identification	FTNIR	Matches Standard	IH158 - FT-NIR
3.	Moisture (%)	Less than 8	3.9	IH149 - 105°C 4 hours
4.	Physical Appearance	Powder, Non Fibrous	Complies	IH112 - Visual
5.	Tap Density (g/cc)	>0.60	0.65	IH116 - USP <616>
<i>Ingredients</i>				
6.	Bulk Density (g/cc)	>0.45	0.46	IH101 - USP <616>
<i>Particle Size</i>				
7.	Wt % through 140 Mesh	>85	92.4	IH131 - USP <786>
CHEMICAL				
8.	Chromium (mcg/g)	No less than 100,000	103,000	IH318 - USP <730>
9.	Nicotinic Acid (mg/g)	Not Less Than 600	661	IH391 - HPLC
10.	pH (1% Solution)	2.5 - 3.5	3.1	IH355 - USP 29 <791>
<i>Heavy Metals</i>				
11.	As (ppm)	Less than 1	0.54	IH305 - USP <730>
12.	Cd (ppm)	Less than 0.3	<0.010	IH308 - USP <730>
13.	Hg (ppm)	Less than 0.3	<0.010	IH350 - USP <730>
14.	Pb (ppm)	Less than 0.5	<0.02	IH345 - USP <730>
MICROBIOLOGICAL				
15.	Coliform (MPN/g)	Less than 3	<3	IH509 - AOAC 966.24
16.	E. Coli (MPN/g)	Less than 3	<3	IH502 - AOAC 966.24
17.	Mold (CFU/g)	Less than 100	<10	IH503 - FDA BAM (18)
18.	Salmonella (ND/25g)	Not Detected	Not Detected	IH504 - AOAC 2004.03
19.	Staphylococcus aureus (CFU/g)	Less than 10	<10	IH505 - AOAC 975.55
20.	Total Plate Count (CFU/g)	Less than 3000	<10	IH507 - AOAC 966.23
21.	Yeast (CFU/g)	Less than 100	<10	IH508 - FDA BAM (18)

Confirmation that specification data from independent laboratory is accurately disclosed on this Certification of Analysis.

By: Fredrick A. Zilz VP, IT

Approval Date: 12/20/2013

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Appendix B. Foods Included in Intake Assessment of Intended Use of Chromium Polynicotinate in
Enhanced Water Beverages

Food Code	Food Description	Additional Description
94210100	Propel Water	all flavors; with calcium
94210200	Glaceau Water	all flavors; Glaceau Vitamin water; Glaceau Fruit water; Glaceau Smart water
94210300	SoBe Lifewater	all flavors
94220200	Glaceau Water, low calorie	Glaceau Vitamin Water 10

Exhibits

Exhibit 1. Report of the Expert Panel

EXPERT PANEL OPINION

The Generally Recognized As Safe (GRAS) Determination for the Use of Chromium Polynicotinate in Enhanced Water Beverages

Introduction

The undersigned, an independent panel of experts, qualified by their scientific training and national and international experience to evaluate the safety of food and food ingredients (the "Expert Panel"), was specially convened to evaluate the safety and "generally recognized as safe" ("GRAS") status of the intended use of the chromium polynicotinate in enhanced water beverages. For purposes of this review, "safe" or "safety" means that there is "a reasonable certainty in the minds of competent scientists that the substance is not harmful under the intended conditions of use," as defined by the U.S. Food and Drug Administration (FDA) in 21 CFR 570.3(i).

Exponent, Inc. ("Exponent") performed a comprehensive search of the scientific literature, through August 2015, relating to the safety of chromium polynicotinate with respect to its proposed use in enhanced water beverages at a maximum use level of 575 µg per liter of beverage (µg/L), equivalent to 575 ppb. Exponent summarized the results of the literature search and prepared a safety dossier, "Documentation Supporting the Generally Recognized as Safe (GRAS) Determination for the Use of Chromium Polynicotinate in Enhanced Water Beverages" for consideration by the Expert Panel.

The Expert Panel (Drs. Anderson, Sobotka, and Tarka) critically evaluated Exponent's safety documentation (the dossier), and other available data and information that the members of the Expert Panel believed to be pertinent to the safety of the proposed use of chromium polynicotinate.

On September 22, 2015, the Expert Panel convened via teleconference, and independently, jointly, and unanimously concluded that chromium polynicotinate, produced consistent with current good manufacturing practice (cGMP) and meeting the stated specifications, is safe for use as a source of chromium in enhanced water beverages. The Expert Panel further concluded unanimously that the intended use of chromium polynicotinate in enhanced water beverages is GRAS based on scientific procedures. It is also the unanimous consensus opinion of this Expert Panel that other qualified experts would concur with these conclusions.

