Safety Assessment of Copper Gluconate as Used in Cosmetics

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All interested persons are provided 60 days from the above release date (i.e., by February 8, 2025) to comment on this safety assessment, and to identify additional published data that should be included or provide unpublished data which can be made public and included. Information may be submitted without identifying the source or the trade name of the cosmetic product containing the ingredient. All unpublished data submitted to CIR will be discussed in open meetings, will be available for review by any interested party and may be cited in a peer-reviewed scientific journal. Please submit data, comments, or requests to the CIR Executive Director, Dr. Bart Heldreth.

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ABBREVIATIONS

ALT	alanine aminotransferase
APP	amyloid precursor protein
AUC	area-under-the-curve
BBN	*N*-butyl-*N*-(4-hydroxybutyl)-nitrosamine
CAS	Chemical Abstracts Service
c-fos	protein c-Fos
CIR	Cosmetic Ingredient Review
CLP	Classification, Labelling, and Packaging regulation
C_{max}	concentration maximum
Council	Personal Care Products Council
CPSC	Consumer Product Safety Commission
CTR1	copper transporter 1
DEN	*N*-nitrosodiethylamine
DHPN	2,2'-dihydroxy-di-*n*-propylnitrosamine
Dictionary	web-based *International Cosmetic Ingredient Dictionary and Handbook* (wINCI)
DMH	1,2-dimethylhydrazine
DMSO	dimethyl sulfoxide
DMT1	divalent metal transporter 1
DNA	deoxyribonucleic acid
ECHA	European Chemicals Agency
EC3	effective concentration to induce a 3-fold increase in local lymph node proliferative activity
ET_{50}	time for the test article to reduce the viability of the skin to 50%
EPA	Environmental Protection Agency
EU	European Union
FDA	Food and Drug Administration
Gadd45α	growth arrest and DNA damage inducible alpha
GGT	gamma glutamyl transpeptidase
GHS	Globally Harmonized System
GRAS	generally recognized as safe
GST-P	glutathione S-transferase placental form
HGF	hepatocyte growth factor
HRIPT	human repeated insult patch test
IL-1α	interleukin 1-alpha
INCHEM	International Programme on Chemical Safety
JECFA	Joint FAO/WHO Expert Committee on Food Additives
Ki67	protein biomarker for cell proliferation
LLNA	local lymph node assay
LOAEL	lowest-observed-adverse-effect-level
MMAS	modified maximum average score
MNU	*N*-methylnitrosourea
MRL	minimal risk level
mRNA	messenger RNA
MT1	metallothionein 1
MT1a	metallothionein 1a
MT2a	metallothionein 2a
MTT	3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide
NA	not applicable
NFκB	nuclear factor kappa-light-chain-enhancer of activated B cells
NOAEL	no-observed-adverse-effect-level
Nos2	nitric oxide synthase
NoG	Notes of Guidance
NR	not reported
OECD	Organisation for Economic Co-operation and Development
OPPTS	Office of Prevention, Pesticides, and Toxic Substances
p21	tumor protein p21
p53	tumor protein p53
Panel	Expert Panel for Cosmetic Ingredient Safety
PDII	primary dermal irritation index
QSAR	quantitative-structure activity relationship
RDA	recommended daily allowance
REACH	Registration, Evaluation, Authorisation, and Restriction of Chemicals
SCCS	Scientific Committee on Consumer Safety

SED	systemic exposure dose
STOT RE	specific target organ toxicity, repeated exposure
$t_{1/2}$	half-life
TG	test guideline
TGFβ	transforming growth factor-β
TNF-α	tumor necrosis factor alpha
TUL	tolerable upper limit
US	United States
USP	US Pharmacopeia
VCRP	Voluntary Cosmetic Registration Program

ABSTRACT

The Expert Panel for Cosmetic Ingredient Safety (Panel) assessed the safety of Copper Gluconate, which is reported to function in cosmetics as a skin-conditioning agent. Industry should minimize impurities, such as heavy metals, according to limits set by the US Food and Drug Administration (FDA) and the Environmental Protection Agency (EPA). The Panel reviewed all available relevant data to determine the safety of this ingredient and concluded that Copper Gluconate is safe in cosmetics in the present practices of use and concentration described in this safety assessment.

INTRODUCTION

This assessment reviews the safety of Copper Gluconate as used in cosmetic formulations. According to the web-based *International Cosmetic Ingredient Dictionary and Handbook* (*Dictionary*), this ingredient is reported to function in cosmetics as a skin-conditioning agent.[1]

In 2019, the Panel published a final report that reviewed the safety of gluconic acid, potassium gluconate, and sodium gluconate, with the conclusion that these ingredients are safe in the present practices of use and concentration in cosmetics described in the safety assessment.[2] The full report can be accessed on the Cosmetic Ingredient Review (CIR) website: (https://cir-reports.cir-safety.org/).

The ingredient reviewed in this safety assessment is generally recognized as safe (GRAS) as a direct human food ingredient and as a nutrient or dietary supplement used in animal drugs, feeds, and related products; hence, daily exposure from food use would result in much larger systemic exposures than those from use in cosmetic products. Thus, the primary focus of the safety assessment of this ingredient as used in cosmetics is on the potential for local effects from topical exposure.

This safety assessment includes relevant published and unpublished data that are available for each endpoint that is evaluated. Published data are identified by conducting an extensive search of the world's literature; a search was last conducted August 2024. A listing of the search engines and websites that are used and the sources that are typically explored, as well as the endpoints that the Panel typically evaluates, is provided on the CIR website (https://www.cir-safety.org/supplementaldoc/preliminary-search-engines-and-websites; https://www.cir-safety.org/supplementaldoc/cir-report-format-outline). Unpublished data are provided by the cosmetics industry, as well as by other interested parties.

Much of the data included in this safety assessment was found on the European Chemicals Agency (ECHA) website.[3] Please note that the ECHA website provides summaries of information generated by industry, and it is those summary data that are reported in this safety assessment when ECHA is cited.

CHEMISTRY

Definition and Structure

Copper Gluconate (CAS No. 527-09-3) is the copper salt of gluconic acid that conforms to the structure depicted in Figure 1.[1]

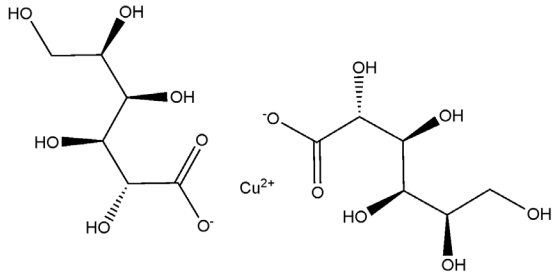

Figure 1. Copper Gluconate

Chemical Properties

Copper Gluconate is a light blue to bluish-green or green solid or crystalline, odorless powder that has a formula weight of 453.9 g/mol (compared to 63.55 g/mol atomic weight of copper) and an estimated log K_{ow} of - 2.98.[3-7] Additionally, Copper Gluconate has a density of 1.78 g/ml and is soluble in water; although slightly soluble in alcohol, it is insoluble in acetone, ether, and other organic solvents. The chemical properties of Copper Gluconate are further outlined in Table 1.

Method of Manufacture

The following are general methods of manufacture, and it is unknown whether these are utilized in the manufacture of Copper Gluconate as a cosmetic ingredient. In one method, a 1.0 M aqueous solution (6 ml) of gluconic acid (0.006 mol) is added to a suspension of copper hydroxide (0.003 mol) in 5 ml of distilled water.[5] The mixture is stirred at 75°C and monitored by infrared spectroscopy; the reaction is conducted until the absorption band for the carboxylic group of gluconic acid is no longer detectable. The solvent is evaporated on a rotary evaporator at 65 - 75°C, at a residual pressure of 10 - 20 mmHg, and the resulting

residue is dried in a desiccator. According to 21CFR184.1260, Copper Gluconate is prepared by reacting gluconic acid solutions with cupric oxide or basic cupric carbonate.

Impurities

According to a supplier, specifications for food-grade Copper Gluconate powder included 98 – 102 % purity, with a 1% maximum limit for reducing substances.[7,8] Results from a certificate of analysis for a food-grade, US Pharmacopeia (USP) Copper Gluconate powder demonstrated a purity of 100.2%, copper content of 14%, reducing substances content of 0.21%, < 0.07% chloride and < 0.05% sulfate (both below maximum limits), 0.10 ppm arsenic (3 ppm maximum limit), 0.02 ppm lead (5 ppm maximum limit), a lack of coliform presence, and aerobic plate count and yeast and mold counts that were below specification limits (< 1000 cfu/g and < 100 cfu/g, respectively).[9,7] In an elemental impurity analysis of a USP Copper Gluconate powder, none of the tested elements were present above typical threshold values.[10] According to specifications provided by another supplier, the presence of cadmium, chromium, mercury, selenium, and thallium (each < 0.1 ppm), arsenic, cobalt, lithium, molybdenum, and vanadium (each < 1 ppm), antimony, barium, and lead (each < 2 ppm), and nickel (< 5 ppm) in Copper Gluconate would be unlikely and minimal.[11] Additionally, specifications for food-grade Copper Gluconate include an acceptance criteria of no more than 5 mg/kg lead in a 1 g sample of Copper Gluconate.[8]

USE

Cosmetic

The safety of the cosmetic ingredient addressed in this assessment is evaluated based on data received from the US Food and Drug Administration (FDA) and the cosmetics industry on the expected use of Copper Gluconate in cosmetics. Data included herein were obtained from the FDA Voluntary Cosmetic Registration Program (VCRP) database and in response to a survey of maximum use concentrations conducted by the Personal Care Products Council (Council), and it is these values that define the present practices of use and concentration.

