Scientific Committee on Consumer Safety

SCCS

SCIENTIFIC ADVICE ON

the safety of triclocarban and triclosan as substances with potential endocrine disrupting properties in cosmetic products

The SCCS adopted this scientific advice
during the plenary meeting on 24-25 October 2022

ACKNOWLEDGMENTS

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This scientific advice has exceptionally been subject to a commenting period of eight weeks after its initial publication (from 25 March to 27 May 2022). Comments received during this period were considered by the SCCS. Main changes of the content occurred in sections 3.2.1, 3.4.3.3, 3.4.3.8, 3.5.2.1, 3.5.2.2, 3.6 as well as respective discussion part and conclusions.

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

1. ABSTRACT

The SCCS concludes the following:

In light of the information submitted via the call for data, the currently available scientific literature, relevant in silico tools and SCCS' expert judgement and taking under consideration in particular the concerns related to potential endocrine disrupting properties, the SCCS is requested:

1. *To identify and justify specific concerns regarding the safe use of triclocarban and triclosan in cosmetic products*

Based on the safety assessment carried out in consideration of all available information, including the potential endocrine effects, the SCCS is of the opinion that:

For Triclocarban

- The use of triclocarban as a preservative in **dermally applied cosmetic product** is safe up to a maximum concentration of 0.2% for both children (0.5-18 years) and adults, when used individually or in combination.
- In addition to the preservative function, the use of triclocarban is also safe up to a maximum concentration of 1.5% **in rinse-off product** when used individually or in combination for both children (0.5-18 years) and adults.
- However, the use of triclocarban to a maximum concentration of 0.2% **in mouthwash** is not safe for adults and children and in toothpaste is not safe for children below 6 years old.
- This assessment does not include exposure of babies through wipes.

For Triclosan

- The use of Triclosan as a preservative at the concentrations reported in entry 25 of Annex V in **dermally applied cosmetic product** is safe except for body lotions, when used individually or in combination, for both adults and children (0.5-18 years).
- The use of Triclosan as a preservative **in toothpaste** is safe at the concentration of 0.3% when used individually for both adults and children (0.5-18 years) but it is not safe when used in combinations for children below 3 years old.
- For adults, the use of Triclosan as a preservative **in mouthwash** is safe at the concentration of 0.2% when used individually but not when used in combination. For children and asdolescents, it is not safe at 0.2%, even when used individually.

2. *To highlight if there is a potential risk for human health from the use of triclocarban and triclosan in cosmetic products.*

The SCCS is not aware of the use of triclocarban and triclosan together in a single product, and, therefore, this has not been assessed.

Keywords: SCCS, scientific advice, triclocarban, triclosan, Regulation 1223/2009, CAS No. 101-20-2, EC No. 202-924-1, CAS No. 3380-34-5, EC No. 222-182-2

Document to be cited as: SCCS (Scientific Committee on Consumer Safety), Request for a scientific advice on the safety of triclocarban (CAS No. 101-20-2, EC No. 202-924-1) and triclosan (CAS No. 3380-34-5, EC No. 222-182-2) as substances with potential endocrine disrupting properties used in cosmetic products, preliminary version of 15-16 March 2022, final version of 24-25 October 2022, SCCS/1643/22

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They are: the Scientific Committee on Consumer Safety (SCCS) and the Scientific Committee on Health, Environmental and Emerging Risks (SCHEER) and are made up of scientists appointed in their personal capacity.

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

SCCS

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

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2. MANDATE FROM THE EUROPEAN COMMISSION

Background

1. 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 explicit 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 to 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. Triclocarban and triclosan are among the above-mentioned 14 substances for which the call for data took place.

2. Existing information on triclocarban

In cosmetic products, the ingredient triclocarban (CAS No. 101-20-2, EC No. 202-924-1) with the chemical name '1-(4-Chlorophenyl)-3-(3,4-dichlorophenyl)urea' is regulated as a preservative (entry 23 of Annex V) at a maximum concentration of 0.2 %. Furthermore, triclocarban is restricted to rinse-off products at a maximum concentration of 1.5 % (entry 100 of Annex III).

Triclocarban has been subject to different safety evaluations by the SCCNFP in 1999[4] and SCCP in 2004 (SCCP/0851/04). In particular, the last SCCP opinion states that '...the use of triclocarban for non-preservative purposes in cosmetic rinse-off hand and body care products up to a maximum concentration of 1.5% does not pose a direct risk to the health of the consumer. However, the SCCP would like to draw the Commission's attention to the possible effects of triclocarban to the environment and, subsequently, on human health from such environmental contaminations'.

[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-cosmeticproducts_en
[3] Benzophenone-3, kojic acid, 4-methylbenzylidene camphor, propylparaben, triclosan, resorcinol, octocrylene, triclocarban, butylated hydroxytoluene (BHT), benzophenone, homosalate, benzyl salicylate, genistein and daidzein
[4] https://ec.europa.eu/health/scientific_committees/consumer_safety/opinions/sccnfp_opinions_97_04/sccp_out59_en.htm

3. Existing information on triclosan

The ingredient triclosan (CAS No. 3380-34-5, EC No. 222-182-2) with the chemical name '5-Chloro-2-(2,4-dichlorophenoxy)phenol' is regulated as a preservative (entry 25 of Annex V) in the following product types:

a) Toothpastes; Hand soaps; Body soaps/Shower gels; Deodorants (non-spray); Face powders and blemish concealers; Nail products for cleaning the fingernails and toenails before the application of artificial nail systems - at a maximum concentration of 0.3 %; and

b) Mouthwashes - at a maximum concentration of 0.2 %.

Triclosan has been subject to different safety evaluations by the SCCNFP in 2002 (SCCNFP/0600/02)[5], by SCCP in 2006 (SCCP/1040/06)[6], 2008 (SCCP/1192/08)[7], 2009 (SCCP/1251/09)[8] and by SCCS in 2011 (SCCS/1414/11)[9]. In particular, the last SCCS opinion resulted in the existing regulatory measures that allow different concentration of triclosan based on the product.

Terms of reference

In light of the information submitted via the call for data, the currently available scientific literature, relevant in silico tools and SCCS' expert judgement and taking under consideration in particular the concerns related to potential endocrine disrupting properties, the SCCS is requested:

1. to identify and justify specific concerns regarding the safe use of triclocarban and triclosan in cosmetic products

2. to highlight if there is a potential risk for human health from the use of triclocarban and triclosan in cosmetic products.