Summarized below are the data, information and interpretive analysis supporting the Expert Panel's conclusions.

Description

Chromium polynicotinate is a complex of trivalent chromium and nicotinic acid. Chromium polynicotinate is also known as chromium nicotinate. The chromium polynicotinate that is the subject of this GRAS determination is sold under the trade name ChromeMate® CM-100M. Chromium polynicotinate is produced under current Good Manufacturer Practices (cGMP) and meets product specifications appropriate for a food ingredient. The specifications establish a minimum level of chromium (III) in the finished product of 100,000 µg/g (i.e., 10% by weight) and a minimum level of niacin of 600,000 µg/g (i.e., 60% by weight). Analytical data from representative non-consecutive batches of chromium polynicotinate demonstrate that the ingredient consistently meets these product specifications.

Intended Use

Chromium polynicotinate is proposed for use in enhanced water beverages at a maximum use level of 575 µg per liter of beverage (µg/L), equivalent to 575 ppb. The addition of chromium polynicotinate to enhanced water beverages provides a dietary source of chromium.

Assessment of Safety

The exact mode of absorption and distribution of chromium polynicotinate in humans is unknown. However, in stomach acid, the nicotinate complex will be partially broken down into its two constituent parts, e.g. chromium (III) and nicotinic acid. It is postulated that chromium (III) and nicotinic acid released from the complex would be absorbed by the usual physiological mechanisms, and the remaining chromium polynicotinate would be absorbed as the complex (EFSA, 2008).

The average bioavailability of chromium from the American food supply has been estimated at 0.5-2% (Anderson and Kozlovsky, 1985). Studies in humans and animals support the low bioavailability of chromium when administered orally as chromium polynicotinate (Anderson et al., 1996; DiSilvestro and Dy, 2007; EFSA, 2008; Lachinsky et al., 2012; Olin et al., 1994).

The potential toxicity of chromium polynicotinate has been investigated in a series of pre-clinical studies. Chromium polynicotinate is not acutely toxic as the oral lethal dose, 50% (LD₅₀), is > 5,000 mg/kg bw (Shara et al., 2005). Chromium polynicotinate is not mutagenic in the bacterial reverse mutation assay and the L5178Y TK (+/-) mouse lymphoma assay (Shara et al., 2005), and is not genotoxic in a chromosome aberration study (Stearns et al., 1995). Four pre-clinical safety studies of chromium polynicotinate were identified in the peer-reviewed literature (Deshmukh et al., 2009a; Deshmukh et al., 2009b; Shara et al., 2005; Shara et al., 2007); the information gleaned from these studies provides pivotal information for assessing the safety of chromium polynicotinate. Other studies and reports including short-term, chronic duration, and

placental transfer studies were identified, however, the studies were not of conventional toxicological design and some were not peer-reviewed or adequately reported; thus not suitable for use in a safety assessment (Anderson et al., 1996; Jensen, 1993; Preuss et al., 2001; Perricone et al., 2010).

In a 90-day oral toxicity study in rats, chromium polynicotinate did not result in adverse effects at the highest dose level tested, 125 ppm (equivalent to 6.25 mg/kg bw/day) (Shara et al., 2005). A two generation-reproductive toxicity study in rats, conducted under GLP and in accordance with the United States Food and Drug Administration (FDA) Redbook Guidelines for Reproduction Studies IV.C.9.a and Guidelines for Developmental Toxicity Studies IV.C.9.b., Food Additive Safety, did not report treatment-related parental toxicity, reproductive effects, or offspring effects at the highest dose tested, 60 ppm, which is equivalent to 5.88 mg/kg bw/day (Deshmukh et al., 2009a). While chromium polynicotinate has been reported by Jensen (1993) to cross the placenta in rats, no treatment-related developmental toxicity has been reported (Deshmukh et al., 2009a, b). Furthermore, the study by Jensen (1993) and its conclusions were not peer-reviewed, and the study was not adequately reported to allow for independent verification of the conclusions made. In the study by Deshmukh et al. (2009b), conducted under GLP and in accordance with the U.S. FDA Redbook Guidelines for Reproduction Studies IV.C.9.a and Guidelines for Developmental Toxicity Studies IV.C.9.b., Food Additive Safety, no treatment-related maternal or developmental toxicity was reported at dose levels up to 5.86 mg/kg bw/day of chromium polynicotinate.

