Scientific Committee on Consumer Safety

SCCS

OPINION on

Resorcinol

The SCCS adopted this document
At plenary meeting on 30-31 March 2021

ACKNOWLEDGMENTS

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

For the preliminary and final version of the Opinion

SCCS members
Dr U. Bernauer
Dr L. Bodin
Prof. Q. Chaudhry (SCCS Chair)
Prof. P.J. Coenraads (SCCS Vice-Chair, Chairperson of the WG and Rapporteur)
Prof. M. Dusinska
Dr J. Ezendam
Dr E. Gaffet
Prof. C. L. Galli
Dr B. Granum
Prof. E. Panteri
Prof. V. Rogiers (SCCS Vice-Chair)
Dr Ch. Rousselle
Dr M. Stepnik (Rapporteur)
Prof. T. Vanhaecke
Dr S. Wijnhoven

SCCS external experts
Dr A. Koutsodimou
Prof. W. Uter
Dr N. von Goetz

All Declarations of Working Group members are available on the following webpage:

Register of Commission expert groups and other similar entities

This Opinion has been subject to a commenting period of eight weeks after its initial publication (from 27 October until 22 December 2020). Comments received during this time period are considered by the SCCS. The final version has been amended, in particular in the following sections: SCCS comment under section 3.4.5.1 fertility and reproduction toxicity, additional information/SCCS comment/SCCS conclusion under section 3.4.10 special investigations – endocrine activity – *in vivo* data, as well as related discussion section and references.

1. ABSTRACT

The SCCS concludes the following:

1. In light of the data provided and taking under consideration the concerns related to potential endocrine disrupting properties of Resorcinol, does the SCCS consider Resorcinol safe when used as an oxidative hair dye in products intended for hair and eyelashes up to 1.25 % and up to 0.5 % in hair lotions and shampoos?

Keeping in view the evidence on endocrine disrupting properties of resorcinol, the SCCS assessment shows that resorcinol is safe when used as an oxidative hair dye in products intended for hair and eyelashes up to 1.25 % and up to 0.5 % in hair lotions and shampoos.

2. Alternatively, what is according to the SCCS, the maximum concentration considered safe for use of Resorcinol as an oxidative hair dye in products intended for hair and eyelashes and for hair lotions and shampoos?

/

3. Does the SCCS have any further scientific concerns with regard to the use of Resorcinol in cosmetic products?

Resorcinol is a moderate skin sensitiser based on data from animal studies. Clinical studies show that the frequency of contact sensitisation in humans is low.

The SCCS mandates do not address environmental aspects. Therefore, this assessment did not cover the safety of resorcinol for the environment.

Keywords: SCCS, scientific opinion, Resorcinol, hair dye, Regulation 1223/2009, CAS Number 108-46-3, EC No 203-585-2

Opinion to be cited as: SCCS (Scientific Committee on Consumer Safety), Opinion on Resorcinol (CAS No 108-46-3, EC No 203-585-2), preliminary version of 16 October 2020, final version of 30-31 March 2021, SCCS/1619/20

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

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

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

Scientific Committee members
Ulrike Bernauer, Laurent Bodin, Qasim Chaudhry, Pieter Jan Coenraads, Maria Dusinska, Janine Ezendam, Eric Gaffet, Corrado Lodovico Galli, Berit Granum, Eirini Panteri, Vera Rogiers, Christophe Rousselle, Maciej Stepnik, Tamara Vanhaecke, Susan Wijnhoven

Contact:
European Commission
Health and Food Safety
Directorate C: Public health
Unit C2- Health information and integration in all policies
L-2920 Luxembourg
SANTE-C2-SCCS@ec.europa.eu

ISSN ISBN

Doi ND

The opinions of the Scientific Committees present the views of the independent scientists who are members of the committees. They do not necessarily reflect the views of the European Commission. The opinions are published by the European Commission in their original language only.

http://ec.europa.eu/health/scientific_committees/consumer_safety/index_en.htm

TABLE OF CONTENTS

2. MANDATE FROM THE EUROPEAN COMMISSION

Background on substances with endocrine disrupting properties

On 7 November 2018, the Commission adopted a review[1] of Regulation (EC) No 1223/2009 on cosmetic products ('Cosmetics Regulation') regarding substances with endocrine disrupting properties. The review concluded that the Cosmetics Regulation provides the adequate tools to regulate the use of cosmetic substances that present a potential risk for human health, including when displaying ED properties.

The Cosmetics Regulation does not have specific provisions on EDs. However, it provides a regulatory framework with a view to ensuring a high level of protection of human health. Environmental concerns that substances used in cosmetic products may raise are considered through the application of Regulation (EC) No 1907/2006 ('REACH Regulation').

In the review, the Commission commits to establishing a priority list of potential EDs not already covered by bans or restrictions in the Cosmetics Regulation for their subsequent safety assessment. A priority list of 28 potential EDs in cosmetics was consolidated in early 2019 based on input provided through a stakeholder consultation. The Commission then organised a public call for data[2] from 16 May 2019 – 15 October 2019 on 14[3] of the 28 substances (to be treated with higher priority) in order to be able to prepare the safety assessment of these substances. Resorcinol is one of the above-mentioned 14 substances for which the call for data took place.

Existing information on Resorcinol

In cosmetic products, the ingredient Resorcinol (CAS No 108-46-3, EC No 203-585-2) with the chemical names 1,3-benzenediol and 1,3-dihydroxybenzene is currently regulated as an oxidative hair dye in hair products and products intended for colouring eyelashes in a concentration up to 1,25 % (Annex IV/22 a, b). Furthermore, Resorcinol is also allowed in a concentration up to 0.5 % in hair lotions and shampoos (Annex IV/22 c).

Resorcinol has been subject to different safety evaluations (1980, 1985, 1987, 1993, 2007, 2009 and 2012). In particular, the SCCS opinion from 2009 states that '…the use of resorcinol as an ingredient in oxidative hair dye formulations with a maximum on-head concentration of 1.25% will not pose a risk to the health of the consumer, apart from its sensitising potential.' In addition, the SCCS opinion from 2012 on oxidative hair substances used in products to colour eyelashes confirmed that Resorcinol is safe up to 1.25% and is not irritant to eyes.

During the call for data, stakeholders submitted scientific evidence to demonstrate the safety of Resorcinol as an oxidative hair dye in cosmetic products. The Commission requests the SCCS to carry out a safety assessment on Resorcinol in view of the information provided.

Terms of reference

1. In light of the data provided and taking under consideration the concerns related to potential endocrine disrupting properties of Resorcinol, does the SCCS consider Resorcinol safe when used as an oxidative hair dye in products intended for hair and eyelashes up to 1.25 % and up to 0.5 % in hair lotions and shampoos?

2. Alternatively, what is according to the SCCS, the maximum concentration considered safe for use of Resorcinol as an oxidative hair dye in products intended for hair and eyelashes and for hair lotions and shampoos?

3. Does the SCCS have any further scientific concerns with regard to the use of Resorcinol in cosmetic products?

[1] https://ec.europa.eu/transparency/regdoc/rep/1/2018/EN/COM-2018-739-F1-EN-MAIN-PART-1.PDF
[2] https://ec.europa.eu/growth/content/call-data-ingredients-potential-endocrine-disrupting-properties-used-cosmetic products_en
[3] Benzophenone-3, kojic acid, 4-methylbenzylidene camphor, propylparaben, triclosan, resorcinol, octocrylene, triclocarban, butylated hydroxytoluene (BHT), benzophenone, homosalate, benzyl salicylate, genistein and daidzein

3. OPINION

3.1 CHEMICAL AND PHYSICAL SPECIFICATIONS

3.1.1 Chemical identity

3.1.1.1 Primary name and/or INCI name

Resorcinol (INCI)

3.1.1.2 Chemical names

1,3-Dihydroxybenzene
1,3-Benzenediol
m-Dihydroxybenzene
m-Hydroquinone
3-Hydroxyphenol
m-Phenylenediol
Resorcin

3.1.1.3 Trade names and abbreviations

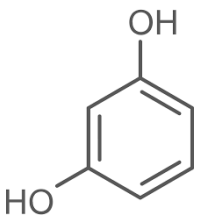
Colorex RES-CG
Covastyle RCN
Jarocol RL
Rodol RS
Rodol RS TECH
Rodol RS TECH SP
Rodol RS USP-C
Rodol RS USP-F
Unichem RSC

COLIPA n° A11

3.1.1.4 CAS / EC number

CAS No 108-46-3, EC No 203-585-2

3.1.1.5 Structural formula



3.1.1.6 Empirical formula

Formula: $C_6H_6O_2$

3.1.2 Physical form

Light pink flakes.
It exists in at least two crystalline modifications. Crystalline resorcinol turns pale red in the presence of light and air and is hygroscopic.

Ref.: WHO (2006)

3.1.3 Molecular weight

Molecular weight: 110.11 g/mol

3.1.4 Purity, composition and substance codes

Information from SCCS/1270/09
All studies submitted in the present dossier were conducted using test batches that were well characterized analytically, i.e.:

- 706030517 (98.8% pure) [1-9,11,13]
- IN-79-7087 (>99% pure) [10]
- 706010501 (99.8% pure) [12]
- 03346009 (98.4% pure) [13]
- SEL/1398 (radiochemical purity >99%) of [U-^{14}C]-resorcinol [13]
- 706061001 (96.8% pure by potentiometry) [34]

Description	**Batch**			
	706030517	**03346009**	**IN-79-7087**	**706010501**
Identification/ characterisation	MS, IR, NMR, UV, HPLC, Elemental analysis	IR, UV, HPLC	IR, NMR UV, HPLC	NMR, UV, GC-FID
Titre[1] (g/100 g)	98.8	> 98.4	> 99	
HPLC content (% peak area)	> 99.5	> 99.5	> 99*	100% (GC peak area)
Impurities[2] (g/100 g)	see 3.1.5	< 0.5	< 0.5	see 3.1.5
Water content (pg/g)	< 50			
Loss on drying (g/100g)	< 0.1			

Bromination in an acetic acid medium, potassium iodide addition and titration of the liberated iodine with sodium thiosulfate.
Informed total impurity
* 102% relative to the USP standard

3.1.5 Impurities / accompanying contaminants

Information from SCCS/1270/09
Batch n° 706030517:

Hydroquinone <0.01% (w/w)
Pyrocatechol <0.01% (w/w)
Orcinol <0.01% (w/w)
Phenol <0.01% (w/w)
Ag, Al, As, Ba, Bi, Cd, Co, Cr, Cu, Fe, Mn, Mo, Ni, Pb, Pd, Pt, Sb, Se, Sn, Ti, V, Zn: each < 1 mg/kg
Hg: < 0.1 mg/kg
Solvent residues: less than 100 µg/g of solvents such as methanol, ethanol, isopropanol, n-propanol, acetone, ethyl-acetate, cyclohexane, methylethyl ketone and monochlorobenzene.