[5] https://ec.europa.eu/health/ph_risk/committees/sccp/documents/out182_en.pdf
[6] https://ec.europa.eu/health/ph_risk/committees/04_sccp/docs/sccp_o_073.pdf
[7] https://ec.europa.eu/health/ph_risk/committees/04_sccp/docs/sccp_o_166.pdf
[8] https://ec.europa.eu/health/scientific_committees/consumer_safety/docs/sccs_o_023.pdf
[9] https://ec.europa.eu/health/scientific_committees/consumer_safety/docs/sccs_o_054.pdf

3. SCIENTIFIC ADVICE

3.1 PHYSICOCHEMICAL PROPERTIES

3.1.1 Triclocarban

INCI name:	Triclocarban
IUPAC name:	1-(4-chlorophenyl)-3-(3,4-dichlorophenyl)urea
Chemical names:	N-(4-chlorophenyl)-N'-(3,4-dichlorophenyl)urea; 3,4,4'-Trichlorocarbanilide urea, N-(4-chlorophenyl)-N'-3,4-dichlorophenyl)
Trade names:	Preventol SB
COLIPA n°:	P29
CAS number:	101-20-2
EINECS number:	202-924-1
Formula:	$C_{13}H_9Cl_3N_2O$
Physical form:	White powder
Molecular weight:	315.59
Solubility:	0.11 mg/L at 20°C in water, 0.624 mg/L at 25 °C in water, 1600 mg/L at 35 °C in methanol
Log P_{ow}:	3.633 at 25 °C
Melting point:	245.3°C at 977.9 hPa
Boiling point:	> 250°C at 978.0hPa
Vapour pressure:	4.81E-9 hPa at 25 °C
Density:	650 kg/m³ (bulk density), 0.336 cm^3 at 20 °C, 1.53 g/cm^3 at 25 °C
Particle size distribution	150 µm to 75 µm
pH:	7.5 (1% w/w at 31 °C)
pKa:	$2.4*10^{-14}$ at 30 °C

Ref.: SCCP 2005; ECHA 2022a

3.1.2 Triclosan

INCI name:	Triclosan
IUPAC name:	5-chloro-2-(2,4-dichlorophenoxy)phenol
Chemical names:	2,4,4'-trichloro-2'-hydroxy-diphenylether
Trade names:	Irgasan® DP300, Irgasan® PG60, Irgacare® MP, Irgacare® CF100, Irgacide® LP10. Triclosan is also referred to as Irgasan, DP300, FAT 80'023), CH 3565, and GP 41-353 in a number of toxicology studies
CAS number:	3380-34-5
EINECS number:	222-182-2
Formula:	$C_{12}H_7Cl_3O_2$
Physical form:	White crystalline powder
Molecular weight:	289.5
Log P_{ow}:	4.9 at 20 °C at pH 5
Melting point:	56.4 °C
Boiling point:	decomposes at >253°C before boiling
Relative density:	1.55 ± 0.04 g/cm^3 at 22 °C
Vapour pressure:	0.0003 Pa at 20 °C ($2.25\ 10^{-6}$ mmHg)
pKA:	8.14 (20 °C)
Solubility:	0.01 g/L at 20 °C in distilled water 0.04 g/L at 50 °C in distilled water

At 25 °C in g/100 g solvent	
1 N caustic soda	31.7
1 N sodium carbonate	0.40
1 N ammonium hydroxide	0.30
Triethanolamine	>100
Acetone	>100
Ethanol 70% or 95%	>100
Isopropanol	>100
Propylene glycol	>100
Polyethylene glycol	>100
Methyl cellosolve	>100
Ethyl cellosolve	>100
Dipropylene glycol	~40
Glycerine	0.15
n-Hexane	8.5
Petroleum jelly	~0.5
Tween 20	>100
Tween 80	>100
Triton X-100	>100
Olive oil	~60
Castor oil	~90
n-octanol	4.81 (at 20 °C)

Ref.: SCCP 2009; ECHA 2022b

3.2 TOXICOKINETICS

3.2.1 Triclocarban

From SCCP/0851/04

Oral route

Triclocarban was moderately absorbed *via* the oral route and, depending on the vehicle and exposure conditions, poorly to moderately absorbed by dermal application. On the basis of a number of ADME investigations in various species, it was estimated that the absorption following oral exposure in humans must be greater than 27%.

Dermal penetration

In humans, it was estimated that without a rinsing step, about 7% of topically applied triclocarban dissolved in acetone was absorbed and systemically available. In a typical rinse-off scenario mimicked by a showering study with human subjects using bar soap containing triclocarban, about 0.39% triclocarban of the total applied dose was systemically available.

In all species investigated, triclocarban was extensively metabolized to compounds that were more water-soluble and hence, more readily excreted than the parent compound. Both direct conjugation and hydroxylation followed by conjugation were observed. The principal metabolites common to all species were the sulphate and glucuronide conjugates of 2', 3'- and 6-Hydroxy-triclocarban. The rat also produced the glucuronide and sulphate of 2',6-Dihydroxy-triclocarban. In none of the species examined was the C-N bond in triclocarban cleaved as a result of metabolism. In humans, the plasma N- and N'-glucuronides of triclocarban were eliminated with a half-life time of 2h into urine, while the ortho-hydroxy sulfates of triclocarban were removed with a half-life time of 20h, presumably into the bile.

The faeces were the major route of excretion of radioactivity in humans after intravenous and dermal absorption of triclocarban. The ratio of amounts of faecal to urinary excretion of radioactivity was about 2:1.

Ref.: SCCP 2009

In vitro taken from SCCP 2005

The dermal absorption of 14C-labeled Triclocarban was investigated in static and flow-through *in vitro* skin cell systems using full thickness human newborn and adult as well as a monkey skin. Triclocarban (4 µL) in acetone was applied onto the skin models at a concentration of 27 µg/cm^2. The static cells had a volume of 3.77 ml and an epidermal surface area of 0.126 cm^2 . The flow cells had the same surface area and a flow rate of 15 ml/h. At 37 °C, 2.5% of the applied dose was absorbed in human newborn foreskin, 0.60 % in human adult foreskin, 0.29 % in human infant abdominal skin, 0.26 % in human newborn abdominal skin and 0.23 % in human adult abdominal skin. In the monkey adult abdominal skin model 0.25 % of the applied dose was absorbed. In the continuous flow system at 23°C, 6% ± 2.0 % of the applied dose was reported to be absorbed in the human adult abdominal skin model. The latter findings were in good correlation with a human *in vivo* investigation (Wester *et al.*, 1985).

