SCCS/1657/23
Final version

Scientific Committee on Consumer Safety

SCCS

OPINION ON

water-soluble zinc salts used in oral hygiene products

- Submission II -

The SCCS adopted this Opinion
during the plenary meeting on 26 October 2023

ACKNOWLEDGMENTS

Members of the Working Group are acknowledged for their valuable contribution to this Opinion. The members of the Working Group are:

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This Opinion has been subject to a commenting period of eight weeks after its initial publication (from 4 July to 8 September 2023). Comments received during this period were considered by the SCCS. For this Opinion, there was no comment received but a clarification was added under SCCS comment in section 3.3 (repeated dose toxicity), under Table 4, as well as in the first conclusion.

All Declarations of Working Group members are available on the following webpage:
Register of Commission expert groups and other similar entities (europa.eu)

1. ABSTRACT

The SCCS concludes the following:

In light of the data provided and taking under consideration the aggregate exposure (including diet) and the concerns on the Tolerable Daily Upper Intake,

(1) Does the SCCS consider that water soluble zinc salts are safe up to 1 % (as zinc) in toothpaste and 0.1% (as zinc) in mouthwash, for both adults and children? If not, the SCCS is requested to provide safe concentrations for each age group.

The SCCS has calculated aggregate exposure to water-soluble zinc salts via toothpaste at the concentrations of 1% and from diet, and concluded that the use of zinc in toothpaste is safe per se except for children under the age of 1 year because the intake exceeds the upper limit level. For children between 6 months and 1 year of age, the SCCS recommends a safe concentration of 0.72% for soluble zinc salts (as zinc) in toothpaste.

The inclusion of zinc in mouthwash at 0.1% Zn is considered safe across all age groups above 6 years.

(2) Does the SCCS consider that the contribution of the cosmetic products among the overall/total exposure to zinc is still of concern?

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Keywords: SCCS, scientific opinion, water-soluble zinc salts, oral hygiene products, zinc acetate CAS: 557-34-6 EC: 209-170-2, zinc chloride CAS: 7646-85-7 EC: 231-592-0, zinc gluconate CAS: 4468-02-4 EC:/, zinc citrate CAS: 546-46-3 EC:/, zinc sulphate/zinc sulphate monohydrate/zinc sulphate heptahydrate CAS: 7733-02-0/7446-19-7/7446-20-0 EC:/, SCCS/1586/17, Regulation 1223/2009

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Two independent non-food Scientific Committees provide the Commission with the scientific advice it needs when preparing policy and proposals relating to consumer safety, public health and the environment. The Committees also draw the Commission's attention to the new or emerging problems which may pose an actual or potential threat.
These Committees are: the Scientific Committee on Consumer Safety (SCCS) and the Scientific Committee on Health, Environmental and Emerging Risks (SCHEER) and they are made up of scientists appointed in their personal capacity.

In addition, the Commission relies upon the work of the European Food Safety Authority (EFSA), the European Medicines Agency (EMA), the European Centre for Disease prevention and Control (ECDC) and the European Chemicals Agency (ECHA).

SCCS
The Committee shall provide Opinions on questions concerning health and safety risks (notably chemical, biological, mechanical and other physical risks) of non-food consumer products (for example cosmetic products and their ingredients, toys, textiles, clothing, personal care and household products such as detergents, etc.) and services (for example: tattooing, artificial sun tanning, etc.).

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2. MANDATE FROM THE EUROPEAN COMMISSION

Background

Water-soluble zinc compounds are used in oral cosmetic products to reduce oral malodour, tartar and plaque formation. Currently, water-soluble zinc salts are regulated under entry 24 of Annex III to Regulation (EC) 1223/2009 (Cosmetics Regulation). More specifically, entry 24 allows the use of Zinc Salts with the exception of Zinc 4-hydroxybenzenesulphonate and Zinc Pyrithione, up to a maximum concentration of 1% (as Zinc).
In July 2014, the Federal Institute for Risk Assessment (BfR) submitted a dossier expressing potential safety concerns related to the use of Zinc salts in oral products such as toothpaste and mouthwash in particular for specific age groups.

In February 2016, Cosmetics Europe submitted a safety dossier to demonstrate that the combined exposure from food and oral care products is safe up to 1% and 0.1% in toothpastes and in mouthwashes, respectively, for all age groups.

In June 2018, the SCCS concluded that the use of Zinc in toothpaste and mouthwash per se is safe. However, SCCS highlighted that the dietary intake was not taken under consideration and the committee '*cannot advise which portion of the upper limit should be allocated to exposure from cosmetic products*'. In its Opinion (SCCS/1586/17)[1], the SCCS stated that when assessing exposure to chemicals, allocation factors that reflect a reasonable level of exposure may be applied, while still being protective. The SCCS also added that any additional source of exposure may lead to exceeding the upper limits, because the default values used in this assessment were based on conservative estimates.