Possible impurities (g/100 g) in USP resorcinol 706010501 Lot No. 02-77RP-1 (described in 2-generation drinking water study), reanalysis by capillary GC:

Phenol	0.002
o-Cresol	< 0.001
2,6-xylenol	< 0.001
m-Cresol	< 0.001
3,5-xylenol	< 0.001
Catechol	< 0.005
Mercaptophenol	< 0.02
Methylresorcinol	< 0.001
Unknowns (No.)	0.035 (3)
2,2'-Biphenyldiol	< 0.001
Unknowns (No.)	0.001(3)
2,5-Biphenyldiol	< 0.001
Unknowns (No.)	< 0.005
3,4-Biphenyldiol	< 0.005
Unknowns (No.)	< 0.005
3,3'-Biphenyldiol	< 0.005
3,4'-Biphenyldiol	< 0.005
4,4'-Biphenyldiol	< 0.01
Unknowns (No.)	< 0.01
THD isomer	< 0.01
Unknowns (No.)	< 0.01
2,4,3'-THD	< 0.01

3.1.6 Solubility

Information from SCCS/1270/09
Water: 678 ± 21 g/L at 20 °C (according to EEC Method A6)
Ethanol: ≥ 20 g/100 mL at 22 °C after 24h
DMSO: ≥ 20 g/100 mL at 22 °C after 24h

3.1.7 Partition coefficient (Log Pow)

Information from SCCS/1270/09 and WHO/IPCS 2006
Log Po/w: 0.04 at 24°C and pH 7.2 (Experimental value according EEC Method A8 – HPLC)
Log Po/w: 0.8 - 0.93 (at 20°C) (WHO)

3.1.8 Additional physical and chemical specifications

Information from SCCS/1270/09, WHO/IPCS 2006, Pubchem 2020

Melting point:	108-111°C
Boiling point:	276-280°C
Flash point:	127°C (Closed cup)
Vapour pressure:	0.027-0.065 Pa at 25°C
Density, solid	
(g/cm^3 at 20^oC):	1.272
α-phase:	1.278
β-phase:	1.327-1.33
Viscosity:	/
Dissociation Constants:	pKa1 = 9.30; pKa2 = 11.06
Refractive index:	1.578 at 25°C/D
pH:	/
UV_Vis spectrum:	absorption maxima at 275.8 nm and at 281.6 nm

3.1.9 Homogeneity and Stability

Information from SCCS/1270/09
In the prenatal developmental study, resorcinol was stable in the dosage forms used for the toxicological studies at 0.1 and 200 mg/mL in purified water over a 6-hour period at room temperature and over a 9-day period at +4°C, protected from light and under inert gas atmosphere; at 0.1 and 250 mg/mL in DMSO and at 0.1, 10 and 500 mg/mL in DMF over a 4-hour period at room temperature, protected from light and under inert gas atmosphere: deviations from the original concentration were in the range of -5 to +3%.

Ref: USR 2004b (also cited as Foulon, 2005)

Batch 706010501 (used in USR 2005a)
Solutions of 300 ng resorcinol/mL and 1000 ng resorcinol/mL in a HPLC mobile phase (water/acetonitrile, 85/15) stored at room temperature were shown to be stable up to 7 days:
300 ng/mL, storage time 7 days, concentration 104% of the original concentration, 1000 ng/mL, storage time 3 days, concentration 90.2% of the original concentration.

The solutions of 5000 ng resorcinol/mL in a HPLC mobile phase (water/acetonitrile, 85/15) stored at room temperature were less stable up to 7 days: concentration 88.4-89.8% of the original concentration. 1000 ng resorcinol/mL and 5000 ng resorcinol/mL plasma were stable at room temperature up to 4 hours: concentrations 90.9-93.7% of the original concentration.
Decay of resorcinol in 1000 ng resorcinol/mL plasma and 5000 ng resorcinol/mL plasma, stored frozen (-20°C), was 10% in 29 days, 20% in 61 days and 50% in 191 days.
The water solutions of resorcinol (120-3000 mg/L), used in the 2-generation drinking water study, were stable up to 24 days: concentration 95.3-100% after storage at room temperature for 15 days, and 87.5-96.1% after storage at room temperature for 24 days.
The water solutions of resorcinol, used in the 2 generation drinking water study, were shown to be homogeneous after storage for 1, 8 and 15 days in a refrigerator (range 95.7-102% of the original concentration).

Ref: USR 2005a (also cited as Nemec 2005)

3.2 TOXICOKINETICS

TUKES 2017 (note: references as stated in this report)**:**

Toxicokinetic studies in rats and rabbits suggest that orally-administered resorcinol is rapidly absorbed, metabolized and excreted in the urine primarily as monoglucuronide conjugate (unpublished report, 2004a, EFSA 2010, Garton *et al.* 1949, Kim and Matthews 1987, Merker *et al.* 1982, unpublished report, 2005). Minor metabolites included a monosulphate conjugate, a mixed sulphate-glucuronide conjugate, and a diglucuronide conjugate. In rats (Kim and Matthews 1987) most of the orally-administered [14C]-resorcinol was excreted via urine (90.8 – 92.8%) with a minimal amount excreted via the faeces (1.5 – 2.1%) within 24 hrs. In rats (Merker *et al.* 1982) after single subcutaneous dosing of [14C]-resorcinol the [14C] activity in plasma decreased rapidly (ca. 90 % clearance within the first 2 hours). The elimination was biphasic, with half-lives of 18–21 min and 8.6–10.5 h. Within 24 h, 98% of the applied dose was excreted via urine and 1% via faeces, mainly as glucuronide conjugate (84%). The available data do not show accumulation in any organ or tissue, including the thyroid gland, when 14C-resorcinol was administered either subcutaneously or orally to rats.

3.2.1 Dermal / percutaneous absorption

From SCCS/1270/09

Human skin samples (4 breast and 4 abdomen) were obtained from eight female donors subjected to plastic surgery.
Under oxidative conditions, it was incorporated into a typical hair colouring formulation at 2.50% (w/w) associated with p-phenylenediamine (PPD) at 2.45% (w/w) before mixing with hydrogen peroxide (1:1, w/w) to give a final concentration of 1.25% (w/w).
Under non-oxidative conditions, it was incorporated into the same formulation devoid of primary intermediate at 2.50% (w/w) before mixing with water (1:1, w/w) to give a final concentration of 1.25% (w/w).
Twenty (20) mg/cm² of oxidative and non-oxidative test preparations were applied to the skin surface for 30 minutes. After this time period, the remaining formulation on the skin surface was removed using a standardized washing procedure.
Twenty-four hours after application, the percutaneous absorption of resorcinol was estimated by measuring its concentration in the following compartments: dislodgeable dose, *stratum corneum* (isolated by tape strippings), skin (living epidermis + dermis) and receptor fluid.
The dermal delivery (sum of the amounts measured in the living epidermis, dermis and receptor fluid) under oxidative conditions was 1.04 ± 0.51 µg/cm² (range 0.37 to 2.0 µg/cm²); 0.40 ± 0.18 % (range 0.15 to 0.74%).

SCCS comment
As too few evaluable chambers were available in the experiment under oxidative conditions, the mean + 2 SD = 2.06 µg/cm² (1.04 + 2 x 0.51) will be used for calculating the MOS of resorcinol under oxidative conditions.

Ref.: Toner 2005

TUKES 2017 (note: references as stated in this report):

In an *in vitro* dermal absorption study using human skin (USR, unpublished report, 2005), dermal absorption of resorcinol was evaluated from a representative hair dye formulation (oxidative and non-oxidative test preparations) that contained [^{14}C]-resorcinol (Table 15 in that report).
The absorbed dose was 0.32 % (oxidative preparation) and 0.82 % at 24 hours (non-oxidative preparation) of the applied dose.

In a human volunteer study (Yeung *et al.* 1983) to measure absorption and metabolic disposition, 2% resorcinol (800 mg resorcinol/day, a maximal exaggerated use level) was applied topically in a hydro-alcoholic vehicle over an application area of 2600 cm^2 twice a day, six days a week for four weeks to three male volunteers with one control volunteer. The test substance penetrated the skin at a rate of 0.37 $\mu g/cm^2$/hour. After two weeks of application, an average of 1.64% of the dose was being excreted in 24-hr urine specimens as the glucuronide or as the sulphate conjugate. There was no resorcinol or its conjugates in blood drawn at week 1, 2, 3, and 4.

In *in vitro* permeability studies using human skin treated with 10% w/v resorcinol, there was a long lag time (80 min) (Roberts *et al.* 1977). A steady state permeability coefficient (Kp) of 0.00024 cm/h was calculated.

In conclusion, the Registrant(s) identified a 2% absorption rate as a conservative absorption rate for risk assessment purposes, while recent studies suggest the dermal absorption to be < 1% (0.82%). The Registrant(s) concluded that when applied to intact skin, dermal absorption is low in humans but utilises the same urinary excretion pathway and forms common metabolites as via the oral route.

The evaluating Member State Competent Autority (eMSCA) performing Substance Evaluation (SEv) of Resorcinol agreed with the Registrant(s) that the available studies suggest the dermal absorption to be low when applied to intact skin.

Data published after SCCS/1270/09

In two recent publications, the metabolism of resorcinol applied to human skin explants was evaluated (Géniès 2019 and Géniès 2020). It was concluded that in human skin the metabolite is only produced at late time points (18-24 h). After 24 hours exposure, the applied dose detected in the medium was 46.7±07% (human skin) and 50.9±1.2% (pig skin) (Géniès 2019). In the second experiment, after 24 hours exposure, the applied dose detected in the medium ranged from 45.8 to 49% (Géniès 2020). After 1 hour, the applied dose detected in the medium was 0.14 to 2.92% and after 2 hours 0.37 to 6.42%.

Following an OECD Test Guideline compliant (OECD, 2004) standardized protocol, human abdominal skin (4 donors; 3 replicates/donor; 1 cm^2) was exposed to 100 $\mu g/cm^2$ resorcinol in phosphate buffered saline for up to 24 h using non-occluding conditions (Hewitt 2020). A finite dose of 10 $\mu L/cm^2$ was used. The cumulative amount in the receptor fluid was 3.09 ± 7.40 µg after one hour and 8.92±11.76 µg after 2 hrs. The total dermal delivery after 24 hrs was 72.6 $\mu g/cm^2$ (SD 8.9). The Flux was estimated to be 5.86 µg/h.

According to additional information supplied to the SCCS by the consortium that performed the Hewitt 2020 study, the flux derived from the finite doses used does not represent the true flux under infinite conditions. The chemicals were applied in a simple PBS solvent as leave-on i.e. for 24 hours (no wash at early time points). The data that were generated cannot be used or extrapolated for the risk assessment of real case scenarios since they do not reflect consumer use-conditions: a different dose (0.9% vs. 1.25% target) was used in a different formulation (PBS vs. a hair dye formulation) for a different exposure scenario (24 hours vs. 45 minutes).

SCCS comment

From the abovementioned skin penetration study by Hewitt *et al.* (Hewitt 2020) and the metabolism studies (Géniès 2019, 2020) it is not possible to use the flux and the percentage resorcinol in the receptor fluid after one hour for estimation of the dermal absorption from a 45-minute hair-dye application of 1.25% resorcinol.

For the calculation of the MoS, the SCCS will use the same dermal absorption value (2.06 µg/cm²) as used in the previous Opinion (SCCS/1270/09), based on the report by Toner (2005).

3.2.2 Other studies on toxicokinetics

See 3.2 above.

3.3 EXPOSURE ASSESSMENT

3.3.1 Function and uses

Information from SCCS/1270/09
Resorcinol is used in oxidative hair colouring products at a maximum concentration of 2.5%, which after mixing in a 1:1 ratio with hydrogen peroxide just prior to use, corresponds to a concentration of 1.25% upon application.

Resorcinol is also used as a food additive and was recently evaluated by EFSA. Resorcinol is a specific inhibitor of polyphenol oxidase and therefore it can act as an anti-browning agent in crustaceans. The EFSA panel established an ADI of 0.12 mg/kg bw/day. The conservative estimates of acute consumption of shrimps (the only category for which experimental data were reported) indicate that dietary exposure to resorcinol for adults and for children would exceed the ADI when the residual concentration of resorcinol in whole raw shrimps is above 35 mg/kg. The EFSA Panel noted that this value is only applicable if other uses of resorcinol are excluded.

Ref.: EFSA, 2010

Resorcinol is included in Annex I as an existing active substance in biocidal products in accordance with the requirements of Article 3(1) of Commission Regulation (EC) 1451/2007 concerning the placing of biocidal products on the market (EC, 2007).
It has found use in a variety of topical medicaments that may be obtained over the counter.

3.3.2 Calculation of SED/LED

See also Safety Evaluation (Including Calculation of the MOS, page 30).

Following the SCCS Notes of Guidance, for absorption through the skin (DA) the mean + 2SD = 2.06 µg/cm² obtained from the study mimicking exposure to a hair dye formulation containing 1.25% resorcinol (see 3.2.1) is used. The skin surface area exposed to hair-dye is 580 cm^2 and the human body weight is set at 60 kg.
Thus, the systemic exposure dose (SED) is SSA x DA x 0.001 / 60 = 0.02 mg/kg bw.

