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March 21, 2023

BY FEDERAL EXPRESS

Dr. Susan Carlson
GRAS Notification Program
Office of Food Additive Safety
Center for Food Safety and Applied Nutrition
U.S. Food and Drug Administration
5001 Campus Drive
College Park, Maryland 20740-3835

Subject: GRAS Notification for the Intended Use of Copper (II) ions as an antimicrobial in packaging for fresh beef, pork, poultry, fresh sausage, salmon, and fresh cheese, and on deli meat.

Dear Dr. Carlson:

In accordance with 21 C.F.R. Part 170, Subpart E - Generally Recognized As Safe (GRAS) Notice, we hereby submit, on behalf of Copperprotek SPA (Copperprotek), this notification that the intended use of copper (II) ions as an antimicrobial in packaging for fresh beef, pork, poultry, fresh sausage, salmon, and fresh cheese, and on deli meat is exempt from the premarket approval requirements of the Federal Food, Drug, and Cosmetic Act because Copperprotek has determined that such use is GRAS based on scientific procedures. Information setting forth the basis for the GRAS conclusion is enclosed for review by the agency.

To facilitate your review, this notification is submitted in the format required under 21 C.F.R. §§ 170.220-255. Enclosed are one paper and one electronic copy of the GRAS notice documents. If you have any questions concerning this submission, please do not hesitate to contact me.

Sincerely,

Riëtte L. van Laack
Counsel to Copperprotek SPA

RVL/eam
Enclosures

Notification of a Generally Recognized As Safe (GRAS) conclusion regarding the safety from exposure to copper (II) ions derived from a microparticle incorporated in packaging used for specified meat, salmon and cheese products via migration from packaging

Copperprotek SPA
Cerro Los Cóndores 9881 A,
Quilicura, Región Metropolitana, Chile

Author:
Leslie Patton, Ph.D.
ChemReg Compliance Solutions LLC
131 N. Donelson Street, Alexandria, VA 22304

Date:
March 8, 2023

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List of Acronyms

AAS	Atomic Absorption Spectrometry
ALP	Alkaline Phosphatase
ALT	Alanine Aminotransferase
AST	Aspartate Aminotransferase
ATSDR	Agency For Toxic Substances And Disease Registry
BMDL	Benchmark Dose Level
bw	Body Weight
CAS RN	Chemical Abstracts Service Registry Number
CF	Consumption Factor
CFR	Code Of Federal Regulations
CFU	Colony-Forming Units
CNS	Central Nervous System
COA	Certificate Of Analysis
DRI	Dietary Reference Intake
EDI	Estimated Daily Intake
EDS	Energy Dispersive Spectroscopy
EFSA	European Food Safety Agency
EPA	U.S. Environmental Protection Agency
FCS	Food Contact Substance
FDA	U.S. Food And Drug Administration
f_T	Food-Type Distribution Factors
GGT	L- γ-Glutamyl Transferase
GLP	Good Laboratory Practice
GRAS	Generally Recognized As Safe
ICC	Indian Childhood Cirrhosis
ICP-MS	Inductively Coupled Plasma Mass Spectroscopy
ICT	Idiopathic Copper Toxicosis
IOM	Institute of Medicine
ISO	International Organization For Standardization
JIS	Japanese Industrial Standard
LDH	Lactate Dehydrogenase
LLDPE	Linear Low Density Polyethylene
LLOQ	Lower Limit Of Quantitation
LOAEL	Lowest-Observed-Adverse-Effect-Level
MRL	Minimal Risk Level
NHANES	National Health And Nutrition Examination Survey
NOAEL	No-Observed-Adverse-Effect-Level
NOEL	No-Observed-Effect-Level
NTP	National Toxicology Program
ppm	Parts Per Million
PSSA	Pellet Size & Shape Analysis System
RDA	Recommended Daily Allowance
RSA	Chilean Food Sanitary Regulations
SCF	Scientific Committee For Food
SEM	Scanning Electron Microscope
TDS	Total Diet Survey
UL	Tolerable Upper Intake Level
USDA	U.S. Department Of Agriculture
WHO	World Health Organization
WWEIA	What We Eat In America

I. Signed Statements and Certification

Copperprotek SPA submits to the U.S. Food and Drug Administration (FDA) this generally recognized as safe (GRAS) notice in accordance with 21 CFR part 170, subpart E.

Name and Address of Notifier:

Juan José Mac-Auliffe, Copperprotek SPA, Cerro Los Cóndores 9881 A, Quilicura, Región Metropolitana, Chile.

Name of GRAS Substance:

The proposed GRAS substance is copper (II) ion. The copper ion is derived from a microstructure, multicomposite copper microparticle.

Intended Use and Consumer Exposure:

The intended use of copper is as an antimicrobial on packaged fresh beef, pork, poultry, sausage, salmon, cheese, and deli meat. Copper is extruded into polymeric packaging material so that it is in contact with the packaged food, controlling and/or reducing the growth of superficial bacteria or fungi. The level of copper in the packaging will not exceed 100 mg/m^2.

Basis for Conclusion of GRAS Status:

Copperprotek SPA's conclusion of GRAS status for the intended use of copper in food packaging is based on scientific procedures in accord with 21 CFR §170.30(a) and (b).

Pre-Market Approval Exclusion Claim:

The intended use of copper ion as an antimicrobial on select packaged foods, is not subject to the premarket approval requirements of the Federal Food, Drug, and Cosmetic Act because Copperprotek SPA has concluded that such use is generally recognized as safe (GRAS) through scientific procedures.

Availability of Information:

The data and information that serve as the basis for this GRAS conclusion, as well as the information that has become available since the GRAS conclusion, will be sent to the FDA upon request, or are available for the FDA's review and copying during customary business hours at the office of Hyman, Phelps, & McNamara, P.C., 700 Thirteenth Street N.W., Suite 1200, Washington, DC 20005.

Exemptions from Disclosure:

It is our view that none of the data and information in Parts 2 through 7 of the GRAS notice are exempt from disclosure under the Freedom of Information Act (FOIA).

FSIS Statement:

The intended conditions of use of the notified substance include use in a product or products subject to regulation by the Food Safety and Inspection Service (FSIS) of the USDA. We authorize FDA to send this document in its entirety to FSIS.

Certification Statement:

On behalf of Copperprotek SPA, I hereby certify that, to the best of my knowledge, this GRAS notice is a complete, representative, and balanced submission that includes unfavorable, as well as favorable information, known to me and pertinent to the evaluation of the safety and GRAS status the use of the substance.

03/17/2023

Juan José Mac-Auliffe
Marketing Manager
Copperprotek SPA

Date

II. Identity, Method of Manufacture, Specifications and (Physical or) Technical Effect of Substance

A. Identity

Unlike a typical food ingredient that is added directly to food during manufacturing, the copper (II) ion that is the subject of this GRAS notification migrates to meats, fish, and cheese from food packaging material. Specifically, Copperprotek SPA has developed a microstructure, multicomposite copper microparticle that has a regular, crystalline, and microstructured composition that comprises of five different crystalline copper sulfate and copper hydroxide compounds in different states of hydration and hydrogenation.

Copper species comprising the microparticle are identified in Table 1.

Table 1. Microparticle composition

Name	**Synonym**	**Formula**	**CAS RN**
Tricopper tetrahydroxide sulfate	Antlerite	$Cu_3^{2+}(SO_4)(OH)_4$	no CAS RN
Tribasic copper sulfate	Brochantite	$Cu_4^{+2}SO_4(OH)_6$	12068-81-4
Copper sulfate pentahydrate	Chalcanthite	$Cu^{+2}SO_4 \cdot 5H_2O$	7758-99-8
Dicopper hydroxide sulfate, sodium salt monohydrate	Natrochalcite	$NaCu_2^{+2}(SO_4)_2OH \cdot H_2O$	no CAS RN
Hydrated copper sulfate hydroxide		$Cu_3(SO_4)_2(OH)_2 \cdot 4H_2O$/ $2CuSO_4 \cdot Cu(OH)_2$	678159-65-4

X-ray diffraction analysis determined the identities of the five copper species present in the microparticle. Imaging of microparticles is pictured below in Figure 1. The microparticles are not a mixture or agglomeration of the five species but are rather a single structure made of these five species.

Scanning electron microscope (SEM) was used to characterize the structure, size, and distribution of the copper microparticles (Figure 2). Each of the five species comprising the microparticle are in crystalline form, maintaining an ordered, non-amorphous structure. Particles are spherical and have a heterogeneous size distribution. The microparticles are between 5 and 50 µm in diameter, with most between 10 and 15 µm. SEM analysis carried out with energy dispersive spectroscopy (EDS) technique determined the elemental composition of the microparticles: copper, sulfur, and oxygen.

Microparticles are mixed with molten resin to form a Masterbatch, which is then pelleted. The Masterbatch is 4% +/- 0.5% (*wt*) copper and 90% LLDPE. The remainder is residual reaction products of the starting materials, which are food grade: water, hydroxide from copper hydroxide, and sulfate from copper sulfate. The Masterbatch is incorporated into polymeric food packaging such that there is a maximum of 100 mg copper per square meter of packaging material. The Masterbatch is intended to be used with packaging (e.g., vacuum-packed, bags, plastic wraps) for fresh meats (beef, poultry, pork), fresh salmon, fresh sausage (of any animal), deli meat, and fresh cheese where the copper-containing plastic will contact the surface of the

food. Upon contact with food, the microparticles release copper ions. Because the solubility of each copper species differs slightly, each has a different release rate, resulting in a controlled release of copper ions over time and giving the packaging antimicrobial properties.

