Scientific Committee on Consumer Safety

SCCS

**OPINION ON**

*water-soluble zinc salts used in oral hygiene products*

- Submission I -

The SCCS adopted this Opinion at its plenary meeting on 21-22 June 2018
About the Scientific Committees

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SCCS

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ISSN 1831-4767
Doi:10.2875/97758

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ACKNOWLEDGMENTS

SCCS members listed below are acknowledged for their valuable contribution to this Opinion.

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All Declarations of Working Group members are available on the following webpage:
http://ec.europa.eu/health/scientific_committees/experts/declarations/sccs_en.htm
This Opinion has been subject to a commenting period of a minimum eight weeks after its initial publication (from 13 March until 14 May 2017). Comments received during this time were considered by the SCCS.

For this Opinion, comments received resulted in the following minor changes: physico-chemical part under section 3.1, age groups and upper limit in % under exposure section 3.5, some miss-spelling of the unit (mg instead of g), and conclusions/references accordingly.


Opinion to be cited as: SCCS (Scientific Committee on Consumer Safety), Opinion on water-soluble zinc salts used in oral hygiene products - Submission I, preliminary version adopted on 7 March 2017, final version adopted on 21-22 June 2018, SCCS/1586/17
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1. BACKGROUND

Water-soluble Zinc salts, including amongst other Zinc Acetate and Zinc Chloride with the exception of Zinc 4-hydroxybenzenesulphonate and Zinc Pyrithione, are regulated in entry 24 of the Annex III of the Regulation (EC) 1223/2009. They are currently allowed for use in cosmetic products in concentrations of up to 1% as Zinc with a wide range of functions ranging from antioxidant to antimicrobial and skin protecting.

Tolerable total uptake level (UL) for Zinc up to 25 mg was established by the Scientific Committee on Food in 2003. Cosmetic products might account for maximum 10% of the UL.

In July 2014, the German authority, Federal Institute for Risk Assessment (BfR), has submitted a dossier expressing potential safety concerns related to the use of Zinc salts in oral products such as toothpastes and mouthwashes. According to BfR, cosmetic products might account for maximum 10% of the UL. While confirming the safety for adults of toothpastes containing zinc (maximum Zinc content: 1%), BfR concluded that:

"The use of mouthwashes with a Zinc content of up to 1%, however, can lead to the 10% share of UL which should be accounted for by cosmetic products being significantly exceeded. The BfR categorises these products as potentially dangerous for the consumer if used regularly and over an extended period."

In addition, BfR has shown concerns for the particular age group of children and adolescents (1 to 17 years old) due to their lower body weight as the use of toothpastes with a maximum content up to 1% of Zinc might lead to a significant excess of the maximum 10% share of UL contribution of the cosmetic products, particularly in the age group 1-10 years old.

To minimize the potential risks, BfR has proposed to lower the maximum Zinc concentration to 0.1% in oral hygiene products for adults while free Zinc should not be present in these products for children and young people aged under 18.

In February 2016, Cosmetics Europe has transmitted an aggregate exposure assessment for children and adults to demonstrate that the combined exposure from food as well as oral care products, at the current allowed concentration of up to 1% as Zinc in toothpastes is safe across all age groups. On the other hand, for mouthwashes they support the maximum use level at concentration of up to 0.1% as Zinc for all age groups.

2. Terms of reference

(1) According to the data available, does the SCCS consider water-soluble Zinc salts safe for all age groups at the current allowed concentration of up to 1% as Zinc when used in toothpastes and at the use level of up to 0.1% as Zinc when used in mouthwashes?

(2) Does the SCCS have any concerns related to the use of water-soluble Zinc salts in oral products for the particular age group 1 to 17-year old?
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. Thus, based on the assumption that the zinc cation is the determining factor for systemic toxicity, this opinion was based on the zinc ionic content.

Ref.: Lynch, 2011; BfR, 2014

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.


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. Furthermore, 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. Thus, SCCS is not concerned about the reported effects after dermal exposure.

Ref.: ATSDR, 2005; Hartwig, 2014

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 leucopaenia, neutropaenia, 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.

It the present Opinion, SCCS applies these ULs for the respective age groups.

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

Reproductive toxicity

In animal studies on Zn sulphate, no potential 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. Based on the available data, SCCS concludes that the available evidence is insufficient to consider the evaluated zinc salts as genotoxic.