3.4 TOXICOLOGICAL EVALUATION

3.4.1. Irritation and corrosivity

3.4.1.1 Skin irritation

General SCCS comment from SCCS/1270/09

A single dose of 0.5 mL of 2.5% resorcinol in purified water was not irritant when applied under a semi-occlusive dressing to the clipped skin of 3 male New Zealand White rabbits.

3.4.1.2 Mucous membrane irritation / eye irritation

General SCCS comment from SCCS/1270/09
A single dose of 0.1 mL of 2.5% aqueous solution of resorcinol caused mild conjunctival irritation in 2/3 animals on day 1 or day 2, when applied to the eye.

Resorcinol is classified as eye irritation cat 2 (H319) and skin irritation cat 2 (H315).

3.4.2 Skin sensitisation

General SCCS comment from SCCS/1270/09
According to the grading scheme used by the SCCS (SCCP/0919/05), resorcinol should be considered as a strong sensitizer.

Data submitted 2019
The applicant re-evaluated the study [Sire, 2005] on which the SCCS had based its 2010 Opinion. According to the applicant, in the first experiment, positive lymphoproliferative responses (SI>3) were noted at all tested concentrations, but no clear dose-response relationship was observed. In the second experiment, a dose-related increase in SI was observed (except at the concentration of 1%) and the threshold positive value of 3 was exceeded at concentrations >5%. The authors of this study calculated an EC3 value of 1.4%, thereby identifying resorcinol as a strong skin sensitizer. However, this calculation appears not to be justified on the basis of the available dose-response.

Test concentration	0.1%	0.5%	1%	5%	25%
Stimulation Index (SI)	1.58	2.87	1.97	3.51	5.74

a) Assuming SI3 is between the concentration 0.5% and 5%: EC3=0.5 + [(3-2.87)/(3.51-2.87)] x (5-0.5) = 1.41
b) Assuming SI3 is between the concentration 1% and 5%: EC3=1 + [(3-1.97)/(3.51-1.97)] x (5-1) = 3.67

A recalculation on the basis of a more transparent dose-response assumption resulted in a EC3 value of 3.67%, thereby identifying resorcinol as a moderate skin sensitizer [Sumitomo Chemical 2012].
The applicant concluded that Resorcinol induced contact sensitization in this study and that according to the LLNA results it should be considered as a moderate sensitizer.

A published study reported the results of an LLNA performed in accordance with the OECD test guideline 429 (Basketter, 2007). It correctly identified resorcinol as a skin sensitizer. Clear evidence of a dose response was apparent. The publication also reviewed the results of older LLNA's. An EC3 value of approximately 6% was calculated.

SCCS comment
The SCCS has noted the re-evaluation of the LLNA data and the results from other LLNA studies. Resorcinol is considered as a moderate skin sensitiser.
Several clinical publications (reviewed in Uter, 2015 and in Darcis, 2016) indicate that, despite its widespread use, the frequency of contact sensitisation to Resorcinol in humans is low.

3.4.3 Acute toxicity

3.4.3.1 Acute oral toxicity

From SCCS/1270/09
One animal (out of 5 female rats) died after a single oral gavage dose of 500 mg/kg bw and one died after receiving a dose of 2000 mg/kg bw. The maximal non-lethal dose of resorcinol after a single administration in rats was 200 mg/kg bw.

Ref: Sire 2004a

3.4.3.2 Acute dermal toxicity

No data submitted.

3.4.3.3 Acute inhalation toxicity

No data submitted.

3.4.4 Repeated dose toxicity

3.4.4.1 Repeated dose (28 days) oral / dermal / inhalation toxicity

Information from SCCS/1270/09
In a 17-day Oral Toxicity Study in F344/N rats and B6C3F$_1$ mice, resorcinol was administered by gavage 5 days per week at dose levels of 0, 27.5, 55, 110, 225 and 450 mg/kg bw/d in male and female rats (5 animals per sex / dose), and at 0, 37.5, 75, 150, 300 and 600 mg/kg bw/d in male and female mice (5 animals per sex / dose).
The following NOAELs based on short term acute effects after oral gavage were derived by EFSA (2010): the NOAEL in rats was 27.5 mg resorcinol/kg bw/d and the NOAEL in mice was 75 mg/kg bw/d.

3.4.4.2 Sub-chronic (90 days) oral / dermal / inhalation toxicity

Information from SCCS/1270/09
In a CIT study, four groups of 10 male and 10 female Sprague-Dawley rats received the test item (A011, batch No 70603051) daily by gavage at 0, 40, 80 or 250 mg/kg bw/day for at least 13 weeks. Under the experimental conditions of the study, the NOEL was reported by the applicant to be 80 mg/kg bw/day. Absolute and relative thyroid gland weight was slightly decreased (respectively -19% and -13%) in the 250 mg/kg bw/day group. According to the study authors, these effects were considered of no toxicological importance (no dose response relationship and without relevant histopathological abnormalities). However, in the opinion of the SCCS, since in the reproductive study some effects on the thyroid were also observed, these effects might be of relevance. The SCCS considered the 80 mg/kg bw/day as a NOAEL.

Ref.: USR 2004 (also cited as Foulon, 2004)

In the NTP 13-week oral toxicity study in F344/N rats and B6C3F1 mice, resorcinol was administered 5 days per week by gavage at dose levels of 0, 32, 65, 130, 260 and 520 mg/kg bw/d to male and female rats (10 animals per dose), and 0, 28, 56, 112, 225 and 420 mg/kg bw/d to male and female mice (10 animals per dose).

All female and 8 male rats receiving 520 mg/kg and 8 mice of each sex receiving 420 mg/kg resorcinol died of chemical-related toxicity during the studies. The final mean body weights of dosed rats and mice were similar to those of the control groups. No chemical-related gross or microscopic lesions were observed.
In rats the few significant differences in various parameters were scattered among the groups, but none were considered biologically significant. The levels of T3 and T4 in the 130 mg resorcinol/kg bw/d 5 days per week group were comparable to the control values. There were no gross or microscopical lesions attributable to resorcinol administration. Changes in organ weights were recorded in the liver of both sexes and in the adrenal glands of males. Absolute and relative liver weights of males dosed with 130 mg/kg bw/d or 260 mg/kg bw/d were statistically significantly ($p<0.01$) increased compared to controls. For females, statistically significantly increased absolute liver weights were recorded after doses higher than 32 mg/kg bw/d. The EFSA Panel (EFSA 2010) noticed that the increases in liver weights in the treated groups were slight, with no marked dose-response relationships, and not accompanied by any changes in clinical chemistry parameters indicative of impaired liver function, or by any histopathological changes. The EFSA Panel considered therefore that the effect on the liver weight was not biologically significant. The absolute and relative weights of the adrenal glands in males from all dosed groups were statistically significantly increased ($p<0.01$) compared to the controls. The EFSA Panel noted that the absolute adrenal weights were low in the male controls, that no dose-response relationship was apparent, and that the changes in adrenal weights were not accompanied by histopathological findings (NTP, 1992). Due to the incorrect dosing of the animals in the 260 mg resorcinol/kg bw/day dose-group, the Panel concluded that this dose-group should not be used to derive a NOAEL.

In mice, seven animals in the high-dose group of each sex died during the first week of the study, another male died during week 4 and another female died during week 12. The authors of the study attributed these deaths to resorcinol-related toxicity. Furthermore, one male died in the 112 mg/kg bw group due to improper gavage technique. The final body weights of the 2 surviving high-dose male mice were statistically significantly lower compared to controls. The final body weights and changes in body weights of all other mice receiving resorcinol were similar to those of the controls. Clinical signs of toxicity recorded for the high-dose animals were dyspnoea, prostration, and tremors. These signs appeared within 30 minutes of dosing. No resorcinol-related, biologically significant changes in haematology or clinical chemistry parameters were seen. Statistically significant decreases ($p<0.01$) were noted in absolute and relative adrenal gland weights in males from all dosed groups. The EFSA Panel noticed that there was no dose-response relationship for the decreased adrenal weights and that the changes were not accompanied by microscopical findings. A few other differences in various organ weights were scattered among the study groups, and none were considered biologically significant. There were no gross or microscopic lesions attributable to resorcinol administration (NTP 1992).

The EFSA Panel considered 130 mg resorcinol/kg bw/day as the NOAEL in rats. There were no gross or microscopical lesions attributable to resorcinol administration. Based on the clinical effects reported, the EFSA Panel concluded that the NOAEL was 225 mg resorcinol/kg bw/d in B6C3F1 mice. The Panel noticed that the dose causing mortality was less than two-fold greater than this NOAEL.

Ref.: NTP 1992, EFSA 2010

SCCS comment
The SCCS agrees with this evaluation. Interestingly, in contrast to other repeated dose toxicity studies, in the NTP study acute toxic effects were only observed at the highest dose of 520 mg/kg bw/day (rats) and 420 mg/kg bw/day (mice).

3.4.4.3 Chronic (> 12 months) toxicity

See section 3.4.7. Carcinogenicity

3.4.5 Reproductive toxicity

3.4.5.1 Fertility and reproduction toxicity

Information from SCCS/1270/09 (taken from SCCP/1117/07)
Five groups of male and female Crl:CD®(SD) rats (30/sex/group) were administered the test article Resorcinol (batch no 706010501) on a continuous basis in drinking water for at least 70 consecutive days prior to mating. Exposure levels were 0, 120, 360, 1000 and 3000 mg/L for the F0 and F1 generations.
No F0 or F1 parental test article-related deaths or clinical findings were reported.
No statistically significant test article-related changes in the mean concentrations of T3, T4 or TSH were noted in the F0 or F1 parental animals or in the F1 or F2 pups selected for analysis (PND 4 or PND 21). The higher (but non-significant) TSH values noted at all dose levels in the F0 males at the scheduled necropsy were not considered test article-related in the absence of effects on T3 or T4, organ weights or adverse macroscopic or microscopic findings. Test article-related decreased colloid within the thyroid glands of the 3000 mg/L F0 males was not considered adverse due to the lack of associated functional effects.
As the mean water consumption was significantly decreased with ~10% in the 1000 mg/L (F_0 animals only) and with ~20% in the 3000 mg/L treatment group (F_0 and F_1 animals), SCCP considers 0.8 * 3000 = 2400 mg Resorcinol/L as the NOAEL. This corresponds to ~186 mg/kg bw/day for males over the entire generation, ~243 mg/kg bw/day for females during premating and gestation and ~528 mg/kg bw/day for females during lactation.

Ref: USR 2005a (also cited as Nemec, 2005)

TUKES, 2017:
No indications of reproductive toxicity were seen in the dose range-finding study or in the two-generation reproductive toxicity study in rats (USR 2003, 2005, Welsch *et al.* 2008a).
Endpoints for neurotoxicity (i.e. brain weight and width, brain histology, functional observation battery (FOB), locomotor activity, acoustic startle response and Biel maze swimming trials) were investigated in a dose range-finding study (unpublished study report, 2003), where dose-related effects on locomotor activity (in cumulative total and ambulatory counts) was observed in sexually mature F1 males at PND 61 (young adult). Locomotor activity was also increased in F1 females but the change was not statistically significant or dose-related. The eMSCA considered that increased motor activity at PND 61 may be an indication of latent alteration in motor activity. However, the eMSCA considered that resorcinol, based on the results from limited developmental neurotoxicity measurements in the dose range-finding study, is probably not a developmental neurotoxicant because significant effects were seen only in males, other behavioral endpoints were not affected, no indications of developmental delay were reported and no concurrent correlating changes in brain histopathology, weight or width were reported.
Overall, the eMSCA concluded that no clear adverse effects were seen on the hypothalamus-pituitary-thyroid axis (HPT axis).

SCCS comment
Considering the Adverse Outcome Pathway on TPO inhibition (OECD-AOP 2019), and the capacity of resorcinol to alter T4 levels in humans and experimental animals, neurobehavioural effects of resorcinol in offspring may occur.