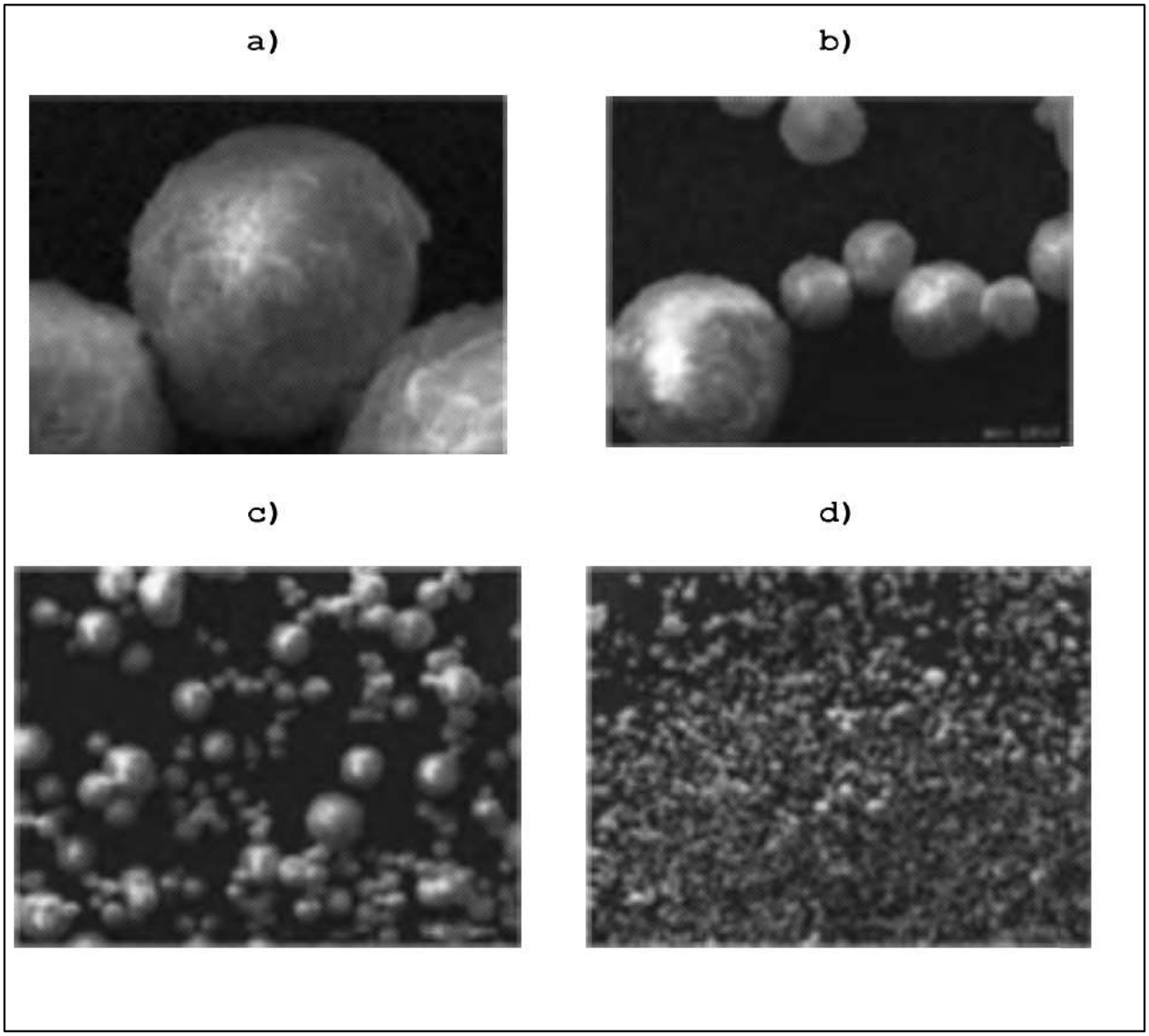

Figure 1. Scanning electron microscope images of copper microparticles at four magnifications: a) 10,000x; b) 2,500x; c) 500x; d) 100x. Zeiss model EVO MA 10 with Penta FET Precision detector, Oxford Instruments X-act.

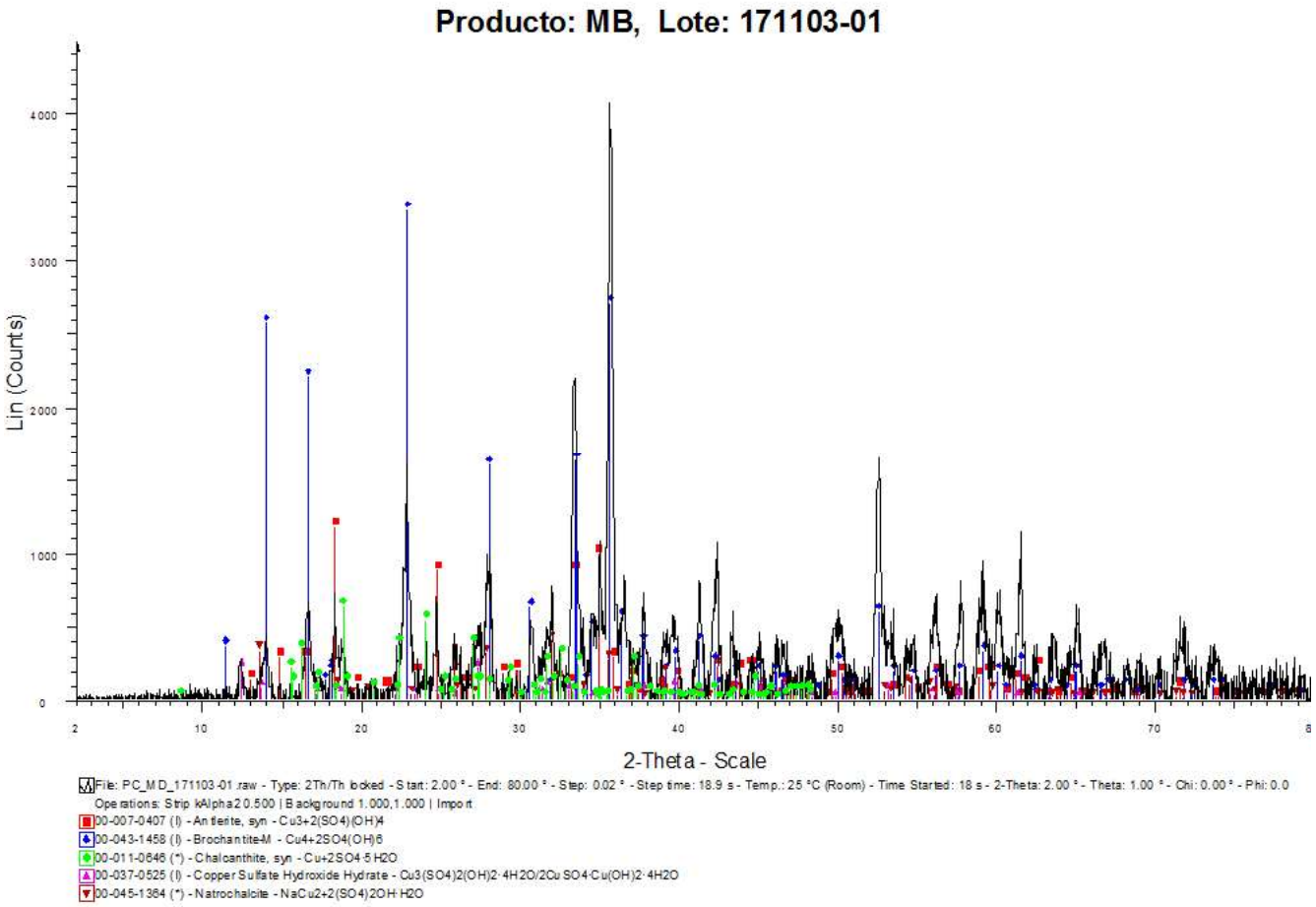

Figure 2. X-ray diffraction of copper microparticle.
Red square: Antlerite $Cu_3^{+2}(SO_4)(OH)_4$;
Blue diamond: Brochantite $Cu_4^{+2}(SO_4)(OH)_6$;
Green circle: Chalcantite $Cu^{+2}SO_4 \cdot 5H_2O$
Purple triangle: Natrochalcite $NaCu_2^{+2}(SO_4)_2OH \cdot H_2O$;
Brown upside down triangle: Hydrated sulfate hydroxide $Cu_3(SO_4)_2(OH)_2 \cdot 4H_20/2CuSO_4 \cdot Cu(OH)_2$

Purity analysis

Three samples from three separate batches of Copperprotek Masterbatch were analyzed for 34 metals by inductively coupled plasma mass spectroscopy (ICP-MS). Results demonstrated consistency in the manufacturing process relative to copper, as well as low levels of heavy metals and other metals. Selected results from this analysis are shown in Table 2.

Table 2. Metals analysis of Copperprotek Masterbatch (ppm)											
	Batch Number (Sample)									LLOQ*	**Mean**
	1(A)	1(B)	1(C)	2(A)	2(B)	2(C)	3(A)	3(B)	3(C)		
Arsenic	---	---	---	---	---	---	---	---	---	0.02	**---**
Cadmium	---	---	---	---	---	---	---	---	---	0.02	**---**
Cobalt	0.41	0.41	0.42	0.42	0.42	0.42	0.42	0.43	0.42	0.02	**0.42**
Copper (x1000)	38	38	38	37	38	38	38	38	38	0.2	**38**
Lead	0.047	0.045	0.046	0.05	0.048	0.16	0.045	0.05	0.045	0.02	**0.06**
Mercury	---	---	---	---	---	---	---	---	---	0.02	**---**

* lower limit of quantitation

The average and highest concentration of lead detected in the Masterbatch was 0.06 ppm and 0.16 ppm, respectively. Using the higher value, this equates to 1.6 mg Pb/kg $CuSO_4$,[1] which is within the Food Chemical Codex (FCC) copper sulfate specification of 4.0 mg/kg $CuSO_4$.

The estimated intake of lead is also below the US FDA lead interim reference levels (IRL) for children and pregnant women of 2.2 µg/day and 8.8 µg/day, respectively (Flannery and Middleton 2022). The estimated intake of lead was derived based on a worst-case scenario, assuming 100% migration of the metal into food and assuming 100% of all LDPE food contact materials contains the Masterbatch. The following FDA default values were used in the calculations:

- Surface area (SA) to food mass ratio (Am/f) = 0.0645 m^2/kg
- LDPE consumption factor (CF) = 0.12
- Polyolefins food-type distribution factor (f_T), aqueous + fatty foods = 0.98
- Total food consumption = 3 kg/day

The mass of Masterbatch (MB) per square meter of packaging is 2500 mg/m^2 (based on 100 mg copper/m^2 packaging and 4% copper in Masterbatch). The lead Estimated Daily Intake (EDI) was calculated to be 0.009 µg/day, well below the IRL values:

- [Pb] on SA of packaging = 0.16 µg/g ÷ 1,000 g/mg x 2500 mg MB/m^2 = 0.400 µg/m^2
- Migration = 0.400 µg/m^2 x 0.0645 m^2/kg = 0.026 µg Pb/kg food
- Dietary concentration = 0.026 µg Pb/kg food x 0.12 x 0.98 = 0.003 µg Pb/kg food
- EDI = 0.003 µg Pb/kg food x 3 kg/day = 0.009 µg/day

The same calculation was carried out for cobalt using 0.43 ppm, the highest result from among the replicates and samples measured and presented in Table 2. The EDI of cobalt was determined to be 0.024 µg/day, 736x less than EPA's chronic p-RfD of 0.0003 mg/kg bw/day (US EPA 2008) or 18 µg/day for a 60-kg person.

[1] 0.16 ppm Pb in Masterbatch (MB) ÷ 40,000 ppm Cu in MB x 10^6 mg/kg = 4.0 mg Pb/kg Cu x 39.82% Cu in $CuSO_4$ by wt. = 1.6 mg Pb/kg $CuSO_4$

B. Manufacturing

Microparticle formation

The production process of the microparticle begins with the preparation of a dispersion of copper hydroxide in a gel state, which is formed by mixing an aqueous solution of copper sulfate pentahydrate with an aqueous solution of sodium hydroxide until the pH is between 4 and 6:

$CuSO_4$ (aq) + 2NaOH (aq) → $Cu(OH)_2$ (s) + Na_2SO_4 (aq)

Once the copper hydroxide precipitate/gel forms, the supernatant is removed and discarded, and the precipitate is emulsified in another copper sulfate solution. That solution is dried with a spray dryer at a very high temperature at which time microparticles comprising five copper species are formed. The copper species are all copper sulfates in various hydration states and/or hydroxylation states (Table 1).

Masterbatch formation

Copper microparticles are incorporated into linear low-density polyethylene (LLDPE) compliant with 21 CFR 177.1520(c)(3.1a). The polymer is pulverized in a mill, cold-mixed with the microparticle, then heated until liquified. The resulting product is extruded into a pellet, which is the Masterbatch that is sold by Copperprotek SPA.