According to 2023 VCRP survey data, Copper Gluconate has 170 reported uses, 140 of which are in leave-on formulations (Table 2).[12] The results of the concentration of use survey conducted by the Council in 2022 and updated in 2024 indicate that the maximum reported concentration of use for Copper Gluconate in a leave-on formulation is 0.008% in non-spray night products; overall, the highest maximum reported concentration of use is 0.36% in other oral hygiene products.[13]

Several uses in products applied near the eye (at up to 0.006% in eyeliners) and in products that can result in incidental ingestion have been reported (e.g., it has 4 reported uses in mouthwashes and breath fresheners, 2 reported uses in lipsticks; and is used at 0.36% in other oral hygiene products; other concentrations not provided). Copper Gluconate is reported to be used in baby shampoos and baby lotions, oils, powders, or creams at 0.00008%.

Copper Gluconate is also reported to be used in face powder formulations (concentration not provided) and could possibly be inhaled. In practice, as stated in the Panel's respiratory exposure resource document (https://www.cir-safety.org/cir-findings), most droplets/particles incidentally inhaled from cosmetics would be deposited in the nasopharyngeal and tracheobronchial regions and would not be respirable (i.e., they would not enter the lungs) to any appreciable amount. Conservative estimates of inhalation exposures to respirable particles during the use of loose powder cosmetic products are 400-fold to 1000-fold less than protective regulatory and guidance limits for inert airborne respirable particles in the workplace.

Some products containing Copper Gluconate may be marketed for use with airbrush delivery systems; however, this information is not available from the VCRP or the Council survey. Airbrush delivery systems are within the purview of the US Consumer Product Safety Commission (CPSC), while ingredients, as used in airbrush delivery systems, are within the jurisdiction of the FDA. Airbrush delivery system use for cosmetic application has not been evaluated by the CPSC, nor has the use of cosmetic ingredients in airbrush technology been evaluated by the FDA. Moreover, no consumer habits and practices data or particle size data are publicly available to evaluate the exposure associated with this use type, thereby preempting the ability to evaluate risk or safety. Without information regarding the frequency and concentrations of use of this ingredient, and without consumer habits and practices data or particle size data related to this use technology, the Panel is not able to determine safety for use in airbrush formulations. Accordingly, the data are insufficient to evaluate the exposure resulting from cosmetics applied via airbrush delivery systems.

Copper Gluconate is not restricted from use in any way under the rules governing cosmetic products in the European Union (EU).[14]

Non-Cosmetic

According to the US National Institutes of Health Office of Dietary Supplements, copper is an essential mineral which is naturally present in the human body and in some foods; 900 µg is the recommended daily allowance (RDA) for adult copper intake.[15] The tolerable upper limit (TUL) for copper intake is 10,000 µg/d.[16]

As indicated in 21CFR184.1260, Copper Gluconate is affirmed as GRAS by the US FDA as a direct human food ingredient, which includes use in nutrient supplements and in infant formula, provided that levels do not exceed current good manufacturing practices. In addition, Copper Gluconate is also considered GRAS as a nutrient or dietary supplement used in animal drugs, feeds, and related products at a level not to exceed 0.005% (21CFR582.5260) and as a trace mineral added to animal feed

(21CFR582.80), both in accordance with good manufacturing or feeding practices. According to 21CFR310.545, Copper Gluconate has been present as an active ingredient in over-the-counter drug products for weight control; however, based on the currently available evidence, there is inadequate data to establish the safety or effectiveness of this use.

In the EU, copper and Copper Gluconate are categorized as mineral substances in Annex II of vitamin formulations and mineral substances which may be added to foods[17] and as minerals in Annex II of vitamin and mineral substances which may be used in the manufacture of food supplements;[18] listing in Annex II indicates the approved form for use in foods and food supplements. Additionally, Copper Gluconate is categorized as a mineral and is allowed in all 4 categories of food intended for infants and young children (i.e., infant formula and follow on formula; processed cereal-based food and baby food; food for special medical purposes; and total diet replacement for weight control).[19]

TOXICOKINETIC STUDIES

Animal

Oral

Groups of 449-d-old male C57BL/6J mice (5/group) were administered 0.005 M Copper Gluconate in drinking water for 92 d.[20] The accumulation of copper (dry weight) in the liver, kidney, brain, and heart of the test animals was compared to that of controls (drinking water). There was a statistically significant increase in copper accumulation in the livers of Copper Gluconate-fed mice, compared to controls (28.6 vs. 13.5 ng/mg). Differences between the amount of copper found in the kidney, brain, and heart of Copper Gluconate-fed mice and control mice were not statistically significant. In a related study, groups of 5 – 7 male C57BL/6J mice were administered 0.005 M Copper Gluconate in drinking water for 104 d, starting from various ages (64, 302, and 540 d of age). The accumulation of copper (dry weight) in the liver and kidney of Copper Gluconate-fed mice and controls (drinking water) was compared at the end of the experiment. The difference between copper accumulation in the liver of Copper Gluconate-fed mice and control mice was statistically significant in all 3 age groups; no statistically significant differences were observed in the amount of copper found in the kidneys of Copper Gluconate-fed mice (in all 3 age groups) compared to controls.

In a biodistribution study of copper (administered as Copper Gluconate), male Wistar rats (total number not specified) received a single dose of 79.5 mg/kg Copper Gluconate, dissolved in deionized water, via gavage, and were observed for up to 168 h prior to necropsy (rats were killed at 0.08, 0.17, 0.25, 0.5, 1, 1.5, 2, 3, 4, 5, 6, 12, 24, 48, 72, and 168 h).[21] Blood samples, brain tissue (striatum and midbrain), and liver samples were collected at each time point (n = 4 – 6). Controls received deionized water and were killed immediately after treatment; copper concentration in control blood and tissue samples was considered baseline. A plasma copper concentration maximum (C_{max}) value of 1.94 ±0.28 µg/ml was observed 1.5 h post-treatment, which was 73.1% higher than the baseline concentration ($p < 0.01$). Copper plasma concentration returned to baseline 72 h after treatment and the half-life ($t_{1/2}$)and area-under-the-curve (AUC) values were about 1.79 h and 2.48 ± 0.36 µg/ml*h, respectively. The C_{max} for copper distribution in the striatum tissue of Copper Gluconate-treated rats was 2.93 ± 0.21 µg copper/g of wet tissue at 0.25 h post-treatment (49.9% higher than baseline values) which returned to baseline after 168 h. A 27.6% increase in copper concentration (3.87 ± 0.25 µg copper/g of wet tissue) was observed in the midbrain of treated rats at 0.25 h post-treatment, however, no significant differences in copper concentration in the midbrain tissue of treated and control rats were observed. The C_{max} of copper in the liver of Copper Gluconate-treated rats was arrived at 12 h post-administration and was 391% higher than baseline (23.25 ± 1.75 vs. 4.735 ± 0.29 µg copper/g of wet tissue). Elimination or redistribution of copper found in the liver was observed 24 h post-administration. The area-under-the-curve $(AUC)_{0-168\ h}$ value for liver copper concentration was about 200 times greater than the AUC value for plasma copper concentration (494.8 ± 47.22 vs. 2.48 ± 0.36 µg/ml*h).

Human

Wilson's disease and Menkes disease are rare genetic defects characterized by abnormal copper metabolism in the human body.[22] Wilson's disease is a defect in copper excretion leading to progressive accumulation of toxic levels in the liver, brain, kidneys, and cornea. Menkes disease is a severe and fatal sex-linked mutation in genes coding for the copper-transport protein that results in copper deficiency in male infants.

TOXICOLOGICAL STUDIES

Acute Toxicity Studies

Details on the acute oral and computational (dermal) toxicity studies on Copper Gluconate summarized below are found in Table 3.

In an acute oral administration study, male Wistar rats (4 - 6/group) were administered a single oral dose of 79.5, 156, or 312 mg/kg Copper Gluconate, in deionized water.[21] The survival rate of rats in the 312 mg/kg group was 31%. No animals from the 79.5 and 156 mg/kg groups died and no significant differences in weight gain or activity levels of the hepatic enzymes gamma glutamyl transpeptidase (GGT) or alanine aminotransferase (ALT) were observed 7 d after exposure compared to the control group. Male and female Wistar rats (5/sex/group) were administered a single dose of up to 3200 mg/kg Copper Gluconate, in water, in an acute oral toxicity study.[3] Five out of 10 of the animals from the 1800 mg/group died within 48 h of exposure, 8 out of 10 animals in the 2400 mg/group died within 48 h of exposure, and all 10 animals from the 3200 mg/kg group died within 24 h

of exposure. The acute oral LD_{50} was determined to be 1709 mg/kg bw for both sexes. According to a quantitative structure-activity relationship (QSAR) model described in an ECHA dossier, the acute dermal LD_{50} for Copper Gluconate was predicted to be 2130 mg/kg bw in rats.[3]

Short-Term and Chronic Toxicity Studies

Details on the oral short-term and chronic toxicity studies and a computational study to predict short-term oral toxicity of Copper Gluconate summarized below are found in Table 4.