3.4.5.2 Developmental Toxicity

Information from SCCS/1270/09
Four groups of Sprague-Dawley Crl CD® (SD) IGS BR rats (24 females/group) were administered with resorcinol by gavage once daily from day 6 to day 19 of gestation at the dose-level of 0, 40, 80 or 250 mg/kg bw/day. The females were sacrificed on day 20 of gestation and subjected to a macroscopic examination.
At 250 mg/kg bw/day the net body weight change was significantly reduced. No other maternal effects were observed. All group mean numbers of implantations and live foetuses and the extent of pre- and post-implantation losses were comparable with the controls. There were no effects of treatment on foetal body weight. In the litters, no external, soft tissue or skeletal malformations or variations were considered to be treatment-related. There was a significant increase in the incidence of foetuses with an incompletely ossified interparietal at 40 and 80 mg/kg bw/day, when compared to controls ($p < 0.05$ and $p < 0.01$, respectively). The incidence of incompletely ossified parietals was also significantly greater at 80 mg/kg bw/day, when compared to controls ($p<0.05$). In the absence of any effects at 250 mg/kg bw/day these observations were not considered to be treatment related.
In the opinion of the SCCS, the maternal NOAEL of resorcinol administered by gavage to pregnant female rats was 80 mg/kg bw/day and the developmental NOAEL was 250 mg/kg bw/day.

Ref: USR 2005b (also cited as Foulon, 2005)

TUKES, 2017:
The eMSCA considered that the findings observed in the evaluated developmental toxicity studies with resorcinol and in the developmental toxicity study with resorcinol bis-diphenylphosphate (BDP) do not raise concern of resorcinol-induced developmental effects. This conclusion is also drawn in each individual study.

ECHA 2020:
Regarding the abovementioned study (USR, 2005b), the ECHA support document to identify Resorcinol as a Substance of very high concern (SVHC) also noted that the incidence of incompletely ossified parietals was significantly greater at 80 mg/kg/day, when compared to controls, but concluded that in the absence of any effects at 250 mg/kg/day, the relation to treatment is uncertain. The proposal noted that there was a significantly greater incidence of incompletely ossified 5th sternebra at 250 mg/kg/day, when compared to controls, and stated that, considering that the incidence of unossified 5th sternebra was (not significantly) lower, overall it cannot be seen as a general delay in ossification of sternebra.

The ECHA proposal also evaluated three older developmental studies:
A study in which pregnant Sprague-Dawley dams (n=23/group) were exposed to 40, 80 or 250 mg/kg/d resorcinol in distilled water from gestational day (GD) 6 to 15 (Unpublished study report, 1982a). An increased incidence of skeletal variations was observed (2%, 7.7%, 8.5% and 10.5% in groups exposed to 0, 40, 80 or 250 mg/kg/d) and consisted of parietal incompletely ossified, interparietal incompletely ossified, splitting of ossification centres, single extra ribs and extra pair of ribs. They were observed in foetuses of normal weight in the study. These variations cannot be linked to weight loss and to excessive toxicity. No historical control data were provided.

Another study in pregnant Sprague-Dawley dams (n=13/group) that were exposed to 0, 125, 250 or 500 mg/kg/d resorcinol in propylene glycol by gavage from GD 6 to 15) reports that resorcinol does not induce any teratogenic effects after visceral and skeletal examinations and assessment of foetal viability and body weights but no detailed information was presented (DiNardo, 1985).

A teratogenicity study with New Zealand White rabbits (n=20-26/group) that were exposed to 0, 25, 50 or 100 mg/kg/d resorcinol in distilled water from GD 6 to 18 showed no effect on the number of *corpora lutea*, implantations, foetal viability, foetal weight and foetal malformations and variations (Unpublished study report, 1982b).

SCCS comment
The SCCS maintains the conclusion of its previous opinion that the maternal NOAEL of resorcinol administered by gavage to pregnant female rats was 80 mg/kg bw/day and the developmental NOAEL was 250 mg/kg bw/day.

3.4.6 Mutagenicity / genotoxicity

3.4.6.1 Mutagenicity / genotoxicity *in vitro*

New data from the open literature
In TK6 cells resorcinol caused concentration-dependent reductions to the relative nuclei count both in the presence and absence of S9, with a considerable attenuating effect in the presence of 0.25% S9. Whereas the p53 responses were modest at 4 hr, strong induction of p53 with and without S9 occurred at 24 hr. The magnitudes of the γH2AX biomarker responses were pronounced at both time points, and similar across S9 conditions. The presence of S9 markedly shifted the dose response curves to the right. Benchmark dose values were reduced by the presence of S9 by an order of magnitude in several instances. The machine learning ensemble (which combines different statistical analyses) characterized resorcinol, with and without S9, as clastogenic.

Ref.: Tian (2020)

Resorcinol (used in the study as a false positive chemical) was assessed for Micronuncleus (MN) induction *in vitro* in three different cell types: p53-competent human lymphoblastoid TK6, p53-mutant mouse lymphoma L5178Y and p53-mutant human WIL2-NS cells. Resorcinol was clearly positive in L5178Y and TK6 cells, and gave an equivocal result in WIL2-NS cells.

Ref.: Whitwell (2015)

Resorcinol was positive in GADD45a–GFP GreenScreen HC assay in the presence of S9-mix.

Ref.: Luzy (2013)

3.4.6.2 Mutagenicity / genotoxicity *in vivo*

No new data.

Overall SCCS comment on mutagenicity based on the information from SCCS/1270/09 and the new *in vitro* studies
Resorcinol was investigated in valid genotoxicity tests for the three types of genotoxic endpoints: gene mutation, structural and numerical chromosome aberration. Overall, resorcinol did not induce mutations in bacteria in a number of studies. Only in one non-guideline study (Gocke, 1981) resorcinol induced point mutations in the *Salmonella typhimurium* strain TA100 without metabolic activation and in strain TA1535 with metabolic activation when tested with a special bacterial minimal medium.
Resorcinol was genotoxic (mutagenic and or clastogenic) in the absence of metabolic activation in the mouse lymphoma assay (tk locus) and a potent clastogen in human peripheral blood lymphocytes. However, resorcinol did not induce gene mutations (hprt locus) in the same mammalian cell line (mouse lymphoma cells). It is therefore concluded

that the positive result observed in the first performed mouse lymphoma assay was a clastogenic effect.
Several studies (Erexson 2005, Lloyd 2009, Luzy 2013, Sire 2004d, Tian 2020, Whitwell 2004, 2015, Williams 2005) showed that resorcinol induced chromosomal aberrations in mammalian cells *in vitro*. The clastogenic effects observed in the *in vitro* assays were not confirmed in one GLP *in vivo* assay. Moreover, in a range of non-GLP studies from the open literature (from the 1980s) resorcinol did not induce micronuclei in the bone marrow of mice. In a well-conducted 2-year carcinogenicity study resorcinol administered in water by gavage to rats and mice did not induce any tumorigenic effect.
It is therefore concluded that resorcinol itself does not have a genotoxic potential *in vivo*. This conclusion is based on the data submitted to SCCS, but it is also supported by information from the open literature.

3.4.7 Carcinogenicity

Information from SCCS/1270/09
A 2-year carcinogenicity study (NTP 1992) was conducted by administering resorcinol (> 99% pure) in water by gavage to groups of F344/N rats and B6C3F1 mice of each sex. Under the conditions of the study, there was no evidence of carcinogenic activity of resorcinol in male F344/N rats given 112 or 225 mg/kg bw/day or female F344/N rats given 50, 100, or 150 mg/kg bw/day. There was no evidence of carcinogenic activity of resorcinol in male or female B6C3F1 mice given 112 or 225 mg/kg bw/day.

Based on the acute clinical signs of toxicity, which were considered a resorcinol-related effect on the CNS, the EFSA Panel (EFSA 2010) concluded that the NOAEL was 50 mg resorcinol/kg bw/d. This NOAEL corresponds to a daily dose of 36 mg/kg/d when adjusted from the 5-day dosing week to a 7-day dosing week.
Since the dosing was performed by gavage and the clinical signs lasted 30-60 minutes after dosing, these signs might be the result of the high (local) dose. In the case of dermal application, such effects are not relevant. Therefore, 50 mg/kg bw/day will not be used as the NOAEL for the calculation of the MOS.

3.4.8 Photo-induced toxicity

3.4.8.1 Phototoxicity / photo-irritation and photosensitisation

No data submitted.

3.4.8.2 Photomutagenicity / photoclastogenicity

No data submitted.

3.4.9 Human data

3.4.10 Special investigations

Endocrine activity

Information from SCCS/1270/09

Evidence of anti-thyroid activity of resorcinol in animals is only demonstrated when administered continuously (diet, subcutaneous injection with oil-based vehicle) at higher doses. Additionally, it was stated that 'effects of resorcinol on the thyroid, particularly in rats, must be interpreted with caution as there are species-specific differences […] that complicate interpretation of goitrogenesis in these species'.
Based on the human data as reviewed by Lynch *et al.* (2002) and IPCS (2006), thyroid effects may occur as a result of dermal exposure to ulcerized skin at resorcinol dose levels greater than 30 mg/kg bw/day. From these data, a thyroid effect threshold value of 10 mg/kg bw/day for dermal exposure was established based on the application of a threefold safety factor. However, high-dose exposure has been rare in the past and has occurred mainly in patients as a result of the treatment of ulcers with large amounts of Resorcinol for a long period of time. Based on Lynch *et al.* (2002), there is no evidence that intermittent or low-dose exposure to Resorcinol causes hypothyroidism or any other adverse health effects.

Based on the results of the 2-generation reproductive study (USR 2005a, also cited as Nemec, 2005) study, the NOAEL was considered to be 3000 mg Resorcinol/L, which corresponds to ~233 mg/kg bw/day for males over the entire generation, 304 mg/kg bw/day for females during premating and gestation and 660 mg/kg bw/day for females during lactation.

Additional information

1) **Non-test information, *in silico*, *in chemico*, read across**:

The proposed identification of Resorcinol as endocrine disrupter has been reviewed in an evaluation by the Danish Centre on Endocrine Disrupters (CEHOS, 2012) and the ECHA support document (ECHA, 2020a).

2) ***In vitro* and other assays**:

Information taken from CEHOS (2012):
Resorcinol and some of its derivates, have been shown to be very potent inhibitors of the enzyme thyroid peroxidase *in vitro*, and to inhibit uptake of radioactive iodide (Lindsey *et al.* 1992). Irreversible loss of thyroid peroxidase activity was also shown in a study by Divi & Doerge (1994), and more recently resorcinol has also been shown to disrupt the thyroid hormone system in the T-screen, by proliferation of the TH-dependent rat pituitary GH3 cell (Ghisari and Bonefeld-Jorgensen 2009). Furthermore, resorcinol has been shown to affect both the aryl hydrocarbon receptor (AhR) and the androgen receptor (AR) *in vitro* (Krüger *et al.* 2008), and to inhibit prostaglandine production (Alanko *et al.* 1995) and affect glucose metabolism by inhibiting phosphorylase (Aiston *et al.* 1999).
The evaluation includes summaries of the following studies: Lindsey *et al.* (1992), Divi & Doerge (1994), Ghisari and Bonefeld-Jorgensen (2009), Krüger *et al.* (2008), Alanko *et al.* (1995) and Aiston *et al.* (1999).