Ref.: 43

New data

Six human volunteers took a shower with commercial 0.6% triclocarban containing soap. Before showering, the participants were questioned about their use of triclocarban-containing products and instructed not to use them during the sampling period. The individuals took a shower, rubbing soap over the whole body except for head and genitals. In order to minimize interindividual differences in shower procedures, the individuals let the foam stand for 15 min prior to wash off. Aliquots from each urination over a time span of 24-48 h and a single sample after 72 h were collected. The major route of renal elimination was excretion as N-glucuronides. The mean soap consumption was 11.7±2.6 g (70±15 mg of triclocarban), corresponding to an average maximal topical dose of 1 mg/kg body weight (40 mg/m^2 body surface area). The absorption was estimated at 0.6±0.2%.

Ref.: Schebb 2011

SCCS comment
Both the study used by SCCP in 2005, (Scharpf *et al.* 1975) and Schebb *et al.* (2011), had similar designs: six human volunteers participated in a body showering experiment, and 7 g soap containing 2% triclocarban applied with a lathering time of 2.5 minutes vs 11.7 g soap containing 0.6% triclocarban with a lathering time of 15 minutes, respectively. The recovery level of 0.39% reported by Scharpf *et al.* was based on levels in faeces after six days and in urine after two days (0.23% and 0.16 % of applied dose, respectively). The recovery level of 0.6±0.2% reported by Schebb *et al.* was based on levels in urine after two days.

The studies reported by Scharpf *et al.* (1975) and Schebb *et al.* (2011) do not meet the SCCS basic criteria for dermal absorption studies as outlined in the SCCS Notes of Guidance (2021) and hence cannot be used for calculation of SED. The SCCS will therefore use the value of 6% + 2 % = 8% (Mean + SD) estimated by Wester *et al.* (1985) in an *in vitro* study.

3.2.2 Triclosan

From SCCP/1192/08 and SCCS/1414/11

Animals

More than 30 non-clinical pharmacokinetics and/or toxicokinetics studies investigating absorption, distribution, metabolism, and excretion of triclosan have been reviewed for this dossier.

Triclosan is rapidly absorbed (via the oral, intraperitoneal, and intravaginal routes of administration) in all species. Specific studies conducted in rats indicated that the level of absorption was between 70 to 80% following oral administration in this species. Subsequent to absorption after oral administration, 2 peaks in plasma triclosan levels were detected in mice and rats at 1 and 4 hours, which is indicative of enterohepatic circulation. Evidence from both hamster and rat studies provide evidence of a lack of bioaccumulation/bioretention of triclosan following repeated oral doses.

Triclosan is widely distributed in organs and tissues, with well-perfused, and excretory, organs such as liver and kidney, as well as lung, heart, GI tract, and gall bladder showing highest levels following oral, dermal, or intravenous. Administration in rodents and monkeys. Levels of triclosan in mouse liver were higher than in plasma following repeated dosing with triclosan.

Following absorption, the parent triclosan compound was found to be metabolised to both glucuronide and sulfate conjugates.

Triclosan was shown to be excreted primarily in the faeces of mice and rats following oral administration, while the predominant excretion route in hamsters and monkeys was via the urine. The faecal excretion route also predominated in rats following dermal applications of triclosan.

Repeated dosing in mice led to an increased half-life for triclosan and its sulfate conjugate as measured in the kidney, and elevated liver triclosan levels (~2- to 3-fold) in male mice (with respect to levels measured in the plasma and kidney). The higher levels of triclosan in mouse liver than in plasma may be correlated with toxicology findings in mouse toxicology studies. Differences between mice, rats, and hamsters in hepatic levels of triclosan also may correlate with differences in the incidence of liver-related findings in these species, with the mouse showing greater sensitivity to liver effects, but both the rat and hamster showing either a lower incidence or no liver effects.

Humans

A total of over 30 pharmacokinetic studies investigating the absorption, metabolism and excretion of triclosan in humans have been reviewed. In the absence of data showing tissue levels of triclosan following single and repeated exposures, evidence of a lack of bioaccumulation or bioretention of triclosan is provided by an examination and comparison of plasma triclosan levels in a number of studies.

Triclosan is very well absorbed following oral ingestion (up to 98% of the dose). However, under normal conditions of toothpaste use (*i.e.*, expectoration and rinsing) or following percutaneous application of several different personal care products, there is only limited absorption (approximately 5 to 10% of the dose via either of these routes of administration). Based on plasma levels and percentage of dose absorbed, it is clear that low exposures to triclosan occur following either toothpaste use or soap/hand wash use and that, with repeated exposures using either route, low steady-state levels of triclosan are reached after approximately 7 to 10 days. Due to a pronounced first-pass effect, there is near total conversion of absorbed triclosan to glucuronic and sulphuric acid conjugates.

The human oral and dermal data provide no evidence for a bioaccumulation potential. Likewise, the kinetic data in rats and hamsters provide no evidence for a bioaccumulation in these species, whilst in mice retention of triclosan (and/or metabolites) appears to occur in liver.

Kinetics of triclosan are qualitatively similar, but the observed quantitative differences between humans and several animals make human data the first choice for the safety evaluation of triclosan-containing consumer products.

Table 1 presents a summary of the values from the *in vitro* studies conducted in human skin samples.

Table 1. Summary of Dermal Absorption Values in Human Skin Samples from *in vitro* studies for triclosan taken from SCCP/1192/08

Test Formulation	% Triclosan in test material	Dermal Absorption (SCCP)	
		%	µg/cm²
w/o Emulsion	0.2%	11.3	0.420
Deodorant formulation	0.2%	7.7	0.303
Soap solution formulation	0.02%	7.2	0.0306
Ethanol/water	--	30.3%	--

Ref.: SCCP 2009; SCCS 2011

SCCS comment
Since no new data on dermal absorption of triclosan were submitted in the call for data, the values taken from SCCP (2009) will be used for the SED calculations.