Groups of 5 male Fischer 344 rats were administered 0, 0.001, 0.03, or 0.6% (equivalent to 0, 10, 300, or 6000 ppm, respectively) Copper Gluconate in the diet for 2 wk, in a short-term oral toxicity study.[23] No differences in final body weight, liver weight, food consumption, or gross or histological changes in the liver were observed in the treated animals, compared to controls. Upon performing gene expression analysis in the liver, hepatic messenger RNA (mRNA) expression of metallothionein 1a (*Mt1a*; a metal metabolism-related gene) and growth arrest and DNA damage inducible alpha (*Gadd45α*; an apoptosis-related gene) were significantly increased in the 0.6% Copper Gluconate group and tumor protein p21 (*p21*; an apoptosis-related gene) expression was significantly increased in the 0.03 and 0.6% dose groups. Expression levels of tumor protein p53 (*p53*; an apoptosis-related gene) and inflammation-related genes, such as tumor necrosis factor alpha (*TNF*-α), interleukin 1-alpha *(IL*- 1α), nitric oxide synthase 2 (*Nos2*), and protein c-Fos (*c-fos*; a proto-oncogene) were not affected.

No adverse effects were noted in food consumption, body weight gain, urinalysis, or gross and microscopic examination of tissues and organs in male and female rats that were administered 0.006 or 0.06% Copper Gluconate (mean daily consumption of 3.46 or 34.9 mg/kg/d, respectively) in the diet for 24 wk.[24] Copper content was elevated in the kidneys of animals fed the diet containing 0.06% Copper Gluconate. In a chronic oral toxicity study, groups of 25 rats were administered 1.14% Copper Gluconate in the diet for up to 44 wk.[25,26] Significant growth retardation was discernible at 26 wk compared to controls, and over 80% of the animals died between week 17 and week 35. Upon necropsy, hypertrophied uteri, ovaries, seminal vesicles and hypertrophied stomachs, occasional ulcers, bloody mucus in the intestinal tract, and bronzed kidneys and livers were observed; chronic exposure to 1.14% Copper Gluconate in the diet was considered toxic. Groups of 6 male and 6 female Beagle dogs were administered 0.012, 0.06, or 0.24% Copper Gluconate in the diet (equivalent to 3, 15, or 60 mg/kg/d, respectively) for up to 1 yr.[25,26] Accumulation of copper was seen in the liver, kidneys, and spleen of animals in the 0.24% group; minimal liver function was observed in 1 out of 12 dogs in the 0.24% group after 1 yr of dosing, which was reversible within a 12-wk withdrawal period. No other test-article related effects were observed. Male C57BL/6J mice (number not specified) received 0.0005, 0.001, or 0.005 M Copper Gluconate in drinking water over the animal lifetime.[20] The survival curve and lifespan were significantly reduced by 11.8, 14.7 and 14.4% in the 0.0005, 0.001 and 0.005 M groups, respectively, indicating the absence of a dose-response relationship for survival. The effect of administering copper to adult Capuchin monkeys (2/sex; 7.5 mg/d) and copper as Copper Gluconate to young Capuchin monkeys (2/sex; 5.5 mg/d), in the diet, was evaluated in a 156-wk (3-yr) oral toxicity study.[27] No differences in food intake, body weight, or weight gain by age or time of exposure were observed in treated adult and young Capuchin monkeys, compared to age-matched controls. After 24 mo, Ki67 (a protein biomarker for cell proliferation) and MT1 (metallothionein 1) protein levels were significantly greater in the liver tissue of treated adult and young monkeys. Upon further analysis of adult liver tissue after 36 mo, hepatic mRNA expression of proteins related to inflammation and hepatic response to injury (nuclear factor kappa-light-chain-enhancer of activated B cells (*NFκB*), hepatocyte growth factor (*HGF)*, and transforming growth factor-β (*TGFβ))*) were significantly greater in treated animals compared to controls, with no further evidence of clinical, hematological, or histological evidence of liver damage.

According to a QSAR model described in an ECHA dossier, the oral lowest-observed-adverse-effect-level (LOAEL) for Copper Gluconate in rats was predicted to be 94.7 mg/kg bw/d.[3] Based on this value and the Classification, Labelling, and Packaging (CLP) regulation, the specific target organ toxicity for repeated exposure-2 (STOT RE-2) designation, indicating presumed toxicity to specific organs with repeated exposure, was considered applicable.

DEVELOPMENTAL AND REPRODUCTIVE TOXICITY STUDIES

Details on the oral developmental and reproductive toxicity studies and computational studies to predict such toxicity for Copper Gluconate summarized below are found in Table 5.

Groups of male albino rats (8/group) were used to examine the toxicological effects of Copper Gluconate upon oxidative biomarkers in testis tissue in a 90-d reproductive toxicity study.[28] The animals received 3.75, 7.5, or 15 mg/kg/d Copper Gluconate, via gavage; 2 control groups received either 1 ml of saline or 0.5 ml dimethyl sulfoxide (DMSO), via gavage, for the duration of the study. Treatment with Copper Gluconate did not significantly affect catalase levels but did significantly reduce glutathione and superoxide dismutase levels (at the medium and high dose). Additionally, malondialdehyde levels were also increased in treated rats, compared to controls; the study results are indicative of the development of oxidative stress in testes tissue. Female Swiss-Webster mice (20/group) and female albino Wistar rats (number/group not specified) received 0, 0.1, 3, or 30 mg/kg/d Copper Gluconate, via gavage, from day 6 to 14 of gestation or from day 5 to 15 of gestation, respectively, in two separate developmental oral toxicity studies.[25,26] Neither embryotoxic nor teratogenic effects were observed in treated animals compared to controls in either study. In another oral developmental toxicity study, female Wistar rats (20/group) received up to 30 mg/kg/d Copper Gluconate, via gavage.[25,26] Female rats were dosed with Copper Gluconate 15 d prior to mating, during gestation,

and for 21 d postpartum. Groups of treated females, from each dose group, were mated with untreated males. To assess the effects of Copper Gluconate on the male rat, 2 additional groups of males that were treated with 3 mg/kg/d Copper Gluconate 60 d prior to mating were mated with a group of untreated females or with a group of females that received the same 60-d pre-treatment. A third group of untreated males mated with untreated females served as controls. Male rat reproductive performance was not affected by Copper Gluconate administration. No significant differences were observed between the percentage of pregnancies, the number and distribution of embryos in each uterine horn, implantation sites, resorption sites, duration of gestation, mean number of fetuses and live pups per litter, litter size, stillborn and live born numbers, gross anomalies and mean weight per pup, compared to controls. Necropsy of dams and pups revealed a lack of visceral abnormalities. Thus, under the conditions of the study, the researchers concluded that Copper Gluconate did not affect the reproductive performance of either male or female rats.

As described in an ECHA dossier, 2 separate models following the REACH Guidance on QSARs and Grouping of Chemicals R.6 were used to predict the developmental and reproductive toxicity of Copper Gluconate in rats.[3] The no-observed-adverse-effect-level (NOAEL) of Copper Gluconate for oral reproductive toxicity in rats was predicted to be 318 mg/kg bw/d and the NOAEL of Copper Gluconate for oral developmental toxicity in rats was predicted to be 793 mg/kg bw/d.

GENOTOXICITY STUDIES

In Vitro

Copper Gluconate was tested at up to 1 mg/plate using *Salmonella typhimurium* strains TA97 and TA102 in an Ames test, according to EPA Office of Prevention, Pesticides, and Toxic Substances (OPPTS) 870.5265.[3] The test article was not genotoxic, with or without metabolic activation. Additionally, Copper Gluconate was evaluated for mutagenicity in various in vitro tests using *S. typhimurium* strains TA1535, TA1537, and TA1538, and *Saccharomyces cerevisiae* strain D4.[25,26] The test article was not considered mutagenic, with or without metabolic activation. No further details were provided.

Computational

QSAR model results predicting the genotoxic potential of Copper Gluconate were described in an ECHA dossier.[3] Using QSAR Toolbox 3.4.0.17, and based on REACH guidance R.6, Copper Gluconate was predicted to be non-genotoxic in an Ames test (with and without metabolic activation) and in a chromosome aberration test. Based on the expert rule-based system, Derek Nexus 6.3.0, Copper Gluconate exposure is not predicted to cause in vivo mutagenicity (*Mutagenicity in vivo* endpoint).[CIR staff]

CARCINOGENICITY STUDIES

Tumor Promotion

Five-wk-old male Fischer 344 rats (9 - 12/group) were given a single intraperitoneal injection of 200 mg/kg bw *N*-nitroso-diethylamine (DEN) as a carcinogenic initiator, and after 2 wk, received 0, 0.001, 0.03, or 0.6% (0, 10, 300, or 6000 mg/kg/d) Copper Gluconate in a basal diet for 6 wk, in a medium-term liver carcinogenicity bioassay.[23] Simultaneously, two additional groups which did not receive the nitrosamine injection prior were fed 0 or 0.6% Copper Gluconate in the diet. Numbers of glutathione *S*-transferase placental form (GST-P) positive lesions, single GST-P-positive hepatocytes, 8-oxoguanine-positive hepatocytes, and levels of cell proliferation and apoptosis in the liver were significantly increased in the 0.6% Copper Gluconate group, with and without nitrosamine pre-treatment. Furthermore, the hepatic mRNA expression of the metal metabolism-related gene *Mt1a*, the apoptosis-related genes *Gadd45α* and *p21*, the inflammation-related genes *TNF-α, IL-1α,* and *Nos2*, and *c-fos* were significantly increased in the 0.6% group, irrespective of nitrosamine treatment, while *p53* expression was significantly increased in the 0.03 and 0.6% Copper Gluconate groups which received the nitrosamine injection and in the 0.6% group which did not receive the nitrosamine injection. In the absence of the DEN treatment, animals treated with Copper Gluconate did not develop GST-P-positive lesions in the liver. While treatment with Copper Gluconate may have been associated with carcinogenic risk toward the liver at a high dose level (0.6%), the researchers indicated there is a considerably large safety margin for Copper Gluconate at the human relevant dose of 0.001 and 0.03% (the 0.001% dose nearly corresponds to the daily human intake of Copper Gluconate, as a food additive).

