Scientific Committee on Consumer Safety

SCCS

ADDENDUM

to the scientific opinion on

Zinc pyrithione (P81)
ref. SCCS/1512/13

The SCCS adopted this document
at its plenary meeting on 21-22 February 2018

ACKNOWLEDGMENTS

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In agreement with the mandating DG, there is no commenting period for this Addendum.

All Declarations of Working Group members are available on the following webpage:
http://ec.europa.eu/health/scientific_committees/experts/declarations/sccs_en.htm

1. ABSTRACT

The SCCS concludes the following:

1. *In light of the new evidence available, does the SCCS still consider that zinc pyrithione, when used in a concentration up to 2.0% as an anti-dandruff agent in rinse-off hair care products, is safe for the consumer as concluded in SCCS/1512/13?*

The newly provided studies on fertility and developmental toxicity did not lead to changes of point of departure for risk assessment compared to SCCS/1512/13. Further additional studies mentioned in the Swedish CLH proposal confirm neurotoxicity as a sensitive endpoint of ZPT toxicity. In view of the additional studies SCCS confirms the LOAEL of 0.5 mg/kg bw/d that was derived in SCCS/1512/13 as a conservative value for risk assessment of ZPT.
Therefore ZPT is considered safe when used at a concentration up to 2.0% as an anti-dandruff agent in rinse-off hair care products.

2. *Does the SCCS have any further scientific concerns regarding the use of zinc pyrithione in cosmetic products?*

The conclusion from SCCS/1512/13 was specifically targeted to risk assessment for the particular use of ZPT in a concentration up to 2.0% as an anti-dandruff agent in rinse-off hair care products. Aggregate exposure from non-cosmetic sources has not been considered.
In view of apparent further (non-cosmetic) uses and in view of the fact that classification as Repr 1B is currently proposed, the SCCS recommends risk assessment taking into consideration all possible sources of exposure in line with Art 15 of Cosmetics Regulation (EU 1223/2009).
Not all relevant toxicological studies performed with ZPT have been made available to the SCCS (see section 3.1. Introduction of SCCS/1512/13).

Keywords: SCCS, scientific opinion, addendum, preservative, P81, Zinc pyrithione, Regulation 1223/2009, CAS 13463-41-7

Opinion to be cited as: SCCS (Scientific Committee on Consumer Safety), addendum to the Opinion on preservative Zinc pyrithione (P81) ref. SCCS/1512/13, 21-22 February 2018, SCCS/1593/18

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SCCS

The Committee shall provide Opinions on questions concerning all types of 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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ISSN ISBN

Doi: ND-

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2. MANDATE FROM THE EUROPEAN COMMISSION

Background

The cosmetic ingredient Zinc Pyrithione (ZPT) (CAS 13463-41-7; EU 236-671-3) with the chemical name: Bis[(2-pyridyl-1-oxo)-thio]zinc was introduced into the Cosmetics Directive as a preservative by Directive 82/368/EEC. It was authorised as a preservative at the maximum concentration of 0.5% with the limitation "Authorized in products rinsed off after use, forbidden in products for oral hygiene".

ZPT 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).
In particular, in the opinion of 2002, experts assessed ZPT safe for the consumer as antidandruff agent in rinse-off hair care products at a maximum concentration of 1.0% and later in 2014 safe at 2.0%.

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 V/8).
Furthermore, ZPT is also allowed in a concentration up to 0.1% in leave-on hair products (Annex III/101).

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

As new studies are available and used in the CLH report for ZPT, the Swedish Medical Products Agency have asked for a re-assessment of the safety of ZPT as an anti-dandruff agent in rinse-off hair care products at a maximum concentration of 2.0%.

Terms of reference

1. *In light of the new evidence available, does the SCCS still consider that zinc pyrithione, when used in a concentration up to 2.0% as an anti-dandruff agent in rinse-off hair care products, is safe for the consumer as concluded in SCCS/1512/13?*

2. *If not, does the SCCS consider that zinc pyrithione, when used in a concentration up to 1.0% as an anti-dandruff agent in rinse-off hair care products, is safe for the consumer as is the current situation?*

3. *Does the SCCS have any further scientific concerns regarding the use of zinc pyrithione in cosmetic products?*

3. OPINION

The SCCS received the following documents to re-assess the safety of zinc pyrithione based on new data that has become available:

A proposal of Swedish authorities for 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 document is also called Swedish CLH proposal in this document.