The Copperprotek Masterbatch can be incorporated during the extrusion process into molten polymer used to form rigid or flexible sheets of polyolefin polymers that will be made into multilayer food contact packaging material.

C. Specifications

The pellet size, color, solubility, and copper content of the Copperprotek Masterbatch are measured in each lot produced.

Specification	**Value**	**Method of Analysis**
Pellet Size	2 – 7 mm	Pellet Size & Shape Analysis System (PSSA)
Copper Content	3.5 – 4.5% w/w	Atomic Absorption Spectrometry (AAS)
Pellet Color	Light green	ASTM D6290-19
Pellet Solubility	Insoluble (99.9%)	EN 13130 (Migration in acid, ethanol and oil)

Specifications do not include heavy metal limits because the purity of the starting materials is high. Heavy metal analysis carried out on the Masterbatch supports this (*see* Table 2).

Data from 3 batches of the Masterbatch are summarized in Table 3. The certificates of analysis (COAs) are provided in Appendix A.

Table 3. Analysis of 3 batches of Copperprotek Masterbatch			
	MB-22-1	**MB-22-2**	**MB-22-3**
Pellet size (mm)	3-6	3-6	3-6
Copper content (% w/w)	3.8%	3.76%	3.73%
Pellet color	Light green	Light green	Light green
Pellet solubility	Insoluble	Insoluble	Insoluble

D. Technical Effect of Substance

The intended technical effect of copper is as an antimicrobial on certain packaged foods. The antimicrobial properties of copper on food are well-established. Copper is a broad-spectrum pesticide active ingredient approved for a wide range of uses, including virtually all food/feed crops (EPA 2009; EPA 2018). In these agricultural applications, copper creates a protective barrier on the surface of plant tissue preventing spore germination in fungi and causing membrane destruction leading to cell lysis in bacteria. Copper also functions as a preservative for wood, paint, and other nonfood surfaces, and is used to treat drinking water.

The Copperprotek copper Masterbatch, when incorporated into packaging, has antibacterial effects on food. Microbial growth, based on mesophilic aerobic bacteria, on sliced ham stored in packaging containing copper Masterbatch under refrigerated conditions (4 +/- 2 ºC) was compared to microbial growth on ham in regular packaging. Microbial growth was monitored over time and stopped when growth exceeded 500,000 cfu/g, the maximum bacteria load allowed under Chile's Sanitary Regulation for Food Products (RSA). The ham stored in copper Masterbatch packaging reached this level after 85 days, whereas ham stored in regular packaging reached this level after 55 days.

E. Stability

The Masterbatch product is labeled with a shelf life of 24 months when stored at room temperature in dry conditions. This value is derived from the shelf life of the LLDPE in the Masterbatch. Copper is stable over time; the only potentially interfering factor in the food packaging application would be moisture accumulation during storage, which may result in copper solubilizing and migrating from the food packaging material.

An accelerated shelf-life study was carried out with plastic sheets extruded with Copperprotek Masterbatch to determine the effect of humidity on copper content over time with respect to both copper content and antimicrobial effectiveness. Conditions of humidity were exaggerated to support a two-year shelf life from a shorter-term study.

The aim of the first part of the study was to determine if there was a reduction in copper in the plastic sheets due to release of copper ions. Four replicate plastic sheets containing Masterbatch were "washed" with a wet sponge for 5-minute periods so that the sheets were constantly wet during the test. Two sheets were washed "normally" while two were washed "intensely;" where more water was used and scrubbing was more vigorous. When not being washed, samples were stored at a humidity of 25% at room temperature. The rinsing regimen was carried out for 132 days. The copper concentration in the plastic was measured using Atomic Absorption Spectroscopy (AAS) at time points throughout the test. Results are summarized in the table and figure below.

Number of days	*Wash intensity*	*% Cu*
18	*Normal*	*2.3*
28	*Normal*	*2.1*
87	*Normal*	*3.0*
132	*Normal*	*2.0*
18	*High*	*3.0*
28	*High*	*3.1*
87	*High*	*3.0*
132	*High*	*1.8*

Table 4. Effect of moisture over time on copper concentration in plastic with Copperprotek Masterbatch

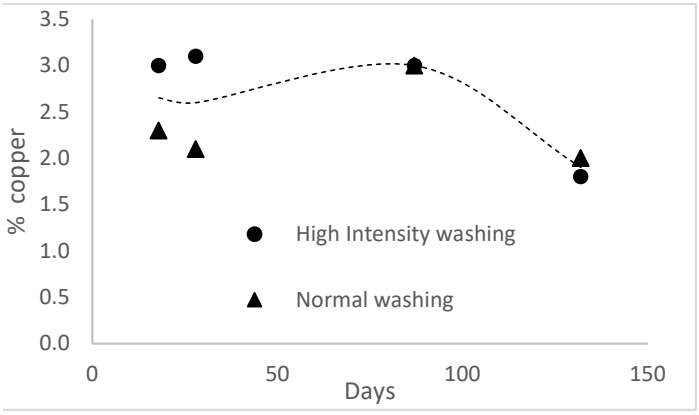

Figure 3. Average % Cu in plastic containing Masterbatch over time with washing. Circle: high intensity washing; Triangle: normal washing; Line: average across both.

The average concentration of copper in the plastic decreased slightly over time. The intensity of washing did not appear to have a significant effect on copper levels, though the final copper concentration was lower in the more intensely washed samples.

The antimicrobial activity of the washed samples of plastic was then tested under GLP ENV/MC/CHEM (98)17 using test guideline JIS Z 2801/ ISO 22196 (Assessment of Antimicrobial Activity of Hard Non-Porous Surfaces). Three washed samples of normal wash intensity, three of high wash intensity and three negative controls (without copper) were inoculated with 2.5×10^5 CFU/mL *Escherichia coli* ATCC 25922. The cell count of the negative controls was determined at time 0 and after 24 hours. The Masterbatch-containing samples were counted after 24 hours.

Results are summarized in the table below. The standard for antimicrobial effectiveness under JIS Z 2801/ ISO 22196 is $\geq$ 2 log reduction. The log reduction of *E. coli* was 5.3[2] and 2.3 for the normal and intense washed samples, respectively. Although growth was higher on the intensely washed sample, where the copper concentration was also lower, both maintained antimicrobial effectiveness even after 132 days under highly exaggerated conditions of moisture.

Table 5. Effect of prolonged moisture on biocidal efficacy of plastic with Copperprotek Masterbatch

Sample	**Average count (cfu)**	**Antimicrobial activity (R)[1]**
Control at T0	11,000	---
Control at 24 hrs	130,000	---
Plastic with Masterbatch at 24 hrs (normal wash)	0.63	5.3
Plastic with Masterbatch at 24 hrs (intense wash)	600	2.3

[2] Example calculation of antimicrobial activity (R) = Log (130,000/11,000) - Log (0.63/11,000) = 5.3

Results of these studies show that while the average concentration of copper decreased over time from 2.7% after 18 days to 1.9% after 132 days under highly exaggerated conditions of humidity, the antimicrobial activity was maintained. These results suggest that under conditions of normal humidity, the Masterbatch extruded in plastic is stable over time, supporting a shelf life of 2 years particularly when labeling recommends storage under dry conditions.

Packaging containing copper Masterbatch was tested for resistance against fungal growth over 28 days. Masterbatch packaging tested under ASTM guideline G 21-15 showed no growth of *Aspergillus niger, Penicillium pinophilum, Chaetomium globosum*, *Trichoderma virens*, or *Aureobasidium pullulans*.

III. Dietary Exposure

A. Proposed Use

Copper Masterbatch is intended to be used in plastic packaging in contact with the following foods:

- Fresh beef
- Fresh poultry
- Fresh pork
- Sausage
- Deli meat
- Fresh salmon
- Fresh cheese

Masterbatch is added to food packaging so that the level of copper is 100 mg/m^2.

B. Migration of Copper from Packaging

A migration test was carried out on sheets of LLDPE containing the copper Masterbatch at the intended use level of 100 mg Cu/m^2. The test was performed under conditions recommended for Condition of Use F under Appendix II of FDA's Guidance for Industry: Preparation of Premarket Submissions for Food Contact Substances (Food Contact Substances Guidance) (FDA 2007). Briefly, the LLDPE was extracted for 10 days at 20°C in 10% and 95% ethanol in water, representing aqueous and fatty food, respectively. Test solutions were analyzed for copper after 24, 48, 120 and 240 hours. Migration was considered in two ways: the average concentration extracting over the 10-day period and the highest concentration from among the 4 time points for each food simulant. Results are presented below in Table 6.

Table 6. Copper migration (µg Cu/kg food)

Food type	**Highest**	**Average**
Aqueous	1157.3	1065.2
Fatty	49.3	32.5

C. Estimated Daily Intake (EDI)

The estimated daily intake of copper from the intended use of the copper Masterbatch in food packaging was determined by first estimating food consumption of the relevant foods.

- Meat, fish, and poultry:
  - Total meat, poultry, and seafood, mean and 90th percentile consumption per day; National Health and Nutrition Examination Survey (NHANES) cycles 2003 to 2004, 2011 to 2012, 2013 to 2014, 2015 to 2016 (Table 7)
- Fresh cheese
  - Total cheese intake, mean and pseudo 90th percentile consumption per day; NHANES cycle 2017-2018 (Table 8)

Table 7: Total meat, poultry and seafood consumption (g/day); NHANES 2003-2004 through 2015-2016 (Bowman et al. 2018)				
Mean consumption				
Age group (years)	**2003 to 2004**	**2011 to 2012**	**2013 to 2014**	**2015 to 2016**
2 to 5	70.874	65.204	59.534	65.204
6 to 11	90.718	90.718	85.049	90.718
12 to 19	121.903	119.068	124.738	110.563
20+	136.078	136.078	138.913	136.078
All	127.573	124.738	127.573	127.573
90th percentile consumption				
Age group (years)	**2003 to 2004**	**2011 to 2012**	**2013 to 2014**	**2015 to 2016**
2 to 5	141.748	130.408	119.068	130.408
6 to 11	181.437	181.437	170.097	181.437
12 to 19	243.806	238.136	249.476	221.126
20+	272.155	272.155	277.825	272.155
All	255.146	249.476	255.146	255.146

Table 8. Total mean and 90th percentile cheese consumption (g/day); NHANES 2017-2018		
Age group (years)	**Average**	**90th percentile**
2 to 5	13.54	27.07
6 to 11	26.89	53.79
12 to 19	59.78	119.57
20+	31.52	63.03
All	32.16	64.33

These values overestimate copper intake from the intended uses of Copperprotek packaging as Table 7 consumption values are for all meat, poultry, and seafood, not just salmon, and Table 8 consumption estimates include all cheese, not just fresh cheese. The percentage of Table 7 values representing fish and seafood intake is approximately 7% (Bentley 2019) and salmon consumption has been estimated at 14% of total fish and seafood consumption (Knapp et al. 2007). Based on USDA cheese consumption data with limited distinction among types, the percentage of natural cheese consumed that is fresh cheese is approximately 40% (USDA-ERS 2022).

