



## **Scientific Committee on Consumer Safety**

### **SCCS**

# **OPINION ON Zinc Pyrithione (ZPT) (CAS No 13463-41-7) - Submission III -**



The SCCS adopted this document  
at its plenary meeting on 03-04 March 2020

## ACKNOWLEDGMENTS

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This Opinion has been subject to a commenting period of a minimum eight weeks after its initial publication (from 16 December 2019 until 17 February 2020). Comments received during this time period are considered by the SCCS. For this Opinion, some changes occurred, in particular in sections 3, 3-3.1.3, 3-4 and relevant discussion parts.

## 1. ABSTRACT

### **The SCCS concludes the following:**

*1. In view of the conditions laid out in Article 15(d) of the Regulation (EC) No 1223/2009 and taking into account the scientific data provided, does the SCCS consider Zinc Pyrithione safe when used as an anti-dandruff in rinse-off hair products up to a maximum concentration of 1%?*

In line with the conditions laid out in Article 15(d) (i.e. 'overall exposure from other sources') of the Regulation (EC) No 1223/2009 and taking into account the scientific data provided, the SCCS considers Zinc Pyrithione (ZPT) as safe when used as an anti-dandruff in rinse-off hair products up to a maximum concentration of 1%.

*2. Does the SCCS have any further scientific concerns with regard to the use of Zinc Pyrithione in cosmetic products?*

/

Keywords: SCCS, scientific opinion, preservative, Zinc Pyrithione, ZPT, P81, submission III, Regulation 1223/2009, CAS 13463-41-7, EC 236-671-3

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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).

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## 2. MANDATE FROM THE EUROPEAN COMMISSION

### Background

The cosmetic ingredient Zinc Pyrithione (ZPT) (CAS No 13463-41-7, EC No 236-671-3) with the chemical name Bis[(2-pyridyl)-1-oxo]-thio]zinc is currently regulated as a preservative in rinse-off products (excluding oral hygiene products) in a concentration up to 0.5% in general and up to 1.0% in hair products (Annex V/8). Furthermore, ZPT is also allowed in a concentration up to 0.1% in leave-on hair products (Annex III/101).

Zinc Pyrithione has been subject to different safety evaluations by the SCC in 1984 (XI/389/84), SCCNFP in 2002 (SCCNFP/0671/03), and the SCCS in 2014 (SCCS/1512/13) and 2018 (SCCS/1593/2018). In particular, in the SCCS opinions from 2014 and 2018, Zinc Pyrithione was found safe as an antidandruff agent in rinse-off hair care products at a maximum concentration of 2.0%.

In October 2016 a CLH dossier was submitted by the Swedish Chemicals Agency ("KEMI") to ECHA to support the harmonised classification and labelling of ZPT as a CMR 1B.

On 14 September 2018, ECHA's Risk Assessment Committee (RAC) adopted an opinion proposing harmonised classification and labelling at EU level of ZPT as a CMR 1B substance under Regulation (EC) No. 1272/2008<sup>1</sup>.

*According to Article 15(2) of the Cosmetics Regulation*, "The use in cosmetic products of substances classified as CMR substances, of category 1A or 1B under Part 3 of Annex VI to Regulation (EC) No 1272/2008 shall be prohibited.

However, such substances may be used in cosmetic products by way of exception where, subsequent to their classification as CMR substances of category 1A or 1B under Part 3 of Annex VI to Regulation (EC) No 1272/2008, all of the following conditions are fulfilled:

- (a) they comply with the food safety requirements as defined in Regulation (EC) No 178/2002<sup>2</sup> of the European Parliament and of the Council of 28 January 2002 laying down the general principles and requirements of food law, establishing the European Food Safety Authority and laying down procedures in matters of food safety;
- (b) there are no suitable alternative substances available, as documented in an analysis of alternatives;
- (c) the application is made for a particular use of the product category with a known exposure; and
- (d) they have been evaluated and found safe by the SCCS for use in cosmetic products, in particular in view of exposure to these products and taking into consideration the overall exposure from other sources, taking particular account of vulnerable population groups"

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<sup>1</sup> <http://eur-lex.europa.eu/LexUriServ/LexUriServ.do?uri=OJ:L:2008:353:0001:1355:en:PDF>

<sup>2</sup> <https://eur-lex.europa.eu/legal-content/EN/TXT/PDF/?uri=OJ:L:2002:031:FULL&from=EN>

In view of the above, regulatory measures must be adopted by the Commission services within 15 months of the classification as CMR 1A or 1B of the substance(s) concerned in Part 3 of Annex VI to Regulation (EC) No 1272/2008.

In April 2019, a safety dossier on ZPT was submitted by Cosmetics Europe to demonstrate the safety of the ingredient as an anti-dandruff in rinse-off hair products.

## **Terms of reference**

- 1. In view of the conditions laid out in Article 15(d) of the Regulation (EC) No 1223/2009 and taking into account the scientific data provided, does the SCCS consider Zinc Pyrithione safe when used as an anti-dandruff in rinse-off hair products up to a maximum concentration of 1%?*
- 2. Does the SCCS have any further scientific concerns with regard to the use of Zinc Pyrithione in cosmetic products?*

### 3. OPINION

The SCCS has re-assessed the safety of zinc pyrithione in its Addendum (SCCS/1593/18), considered here as submission II, based on the following information:

- A proposal by the Swedish authorities for the classification and labelling of zinc pyrithione as Repr. 1B (hazard statement H360D- may damage the unborn child) and STOT RE1 (hazard statement H372 – Causes damage to organs through prolonged or repeated exposure) according to Regulation (EC) No. 1272/2008 (CLP-Regulation) (ECHA, 2017). The proposal is referred to as Swedish CLH proposal in this document.
- Three study reports on recently performed developmental and reproductive toxicity studies (Thor, 2015a; Thor, 2015b; Thor, 2015c), along with documents/comments from industry on developmental toxicity and classification (Daston et al., 2016; Thor GmbH, 2017; ZnPT Industry CLH Consortium, 2017a and b). These studies were performed after the animal testing ban of 11 March 2013 that banned the sale of cosmetics in Europe that had been tested on animals using *in vivo* studies. However, as the studies were performed in the context of the biocides regulatory framework, the studies can be accepted for the safety assessment of cosmetics.

In addition, the SCCS has noted that the Committee for Risk Assessment (RAC), in its Opinion adopted on 14 September 2018, proposed to classify zinc pyrithione for the following human health hazards (Acute Tox 3; H301, ATE oral = 221 mg/kg bw, Acute Tox 2; H330, ATE inhalation = 0.14 mg/l, Eye Dam. 1; H318, STOT RE 1, H372, Repr. 1B; H360D). A nose-inhalation study (2014) derived an ATE inhalation of 0.05-0.5 mg/l.