The toxicity of chromium polynicotinate was also assessed in a long-term (up to 52 weeks) study (Shara et al., 2007). Dietary chromium polynicotinate intake in the study was reported by EFSA (2014) as 1.7 mg/kg bw/day for males and 2.2 mg/kg bw/day for females. This was the only dose tested (25 ppm) in addition to controls. The authors reported no changes in the mean absolute body weights of the treated group when compared to control groups at 26, 39 and 52 weeks. Body weight gain was significantly reduced in the treated group at 26, 39, and 52 weeks by 7.7%, 8.1% and 14.9% in male rats, respectively, and by 5.5%, 11.4% and 9.6% in female rats, respectively. No other effects were reported in this study. Although reductions in body weight gains were reported in the study, the reductions were not considered to be biologically or toxicologically relevant and were therefore not considered to be adverse effects. Furthermore, the effect on body weight gain is not supported by the results reported in the available subchronic, reproductive and developmental toxicity studies, with the same strain of rats (Sprague-Dawley) at higher dietary doses of 60 and 125 ppm, respectively (Deshmukh et al., 2009 a, b; Shara et al., 2005). Other studies of similar duration (26-52 weeks) did not report measurement of body weight gain (Perricone et al., 2010; Preuss et al., 2001). The European Food Safety Authority (EFSA, 2014) reviewed Shara et al. (2007) and concluded that the reductions in body weight gain were non-adverse and subsequently identified 25 ppm as the No-Observed-Adverse-Effect-Level (NOAEL). Therefore, in this safety review the effects on body weight gain in the chronic study were considered to be non-adverse and the highest dose tested

(25 ppm, 1.7 mg/kg bw/day for males and 2.2 mg/kg bw/day for females) was interpreted as the NOAEL.

In reviewing the totality of the identified pre-clinical data available for chromium, the subchronic NOAEL identified by Shara et al. (2005) of 125 ppm, corresponding to a test material intake of 6.25 mg/kg bw/day is recommended as the endpoint for risk assessment with an uncertainty factor of 1000x. This endpoint is supported by a two-generation reproductive study in rats (Deshmukh et al., 2009a) which had a NOAEL of 60 ppm, the highest dose tested, estimated to be 5.88 mg/kg bw/day and also by the developmental toxicity studies with chromium polynicotinate which did not report toxicity at doses up to 60 ppm (highest dose tested, equivalent to 5.86 mg/kg bw/day). The NOAELs based on these sub-chronic, 2 generation reproduction, and developmental toxicity studies for chromium polynicotinate are in the range of 5.86 – 6.25 mg/kg bw/day.

Chromium polynicotinate is intended for use in enhanced water beverages at a maximum use level of 575 µg/L. In the U.S. population 2 years and older, the mean and 90th percentile *per user* EDIs of chromium polynicotinate from the proposed use in enhanced water beverages are 202 and 342 µg/day, respectively, or 3.1 and 5.6 µg/kg bw/day, respectively. On a body weight basis, the 90th percentile *per user* EDI of chromium polynicotinate was lowest among the U.S. population 2 years and older and adults 19 years and older (5.6 µg/kg bw/day in each group) and highest among children ages 2-18 years (6.2 µg/kg bw/day).

The margin of exposure (MOE) between the chromium polynicotinate NOAELs and the *per user* 90th percentile EDIs of the complex for the U.S. population ages 2 years and older and subpopulations of children (ages 2-18 years) and adults (ages 19 years and older) range from 945 to 1116. A MOE of 1000 provides a conservative margin to assure safety for human consumption. Given that the MOE is approximately 1000, the proposed use can be concluded to be safe.

Clinical studies of chromium polynicotinate supplementation at levels of intake ranging from 400 to 8000 µg/day provide no evidence of untoward effects under these conditions of use and therefore provide further support for the conclusion of safety. The *per user* 90th percentile EDIs of chromium polynicotinate for the U.S. population and subpopulations from the proposed uses in enhanced water beverages range from 207 µg/day (children 2-18 years) to 359 µg/day (adults 19 years and older), which are below levels examined in the clinical studies that presented no safety concerns.

The conclusion of safety of consumption from the proposed use of chromium polynicotinate in enhanced water beverages based on the MOE between the chromium polynicotinate NOAELs and the *per user* 90th percentile EDIs is further supported by the evaluation of EDIs of chromium and niacin from the proposed use and comparison of cumulative intakes to established

upper levels of intakes for each nutrient that have been previously established. The constituents of chromium polynicotinate, chromium and nicotinic acid, are both nutrients for which Dietary Reference Intakes (DRIs) have been established (IOM, 1998; IOM, 2001). The compounds are consumed as natural constituents in foods and may be added to foods as fortification or enrichment nutrients.