Groups of male Brl:Han Wistar rats (3 rats/group) were used to evaluate the toxicologic and carcinogenic risk of Copper Gluconate in a 13-wk medium-term multi-organ carcinogenesis assay.[29] Throughout the experiment, animals were fed a diet containing 0, 0.1, 0.3, 0.48, or 0.6% (equivalent to 0, 1000, 3000, 4800, or 6000 mg/kg/d, respectively) Copper Gluconate, or 1.2% (12,000 mg/kg/d; 1 animal) Copper Gluconate, while being exposed to multiple carcinogens. All animals received a single intraperitoneal administration of 100 mg/kg bw DEN followed by 4 intraperitoneal injections of 20 mg/kg bw *N*-methylnitrosourea (MNU) and 0.05% *N*-butyl-*N*-(4-hydroxybutyl)-nitrosamine (BBN), administered in drinking water, during the initial 2 wk. In the following 2 wk, the animals received 4 subcutaneous injections of 40 mg/kg bw 1,2-dimethylhydrazine (DMH) and 0.1% 2,2'-dihydroxy-di-*n*-propylnitrosamine (DHPN), in drinking water. The animals were killed and necropsied after 13 wk. Blood samples were taken from the abdominal aorta, urine samples were taken from the bladder, and major organs and tissues were removed; the liver was weighed and fixed for histopathological, histochemical, and immunohistochemical analyses. All animals survived until killed. Body weight and food consumption were similar between groups. Black stool was found in rats exposed to ≥ 0.3% Copper Gluconate. Copper levels in the serum, urine, and liver were significantly increased in animals dosed with ≥ 0.6%

Copper Gluconate. Absolute and relative liver weights were similar among groups but appeared to increase in the 1 animal that received 1.2% Copper Gluconate. Livers were macroscopically and histologically normal in the groups dosed with ≤ 0.48%; slight or moderate granulomas were scattered in livers of animals in the 0.6% group. Copper accumulation and metallothionein induction were apparent at doses of ≥ 0.3% and ≥ 0.1% Copper Gluconate, respectively. Marked diffuse granulomas and hepatocellular necrosis were observed in the liver of the animal in the 1.2% Copper Gluconate group (1 rat in this group). Putative preneoplastic lesions appeared in the rat dosed with 1.2% Copper Gluconate and 8-hydroxydeoxyguanosine formation was enhanced in the 0.6% group. The researchers indicated that under the current experimental conditions with co-exposure to multiple carcinogens, Copper Gluconate did not exert significant systemic toxicity, i.e., there were no differences in mean body weights among groups and in any treatment-related alternations in extrahepatic organs/tissues; however, it was noted that Copper Gluconate may cause toxic and carcinogenic risks towards the liver at high doses.

OTHER RELEVANT STUDIES

Nephrotoxicity

In a 90-d oral toxicity study examining the effects of Copper Gluconate on renal function, groups of 8 male albino Swiss rats were administered 3.75, 7.5, or 15 mg/kg Copper Gluconate, in saline, via gavage.[30] Controls received either 1 ml saline or 0.5 ml DMSO. Two animals per group were killed and blood samples were collected via cardiac puncture on days 30, 45, 60, and 90 for serum analysis. A statistically significant increase in urea, creatinine, sodium, and potassium levels was observed in renal serum obtained from treated animals, compared to controls. The results indicated development of renal failure and oral ingestion of the test article was considered nephrotoxic.

DERMAL IRRITATION AND SENSITIZATION STUDIES

Details of the human repeated-insult patch tests (HRIPT) and computational studies on Copper Gluconate summarized below are found in Table 6.

A leave-on baby product formulation and a rinse-off adult product formulation, each containing 0.00008% Copper Gluconate (dose/unit area: 0.00004 mg/cm^2), were found to be non-irritating and non-sensitizing when applied neat in 2 separate HRIPTs, using 210 and 211 subjects, respectively.[31,32] A powder containing 0.1% Copper Gluconate (up to 0.038 mg/cm^2) was not irritating or sensitizing when applied in distilled water to 52 subjects in an HRIPT.[33] A rinse-off baby product formulation containing 0.2% Copper Gluconate (0.1 mg/cm^2) was also non-irritating and non-sensitizing when applied neat in an HRIPT using 217 subjects.[34] Based on QSAR models described in an ECHA dossier, Copper Gluconate was predicted to produce a primary dermal irritation index (PDII) of 2.26 in rabbit skin and 5.08% Copper Gluconate was predicted to be the effective concentration needed to induce a 3-fold increase in local lymph node proliferative activity (EC3) in a mouse skin model.[3] Based on an EC3 value > 2%, Copper Gluconate was classified according to Globally Harmonized System (GHS) criteria as having low to moderate skin-sensitizing potential (Skin Sensitizer Category 1B, under GHS category 1: substances that show a low to moderate frequency of occurrence in humans and/or low to moderate potency in animals and can be presumed to potentially produce significant sensitization in humans.[3,35]

OCULAR IRRITATION STUDIES

Details of the in vitro and computational ocular irritation studies described below can be found in Table 7.

The potential for a face cream containing 0.0025% Copper Gluconate to cause ocular irritation was evaluated in a 3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide (MTT) assay using an in vitro tissue model.[36] EpiOcular™ tissues were treated with the test article for up to 24 h. More than 24 h of treatment time was required to achieve a 50% reduction in tissue cell viability; the test article was classified as minimally or not irritating to eyes. Using QSAR prediction software (QSAR Toolbox 3.4.0.17) and the REACH guideline on QSAR, the modified maximum average score (MMAS) for Copper Gluconate was predicted to be 49.5 in rabbit eyes.[3] Copper Gluconate was predicted to be mildly toxic, considering that the maximum value for damage to the cornea, conjunctiva, and iris is 110. Based on GHS criteria, Copper Gluconate was considered to be a potential mild irritant to the eyes (Category 2B).

CLINICAL STUDIES

Oral Supplementation

The effect of copper supplementation, in the form of Copper Gluconate, was evaluated in a 12-wk, double-blind, randomized study.[37] Seven subjects (3 men and 4 women) received either a 5 mg capsule of Copper Gluconate or placebo twice a day. Blood, serum, urine, and hair samples were collected at the beginning of the study, 6 wk after supplementation, and at the end of the 12 wk. Copper, zinc, and magnesium levels were determined in all the samples; no significant changes were observed in serum, urine, or hair for the study duration. No significant changes in hematocrit, mean corpuscular volume, serum cholesterol, triglyceride, glutamic-oxaloacetic transaminase, alkaline phosphatase, gamma-glutamyl transferase, or lactate dehydrogenase levels were observed in treated subjects. Serum potassium levels did change from a mean of 4.3 mEq/l to 4 mEq/l ($p < 0.05$). The incidence of nausea, diarrhea, and heartburn was the same in both treated subjects and controls.

EXPOSURE ASSESSMENT

Copper is an essential mineral, which is naturally present in some foods and can also be taken as a dietary supplement. As a food additive, Copper Gluconate may serve as a nutritional supplement for copper.[15] The daily copper intake needed to fulfill the nutritional needs averages 900 µg/d for adults (aged 19+ yr) and 340 µg/d for babies (aged 1-3 yr). Additionally, the highest daily intake that is unlikely to lead to adverse health effects is set at 10,000 µg/d for adults (aged 19+ yr) and 1000 µg/d for babies (aged 1-3 yr).

CIR staff applied exposure parameters identified from literature and the in silico tool VERMEER Cosmolife (previously named SpheraCosmolife)[38] to estimate the daily exposure to copper that results from the highest use concentration of Copper Gluconate (e.g., 0.36% in mouthwash) and from exposure to other product categories (e.g., 0.1% in make-up remover, and 0.008% in body lotion).

i) Copper Gluconate at 0.36% in oral hygiene products (e.g., mouthwash)

The following parameters are retrieved from a 2008 dermal sensitization risk assessment[39]:
Estimated amount applied of mouthwash per application: 10 g (or 10,000mg)
Frequency of application: 3/d
Retention factor: 0.01
Type of exposure: incidental ingestion
Relative daily exposure of mouthwash: 10,000 mg/d × 3 (application times) × 0.01 (retention factor) = 300 mg/d
Exposure to Copper Gluconate as used in mouthwash: 300 mg/d × 0.36% (use concentration) = 1.08 mg/d

The proportion of copper in Copper Gluconate is approximately 14%; therefore, daily exposure to copper from Copper Gluconate in mouthwash: 1.08 mg/d × 14% = 0.1512 mg/d = 151.2 µg/d
Systemic exposure dose (SED) with 100% absorption (oral absorption): 151.2 µg/d

ii) Copper Gluconate at 0.1% in skin cleansing preparations (e.g., make-up remover)