In May 2021, Cosmetics Europe submitted a new dossier reviewing the available database and in particular, the methodology and choices that led to the definition by the Scientific Committee on Food (SCF) of Tolerable Daily Upper Intake levels. Submission II includes considerations of the reported dietary exposures, absorption kinetics, and the age-dependent usage of oral care products by consumers.

Terms of reference

In light of the data provided and taking under consideration the aggregate exposure (including diet) and the concerns on the Tolerable Daily Upper Intake,

1. *Does the SCCS consider that water soluble zinc salts are safe up to 1 % (as zinc) in toothpaste and 0.1% (as zinc) in mouthwash, for both adults and children? If not, the SCCS is requested to provide safe concentrations for each age group.*

2. *Does the SCCS consider that the contribution of the cosmetic products among the overall/total exposure to zinc is still of concern?*

[1] https://ec.europa.eu/health/sites/default/files/scientific_committees/consumer_safety/docs/sccs_o_207.pdf

3. OPINION

3.1 Chemical and Physical Specifications

Several water-soluble compounds can be used in oral hygiene products, but the zinc compounds generally used in oral hygiene products include zinc acetate (Zn^{2+}- proportion: 35.64 %), zinc chloride (Zn^{2+}- proportion: 47.98 %), zinc gluconate (Zn^{2+}- proportion: 13.29 %), zinc citrate (Zn^{2+}- proportion: 22.77 %), zinc sulphate (Zn^{2+}- proportion: 40.50 % / 22.74 %).

Since water-soluble zinc salts are ionically bonded compounds consisting of cationic zinc and acid residue anion(s), dissolution of these salts in aqueous media causes dissociation by creating solvated zinc cations and respective anion(s). In the dissolved state, zinc and anions are no longer ionically bound but interact independently with water molecules instead. As a consequence, they exert their biological activity independent from each other under physiological conditions. However, while the anions may possess different biological activities of their own at different concentrations, it is the effects that are driven by zinc that all water soluble zinc salts have in common.

Ref.: Lynch, 2011; BfR, 2014

SCCS comment
The SCCS bases this Opinion on the zinc ionic content, considering that the zinc cation is the determining factor for systemic toxicity.

3.2 Function and uses

Zinc compounds are added to oral hygiene products to reduce oral malodour, to reduce tartar formation and as an anti-bacterial agent to help to control plaque.

Ref.: Lynch, 2011; BfR, 2014

3.3 Toxicological Evaluation

Several reports have been published representing extensive reviews of the effect of water-soluble zinc salts on human health.

Ref.: WHO, 2001; SCF 2003; ATSDR 2005; EU 2008; BfR 2014; Hartwig 2014

Acute toxicity

Information on acute toxicity of zinc in humans is rare, although there are cases of food poisoning resulting from storage of food and drink in galvanised containers. Symptoms of acute toxicity of zinc are gastrointestinal disturbances with nausea, vomiting, epigastric pain, abdominal cramps and diarrhoea, as well as lethargy, headaches and circulation problems. An emetic dose of zinc corresponds to 225-450 mg.

Ref.: SCF 2003; BfR 2014

Irritation, corrosivity, skin sensitisation

Generally, dermal exposure to water soluble zinc salts does not result in any noticeable toxic effects, with the exception of the skin irritancy that has been reported. In a study on skin-irritating effects of different zinc compounds, open-patch test were performed with

rabbits, guinea pigs and mice. Skin-irritating effects (epidermal hyperplasia, erythema and ulceration) were reported after application of zinc chloride (1% in water). Application of zinc acetate (20% in water) revealed acanthosis, hyperkeratosis and parakeratosis. In addition, mildly irritating effects were found with zinc sulphate (1% in water), including slight epidermal hyperplasia. Furthermore, zinc sulphate was considered to induce ocular irritation (such as corneal injury, epithelial damage and conjunctival irritation).

There are a few studies reporting that dental prosthetic materials containing zinc can possibly induce conditions or changes in the buccal mucosa. Despite a wide range of possible exposures to water-soluble zinc salts from cosmetics and pharmaceuticals, skin sensitisation has been reported only in a few individual cases. Animal studies with zinc sulphate have revealed negative results.

With regard to oral hygiene products containing water-soluble zinc salts, oral exposure is more important than dermal exposure.

Ref.: ATSDR, 2005; Hartwig, 2014

SCCS comments
The SCCS is of the opinion that effects reported after dermal exposure are not a concern.

Repeated dose toxicity

Studies on chronic and sub-chronic toxicity of zinc show that prolonged intakes of zinc supplements ranging from 50 to 300 mg/day are associated with a range of biochemical and physiological changes, such as leucopenia, neutropenia, sideroblastic anaemia, decreased concentrations of plasma copper and decreased activity of copper-containing enzymes (superoxide dismutase and caeruloplasmin), altered lipoprotein metabolism and impaired immune function. Many of the reported biochemical and physiological changes are comparable to those observed during copper deficiency, and the reduction in superoxide dismutase activity might mark the range where effects on copper balance begin.

Based on an oral zinc intake level where no effects on parameters of the copper balance occur, a NOAEL of 0.43 mg zinc/kg body weight and day (corresponding to 25.8 mg/day for an adult with a body weight of 60 kg) after oral intake was defined by Hartwig *et al.* (2014).