Information taken from ECHA (2020a):
Studies investigating potential effects of resorcinol on endocrine systems other than thyroid detected no estrogenic or anti-estrogenic activity. Antagonist activities to AhR and AR were detected (Krueger *et al.*, 2008). A number of ED activities were screened in Waring *et al.* (2012) and a positive response was observed only for the inhibition of the aromatase activity. In the US EPA Toxcast program, resorcinol was found active in 6 assays related to endocrine disruption and inhibition of thyroid peroxydase (TPO) (as reported in more detail in Friedman 2016) was the most sensitive target of resorcinol.
Several studies investigated the effects of resorcinol on TPO, using either TPO purified from porcine thyroid tissues or human thyroid cell lines or rat thyroid microsomes and using different substrates (tyrosine, guaiacol, BSA, fluorescent Amplex Ultrared, luminol). Inhibition of TPO was consistently identified in these studies independently of the test

system. Differences in potency were reported across studies. The lowest potency was measured in rat microsomes (IC50=253 µM, Paul *et al.* 2014) whereas a subsequent study using an identical protocol determined a much higher potency (IC50=0.025 µM, Paul Friedman *et al.* 2016). A difference in purity of resorcinol was mentioned by the authors as a possible explanation for the discrepancy in the results but may hardly explain the strong variability in values.

3) *In vivo* data:

The ECHA/EFSA guidance on ED and its specific appendix on thyroid-disruption recognise that in the absence of substance-specific data, which provide proof of the contrary, humans and rodents are considered to be equally sensitive to thyroid-disruption.

From CEHOS (2012):
Rat studies performed in the 1950s quite unambiguously show effects on the thyroid hormone system of rats treated with resorcinol, shown as decreased uptake levels of radioactive iodine (Doniach & Fraser 1950, Arnott & Doniach 1952) and increased thyroid weight and altered thyroid histopathology (Samuel 1955, Doniach and Logothetopoulos 1953). In their conclusions, Doniach and Logothetopoulos (1953) stress the importance of maintaining a continuous high antithyroid drug level in the blood stream. Since resorcinol is rapidly cleared from the plasma through urinary excretion, a mode of exposure that allows for a slower and more continuous release of resorcinol to the systemic circulation is likely required to produce histological evidence of goiter in rats i.e., resorcinol administered by gavage or subcutaneously in an aqueous vehicle is rapidly cleared from circulation and, therefore, resorcinol is not present systemically for a sufficient time to inhibit thyroid hormone synthesis. In two more recent studies, effects of resorcinol exposure in rats have been seen at a very low dose levels (5 mg/kg/day), however both studies used only one dose level. In the first study resorcinol caused decreases in T3 and T4 levels and increased size of the thyroid after 30 days of dosing (Cooksey *et al.* 1985) while altered thyroid histopathology was seen after 12 weeks of dosing in the other study (Seffner *et al.* 1995). In both studies, resorcinol was added to the drinking water.
In 1992, the National Toxicology Program of the US EPA tested the effects of resorcinol given to rats by gavage for 13 weeks and no significant effects on T4 levels were seen (NOAEL 130 mg/kg/day). In a more recent two-generation study examining the effects of resorcinol dosing through the drinking water on the thyroid system in rats, the only significant effect was histopathological changes in the thyroid of males from the parental generation, while no effects on thyroid hormone levels or thyroid gland weights were seen at any time point in the parental or offspring generations (Welsch *et al.* 2008a). The LOAEL from this study was 233 mg/kg/day in males and 340-660 mg/kg/day in females.
The discrepancy between available data is most likely due to different administration routes and forms. In the animal studies reporting negative results, resorcinol has been administered via gavage or drinking water.
Free resorcinol is extremely efficiently metabolized (possibly by first pass through the liver) and effectively removed from the body via the urine, which may explain the lack of thyroid effects seen in some of these studies.

The evaluation includes summaries of the following studies:
Doniach & Fraser (1950), Arnott & Doniach (1952), Doniach and Logothetopoulos (1953), Samuel *et al.* (1955), Cooksey *et al.* (1985), Seffner *et al.* (1995), NTP (1992) and Welsch *et al.* (2008a).

TUKES (2017) In the context of a substance evaluation under REACH the effects on the thyroid in the two-generation reproductive study (USR 2005a, Welsch 2008a) were evaluated. The eMSCA considered that the toxicological significance of changes in thyroid/pituitary hormone levels (i.e. serum T3, T4 and TSH) should be interpreted in conjunction with histopathological changes in thyroid gland, weights of thyroid/pituitary glands and overall toxicity. The changes in the hormone levels represent a measurement at a single point in time and can be transient and affected by several factors, whereas thyroid

weight and histopathology are endpoints that may represent cumulative effects. The decreased colloid content in the follicular lumen could be interpreted as an indication of increased biological activity (increased endocytosis of colloid into the follicular cells), compensatory reaction, of the thyroid gland rather than clear adverse effect. Not studied in the aforementioned studies, but the change in the colloid amount may be reversible depending on the level of biological activity.
The slight non-consistent changes in circulating T3, T4 and TSH hormone values and in follicular colloid content seen in the two-generation reproductive toxicity study (without any other histopathological alterations, effects on thyroid/pituitary weights or reproductive toxicity) were not considered toxicologically significant by the eMSCA. Overall, the eMSCA concluded that no clear adverse effects were seen on the hypothalamus-pituitary-thyroid axis (HPT axis).

From ECHA (2020a):
When administered in diet or drinking water, an effect on thyroid weight as well as on thyroid hormones was observed in rats after exposure to approximately 2000 - 2500 mg/kg/d for 14 days (Berthezene *et al.,* 1979) or 9.9 mg/kg/d for 30 days (Cooksey *et al.*, 1985). Microscopic findings were investigated in Seffner *et al.* (1995) and some changes in thyroid structure that are indicative of compensatory mechanisms were observed at doses as low as approximately 2.5 mg/kg/d after administration for 12 weeks. The decrease of iodine uptake observed in Doniach & Fraser (1950) after a short exposure to 2% resorcinol in drinking water also provides supporting evidence of thyroid effects of resorcinol via drinking water.

A 90-day study was conducted in Sprague Dawley rats by gavage (Unpublished study Report 2004a). Animals were exposed to 0, 40, 80 or 250 mg/kg/d resorcinol in purified water for 13 weeks. Six controls and high-dose animals of each sex were then kept for a 4-week treatment-free period. Thyroids were weighted and histopathological analyses performed. The levels of thyroid hormones were not determined.
No treatment-related mortality was observed. Animals of the high-dose group showed intermittent convulsive movements and excessive salivation, starting approximately between weeks 6 and 8. Body weight was transiently reduced in females between weeks 4 and 8 but no effect on body weight was observed at the end of the exposure period. At week 13, plasma levels were quantifiable only at 0.5 to 2 hours for the 80 and 250 mg/kg/d groups (LOQ=0.5 µg/mL). AUC in females was approximately 3 times higher than in males. The functional observation battery (FOB) performed after week 10 revealed an increased landing foot splay in females exposed to 80 and 250 mg/kg/d. Motor activity was unaffected by treatment. Absolute thyroid weight was significantly decreased by 19% in high-dose females at the end of exposure period and significantly increased by 37% after 4-week without exposure. These changes are substantial but not significant when relative weight is considered (-13% at the end of exposure and +30% after recovery). No significant changes in any other organ weight were observed and there were no histopathological findings in any organ.

In a preliminary reproductive toxicity study of 2003 and a main study finalised in 2005 (unpublished study reports), sporadic statistically significant changes were noted:

In the preliminary study:
- an increase in T3 in F0 females exposed to the highest dose of approximately 40 mg/kg/d (360 mg/L),

In the main study:
- decreased colloid in the thyroid in F0 males exposed to the highest dose of approx. 300 mg/kg/d (3000 mg/L),
- increased TSH in male F1 pups at PND21 at the intermediate dose of approx. 40 mg/kg (360 mg/L) and
- increased thyroid weight and decreased T4 in female F2 pups at PND21 at the intermediate dose of approx. 237 mg/kg/d (1000 mg/L).

The ECHA/EFSA guidance (2018) on identification of ED in Biocides and Plant Protection Products states that "Using the current understanding of thyroid physiology and toxicology (European Commission, 2017), it is proposed that the following be applied when interpreting data from experimental animals:
1) Substances inducing histopathological changes (i.e. follicular cell hypertrophy and/or hyperplasia and/or neoplasia) in the thyroid, with or without changes in the circulating levels of THs, would pose a hazard for human thyroid hormone insufficiency in adults as well as pre- and post-natal neurological development of offspring.
2) Substances that alter the circulating levels of T3 and/or T4 without histopathological findings would still present a potential concern for neurodevelopment.
A modification of thyroid histology is considered as a sensitive and early endpoint to demonstrate thyroid disruption (Bianco *et al.*, 2014). As it reflects an attempt to compensate for insufficient levels of TH, it is considered as a reliable indicator of repeated TH disturbance.

Table 3. Summary of findings in studies investigating thyroid (from Table 25 in ECHA, 2020a)

Reference	TOX R-tool	Species	Vehicle	Duration	Doses (M/F)	Parameter measured						
						Thyroid weight	Histology	TSH	T3	T4	MIT/DIT	I uptake
SUBCUTANEOUS												
Klein 1950	3	Rabbits	Saline	4 or 15 d	50 or 75 mg/kg/d	=	=					
Cheymol 1951	3	Wistar	Aqueous solution	Every 2 d for 1	50 mg/kg/d	(+)	(+)					
Arnott & Doniach 1952	2	Rats	Water or ethanol: water	Single	42 to 180 mg/kg							↘
Doniach & L. 1953	2	Rats	Oil	10 to 69 days	308 mg/kg/d	+	+					
			Water	Single	55 mg/kg							-
Samuel 1955	3	Wistar rats	Peanut oil	21 to 38 d	308 to 396 mg/kg/d	+	+					
			Beeswax in peanut oil	21 to 79 d	792 mg/kg/d	+	+					
DERMAL												
Doniach & L.	2	Rats	Ointment	3 wk	NA	=						
Samuel 1955	3	Wistar	Ointment	28 d	8 000 mg/kg/d	+	+					
GAVAGE												
NTP 1992	1	B6C3F1 mice	Water	90 days	28, 56, 112, 225 or 420		=					
				2 years	112 or 225 mg/kg/d		=					
		F344 rats		90 days	32, 65, 130, 260 or 520		=		=	=		
				2 years	50, 112/100 or 225/150		=					
USR, 2004a	1	SD rats	Water	90 days	40, 80 or 250 mg/kg/d	F: ↘	=					

DIET OR DRINKING WATER												
Berthezene 1979	3	Rats	Diet	14 days	2 000-2 500 mg/kg	↗				↘	↗	
Cooksey 1985	2	Wistar	DW	30 days	9.9 mg/kg/d	↗			↘ T3+T4			
Seffner 1995	2	Rats	DW	84 days	2.56-2.92 mg/kg/d		+					
USR, 2003	1	SD rats	DW	F0: approx. 81	0.8/0.8, 3.9/5.1, 13.1/15.6 or 36.9/46.6	=	M/F:	M:(↗)	F:↗	=		
				F1: GD0- PND4				=	(↗)	(↗)		
				F1: GD0-PND28	5.0, 18.5, 58.7 or 174.4 mg/kg/d	=		M:(↗)	F:(↗)	=		
USR, 2005a (Welsch, 2008a)	1	SD rats	DW	F0: approx. 133 days	11/17, 33/51, 88/123 or 246/294 mg/kg/d	=	M:+	M:(↗)	M:(↗)	=		
				F1 pups: GD0-PND21	31, 98, 245 or 674 mg/kg/d	=	=	M:↗	=	=		
				F1 adults: GD0 to	14/18, 41/48, 115/141 or 304/347 mg/kg/d	=	=	=	=	=		
				F2 pups: GD0-PND21	28, 85, 237 or 645 mg/kg/d	F: ↗ M:(↗)		=	=	F:↘ M:(↘)		
INHALATION												
USR, 1977	3	SD rats	-	90 days	220 ppm	=	+					

USR: unpublished study report; NA: data not available; F: females; M: males; DW: drinking water
= : no effect observed
+ : effect observed (not significant but >10% and p<0.3 when into brackets)
↗: increase observed (not significant but >10% and p<0.3 when into brackets)
↘: decrease observed (not significant but >10% and p<0.3 when into brackets)
Cell left empty when parameter not investigated

It is also stated in the ECHA (2020a) support document that the relevance of subchronic studies in rodents is questionable. In some studies, significant effects were observed but the absence of a dose-response was noted. In the gavage 90-day study (USR, 2004a), the effect on thyroid weight was in contradiction with other studies. The experimental observation of effects that are inconsistent or without a clear dose-response illustrates that the complexity of the response in reaction to thyroid disturbance is not fully characterised and understood. Considering the wide range of functions influenced by TH, it is also highly challenging to fully characterise these effects and their dose-response in experimental studies.