EDI values were calculated using the highest migration values from Table 6 above to give a conservative estimate. Migration values were weighted as a factor of the percent aqueous versus fat content, where meats and fish are assumed to be 95% water soluble and 5% fat soluble. The relative percentages of water and fat-soluble components vary among fresh cheese types. For example, full fat cream cheese is 55% water, 6% protein, and 33.5% fat, while low moisture, part skim mozzarella cheese is 48% water, 24% protein, and 20% fat (USDA-ARS 2019). As a conservative calculation, the water and protein content of cheese was assumed to be at the high end of this range at 80%. The results of the EDI calculations are in Table 9.

Table 9. Copper EDI from Masterbatch use in food packaging (µg/day)						
Age group (years)	**Average consumer**			**90th percentile consumer**		
	From packaged meat, poultry, seafood	**From cheese**	**Total**	**From packaged meat, poultry, seafood**	**From cheese**	**Total**
2 to 5	71.8	12.7	**84.5**	143.7	25.3	**169.0**
6 to 11	98.4	25.2	**123.6**	196.8	50.3	**247.1**
12 to 19	131.2	55.9	**187.1**	262.4	111.9	**374.3**
20+	150.7	29.5	**180.2**	301.4	59.0	**360.4**
All	139.8	30.1	**169.9**	279.6	60.2	**339.8**

Alternate EDI calculation for food contact substances

The EDI can also be calculated using standard assumptions about food packaging recommended by the Food Contact Substances Guidance (FDA 2007).

The migration estimate accounts for the nature of the food contacting the packaging. FDA has derived default "food-type distribution factors" (f_T) for each packaging material to reflect the fraction of all food contacting each material that is aqueous, acidic, alcoholic, and fatty. However, because this packaging is specific to the foods previously described, the fractions of aqueous- and fatty- food contacting this packaging described above are more accurate: 0.95/0.05 aqueous/fatty for meats and 0.8/0.2 for cheese:

$<M> = (f_{aqueous})(M_{10\% \text{ ethanol}}) + f_{fatty}(M_{95\% \text{ ethanol}}) = (0.95)(11.57.3 \text{ µg/kg}) + (0.05)(49.3 \text{ µg/kg})$

$= 1102 \text{ µg Cu/kg food}$

The dietary concentration is calculated using a consumption factor (CF), which describes the fraction of the daily diet expected to contact the specific packaging material of interest. FDA has derived default CFs for various packaging types, but for specialized applications, a production volume-based CF can be derived. A CF was calculated based on the maximum estimated annual production volume in the fifth year of production: 45.2 tons (4.1×10^{10} mg) of copper Masterbatch. Considering a 4% concentration of copper in Masterbatch and an addition of the Masterbatch at a rate of 100 mg copper per square meter, a maximum of 1.64×10^7 m^2 of food contact plastic with Masterbatch is produced per year.[3] Assuming 1.0 in^2 of packaging is in contact with 10 g food (equivalent to 6.45×10^{-5} m^2/g), the total weight of food in contact with Masterbatch packaging is 2.54×10^{11} g/yr. Assuming an estimated US population over age 2 of 3.1×10^8 and assuming the average individual consumes a daily diet of 3000 g, total food intake is estimated to be 3.37×10^{14} g/yr.

The CF is the ratio of the total food packaged in contact with the FCS divided by the total population diet:

$CF = 2.54 \times 10^{11}$ g food/yr ÷ 3.37×10^{14} g food/yr = **0.00075**

[3] 4.1×10^{10} mg Cu-MB/yr produced x 4% Cu by wt. ÷ 100 mg Cu/m^2

The EDI is the product of migration and the CF and assumes a daily consumption of food of 3 kg/day:

EDI = CF x <M> = 0.00075 x 1102 µg/kg = 0.831 µg/kg food x 3 kg food/day

= 2.5 µg Cu/person/day

Although estimating EDI by this method does not reflect consumption by a consumer (i.e., it is more of a per capita estimate), it is a more accurate representation of the average copper intake derived from Masterbatch food packaging than the first estimate, which assumed 100% of meat and cheese is packaged in copper Masterbatch food packaging. Even given the possibility that additional producers of copper Masterbatch come to the market, this calculation illustrates the magnitude of increase in dietary copper predicted from this use.

D. Background Exposure

Copper is an essential trace element that is present in a variety of foods. Of the foods sampled in FDA's 2018-2020 Total Diet Survey (TDS), the copper concentration was as high as ~20 mg/kg, with the highest in sunflower seeds, walnuts, almonds, infant formula (milk-based, dry), and peanuts (FDA 2022). Other significant dietary sources of copper include seafood, wheat-bran cereals, and whole-grain products. Organ meats like beef liver contain the highest levels of copper, as high as 175 mg/kg (FDA 2017), but were not a significant part of the U.S. diet in recent years. The copper content of baby foods varied by type and was highest in teething biscuits, which had an average content of 1.6 mg /kg (US FDA 2017). Average copper levels in human milk ranged from 0.02–0.08 µg per 100 g in women one-to-six months postpartum and from 0.017–0.02 µg per 100 g in women seven-to-twelve months postpartum.

The other major source of dietary copper is dietary supplements, which typically contain copper in the range of a few micrograms to 15-mg (NIH 2022a). Drinking water is another source of copper. Data from EPA indicated that most of the U.S. population receives less than 100 to 900 µg/day of copper from drinking water (IOM 2001) with an average of 150 µg/day (ATSDR 2022). Other sources of dietary copper in the U.S., such as from residues of pesticides, fertilizers, and animal feed additives have not been quantified but are unlikely to be significant. According to EPA (2016), exposure to copper from pesticide residues is not expected to significantly add to background environmental copper levels.

Based on data from the 2017-2020 (pre-pandemic) NHANES/WWEIA survey, the mean intake of dietary and supplemental copper in all individuals (excluding pregnant, lactating, and breast-fed individuals and those with incomplete supplement data) was 1300 µg/day, approximately 200 µg/day greater than the mean intake from food alone (USDA-ARS 2022). IOM (2006) reported similar values from NHANES III, 1988–1994. In the 1988-1994 survey, the highest intake from food and supplements at the 90th percentile was 3,580 µg/day in lactating women, with the next highest reported intake at the 90th percentile of 3,550 µg/day in pregnant women. Table 10 summarizes mean and 90th percentile dietary copper intakes for all groups surveyed in NHANES III.

Table 10. Background copper intake from food and supplements (µg/day) (IOM 2006)			
Sex	**Age/category**	**Mean copper intake**	**90th percentile intake**
Both	1-3 y	740	1,100
	4-8 y	1,050	1,250
Male	9-13 y	1,280	1,640
	14-18 y	1,580	2,240
	19-30 y	1,850	2,880
	31-50 y	1,850	2,790
	51-70 y	1,790	3,150
	71-71+ y	2,200	3,020
Female	9-13 y	1,130	1,420
	14-18 y	1,150	1,610
	19-30 y	1,320	1,980
	31-50 y	1,450	2,730
	51-70 y	1,450	3,010
	71-71+ y	1,520	2,980
	Pregnant	1,860	3,550
	Lactating	2,140	3,580
All Individuals		1,490	2,360
All Indiv (+P/L)*		1,500	2,400

*Pregnant and Lactating

The background copper intake of the U.S. population ranges from 740 to 3,580 µg/day, depending on age and pregnancy or lactation status. The estimated additional daily copper intake from use of copper Masterbatch in food packaging is conservatively predicted to be between 84.5 and 374 µg/day. Therefore, this use of copper is predicted to increase daily copper intake by approximately 11%-14%.

IV. Self-Limiting Levels of Use

The level of copper in the final food packaging is not intended to exceed 100 mg/m^2; however, there is no technical limitation at this level.

V. Experience Based on Common Use in Food Before 1958

N/A.

VI. Narrative

This summary of publicly available and other relevant information was developed to assist a panel of independent scientists (the GRAS Panel), qualified by their scientific training and relevant national and international experience to conduct an independent, critical, and comprehensive evaluation of the available information on the safety of copper, and to determine whether the proposed use is suitable and Generally Recognized as Safe (GRAS) based on scientific procedures when used as an antimicrobial food packaging additive. For the purpose of this review, the term “safe” or “safety” is defined as a reasonable certainty in the minds of competent scientists that the substance is not harmful under the intended conditions of use (21 CFR 170.3(i)).

As an essential trace element, the toxicity of dietary copper has been well-characterized in animals and humans. As noted above in Part III (D), many foods contain copper. FDA considers copper sulfate to be GRAS when used as a nutrient supplement or processing aid with no limitation other than current good manufacturing practice (21 CFR 184.1261). FDA also allows 1.0 mg Cu/L in bottled water (21 CFR 165.110). International regulatory bodies that recognize copper sulfate as a food additive include Health Canada and the Japanese Minister of Health, Labour and Welfare. Most authoritative bodies relevant to food safety and nutrition, including the Institute for Medicine (IOM), the Joint Food and Agricultural Organization/World Health Organization Expert Committee on Food Additives (JECFA), and European Food Safety Agency (EFSA) have conducted comprehensive reviews of safety data related to copper. Their well-established conclusions about dietary copper are summarized in this section. In addition, a literature review was conducted by Leslie Patton, Ph.D. at ChemReg Compliance Solutions LLC for literature published at any time through the date October 27, 2022, which included relevant publications from the “PubMed” database that accesses MEDLINE, life science journals, and online books. The search criteria were “copper,” “dietary copper and toxicity,” and “copper and toxicity and food.”

It is worth noting that, although five forms of copper are produced during the manufacture of the copper microparticles (*see* Table 1), it is not the copper sulfate and hydroxide species being released onto the surface of food but rather the copper (II) ion itself. Furthermore, there is no significant difference in various copper species with respect to the biological response. EFSA reported a study comparing the toxicokinetics of copper hydroxide, copper oxychloride, Bordeaux mixture, tribasic copper sulfate, and copper (I) oxide with copper sulfate pentahydrate and found similar absorption, distribution and excretion rates following oral exposure in bile-cannulated rats (EFSA 2018). Hence, in the toxicology review in this section, effects are expressed on the basis of copper ions rather than copper salts or compounds.

When considering the latest toxicological research on copper and comparing the current intake of copper to the safety levels identified by various expert groups, the intended use of the copper product used in food packaging product can be reasonably expected to be safe.

A. Introduction

Copper is an essential trace element and constituent of animal and human tissue. Copper is important in the formation of red blood cells and in a number of metalloenzymes that reduce molecular oxygen, including diamine oxidase, monoamine oxidases including lysyl oxidase, cytochrome c-oxidase, ferroxidases, dopamine beta-monooxygenase, and copper/zinc superoxide dismutase.

U.S. Dietary Reference Intakes (DRI) for copper are summarized in Table 11. For adult men and women, the Recommended Daily Allowance (RDA) is 900 µg/day and the Tolerable Upper Intake (UL) is 10,000 µg/day (IOM 2006).

Table 11. Dietary reference intakes for copper (IOM 2006)

Life Stage	**Recommended daily allowance (µg/day)**	**Tolerable upper intake level (µg/day)**
1-3 years	340	1000
4-8 years	440	3000
9-13 years	700	5000
14-18 years	890	8000
≥19 years	**900**	**10,000**
Pregnant females, ≤18 years	1000	8000
Pregnant females, 19-50 years	1000	10,000
Lactating females, ≤18 years	1300	8000
Lactating females, 19-50 years	1300	10,000

Frank copper deficiency in humans is rare. Copper has the potential to compete with other nutrients, most notably zinc, by competitive absorption in the gut and/or onto metallothionein. A diet high in zinc can result in copper deficiency. Effects of a diet low in copper include defective connective tissue synthesis and osteogenesis, neutropenia, and iron-resistant anemia (WHO 1996).