From the data available, the experts of the SCF (2003) drew the conclusion that no adverse effects are to be expected at zinc doses below 50 mg/day. This NOAEL was based on the absence of any adverse effects on a wide range of relevant indicators of copper status (such as erythrocyte copper-zinc superoxide dismutase activity, lipoprotein metabolism, and haemoglobin and blood profiles). It is also inferred that, taking into account an uncertainty factor of 2 due to the sometimes small number of test persons in the short-term studies, an upper limit (UL) of 25 mg/day of zinc for adults should not be exceeded. Available studies indicate no increased susceptibility to zinc supplementation in pregnant women. Thus, an UL of 25 mg zinc/day applies also to pregnant and lactating women. The following ULs were extrapolated by SCF for children and young people: 1-3 yrs: 7 mg/day; 4-6 yrs: 10 mg/day; 7-10 yrs: 13 mg/day; 11-14 yrs: 18 mg/day, 15-17 yrs: 22 mg/day.

Ref.: SCF, 2003, 2006; Hartwig, 2014

SCCS comments
In the previous Opinion, SCCS had applied the following ULs for children and young people: 1-3 yrs: 7 mg/day; 4-6 yrs: 10 mg/day; 7-10 yrs: 13 mg/day; 11-14 yrs: 18 mg/day, 15-17 yrs: 22 mg/day. In this Opinion, the SCCS used a linear UL according to the age (and did not use the same UL for age 1 to 3 and 4 to 6) (see section Safety evaluation).

Reproductive toxicity
In animal studies on Zn sulphate, no indications for prenatal developmental toxicity were found at the doses of 200 mg/kg bw/day in rats and 6.8 mg/kg bw/day in mice (highest doses tested). In a number of studies with healthy pregnant women, a daily oral zinc supplement of 20-90 mg has shown no indication of adverse effects.

Ref.: SCF, 2003; Hartwig, 2014

Mutagenicity / Genotoxicity

Existing data on genotoxicity/mutagenicity of zinc salts (zinc acetate and zinc chloride) are inconclusive, showing mostly negative but in some cases positive effects. There is an indication of genotoxic/mutagenic/clastogenic potential of zinc ions (released from zinc oxide nanoparticles) *in vitro* and *in vivo,* acting most likely via secondary mechanisms, *e.g.* via oxidative stress and inflammation, and thus considered threshold-dependent.

Ref.: Pati, 2016; Ghosh, 2016; Khan, 2015; Pandurangan, 2015

SCCS comments
The SCCS concludes that potential genotoxicity of zinc salts is threshold-dependent and thus these can be considered non-genotoxic below the safe concentrations as described in the safety evaluation section.

Carcinogenicity

Studies on zinc-induced carcinogenicity have not adequately demonstrated increased cancer incidence after long-term exposure.

Ref.: ATSDR, 2005; SCF, 2003

Special investigations

Effects on copper status

In humans, a disproportionate oral intake of zinc in relation to copper has been shown to induce copper deficiency resulting in increased copper requirements, increased copper excretion and impaired copper status. Associations between pharmacological intakes of zinc and effects ranging from leukopenia and/or hypochromic microcytic anaemia to decreases in serum high-density lipoprotein concentrations have been reported. Oral intake of zinc may inhibit copper absorption through interaction with metallothionein at the brush border of the intestinal lumen. Both copper and zinc appear to bind to the same metallothionein protein, but copper has higher affinity than zinc. Copper is incorporated into metalloenzymes. These copper-dependent enzymes function mainly to reduce molecular oxygen. Excess zinc may alter the levels or activity of these enzymes before the manifestation of the more severe symptoms of copper deficiency (including anemia and leucopenia). While studies do not always show consistent results, the available studies on volunteers have identified 40–50 mg supplemental zinc/day (0.68-0.83 mg zinc/kg/day) as the level at which subtle changes in copper-containing enzymes can be observed. In humans, long-term administration (1-8 years) of high levels of zinc (2-11.6 mg/kg/day) is reported to cause anaemia. Adequate studies of chronic effects from lower levels of zinc on copper status are, however, not available. In experimental animals exposed to high zinc doses, decreased haemoglobin and haematocrit and anaemia development have been observed.

Ref.: WHO, 2001; ATSDR, 2005

Other adverse effects

Daily oral intakes of 300 mg zinc for six weeks can impair immune responses, i.e. reduction in lymphocyte stimulation response to phytohaemagglutinin as well as chemotaxis and phagocytosis of bacteria by polynuclear leucocytes. Furthermore, daily zinc supplementations of 53 mg for 90 days can increase bone-specific alkaline phosphatase (a possible indicator of bone formation), as demonstrated in 25 post-menopausal women.

Ref.: SCF 2003

3.4 Toxicokinetics

Most orally-ingested zinc is absorbed in the upper small intestine, although small quantities of zinc may be absorbed throughout the entire gastro-intestinal tract. Depending on the nutrition, absorption of zinc from the gastrointestinal tract varies between 8 to 80%. However, in persons with an adequate zinc intake, the absorption varies between 20 to 30%.