In the U.S. population ≥ 2 years, the mean and 90th percentile *per user* EDIs of chromium from the proposed use are 22 and 38 $\mu\text{g/day}$, respectively. Based on the mean chromium content measured in 22 well-balanced diets, adult women in the United States are estimated to consume about 23 to 29 $\mu\text{g/day}$ of chromium (III) from food, and adult men are estimated to consume on average 39 to 54 $\mu\text{g/day}$; intakes by children and adolescents were estimated by extrapolation and are lower or comparable to intakes by adults (IOM, 2001). Cumulative chromium intakes from food sources and the 90th percentile proposed use in enhanced water beverages are therefore estimated at up to 77 to 92 μg of chromium (III) based on dietary chromium intakes for men (39 to 54 $\mu\text{g/day}$), which represent the highest intakes across the U.S. population, and assuming all individuals are 90th percentile consumers of the enhanced water beverages (providing 38 μg chromium/day). Assuming enhanced water consumers are also 90th percentile consumers of chromium-containing dietary supplements (providing 120 μg chromium/day), total chromium intakes are estimated at up to 212 $\mu\text{g/day}$. The Institute of Medicine (IOM) did not establish a Tolerable Upper Intake Level (UL) for chromium (III) as data on adverse effects were limited. The EFSA, however, concluded that chromium (III) as a food supplement is not a concern provided that the intake of chromium (III) does not exceed 250 μg chromium/day (EFSA, 2010). Given that the conservatively high cumulative estimate of chromium intake of 212 $\mu\text{g/day}$ is below the 250 μg chromium/day recognized as an upper level of intake, the proposed use can be concluded to be safe.

The mean and 90th percentile *per user* EDIs of niacin from the proposed use in enhanced water beverages are 0.14 and 0.23 mg/day , respectively. The mean intake of niacin from food and beverages for total U.S. population ages two years and over is 25.1 mg/day and the estimated total intake of niacin from food and supplements combined by the total U.S. population ages two years and older is 32.9 mg/day (USDA, 2014). The proposed use of chromium polynicotinate therefore results in a negligible increase in niacin for the U.S. population. The UL for niacin, which applies only to synthetic forms of nicotinic acid and niacinamide, is between 10 and 30 mg/day for children and adolescents and 35 mg/day for adults (IOM, 1998). The estimated intakes of niacin for the U.S. population do not distinguish between synthetic and intrinsic forms though the IOM noted that only a small percentage of the U.S. population is likely to exceed the UL for niacin (IOM, 1998). Given the negligible amount of niacin provided by the proposed use in enhanced water beverages, the proposed use can be concluded to be safe.

Summary

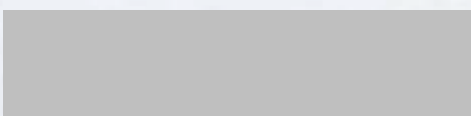
In summary, the MOE between the chromium polynicotinate recognized NOAEL and the *per user* 90th percentile EDIs provides a conservative margin to assure safety for human consumption. General recognition of safety through scientific procedures requires common knowledge throughout the scientific community knowledgeable about the safety of food ingredients that there is a reasonable certainty that a substance is not harmful under the intended conditions of use in foods. The aforementioned regulatory and scientific reviews related to the consumption and safety of chromium polynicotinate have been published in the scientific literature, and therefore are generally available and generally known among the community of qualified food ingredient safety experts. There is broad-based and widely disseminated knowledge concerning chromium polynicotinate and its constituents, chromium and niacin. The data and publicly available information supporting the safety of the proposed use of chromium polynicotinate in enhanced water beverages as proposed in this document are not only widely known and disseminated, but are also commonly accepted among qualified food safety experts. The proposed use of chromium polynicotinate in enhanced water beverages therefore can be concluded to be safe and generally recognized as safe through scientific procedures.

Expert Panel Conclusion

We, the undersigned expert panel members, have individually and collectively critically evaluated published and unpublished data and information pertinent to the safety of the intended use of chromium polynicotinate, produced consistent with cGMP and meeting appropriate food grade specifications, in enhanced water beverages at a maximum use level of 575 µg per liter of beverage (µg/L), equivalent to 575 ppb, and unanimously conclude that such use is safe and "generally recognized as safe" (GRAS) based on scientific procedures.

It is our unanimous consensus opinion that other qualified experts would concur with our conclusion.

By:



Richard A. Anderson, Ph.D., CNS, MACN
PolyChrom Technology LLC

10/21/2015
Date

Thomas J. Sobotka, Ph.D.
Consultant

Date

Stanley M. Turka, Jr., Ph.D. (Panel Chair)
The Turka Group, Inc.

Date

Expert Panel Conclusion

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Richard A. Anderson, Ph.D., CNS, MACN
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Thomas J. Sobotka, Ph.D.
Consultant

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10/21/2015

Stanley M. Tarka, Jr., Ph.D. (Panel Chair)
The Tarka Group, Inc.

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Expert Panel Conclusion

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21 October 2015

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