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

**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 polymuclear 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 of 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.
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<table>
<thead>
<tr>
<th>Age group</th>
<th>Product</th>
<th>Zinc (%)</th>
<th>Daily amount applied (g)</th>
<th>Retention factor</th>
<th>Conversion factor (to mg/g)</th>
<th>Daily intake level (mg/day)</th>
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</thead>
<tbody>
<tr>
<td>Adults (≥18 yrs)</td>
<td>Toothpaste</td>
<td>1.0</td>
<td>2.75</td>
<td>0.05</td>
<td>1000</td>
<td>1.38</td>
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<td>21.61</td>
<td>0.10</td>
<td>1000</td>
<td>2.16</td>
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<td>Aggregated exposure adults (≥18 yrs)</td>
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<td></td>
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<tr>
<td>Children (6-17 yrs)</td>
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<td>1000</td>
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<tr>
<td></td>
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<tr>
<td>Aggregated exposure children (6-17 yrs)</td>
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</table>

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

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

3.6 Safety evaluation

For all age groups the estimated daily intake levels of zinc from the use of toothpaste and mouthwash is below the ULs of 7, 10, 13, 18 and 22 mg/day for children aged 1-3, 4-6, 7-10, 11-14 and 15-17 years, respectively, and the UL of 25 for adults.

Based on the estimations of oral intake from the oral hygiene products, exposure to zinc may lead to daily intake levels of:
- 3.54 mg in adults, which constitutes up to 14% of the UL of 25 mg/day for adults
- 3.54 mg in children aged 15-17 years, which constitutes up to 16% of the UL of 22 mg/day for this age group
- 3.54 mg in children aged 11-14 years, which constitutes up to 20% of the UL of 18 mg/day for this age group
3.54 mg in children aged 7-10 years, which constitutes up to 27% of the UL of 13 mg/day for this age group
- 3.54 mg in children aged 6 years, which constitutes up to 35% of the UL of 10 mg/day for this age group
- 1.00-2.00 mg in children aged 4-5 years, which constitutes up to 10-20% of the UL of 10 mg/day for this age group
- 1.00-2.00 mg in children aged 0.5-3 years, which constitutes up to 14-29% of the UL of 7 mg/day for this age group

4. CONCLUSION

1. According to the data available, does the SCCS consider water-soluble Zinc salts safe for all age groups at the current allowed concentration of up to 1% as Zinc when used in toothpastes and at the use level of up to 0.1% as Zinc when used in mouthwashes?

The SCCS has estimated that exposure to water-soluble zinc salts via toothpaste and mouthwash at the concentrations of 1 and 0.1%, respectively, may lead to a daily intake level of 3.54 mg for adults and children aged 6-17 years. This exposure constitutes between 14 and 35% of the Upper Limit (UL) for these age groups. Therefore, the SCCS considers that the use of zinc in toothpaste and mouthwash per se is safe for adults and children aged 6-17 years.

The SCCS has estimated that exposure to water-soluble zinc salts via toothpaste at the concentrations of 1% may lead to a daily intake level of 1.0-2.00 mg for children aged 0.5-5 years. This exposure constitutes between 10 and 29% of the UL for this age group. Therefore, the SCCS considers that the use of zinc in toothpaste per se is safe for children aged 0.5-5 years.

2. Does the SCCS have any concerns related to the use of water-soluble Zinc salts in oral products for the particular age group 1 to 17-year old?

Exposure to zinc may also occur from sources other than oral hygiene products. An important source of zinc in the population is the diet. This assessment has not taken into account the daily dietary intake of zinc.

The dietary zinc intake (estimated by EFSA in 2014) ranges 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. Therefore, exposure to zinc via the diet may already exceed or be close to exceeding the upper limits of 18, 13, 10 and 7 mg/day for the age groups 11-14, 7-10, 3-7 and 1-3 years, respectively. Any additional source of exposure, including cosmetics, may lead to exceeding the upper limits for children.

The SCCS cannot advise which portion of the upper limit should be allocated to exposure from cosmetic products. When assessing exposure to chemicals, allocation factors that reflect a reasonable level of exposure while still being protective may be applied. For exposure via toys or drinking water, for example, allocation factors of 10% or 20% of the reference value may be considered as safe. In the case of zinc, the use of 1% in toothpaste and 0.1% in mouthwash constitutes between 10 and 35% of the upper limit depending on the age group. The SCCS is aware that upper limits may be exceeded in some cases because the default values used in this Opinion are based on conservative estimates.
5. MINORITY OPINION

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6. REFERENCES


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safety of fluorine compounds in oral hygiene products for children under the age of 6 years, adopted by the SCCP by written procedure on 20 September 2005.