Likewise, overconsumption of copper is not common; however, several rare genetic conditions can render a person susceptible to copper toxicity. Wilson's disease is a recessive genetic condition that results in the accumulation of copper in the liver, resulting in liver failure and cirrhosis. There are an estimated 30-50 cases per million of Wilson's disease around the world and in Western countries, the gene frequency is generally lower at 0.36% (Liu et al. 2017). Menkes disease primarily affects male infants and is associated with a defect in the gene encoding the ATP7A protein that helps control absorption of copper from food and transport, resulting in poor distribution of copper in the body. As a result, copper accumulates in the small intestine and kidneys while levels in liver and brain remain unusually low. Indian childhood cirrhosis (ICC) is characterized by increased copper levels in serum and liver. The etiology of the disease is uncertain; it is thought to result from excessive copper exposure from brass food containers, but there is some evidence that a genetic component exists. Idiopathic copper toxicosis (ICT) is a rare condition believed to be caused by an autosomal-recessive genetic defect in copper metabolism combined with excess dietary copper (Müller et al. 1998).

In healthy people, copper is regulated by tightly controlled homeostasis in the body, preventing short-term toxicity; if the dietary supply of copper is in excess, more is excreted (Turnlund et al. 2005). The most commonly reported adverse health effect of high copper intake is gastrointestinal (GI) distress, which can result from single acute or repeated ingestion of large doses of copper substances (Araya et al. 2001, 2003a; Olivares et al. 2001; Pizarro et al. 1999). In extreme cases where a large dose of copper has been ingested accidentally or intentionally,

GI symptoms may be followed by evidence of kidney and/or liver damage, CNS symptoms, organ failure, and death (ATSDR 2022; Sood and Verma 2011; Akintonwa et al. 1989; Ahasan et al. 1994).

Studies on the effect of a "priming" diet of copper sulfate prior to a large dose indicated kidneys and liver of rats adapt to excess dietary copper. In one such study, Wistar rats (16 males/group) received diets containing either 0 or 3,000 mg Cu/kg of copper sulfate, equivalent to ~270 mg Cu/kg bw/day (Haywood and Loughran 1985). After 15 weeks, 4 rats/group were killed and livers examined. The remaining rats from both groups were then given 6,000 mg Cu/kg diet of copper sulfate for 3 weeks. The rats that had initially received no dietary copper showed clinical effects of toxicity and suffered hepatocellular necrosis and inflammation after the 3-week copper exposure. The "primed" rats did not display the clinical effects or have hepatoxicity. This phenomenon has been noted in humans too. From clinical studies and surveys, the threshold for acute GI effects from copper in water is about 4.8 mg/day (IOM 2001). However, no adverse GI effects were reported in U.S. adults who consumed water containing approximately 8.5 to 8.8 mg/L of copper for over 20 years beginning in childhood (aged 0 through 5 years) (Scheinberg and Sternlieb 1996). Homeostatic data indicated that a 10-fold increase in dietary copper resulted in the absorption of only twice as much copper and that indices of copper status, as a result of the body's regulation of copper, are resistant to change except under extreme dietary conditions (Turnlund et al. 1991).

Various domestic and international scientific and regulatory groups have reviewed the safety of dietary copper over the years. The present review relies on some of these reviews as the toxicity of copper is so well characterized. Reference values relating to dietary copper are summarized below in Table 12.

Table 12. Copper reference values

Reference value type	**Value**	**Endpoint (study)**	**Source**
Acute- and intermediate-duration oral provisional Minimal Risk Level (MRL)	0.02 mg Cu/kg/day	Gastrointestinal (GI) symptoms in women (Pizarro et al. 1999)	Agency for Toxic Substances and Disease Registry (ATSDR) 2022
Tolerable Upper Intake Level (UL)	10 mg/day for adults (extrapolated to children based on body weight - *see* Table 11)	Absence of adverse effects on liver (Pratt et al. 1985)	IOM 2006
Maximum Contaminant Level Goal (MCLG) in drinking water	1.3 mg/L		US EPA; 40 CFR Part 141
Acceptable Daily Intake (ADI)	0.07 mg/kg bw (5 mg/day)	No retention of copper intake (Turnlund et al. 2005, weight of evidence)	EFSA 2022

Previous ADI	0.15 mg Cu/kg bw per day	Elevation of ALT in 1-year dog study (Shanaman et al., 1972)	EFSA 2018, 2008
UL	5 mg/day for adults (extrapolated to children based on body weight)	Absence of adverse effects on liver (Pratt et al. 1985; O'Connor et al., 2003)	SCF 2003
UL	0.18 mg/kg bw/day (10-12 mg/day)	References not cited	WHO 1996
Provisional Tolerable Daily Intake (PTDI)	0.5 mg/kg bw/day		WHO 1982

B. Toxicokinetics

Dietary copper (II) is reduced to Cu(I) by reductases at the apical membrane of intestinal epithelial cells (Ohgami et al. 2006). In this state, copper can be transported across cellular membranes via carrier protein, Ctr1. The ion is primarily absorbed in the stomach and small intestine (Taylor et al. 2020; van den Berghe and Klomp 2009). Copper absorption is controlled by homeostasis, with absorption decreasing as consumption increases (van den Berghe and Klomp 2009). Absorption of dietary copper in adults ranges from 12 to 71%, and in infants, 75 to 84%. For a diet ranging from 0.7 to 6.0 mg/day, true absorption (i.e. excluding the fraction of copper that is lost endogenously, for example via bile, salivary, and gastric routes) was measured to be close to 50% (Harvey et al. 2005). In addition to dietary copper levels, absorption is affected by age, gender, food type, chemical speciation, and pregnancy or contraception status (Bost et al. 2016).

There is a well-characterized decrease in copper absorption in rats and humans when dietary zinc levels are high. Zinc outcompetes copper for serosal transport in the gut, and at the same time, high zinc levels induce metallothionein synthesis, for which copper has the higher binding affinity. Consequently, the presence of high zinc levels results in less copper being transported across the gut and more being bound to metallothionein. The European Scientific Committee on Food (SCF) set a Tolerable Upper Intake Level (UL) of 25 mg/day for zinc based on the absence of any adverse effect on a wide range of indicators of copper status in controlled metabolic studies (EFSA 2014).

An overview of copper distribution and metabolism in humans is pictured below in Figure 4. Following absorption, the distribution of copper in the body is biphasic, where the first phase is transport via the ATPase, ATP7A, into the portal circulation (van den Berghe and Klomp 2009). In the portal circulation, copper is bound to other carriers, including histidine and albumin, as it is transported into the liver. About 75% of absorbed copper is taken up by the liver (Harvey et al. 2005). Most of the remaining 25% flows into the peripheral circulation, mainly bound to albumin. The second phase of distribution begins when a portion (~80%) of the copper in the liver binds to ceruloplasmin and is released into peripheral circulation. This pool of copper is redistributed to the brain, kidneys, muscles, and connective tissue. The other 20% of the liver copper is stored as metallothionein or shunted back to the intestine in bile via another ATPase, ATP7B.

Metabolism is regulated primarily by copper-transport ATPases. Copper is stored in tissues bound to metallothionein and amino acids in association with copper-dependent enzymes (Taylor et al. 2020). Copper exposure induces metallothionein synthesis, an important part of

copper homeostasis (Mercer et al. 1981; Wake and Mercer 1985). Ceruloplasmin and other binding proteins are important in the uptake, storage, and release of copper from tissues.

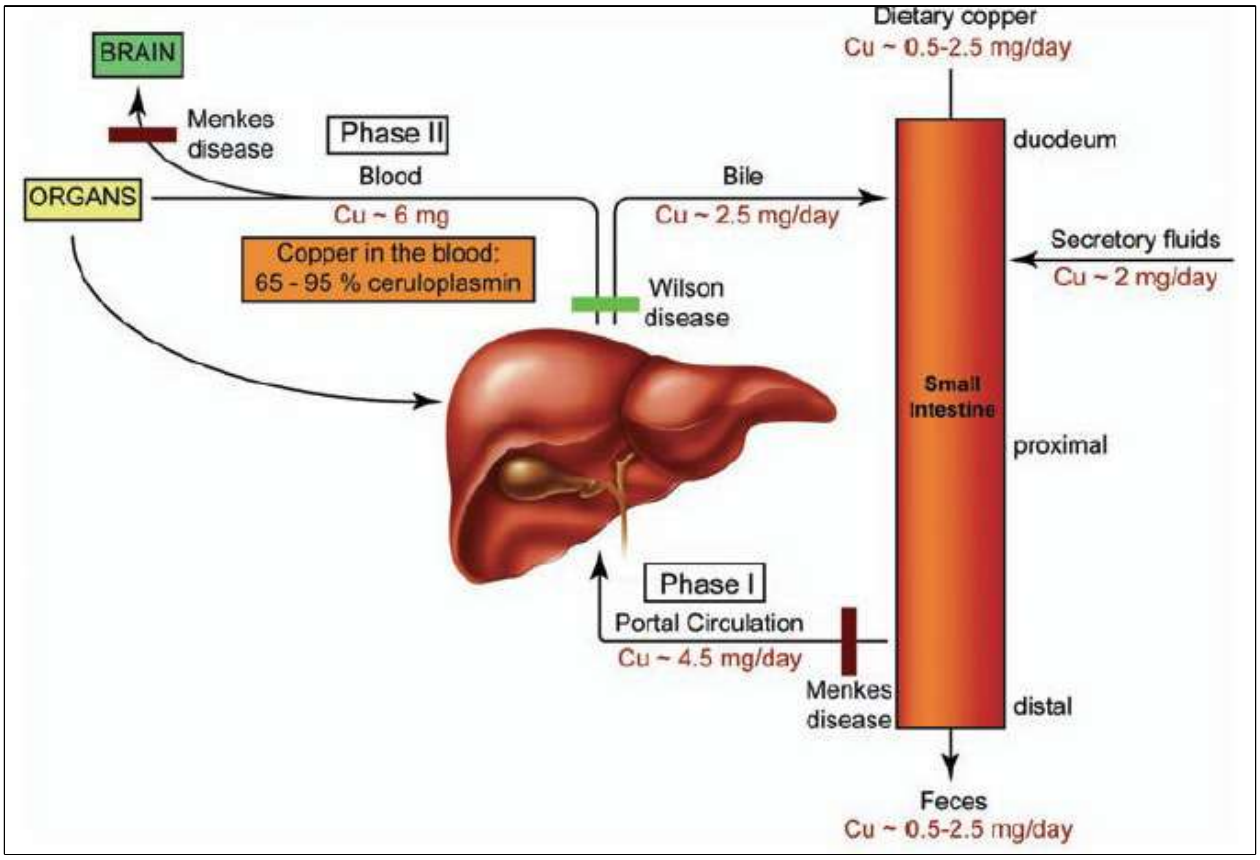

Figure 4. Overview of copper metabolism in humans (van den Berghe and Klomp 2009). In Wilson's disease, copper accumulates in the liver due to a genetic mutation that impairs its biliary excretion. In Menkes disease, copper distribution is affected resulting in accumulation in the kidney and intestinal lining.