In addition, the SCCS received 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 have been performed after the deadline of 11 March 2013 to conduct animal *in vivo* studies for the purpose of Cosmetics Directive (EC 1223/2009). However, as the studies have been performed in the context of the biocides regulatory framework, the studies can be used for assessment for the purpose of Cosmetics Directive.

The SCCS notes that the Swedish CLH proposal concerns **hazard** identification, specifically the hazard developmental toxicity.

The Swedish CLH proposal and the industry documents indicated that further studies have been used in the evaluation from Sweden (see from page 20 onwards of the Swedish CLH proposal). These studies have not been considered in the previous SCCS Opinion and have not been made available to the SCCS for this submission.
As the expected SCCS Opinion is a **risk** assessment and not a **hazard** assessment like the CLH proposal, the additional studies mentioned in the CLH dossier (but not specifically targeted to reproductive or developmental toxicity) must also be taken into consideration when performing a **risk** assessment (i.e. to see whether additional information would lead to a lower NOAEL than that identified in SCCS/1512/13).
As not all reports mentioned in the Swedish CLH proposal were made available to the SCCS, conclusions from SCCS/1215/13 were updated for those endpoints where additional information is available, according to the Swedish CLH dossier.

3.1 CHEMICAL AND PHYSICAL SPECIFICATIONS

The values of some physico-chemical properties varied, depending on the information source.

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 V/8). Furthermore zinc pyrithione is also allowed in a concentration up to 0.1% in leave-on hair products (Annex III/101).

According to the EC Commission Regulation (No. 1451/2007), Zink pyrithione is also used as a biocide in biocidal product categories 2, 6, 7, 9, 10, 11, 12 and 22 of Annex V of the EU

Biocide Directive (Directive 98/8/EC).

3.3 TOXICOLOGICAL EVALUATION

3.3.1 Acute toxicity

In addition to acute oral toxicity studies evaluated in SCCNFP/0671/03, further studies have been performed, amongst them an acute oral neurotoxicity study performed according to OECD TG 424 and GLP where possible neurotoxic effects were considered to be transient and of low magnitude. The data was not made available to the SCCS. The SCCS notes, however, that classification as Acute Tox 3; H301 (toxic if swallowed) is suggested, according to CLP-Regulation (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 (ECHA, 2017).
The acute dermal toxicity of ZPT appears to be higher than 2000 mg/kg. Local and systemic effects are observed upon acute inhalation exposure. The SCCS notes that classification as Acute Tox 3; H331 (toxic if inhaled) according to CLP-Regulation (ECHA, 2017) is currently suggested.

3.3.2 Irritation and corrosivity

3.3.2.1 Skin irritation

Skin irritation studies performed with ZPT were not made available to the SCCS. However, 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. Eye irritation tests performed with ZPT were not made available to the SCCS. 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).

3.3.3 Skin sensitisation

ZPT is not sensitising in animal studies. 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

A 1% dermal absorption is taken for risk assessment as a conservative value as this 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%.

A systemic exposure load of 5.25 µg/kg/d 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) has been derived, 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

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3.3.5 Repeated dose toxicity

A NOAEL of 500 µg/kg/d obtained from a chronic oral study (Larson, 1958) performed with ZPT based on paralysis/hind-limb weakness has been derived in SCCNFP 0671/03.
The SCCS is aware that HSE (2003) considered the Larson 1958 study as inadequate due to insufficiently large group sizes to ensure statistical power. However, a 90-day oral study performed with sodium pyrithione (not available to the SCCS) which was considered adequate by HSE, also lead to a NOAEL of 500 µg/kg/d, supporting the outcome of the Larsson study.
Two oral chronic studies performed with NaPT have been provided by the applicant. In a combined chronic toxicity/carcinogenicity study the dose of 500 µg/kg bw/d was considered as LOAEL by the SCCS.
One study (assigned a reliability of 3) mentioned in ECHA (2017) points to NOAELs of 0.35 and 0.39 mg/kg bw/d in males and females and another study mentioned in ECHA (2017) pointed to an LOAEL for neurotoxic effects between 2.5 and 5 mg/kg/d. In a 90-day oral toxicity study on rats, combined with a neurotoxicity study performed according to OECD TG 408 and 424 and in compliance with GLP using doses of 0, 0.2, 0.5 and 2.5 mg/kg bw/d (the study was not made available to the SCCS, a NOAEL of 0.5 mg/kg bw was derived based on clinical signs, body weight reduction and neurotoxic findings at the highest dose.
These additional studies, which were not made available to the SCCS, also identify neurotoxicity as a sensitive endpoint of ZPT toxicity. In view of the additional studies, the SCCS confirms the LOAEL of 0.5 mg/kg bw/d that was derived in SCCS/1512/13 as a conservative value for the risk assessment of ZPT.