SCCS comment
After reviewing studies listed in table 1 above, the following NOAELs regarding endocrine activity in rats could be derived from each study. From the drinking water main study (USR 2005a), the lowest water intake values were taken.

Table 2. NOAEL's for endocrine activity derived by the SCCS.

Study	Route of exposure	Comment	Parameter	NOAEL (mg/kg bw/d)
NTP 1992	gavage	2 years carcinogenicity study	No changes in thyroid parameters	520
USR 2004a / Foulon 2005	gavage	90-day study	Decreased thyroid weight Females	80 *)
Cooksey 1985	drinking water	Effects noted, but only single dose was used, insufficient reporting, not complying with current guidelines		//
Seffner 1995	drinking water	Effects noted, but publication lacking in details about methods, calculation of oral dose		//
USR 2003	drinking water	Dose range finding study for key study USR 2005a	F0: T3 increase in Females treated with the highest concentration of 360 mg/L (46.6 mg/kg/d)	// **)
USR 2005a, Welsch 2008a	drinking water	Key study 2 generation reproductive toxicity study	F0: -colloid decrease Males -thyroid weight -increased TSH -T3 increase males -T4 changes F1: -decreased colloid -thyroid weight -TSH increase Males ****) -T3 changes -T4 changes F2: -decreased colloid -thyroid weight Female ***) -increased TSH -T3 changes	F0: 177 mg/kg/d 177 177 177 177 F1: 173 mg/kg/d 173 101 173 173 F2: 177 mg/kg/d 177 177 177

			-T4 decrease Females ***)	177 177

*) Decreased thyroid weight in contradiction with other studies.
**) Increase of T3 noted at intake of 360 mg/L drinking water (46.6 mg/kg bw/d), but absence of any effect on T3 at much higher doses in the main study (USR 2005a).
***) statistical differences in the mean values for the different doses reported in ECHA (2020), but biological relevance implausible because of single outliers and absence of effect at higher dose steps.
****) LOAEL based on exposure to 3000 mg/L resorcinol in drinking water (304 mg/kg bw/d), hence NOAEL = 101.

The SCCS concurs with the ECHA SVHC (2020a) evaluation that the USR 2005a report (with the overlapping Welsch 2008a publication) is a reliable study to evaluate the effects on the thyroid. The NOAEL in the table above, derived from the 2004 gavage study (USR 2004a) will not be taken into account for the endocrine activity because the decreased thyroid weight is in contradiction with the findings in other studies. In this study only thyroid weight was monitored without providing any supportive measurements of thyroid hormones. Furthermore, the animals were exposed by gavage leading to short peak doses. Based on these uncertainties concluding on the endocrine disrupting effect in this study is difficult.
Changes in parameters of thyroid function were reported in the ECHA (2020a) evaluation. But, based on the SCCS's own evaluation of the data in the study report regarding statistical differences in the mean values for the different doses, the biological relevance is considered implausible because of single outliers and absence of effect at higher dose steps, except for the slight increase of the TSH in the F1 males at the highest dose.

In its previous opinion (SCCS/1270/09) the SCCS concluded that no significant test article-related changes in the mean concentrations of T3, T4 or TSH were noted in the F0 or F1 parental animals or in the F1 or F2 pups selected for analysis (PND 4 or PND 21). The higher (but non-significant) TSH values noted at all dose levels in the F0 males at the scheduled necropsy were not considered test article-related in the absence of effects on T3 or T4, organ weights or adverse macroscopic or microscopic findings. Test article-related decreased colloid within the thyroid glands of the 3000 mg/L F0 males was not considered adverse due to the lack of associated functional effects.
After a re-examination of the original data regarding the TSH in the F1 males PND 21 (table 213, page 2046-2050 of the USR 2005a study report), the SCCS did not see a clear dose-response, but noted that a statistical test on outliers allowed one value in the mid-concentration of 360 mg/L to be excluded and 2 outlying values in the highest drinking-water exposure to be taken into account for statistical analysis. Based on the analysis, the highest drinking-water exposure (3000 mg/L, converted to 304 mg/kg bw/d based on the drinking-water intake) can be designated as a LOAEL. Consequently, the NOAEL for endocrine effects will be 101 mg/kg bw/d.

4) **Human data**:

The CEHOS (2012) evaluation states that according to human case reports, resorcinol indeed exerts antithyroid functions. Data are old (all from before 1973), but quite clear:

long-term administration of resorcinol to permeable (damaged) skin can cause myxoedema (reduced thyroid function). Cessation of exposure causes the myxoedema to disappear.
The evaluation includes summaries of the following studies: Bull and Fraser (1950), Quentin *et al.* (1951), Berthezene *et al.* (1973), Katin *et al.* (1977), Yeung *et al.* (1983) and Roberts *et al.* (1990).
A study among factory workers with potential exposure to thiourea and resorcinol was unable to link 4 cases of hypothyroidism to this exposure (Roberts, 1990).

CEHOS (2012) states in its weight of evidence that resorcinol is evaluated as an ED in category 1 ('known to have produced ED adverse effects in humans or animal species living in the environment or when there is evidence from animal studies'). This is mainly based on human case studies showing antithyroid effects, but also supported by some *in vivo* animal and *in vitro* studies showing that resorcinol can affect the thyroid hormone system.

ECHA (2020):
The ECHA (2020a) support document also evaluated the abovementioned studies. Additional case reports on patients with hypothyroidism related to medical use of resorcinol on the skin were reviewed (Thomas 1961, Guinet 1967, Hart 1951, Hobson 1951).
The evaluation concludes that the adverse effects of resorcinol on thyroid function as well as its property to disrupt thyroid hormone synthesis have been established in humans.
In human cases, the effects were induced by daily doses of approximately 2 to 140 mg/kg/d for 3 months to 13 years.
Large uncertainties remain on the level of systemic exposure to resorcinol that induces effects on the thyroid and on the level of systemic exposure to resorcinol after different routes of exposure.

At its June 2020 meeting, ECHA's Member State Committee did not unanimously agree with the support document to classify resorcinol as an SVHC (substance of very high concern). However, the committee acknowledged that there is scientific evidence that resorcinol is an endocrine disruptor as defined by the World Health Organization (WHO).

Ref: ECHA 2020b, ECHA 2020c.

SCCS conclusion on potential ED disruption in humans

The SCCS concurs with CEHOS (2012) and ECHA (2020a) that resorcinol exerts anti-thyroid effects. However, while a clear level of exposure needed for such an effect cannot be derived from the available studies in humans, most of these studies point to a relatively much higher level of exposure than is the case from cosmetics.
The SCCS concurs with the ECHA (2020) evaluation that the USR 2005a report (with the overlapping Welsch 2008a publication) is relevant and regards it as the key study to evaluate the effects on the thyroid in rats. From this study, an overall NOAEL of 101 mg/kg/d is derived from the LOAEL of 304, which is based on the slightly increased TSH in F1 male rates receiving 3000 mg/L resorcinol in their drinking water.

SAFETY EVALUATION (INCLUDING CALCULATION OF THE MOS)

For the calculation of the MoS, the lowest NOAEL among those obtained from the different toxicological endpoints will be used, in accordance with the SCCS Opinion SCCS/1270/09. This NOAEL is 80 mg/kg bw/d, and was derived from the prenatal developmental toxicity study by gavage (USR 2005b, also cited as Foulon, 2005) and the 13-week toxicity study (USR 2004, also cited as Foulon, 2004).
Because of the rapid and almost complete absorption from the stomach, and because there is almost no metabolism in the skin upon topical application, a bioavailability adjustment will not be applied to the NOAEL.

Absorption through the skin (mean + 2SD)	DA	= 2.06 µg/cm²
Skin Surface area	SSA	= 580 cm^2
Dermal Absorption per treatment	SSA x DA x 0.001	= 1.19 mg
Typical body weight of human		= 60 kg
Systemic exposure dose (SED)	SSA x DA x 0.001 / 60	= 0.02 mg/kg bw

Hair and eyelashes up to 1.25 % and up to 0.5 % in hair lotions and shampoos:
No observed adverse effect level NOAEL = 80 mg/kg bw/d
(90-day study and maternal toxicity in prenatal developmental study, oral, rat)

Margin of Safety	**NOAEL/SED**	**=**	**4000**

3.5 DISCUSSION

Physicochemical properties

Toxicokinetics

In the skin, metabolism is slow and 5-77% of resorcinol is present as parent resorcinol after 24h. In hepatic cells, metabolism is efficient (half-life of 22 to 55 min). Fast systemic metabolism and excretion is observed but small amounts of free resorcinol (1.2-4.6%) are detected in urine after gavage administration.
The available data do not show accumulation in any organ or tissue, including the thyroid gland.

Exposure

Toxicological Evaluation

Irritation and corrosivity

A single dose of 0.1 mL of 2.5% aqueous solution of resorcinol caused mild conjunctival irritation in 2/3 animals on day 1 or day 2, when applied to the eye.

Skin sensitisation

Based on a re-evaluation of the submitted LLNA data, together with LLNA data reported in the open literature, resorcinol can be considered as a moderate skin sensitiser. Clinical publications indicate that, despite its widespread use, the prevalence of contact sensitisation to resorcinol in humans is very low.

Acute toxicity

The maximal non-lethal dose of resorcinol after a single administration in rats was 200 mg/kg bw. In a 17-day 5 d/wk gavage study in rats up to 450 mg/kg bw/d, no deaths occurred.

Repeated dose toxicity
In a 93-day gavage toxicity study (USR 2004, also cited as Foulon, 2005), at 250 mg/kg bw/day for all males and females (including satellites), showed intermittent convulsive movements, starting between weeks 6 and 8 and lasting until the end of the treatment period. Excessive salivation (majority of animals) and loud breathing (2 males) were also reported in the 250 mg/kg bw/day group. Mortality was mentioned in the 80 mg/kg bw/day (2 males) and the 250 mg/kg bw/day dosage group (1 female). According to the study report, observed deaths at these dose levels were not treatment-related but may be caused by lung lesions due to incidental gavage errors. With the exception of the two males that had convulsions and died, no clinical observations were recorded at 80 mg/kg bw/day. No treatment-related effects on body weight, food consumption, blood and urine parameters, organ weights and necropsy findings were noted. The female group receiving 250 mg/kg bw/day gained slightly less weight from week 4 to week 8. Examination of the animals during the Functional Observation Battery did not reveal any treatment-related effect.
Under the experimental conditions of the study, the NOEL was reported by the applicant to be 80 mg/kg bw/day.

In a 13-week oral toxicity study (NTP 1992) all female and 8 male rats from the high-dose group died from resorcinol-related toxicity during the first four weeks of the study. On day 2 of the study, rats from the 260 mg/kg bw/d group were given 520 mg/kg bw/d by mistake. Within 5 days, two males and four females in this group died. These deaths were attributed to incorrect dosing because no further deaths occurred among rats receiving the correct dose during the study.
The final mean body weights and changes in mean body weights of rats receiving resorcinol were similar to those of the controls. Tremors were observed in high-dose rats of both sexes. No differences were observed in haematology or clinical chemistry parameters that could be attributed to the resorcinol administration. The few significant differences in various parameters were scattered among the groups, but none were considered biologically significant. The levels of T3 and T4 in the 130 mg resorcinol/kg bw/d 5 days per week group were comparable to the control values. There were no gross or microscopical lesions attributable to resorcinol administration. Changes in organ weights were recorded in the liver of both sexes and in the adrenal glands of males. Absolute and relative liver weights of males dosed with 130 mg/kg bw/d or 260 mg/kg bw/d were statistically significantly increased compared to controls. For females, statistically significant increased absolute liver weights were recorded after doses higher than 32 mg/kg bw/d. The EFSA Panel (EFSA 2010) noticed that the increases in liver weights in the treated groups were slight, with no marked dose-response relationships, and not accompanied by any changes in clinical chemistry parameters indicative of impaired liver function, or by any histopathological changes. Therefore it was considered that the effect on the liver weight was not biologically significant. The absolute and relative weights of the adrenal glands in males from all dosed groups were significantly increased statistically compared to the controls. The absolute adrenal weights were low in the male controls, but no dose-response relationship was apparent, and changes in adrenal weights were not accompanied by histopathological findings. Due to the incorrect dosing of the animals in the 260 mg resorcinol/kg bw/day dose-group EFSA (2010) concluded that this dose-group should not be used to define the NOAEL, and established 130 mg/kg bw/d as the NOAEL in rats.