The major excretory pathway for copper is biliary. Copper in the liver is transported with bile back to the intestine and excreted in the feces. In addition, some copper passes directly from the small to large intestine and is excreted with feces. Very little copper is excreted in urine: 1 to 2% of total turnover (Turnlund et al. 2005). Copper half-life in various organs have been calculated to be: 3.9-21 days in the liver, 5.4-35 days in the kidney, 23-662 days in the heart, and 457 days in the brain (Levenson and Janghorbani 1994). The half-life of copper-ceruloplasmin in the body was modeled to be 27 days (Harvey et al. 2005).

C. Acute Toxicity

Oral LD_{50} values of 300 to 960 mg/kg bw copper sulfate (119-382 mg Cu/kg bw) have been determined in rats (Lehman 1951; Smyth et al. 1969). EPA (2009) reported acute oral LD_{50} values for copper sulfate pentahydrate (99% purity) in male and female rats to be 790 and 450 mg/kg bw, respectively (111 and 196 mg Cu/ kg bw). An oral LD_{50} for mice was determined to be 39.8 mg Cu/kg bw using the standard up and down procedure (Kadammattil et al. 2018).

D. Repeated Dose Toxicity

Male and female B6C3F1 mice and F344/N rats (5/species/sex/group) were fed copper (II) sulfate pentahydrate in the diet at a concentration of up to 16,000 mg/kg food for 15 days (Herbert 1993). The top dose was equivalent to approximately 781 mg Cu/kg bw/day in mice and 305 mg Cu/kg bw/ day in rats. In mice, there was no mortality in any dose group. The gastrointestinal system was most sensitive to copper sulfate with minimal hyperplasia and hyperkeratosis in the forestomach observed at 197-216 mg Cu/kg bw/day. The No Observed Adverse Effect Level (NOAEL) for mice in this study was 92 mg Cu/kg bw/day in males and 104 mg Cu/kg bw/day in females. In rats, weight gain was reduced starting at a dose of 194 mg Cu/kg bw/day, but there were no other overt signs of toxicity. Effects on the forestomach were evident from 45 mg Cu/ kg bw/day, on the kidneys from 93 mg Cu/ kg bw/day, and on the liver (inflammation, massive fatty liver change and centrilobular necrosis) and bone marrow from 194 mg Cu/ kg bw/day. The NOAEL in rats in this study was 23 mg Cu/kg bw/day in both sexes.

Two-week drinking water studies in mice and rats were also carried out by NTP at concentrations up to 30,000 ppm copper sulfate pentahydrate in water (estimated intakes up to 97 mg Cu/kg bw/day). Poor palatability of the water at high concentrations lead to dehydration, which precluded interpretation of the study with respect to copper.

NTP also ran comprehensive 90-day studies in rats and mice on the oral toxicity of copper (II) sulfate pentahydrate (Herbert 1993). Ten animals of each species/sex/group received the substance in the feed at up to 8000 mg/kg diet in rats (up to 138 mg Cu/kg bw/day) and up to 16,000 mg/kg diet in mice (up to ~1050 mg Cu/kg bw/day). The only overt sign of toxicity was a dose-related reduction in growth, which was statistically significant in male and female rats starting at 67 and 138 mg Cu/ kg bw/day, respectively, and in male and female mice at 97 and 267 mg Cu/ kg bw/day respectively. Hyperplasia and hyperkeratosis in the forestomach were noted in both species (from 34 mg Cu/ kg bw/day in rats and from 187-267 mg Cu/ kg bw/day in mice), and liver and kidney effects in the rats only (from 67 mg Cu/kg bw/day). The rat liver and kidney effects included inflammation of the liver and degeneration of the kidney tubule epithelium. Iron levels were reduced in male and female rat spleens, and hematological changes indicative of microcytic anemia were observed at 34 mg Cu/ kg bw/day and higher. The NOAEL was 17 mg Cu/kg bw/day in male and female rats and 97 and 126 mg Cu/kg bw/day in male and female mice, respectively.

In a more recent study, Wistar rats (18 males/group) were treated with 0, 100, or 200 mg/kg bw/day of copper sulfate pentahydrate (~25 and 51 mg Cu/kg bw/day) for 30, 60, or 90 days (n=6 at each time point) (Kumar et al. 2015). There were statistically significant increases in copper levels in the liver, kidney, and brain at both dose levels and all treatment durations (up to 29-fold, 3-fold, and 1.5-fold in liver, kidney, and brain, respectively). At the lower dose, body weight decreased 21.5% after 90 days, perhaps due to GI effects and/or hepatotoxicity. Rats exposed to both doses of copper demonstrated impaired motor coordination and cognitive function, as indicated by grip strength, latency to fall time, and attention scores. Other less severe effects at the lower dose included reduced hemoglobin at all time points; increased alanine transaminase, aspartate transaminase, and bilirubin after 90 days, and increased blood urea nitrogen (BUN) and BUN:creatinine ratio after 90 days. NOAEL was not derived in this study.

Neurotoxicity

In the NTP studies discussed above, female and male mice in the 90-day study who received 267 mg Cu/ kg bw/day had a 10-13% increase in relative brain weight (Herbert 1993). No neurological effects were seen following exposure to doses of 44-97 mg Cu/kg bw/day (male mice) or 52-267 mg Cu/kg bw/day (female mice). Additionally, in the 15-day mouse study, neurological effects were not reported in males receiving 10-58 mg Cu/kg bw/day or in females receiving 15-62 mg Cu/kg/day.

The Lowest Observed Adverse Effect Level (LOAEL) for neurotoxicity was identified in a study in which 5 male Sprague Dawley rats/group received gavage doses of 0, 10, or 20 mg/kg bw/day copper sulfate (~4 or 8 mg Cu/kg bw/day) for 16 weeks (Kumar et al. 2019). The ages of the rats were not given. The study investigated the effects on brain copper concentration and neurobehavioral functions. Copper-dosed animals showed a significant increase in brain copper concentration and a depleted ceruloplasmin level. Neurobehavioral effects observed at both doses indicated an effect on memory and motor coordination and included decreased passive avoidance response, increased immobility time in a forced-swim test, decreased entries in an open-arm test, decreased exploration time, and impaired muscle strength and coordination. The severity of the neurotoxic effects increased with dose.

Chronic toxicity and carcinogenicity

The chronic toxicity and carcinogenicity of copper are not well characterized in animal studies. Increased mortality and growth retardation or effects on the liver, kidneys, or stomach have been observed in rats following long-term ingestion of 27-150 mg Cu/kg bw/day as copper (II) sulfate.

There is no scientific evidence to suggest copper sulfate or other copper salts are carcinogenic in test animals.

Reproductive/Developmental toxicity

Scientific data in test animals suggest that exposure to copper compounds can affect reproduction. In some rat studies, the weights and/or histology of the testes, seminal vesicles, uterus, or ovaries were affected by chronic oral intakes of 27-120 mg Cu/kg body weight per day of copper (II) sulfate, acetate, or gluconate (ATSDR 2022). Studies in male rats and mice exposed to copper suggest that copper plays a role in spermatogenesis and male infertility (Kadammattil et al. 2018; Sakhaee et al. 2016). Female mice receiving ~40 mg Cu/kg/day for 14 or 35 days had a reduced number of antral follicles, ovarian cell damage, a decrease in the corpus luteum, and decreases in other follicles and changes to follicle structure (Babaei et al. 2012). In mice, doses between 398 and 537 mg Cu/kg body weight per day of copper (II) sulfate in the diet did not affect male or female reproductive organs (ATSDR 2022). In the NTP 90-day oral toxicity study described above, no effects of $CuSO_4$ were observed on testis, epididymis or cauda epididymis weight, spermatid counts, or sperm motility in either species at any dose (highest dose in rats was ~67 mg Cu/kg bw/day, highest dose in mice was ~398 mg Cu/kg bw/day) (Herbert 1993). There was no statistically significant change in estrus cycle length or duration of estrus in either species.

Data on the developmental toxicity of copper in experimental animals are limited. Some delayed growth and development were noted in rats and rabbits exposed to copper while *in utero* (Haddad et al. 1991; Munley 2003).

E. Genotoxicity

Scientific evidence supports the idea that copper is not genotoxic in humans following oral exposure, although animal models give mixed results. This has been well-described in the literature and by regulatory bodies including the EFSA, European Commission Scientific Committee on Health and Environmental Risks (SCHER), and WHO (EFSA 2022; SCHER 2008; IPCS 1998). Mutagenicity noted *in vitro* and *in vivo* in animal studies often occurs only at high cytotoxic doses (Taylor et al. 2020). Such conditions are unlikely under normal physiological conditions where copper remains bound to proteins.

F. Human Studies

Incidence of acute and chronic copper toxicity in humans is rare and typically restricted to certain subpopulations, such as populations with high copper concentrations in drinking water, populations that utilize copper cooking or food storage vessels, and individuals who have a hereditary predisposition to a disease of copper toxicity. The most sensitive targets of oral copper exposure are the gastrointestinal and neurological systems (Pizarro et al. 1999; Araya et al. 2001; 2003a; 2003b; Olivares et al. 2001). Hepatic effects occur at much higher doses typically associated with accidental ingestions or long-term supplementation (Du and Mou 2019; O'Donohue et al. 1993). There is no strong evidence that copper supplementation in the diet results in cardiovascular disease, cognition decline, or cancer in the general population (ATSDR 2022).

In healthy people, copper is regulated by tightly controlled homeostasis in the body, preventing short-term toxicity; if the dietary supply of copper is in excess, more is excreted. Results from human studies do not support an association between dietary copper level and plasma copper concentrations. In six clinical trials where the range of dietary copper was 0.57–6.9 mg/day, no significant increases in plasma copper were noted among people with higher dietary copper intakes (Harvey et al. 2009). Similarly, copper levels in serum, urine, and hair were not affected by copper supplementation of 10 mg/day for 12 weeks (Pratt et al. 1985). In another study, serum copper levels changed in response to dietary copper supplementation of 1-3 mg/day, although this was more remarkable in individuals with copper deficits. Total ceruloplasmin protein was related to copper status but reflected changes in copper-deficient individuals only.

Gastrointestinal

Gastrointestinal effects are well documented in acute copper poisoning. Case studies of humans accidentally or intentionally ingesting copper compounds typically show gastrointestinal effects. The most common GI effects include abdominal pain, nausea, vomiting, diarrhea, and melena (black stool), leading to local corrosion, intravascular hemolysis, hemolytic anemia, methemoglobinemia, and acute renal and hepatic impairment. Acute GI symptoms result from the maximum serum concentration (C_{max}) of copper at a certain time point rather than an intake over time, suggesting the effect is one of direct contact. In acute studies on human volunteers, mild GI effects have been reported after a single dose of copper (Araya et al. 2001, 2003a; Olivares et al. 2001). In a study conducted in 53 men and women, an increased incidence of nausea at 0.012 mg Cu/kg bw (4 mg Cu/L in water) was reported; no nausea was reported by subjects exposed to lower doses (Olivares et al. 2001). Two drinking water studies reported LOAEL of 6 mg Cu/L in drinking water and NOAEL of 4 mg Cu/L for increased incidence of nausea (Araya et al. 2001; 2003a). The LOAELs were equivalent to doses of 0.09-0.018 mg/kg bw, and the NOAELs, ≤0.012 – 0.06 mg Cu/kg bw, with females being more sensitive.