During the preparation of this Opinion (submission III), additional information became available for the SCCS. These reports have been referenced by ECHA under the numbers:

ECHA ZnPT CAR Doc IIIA A6.1.1/01 Year: 1986  
ECHA ZnPT CAR Doc IIIA A6.1.1/02 Year: 1997  
ECHA Thor GmbH Art. 95 dossier, 2014 (including 12 studies)  
ECHA ZnPT CAR Doc IIIA A6.1.2/01 Year: 1997  
ECHA ZnPT CAR Doc IIIA A6.1.4/01 Year: 2001  
ECHA Thor GmbH Art. 95 dossier, 2014  
ECHA ZnPT dossier Doc IIIA A6.1.4/02 Year: 2001  
ECHA ZnPT CAR Doc IIIA A6.1.5/01 Year: 2002  
ECHA ZnPT CAR Doc IIIA A6.2/03 Year: 2005  
ECHA Thor GmbH Art. 95 dossier, 2015  
ECHA ZnPT CAR Doc IIIA A6.3.1/01 Year: 1992  
ECHA ZnPT CAR Doc IIIA A6.4.1/01 Year: 1973  
ECHA ZnPT CAR Doc IIIA A6.4.3/01 Year: 1993  
ECHA ZnPT CAR Doc IIIA A6.3.3/02 Year: 2009  
ECHA ZnPT CAR Doc IIIA A6.6.1/01 Year: 2002  
ECHA ZnPT CAR Doc IIIA A6.6.2/01 Year: 2002  
ECHA ZnPT CAR Doc IIIA A6.6.3/01 Year: 2002  
ECHA ZnPT CAR Doc IIIA A6.6.5/01 Year: 1992  
ECHA ZnPT CAR Doc IIIA A6.6.4/01 Year: 2001

The SCCS is also aware that zinc pyrithione is under assessment for biocides <https://echa.europa.eu/fr/substance-information/-/substanceinfo/100.033.324>.



### 3.1 Chemical and Physical Specifications

#### 3.1.1 Chemical identity

##### 3.1.1.1 Primary name and/or INCI name

Zinc pyrithione (INCI name)

##### 3.1.1.2 Chemical names

Bis [1-hydroxy-2(1 H)-pyridinethionato-O,S] (T-4) zinc (IUPAC)

Pyrithione zinc

Zinc bis(2-pyridylthio)-N-oxide

Zinc pyridinethione

Zinc 2-pyridinethione-I-oxide

Bis (N-oxopyridine-2-thionato) zinc (II)

ZP, ZnPT, ZnPTO, BOTZ

Note: the chemical names mentioned here are only those related to cosmetic uses. Other names are also mentioned at ECHA website:

<https://echa.europa.eu/fr/brief-profile/-/briefprofile/100.033.324>

##### 3.1.1.3 Trade names and abbreviations

Zinc Omadine

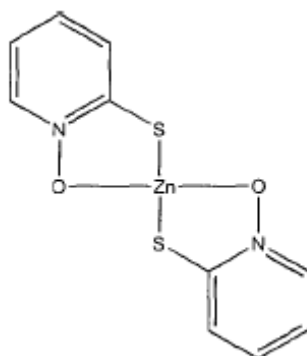
Vancide ZP

##### 3.1.1.4 CAS / EC number

CAS: 13463-41-7

EC 236-671-3

##### 3.1.1.5 Structural formula



##### 3.1.1.6 Empirical formula

C<sub>10</sub>H<sub>8</sub>N<sub>2</sub>O<sub>2</sub>S<sub>2</sub>Zn

**3.1.2 Physical form**

White to slightly yellow crystals

**SCCS comment**

Additional information is available on ECHA's website.

**3.1.3 Molecular weight**

Molecular weight: 317.7 g/mol

**3.1.4 Purity, composition and substance codes**

Zinc pyrithione is commercially supplied as a 24-26% aqueous solution.

**3.1.5 Impurities / accompanying contaminants**

No data submitted.

**3.1.6 Solubility**

Very low solubility in most solvents

Water at 20°C: 4.93 mg/L (reported at ECHA Website)

Ethanol: /

Acetone: /

Chloroform: /

Mineral oil, light: /

**SCCS comment**

Concerning solubility in solvents (other than water), temperature is not provided by the applicant. No further information is available on ECHA's website.

**3.1.7 Partition coefficient (Log P<sub>ow</sub>)**

Log P<sub>ow</sub>: 0.9 (HSE, 2003)

0.97 (MAK, 2012)

0.883 (EU Method A.8, ECHA Website)      0.9 (OECD 107, ECHA Website)

**3.1.8 Additional physical and chemical specifications**

Melting point: 240°C (Decomposition at 240°C)

Boiling point: /

Flash point: /

Vapour pressure : < 0.000001 Pa at 25°C (OECD 104)

Density: 1.782 at 25 °C

Viscosity: 1.76 g/cm<sup>3</sup> at 20°C (OECD 109)

pKa: /

Refractive index: /

UV\_Vis spectrum (200-800 nm): /

**SCCS comment**

Slightly different values for the melting point were given by ECHA and HSE (2003). According to HSE (2003), the substance decomposes before melting (200°C). HSE (2003)

has also cited vapour pressure of <0.532 Pa at 21°C, whereas according to MAK (2012), vapour pressure is  $2.49 \times 10^{-9}$  hPa at 25°C.

### 3.1.9 Stability

Homogeneity and stability of Zn pyrithione in test solutions have been reported in some of the studies performed. In the toxicokinetic investigations described in section 3.3.9.3., the stability of zinc pyrithione in frozen rat plasma was evaluated by analysing the stability of the samples stored under the same conditions as the study samples. Results indicate a frozen-state stability of approximately 377 days at -70°C.

### SCCS general comments to physico-chemical characterisation

Information on purity, composition and impurities of the test substance should be provided according to the SCCS Notes of Guidance, 10<sup>th</sup> revision (SCCS/1602/18). There are different values available on some physicochemical properties of zinc pyrithione from different sources.

## 3.2 Function and uses

Zinc pyrithione (ZPT) is currently regulated as a preservative in rinse-off products (excluding oral hygiene products) in a concentration up to 0.5% in general and up to 1.0% in hair products (Annex VI/1, 8). ZPT is also allowed at a concentration up to 0.1% in leave-on hair products (Annex III/1, 101). According to the EC Commission Regulation (No. 1451/2007), ZPT is also used as a biocide in biocidal product categories 2, 6, 7, 9, 10, and 21 of Annex V of the EU Biocide Directive (Directive 98/8/EC).

- Product Type (PT)2 – Disinfectants and algacides not intended for direct application to humans or animals
- Product Type (PT)6 – Preservatives for products during storage
- Product Type (PT)7 – Film preservatives
- Product Type (PT)9 – Fibre, leather, rubber and polymerised materials preservatives
- Product Type (PT)10 – Construction material preservatives
- Product Type (PT)21 – Antifouling products

## 3.3 Toxicological Evaluation

### SCCS comments

A search of scientific literature was conducted from the time the last Opinion was published in 2014 (SCCS/1512/13) until March 2019. In addition, studies submitted to ECHA and KEMI by two companies under REACH were also provided to the SCCS. The summaries of toxicological data for zinc pyrithione (ZPT) submitted by the applicant were taken from the ECHA website.