The major transporter of zinc in blood is albumin and virtually no zinc circulates in unbound form.

Zinc is found in all tissues of the body. In adults, the total body zinc is about 2.5 and 1.5 g in men and women, respectively. The majority of total body zinc is in the muscle and bone (ca 85%), in addition to skin and hair (ca 8%), liver (ca 5%) and in the gastrointestinal tract and pancreas (ca 3%). Only about 0.1% of zinc is circulating in the blood. In healthy subjects, plasma concentrations of zinc are affected by intake. However, homeostatic mechanisms that act to maintain plasma zinc concentrations within the physiological range may prevent high levels from being sustained over a prolonged period.

There is a rapid turnover of plasma zinc reflecting its exchange with all tissues and organs in the body. This exchanging pool of zinc fully exchanges with zinc in plasma and accounts for about 10% of total body zinc.

As zinc is present in the body as a bivalent cation, electrostatic interaction with anions and negatively-charged groups in proteins or other molecules is possible. However, as a metallic element, zinc is not metabolised.

About 70-80% of ingested zinc is eliminated with the faeces. However, the elimination rate depends on both zinc intake and status. There is a tight homeostatic control of zinc by the small intestine where the fundamental regulation factor is the targeted, transport-dependent absorption of zinc from the gut with a controlled discharge of endogenous zinc in the stool. Thus, in the case of a lack of zinc, endogenous extraction is reduced. Depending on zinc intake, between 14 to 25% is eliminated in the urine. Other elimination routes are via saliva, hair, breast milk and sweat.

Ref.: Hartwig, 2014; EFSA, 2014; BfR, 2014

3.5 Exposure assessment

3.5.1 Exposure from toothpaste and mouthwash

Toothpaste
The recommended 'pea size' amount of toothpaste for children at age 5 years or younger is taken as 0.25 g. Thus, by brushing the teeth twice daily, children in this age group will be exposed to 0.5 g toothpaste daily. Due to not sufficiently developed swallowing reflexes in these children, the retention factor is higher compared to older children and adults. Most studies on oral retention in young children report a retention factor of about 30%. The estimations of oral exposure in children aged 0.5-5 years are thus based on a daily exposure to 0.5 g toothpaste and a retention factor of 20 and 40%.

For children aged 6 to 17 years and adults, the estimation of oral exposure to zinc is based on a daily applied amount of 2.75 g toothpaste with a retention factor of 5%.

Mouthwash
Since the use of mouthwash is not recommended for children aged 5 years of younger, an exposure assessment with regard to mouthwash for this age group is not performed.

For children aged 6 to 17 years and adults, the estimation of oral exposure to zinc is based on a daily applied amount of 21.61 g with a retention factor of 10%.

Estimated amounts of zinc exposure for both the separate products and aggregated exposure for children (0.5-5 years and 6-17 years) and adults.

Age group	Product	Zinc (%)	Daily amount applied (g)	Retention factor		Conversion factor (to mg/g)	Daily intake level (mg/day)	
Adults (≥18 yrs)	Toothpaste	1.0	2.75	0.05		1000	1.38	
	Mouthwash	0.1	21.61	0.10		1000	2.16	
Aggregated exposure adults (≥18 yrs)							3.54	
Children (6-17 yrs)	Toothpaste	1.0	2.75	0.05		1000	1.38	
	Mouthwash	0.1	21.61	0.10		1000	2.16	
Aggregated exposure children (6-17 yrs)							3.54	
Children (0.5-5 yrs)	Toothpaste	1.0	0.5	0.20	0.40	1000	1.00	2.00

Ref.: SCCNFP, 2003; SCCP, 2005; SCCS, 2015, SCCS 2023

3.5.2 Exposure from the diet

Dietary zinc intakes were estimated by EFSA (2014) using the EFSA Comprehensive Food Consumption Database and the EFSA Food Composition Database. The average zinc intake ranged from 8.0 to 14.0 mg/day in adults, from 6.8 to 14.5 mg/day in adolescents aged 10 to < 18 years, from 5.5 to 9.3 mg/day in children aged 3 to < 10 years and from 4.6 to 6.2 mg/day in children aged 1 to <3 years.

Ref.: EFSA, 2014

The European Food Safety Authority published an authoritative compilation of European studies on dietary zinc intake in 2014. To best utilize this wealth of data on the European landscape of dietary zinc exposures, every study was considered by calculating a weighted median for each age group.
Use of the weighted median is sensible for at least two reasons. First, all studies contribute to the overall estimate. Secondly each study contribution to the overall estimate is weighted by the inverse of the study standard deviation (a measure of the uncertainty or noise in the study) divided by the study sample size. This means that studies with high precision (from either a small standard deviation or large sample size) receive more weight in the overall estimate. This weighing function is commonly used in meta analysis where results from many studies are combined to create better estimates.
Studies where EFSA concluded that "the results may not be statistically robust", and for which EFSA decided that, therefore, "the 5th and 95th percentile estimates will not be presented in the intake results" were excluded from this consideration as well. Variance was calculated by consideration of 5th and 95th percentiles, and weight was determined by dividing the number of individuals in each population group of each study by the respective study's variance. Study data as well as weighted median values are shown in Table 1.