The following parameters are retrieved from the SCCS NoG.[40]
Estimated daily amount of make-up remover applied: 5 g/d = 5000 mg/d
Retention factor: 0.1
Type of exposure: rinse-off
Surface area for application: 565 cm^2
Relative daily exposure of make-up remover: 5000 mg/d × 0.1 (retention factor) = 500 mg/d
Exposure to Copper Gluconate as used in make-up remover: 500 mg/d × 0.1% (use concentration) = 0.5 mg/d
Daily exposure to copper from Copper Gluconate in make-up remover: 0.5 mg/d × 14% = 0.07 mg/d = 70 µg/d
SED with 100% absorption (oral absorption): 70 µg/d
Skin surface exposure: 70 µg/d ÷ 565 cm^2 = 0.124 µg/cm^2/d

iii) Copper Gluconate at 0.008% in non-spray night products (e.g., body lotion, leave-on)

The following parameters are retrieved from the SCCS NoG.[40]
Estimated daily amount of body lotion applied: 7.82 g/d = 7820 mg/d
Retention factor: 1.0
Type of exposure: leave-on
Surface area for application: 15,670 cm^2
Relative daily exposure of body lotion: 7820 mg/d × 1.0 (retention factor) = 7820 mg/d
Exposure to Copper Gluconate as used in body lotion: 7820 mg/d × 0.008% (use concentration) = 0.6256 mg/d
Daily exposure to copper from Copper Gluconate in body lotion: 0.6256 mg/d × 14% = 0.0876 mg/d = 87.6 µg/d
SED with 100% absorption (oral absorption): 87.6 µg/d
Skin surface exposure: 87.6 µg/d ÷ 15,670 cm^2 = 0.0056 µg/cm^2/d

The exposure assessment indicates that the daily exposure to copper from Copper Gluconate in mouthwash, make-up removers, and body lotions does not exceed 151.2 µg/d, 70 µg/d, and 87.6 µg/d, respectively. These exposure levels are substantially below the RDA of 900 µg/d for adults or 340 µg/d for babies (1-3 yr), as well as the TUL of 10,000 µg/d for adults or 1000 µg/d for babies.

SUMMARY

The safety of Copper Gluconate is reviewed in this safety assessment. As per the *Dictionary*, this ingredient is reported to function as a skin conditioning agent in cosmetics. According to 2023 VCRP and 2024 Council survey data, Copper Gluconate is

reported to be used in 170 formulations, 140 of which are leave-ons. The highest reported concentration of use is at 0.36% in other oral hygiene products; the highest reported concentration in a leave-on formulation is at up to 0.008% in non-spray night products. Copper Gluconate is also reported to be used in baby shampoos and baby lotions, oil, powders or creams at 0.00008%. Copper is an essential mineral which is naturally found in the human body and in foods; the RDA and TUL for adult copper intake is 900 µg and 10,000 µg/d, respectively. Notably, Copper Gluconate is considered GRAS as a direct food substance for human consumption, which includes use in nutrient supplements and in infant formula.

Groups of male C57BL/6J mice (5/group) were administered 0.005 M Copper Gluconate in drinking water for 92 d. A statistically significant increase in copper accumulation in the livers of Copper Gluconate-fed mice was observed, compared to controls. Differences between the amount of copper found in the kidney, brain, and heart of Copper Gluconate-fed mice, compared to controls (drinking water) were not statistically significant. Groups of male C57BL/6J mice (5 -7/group) were administered 0.005 M Copper Gluconate in drinking water for 104 d, starting from 64, 302, and 540 days of age. The difference between copper accumulation in the liver of Copper Gluconate-fed mice and control mice was statistically significant in all 3 age groups; no statistically significant differences were observed in copper accumulation in the kidneys (in all 3 age groups), compared to controls. In a biodistribution study of copper, male Wistar rats received a single dose of 79.5 mg/kg Copper Gluconate, dissolved in deionized water, via gavage and were observed for up to 168 h. A C_{max} of 2.93 ± 0.21 µg copper/g in brain striatum tissue at 0.25 h returned to baseline after 168 h. No significant differences in copper concentration in the midbrain tissue of treated and control rats was observed. The C_{max} of copper in the Copper Gluconate-treated liver was 391% higher than baseline (elimination and redistribution of copper occurred 24 h after administration) and the AUC value for copper in the liver was about 200 times greater than the AUC for plasma copper concentration (494.8 ± 47.22 vs. 2.48 ± 0.36 µg/ml*h).

No significant differences in weight gain or hepatic enzyme activity were observed in male Wistar rats that were administered a single oral dose of 79.5, 156, or 312 mg/kg Copper Gluconate. The survival rate of rats in the 312 mg/kg group was 31%; no animals in the 79.5 or 156 mg/kg groups died. Male and female Wistar rats received a single dose of 1800, 2400, or 3200 mg/kg bw Copper Gluconate, in water, via gavage, in another acute oral toxicity study. Five out of 10 of the animals from the 1800 mg/group died within 48 h of exposure, 8 out of 10 animals in the 2400 mg/group died within 48 h of exposure, and all 10 animals from the 3200 were found dead within 24 h of dosing. The acute oral LD_{50} was determined to be 1709 mg/kg bw (males and females combined). An acute dermal LD_{50} of 2130 mg/kg Copper Gluconate was predicted for rats, based on a QSAR model.

No differences in final body weight, liver weight, food consumption, or gross or histological changes were observed in male Fischer 344 rats (5/group) that were administered 0, 0.001, 0.03, or 0.6% Copper Gluconate in the diet for 2 wk in a short-term oral toxicity study. Hepatic mRNA expression of *Mt1a* and *Gadd45α* were significantly increased in the 0.6% group and *p21* expression was significantly increased in the 0.3 and 0.6% groups; other gene expression levels were unaffected.

Male and female rats that were administered 0.006 or 0.06% Copper Gluconate in the diet for 24 wk exhibited no adverse effects in food consumption, body weight gain, urine analysis, or gross or microscopic examination of tissues and organs; copper content was elevated in the kidneys of animals in the 0.06% Copper Gluconate group. Groups of 25 male and female rats received 1.14% Copper Gluconate in the diet for up to 44 wk in a chronic oral toxicity study. Significant growth retardation was discernable at 26 wk, compared to controls, and over 80% of the animals died by week 35. Hypertrophied uteri, ovaries, seminal vesicles and hypertrophied stomachs, occasional ulcers, bloody mucus in the intestinal tract, and bronzed kidneys and livers were observed upon necropsy; chronic exposure to 1.14% Copper Gluconate in the diet was considered toxic. Male and female Beagle dogs (6/sex/group) were administered 0.012, 0.06, or 0.24% Copper Gluconate, in the diet, for up to 1 yr; aside from copper accumulation in the liver, kidney, and spleen of animals in the 0.24% group, and reversible minimal liver function in 1 dog from the 0.24% group, no other test-article related effects were observed. The survival curve and lifespan of male C57BL/6J mice (number not specified) which received 0.0005, 0.001, or 0.005 M Copper Gluconate in drinking water during the lifetime were significantly reduced by up to 11.8, 14.7 and 14.4%, respectively, indicating the absence of a dose-response relationship for survival. No differences in food intake, body weight, or weight gain by age or time of exposure were observed in adult Capuchin monkeys (2/sex) that were fed up to 7.5 mg/d copper, and in young Capuchin monkeys (2/sex) fed up to 5.5 mg/d copper (as Copper Gluconate), in a 3-yr oral toxicity study. In the adult monkeys, the hepatic mRNA expression of proteins related to inflammation and hepatic response to injury (*NFκB*, *HGF*, and *TGFβ*) were significantly greater in treated animals compared to controls, with no further evidence of clinical, hematological, or histological evidence of liver damage. Using a QSAR model, the oral LOAEL for Copper Gluconate in rats was predicted to be 94.7 mg/kg bw/d; toxicity to specific organs with repeated exposure, as outlined in the specific target organ toxicity for repeated exposure-2 designation, was considered applicable.

Male albino rats (8/group) received 3.75, 7.5, or 15 mg/kg/d Copper Gluconate, via gavage, in a 90-d reproductive toxicity study. Oxidative biomarkers in rat testis tissue revealed that Copper Gluconate did not significantly affect catalase levels but did significantly reduce glutathione and superoxide dismutase levels (at the medium and high dose), while increasing malondialdehyde levels, compared to controls. These findings indicated the development of oxidative stress. In two separate developmental oral toxicity studies, neither embryotoxic nor teratogenic effects were observed in female Swiss-Webster mice (20/group) or female albino rats (number not specified) that received 0, 0.1, 3, or 30 mg/kg/d Copper Gluconate, via gavage, during gestation. Groups of female Wistar rats (20/group), mated with untreated males and males treated with 3 mg/kg/d Copper Gluconate (both 10/group), received up to 30 mg/kg/d Copper Gluconate in another developmental toxicity study. No significant differences were observed

between the percentage of pregnancies, the number and distribution of embryos in each uterine horn, implantation sites, resorption sites, duration of gestation, mean number of fetuses and live pups per litter, litter size, stillborn and live born numbers, gross anomalies and mean weight per pup, compared to controls. Under the conditions of this study, Copper Gluconate did not affect the reproductive performance of either male or female rats. Based on 2 QSAR models described in an ECHA dossier, the NOAEL of Copper Gluconate for oral reproductive toxicity in rats was predicted to be 318 mg/kg bw/d and the NOAEL of Copper Gluconate for oral developmental toxicity in rats was predicted to be 793 mg/kg bw/d.