3.3.6 Reproductive toxicity

3.3.6.1 Fertility and reproduction toxicity

Two-Generation Reproductive Toxicity Study in Rats

Guideline:	OECD TG 416, EU B.35, OPPTS 870.3800
Species/strain:	Rat, Han Wistar
Group size:	24 animals/sex/dose
Test substance:	Zinc pyrithione
Batch No.:	not given (blacked-out in the report)
Purity:	97.55%
Dose level:	0, 0.2, 0.5 and 2.5 mg/kg bw/d
Route:	oral (gavage)
Vehicle:	1% aqueous carboxymethyl cellulose
Dosing schedule:	once daily, 7 days per week
(parental (F0) animals):	70 days prior to mating, 15 days during mating and in females continued until lactation day 21 – 23
(F1 animals):	after weaning, similar to parental animals
GLP:	Yes
Study Period:	10 January 2014 – 1 October 2014
Report Date:	31.8.2015

Dose levels were selected based on a 14-day range-finding study. Parental (F0) animals were gavaged for a minimum of 70 days prior to mating, during mating and then until scheduled necropsy (except for females during littering). F1 animals were gavaged accordingly after weaning. F1 and F2 animals were in addition exposed indirectly in utero and during weaning and lactation. Animals were observed for mortality, clinical signs, body weights, food consumption and water consumption throughout the study. At necropsy, a variety of parameters according to the guideline were determined, focussing on reproductive parameters.

Results:
Stability of test item formulation for 6 hours at room temperature in concentrations between 0.1 and 1.25 mg/ml was confirmed during a 14-day range-finding study.
At the highest doses tested, the following treatment-related observations were made in female parental animals:
- reduced femoral muscle size in one of the 2 females euthanised due to total litter loss
- hunched posture, piloerection and lean appearance in some animals
- statistically significantly lower body weights and body weight gains compared to controls during days 22 – 64 of the premating period
- reduced size of skeletal muscle in 3 animals
- atrophy of femoral muscle in 7 of 10 animals (2 minimal, 2 slight, 3 moderate)
- fat replacement in 6 of 10 animals (4 minimal, 2 slight)
- minimal axonal degeneration in 4 of 10 animals

One of 10 high-dose females of the F1 generation exhibited slight atrophy of the skeletal muscle. There were no treatment-related effects on pup-development of filial generations. There were no treatment-related adverse effects on reproductive or developmental parameters in any generation or any dose level tested.

From the results of this study, a NOAEL of 0.5 mg/kg bw/d can be derived.

Ref.: Thor, 2015a

SCCS comment
This study has been performed after the deadline of 11 March 2013 to conduct animal in vivo studies for the purpose of Cosmetics Directive (EC 1223/2009). However, as the study has been performed in the context of the biocides regulatory framework, the study can be used for assessment for the purpose of Cosmetics Directive.
This study confirms neurotoxic properties of Zinc pyrithione as already expressed in SCCS/1512/13. A NOAEL of 0.5 mg/kg bw/d was derived from that study. Thus, the study does not result in a lower point of departure for risk assessment compared to that derived in SCCS/1512/13 (the SCCS based MoS calculation on a LOAEL of 0.5 mg/kg bw/d for neurotoxic effects as the point of departure for risk assessment, which was adjusted to a NOAEL of 0.167 mg/kg bw/d by application of an assessment factor of 3).