Neither SCF nor other authorities characterized a gender difference in children regarding the susceptibility to the effects of zinc. Furthermore, Tolerable Upper Intake Levels by SCF were published without consideration of gender, and applied to all groups of the general population (SCF 2006). Therefore, the weighted median dietary intake data was calculated across genders.

This meta analysis furthers the ideal of objective data representation by the utilization of all population groups studied across Europe - instead of using a single maximum data point from a single study for an entire age group.

Table 1 – Weighted Median Dietary Zinc Intake in Europe in mg/day. (n = Number of individuals in the population group.)

	age (years)		From EFSA (2014) n	Ave	Med	P5	P95	Variance	Weight	Weighted Median
male	1 to <3	Finland	245	5.5	5.4	3.2	8.4	2.50	98	
		Germany	174	5.0	4.8	2.9	7.3	1.79	97	
		UK	107	5.8	5.6	3.6	9.0	2.69	40	
female		Finland	255	5.3	5.0	2.9	8.3	2.69	95	
		Germany	174	4.6	4.6	2.8	6.7	1.41	124	
		UK	78	5.3	5.3	3.1	7.8	2.04	38	**5.01**
male	3 to <10	Finland	381	8.5	8.4	5.3	12.1	4.27	89	
		France	239	8.8	8.5	4.9	12.9	5.91	40	
		Germany	426	9.3	9.0	5.9	13.1	4.79	89	
		Germany	146	6.1	5.8	3.9	8.7	2.13	69	
		Italy	94	9.3	8.9	5.3	13.9	6.83	14	
		Netherlands	231	8.0	7.7	4.6	12.6	5.91	39	
		UK	326	6.7	6.6	3.9	10.3	3.78	86	
female		Finland	369	7.7	7.6	5.3	10.9	2.90	127	
		France	243	7.9	7.8	5.0	12.4	5.06	48	
		Germany	409	8.4	8.1	5.5	12.4	4.40	93	
		Germany	147	5.5	5.3	3.5	8.4	2.22	66	
		Italy	99	8.9	8.5	5.0	13.1	6.06	16	
		Netherlands	216	7.5	7.3	4.3	11.7	5.06	43	
		UK	325	6.4	6.3	3.7	9.6	3.22	101	**7.40**
male	10 to <18	Finland	136	12.2	11.9	7.5	17.5	9.24	15	
		France	449	10.7	10.3	6.0	16.9	10.98	41	
		Germany	197	10.0	9.6	6.3	14.9	6.83	29	
		Italy	108	12.2	11.4	7.2	18.0	10.78	10	
		Netherlands	566	10.2	9.8	5.6	16.5	10.98	52	
		UK	340	8.7	8.4	4.9	13.5	6.83	50	
female		Finland	170	9.7	9.5	5.7	15.0	7.99	21	
		France	524	8.4	8.2	4.7	12.9	6.21	84	
		Germany	196	9.3	9.0	6.0	13.5	5.20	38	
		Italy	139	9.8	9.6	5.8	14.4	6.83	20	
		Netherlands	576	8.4	8.2	4.9	12.5	5.34	108	
		UK	326	6.8	6.7	3.4	10.6	4.79	68	**8.74**
male	18 to <65	Finland	585	12.7	12.2	6.6	20.7	18.37	32	
		France	936	11.6	11.4	6.3	18.2	13.08	72	
		Ireland	634	12.2	11.9	7.0	18.8	12.86	49	
		Italy	1068	11.3	11.0	6.6	17.0	9.99	107	
		Netherlands	1023	12.0	11.6	6.6	18.9	13.98	73	
		Sweden	623	13.7	13.2	7.4	21.7	18.89	33	
		UK	560	9.9	9.5	5.3	15.9	10.38	54	
female		Finland	710	9.8	9.5	5.2	15.5	9.80	72	
		France	2340	8.9	8.6	4.7	14.0	7.99	293	
		Ireland	640	0.0	8.8	5.0	13.8	7.15	89	
		Italy	1245	9.4	9.2	5.4	13.8	6.52	191	
		Latvia	990	14.0	13.3	7.9	22.8	20.51	48	
		Netherlands	1034	9.5	9.0	5.3	15.0	8.69	119	
		Sweden	807	10.5	10.1	5.8	16.6	10.78	75	
		UK	706	8.0	7.8	4.2	12.3	6.06	116	**9.76**

SCCS comments

The SCCS appreciates the approach proposed by the Applicant but considers that it is not valid for the following reason:

The food consumption data gathered by EFSA were collected by different methodologies and thus direct country-to-country comparisons should be interpreted with caution.

It is not in EFSA's methodology to mix/group different studies where the measurement and sampling methodologies differ between studies. This is the reason why EFSA only presents medians, P5 and P95 from each study but does not combine them.