Pizarro et al. (1999) reported a dose-response relationship between copper sulfate and GI symptoms in healthy adult women consuming 0, 1, 3, or 5 mg/L of copper as copper sulfate in drinking water for two weeks, equivalent to 0.0006, 0.03, 0.07, and 0.1 mg Cu/kg/day, respectively. This was followed by a 1-week rest, followed by another dose of copper in the sequence until each woman had received a 2-week course of each dose. Incidences of abdominal pain, nausea, and vomiting were dose-dependent and uniformly distributed during the study period, while the incidence of diarrhea was not dose-dependent and presented within the first few weeks, then declined regardless of copper dose. ATSDR (2022) derived a provisional acute- and intermediate duration oral MRL of 0.02 mg Cu/kg/day for copper based on GI effects observed in the study (Pizarro et al. 1999). The MRL was based on a $BMDL_{10}$ of 0.05 mg/kg/day and a total uncertainty factor of 3 for human variability.

Hepatic

Hepatic effects following accidental or intentional ingestion of copper substances are well documented in humans. The most common effect is altered liver enzyme activity, including aspartate aminotransferase (AST), alanine aminotransferase (ALT), alkaline phosphatase (ALP), and lactate dehydrogenase (LDH) (Du and Mou 2019; Malik and Mansur 2011). Liver damage is the most reliable indicator of long-term exposure to high levels of copper, which is seen almost exclusively in people with Wilson's disease, ICC, or ICT. One report described a man who had no known genetic defect who developed acute liver failure following 30 mg/day supplementary copper for two years followed by 60 mg/day for an unspecified period (O'Donohue et al. 1993).

Human toxicity data from longer-term exposures at lower/typical intake levels are limited likely because copper is initially sequestered in the liver as a protective mechanism, preventing adverse effects. For instance, in adult volunteers given between 2 and 6 mg Cu/day in drinking water (0.042 to 0.17 mg Cu/kg/day) for two months, no changes in hepatic enzyme levels were observed (Araya et al. 2003b). Similarly, diets supplemented with either a placebo or 10 mg/day copper (0.15 mg Cu/kg/day) for 12 weeks had no effect on markers of liver damage, including serum AST, L-γ-glutamyl transferase (GGT), LDH, or ALP in 7 healthy adult volunteers (Pratt et al. 1985). Cross-sectional and intervention studies of copper present in infants' drinking water also did not result in changes in liver function (Dassel de Vergara et al. 1999; Zietz et al. 2003; Olivares et al. 1998). In healthy 3-12 month old infants, one group (n = 48) received water with <0.1 mg Cu/L (control) and one group (n = 80) with 2 mg Cu/L (Olivares et al. 1998). Estimated average copper supplementation in formula-fed infants ranged between approximately 248-318 µg/kg bw/day for the high-exposure group and between 123-158 µg/kg bw/day for the low exposure (control) group. In breast-fed infants, intake was 52-179 µg/kg bw/day in the high-exposure group and 38-174 µg/kg bw/day in the low group. There were no differences in copper status or liver function among groups. A few minor differences were noted in this study including statistically higher ceruloplasmin activity in 9-month old subjects who received copper supplementation versus those who did not. Reports of liver damage in healthy children exposed to high levels of copper have not been identified. There were no deaths from any form of liver disease in adults in Massachusetts who had consumed water containing approximately 8.5 to 8.8 mg/L of copper for 23 years beginning at ages 0 through 5 years (Scheinberg and Sternlieb 1996).

Neurotoxicity

Besides liver effects, the toxicity associated with Wilson's disease, and other conditions where copper transport is impaired, is predominantly neurological. Neurological effects are associated

with low plasma ceruloplasmin and the presence of Kayser–Fleischer rings reflecting copper deposition in the cornea (Członkowska et al. 2018; Espinós and Ferenci 2020). The most common neurological effects associated with high copper intake in human studies are headache, dizziness, agitation, and drowsiness (Du and Mou 2019; Malik and Mansur 2011).

A group of 60 healthy women (ages 32 to 36 years) consumed water containing 0, 1, 3, or 5 mg/L ionic copper as copper sulfate pentahydrate (equivalent to 0.0006, 0.0272, 0.0731, and 0.124 mg Cu/kg bw/day, respectively) for a 2-week period followed by a 1-week rest, followed by the next dose of copper in the sequence (Pizarro et al. 1999). Each woman received a 2-week regimen of each dose. In total, six of the women experienced increased salivation and headache when receiving the dose of 0.07 mg Cu/kg bw/day. This was significantly higher than the incidence of these effects at the next lowest dose of 0.03 mg/kg bw/day. This study's LOAEL of 0.07 mg/kg bw/day was the lowest for neurotoxicity noted by ATSDR (2022) in its review.

A link between copper and cognitive decline was explored because this relationship has been suggested in the popular (non-scientific) literature. No studies demonstrating a clear, direct relationship between copper intake and cognition or neurodegenerative disease were identified in the literature search. A cohort study of 3,718 males and females over age 64 attempted to identify a correlation between copper intake and cognition (Morris et al. 2006). Overall, subjects with high copper intakes were more likely to have healthy lifestyle behaviors and higher cognitive ability. A potentially adverse effect of copper dietary supplementation was noted only in subjects who also had high saturated and trans fatty acids. In these individuals, an average Cu intake of 2.75 mg/day (slightly below the 90th percentile intake of copper in the U.S. for people ages 51-70; *see* Table 10) resulted in a rate of mental decline almost 50% higher than that of individuals whose average Cu intake was 0.88 mg/day. Clear conclusions about copper intake could not be made because factors other than copper intake were not considered. The authors noted that dietary fat intake itself has been associated with a higher incidence of Alzheimer's disease and faster cognitive decline. Furthermore, copper and fatty acid intakes were derived from diet questionnaires, which are not highly reliable.

Cardiovascular

There is limited evidence for an association between copper blood levels and coronary heart disease (CHD). In a cohort study, the adjusted risk of death from cardiovascular disease was about four times higher for subjects in the highest serum copper group (>1.43 mg/L) compared with those with normal levels (Singh et al. 1985). NHANES II data of 4574 adults indicated that age-adjusted serum copper was 5% higher in subjects who died from CHD than in those who did not (129.8 µg/dl ± 3.7 SD versus 122.9 µg/dl ± 0.5 SD, p=0.072) (Ford 2000). Hazard ratios for death by CHD and serum copper quartile showed that subjects in quartiles 3 and 4, but not 2, had significantly higher risk of death by CHD compared to quartile 1. The mechanisms underlying this association were not clear. In more recent studies, elevated serum Cu levels as well as ceruloplasmin levels were linked to obesity. In a longitudinal study of 1911 men, serum copper was further linked to an increased risk of cardiovascular disease death across BMI categories (Isiozor et al 2022). However, the risk of cardiovascular disease death did not clearly increase with serum copper levels; the men in the fourth quartile for serum copper concentration had a lower risk than those in the 3rd quartile. The mechanism linking excess serum Cu to cardiovascular disease was not explained. In a study of 1054 subjects aged 65 years old and older, dietary copper intake was not predictive of cardiovascular mortality over 14 years (Bates 2011).

Because serum copper and ceruloplasmin levels are increased as part of the acute-phase response in inflammatory conditions such as CHD (DiSilvestro 1990), the relationship between the two is not clear. Furthermore, there is no evidence for higher rates of CHD in Wilson's disease patients.

Immunotoxicity

No evidence for immunotoxicity has been observed at realistic levels of copper exposure (EFSA 2018).

Cancer

Neither the Department of Health and Human Services (HHS), the International Agency for Research on Cancer (IARC), nor EPA have classified copper regarding its carcinogenicity. The World Cancer Research Fund considered the role of micronutrients in cancer development and concluded there was no evidence for an association between copper intake/status and cancers with an immunotoxicity origin or with lung cancer (WCRF/AICR 2007). In a cohort study including 482,875 subjects, no association between total (dietary and supplemental) copper intake and lung cancer risk was identified (Mahabir et al. 2010).

G. Safety Summary

Potential adverse effects of copper intake have been well characterized over the years by regulatory bodies and scientific research. Copper levels in the body are tightly controlled by homeostasis and copper toxicity is rare. Data from human studies generally do not support an association between copper supplementation and increased body burden of copper in healthy individuals. The most common adverse health effect is gastrointestinal, which is likely an effect of direct contact of copper. ATSDR (2022) derived a provisional acute- and intermediate duration oral MRL of 0.02 mg Cu/kg/day for copper based on GI effects. For a 13-kg child (1-3 years old), the MRL is 260 µg/day and for adult men and women, the MRL is 1520 and 1220 µg/day, respectively, all of which are greater than the estimated daily copper intake from copper Masterbatch summarized in Table 9 for 90th percentile consumers.

It is reasonable to conclude that, except for individuals who suffer from specific genetic disorders (e.g., Wilson's disease), the general population will not be affected by the additional copper exposure from the copper (II) ions of food packaging containing 100 mg/m^2 copper, as described in this dossier. The contribution to daily copper intake from the proposed use of copper is estimated to be between 169 and 340 µg/day based on conservative assumptions. There is a wide enough margin between copper intake even at the 90th percentile and the UL for most age groups (Table 13), so that the addition of copper Masterbatch will not exceed that UL threshold. The UL is defined as the highest level of daily nutrient intake that is likely to pose no risk of adverse effects for almost all people. It includes intake from food, water, and supplements. The margin of exposure between the 90th percentile copper intake individuals and respective ULs is greater than the most conservative copper intake estimate from the proposed use for all but one age group: 1-3 year old children. This group is estimated to be ingesting more copper from food and supplements than the UL, even before considering adding the 169 µg Cu/day estimated for this age group from the proposed use of copper. This additional exposure is small when considering overall background exposure from food, water, and supplements.

The UL for copper is based on liver damage, although copper-associated liver damage in humans is observed almost exclusively in individuals with genetic defects in copper homeostasis, which is extremely rare in the United States. The UL for adults was derived from a double-blind study of seven subjects given 10,000 µg/day of copper gluconate for 12 weeks who sustained no liver damage (Pratt et al. 1985). To derive UL values for children, the adult UL was adjusted on the basis of relative body weight: $UL_{child} = UL_{adult} \times BW_{adult}/BW_{child}$. It is notable that the copper RDA for children is higher than that for adults on a weight basis and that this method of UL derivation does not account for that. It is further important to bear in mind that the UL is not an adverse effect level. Hence, although the estimated dietary intake in some children aged 1-3 may exceed the UL, intake above this level is unlikely to result in adverse health effects. Reports of liver damage in healthy children exposed to high levels of copper have not been identified. In fact, adults who had been exposed to levels of copper between 8.5 and 8.8 mg/L in drinking water for over 20 years starting between ages 0 and 5 did not have liver damage (Scheinberg and Sternlieb 1994).

This analysis supports the conclusion that the use of polyolefin food packaging containing 100 mg/m^2 copper will not affect the health of the people eating that food. The intended use of copper (II) ions as an antimicrobial on packaged fresh beef, pork, poultry, sausage, salmon, cheese, and deli meat delivered via food packaging is safe.