3.3.6.2 Developmental Toxicity

Developmental Toxicity study in rabbits

Guideline:	OECD TG 414, EU B31, OPPTS 870.3700
Species/strain:	Rabbit, White New Zealand
Group size:	22 pregnant females per dose level
Test substance:	Zinc pyrithione
Batch No.:	not given (blacked-out in the report)
Purity:	97.55 %
Dose level:	0; 0.5; 1.5 and 4.0 mg/kg bw/d
Route:	oral (gavage)
Vehicle:	1 % aqueous carboxymethyl cellulose
Dosing schedule:	once daily from day 7 to day 28 post coitum (p.c.)
Dose volume:	1 ml/kg
GLP:	yes
Study Period:	2013
Report Date:	2015

The doses selected were based on a preceding range-finding study. Formulations of the test item were analysed for homogeneity, accuracy of preparation and stability in vehicle at room temperature. Mated female animals were allocated to 4 dose groups (0; 0.5; 1.5 and 4.0 mg/kg bw/d) and received daily oral gavages of the test item in vehicle from day 7 to day 28 post coitum. Animals were observed for mortality, clinical signs, body weights, food consumption and water consumption throughout the study. At the end of the study period, animals were killed and subjected to external, thoracic and abdominal examination. Ovaries, uteri and placentas were examined, numbers of foetuses, early and late resorptions, implantations and corpora lutea were recorded and foetuses were examined for weight, malformations and developmental variations.

Results:
Formulations of target concentrations of 0.5 and 4.0 mg/g were reported to be stable when stored for 4 hr at room temperature. One female at the highest dose aborted on day 20 p.c. and one female of the mid dose aborted just before necropsy. Red/orange discoloured urine containing blood was observed in animals which also had early resorptions (1 control for 1 day, one animal at 1.5 mg/kg/d for 2 days and 10 animals from 4.0 mg/kg/d for 10 days).

In maternal animals, body weight (-8 to -9% during GD 20-29), body weight gain (-55 to –100% during GD 13-29) and food consumption were statistically significantly reduced at the highest dose tested.
At 4 mg/kg/d only 9 litters with viable foetuses remained, as 10 females had only early resorptions, 2 animals were not pregnant and one animal aborted on day 20 p.c. The mean of viable foetuses was statistically significantly decreased (33% compared to 92% in controls), post-implantation loss was statistically significantly increased (67% compared to 8% in controls). At 1.5 mg/kg/d the mean of viable foetuses was statistically significantly decreased (77% compared to 92% in controls) and there was a statistically significant increase in post-implantation loss (23% compared to 8% in controls).

Findings in foetuses:
Omphaloceles were observed in two foetuses at 1.5 and 4.0 mg/kg/, respectively. Of these animals, one of the mid- and one of the high-dose group also had an absent tail. In addition to omphalocele and absent tail, one foetus of the high-dose group also had absent right kidney and urether, dilated urether and absent urine bladder. Skeletal examination revealed several malformations at the highest dose tested (fused sternebrae, rib anomaly, vertebral anomaly, fused skull bones, costal cartilage anomaly and bent limb bones). Skeletal variations included branched sternebrae and vertebral supernumerary sites.
From the results of this study, a NOAEL of 0.5 mg/kg /d can be derived for maternal and developmental effects.

Ref.: Thor (2015b)

SCCS comment
This study has been performed after the deadline of 11 March 2013 to conduct animal *in vivo* studies for the purpose of Cosmetics Directive (EC 1223/2009). However, as the study has been performed in the context of the biocides regulatory framework, the study can be used for assessment for the purpose of Cosmetics Directive.
The study demonstrates adverse effects of zinc pyrithione on development in rabbits. A NOAEL of 0.5 mg/kg bw/d was derived for maternal and developmental effects, also considering the study amendment. Thus, the study does not result in a lower point of departure for risk assessment compared to that derived in SCCS/1512/13 (the SCCS based MoS calculation on a LOAEL of 0.5 mg/kg bw/d for neurotoxic effects as point of departure for risk assessment, which was adjusted to a NOAEL of 0.167 mg/kg bw/d by application of an assessment factor of 3).