Data relating to acute oral toxicity had already been assessed in the previous Opinion (SCCS/1512/13). Therefore, only the comments/conclusions from the previous Opinion have been included in this section, along with any new information.

**3.3.1 Acute toxicity****3.3.1.1 Acute oral toxicity****Taken from SCCNFP/0671/03**

LD<sub>50</sub> values for zinc pyrithione have been determined in various species after oral administration. The values in rats ranged from 92 to 266 mg/kg and in mice from 160 to 1000 mg/kg. Six hundred mg/kg was found to be the LD<sub>50</sub> when administered orally to dogs.

Further studies have been performed in addition to acute oral toxicity studies evaluated in SCCNFP/0671/03. These studies (ECHA ZnPT CAR Doc IIIA A6.1.1/01 Year: 1986, ECHA ZnPT CAR Doc IIIA A6.1.1/02 Year: 1997, Thor GmbH Art. 95 dossier, 2014, have been evaluated by ECHA and KEMI, who reached the same conclusion as the SCCS (SCCNFP/0671/03 and SCCS/1512/13).

The SCCS notes, however, that classification as Acute Tox 3; H301 (toxic if swallowed). according to CLP Regulation (EC) No 1272/2008 of the European Parliament and of the Council of 16 December 2008 on classification, labelling and packaging of substances and mixtures, is suggested by the registrant(s) under REACH.

**3.3.1.2 Acute dermal toxicity**

In addition to acute dermal toxicity studies evaluated in SCCNFP/0671/0 that led to the conclusion that the acute dermal toxicity of zinc pyrithione appears to be higher than 2000 mg/kg. These studies have been evaluated by ECHA and KEMI and did not lead to changes of the conclusions of the SCCS (SCCS/1512/13).

**3.3.1.3 Acute inhalation toxicity**

In addition to acute inhalation toxicity studies evaluated in SCCNFP/0671/03, further studies have been performed. These studies have been evaluated by ECHA and KEMI (ECHA Thor GmbH Art. 95 dossier Year: 2014, ECHA ZnPT CAR Doc IIIA A6.1.3/01 Year: 1996)) did not lead to changes the conclusions of the SCCS (SCCS/1512/13).

In HSE (2003), a whole body inhalation study performed in male and female Sprague-Dawley rats is mentioned, in which a LC<sub>50</sub> value of 0.14 mg/l was derived.

Local and systemic effects were observed upon acute inhalation exposure. The SCCS notes that classification as Acute Tox 2; H330 (fatal if inhaled) according to RAC opinion (2018) is currently suggested.

**3.3.2 Irritation and corrosivity****3.3.2.1 Skin irritation**

In addition to skin irritation studies evaluated in SCCNFP/0671/03, further studies have been performed. These studies have been evaluated by ECHA and KEMI (ECHA: ZnPT CAR Doc IIIA A6.1.4/01 Year: 2001, ECHA Thor GmbH Art. 95 dossier, 2014, ECHA Thor GmbH Art. 95 dossier, 2014 did not lead to changes the conclusions of the SCCS (SCCS/1512/13). From product-based data evaluated in SCCNFP/0671/03, from the description of skin irritation studies performed with ZPT and from human HRIPT tests, it can be inferred that ZPT is – at least - a mild skin irritant.

### 3.3.2.2 Mucous membrane irritation / Eye irritation

Eye irritation potential of shampoo in rabbit eyes was not increased by the incorporation of ZPT. HSE (2003) concluded that ZPT is a severe eye irritant: MAK (2012) states that ZPT is corrosive to the eye. The SCCS notes that classification as Eye Damage 1; H318 (causes serious eye damage) according to CLP Regulation is suggested in ECHA (2017).

In addition to eye irritation studies evaluated in SCCNFP/0671/03 further studies have been performed. These studies have been evaluated by ECHA and KEMI (ECHA ZnPT dossier Doc IIIA A6.1.4/02 Year: 2001, ECHA Thor GmbH Art. 95 dossier, 2013, ECHA Thor GmbH Art. 95 dossier, 2014) and did not lead to changes of the conclusions of the SCCS (SCCS/1512/13).

### 3.3.3 Skin sensitisation

In addition to skin sensitisation studies evaluated in SCCNFP/0671/03, further studies have been performed. These studies have been evaluated by ECHA and KEMI (ECHA: ZnPT CAR Doc IIIA A6.1.5/01 Year: 2002, ECHA Thor GmbH Art. 95 dossier, 2014) and did not lead to changes of the conclusions of the SCCS (SCCS/1512/13).

ZPT was tested in guinea pig studies and the LLNA. Based on these studies, ZPT was considered not to be a skin sensitizer. Concerning human data, ZPT (or the PT moiety part) has a low potential to induce contact hypersensitivity when tested per se or as part of a cosmetic formulation. However, in some human HRIPT studies, evaluation was partly hindered by the erythematous reactions observed.

### 3.3.4 Toxicokinetics

#### 3.3.4.1 Dermal / percutaneous absorption

##### ***In vitro* percutaneous absorption**

In addition to skin penetration studies evaluated in SCCNFP/0671/03, a further study has been performed. This study has been evaluated by ECHA and KEMI (ECHA Thor GmbH Art. 95 dossier, 2014) and did not lead to changes of the conclusions of the SCCS (SCCS/1512/13)

##### ***In vivo* dermal absorption**

##### **Taken from SCCNFP/0671/03**

In addition to skin penetration studies evaluated in SCCNFP/0671/03, a further study has been performed. This study has been evaluated by ECHA and KEMI (ECHA ZnPT CAR Doc IIIA A6.2/03) and did not lead to changes of the conclusions of the SCCS (SCCS/1512/13)

## Human studies

Data related to dermal absorption were assessed in the previous Opinion. SCCS' comments and main conclusions are included in this section.

In conclusion, a 1% dermal absorption is taken for risk assessment as a conservative value, as this is supported by the *in vitro* OECD study (<https://echa.europa.eu/fr/registration-dossier/-/registered-dossier/14333/7/2/3>) and by a human clinical study using 2% ZPT shampoo formulations in combination with 0.1% or 0.25% ZPT-containing leave-on formulations. In this study, up to 0.22% of the applied dose was excreted via urine. Taking into consideration that further amounts could have been excreted at later time points not considered in the test interval or by faecal excretion and also considering some tissue retention, total absorption is most probably not higher than 1%.