Copper Gluconate was not genotoxic when tested at up to 1 mg/plate in *S. typhimurium* TA97 and TA102 strains, with or without metabolic activation, in an Ames test. Additionally, Copper Gluconate was not mutagenic when evaluated in various in vitro tests using *S. typhimurium* strains TA1535, TA1537, TA1538, and *S. cerevisiae* strain D4, with or without metabolic activation. In a QSAR Toolbox 3.4.0.17 prediction described in an ECHA dossier, Copper Gluconate was predicted to be non-genotoxic in an Ames test (with and without metabolic activation) and in a chromosome aberration test. Additionally, based on the expert rule-based system, Derek Nexus 6.3.0, Copper Gluconate is not predicted to be mutagenic.

After an injection with DEN, male Fischer 344 rats (9 – 12 /group) received 0, 0.001, 0.03, or 0.6% Copper Gluconate in a basal diet for 6 wk in a medium-term liver carcinogenicity bioassay. Numbers of GST-P-positive lesions, single GST-P-positive hepatocytes, 8-oxoguanine-positive hepatocytes, and levels of cell proliferation and apoptosis in the liver were significantly increased in the 0.6% Copper Gluconate group, with and without nitrosamine pre-treatment. The hepatic mRNA expression of *Mt1a, Gadd45α*, *p21*, *TNF- α, IL -1α, Nos2*, and *c-fos* were significantly increased in the 0.6% group, irrespective of nitrosamine treatment, while *p53* expression was significantly increased in the 0.03% and 0.6% groups which received the nitrosamine injection and in the 0.6% group which did not receive the nitrosamine injection. While treatment with Copper Gluconate may have been associated with carcinogenic risk toward the liver at the 0.6% dose, the researchers noted a considerably large safety margin for Copper Gluconate at the human relevant dose of 0.001 and 0.03% (0.001% nearly corresponding to the daily human intake, as a food additive).

In a 13-wk medium-term, multi-organ carcinogenesis assay, male Brl:Han Wistar rats (3/group) were fed a diet containing 0, 0.1, 0.3, 0.48, 0.6, or 1.2% Copper Gluconate, while being exposed to multiple carcinogens (DEN, MNU, DMH, and DHPN). Black stool was found in rats exposed to ≥ 0.3% Copper Gluconate, copper levels in the serum, urine, and liver were significantly increased in rats dosed with 0.6% Copper Gluconate, and marked diffuse granulomas and hepatocellular necrosis were observed in the liver of the single (1) rat in the 1.2% Copper Gluconate group. Copper Gluconate did not exert significant systemic toxicity; however, it was noted that Copper Gluconate may cause toxic and carcinogenic risks to the liver at high doses.

In a 90-d oral toxicity study, evaluating the effects of Copper Gluconate on renal function, a statistically significant increase in renal urea, creatine, sodium, and potassium levels was observed in male albino Swiss rats (8/group) that were administered 3.75, 7.5, or 15 mg/kg Copper Gluconate, in saline, via gavage. These results were indicative of renal failure and the test article was considered nephrotoxic.

A leave-on baby product formulation and a rinse-off adult formulation, each containing 0.00008% Copper Gluconate (0.00004 mg/cm^2) and a rinse-off baby product formulation containing 0.2% Copper Gluconate (0.1 mg/cm^2) were not irritating or sensitizing when tested neat in 3 separate HRIPTs using 210, 211, and 217 subjects, respectively. A powder formulation containing 0.1% Copper Gluconate (up to 0.038 mg/cm^2) was not irritating or sensitizing when tested in distilled water in an HRIPT using 52 subjects. Based on a QSAR model described in an ECHA dossier, the PDII of Copper Gluconate was predicted to be 2.26 in rabbit skin. In another QSAR-based prediction described in an ECHA dossier, Copper Gluconate was predicted to produce an EC3 value of 5.08% in an in vivo LLNA of mice; the test article was predicted to have low to moderate skin-sensitizing potential.

The ocular irritation potential of a face cream containing 0.0025% Copper Gluconate was evaluated in an MTT assay using an in vitro tissue model. The test article was classified as minimally or not irritating to the eyes. Based on a QSAR model for ocular irritation, the MMAS for Copper Gluconate in rabbit eyes was predicted, as described in an ECHA dossier, to be 49.5 out of a maximum damage value of 110; the test article was considered to be a potential mild irritant to the eyes.

In a 12-wk, double-blind, randomized clinical trial, subjects received either a 5 mg capsule of Copper Gluconate or placebo, twice a day. No significant changes in copper, zinc, and magnesium levels were observed in the serum, urine, or hair. Similarly, no significant changes in hematocrit, mean corpuscular volume, serum cholesterol, triglyceride, glutamic-oxaloacetic transaminase, alkaline phosphatase, gamma-glutamyl transferase, or lactate dehydrogenase levels were observed in treated subjects. Serum potassium levels did change from a mean of 4.3 mEq/l to 4 mEq/l ($p < 0.05$). The incidence of nausea, diarrhea, and heartburn was the same in both treated subjects and controls.

Using the in silico tool, VEERMEER Cosmolife, daily exposures to copper from Copper Gluconate were estimated to not exceed 151.2 µg/d in mouthwash, 70 µg/d in make-up removers, and 87.6 µg/d in body lotions. These exposure levels are substantially lower than the RDA values for copper in adults and babies (900 and 340 µg/d), as well as corresponding TUL values (10,000 µg/d and 1000 µg/d).

DISCUSSION

This assessment reviews the safety of Copper Gluconate as used in cosmetic formulations, in accordance with the product categories and concentrations of use identified in the Use section and Use table. The Panel noted that while there is a paucity of genotoxicity data in this safety assessment, carcinogenicity data from dietary studies on Copper Gluconate are available. While some carcinogenic effects were observed in these studies, along with nephrotoxic effects in a gavage study, the concentrations at which these adverse effects were observed are much greater than those used in cosmetic formulations. The US FDA has designated Copper Gluconate as GRAS as a direct food ingredient, and the Panel noted copper is an essential nutrient. Additionally, Copper Gluconate is not a dermal irritant or dermal sensitizer in several HRIPTs. The Panel considered these findings, coupled with the low concentration of use in cosmetic products and negative developmental and reproductive toxicity data, and determined that the data were sufficient to conclude that Copper Gluconate is safe in cosmetics in the present practices of use and concentration.

The Panel expressed concern regarding other heavy metals that may be present in this ingredient. They stressed that the cosmetics industry should continue to use the necessary procedures to minimize impurities in cosmetic formulations according to limits set by the US FDA and EPA.

The Panel also discussed the issue of incidental inhalation resulting from exposure to this ingredient; for example, Copper Gluconate is reported to be used in face powder formulations (concentration not provided) and could possibly be inhaled. Inhalation toxicity data were not available. However, coupled with the small actual exposure in the breathing zone and the low concentrations at which this ingredient is used (or is expected to be used) in potentially inhaled products, the available information indicates that the incidental inhalation would not be a significant route of exposure that might lead to local respiratory or systemic effects. A detailed discussion and summary of the Panel's approach to evaluating incidental inhalation exposures to ingredients in cosmetic products is available at https://www.cir-safety.org/cir-findings.

The Panel's respiratory exposure resource document (see link above) notes that airbrush technology presents a potential safety concern, and that no data are available for consumer habits and practices thereof. As a result of deficiencies in these critical data needs, the safety of cosmetic ingredients applied by airbrush delivery systems cannot be assessed by the Panel. Therefore, the Panel has found the data insufficient to support the safe use of this cosmetic ingredient applied via an airbrush delivery system.

CONCLUSION

The Expert Panel for Cosmetic Ingredient Safety concluded that Copper Gluconate is safe in cosmetics in the present practices of use and concentration described in this safety assessment.

TABLES

Table 1. Chemical properties

Property	Value	Reference
Physical Form	solid; crystalline powder powder fine powder	3,4 5 21CFR184.1260
Color	light blue to bluish-green green	3,4 21CFR184. 1260 5
Odor	odorless	3,4
Formula Weight (g/mol)	453.9 (compared to 63.55 g/mol atomic weight of copper)	6,7
Topological Polar Surface Area (Å2)	283	4
Density (g/ml @ 20 ºC)	1.78	3
Vapor pressure (mmHg @ 20 ºC)	0.01	3
Melting Point (ºC)	155 - 157	3,4
Water Solubility (g/l @ 25 °C)	300	3,4
Solubility *Soluble* *Insoluble*	 water, alcohol (slightly) acetone, ether, organic solvents	3,4
log K_{ow}	-2.98 (estimated)	3

Table 2. Frequency (2023)[12] and concentration (2022)[13] of use according to likely duration and exposure and by product category