Developmental Toxicity study in rats

Guideline:	OECD TG 414, EU B31, OPPTS 870.3700
Species/strain:	Rat, Wistar Han
Group size:	22 pregnant females per dose level
Test substance:	Zinc pyrithione
Batch No.:	not given (blacked-out in the report)
Purity:	97.55 %
Dose level:	0, 5, 15 and 25 ppm in diet, corresponding to 0; 0.4, 1.18 and 1.68 mg/kg bw/d
Route:	oral (diet)
Vehicle:	standard powder rodent diet
Dosing schedule:	from day 6 – day 20 p.c.
GLP:	yes
Study Period:	August – September 2013
Report Date:	17 Feb 2015

22 mated female animals were assigned to 4 different dose groups receiving the test substance admixed to diet at 0, 5, 15 and 25 ppm from days 6 to 20 p.c. Animals were observed for mortality, clinical signs, body weights, food consumption and water consumption throughout the study. At the end of the study period, animals were killed and subjected to external, thoracic and abdominal examination. Ovaries, uteri and placentas were examined, numbers of foetuses, early and late resorptions, implantations and corpora lutea were recorded and foetuses were examined for weight, malformations and developmental variations.

Results:
Based on stability of substance in diet, there was one occasion where admixed diet stored at room temperature was used over 4 days although it was stated that admixed diets were not stable for 4 days. All animals survived until scheduled necropsy and there were no indications of abortion or premature birth. In the high dose group, absolute body weights and body weight gains were statistically significantly decreased compared to controls from day 15 – 20 p.c. Body weight gains corrected for uterine weights were also statistically significantly lower. Absolute and relative food consumption was statistically significantly lower compared to controls from days 14 – 20 p.c. Abnormal gait after about 10 days of treatment, piloerection and pale faeces were also observed at the highest dose level.
There were no treatment-related macroscopic findings and no treatment-related effects on maternal pregnancy parameters up to the highest dose tested.
Weights of male and female foetuses were statistically significantly lower compared to controls. There were no other treatment-related developmental findings.
From the results of this study, a NOAEL of 15 ppm in diet (corresponding to 1.18 mg/kg bw/d) can be derived for maternal and developmental effects.

Ref.: Thor 2015c

SCCS comment
This study has been performed after the deadline of 11 March 2013 to conduct animal *in vivo* studies for the purpose of Cosmetics Directive (EC 1223/2009). However, as the study has been performed in the context of the biocides regulatory framework, the study can be used for assessment for the purpose of Cosmetics Directive.
The study demonstrates adverse effects of zinc pyrithione on development in rabbits. A NOAEL of 1.18 mg/kg bw/d was derived for maternal and developmental effects. Thus, the study does not result in a lower point of departure for risk assessment compared to SCCS/1512/13 (the SCCS based MoS calculation on a LOAEL of 0.5 mg/kg bw/d for neurotoxic effects as point of departure for risk assessment, which was adjusted to a NOAEL of 0.167 mg/kg bw/d by application of an assessment factor of 3)

SCCS conclusion on reproductive toxicity
In SCCNFP 0671/03, the following conclusions were drawn with respect to 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 have been performed with ZPT and NaPT as well as developmental toxicity studies with ZPT. Based on the data available and newly provided 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

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, not all of them which were made available to the SCCS. In vitro studies are incomplete and in case of *hprt* gene mutation, results are inconclusive with signs of potential mutagenicity that warrant further investigation. In vivo micronucleus test only discriminates mutagenic compounds with chromosomal aberration/clastogenic or aneugenic effect and does not detect gene mutation-inducing compounds.
Therefore, no firm conclusion with respect to genotoxicity/mutagenicity can be drawn by the SCCS. The SCCS, however, is 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.

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 sodium pyrithione (from which a read across to ZPT is considered adequate) using the oral and dermal uptake pathway have become available.
These studies were not made available to the SCCS. Therefore, no firm conclusion with respect to oral and dermal carcinogenicity of ZPT can be drawn by the SCCS. The SCCS, however, is aware that HSE (2003) and MAK (2012) considered ZPT as non-carcinogenic.
Carcinogenicity of ZPT has not been investigated by the inhalation route.

4. CONCLUSION

1. *In light of the new evidence available, does the SCCS still consider that zinc pyrithione, when used in a concentration up to 2.0% as an anti-dandruff agent in rinse-off hair care products, is safe for the consumer as concluded in SCCS/1512/13?*

The newly provided studies on fertility and developmental toxicity did not lead to changes of point of departure for risk assessment compared to SCCS/1512/13. Further additional studies mentioned in the Swedish CLH proposal confirm neurotoxicity as a sensitive endpoint of ZPT toxicity. In view of the additional studies SCCS confirms the LOAEL of 0.5 mg/kg bw/d that was derived in SCCS/1512/13 as a conservative value for risk assessment of ZPT.
Therefore ZPT is considered safe when used at a concentration up to 2.0% as an anti-dandruff agent in rinse-off hair care products.