A systemic exposure load of 5.25 µg/kg/d has been derived from the use of a shampoo containing 2% ZPT (either in combination with leave-on tonics containing 0.1 and 0.25 % ZPT or with a leave-on tonic containing 0.25% ZPT only). This is based on a study in human volunteers in a 4-day treatment regimen systemic exposure loads up to 4.66 µg/kg/d were derived. 1 SD has been added based on the fact that (a) low recoveries were obtained and (b) even higher systemic amounts of exposure cannot be excluded after repeated prolonged exposure to ZPT-containing products.

### 3.3.4.2 Other studies on toxicokinetics

Two *in vitro* skin penetration studies were published since 2014. While neither of these alter the conclusion that 1% is a maximum absorption in humans, they provide technical knowledge related to the lateral diffusion of ZPT and the probable dissociation of zinc from pyrithione following topical application (Rush *et al.* 2015 and Holmes *et al.* 2018).

#### 3.3.4.2.2. General information on Metabolism and Toxicokinetics of ZPT

The metabolism and toxicokinetics of ZPT have been well investigated in different species. Data related to dermal absorption were assessed in the previous Opinion (SCCS/1512/13).

In addition to toxicokinetics studies evaluated in SCCNFP/0671/03, a further study was performed. This study was submitted to the SCCS and is now available. It was evaluated by ECHA and KEMI (ECHA Thor GmbH Art. 95 dossier 2015), and did not lead to changes of the conclusions of the SCCS (SCCS/1512/13).

Therefore, as experimental data on systemic human exposure from formulations containing 2% ZPT are available, SCCS gives preference to the experimental human data for risk characterisation.

### 3.3.5 Repeated dose toxicity

Data related to repeated toxicity were assessed in the previous Opinion (SCCS/1512/13). Only new elements, along with SCCS comments/ conclusions, are included in this section.

**3.3.5.1 Repeated Dose: oral / dermal / inhalation toxicity****Repeated Dose oral toxicity**

In the previous Opinion (SCCS/1512/13) a LOAEL of 0.5mg/kg/d was derived based on paralysis/hind-limb weakness.

Further information on repeated-dose toxicity was made available to the SCCS and was evaluated:

In the 90-day oral toxicity study combined with a neurotoxicity study, doses of 0, 0.2, 1.0 and 2.5 mg/kg bw/d (reduced from 5 mg/kg/days from 17 days) were administered by gavage in 10 male and 10 female Sprague rats. At the highest dose, significantly increased neurotoxic effects were observed (such as limited movement, loss of movement of the hind limbs, increased salivation). According to ECHA (and reported in the CLH report), the L(O)AEL for neurotoxic effects would be somewhere between 2.5 and 5.0 mg/kg bw/day. In this study, the authors considered the doses of 0.2 mg/kg/day as a NOEL, based on irritancy in the non-glandular forestomach epithelium. This effect is considered as not relevant for humans. Other effects were also noted, such as increased salivation and isolated incidents of red/brown staining around the mouth at dose 1.0 mg/kg/days.

More details of the combined study (chronic toxicity/carcinogenicity) have become available. Sodium pyrithione (NaPT) doses of 0, 0.5, 1.5 and 3.50 mg/kg bw/d (reduced from 5 mg/kg/days from 12 weeks) were administered by gavage in 50 male and 50 female CD rats for 104 weeks.

Animals were observed daily. Bodyweight and food consumption were recorded weekly for the first 16 weeks and every 4<sup>th</sup> week thereafter. Ophthalmoscopic examinations were performed on all animals before the study and on all surviving high-dose animals at the end of the study. Clinical laboratory investigations were performed on ten animals during weeks 27, 53, 79 and 103. At necropsy, a wide range of tissues were taken and preserved. Histopathological examinations were performed on the liver, kidneys and lungs from all animals and on selected further tissues for control and high-dose animals.

**Results:**

121 males and 90 females died or were killed in extremis, deaths were considered not related to treatment by the authors. Clinical signs observed were hindlimb muscle atrophy in high-dose animals. Body weight was reduced in high-dose females. Relative lung weights were increased in mid- and high-dose males. Haematology revealed reductions in red blood cell count and haematocrit in high-dose females. Concerning clinical chemistry and urinalysis, there were no toxicologically relevant treatment-related findings.

Non-neoplastic findings observed at the high dose were degeneration of muscle fibres, degeneration of spinal cord and sciatic nerve fibres and peripheral retinal atrophy at the high dose. The effects were also observed to a lesser degree at 1.5 mg/kg bw/d.

The incidence of neoplastic findings was not influenced by substance treatment.

Under the conditions of this study, NaPT was not carcinogenic to rats. Based on the non-neoplastic findings observed, a NOAEL of 0.5 mg/kg bw/d can be derived from this study.

Data on metabolism of ZPT (assessed in the previous Opinion SCCS/1512/13) demonstrated that Zn is cleaved from the molecule after uptake and that the ADME of the metal ion and the pyrithione moiety is different. Studies performed in pigs using NaPT and ZPT pointed to a common metabolic pathway (references B.68, B.69, B.70). Further, both Zn<sup>2+</sup> and Na<sup>+</sup> ions are not considered to be neurotoxic. Thus, it can be assumed that neurotoxic effects observed after ZPT exposures are due to the pyrithione moiety. It can thus be concluded that results from other pyrithione-liberating salts might support the findings obtained with



ZPT. In this respect, chronic studies performed with NaPT can be used as supporting studies.

### SCCS comment

- (1) Individual animal data were presented in this study;
- (2) As there were treatment-related degenerative changes of sciatic nerve and skeletal muscle described in all treatment groups from the carcinogenic part of the study, SCCS considers 0.5 mg /kg bw/d as NOAEL for NaPT.

In addition to repeated toxicity studies evaluated in SCCNFP/0671/03, three further studies were performed. These studies have been made available and evaluated by the SCCS (ECHA ZnPT CAR Doc IIIA A6.3.1/01 Year: 1992, ECHA: ZnPT CAR Doc IIIA A6.4.1/01 Year: 1973, Thor GmbH Art. 95 dossier, 2014). They were also evaluated by ECHA and KEMI and confirmed the NOAEL of 0.5 mg/kg bw/d.

### Dermal:

Several dermal repeated dose studies have been performed with ZPT. Interpretation of the findings is partly hampered by the fact that grooming was not always prevented and that intermittent exposure regimens (causing recovery) have been applied. From a 28-day dermal neurotoxicity study in which grooming was prevented, NOAELs of 25 and 50 mg/kg bw/d were derived in female and male animals, respectively based on reduced electrophysiological parameters and muscle tone. In a two-year dermal chronic study performed with NaPT, a local NOEL of 5 mg/kg bw/d was derived.

### Inhalation:

Three inhalation studies of different durations have been performed, two of them are available for evaluation. In a 21-day nose-only study performed in Sprague-Dawley rats, a LOAEC of 2 mg/m<sup>3</sup> is derived based on histopathological data in tissues of the respiratory tract and non-respiratory tissues. In a 28-day nose-only study performed in Sprague-Dawley rats, no NOAEC could be derived for local effects in the lung and an NOAEC of 1.5 mg/m<sup>3</sup> was derived for systemic effects.