	# of Uses	Max Conc of Use (%)
Totals*	**170**	**0.000025 - 0.36**
summarized by likely duration and exposure**		
Duration of Use		
Leave-On	*140*	*0.00008 - 0.008*
Rinse-Off	*30*	*0.000025 - 0.36*
Diluted for (Bath) Use	*NR*	*NR*
Exposure Type*		
Eye Area	13	0.0005 - 0.006
Incidental Ingestion	6	0.36
Incidental Inhalation-Spray	53[a]; 46[b]	0.0008[b]
Incidental Inhalation-Powder	5; 46[b]	0.0008[b]; 0.0008 - 0.003[c]
Dermal Contact	156	0.0008 - 0.1
Deodorant (underarm)	NR	NR
Hair - Non-Coloring	8	0.000025 - 0.0008
Hair-Coloring	NR	NR
Nail	NR	NR
Mucous Membrane	8	0.36
Baby Products	2	0.00008
as reported by product category		
Baby Products		
Baby Shampoos	2	0.00008
Baby Lotions/Oils/Powders/Creams	NR	0.00008
Eye Makeup Preparations		
Eyeliner	NR	0.006
Eye Lotion	7	0.0005
Eye Makeup Remover	1	0.0008
Other Eye Makeup Preparations	5	NR
Hair Preparations (non-coloring)		
Hair Conditioner	NR	0.000025
Rinses (non-coloring)	NR	0.0008
Shampoos (non-coloring)	4	0.000025
Tonics, Dressings, and Other Hair Grooming Aids	1	NR
Other Hair Preparations	1	NR
Makeup Preparations		
Blushers (all types)	2	NR
Face Powders	5	NR
Foundations	5	NR
Lipstick	2	NR
Makeup Bases	1	NR
Makeup Fixatives	3	NR
Other Makeup Preparations	4	0.0025
Oral Hygiene Products		
Mouthwashes and Breath Fresheners	4	NR
Other Oral Hygiene Products	NR	0.36
Personal Cleanliness Products		
Bath Soaps and Detergents	1	NR
Other Personal Cleanliness Products	1	NR
Skin Care Preparations		
Cleansing	17	0.0016 - 0.1
Face and Neck (exc shave)	39	not spray: 0.0008 - 0.003
Body and Hand (exc shave)	7	not spray: 0.0008
Moisturizing	35	not spray: 0.0025
Night	5	not spray: 0.005 – 0.008
Paste Masks (mud packs)	NR	0.0001 - 0.005
Skin Fresheners	7	NR
Other Skin Care Preparations	10	0.0005

NR – not reported

* Because each ingredient may be used in cosmetics with multiple exposure types, the sum of all exposure types may not equal the sum of total uses.

**likely duration and exposure is derived based on product category (see Use Categorization https://www.cir-safety.org/cir-findings)

[a] It is possible these products are sprays, but it is not specified whether the reported uses are sprays.

[b] Not specified whether a spray or a powder, but it is possible the use can be as a spray or a powder, therefore the information is captured in both categories

[c] It is possible these products are powders, but it is not specified whether the reported uses are powders.

Table 3. Acute toxicity studies on Copper Gluconate

Vehicle	Animals/Group	Dose	Protocol	LD_{50}/Results	Reference
			ORAL		
deionized water	Male Wistar rats (4 - 6/group)	79.5, 156, or 312 mg/kg	Administered via gavage; body weights were recorded for 7 d. Animals were killed on day 7 and samples from the blood and liver were obtained for analysis. Controls received equivalent doses of calcium gluconate.	No animals from the 79.5 and 156 mg/kg groups died. No significant differences in weight gain or hepatic activity (measured via GGT and ALT levels) were observed compared to the control group. Survival rate for the 312 mg/kg group was 31%.	[21]
water	Wistar rats (5/sex/group)	0, 1800, 2400, or 3200 mg/kg bw	OECD TG 401; administered via gavage; animals were observed for up to 14 d.	LD_{50} = 1709 mg/kg bw (combined for males and females) 5 animals in the 1800 mg/kg group died within 48 h; all animals in the 2400 and 3200 mg/kg died within 48 or 24 h, respectively In the animals that were found dead, local hemorrhages and necrosis were found in the fundus of the stomach, and the intestinal tracts were congested; surviving animals did not exhibit any treatment-related gross abnormalities upon necropsy.	[3]
			COMPUTATIONAL		
NA	NA	NA	Results from a QSAR model (described in an ECHA dossier); based upon REACH Guidance QSAR R6; was used to predict the acute dermal LD_{50} in rats.	LD_{50} = 2130 mg/kg bw (dermal)	[3]

Table 4. Repeated dose toxicity studies on Copper Gluconate

Vehicle	Animals/Group	Study Duration	Dose/Concentration	Protocol	Results	Reference
				ORAL		
feed	Male Fischer 344 rats (5/group)	2 wk	0, 0.001, 0.03, or 0.6% (0, 10, 300, or 6000 ppm)	The liver was removed and weighed upon study termination. Liver tissue was fixed for histopathological analysis and the remainder was assessed for genes related to metal metabolism (*Mt1a*), apoptosis (*Gadd45α*, *p21*, *p53*), inflammation (*TNF*-α, *IL-1*α, *Nos2*), and normal cell growth (*c-fos*).	The test article did not affect final body weight, liver weight, or food consumption and no gross or histological changes were observed in the liver of treated animals, compared to controls. Hepatic mRNA expression of metal metabolism-related gene *Mt1a* and apoptosis-related gene *Gadd45α* were significantly increased in the 0.6% group. The expression of apoptosis-related gene *p21* was significantly increased in the 0.03 and 0.6% groups. The expression of *p53* (apoptosis-related), *TNF*- α, *IL-1*α, *Nos2* (inflammation-related), and *c-fos* (related to cell growth) expression were not affected at any dose level.	[23]
feed	Male and female rats (number not specified)	6 mo (24 wk)	0.006 or 0.06% in the diet (mean consumption of 3.46 or 34.9 mg/kg/d)	No further details were provided.	No adverse effects were noted in food consumption, body weight gain, urinalysis, or gross and microscopic examination of tissues and organs at necropsy. Copper content was elevated in the kidneys of test animals fed the test diet.	[24]
feed	Rats (25/sex/group)	Up to 44 wk	1.14% in the diet (equivalent to 0.16% copper)	A control group was also maintained. No further details were provided.	Significant growth retardation was discernible at 26 wk, compared to controls. Over 80% of the animals died between weeks 17 and 35. Hematology and urine components were within the normal range except for high blood non-protein nitrogen in males. Upon necropsy, hypertrophied uteri, ovaries, seminal vesicles and hypertrophied stomachs, occasional ulcers, bloody mucus in the intestinal tract, and bronzed kidneys and livers were observed. Abnormal hepatic and renal changes, varying degrees of testicular damage, and a marked depression in tissue storage of iron was also observed. Chronic exposure to 1.14% Copper Gluconate in the diet was considered toxic.	[26,25]

Table 4. Repeated dose toxicity studies on Copper Gluconate

Vehicle	Animals/Group	Study Duration	Dose/Concentration	Protocol	Results	Reference
feed	Male and female Beagle dogs (6/group/sex)	Up to 1 yr (52 wk)	0.012, 0.06, or 0.24% in the diet (equivalent to 3, 15, or 60 mg/kg/d)	Clinical chemistry parameters and urine samples were obtained at 4, 13, or 26 wk. Interim sacrifice and necropsy of 2 animals/sex/group was performed after 6 mo of treatment . No further details were provided.	After 6 mo of dosing, no differences were noted in overall health, hematology, urinalysis, food consumption, or body weight gain, between test animals and controls. After 1 yr of dosing, 1 out of 12 dogs from the 0.24% group exhibited minimal liver function, which was reversible with a 12-wk withdrawal period. No test-article related deaths occurred and gross or microscopic pathologic lesions were not observed upon sacrifice. Accumulation of copper was seen in the liver, kidneys, and spleen in the 0.24% group; no other test article-related effects were observed at the lowest dose or in any dog.	26,25
drinking water	Male C57BL/6J mice (number not specified)	animal lifetime	1st experiment: 0.005 M Copper Gluconate (317 ppm copper) in ~ 4 ml water/d) 2nd experiment: 0.0005 or 0.001 M Copper Gluconate (12.7 or 63.5 ppm copper)	Mice also received copper in the diet ad libitum (incidentally containing 18 ppm copper in the ash) from the beginning of the study; controls received distilled water, ad libitum 1st experiment: mice received Copper Gluconate in drinking water from 58 d of age. 2nd experiment: mice received Copper Gluconate in drinking water from 31 d of age.	Survival curves and lifespan were significantly reduced by14.4% (0.005 M; $p < 0.01$) for treated mice in the 1st experiment and by 11.8% (0.0005 M; $p > 0.05$) and 14.7% (0.001 M; $p < 0.01$) for mice in the 2nd experiment. These results indicated the absence of dose-response relationship for survival. Animals that consumed Copper Gluconate weighed slightly less than controls throughout the experiment.	20
Cow milk infant formula	Young Capuchin monkeys (2/sex) -treated group -age-matched controls	3 yr (156 wk)	3.5 mg/d, increased to 5.5 mg/d (of copper, as Copper Gluconate) over initial 2 mo	Newborn monkeys received a daily Copper Gluconate dose in formula, adjusted to the monkey's body weight every 2 wk, even after fruits and vegetables were introduced to the diet at 4 - 6 mo. Blood samples were collected every 2nd month during the 1st year and every 3rd month thereafter. Hematological indicators, liver aminotransferases (serum aspartate aminotransferase, alanine aminotransferase, and gamma-glutamyl transpeptidase), and serum and hair copper concentrations were measured. The liver was biopsied every 3rd month during the 1st year and every 6 mo thereafter, to assess general hepatic structure and visualize copper distribution.	No differences in food intake or body weight were observed, including weight gain by age or time of exposure, between the treated animals and controls. Gamma glutamyl-transpeptidase was significantly greater in treated animals compared to controls; no differences were observed in the other hematological indicators or liver aminotransferases. At 24 mo, levels of the antibodies Ki67 and MT1 in liver tissue were greater in treated animals compared to controls. After 36 mo, copper hair and liver concentrations were significantly greater in treated animals (4 -5 times that of controls).	27
In food (fruits or sauces)	Adult tufted Capuchin monkeys - treated group (2/sex) - age-matched controls (3 males/1 female)	3 yr (156 wk)	5 mg/d, increased to 7.5 mg/d (of copper as Copper Gluconate) over initial 2 mo	The monkeys were 3 - 3.5 yr old at enrollment. Blood, hair and liver samples were collected and analyzed as described above. At the end of the experiment, liver biopsies were assessed for the relative abundance of 4 transcripts encoding proteins related to copper uptake, storage and metabolism (*MT2a*, *APP*, *DMT1*, and *CTR1*) and 3 proteins related to hepatic responses to injury (*HGF*, *TGFβ*, and *NFκB*).	No differences in food intake or body weight were observed between the treated animals and controls. Hemoglobin and mean corpuscular volume were significantly lower and free erythrocyte protoporphyrin was significantly greater in treated animals compared to controls; liver aminotransferases did not differ between groups. At 24 mo, levels of Ki67 and MT1 proteins in liver tissue were significantly greater in treated animals compared to controls. When assessed after 36 mo, the hepatic mRNA expression of *NFκB*, *HGF*, and *TGFβ* was significantly greater in the treated animals, compared to controls, with no further evidence of clinical, hematological, or histological evidence of liver damage. Copper hair and liver concentrations were significantly greater (4 - 5 times that of controls) in treated animals.	27