3.3 FUNCTION AND USES

Triclocarban

Triclocarban is an antibacterial agent used as an ingredient in personal care products, especially dermal cleaning products such as antibacterial bar/liquid soaps, body lotions, deodorants, detergents, medical disinfectants, aftershave soaps, hand sanitizers, toothpaste, handwash and mouthwash, body washes, cleansing lotions, baby teethers and wipes for its sanitizing properties and detergents. It acts as a fungicide and preservative in air fresheners, fabric and leather finishing agents.
In 2016, the U.S. Food and Drug Administration banned its use in over-the-counter hand and body washes.

Ref.: Iacopetta 2021

Triclosan

Triclosan is effective against many different bacteria as well as some fungi and protozoa. It is used as an antiseptic, preservative and disinfectant in healthcare and in consumer products including cosmetics, household cleaning products, plastic materials, toys and paints. It is also included in surface of medical devices, plastic materials, textiles and kitchen utensils where it acts as a bactericide for extended periods of time.

Ref.: EU 2010

3.4 TOXICOLOGICAL EVALUATION

3.4.1 Toxicological evaluation of triclocarban

Irritation / sensitisation
Data from experimental animal and/or human studies indicate that triclocarban is a weak skin irritant but not an eye irritant. Experimental and clinical data show no evidence of skin sensitisation. Triclocarban has been found to be non-photoallergenic in an experimental animal study.

Acute / repeated dose toxicity
Triclocarban was found to be low acute oral, dermal and intraperitoneal toxicity.

In SCCP (2005) the following rationale was given on the choice of NOEL:
In the 2-year chronic feeding study, the rats were fed with a diet containing triclocarban at doses of 25, 75, and 250 mg/kg bw/d. At the highest administered dose, the investigators observed a reduction in food consumption, mean body weight and some changes in organ weights and the blood chemistry (i.e., increases in alkaline phosphatase, blood urea nitrogen, glucose, and bilirubin at various time points in the male animals). Decrease in food consumption, body weights, and organ weights (e.g., liver, spleen) were also observed in the animals in the mid dose group of 75 mg/kg bw/d. The NOEL was established at 25 mg/kg bw/d and the lowest observed effect level (i.e., LOEL) at 75 mg/kg bw/d.

Reproductive/developmental Toxicity
Triclocarban may affect the reproductive function of males (fertility and/or male sexual behaviour) and females (pre-implantation and/or implantation development) and cause adverse effects on the offspring via lactation.

The SCCP (2005) derived a NOAEL for reproductive and developmental toxicity based on a three-generation study in rats: F0 generation NOAEL = 3000 ppm (*i.e.*, approximately 280 mg/kg/day); F1 generation NOAEL = 1000 ppm (*i.e.*, approximately 95 mg/kg/day; F2 generation NOAEL = 3000 ppm (*i.e.*, approximately 300 mg/kg/day).

Mutagenicity / genotoxicity
Triclocarban was not found to be mutagenic in the Ames test or clastogenic in the chromosomal aberration test with and without metabolic activation.

Carcinogenicity
In a two-year rat chronic feeding study, there was no evidence for a dose-related increase in tumour incidence and it was concluded that triclocarban was not carcinogenic under the conditions of the study.

Human data
/

Ref.: SCCP 2005

3.4.2 Toxicological evaluation of triclosan

Irritation / sensitisation
Data from human use evaluating the skin and oral mucosa irritation effects of triclosan alone, or in combination with SLS, indicate that triclosan 0.3% is not a skin or oral mucosal irritant. Triclosan at concentrations of 1 to 10% produced only slight, reversible irritation in the rabbit

eye. Clinical experience has shown that triclosan does have a low sensitisation potential in humans. Possible photocontact allergy has been rarely reported.

Acute / repeated dose toxicity
Triclosan is not acutely toxic via the oral route of administration, with high oral intubation LD50 values in the range of 3,750 to 5,000 mg/kg body weight in mice and rats, and an oral capsule LD50 value of greater than 5,000 mg/kg body weight in dogs.

In the SCCP Opinion SCCP/1192/08 (SCCP, 2009) the following rationale was given on the choice of NOAEL: *"The derived NOAELs from subchronic and chronic studies in different species were compiled. EPA in its recent evaluation selected the NOAEL of the baboon study (30 mg/kg bw/d) for risk assessment based on clinical signs of toxicity which are presumably due to oral treatment. This might not be relevant for cosmetic uses. The applicant in its safety evaluation used the NOAEL of the 95-week study in hamsters as this species was judged to be the most relevant to humans based on pharmacokinetics (75 mg/kg bw/d). Alternatively, as a more conservative value, the NOAEL of the 104-week rat study (≈ 48 mg/kg bw/d for both sexes) was used. SCCP considers the NOAEL of this long-term toxicity study in rats as 12 - 17 mg/kg bw/d (≈ 14.5 mg/kg bw/d) due to haematotoxicity and decreased absolute and relative spleen weights. Haematotoxicity was also detected in the 13-week subchronic oral toxicity studies in mice and rats, in hamsters only at higher doses and in the 1-year toxicity study in baboons. This was further confirmed by changes in haematology parameters in the long-term studies in mice and hamsters. Interestingly, also in the 13-week subchronic dermal toxicity study in rats changes in erythrocytes parameters were observed. The SCCP will use the NOAEL of 12 mg/kg bw/d of the long-term toxicity study in rats for risk assessment."* The LOAEL from the 104-week rat study was 40 mg/kg bw/day.

Reproductive / developmental toxicity
The SCCP (2009) derived a NOAEL of 65 mg/kg bw/d based on decreases in foetal body weights and the mean number of live pups reported in previous reproductive toxicity studies in the rat.

Mutagenicity / genotoxicity
Triclosan can be considered to have no relevant genotoxic potential *in vivo*.

Carcinogenicity
Triclosan is not classified as carcinogen according to CLP regulation. It should be noted that triclosan is a peroxisome proliferator in mice liver.

Human data
In addition to the indications of good tolerability and safety from historical and consumer use of personal care products containing triclosan, a number of clinical studies showed no signs of overt toxicity in over 3,000 subjects that used triclosan-containing toothpaste for 12 weeks to 3 years.