In a 90-day study, animals were whole-body exposed and oral intake cannot be excluded.

In addition to repeated toxicity studies evaluated in SCCNFP/0671/03, further studies have been performed. These studies have been made available and assessed by the SCCS (ECHA ZnPT CAR Doc IIIA A6.4.3/01 YEAR: 1993, ECHA ZnPT CAR Doc IIIA A6.3.3/02 Year: 2009). These studies have also been evaluated by ECHA and KEMI. ECHA mentions a 90-d whole-body study performed in Sprague-Dawley. Fifteen rats/sex/dose were administered zinc pyrithione at doses of 0.5, 2.5 and 10 mg/m<sup>3</sup> for 6 hours daily. According to ECHA, clinical signs of toxicity including laboured breathing, rales (noises when breathing), increased salivation, decreased activity and dry red-brown material around the nose. From this study, a NOAEC of 0.5 mg/m<sup>3</sup> air was derived.

## **3.3.6 Reproductive toxicity**

Data related to reproductive toxicity were assessed in the previous Opinion. Only new elements, SCCS comments and main conclusions are included in this section.

A previous Opinion (SCCNFP 0671/03) made the following conclusions with respect to the reproductive toxicity of ZPT:

- 2.5 mg/kg/d administered orally to rats has a no effect level for teratological effects
- no reproductive effects have been observed when ZPT was applied topically to rats and rabbits at levels up to 15 and 100 mg ZPT/kg/d respectively (highest doses tested) and ingestion of the test material was controlled.



- no reproductive or teratogenic effects have been observed in rabbits and pigs following topical application of shampoo formulations containing 50 and 400 mg ZPT/kg/d respectively.

Since then, further generation studies were performed with ZPT and NaPT, as well as developmental toxicity studies with ZPT. Based on the data available and newly provided data, it can be concluded that ZPT is unlikely to be of concern with respect to fertility.

However, the SCCS acknowledges that adverse effects on development have been identified. These effects were observed at higher dosages than those leading to neurotoxic effects, which were considered by the SCCS as the leading health effects. The new studies did not lead to lower N(L)OAELs compared to SCCS/1512/13.

### 3.3.7 Mutagenicity / Genotoxicity

Data related to mutagenicity/genotoxicity were assessed in the previous Opinion (SCCS/1512/13). Only new elements, along with SCCS comments/ conclusions are included in this section.

From the studies available for SCCNFP/0671/03 and Addendum to the scientific Opinion on Zinc pyrithione (P81) SCCS/1593/18, it was concluded that ZPT is not mutagenic. Since then, further *in vitro* and *in vivo* genotoxicity/mutagenicity studies have been performed. New studies show that ZPT is mutagenic in the mammalian MLA test, negative in the Ames test, and positive results are obtained in a chromosomal aberration test although at cytotoxic concentration. None of the positive results from *in vitro* assays were confirmed *in vivo* in two different mammalian erythrocyte micronucleus tests (one in mice and one in rats).

Additionally, despite some methodological limitations of the study, the SCCS considered the *in vivo* comet assay results in the liver, blood and duodenum cells as negative.

The SCCS is also aware that HSE (2003) and MAK (2012) considered ZPT as non-genotoxic and non-mutagenic. The more recent analysis of genotoxicity presented in ECHA (2017) also came to the conclusion that ZPT does not fulfil classification criteria for germ-cell mutagenicity.

Thus, with respect to genotoxicity/mutagenicity, SCCS concludes that ZPT is not genotoxic/mutagenic *in vivo*.

Mutagenicity/genotoxicity studies evaluated and presented in ECHA (2017).

These studies have been evaluated by ECHA and KEMI (ECHA ZnPT CAR Doc IIIA A6.6.1/01 Year: 2002, ZnPT CAR Doc IIIA A6.6.2/01 Year: 2002, ZnPT CAR Doc IIIA A6.6.3/01 Year: 2002, ZnPT CAR Doc IIIA A6.6.5/01 Year: 1992, ZnPT CAR Doc IIIA A6.6.4/01 Year: 2001, Thor GmbH Art 95 dossier Year: 2014, and did not lead to changes of the conclusions of the SCCS (SCCS/1512/13).

### 3.3.8 Carcinogenicity

From chronic oral and dermal studies available in submission I, SCCNFP 0671/03 concluded: "no evidence of a carcinogenic response was seen when ZPT was applied topically (up to 100 mg/kg/d) or given orally (up to 5 mg/kg/d) in lifetime studies using mice and rats." Since then, further chronic (lifetime) studies performed with ZPT and NaPT (from which read across to ZPT is considered adequate) using the oral and dermal uptake pathway have become available.

From the studies performed by the oral or dermal route with either ZPT or NaPT, there was no evidence for a carcinogenic potential up to dermal doses of 100 mg/kg bw day and up to oral doses of 2.5 mg/kg bw/d ZPT and 3.5 mg/kg bw/d NaPT (based on systemic findings, higher doses of ZPT/NaPT could not be tested in chronic oral studies). The carcinogenicity of ZPT has not been investigated by the inhalation route.

From chronic oral and dermal studies available in submission I, SCCNFP 0671/03 concluded: "no evidence of a carcinogenic response was seen when ZPT was applied topically (up to 100 mg/kg/d) or given orally (up to 5 mg/kg/d) in lifetime studies using mice and rats." Since then, further chronic (lifetime) studies performed with ZPT and NaPT (from which a read across to ZPT is considered adequate) using the oral and dermal uptake pathway have become available.

These studies are available to the SCCS. The SCCS considered ZPT as non-carcinogenic.

### **3.3.9 Photo-induced toxicity**

#### **3.3.9.1 Phototoxicity / photo-irritation and photosensitisation**

No data available

#### **3.3.9.2 Phototoxicity / photomutagenicity / photoclastogenicity**

No data available

### **3.3.10 Human data**

See section on skin sensitisation and section on *in vivo* dermal absorption.

### **3.3.11 Special investigations**

Data related to special investigation including mode of action and ocular toxicity were assessed in the previous Opinion. Only new elements, SCCS comments and main conclusions are included in this section.

Reversible hind-limb paralysis is the most prominent effect observed in rats after repeated oral administration of ZPT. In the first instance, dermal administration was considered not to cause hind-limb paralysis. However, mechanistic studies and further dermal repeat-dose studies have demonstrated that dermal administration of ZPT caused electrophysiological changes and decreases in hind-limb and fore-limb grip strength and muscle tone. An acute inhalation study (described in section 3.4.1.3) demonstrates that neurotoxic (hindlimb) effects are also exerted after uptake by the inhalation route.

The loss of hind-limb function is mediated by peripheral axonopathy. Thus, muscle atrophy is considered as a secondary event due to underlying nerve damage.

Species differences have been observed with respect to loss of hind-limb function, with monkeys being appreciably less sensitive to ZPT-induced loss of hind-limb function.