The SCCS notes that the P95 Dietary Intake value based on food consumption data values exceed the tolerable upper limits for children up to age 11. Therefore, the SCCS is in agreement with EFSA and prefers to use the largest median values reported by EFSA as presented in Table 2.

Table 2 –Dietary Zinc Intake in Europe in mg/day. (n = Number of individuals in the population group.)

Age class (years)	Country	Survey		Intake expressed in mg/day			
			n	Average	Median	P5	P95
1 to <3	UK	NDNS–RollingProgrammeYears1–3	107	5.8	5.6	3.6	9
3 to <10	Germany	EsKiMo	426	9.3	9	5.9	13.1
10 to < 18	Finland	NWSSP07_08	136	12.2	11.9	7.5	17.5
18 to < 65	Latvia	FC_PREGNANTWOMEN_2011	990	14	13.3	7.9	22.8

3.6 Safety evaluation

The applicant has been asked to review the aggregate exposure to zinc from cosmetics for the groups that might be affected if dietary consumption of zinc is included in the calculations. More specifically, for children of 3 and 6 years the aggregate daily exposure to zinc is 9.40 and 11.56 mg Zn/d compared with the Tolerable Upper Intake Levels of 7 and to 10 mg Zn/d, respectively, when dietary intake is added to potential exposure from Oral Care (OC) products (Table 3).

There are two ages where aggregate exposures appear to exceed ULs: Age 3 and age 6. At these two ages, the very conservatively derived aggregate intake from OC adds a theoretical amount to the weighted median dietary intake. That total exceeds a numerical value found by authoritative bodies to be safe. The following considerations will, however, rebut any concerns these numbers may have elicited:

-First, peer-reviewed research sponsored by Health Canada (Bertinato *et al.* 2013) challenges the current ULs and provides "evidence in support of the need for reexamining the current UL for zinc for children" for setting the ULs higher.

-Secondly, and as a direct consequence, it is imperative to emphasize that the exceeding of a UL does not imply toxicity. By definition, a UL is a known safe level, not a threshold for toxicity.

-Thirdly, the absorption kinetics outlined above, clearly demonstrate that the human body effectively maintains zinc homeostasis by regulating absorption within the dose range of consideration, even at higher exposures.

-Lastly, the apparent exceeding of ULs at ages 3 and 6 is a data artefact (aliasing) caused by combination of age groups by authoritative bodies. Obviously, body weight should factor into ULs, not just age. As such, the increase in ULs should be linear, not step-wise. Nevertheless, the same ULs apply for ages 1-3 and 4-6 (and all others). They were developed with the youngest members of each age group in mind. Applying the same UL to children of the age of 1 and 3 means that this value is exceedingly conservative for a 3 year-old child. The same holds true for ages 4 and 6: The published UL for 6 year-olds is the value for age 4, while it should instead be closer to the UL for age 7. In addition, dietary intakes were also grouped - by even larger age differentials. Thus, the dietary intake for age 3 is dominated by data from older children (up to age 9). Consequently, dietary intake data for 3 year-olds must be considered exceedingly conservative as well.

In conclusion, Table 3 might provide the incorrect impression that zinc exposure randomly peaks above known safe levels (but still below the NOAEL) for ages 3 and 6. It is important to emphasize that these levels do not pose a health hazard, that the body maintains the homeostasis of this essential element at these exposure levels, and that the arbitrarily set ULs and dietary intake age groups artificially create false concerns. Zinc does not spontaneously exert toxicity with the 3rd and 6th birthday.

Table 3 – Aggregate exposures in comparison to ULs and NOAEL.

Age	Intake from Toothpaste at 1.0 % Zn	Intake from Mouthwash at 0.1 % Zn	Aggregate Intake from Oral Care	Weighted Median Dietary Intake based on food consumption data	SCF Tolerable Upper Intake Levels	IOM Tolerable Upper Intake Levels	**Aggregate Exposure Oral Care + Weighted Dietary Average**	NOAEL by Yadrik *et al.* (1989)
[years]	[mg Zn/d]	[mg Zn/d]	[mg Zn/d]	[mg Zn/d]	[mg Zn/d]	[mg Zn/d]	**[mg Zn/d]**	[mg Zn/d]
1	2.00	0	2.00	5.01	7	7	**7.01**	10
2	2.00	0	2.00	5.01	7	7	**7.01**	10
3	2.00	0	2.00	7.40	7	7	**9.40**	10
4	2.00	0	2.00	7.40	10	12	**9.40**	16
5	2.00	0	2.00	7.40	10	12	**9.40**	16
6	2.00	2.16	4.16	7.40	10	12	**11.56**	16
7	1.38	2.16	3.54	7.40	13	12	**10.94**	24
8	1.38	2.16	3.54	7.40	13	12	**10.94**	24
9	1.38	2.16	3.54	7.40	13	23	**10.94**	24
10	1.38	2.16	3.54	8.74	13	23	**12.28**	24
11	1.38	2.16	3.54	8.74	18	23	**12.28**	37
12	1.38	2.16	3.54	8.74	18	23	**12.28**	37
13	1.38	2.16	3.54	8.74	18	23	**12.28**	37
14	1.38	2.16	3.54	8.74	18	34	**12.28**	37
15	1.38	2.16	3.54	8.74	22	34	**12.28**	50
16	1.38	2.16	3.54	8.74	22	34	**12.28**	50
17	1.38	2.16	3.54	8.74	22	34	**12.28**	50
adult	1.38	2.16	3.54	9.76	25	40	**12.28**	53