Ref.: Ciba-Geigy 1986; SCCP 2009; SCCS 2011

3.4.3 Special investigations

3.4.3.1 Endocrine activity of triclocarban and triclosan: Non-test information, *in silico*, read across, *in chemico* (Level 1)

Plosnik *et al.* (2015) and Kenda *et al.* (2020) have assessed the endocrine-disrupting potential of triclocarban and triclosan using two *in silico* platforms Endocrine Disruptome and VirtualToxLab (Table 2). Endocrine Distruptome predicted moderate binding to antagonist conformation of androgen receptor (AR) and agonist conformation of estrogen receptor α (ERα) for triclocarban. Further, high probability of binding was assigned to antagonist

conformation of ERβ for triclocarban. In VirtualToxLab triclocarban was predicted to interact with nuclear receptors in nanomolar concentrations or lower for glucocorticoid receptor (GR) and triclosan for progesterone receptor (PR) and both isoforms of thyroid receptor (TRα and β).

Ref.: Plosnik 2015; Kenda 2020

3.4.3.2 Endocrine activity of triclocarban and triclosan: *In vitro* and other assays (Level 2)

Results from studies on triclocarban and triclosan using cell based *in vitro* assays and binding affinity assays are summarised in Table 2.

In vitro data detailed in Table 2 underneath suggest some evidence of estrogenic activity of triclocarban, with weak to strong capacity to bind both ERα and ERβ, depending on the assay and the cell model, as detail in the table. Regarding androgenic activity, triclocarban is a weak agonist of AR and a moderate anti-androgenic compound. Data regarding the affinity of triclocarban to GR are in favour for a weak binding capacity, depending also on the cell line and the assay. Regarding TH, triclocarban is able to bind TRα and β, but as a weak antagonist. Interestingly, triclocarban is able to strongly bind MR and activate CAR. To summarize and as mentioned by the Danish Centre on endocrine disrupters (2018), *in vitro* MoA of triclocarban should be considered as moderate, with an amplification of androgen- and estrogen-mediated activity, including non-direct effects as detailed under Table 2.

Regarding triclosan, as already mentioned in the DTU report (2019), *in vitro* data show some evidence of estrogenic activity of triclosan. The antiandrogenic mode of action *in vitro* is better-documented. Few data are suggesting that triclosan is a weak antagonist to TR, and is able to bind some other receptors such as LXR, MR, PR, PPARγ and TTR. Some indirect effects were also reported confirming the androgen- and estrogen-mediated activity of triclosan.

Ref.: Danish Centre on Endocrine Disrupters 2018; DTU 2019

Table 2. Summary of *in silico* and *in vitro* data for triclocarban and triclosan

	AR	ER	GR	TR	other NRs
Triclocarban *In silico*					
Endocrine Disruptome binding prediction					
Kenda *et al.* 2020	Intermediate (ARan)	Intermediate (ERα) Weak (ERβ) Strong (ERβan)	Weak	Weak (TRα) Weak (TRβ)	No binding
Plosnik *et al.* 2015			Weak affinity	Weak affinity (α, β)	MR: strong affinity
VirtualToxLab™ binding prediction					
Kenda *et al.* 2020	No binding	81.4 µM (ERα), 47.6 µM (ERβ)	633 nM	No binding	3.62 µM (MR)
Triclocarban *In vitro*					
Cell-based in vitro assays					

	AR	ER	GR	TR	other NRs
Ahn *et al.* 2008 Chen *et al.* 2008 Christen *et al.* 2010 Yueh *et al.* 2012 Huang *et al.* 2014 Tarnow *et al.* 2013 Kolsek *et al.* 2014a Kenda *et al.* 2020	Enhancer of T activity in T47D-ARE cells Enhancer of T activity in HEK-2933Y cells Enhancer of DHT activity in MDA-kb2 cells Agonist in AR-EcoScreen cells Agonist (1-2.5 µM in AR EcoScreen Cells)	Enhancer of E2 activity in BG1-ERE cells (Erα) Enhancer of E2 activity in HeLa9903 cells Erα (activated ER) reporter gene assay in CV1 cells → weak estrogenic effect Agonist in BG1-ERE cells ERα activated (strong estrogen, similar potency as estradiol) in transfected CV1 cells. Agonist in hERα-HeLa-9903 cells Agonist in, MCF-7 cells (E-Screen assay)	Enhancer of HC activity in MDA-kb2 cells Antagonist in MDA-kb2 cells	Antagonist in GH3.TRE-Luc cells	CAR activated in transfected CV1 cells
Binding affinity assay					
Chen *et al.* 2008 Kenda *et al.* 2020	Negative for recombinant AR Negative on isolated AR		Negative in binding affinity Assay	Antagonist	
Triclosan *In silico*					
Endocrine Disruptome binding prediction					
Kenda *et al.* 2020	Weak (ARan)	No binding	Weak	No binding (TRα), No binding (TRβ)	No binding
VirtualToxLab™ binding prediction					
Kenda *et al.* 2020	6.22 µM	79.4 µM (Erα)	7.36 µM	190 nM (TRα) 368 nM (TRβ)	32.6 µM (LXR) 4.82 µM (MR) 37.6µM(PPARγ) 646 nM (PR)
Triclosan *In vitro*					
Cell based in vitro assays					
Houtman *et al.* 2004	Enhancer of DHT activity	Erα (activated ER) reporter	No effect in MDA-kb2 at 5	Antagonist in GH3.TRE-Luc	TTR agonist hPXR

	AR	ER	GR	TR	other NRs
Tamura *et al.* 2006 Ahn *et al.* 2008 Chen *et al.* 2008 Christen *et al.* 2010 Blake *et al.* 2010 Rostkowski *et al.* 2011 Huang *et al.* 2014 Kolsek *et al.* 2014 Gee *et al.* 2008 Lange *et al.* 2015 Cavanagh *et al.* 2018 Kenda *et al.* 2020	in MDA-kb2 cells Agonist in MDA-kb2 cells Antagonist in HEK-2933Y cells Antagonist in stably transfected LTR-CAT gene in S115 +A cells Antagonist in transiently transfected LTR-CAT gene in T47D cells Antagonist in MDA-kb2 cells, antagonist in T47D-ARE cells Antagonist at 10 µM in a stickleback AR reporter assay Antagonist in AR-EcoScreen cells Antiandrogenic in PALM cells Antiandrogenic in S115 mouse mammary tumor cells	gene assay in CV1 cells → weak estrogenic effect Agonist in MCF-7 cells (E-Screen assay) Negative for agonism in ER-CALUX Antagonist in BG1-ERE cells Antagonist in stably transfected ERE-CAT gene in MCF7 cells Antagonist in hERα-HeLa-9903 cells	µM Antagonist in MDA-kb2 cells	cells	activation
Yeast based in vitro assays					
Rostkowski *et al.* 2011	Antagonist				
Binding affinity assays					
Gee *et al.* 2008 Kenda *et al.* 2020	Positive for recombinant AR Positive on isolated AR	Positive for ER of MCF7 cytosol (18:1 ERα to ERβ ratio) Positive for recombinant ERα and recombinant Erβ	Positive in binding affinity assay		