*In vitro* studies so far contributed to a mechanistic understanding of ZPT-induced neurological effects: Pyrithione stimulates an influx of calcium into both rat and Rhesus

monkey motor neuron preparations. This influx is mediated via pyrithione-stimulated  $\text{Ca}^{2+}$  release-activated  $\text{Ca}^{2+}$  channels. Although quantitative differences in  $\text{Ca}^{2+}$  influx were observed between rat and monkey motor neurons *in vitro*, which might be used to explain differences in sensitivities to the neurotoxic effects of ZPT in rats and monkeys, no conclusions with respect to human sensitivity can be drawn from these studies.

Furthermore, it has to be kept in mind that in the *in vitro* studies, no attempt had been made to relate the *in vitro* pyrithione concentration to *in vivo* blood levels.

Apart from an interaction with  $\text{Ca}^{2+}$  channels, ZPT is also able to activate KCNQ potassium channels.

### 3.4 Safety evaluation (including calculation of the MoS)

#### MoS calculation (cosmetic use only):

The individual exposures and calculated MoS for use at 1% in such products are presented in the Table below. Because 1% ZPT in shampoo and conditioner represents the greatest cosmetic exposure to ZPT in terms of maximum concentration and marketed products, these combined uses will be used in the deterministic aggregate exposure and calculation of MoS.

The previous SCCS Opinion (2014) and the Addendum (SCCS 2018) use oral bioavailability of ZnPT at 88% for MoS calculation. In this assessment, the SCCS has considered that the bioavailability value is almost 100% and therefore uses 100% bioavailability value in MoS calculations. For the sake of clarity, both MoS calculations have been presented in this Opinion.

Using the NOAEL, the individual and total MoS for product use are presented below: the MoS is 2913 for shampoo and 6567 for conditioner products containing 1% ZPT. The individual exposures used to calculate the SED are taken from Table 4 of the SCCS Notes of Guidance (SCCS/1602/18).

Data related to dermal absorption were assessed in the previous Opinion (2014). A 1% dermal absorption in humans is supported by a human clinical study using 2% ZPT shampoo formulations in combination with 0.1% or 0.25% ZPT containing leave-on formulations. In this study, up to 0.22% of the applied dose was excreted via urine. Taking into consideration that further amounts could have been excreted at later time points not considered in the test interval or by faecal excretion and also considering some tissue retention, total absorption is most probably not higher than 1%.

#### For shampoo:

|   |                                     |                    |
|---|-------------------------------------|--------------------|
| <b>Absorption through the skin</b>  | <b>DA<sub>p</sub></b>               | = 1%               |
| <b>Amount of product applied daily</b>  | <b>A</b>                            | = 1.51 mg/kg/d     |
| <b>Concentration of ingredient in product</b>                                   | <b>C</b>                            | = 1%               |
| <b>Systemic exposure dose (SED)</b>   | <b>A x C / 100 x DA<sub>p</sub></b> | = 0.000151 mg/kg/d |
| <b>No adverse observed effect level</b><br>(oral chronic/carcinogenicity study) | <b>NOAEL</b>                        | = 0.5 mg/kg/d      |
| <b>Bioavailability 100%</b>   |                                     | = 0.5 mg/kg/d      |
| <b>Bioavailability 88%</b> (based on SCCS 2014)                                 |                                     | = 0.44 mg/kg/d     |

|  |                  |               |
|--|------------------|---------------|
| <b>Margin of Safety</b><br><b>(Bioavailability 100%)</b> | <b>NOAEL/SED</b> | <b>= 3312</b> |
|--|------------------|---------------|

|   |                  |               |
|---|------------------|---------------|
| <b>Margin of Safety<br/>(Bioavailability 88%)</b> | <b>NOAEL/SED</b> | <b>= 2913</b> |
|---|------------------|---------------|

**For conditioner:**

|   |                                     |                    |
|---|-------------------------------------|--------------------|
| <b>Absorption through the skin</b>            | <b>DA<sub>p</sub></b>               | = 1%               |
| <b>Amount of product applied daily</b>        | <b>A</b>                            | = 0.67 mg/kg/d     |
| <b>Concentration of ingredient in product</b> | <b>C</b>                            | = 1%               |
| <b>Systemic exposure dose (SED)</b>           | <b>A x C / 100 x DA<sub>p</sub></b> | = 0.000067 mg/kg/d |
| <b>No adverse observed effect level</b>       | <b>NOAEL</b>                        | = 0.5 mg/kg/d      |

(oral chronic/carcinogenicity study)

**Bioavailability 100%** = 0.5 mg/kg/d**Bioavailability 88%** (based on SCCS 2014) = 0.44 mg/kg/d

|  |                  |               |
|--|------------------|---------------|
| <b>Margin of Safety<br/>(Bioavailability 100%)</b> | <b>NOAEL/SED</b> | <b>= 7462</b> |
|--|------------------|---------------|

|   |                  |               |
|---|------------------|---------------|
| <b>Margin of Safety<br/>(Bioavailability 88%)</b> | <b>NOAEL/SED</b> | <b>= 6567</b> |
|---|------------------|---------------|

**For shampoo and conditioner:**

|   |                                     |                    |
|---|-------------------------------------|--------------------|
| <b>Absorption through the skin</b>            | <b>DA<sub>p</sub></b>               | = 1%               |
| <b>Amount of product applied daily</b>        | <b>A</b>                            | = 2.17 mg/kg/d     |
| <b>Concentration of ingredient in product</b> | <b>C</b>                            | = 1%               |
| <b>Systemic exposure dose (SED)</b>           | <b>A x C / 100 x DA<sub>p</sub></b> | = 0.000217 mg/kg/d |
| <b>No adverse observed effect level</b>       | <b>NOAEL</b>                        | = 0.5 mg/kg/d      |

(oral chronic/carcinogenicity study)

**Bioavailability 100%** = 0.5 mg/kg/d**Bioavailability 88%** (based on SCCS 2014) = 0.44 mg/kg/d

|  |                  |               |
|--|------------------|---------------|
| <b>Margin of Safety<br/>(Bioavailability 100%)</b> | <b>NOAEL/SED</b> | <b>= 2304</b> |
|--|------------------|---------------|

|   |                  |               |
|---|------------------|---------------|
| <b>Margin of Safety<br/>(Bioavailability 88%)</b> | <b>NOAEL/SED</b> | <b>= 2027</b> |
|---|------------------|---------------|

**Conclusion on MoS calculation for cosmetic use only**

Based on all above considerations, the substance is considered safe under cosmetic use conditions.

**Aggregate exposure and MoS calculation (cosmetic use and non-cosmetic product):**

Aggregate exposure to cosmetic and non-cosmetic (biocidal) products containing ZPT have been estimated and used to determine the Systemic Exposure Dose or SED in calculating the Margin of Safety (MoS). The Point of Departure (PoD) derived for cosmetic uses of ZPT, i.e., 0.440 mg/kg bw/d (based on 88% bioavailability as the worst case), has been applied to all products and scenarios.