Table 13. 90th percentile copper intake compared to copper UL (µg/day)

Sex	Age/ category	Background 90th %ile intake	90th %ile intake from MB	Total 90th %ile Cu intake	UL
Both	1-3 y	1,100	169	1,269	1,000
	4-8 y	1,250	169	1,419	3,000
Male	9-13 y	1,640	247	1,887	5,000
	14-18 y	2,240	374	2,614	8,000
	19-30 y	2,880	360	3,240	10,000
	31-50 y	2,790	360	3,150	
	51-70 y	3,150	360	3,510	
	71-71+ y	3,020	360	3,380	
Female	9-13 y	1,420	247	1,667	5,000
	14-18 y	1,610	374	1,984	8,000
	19-30 y	1,980	360	2,340	10,000
	31-50 y	2,730	360	3,090	
	51-70 y	3,010	360	3,370	
	71-71+ y	2,980	360	3,340	
	Pregnant	3,550	360	3,910	8,000
	Lactating	3,580	360	3,940	10,000

Discussion of information inconsistent with the GRAS determination

No reports or other information are available that are deemed inconsistent with this GRAS determination.

Basis for conclusion regarding safety

The data and information summarized herein provides the basis for concluding that there is a reasonable certainty that under the conditions of use described above, the proposed use of copper in food packaging is not harmful to humans who consume the food in which it is packaged.

VII. List of Supporting Data and Information

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Appendix A. Certificates of Analysis

COPPERPROTEK®
EXTENDING YOUR QUALITY

Certificate of Analysis.

MB – PE with micro-structured Cu^{+2} as an active ingredient.

Batch n°: MB-22-1

Masterbatch for food packaging

	Spec. Value	Batch Value
Pellet Size	2 – 7 mm	3 – 6 mm
Copper Content	3.5 – 4.5% w/w	3.8% w/w
Pellet Color	Light green	Light green
Pellet Solubility	Insoluble (99.9%)	Insoluble (99.9%)
Carrier	Polyethylene Dowlex IP 20 Polyethylene resin	

Shelf-life:

24 months, at room temperature, in a cool, dry place. Away from sources of heat and humidity.

M.Sc. Noelle Blanc Schilling

Chief of Laboratory

Date of release (DD.MM.YYYY): 05.05.2022

Done by: Samantha Núñez Date: 05/05/2022	Revised by: Noelle Blanc Date: 05/05/2022	Approved by: Javier Lavín Date: 05/05/2022

COPPERPROTEK®
EXTENDING YOUR QUALITY

Certificate of Analysis.

MB – PE with micro-structured Cu^{+2} as an active ingredient.

Batch: MB-22-2

Masterbatch for food packaging

	Spec. Value	Batch Value
Pellet Size	2 – 7 mm	3 – 6 mm
Copper Content	3.5 – 4.5% w/w	3.76% w/w
Pellet Color	Light green	Light green
Pellet Solubility	Insoluble (99.9%)	Insoluble (99.9%)
Carrier	Polyethylene Dowlex IP 20 Polyethylene resin	

Shelf-life:

24 months, at room temperature, in a cool, dry place. Away from sources of heat and humidity.

M.Sc. Noelle Blanc Schilling

Chief of Laboratory

Date of release (DD.MM.YYYY): 10.05.2022

Done by: Samantha Núñez Date: 10/05/2022	Revised by: Noelle Blanc Date: 10/05/2022	Approved by: Javier Lavín Date: 10/05/2022

COPPERPROTEK®
EXTENDING YOUR QUALITY

Certificate of Analysis.

MB – PE with micro-structured Cu^{+2} as an active ingredient.

Batch: MB-22-3

Masterbatch for food packaging

	Spec. Value	Batch Value
Pellet Size	2 – 7 mm	3 – 6 mm
Copper Content	3.5 – 4.5% w/w	3.73% w/w
Pellet Color	Light green	Light green
Pellet Solubility	Insoluble (99.9%)	Insoluble (99.9%)
Carrier	Polyethylene Dowlex IP 20 Polyethylene resin	

Shelf-life:

24 months, at room temperature, in a cool, dry place. Away from sources of heat and humidity.

M.Sc. Noelle Blanc Schilling

Chief of Laboratory

Date of release (DD.MM.YYYY): 15.05.2022

Done by: Samantha Núñez Date: 15/05/2022	Revised by: Noelle Blanc Date: 15/05/2022	Approved by: Javier Lavín Date: 15/05/2022

Appendix B. GRAS Panel Opinion

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 "GRAS Panel"), was specially convened by Hyman, Phelps & McNamara, on behalf of Copperprotek SPA, to evaluate the safety and "generally recognized as safe" ("GRAS") status from the exposure of the intended use of copper (II) ions as an antimicrobial in packaging for fresh beef, pork, poultry, fresh sausage, salmon, and fresh cheese, and on deli meat. Copper in microparticle form is incorporated into LLDPE and this mixture is extruded into polymeric packaging material so that it is in contact with the packaged food, controlling and/or reducing the growth of superficial bacteria or fungi. The level of copper in the packaging will not exceed 100 mg/m^2. The GRAS panelists were Stanley Tarka Jr., Ph.D., FATS (The Tarka Group, Inc.), Michael Pariza, Ph.D. (Michael W. Pariza Consulting, LLC*)*, and P. Michael Bolger, Ph.D., DABT (Exponent, Inc.). For the purpose 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 conditions of its intended use," as defined by the U.S. Food and Drug Administration (FDA or the "Agency") in 21 C.F.R. § 170.3(i). Curricula vitae evidencing their expert qualifications for evaluating the safety of food ingredients are available upon request.

The GRAS Panel, independently and collectively, critically evaluated a supporting dossier [Notification of a Generally Recognized As Safe (GRAS) conclusion regarding the safety from exposure to copper (II) ions derived from a microparticle incorporated in packaging used for specified meat, salmon, and cheese products via migration from packaging] containing a review of publicly available scientific materials compiled from the literature and other public sources by Leslie Patton, Ph.D. of ChemReg Compliance Solutions LLC. The dossier includes information compiled from a comprehensive search of the publicly available scientific literature through October 27, 2022, and a comprehensive package of data and information pertaining to the method of manufacture, product specifications and analytical data, stability, and dietary consumption estimates for the conditions of intended use of copper.

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

Description

The copper microparticle comprises five crystalline copper sulfate and copper hydroxide species in different states of hydration and hydrogenation. The microparticle is combined with LLDPE to form a pelleted Masterbatch, which is the product that Copperprotek SPA sells to food packaging manufacturers. Copperprotek Masterbatch contains 4.0% +/- 0.5% copper. The Masterbatch is incorporated during the extrusion process into polyolefin polymers that will be made into multilayer food contact packaging material. The level of copper in the packaging is intended to be 100 mg/m^2. The layer of food packaging containing the Masterbatch is intended to be directly in contact with the packaged food, releasing copper (II) ions into the food, thereby controlling and/or reducing the growth of superficial bacteria or fungi.

Estimated Daily Intake (EDI)

The EDIs for copper were calculated based on the results of a migration test on sheets of LLDPE containing the copper Masterbatch at the intended use level of 100 mg Cu/m^2. Migration was measured for 10 days at 20° C into an aqueous and a fatty food simulant. Using the worst-case migration results, EDIs from use of the copper Masterbatch in food packaging

were determined by estimating food consumption of the relevant foods from data collected in the National Health and Nutrition Examination Surveys (NHANES). Consumption values for *all* seafood, not just salmon, and all cheese, not just fresh cheese, were used, resulting in a conservative intake estimate. The 90th percentile EDI of copper using this method was determined to be 339.8 µg/day for all populations, ranging from 360.4 µg/day for adults ages 20 years and older to 169.0 µg/day for children ages 2-5 years.

The background intake of copper from food and dietary supplements was also determined from NHANES data. The 90th percentile EDI of background copper was determined for a range of ages, as well as for pregnant and lactating women. The 90th percentile background copper intake for all individuals was 2,360 µg/day and ranged from 1,100 to 3,580 µg/day across the populations sampled.

Safety

The safety of dietary copper is well characterized based on its status as an essential trace element. Some of the major animal and human studies on copper were summarized in the dossier. There is a robust human data set for copper. The most sensitive targets of oral copper exposure in humans are the gastrointestinal, hepatic, and neurological systems, while there is no strong evidence that copper supplementation in the diet results in cardiovascular disease, cognition decline, or cancer in the general population. Incidence of acute and chronic copper toxicity in humans is rare and typically restricted to subpopulations with high copper concentrations in drinking water, populations that utilize copper cooking or food storage vessels, or individuals who have a hereditary predisposition to a disease of copper toxicity.

USDA has established Dietary Reference Intakes (DRIs) for copper for different populations in the United States, including Tolerable Upper Intake Level (ULs) established by the Institute of Medicine of the National Academies of Sciences, Engineering, and Medicine (NASEM). DRIs represent the highest level of a daily nutrient intake that is likely to pose no risk of adverse effects for almost all people. The copper UL for males and females aged 19 years and older is 10,000 µg/day. This safety assessment relies on ULs to establish the safety of exposure to the additional dietary dose of copper from the proposed copper ion that is derived from a microstructure, multicomposite copper microparticle used in the packaging of select foods identified in this dossier. Comparing the 90th percentile intake of copper for each U.S. subpopulation to the respective UL, the addition of 169.0 to 360.4 µg copper/day to the diet does not result in the EDI exceeding the UL except minimally in 1-3 year olds at the 90th percentile, a population whose copper intake exceeds the UL even before considering the addition of copper from the proposed use.

Summary

Based on the information provided to support safety, the intended use of copper (II) ions derived from a microstructure, multicomposite copper microparticle that is incorporated into packaging as an antimicrobial on packaged fresh beef, pork, poultry, fresh sausage, salmon, fresh cheese, and deli meat can be concluded to be safe. Therefore, the proposed use of 4% copper in a Masterbatch added to polyolefin food packaging at 100 mg/m^2 meets the standard of reasonable certainty of no harm and therefore is safe within the meaning of the Federal Food, Drug, and Cosmetic Act.

Conclusion of the GRAS Panel

We, the undersigned qualified GRAS panel members, have, both individually and collectively, critically evaluated published and unpublished data and information pertinent to the safety of the copper (II) ions incorporated in polyolefin food packaging at 100 mg/m^2 used in packaging fresh beef, poultry, fresh sausage, salmon, fresh cheese, and deli meat.

We unanimously conclude that the intended use of copper (ii) ions manufactured in accordance with current good manufacturing practice (cGMP), and meeting appropriate food grade specifications, is safe.

We further unanimously conclude that the intended use of this copper (ii) ions is Generally Recognized as Safe (GRAS) based on scientific procedures.

It is our opinion that other qualified experts reviewing the same information would concur with our conclusions.

Michael Bolger, Ph.D., DABT
Exponent, Inc.

[redacted]
14 March 2023

Michael Pariza, Ph.D.
Michael W. Pariza Consulting LLC

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Stanley Tarka, Jr. Ph.D., FATS
President
The Tarka Group, Inc.

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14 March 2023

Stanley Tarka, Jr. Ph.D., FATS
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14 March 2023