AR: androgen receptor; CAR: constitutive androstane receptor; ER: estrogen receptor; GR: glucocorticoid receptor; MR: mineralocorticoid receptor; NR: nuclear receptor; TCC: Triclocarban; TCS: Triclosan; TR: thyroid receptor

Triclocarban

Wu *et al.* (2016) studied the effects of triclocarban on FRTL-5 cells (Rat thyroid follicular cells) from 0.01-1000 µM and observed a concentration-dependent decrease of iodide uptake, with a Vmax decrease in a concentration-dependent manner. Triclocarban displayed a concentration dependent inhibitory effect on thyroid peroxidase activity, but the potency remained low (IC_{50} value being >300 µM).

Ref.: Wu 2016

Yueh *et al.* (2012) showed that triclocarban promotes both constitutive androstane receptor (CAR) and estrogen receptor alpha (ERα) activities as mentioned in Table 2. Moreover, CYP1B1 and CYP 2B6 promoter activities, which are regulated by ERα, was significantly induced by triclocarban in a dose-dependent manner. Humanized UGT1 mice exposed to 16 mg triclocarban/kg bw intraperitoneally for 2 days had an induction of UGT1A genes in liver, which dependent of CAR (as no induction was observed in hUGT1Car$^{-/-}$ mice. They also showed that activation of ERα by triclocarban (10 µM) in receptor-based assays also promotes induction of human CYP2B6.

Ref.: Yueh 2012

According to Li *et al.* (2017), in JEG-3 cell microsomes, triclocarban (100 µM) was a non-competitive inhibitor of human CYP19A1 with a decrease of 5 to 9% of the control.

Ref.: Li 2017

Triclosan

Regarding non-direct effects, Ajao et al (2015) reported that triclosan treatment inhibits boar sperm motility. They showed that exposure of sperm cells (boar) to triclosan (1 to 2.5 µg/mL) led to hyperpolarisation of the cytoplasmic membranes in the acrosomal area (the forehead) and of the fibrous sheath (the principal piece of the boar sperm flagellum).

Ref.: Ajao 2015

In sheep, James *et al.* (2010) found that triclosan at 1 µM was not a substrate for glucuronidation in sheep placental microsomes, but was as an inhibitor of estrogen sulfotransferase which raises concern about its possible effects on the ability of the placenta to supply estrogen to the fetus, and in turn on fetal growth and development.

Ref.: James 2010

Kumar *et al.* (2008) worked on male Wistar rats from which they collected the testes to isolate and purify the Leydig cells. Cells were exposed to triclosan (1nM to 10 µM). Although no significant reduction in cellular proliferation was observed, triclosan severely impaired the LH-induced testosterone production in Leydig cells in a dose-dependent manner with a 50% inhibition of LH-induced testosterone production at 1µM triclocarban. The transcription of three major steroidogenic enzymes: $P450_{SCC}$, 3b-HSD, 17b-HSD and StAR protein decreased a dose-dependent manner, as well as at the protein activity level for 3b-HSD and 17b-HSD. The activity of adenylyl cyclase was also observed at 10 nM and 1 µM leading to a decrease of the cell cAMP production. The authors concluded that triclosan acts as a potent endocrine disruptor in Leydig cells and the inhibition of androgen production is initiated when this chemical disrupts the activity of adenylyl cyclase enzyme disrupting the entire cAMP-dependent steroidogenic pathway, StAR expression responsible for cholesterol transport to inner mitochondrial membrane.

Ref.: Kumar 2008

According to Wang *et al.* (2004), triclosan (0 to 500 µM) is an inhibitor of phase I (CYP450) and the phase II xenobiotic metabolizing enzymes 3'-phosphoadenosine 5'-phosphosulfate-sulfotransferases and UDP-glucuronosyltransferases in human liver cytosol and microsomes. Triclosan is metabolized (sulfonation and glucuronidation), but also inhibited selectively the

hepatic cytosolic sulfonation of phenolic compound such as 3-hydroxybenzo(a)pyrene (3-OH-BaP), bisphenol A, p-nitrophenol, and acetaminophen but not morphine.

Ref.: Wang 2004

Wu et al (2016) studied the effects of triclosan on FRTL-5 cells (Rat thyroid follicular cells) from 0.625-40 µM and observed a concentration-dependent decrease of the iodide uptake, with a Vmax decrease in a concentration-dependent manner. No changes were noticed in the expression of genes involved in thyroid hormone synthesis (Slc5a5, Tpo, and Tg) in these cells. Triclosan inhibited thyroid peroxidase (TPO) activity in a concentration-dependent manner, (IC_{50} = 165.8 µM).

Ref.: Wu 2016

According to Li *et al.* (2017), in JEG-3 cell microsomes, triclosan (100 µM) was a competitive inhibitor of the human CYP19A1 (which catalyzes the conversion of testosterone to estradiol) by 5 to 9% of the control.

Ref.: Li 2017

SCCS comment on *in silico* and *in vitro* endocrine activity of triclocarban and triclosan

Several studies performed *in vitro* and *in silico* have indicated some estrogenic and androgenic activity of triclocarban that could be considered as moderate and weak affinity for thyroid receptor.

Regarding triclosan, several studies have demonstrated estrogenic activity and an anti-androgenic activity through both direct and indirect MoA, confirming the androgen- and estrogen-mediated activity of triclosan.

Taken together, this presents a clear evidence that triclocarban and triclosan bind androgen and estrogen receptors, with effects observed even at low doses of exposure. Both compounds exert their effect not only through binding the endocrine receptors, but also through modulating enzyme activities, such as phase I and II xenobiotic metabolising enzymes.