As there are no detailed data available to accurately determine patterns of use of cosmetics in combination with worker and/or consumer exposures to biocidal products containing ZPT, for purposes of this dossier, a low tier, "Tier 0", worst-case approach has been used. A deterministic approach was employed to determine the discrete exposure to rinse-off hair products, i.e., shampoo, conditioner, using values from SCCS Notes of Guidance (SCCS/1602/18) to estimate SED.

In spite of this evolving regulatory state of ZPT, this material is found in a wide variety of diverse non-cosmetic applications. Currently, biocidal dossiers are under review, as according to EU 2017/698, for the following Product Types (PT):

- Product Type (PT)2 – Disinfectants and algaecides not intended for direct application to humans or animals
- Product Type (PT)6 – Preservatives for products during storage
- Product Type (PT)7 – Film preservatives
- Product Type (PT)9 – Fibre, leather, rubber and polymerised materials preservatives
- Product Type (PT)10 – Construction material preservatives
- Product Type (PT)21 – Antifouling products

Over the range of biocidal applications for ZPT, the likely concentrations at which the active substance is used ranges from 0.02 to 0.25% in articles, e.g. hygienic surface layers (PT 2, PT 7, PT 9, PT 10), up to 0.5% in aqueous dispersions, e.g. interior paints (PT 6, PT 7), etc., and up to 5% in antifouling paints (PT 21).

Using the PoD, both the current non-cosmetic exposures and aggregate exposures with cosmetics have a MoS higher than 100 (see Table 1 below).

Table 1: Margin of Safety Calculations for Non-cosmetic (worst cases) + Cosmetic (Shampoo + Conditioner) or Aggregate Exposure Dose (AED)

| PT    | Prof/ Non-prof | Product exposed to                       | Conc of ZPT considered          | Exposed individual | Total Systemic Exposure Dose <b>Non-cosmetic</b> (mg/kg bw/d) | MoS <b>(NOAEL/SED)N</b> on-cosmetic | Aggregate Exposure Dose (AED) - Non-cosmetic + cosmetic + Cosmetic 0,000217 mg/kg bw/d cosmetic) | MoS <b>(NOAEL/SED) Non-cosmetic + Cosmetic</b> |
|-------|----------------|--|---------------------------------|--------------------|---|-------------------------------------|--|--|
| PT2   | Prof           | Product containing ZPT                   | 52,78% (high level concentrate) | Manufacturer       | 0.0002755   | <b>1597</b>                         | 0.0004925  | <b>893</b>                                     |
| PT 6  | Prof           | Paints and coatings, Glues and Adhesives | 0,5% (maximum level)            | Manufacturer       | 0.0003931   | <b>1119</b>                         | 0.0006101  | <b>721</b>                                     |
| PT 7  | Prof           | Paints and coatings, Glues and Adhesives | 0,5% (maximum level)            | Manufacturer       | 0.0003931   | <b>1119</b>                         | 0.0006101  | <b>721</b>                                     |
| PT 9  | Prof           | Product containing ZPT                   | 48% concentrate                 | Manufacturer       | 0.0005327   | <b>826</b>                          | 0.0007497  | <b>587</b>                                     |
| PT 10 | Prof           | Plaster and stucco                       | 0,5% (maximum level)            | Manufacturer       | 0.0003931   | <b>1119</b>                         | 0.0006101  | <b>721</b>                                     |
| PT 21 | Non-prof       | AF paint                                 | 5% (high level)                 | Painter            | 0.003899  | <b>113</b>                          | 0.004116   | <b>107</b>                                     |
| PT 21 | Prof           | AF paint                                 | 5% (high level)                 | Sprayer            | 0.001692  | <b>260</b>                          | 0.001909   | <b>230</b>                                     |
| PT 21 | Non-prof       | AF paint                                 | 5% (high level)                 | Hobbyist           | 0.004132  | <b>106</b>                          | 0.004349   | <b>101</b>                                     |

**SCCS comments**

The SCCS is of the opinion that adding ZPT exposure from cosmetic use to non-cosmetic use will have little impact on the total MoS. ZPT is safe even when worst-case scenario deterministic aggregate exposures are considered.

### 3.5 Discussion

#### ***Physicochemical properties***

Different values for some physicochemical properties are available from different sources. Impurities data are missing and should be provided according to the SCCS Notes of Guidance (SCCS/1602/18).

#### ***Toxicological Evaluation***

There are additional studies, which were submitted under REACH evaluation, but were not available to the SCCS (submission I). These studies were available for the current assessment by the SCCS. These studies have also been evaluated by ECHA and KEMI and did not lead to changes of the conclusions of the SCCS (SCCS/1512/13). Therefore, considering these studies does not result in a lower (or different) point of departure for risk assessment compared to that derived in the previous Opinion (SCCS/1512/13).

#### ***Acute oral toxicity***

LD<sub>50</sub> values for zinc pyrithione have been determined in various species after oral administration. The values in the rat ranged from 92 to 266 mg/kg and in the mouse from 160 to 1000 mg/kg. Six hundred mg/kg was found to be the LD<sub>50</sub> when administered orally to dogs.

#### ***Acute dermal toxicity***

In addition to acute dermal toxicity studies evaluated in SCCNFP/0671/0 that led to the conclusion that the acute dermal toxicity of zinc pyrithione appears to be higher than 2000 mg/kg. These studies have been evaluated by ECHA and KEMI and did not lead to change the conclusions of the SCCS (SCCS/1512/13).

#### ***Acute inhalation toxicity***

Acute inhalation studies have been performed with ZPT. According to one of the studies, classification as Acute Tox 2; H330 (fatal if inhaled) according to CLP as suggested by the registrant(s) under REACH is justified.

#### ***Irritation and corrosivity***

From product-based data evaluated in SCCNFP/0671/03, from the description of skin irritation studies performed with ZPT and from human HRIPT tests, it can be inferred that ZPT is – at least – a mild skin irritant.

HSE concludes that ZPT is a severe eye irritant, whereas MAK (2012) states that ZPT is corrosive to the eye. SCCS notes that classification as Eye Damage 1; H318 (causes serious eye damage) according to CLP is suggested by the registrant(s) under REACH.

#### ***Skin sensitisation***

ZPT was tested in guinea pig studies and the LLNA and based on these studies, it was considered not to be a skin sensitiser. Concerning human data, ZPT (or the PT moiety part) has a low potential to induce contact hypersensitivity when tested per se or as part of a cosmetic formulation. However, in some human HRIPT studies, evaluation was partly hindered by the erythematous reactions observed.

#### ***Toxicokinetics-Dermal absorption***

Dermal absorption was assessed in two clinical studies in humans. Based on these studies, the SCCS has assumed 1% dermal absorption in humans.