The 13-week oral toxicity study was also conducted in mice. Clinical signs of toxicity recorded for the high-dose animals were dyspnoea, prostration, and tremors. These signs appeared within 30 minutes of dosing. No resorcinol-related, biologically significant changes in haematology or clinical chemistry parameters were seen. Statistically significant

decreases were noted in absolute and relative adrenal gland weights in males from all dosed groups. According to EFSA (EFSA 2010), there was no dose-response relationship for the decreased adrenal weights and the changes were not accompanied by microscopical findings. A few other differences in various organ weights were scattered among the study groups, and none were considered to be biologically significant. There were no gross or microscopic lesions attributable to resorcinol administration.

From the carcinogenicity study (NTP 1992), based on the acute clinical signs of toxicity that were considered a resorcinol-related effect on the CNS, the EFSA Panel (EFSA 2010) concluded that the NOAEL was 50 mg resorcinol/kg bw/d. This NOAEL corresponds to a daily dose of 36 mg/kg/d when adjusted from the 5-day dosing week to a 7-day dosing week.
Since the dosing was performed by gavage and the clinical signs lasted 30-60 minutes after dosing, these signs might be the result of the high (local) dose. In the case of dermal application, such effects are not relevant. Therefore, 50 mg/kg bw/day will not be used as the NOAEL for the calculation of the MOS.

Reproductive toxicity

In a prenatal developmental study in rats (USR 2005b) there were no effects of treatment on foetal body weight. In the litters, no external, soft tissue or skeletal malformations or variations were considered to be treatment-related. There was an increase in the incidence of foetuses with an incompletely ossified interparietal at 40 and 80 mg/kg bw/day, when compared to controls, but in the absence of any effects at 250 mg/kg bw/day these observations were not considered to be treatment related. In the opinion of the SCCS the maternal NOAEL of resorcinol administered by gavage to pregnant female rats was 80 mg/kg bw/day and the developmental NOAEL was 250 mg/kg bw/day.

According to TUKES (2017), no indications of reproductive toxicity were seen in a dose-range finding study (USR, 2003) or in the two-generation reproductive toxicity study in rats (USR 2005a, Welsch 2008a).
Endpoints for neurotoxicity (i.e. brain weight and width, brain histology, functional observation battery (FOB), locomotor activity, acoustic startle response and Biel maze swimming trials) were investigated in the dose range-finding study (USR 2003), where dose-related effects on locomotor activity (in cumulative total and ambulatory counts) were observed in sexually mature F1 males at PND 61 (young adult). Locomotor activity was also increased in F1 females but the change was not statistically significant or dose-related. TUKES (2017) considered that increased motor activity at PND 61 may be an indication of latent alteration in motor activity. However, it was also considered that resorcinol, based on the results from limited developmental neurotoxicity measurements in the dose range-finding study is probably not a developmental neurotoxicant because significant effects were seen only in males, other behavioural endpoints were not affected, no indications of developmental delay were reported and no concurrent correlating changes in brain histopathology, weight or width were reported.

Mutagenicity / genotoxicity

Although induction of chromosomal aberrations in mammalian cells *in vitro* has been shown, this was not confirmed in one GLP *in vivo* assay. Moreover, in a range of non GLP studies from the open literature (from the 1980s), resorcinol did not induce micronuclei in the bone marrow of mice. In a well-conducted 2-year carcinogenicity study, resorcinol administered in water by gavage to rats and mice did not induce any tumorigenic effect.
It is therefore concluded that resorcinol itself does not have a genotoxic potential *in vivo*.

Carcinogenicity

There was no evidence of carcinogenic activity of resorcinol in male F344/N rats given 112 or 225 mg/kg bw/day or female F344/N rats given 50, 100, or 150 mg/kg bw/day. There was no evidence of carcinogenic activity of resorcinol in male or female B6C3F1 mice given 112 or 225 mg/kg bw/day.

Human data

Human case reports indicate that resorcinol exerts anti-thyroid effects. Data are old (all from before 1973), but indicate clearly that long-term administration of resorcinol to permeable (damaged) skin can cause myxoedema (reduced thyroid function). Cessation of exposure causes the myxoedema to disappear. While a dose-response cannot be derived from these studies, the exposures were in a medical setting with relatively high doses. A study in factory workers with hypothyroidism exposed to thiourea and resorcinol did not lead to any conclusions about a causal link.

Special investigation: endocrine activity

Resorcinol has been shown to be an inhibitor of the enzyme thyroid peroxidase *in vitro*. This explains the alterations in thyroid function and structure observed in animal studies following oral administration and the thyroid effects described in case reports about humans exposed to resorcinol in a medical setting. ECHA's eMSCA (TUKES 2017) considers that extrapolation of effects on follicular colloid content and thyroid hormone levels from rodents to human is not straightforward, due to suggested species differences in thyroid hormone homeostasis, i.e. healthy adult humans have lower thyroid hormone turnover rates (due to binding to thyroxine-binding globulin), the rat follicles contain much less colloid than primate follicles and humans have larger reserves of iodinated thyroglobulin, allowing them to compensate for reduced hormone synthesis in the thyroid.
In a two-generation study in rats (USR 2005a, considered to be a key study), preceded by a preliminary dose-range finding study, following administration of resorcinol in drinking water, sporadic statistically significant differences between mean doses in relation to various aspects of the thyroid function were noted. However, the biological relevance is questionable because of single outliers and/or absence of effects at higher dose steps.
In the preliminary study dose-range finding study, an increase in T3 in F0 females exposed to the highest dose of approximately 46 – 174 mg/kg/d (360 mg/L drinking water) was noted, but this effect was absent at higher doses in the key study. Moreover, there was no indication of an increased TSH. The increased locomotor activity (assessed as part of FOB) in the preliminary study occurred in the absence of other neurobehavioural changes.
The increased thyroid weight in female F2 is in contradiction to a decreased thyroid weight in the 13-week gavage study. A decreased T4 in female F2 pups at PND21 at the intermediate dose of approx. 237 mg/kg/d (1000 mg/L) was reported, but the decrease was absent at a higher dose and not statistically significant.
In the key study, an increased average TSH in male F1 pups at PND21 was reported at the intermediate dose of approx. 40 mg/kg (360 mg/L). On examination of the individual data, this was clearly based on a single outlier. A statistical test on outliers allowed the outlying values in the highest drinking-water concentration to be taken into account and therefore, 3000 mg/L, converted to 304 mg/kg bw/d based on the drinking-water intake can be designated as a LOAEL.
Overall from the 2-generation key study, for the majority of the thyroid parameters NOAELs can be derived from the absence of a biologically relevant effect at the highest test dose. From the TSH values in F1 males, an overall NOAEL for endocrine (thyroid) effects of 101 mg/kg bw/d can be derived.

4. CONCLUSION

1. In light of the data provided and taking under consideration the concerns related to potential endocrine disrupting properties of Resorcinol, does the SCCS consider Resorcinol safe when used as an oxidative hair dye in products intended for hair and eyelashes up to 1.25 % and up to 0.5 % in hair lotions and shampoos?

Keeping in view the evidence on endocrine disrupting properties of resorcinol, the SCCS assessment shows that resorcinol is safe when used as an oxidative hair dye in products intended for hair and eyelashes up to 1.25 % and up to 0.5 % in hair lotions and shampoos.

2. Alternatively, what is according to the SCCS, the maximum concentration considered safe for use of Resorcinol as an oxidative hair dye in products intended for hair and eyelashes and for hair lotions and shampoos?

/

3. Does the SCCS have any further scientific concerns with regard to the use of Resorcinol in cosmetic products?

Resorcinol is a moderate skin sensitiser based on data from animal studies. Clinical studies show that the frequency of contact sensitisation in humans is low.

The SCCS mandates do not address environmental aspects. Therefore, this assessment did not cover the safety of resorcinol for the environment.

5. MINORITY OPINION

/

6. REFERENCES

Aiston (1999) Aiston, S. and Agius, L.. *Leptin enhances glycogen storage in hepato-cytes by inhibition of phosphorylase and exerts an additive effect with insu*lin. Diabetes 1999;48(1), 15-20. doi: 10.2337/diabetes.48.1.15.

Alanko (1995) Alanko, J., Riutta, A., and Vapaatalo, H.. *Phenols Inhibit Prostaglandin E(2) Synthesis in A23187- Stimulated Human Whole-Blood and Modify the Ratio of Arachidonic-Acid Metabolite*s. Prostaglandins Leukotrienes and Essential Fatty Acids 1995;52(5), 299-301. doi: 10.1016/0952-3278(95)90030-6.

Arnott (1952) Arnott, D.G. and Doniach, I.. *The Effect of Compounds Allied to Resor-cinol Upon the Uptake of Radioactive Iodine (I-131) by the Thyroid of the Rat*. Biochemical Journal 1952;50(4), 473-479. doi: 10.1042/bj0500473

Basketter (2007) Basketter DA, Sanders D, Jowsey IR . *The skin sensitization potential of resorcinol: experience with the local lymph node assay*. Contact Dermatitis 2007; 56(4), 196–200. d oi: 10.1111/j.1600-0536.2006.01008.x

Berthezene (1973) Berthezene F. Resorcin induced hypothyroidism. Report of 2 cases. Lyon. Med. 230:319; 1973

Berthezene (1979) Berthezene, F., Perrot, L., Munari, Y., and Ponsin, G.. *Multiple Effects of Resorcinol on Thyroid- Function*. Annales D Endocrinologie 1979;40(1), 67-68.

Bull (1950) Bull GM, Fraser R . *Myxedema from Resorcinol ointment applied to leg ulcers*. Lancet 1950; 1 (6610), 851-855. doi: 10.1016/s0140-6736(50)90689-1

CEHOS (2012) Evaluation of 22 SIN List 2.0 substances according to the Danish proposal on criteria for endocrine disrupters. Danish Center on Endocrine Disrupters 2012, May 2012.

Cooksey (1985) Cooksey RC, Gaitan E, Lindsay RH, Hill HB, Kelly K . *Humic substances, a possible source of environmental goitrogens*. Organic Geochemistry 1985; 8(1):77–80. doi : 10.1016/0146-6380(85)90054-3

Darcis (2016) Darcis J, Goossens A, 2016. *Resorcinol: a strong sensitizer but a rare contact allergen in the clinic*. Contact Dermatitis 2016;74(5), 310-312. doi: 10.1111/cod.12532.

DiNardo (1985) DiNardo JC, Picciano JC, Schnetzinger RW, Morris WE, Wolf BA. *Teratological assessment of five oxidative hair dyes in the rat*. Toxicol Appl Pharmacol 1985;78(1):163-166. doi : 10.1016/0041-008X(85)90316-3

Divi (1994) Divi, R.L. and Doerge, D.R.. *Mechanism-Based Inactivation of Lactoperoxidase and Thyroid Peroxidase by Resorcinol Derivatives*. Biochemistry 1994;33(32), 9668-9674. doi: 10.1021/bi00198a036

Doniach and Fraser (1950) Doniach, I., Fraser. R.. *Effect of resorcinol on the thyroid uptake of I131 in ra*ts. Lancet 1950; 1 (6610):855-856. doi: 10.1016/s0140-6736(50)90690-8.