Table 4. Repeated dose toxicity studies on Copper Gluconate

Vehicle	Animals/Group	Study Duration	Dose/Concentration	Protocol	Results	Reference
COMPUTATIONAL						
NA	NA	NA	NA	Results from a QSAR model (described in an ECHA dossier); based on REACH guidance QSARs R.6 and were used to predict the oral LOAEL for Copper Gluconate in rats.	LOAEL = 94.7 mg/kg bw/d (oral) According to this value and the GHS/CLP classification, the STOT RE -2 designation, indicating presumed toxicity to specific organs with repeated exposure, was considered applicable.	[3]

Table 5. Developmental and reproductive toxicity studies on Copper Gluconate

Vehicle	Animals/Group	Dose	Procedure	Results	Reference
ORAL					
Not specified	Male albino rats (8/group)	3.75, 7.5, or 15 mg/kg/d	Animals were dosed via gavage for 90 d. Two control groups received either 1 ml of saline or 0.5 ml DMSO for the duration of the study. Several antioxidant enzymes activities in the testis tissue of rats were determined spectrometrically.	Copper Gluconate did not significantly affect catalase levels but did significantly reduce glutathione and superoxide dismutase levels (at the medium and high dose), while increasing malondialdehyde levels, compared to controls. These findings are indicative of the development of oxidative stress.	[28]
Not specified	Female Swiss-Webster mice (20/group)	0, 0.1, 3, 30 mg/kg/d	The test article was administered, via gavage, to pregnant mice on days 6 to 14 of gestation.	Neither embryotoxic nor teratogenic. The average length and weight of the fetuses, their number per litter, and the incidence of skeletal and soft tissue abnormalities did not differ in test animals as compared to controls.	[26,25]
Not specified	Female albino Wistar rats (number not specified)	0, 0.1, 3, 30 mg/kg/d	The test article was administered, via gavage, to pregnant rats on days 5 to 15 of gestation.	Neither embryotoxic nor teratogenic. Weekly body weights and food intake were similar among all groups. Corpora lutea, implantation sites, implantation loss were not affected by treatment. The mean number of fetuses/litter, fetal viability, and resorption sites in the treated groups did not differ from the control group. Measurements of fetal weight and length as well as incidence of skeletal and soft tissue abnormalities were also unaffected by treatment.	[26,25]
Not specified	Male and female Wistar rats (males: 10/group; females: 20/group)	Female rats: 0, 3, or 30 mg/kg/d Male rats: 0 or 3 mg/kg/d	Female rats were dosed (via gavage) with Copper Gluconate 15 d prior to mating with untreated males, during gestation, and for 21 d postpartum. Two groups of male rats were treated 60 d prior to mating (via gavage). One group of treated males was mated with untreated females and the 2nd group of treated males was mated with females who had also received 3 mg/kg/d Copper Gluconate 60 d prior to mating. A third group of untreated males mated with untreated females served as controls.	Male rat reproductive performance was not affected by Copper Gluconate. No significant differences were observed between the percentage of pregnancies, the number and distribution of embryos in each uterine horn, implantation sites, resorption sites, duration of gestation, mean number of fetuses and live pups per litter, litter size, stillborn and live born numbers, gross anomalies and mean weight per pup, compared to controls. At the end of the 21-d postpartum period, necropsies of the dams and pups from all groups revealed a lack of visceral abnormalities. Under the conditions of this study, the researchers concluded that Copper Gluconate did not affect the reproductive performance of either male or female rats.	[26,25]
COMPUTATIONAL					
NA	NA	NA	As described in an ECHA dossier, an oral NOAEL reproductive toxicity in rats was determined using a QSAR model following the REACH Guidance on QSARs and Grouping of Chemicals R.6. However, the specifics of how these values were derived were not provided.	NOAEL = 318 mg/kg bw/d	[3]
NA	NA	NA	as above, but for developmental toxicity in rats	NOAEL = 793 mg/kg bw/d	[3]

Table 6. Dermal irritation and sensitization studies

Test Article	Vehicle	Dose	Test Population	Protocol	Results	Reference
HUMAN REPEATED-INSULT PATCH TESTS						
Leave-on baby product containing 0.00008% Copper Gluconate	applied neat	0.2 ml/mg Copper Gluconate dose applied: 0.00004 mg/cm^2	210 subjects	HRIPT; occlusive conditions (patch size 4 cm^2); 9 induction patches; challenge patch was applied to an untreated site after 2 wk. Challenge readings were taken 24, 48, 72, and 96 h after patch removal.	non-irritating; non-sensitizing	[31]
Rinse-off adult product containing 0.00008% Copper Gluconate	applied neat	0.2 ml/mg Copper Gluconate dose applied: 0.00004 mg/cm^2	211 subjects	HRIPT; occlusive conditions (patch size 4 cm^2); 9 induction patches; challenge patch was applied to an untreated site after 2 wk. Challenge readings were taken 24, 48, 72, and 96 h after patch removal.	non-irritating; non-sensitizing	[32]
Powder containing 0.1% Copper Gluconate	distilled water	0.1 – 0.15 g Copper Gluconate dose applied: 0.025 – 0.038 mg/cm^2 (equivalent to 0.0036 – 0.0054 mg/cm^2 copper)	52 subjects	HRIPT; occlusive conditions; 9 induction patches (~0.025 – 0.038 mg/cm^2 of test material per patch); challenge patch was applied to an untreated site after ~ 2 wk. Challenge readings were taken 24 and 72 h after patch removal.	non-irritating; non-sensitizing	[33]
Rinse-off baby product containing 0.2% Copper Gluconate	applied neat	0.2 ml/mg Copper Gluconate dose applied: 0.1 mg/cm^2	217 subjects	HRIPT; occlusive conditions (patch size 4 cm^2); 9 induction patches; challenge patch was applied to an untreated site after 2 wk. Challenge readings were taken 24, 48, 72, and 96 h after patch removal.	non-irritating; non-sensitizing	[34]
COMPUTATIONAL						
Copper Gluconate	NA	NA	NA	Results from a QSAR model (described in an ECHA dossier) are based on REACH guidance and were used to predict a PDII of 2.26 in rabbit skin.	Prediction of being non-irritating and non-sensitizing	[3]
Copper Gluconate	NA	NA	NA	Results from a QSAR model (described in an ECHA dossier) were used to predict that the EC3 for Copper Gluconate in a local lymph node proliferative assay is 5.08%.	Based on an EC3 value > 2%, Copper Gluconate was classified as having low to moderate skin-sensitizing potential (Skin Sensitizer Category 1B, under GHS category 1)*	[3]

*substances that show a low to moderate frequency of occurrence in humans and/or low to moderate potency in animals and can be presumed to potentially produce significant sensitization in humans.

Table 7. Ocular irritation studies

Test Article	Vehicle	Concentration/Dose	Test System	Procedure	Results	Reference
				IN VITRO		
Face cream containing 0.0025% Copper Gluconate	applied neat	100 µl	EpiOcular™ tissues, tested in duplicate	Tissues were treated for 4, 8, 16 and 24 h in a MTT assay. 0.3% Triton X-100 and distilled water served as positive and negative controls, respectively. Because the treatment with the test article reduced MTT in the absence of viable tissue, a killed control experiment was conducted. Little or no direct MTT reduction was observed in test article-treated killed controls compared to negative controls with killed cells; MTT reduction in the test article-treated viable tissue was ascribed to the viable cells.	ET_{50} > 24 h (compared to 24 min for the positive control); classified as minimally or not irritating Cell viability after each treatment time: After 4 h: 111.1% 8 h: 107.2% 16 h: 92.2% 24 h: 63.7%	[36]
				COMPUTATIONAL		
Copper Gluconate	NA	NA	NA	Using QSAR Toolbox 3.4.0.17 and REACH guideline on QSAR, the MMAS for Copper Gluconate was predicted in rabbit eyes.	MMAS = 49.5 Copper Gluconate predicted to be mildly toxic, considering the maximum value for damage to the cornea, conjunctiva, and iris is 110. Based on GHS criteria, Copper Gluconate was classified as a possibly mild irritant to the eyes (Category 2B).	[3]

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