The previous SCCS Opinion (2014) and the Addendum (SCCS (2018) use oral bioavailability of ZnPT at 88% for MoS calculation.

**Repeated dose toxicity**

Several oral repeated dose toxicity studies of different durations have been performed with ZPT. In a combined chronic toxicity/carcinogenicity study, the dose of 0.5mg/kg bw/d is considered as NOAEL by the SCCS. The Point of Departure (PoD) derived for cosmetic uses of ZPT, i.e., 0.440 mg/kg bw/d (based on 88% bioavailability as the worst case), has been applied to all products and scenarios.

Several dermal repeated dose toxicity studies have been performed with ZPT. Interpretation of the findings is partly hampered by the fact that grooming was not always prevented and that intermittent exposure regimens (causing recovery) have been applied.

**Reproductive toxicity**

The SCCS is aware that HSE (2003) did not identify any potential concern to humans regarding adverse effects on fertility. Furthermore, both MAK (2012) and HSE (2003) concluded that adverse effects on development were most likely attributable to maternal toxicity.

**Mutagenicity / genotoxicity**

From the studies available for SCCNFP/0671/03, it was concluded that ZPT is not mutagenic. Since then, further *in vitro* and *in vivo* genotoxicity/mutagenicity studies have been performed. *In vitro* studies are incomplete and in case of *Hprt*, gene mutation results are positive with signs of potential mutagenicity that deserve further investigation. *In vivo* micronucleus tests only identify mutagenic compounds with chromosomal aberration/clastogenic or aneugenic effect and do not detect gene-mutation inducing compounds.

The SCCS considers ZPT as non-genotoxic and non-mutagenic *in vivo*.

**Carcinogenicity**

From the studies performed by the oral or dermal route with either ZPT or NaPT, there was no evidence for a carcinogenic potential up to dermal doses of 100 mg/kg bw day and up to oral doses of 2.5 mg/kg bw/d ZPT and 3.5 mg/kg bw/d NaPT (based on systemic findings: higher doses of ZPT/NaPT could not be tested in chronic oral studies).

Carcinogenicity of ZPT has not been investigated by the inhalation route.



#### 4. CONCLUSION

*1. In view of the conditions laid out in Article 15(d) of the Regulation (EC) No 1223/2009 and taking into account the scientific data provided, does the SCCS consider Zinc Pyrithione safe when used as an anti-dandruff in rinse-off hair products up to a maximum concentration of 1%?*

In line with the conditions laid out in Article 15(d) (i.e. 'overall exposure from other sources') of the Regulation (EC) No 1223/2009 and taking into account the scientific data provided, the SCCS considers Zinc Pyrithione (ZPT) as safe when used as an anti-dandruff in rinse-off hair products up to a maximum concentration of 1%.

*2. Does the SCCS have any further scientific concerns with regard to the use of Zinc Pyrithione in cosmetic products?*

/

#### 5. MINORITY OPINION

/

## 6. REFERENCES

References from the Submission I and Addendum are included in:

SCCS (2014). Scientific Committee on Consumer Safety SCCS OPINION on Zinc pyrithione COLIPA n P81. European Commission. SCCS/1512/13 Revision of 18 June 2014 [https://ec.europa.eu/health/scientific\\_committees\\_en](https://ec.europa.eu/health/scientific_committees_en)

SCCS (2018) Addendum to the scientific opinion on Zinc pyrithione (P81) ref. SCCS/1512/13. SCCS/1593/2018 Final Opinion, adopted 21-22 February 2018.

References included in the Submission III

ECHA (2017): Proposal for a Harmonised Classification and Labelling Based on Regulation (EC) No 1272/2008 (CLP Regulation), Annex VI, Part 2 International Chemical Identification: pyrithione zinc; (T-4)-bis[1-(hydroxy-.kappa.O)pyridine-2(1H)-thionato-.kappa.S]zinc (Dossier submitter: Swedish Chemicals Agency). Available at: <https://echa.europa.eu/documents/10162/4183133f-3ef2-ceaa-dadb-4e7789aeb7c4>

During the preparation of this Opinion (submission III), additional information became available for the SCCS. These reports have been referenced by ECHA under the numbers:

ECHA ZnPT CAR Doc IIIA A6.1.1/01 Year: 1986

ECHA ZnPT CAR Doc IIIA A6.1.1/02 Year: 1997

ECHA Thor GmbH Art. 95 dossier, 2014 (including 12 studies)

ECHA ZnPT CAR Doc IIIA A6.1.2/01 Year: 1997

ECHA ZnPT CAR Doc IIIA A6.1.4/01 Year: 2001

ECHA Thor GmbH Art. 95 dossier, 2013

ECHA ZnPT dossier Doc IIIA A6.1.4/02 Year: 2001

ECHA ZnPT CAR Doc IIIA A6.1.5/01 Year: 2002

ECHA ZnPT CAR Doc IIIA A6.2/03 Year: 2005

ECHA Thor GmbH Art. 95 dossier, 2015

ECHA ZnPT CAR Doc IIIA A6.3.1/01 Year: 1992

ECHA ZnPT CAR Doc IIIA A6.4.1/01 Year: 1973

ECHA ZnPT CAR Doc IIIA A6.4.3/01 Year: 1993

ECHA ZnPT CAR Doc IIIA A6.3.3/02 Year: 2009

ECHA ZnPT CAR Doc IIIA A6.6.1/01 Year: 2002

ECHA ZnPT CAR Doc IIIA A6.6.2/01 Year: 2002

ECHA ZnPT CAR Doc IIIA A6.6.3/01 Year: 2002

ECHA ZnPT CAR Doc IIIA A6.6.5/01 Year: 1992

ECHA ZnPT CAR Doc IIIA A6.6.4/01 Year: 2001

SCCS/1602/18, 10th Revision of the SCCS Notes of Guidance for the Testing of Cosmetic Ingredients and their Safety Evaluation.

## 7. GLOSSARY OF TERMS

See SCCS/1602/18, 10th Revision of the SCCS Notes of Guidance for the Testing of Cosmetic Ingredients and their Safety Evaluation – from page 141

### Abbreviations in Addendum SCCS/1593/2018

|          |  |
|----------|--|
| CLH:     | Harmonized Classification and Labelling                |
| GD:      | Gestation Day  |
| HSE:     | Health and Safety Executive                            |
| HRIPT:   | Human Repeat Insult Patch Testing                      |
| KEMI:    | Swedish Chemicals Agency                               |
| MAK:     | Maximale Arbeitsplatzkonzentration                     |
| STOT RE: | Specific Target Organ Toxicity after Repeated Exposure |
| ZPT:     | Zinc Pyrithione (as used in this dossier)              |
| ZnPT:    | Zinc Pyrithione (as used in the reports from industry) |

## 8. LIST OF ABBREVIATIONS

See SCCS/1602/18, 10th Revision of the SCCS Notes of Guidance for the Testing of Cosmetic Ingredients and their Safety Evaluation – from page 141