Doniach and Logothetopoulos (1953) Doniach, I, Logothetopoulos J. *The goitrogenic action of resorcinol in rats*. Br J Exp Pathol. 1953 Apr;34(2):146-51.

ECHA (2020a) Support Document to the opinion of the Member State Committee on identification of Resorcinol as a Substance of Very High Concern because of its endocrine disrupting properties (Article 57(f) - Human Health) Adopted on 12 June 2020. https://echa.europa.eu/documents/10162/7d16c5c3-4fe7-21c4-462c-7ef8234c1c36

ECHA (2020b) MSC opinion. https://echa.europa.eu/documents/10162/5ff2f41c-409e-7ab8-636e-e74aa17c49f0 (accessed july 2020)

ECHA (2020c) Minority opinion. https://echa.europa.eu/documents/10162/736eeb34-238e-a626-8217-4255adf92cba (accessed July 2020)

EFSA (2010). EFSA Panel on Food Additives and Nutrient Sources added to Food (ANS); Scientific Opinion on the use of Resorcinol as a food additive on request from the European Commission. EFSA Journal 2010;8(1):1411

Erexson (2005) G. Erexson. Resorcinol (A011): *In Vivo* Rat Micronucleus Assay in Resorcinol (A011). Covance Study No. 6182-114, 2005

Foulon (2004). Resorcinol (A011): 13-Week Toxicity Study by Oral Route (Gavage) in Rats Followed by a 4-Week Treatment-Free Period. CIT Study No. 26890 TCR, 2005. Also cited as USR 2004a.

Foulon (2005). Resorcinol (A011): Prenatal Developmental Toxicity Study by Oral Route (Gavage) in Rats. CIT Study No. 26889 RSR, 2005. Also cited as USR 2005b.

Géniès (2019) Géniès C, Jamin EL, Debrauwer L, *et al. Comparison of the metabolism of 10 chemicals in human and pig skin explants*. J. Appl. Toxicol. 2019;39(2):385–397. doi : 10.1002/jat.3730

Géniès (2020) Géniès C, Jacques-Jamin C, Duplan H, *et al.* Comparison of the metabolism of 10 cosmetics-relevant chemicals in EpiSkin™ S9 subcellular fractions and *in vitro* human skin explants. J. Appl. Toxicol. 2020;40(2) :313–326. doi : 10.1002/jat.3905

Ghisari (2009) Ghisari, M. and Bonefeld-Jorgensen, E.C., . *Effects of plasticizers and their mixtures on estrogen receptor and thyroid hormone functions*. Toxicology Letters 2009; 189(1), 67-77. doi: 10.1016/j.toxlet.2009.05.004

Gocke (1981) Gocke E, King M-T, Eckhardt K and Wild D (1981). *Mutagenicity of cosmetics ingredients licensed by the European Communities*. Mutation Research 1981; 90(2) 91-109. doi: 10.1016/0165-1218(81)90072-0

Hewitt (2020) Hewitt NJ, Grégoire S, Cubberley R, *et al.* Measurement of the penetration of 56 cosmetic relevant chemicals into and through human skin using a standardized protocol. J Appl Toxicol. 2020;40(3):403–415. doi : 10.1002/jat.3913

IPCS (2006) International Programme on Chemical Safety (2006). RESORCINOL (first draft). Concise International Chemical Assessment Document 71. World Health Organization. ISBN 92 4 153071 5

Katin (1977) Katin MJ, Teehan BP, Sigler MH, Schleifer CR, Gilgere GS. Resorcinol-induced hypothydroidism in a patient on chronic hemodialysis. Ann Intern Med. 1977;86(4):447-9. doi: 10.7326/0003-4819-86-4-447

Lloyd (2009) M. Lloyd. Resorcinol (A011): Mutation at the hprt locus of L5178Y Mouse Lymphoma cells using the Microtitre® fluctuation technique. Covance Study Number 413/172, 2009

Luzy (2013) Luzy AP, Orsini N, Linget JM, Bouvier G. Evaluation of the GADD45α-GFP GreenScreen HC assay for rapid and reliable *in vitro* early genotoxicity screening. J Appl Toxicol. 2013;33(11):1303-15. doi: 10.1002/jat.2793.

Lynch (2002) Lynch BS, Delzell ES, Bechtel DH. Toxicology Review and Risk Assessment of Resorcinol: Thyroid Effects. Reg. Tox. Pharm 2002; 36(2), 198-210. doi : 10.1006/rtph.2002.1585

Nemec (2005). A Drinking Water Two-Generation Reproductive Toxicity Study of Resorcinol in Rats. WIL Study No. 455003, 2005. Also cited as USR (2005a) Unpublished study report.

NTP (1992) National Toxicology Program. Toxicology and Carcinogenesis Studies of Resorcinol in F344/N Rats and B6C3F1 Mice. Technical Report Series No. 403. NIH Publication No. 92-2858, July 1992

OECD-AOP (2019) Crofton K, Gilbert M, Paul Friedman K, Demeneix B, Marty MS, Zoeller TR (2019). Adverse Outcome Pathway on inhibition of Thyroperoxidase and subsequent adverse neurodevelopmental outcomes in mammals, OECD Series on Adverse Outcome Pathways, n° 13, Éditions OCDE, Paris https://doi.org/10.1787/ea5aa069-en

Paul Friedman (2016) Paul Friedman KP, Watt ED, Hornung MW, Hedge JM, Judson RS, Crofton KM, Houck KA, Simmons SO *Tiered high-throughput screening approach to identify thyroperoxidase inhibitors within the toxcast phase i and ii chemical libraries*. Toxicol Sci 2016; 151:160-180. doi : 10.1093/toxsci/kfw034

Roberts (1990) Roberts FP, Wright AL, O'Hagan SA. *Hypothyroidism in textile wor*kers. J Soc Occup Med. 1990;40(4):153-6. doi: 10.1093/occmed/40.4.153.

Samuel KC. (1955). Experimental production of goiter in rats: With resorcinol and its
derivatives. Lab Invest 4:90-105

Seffner (1995) Seffner, W., Schiller, F., Heinze, R., and Breng, R. . *Subchronic application of humic acids and associated compounds provokes histological changes of goitre in the ra*t. Exp. Toxicol. Pathol. 1995; 47(1), 63–70. doi: 10.1016/S0940-2993(11)80288-5.

Sire (2004a) G. Sire. Resorcinol (A011): Acute Oral Toxicity in Rats – "Fixed Dose Method". CIT Study No. 26937TAR, 2004

Sire (2004b) G. Sire. Resorcinol (A011): Acute Dermal Irritation in Rabbits. CIT Study No. 26939 TAL, 2004

Sire (2004c) G. Sire. Resorcinol (A011): Acute Eye Irritation in Rabbits. CIT Study No. 26938 TAL, 2004

Sire (2004d) G. Sire. Resorcinol (A011): *In Vitro* Mammalian Cell Gene Mutation Test in L5178Y TK+/- Mouse Lymphoma Cells. CIT Study No. 27065 MLY, 2004

Sire G (2005). Resorcinol (A011): Evaluation of Skin Sensitisation Potential in Mice using the Local Lymph Node Assay (LLNA). CIT Study N° 26940 TSS, 2005

Sumitomo Chemical (2012). Resorcinol: GHS Classification of Skin Sensitization, 5 November 2012

Tian (2020) Tian S, Cyr A, Zeise K, Bryce SM, Hall N, Bemis JC, Dertinger SD. *3Rs-Friendly Approach to Exogenous Metabolic Activation that Supports High-Throughput Genetic Toxicology Testing*. Environ Mol Mutagen. 2020;61(4):408-432.. doi: 10.1002/em.22361.

Toner (2005) Toner F. The *In Vitro* Percutaneous Absorption of Radiolabelled Resorcinol Through Human Skin. Inveresk Study No. 774075, Report No. 24566, 2005

TUKES (2017) Finnish Safety and Chemicals Agency. Substance evaluation conclusion as required by REACH Article 48 and evaluation report for Resorcinol EC No 203-585-2 CAS No 108-46-3. 24 October 2017. Published at ECHA website: https://echa.europa.eu/documents/10162/97172844-3552-65bd-a03e-c75e445c0b62

USR (2003) Unpublished study report. M. Nemec: A Drinking Water Dose Range-Finding Reproductive Toxicity Study of Resorcinol in Rats. WIL Study No. 455002, 2003. Also cited as Nemec 2003.

USR (2004) Unpublished study report. O. Foulon. Resorcinol (A011): 13-Week Toxicity Study by Oral Route (Gavage) in Rats Followed by a 4-Week Treatment-Free Period. CIT Study No. 26890 TCR, 2005. Also cited as Foulon, 2004.

USR (2005a) Unpublished study report. M. Nemec: A Drinking Water Two-Generation Reproductive Toxicity Study of Resorcinol in Rats. WIL Study No. 455003, 2005. Also cited as Nemec, 2005.

USR (2005b) Unpublished study report. O. Foulon: Resorcinol (A011): Prenatal Developmental Toxicity Study by Oral Route (Gavage) in Rats. CIT Study No. 26889 RSR, 2005. Also cited as Foulon, 2005.

Uter (2015) Uter W, Bensefa-Colas L, Frosch P, Giménez-Arnau A, John SM, Lepoittevin JP, Lidén C, White IR, Duus Johansen J . *Patch testing with hair cosmetic series in Europe: a critical review and recommendation*. Contact Dermatitis 2015;73(2), 69-81. doi: 10.1111/cod.12424.

Waring (2012) Waring RH, Ramsden DB, Jarratt PDB, Harris RM. *Biomarkers of endocrine disruption: Cluster analysis of effects of plasticisers on phase 1 and phase 2 metabolism of steroids*. Int J Androl 2012;35:415-423.10.1111/j.1365-2605.2012.01248.x

Welsch (2008a) Welsch F, Nemec MD, Lawrence WB . *Two-generation reproductive toxicity study of Resorcinol administered via drinking water to CRL:CD (SD) rats*. Int. J. Toxicol 2008;27(1), 43-57. doi: 10.1080/10915810701876679.

Welsch (2008b) Welsch, F.. *Routes and modes of administration of resorcinol and their relationship to potential manifestations of thyroid gland toxicity in animals and man*. International Journal of Toxicology 2008;27(1), 59-63. doi: 10.1080/10915810701876687.

Whitwell (2004) J. Whitwell. Resorcinol (A011): Induction of micronuclei in cultured human peripheral blood lymphocytes. Covance Study No. 413/68, 2004

Whitwell (2015) Whitwell J, Smith R, Jenner K, Lyon H, Wood D, Clements J, Aschcroft-Hawley K, Gollapudi B, Kirkland D, Lorge E, Pfuhler S, Tanir JY, Thybaud V. *Relationships between p53 status, apoptosis and induction of micronuclei in different human and mouse cell lines in vitro: Implications for improving existing assay*s. Mutat Res Genet Toxicol Environ Mutagen 2015;789-790:7-27. doi: 10.1016/j.mrgentox.2015.05.011

WHO (2006) WHO/International Programme on Chemical Safety; Concise International Chemical Assessment Document 71 Resorcinol pp.1-72 (2006), Available from, as of 2020: https://www.who.int/ipcs/publications/cicad/cicad71.pdf?ua=1

Yeung (1983) Yeung D, Kantor S, Nacht S, Gans EH. *Percutaneous absorption, blood levels and urinary excretion of Resorcinol applied topically in humans*. Int J Dermatolol 1993;22(5), 321-324. doi: 10.1111/j.1365-4362.1983.tb02149.x.

7. GLOSSARY OF TERMS

See SCCS/1628/21, 11th Revision of the SCCS Notes of Guidance for the Testing of Cosmetic Ingredients and their Safety Evaluation – from page 181

8. LIST OF ABBREVIATIONS

See SCCS/1628/21, 11th Revision of the SCCS Notes of Guidance for the Testing of Cosmetic Ingredients and their Safety Evaluation – from page 181