2. *If not, does the SCCS consider that zinc pyrithione, when used in a concentration up to 1.0% as an anti-dandruff agent in rinse-off hair care products, is safe for the consumer as is the current situation?*

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3. *Does the SCCS have any further scientific concerns regarding the use of zinc pyrithione in cosmetic products?*

The conclusion from SCCS/1512/13 was specifically targeted to risk assessment for the particular use of ZPT in a concentration up to 2.0% as an anti-dandruff agent in rinse-off hair care products. Aggregate exposure from non-cosmetic sources has not been considered.
In view of apparent further (non-cosmetic) uses and in view of the fact that classification as Repr 1B is currently proposed, the SCCS recommends risk assessment taking into consideration all possible sources of exposure in line with Art 15 of Cosmetics Regulation (EU 1223/2009).
Not all relevant toxicological studies performed with ZPT have been made available to the SCCS (see section 3.1. Introduction of SCCS/1512/13).

5. MINORITY OPINION

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6. REFERENCES

A: References related to dossier on P81 – Addendum

Daston, G., Moore, N. and Laepple, F. (2016): Zinc Pyrithione (CAS: 13463-41-7): Assessment of Developmental Effects. Confidential Document submitted to KEMI by Procter & Gamble; Lonza; Thor GmbH; Janssen.

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ZnPT Industry CLH Consortium (2017b): Document from the ZnPT Industry CLH Consortium with Comments on Reproductive Toxicity on the harmonized Classification and Labelling Report (the 'CLH Report' submitted by the Swedish Chemicals Agency ('KEMI') to the European Chemicals Agency ('ECHA') on Zinc Pyrithione (EC 236-671-3; CAS 13463-41-7) ("ZNPT").

(Daston et al., 2016; Thor GmbH, 2017; ZnPT Industry CLH Consortium, 2017a and b).

ANNEX – MOS Calculations

Product type	Exposure according to table 4 of the SCCS NoG SCCS/1564/15	Concentration of ZPT in finished cosmetic products [%]	SED [mg/kg bw/d]	NOAEL [mg/kg bw/d]	MoS
Shower gel and hand wash soap (rinse-off)	6.12 mg/kg bw/d	0.5	0.00031	0.147	480
Shampoo and hair conditioner (rinse-off)	2.18 mg/kg bw/d	1.0	0.00022	0.147	668
Shampoo and hair conditioner (rinse-off)	2.18 mg/kg bw/d	2.0	0.00042	0.147	350
Leave-on hair products	5.74 mg/kg bw/d	0.1	0.000057	0.147	2561
Combined use (rinse-off with shampoo and conditioner containing 1 % ZPT + leave-on hair products)			0.0006	0.147	250
Combined use (rinse-off with shampoo and conditioner containing 2 % ZPT + leave-on hair products)			0.0008		187

The following parameters were used to determine SED for dermally applied cosmetic products:

Concentration of ingredient in finished product C (%) = 0.1, 0.5, 1.0 and 2.0 %
Typical body weight of human = 60 kg
Systemic exposure dose (SED) calculated according to:
A (mg/kg bw/d) x 1000 mg/g x C (%)/100 x Dap (%)/100

LOAEL = 500 µg/kg bw/d
(systemic LOAEL, chronic/carcinogenicity study, rat)

Adjusted to NOAEL (application of adjustment factor of 3): = 167 µg/kg bw/d

Adjusted for 88 % Bioavailability = 147 µg/kg bw/d

7. GLOSSARY OF TERMS

See SCCS/1564/15, 9th Revision of the SCCS Notes of Guidance for the Testing of Cosmetic Ingredients and their Safety Evaluation – from page 144

8. LIST OF ABBREVIATIONS

See SCCS/1564/15, 9th Revision of the SCCS Notes of Guidance for the Testing of Cosmetic Ingredients and their Safety Evaluation – from page 144

And the following additional Abbreviations

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)