SCCS comment

The SCCS acknowledges the fact that grouping data for both exposure and UL in a non-linear step could create an artificial concern for children of a specific age. Therefore, the SCCS agreed to use a linear UL according to the age (and not to use the same UL for age 1 to 3 and 4 to 6).

This was done by using a body weight equation, based on a French survey. This study (EAT for French total Diet Study) included 4,078 subjects aged between 3 and 60 years, and 703 subjects under the age of 3. The reported data (weight, age) from this study made it possible to derive an equation describing the increase in weight according to age (see Anses cadmium 2017, EFSA PFAS Opinion 2020).

The following equation was used:

BW= 3.68+4.47*year-0.093*year^2+0.00061*year^3

The SCCS disagrees with using the NOAEL as proposed by the Applicant and considers the international Tolerable Upper Intake Levels (UL) (published by the European Commission Scientific Committee on Food (EU SCF 2003) as the reference level for the safety evaluation. The UL were based on a NOAEL of 50mg/day for adults and extrapolated to children by allometric scaling, with an uncertainty factor of 2 (due to the small number of subjects) by the EU SCF 2003.

The following equation was then used by the SCCS to calculate UL in a linear fashion:

Tolerable Upper Intake Levels (UL) =25*((BW/60)^0.75)

The SCCS calculated the aggregate exposure to zinc from cosmetics and diet according to the largest median reported by EFSA. Table 4 and Figure 1 below summarise the total aggregated oral exposure for zinc from all sources (food and dental care products) across age groups:

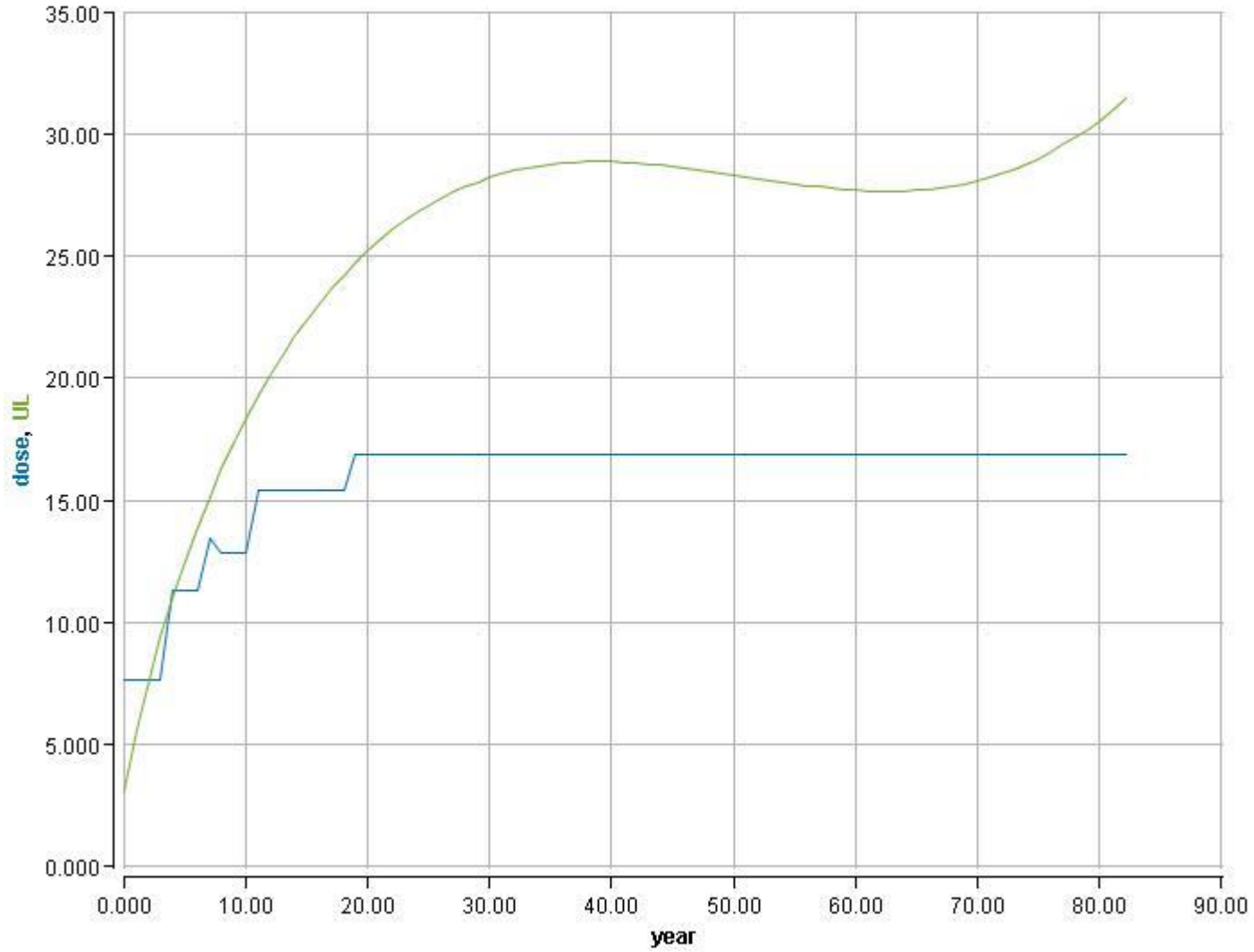

Figure 1: dose: aggregated exposure for Zinc in oral products and diet (median) by age is represented by blue line. The UL are represented by the green line, and calculated according the body weight.

Table 4: aggregated oral exposure for Zinc in oral products and diet (median) calculated by the SCCS

Age	Intake from Toothpaste at 1.0 % Zn	Intake from Mouthwash at 0.1 % Zn	Aggregate Intake from Oral Care	Median Dietary Intake based on food consumption data	**Aggregate Exposure Oral Care + Dietary (median)**	SCF Tolerable Upper Intake Levels
[years]	[mg Zn/d]	[mg Zn/d]	[mg Zn/d]	[mg Zn/d]	[mg Zn/d]	[mg Zn/d]
1	2	0	2	5.6	7.6	6
2	2	0	2	5.6	7.6	8
3	2	0	2	9	11	9
4	2	0	2	9	11	11
5	2	0	2	9	11	12
6	2	2.16	4.16	9	13.16	14
7	1.38	2.16	3.54	9	12.54	15
8	1.38	2.16	3.54	9	12.54	16
9	1.38	2.16	3.54	9	12.54	17
10	1.38	2.16	3.54	11.9	15.44	18
11	1.38	2.16	3.54	11.9	15.44	19
12	1.38	2.16	3.54	11.9	15.44	20
13	1.38	2.16	3.54	11.9	15.44	21
14	1.38	2.16	3.54	11.9	15.44	22
15	1.38	2.16	3.54	11.9	15.44	22
16	1.38	2.16	3.54	11.9	15.44	23
17	1.38	2.16	3.54	11.9	15.44	24
adult	1.38	2.16	3.54	13.3	16.84	25

The SCCS is of the opinion that the aggregate exposure (oral care and diet exposure) in children below the age of 1 exceed the tolerable daily upper intake, and therefore raise a concern.
The SCCS recognises that the calculated aggregated zinc exposure of 11 mg/day exceeds the tolerable upper intake level of 9 mg/day at 3-year-old children. Nevertheless, the SCCS is of the opinion that this apparent exceeding of ULs could be considered as an artefact caused by combination of age groups exposure.
For children at age 3-year-old, the calculated aggregated zinc exposure is dominated by the median dietary intake based on food consumption data from age class 3 to 10 *(e.g.* 9 mg/day). It should be noted that the use of median dietary intake based on food consumption data from age class 0 to <3 (*e.g.* 5.6 mg/day), the calculated aggregated zinc exposure does not exceed the tolerable upper intake level of 9 mg/day.

The SCCS recommends a safe concentration for soluble zinc salts (as zinc) in toothpaste of 0.72 % for children up to 1 year of age.

4. CONCLUSION

In light of the data provided and taking under consideration the aggregate exposure (including diet) and the concerns on the Tolerable Daily Upper Intake,

1. *Does the SCCS consider that water soluble zinc salts are safe up to 1 % (as zinc) in toothpaste and 0.1% (as zinc) in mouthwash, for both adults and children? If not, the SCCS is requested to provide safe concentrations for each age group.*

The SCCS has calculated aggregate exposure to water-soluble zinc salts via toothpaste at the concentrations of 1% and from diet, and concluded that the use of zinc in toothpaste is safe per se except for children under the age of 1 year because the intake exceeds the upper limit level. For children between 6 months and 1 year of age, the SCCS recommends a safe concentration of 0.72% for soluble zinc salts (as zinc) in toothpaste.

The inclusion of zinc in mouthwash at 0.1% Zn is considered safe across all age groups above 6 years.

2. *Does the SCCS consider that the contribution of the cosmetic products among the overall/total exposure to zinc is still of concern?*

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5. MINORITY OPINION

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7. GLOSSARY OF TERMS

See SCCS/1647/22, 12th Revision of the SCCS Notes of Guidance for the Testing of Cosmetic Ingredients and their Safety Evaluation – Appendix 15 - from page 158

8. LIST OF ABBREVIATIONS

See SCCS/1647/22, 12th Revision of the SCCS Notes of Guidance for the Testing of Cosmetic Ingredients and their Safety Evaluation – Appendix 15 - from page 158