3.4.3.3 Endocrine activity of triclocarban: *In vivo* animal (Level 3 and 4)

Kennedy *et al.* (2015) investigated whether triclocarban exposure during early life affects the trajectory of fetal and/or neonatal development. Sprague Dawley rats were provided chow supplemented with 0.2% w/w or 0.5% w/w triclocarban, or raw chow without triclocarban (control), through a series of three experiments that limited exposure to critical growth periods: gestation, gestation and lactation, or lactation only (cross-fostering) to determine the susceptible windows of exposure for developmental consequences. Exposures started on GD 5 and there was 4-5 animals/group.

Levels of triclocarban on PND 6 were measured in maternal blood and milk. The level of triclocarban in pooled blood samples collected from neonates on PND 5 was also analysed. Maternal serum levels significantly increased with either triclocarban exposure groups (0.2% w/w: 134.6 ± 15.4 ng/mL; 0.5% w/w: 230.3 ± 77.3 ng/mL) compared to controls (0.19 ± 0.11 ng/mL). Following the same pattern, a dose-dependent increase of triclocarban in maternal milk samples was observed among groups (control: 0.23 ± 0.14 ng/mL; 0.2% w/w: 510.99 ± 122.8 ng/mL; 0.5% w/w: 917.8 ± 88.9 ng/mL). High levels of triclocarban were also detected in serum samples of neonates from triclocarban-treated dams in both groups compared to controls (control: 0.56 ± 0.23 ng/mL; 0.2% w/w: 13.87 ± 8.5 ng/mL; 0.5% w/w: 136.20 ± 55.86 ng/mL).

Exposure during pregnancy: Maternal body weight gain from GDs 5 to 19 in 0.5% w/w-treated dams was lower compared to control dams on 0.2% w/w treated dams. Levels of T3 were significantly decreased in dams provided 0.5% w/w triclocarban compared to control and 0.2% w/w-treated dams. Triclocarban had no effect on the levels of estradiol, progesterone, testosterone, T4 and TSH, implantation number, organ weight or histology.

***In utero*/lactational exposure (cross-fostering where each dam nursed two of their own pups and two pups from each of the other two treatment groups):** At birth, no statistical difference in number of live births or average birth weight per litter between groups was noted (maternal data). There was no initial statistical body weight difference in female pups born to control dams or pups born to either group of treated dams prior to culling on PND 0. Reduced offspring survival occurred when offspring were exposed to triclocarban at concentrations of 0.2% w/w and 0.5% w/w during lactation (until PND 21), in which only 13% of offspring raised by 0.2% w/w triclocarban dams survived beyond weaning and no offspring raised by 0.5% w/w triclocarban dams survived to this period. *In utero* exposure status had no effect on survival, as all pups nursed by control dams survived regardless of their *in utero* exposure status. The abdomens of all pups raised by dams exposed to either triclocarban concentrations were distended and all pups had diarrhea. Gross pathological examination of randomly selected pups raised by the 0.5% w/w dams on PNDs 4 and 5 showed small acute gastric ulcers and fatty vacuolation of hepatocytes.

Microscopic evaluation of dam mammary tissue revealed involution to be a secondary outcome of triclocarban exposure rather than a primary effect of compound administration.

The authors concluded that these results demonstrate that gestational triclocarban exposure does not affect the ability of dams to carry offspring to term but triclocarban exposure during lactation has adverse consequences on the survival of offspring although the mechanism of reduced survival is currently unknown. Based on T3 levels: NOAEL = 0.2% w/w. Based on pup survival: LOAEL = 0.2% w/w corresponding to maternal serum levels of 134.6 ± 15.4 ng/mL on GD5.

Ref.: Kennedy 2015

Using experimental rodent studies, low doses of triclocarban were reported to induce hepatic steatosis. It is plausible that this effect resulted from an ED mode of action involving changes in the expression levels of leptin and adiponectin and/or AhR activation. *In vitro* studies support also an interaction of triclocarban with AhR, which is known to be involved in metabolic disorders (metabolic syndrome, hepatic metabolism and liver.

Ref.: ANSES 2020

Costa 2020a and 2020b are based on the same experiment where outcomes are reported for female and male offspring, respectively.

Pregnant female Wistar rats were given 0, 0.3, 1.5 or 3.0 mg/kg bw/day of triclocarban (n = 8–11/group) daily by oral gavage from gestational day 0 to lactational day 21 (Costa *et al.* 2020a). The female pups (F1 generation) were weaned on postnatal day 21 and included in the study. The study was based on OECD 421. There were no significant differences in the maternal body weight gain, maternal behaviour and fertility between the experimental groups. Female offspring on PND1 and PND21 showed no significant differences in bodyweight and bodyweight gain. No differences in AGD or reproductive organ weights were noted between the groups on PND 21. During PND 21-90, no differences were noted in bodyweight gain, puberty onset, or estrous cycle. On PND 90, there were no differences in body and reproductive organ weights, or histopathological findings of the ovaries and uterus. In relation to hormones, there was a statistically significant decrease in progesterone levels at 3.0 mg/kg bw/day and in estradiol levels at 0.3 and 3.0 mg/kg bw/day of triclocarban (but not at 1.5 mg/kg bw/day) compared to the control. An increase in preimplantation loss was observed in

female offspring given 3.0 mg/kg bw/day of triclocarban when compared to the control. The NOAEL derived from this study was 1.5 mg/kg bw/day.

Ref.: Costa 2020a

In the Costa *et al.* (2020b) study, pregnant female Wistar rats were given 0, 0.3, 1.5 or 3.0 mg/kg bw/day of triclocarban (n = 8–11/group) daily by oral gavage from gestational day 0 to lactational day 21. The male pups (F1 generation) were weaned on PND 21 and included in the study. The study was based on OECD 421. On PND 21, three male pups from each litter were selected for different time point evaluations: infancy (PND 21), puberty (PND 50) and adult life (PND 90–120). The surplus pups were euthanised. There were no significant differences in the maternal body weight gain, maternal behaviour and fertility between the experimental groups. In male offspring on PND 1-21, there were no differences in bodyweight gain and normalised AGD between groups.
On PND 21, there were no differences in body and testis weights. Increased testosterone levels (111.10 ng/dL [39.96- 182.00]) compared to the control (34.21 ng/dL[13.97-65.65]) and decreased interstitial volume of testis was noted at 3.0 mg/kg bw/day of triclocarban (21.49 µL +/- 2.05) when compared to the control (31.85 µL +/- 2.14).
On PND 40, there were no differences in puberty onset, and on PND 50, no differences in body and reproductive organs weights or testosterone levels. There was a decrease in the diameter of seminiferous tubules 3.0 mg/kg bw/day of triclocarban (172.42 µm [170.44-177.69) when compared to the control (202.23 µm [186.76-218.17]).
On PND 90, 4 of 8 animals of 3.0 mg/kg bw/day of triclocarban group were considered sexually competent compared to the control, whereas the other parameters of sexual behaviour were not significant different between groups latency to the first intromission, no. of intromissions until the first ejaculation, latency to the first ejaculation, latency to the first post-ejaculatory intromission, no. of post-ejaculatory intromissions, no. of ejaculation, preference score).
On PND 120, no significant differences were noted between groups for final body weight, reproductive organs weight, testosterone levels, testis histomorphometric parameters, sperm motility, viability, morphology sperm count through testis, epididymis and vas deferens. The NOAEL derived from this study was 1.5 mg/kg bw/day.

Ref.: Costa 2020b

SCCS comment
Costa *et al.* (2020a and 2020b) have evaluated the effects of maternal exposure to triclocarban on the reproductive parameters of female and male offspring respectively.
Among the several measured parameters in the female offspring, the statistically significant effects were a decrease in the progesterone levels at the highest tested dose, a decrease in estradiol levels at the lowest and the highest doses (but not the middle dose), and an increase in preimplantation loss at the highest tested dose compared to the control (Costa, 2020a). In the male offspring, the statistically significant changes were a decrease in the testis interstitial volume, an increase in testosterone levels in the highest dose group during infancy; a decrease in the seminiferous tubule diameters at puberty, and a decrease in sexual competency in adulthood (Costa, 2020b). Any statistically significant differences (compared to control group) are largely limited to the highest tested dose. No apical effects on reproductive performance were reported in these studies.

The SCCS considers that the hormonal/behavioural parameters evaluated in both female and male offspring following maternal exposure of Wistar rat to triclocarban are sensitive paramaters that may be indicative of an endocrine activity, but that as such as they are not directly linked to an adverse effect and therefore cannot be used to derive a NOAEL/LOAEL.

3.4.3.4 Endocrine activity of triclocarban: human data

Geer *et al.* (2017) examined the relationship between human exposure triclocarban and birth outcomes including birth weight, body length and head size, and gestational age at birth. Maternal third trimester urinary and umbilical cord blood plasma concentrations of triclocarban were measured in 185 mothers and 34 paired singleton neonates.

Mean plasma level of triclocarban was 0.13 µg/L (min, max: 0.04, 1.17) and mean urinary level was 3.44 µg/L (min, max: 0.01, 101.7). Cord serum levels of triclocarban were significantly inversely associated with gestational age at birth. In addition, the metabolite 3'-OH-triclocarban was positively associated with low birth weight. No associations were observed between urinary triclocarban and its metabolites and the birth outcomes.

Ref.: Geer 2017

Smarr *et al.* (2017) aimed to prospectively assess couples' urinary concentrations of triclocarban in the context of fecundity, measured as time to pregnancy (TTP) using a prospective cohort of 501 couples. Preconception urinary triclocarban levels were measured. The urinary creatinine- level of triclocarban was in females 0.02 µg/g (0.00–0.06; Median (IQR)) and males 0.01 µg/g (0.00–0.03). Overall, 347 (69%) couples became pregnant. No associations were observed with couple fecundity and triclocarban.

Ref.: Smarr 2017

Wei *et al.* (2017) investigated the potential impact of exposure to triclocarban on fetal abnormalities (classified according to ICD-10 guidelines). Triclocarban levels were measured in maternal and umbilical cord blood samples from 39 pregnant women diagnosed with fetal or post-birth. Controls were 52 pregnant women who gave birth to healthy neonates during the same period of time. Congenital malformations of the circulatory system, eye, ear, face, neck, urinary system and musculoskeletal system were among the most frequent abnormalities. No significant differences in triclocarban levels in maternal and cord serum were found between cases and controls (Case: 0.190 ± 0.365 ng/mL and 0.103 ± 0.187 ng/mL in maternal and cord serum, respectively; Controls: 0.292 ± 0.586 ng/mL and 0.106 ± 0.171 ng/mL in maternal and cord serum, respectively).

Ref.: Wei 2017

Aker *et al.* (2018) investigated the association between triclocarban and four plasma thyroid hormones in 439 pregnant women in a case-control sample nested within a longitudinal birth cohort (USA). Urine and blood samples were collected from up to four visits during pregnancy Linear mixed models were constructed to take into account the repeated measures jointly, followed by multivariate linear regression models stratified by gestational age to explore potential windows of susceptibility. Triclocarban was detected in less than 25% of the samples and therefore categorized into a dichotomous variable (below/above level of detection (LOD)). Triclocarban at levels above the LOD were negatively associated with T3. There were no significant associations between triclocarban and any thyroid hormone in models stratified by gestational age.

Ref.: Aker 2018

Aker *et al.* (2019) examined the association between triclocarban exposure with maternal reproductive and thyroid hormones in 602 pregnant women in Puerto Rico. Urinary triclocarban and serum hormones (estriol, progesterone, testosterone, sex-hormone-binding globulin (SHBG), corticotropin-releasing hormone (CRH), total T3, total T4, free T4 and TSH) were measured at two visits during pregnancy. Specific gravity-corrected urinary level of triclocarban was 4.34 ± 10.27 µg/L (geometric mean and SD) for weeks 16-20 and 4.86 ± 56.2 µg/L for weeks 24-28. An inter-quartal range increase in triclocarban was associated with a 6% increase in T3 and T3/T4 ratio at 16-20 weeks of gestation, and a 6% increase in

T3 at 24-28 weeks of gestation. No statistically significant associations were observed for TSH and T4. Further, no statistically significant associations were observed for the reproductive hormones except a negative association between triclocarban and SHBG at 24–28 weeks of gestation.

Ref.: Aker 2019

SCCS comment on *in vivo* animal and human data for triclocarban
The SCCS considers that the health effects observed in Costa *et al.* studies (2020a and 2020b) cannot be regarded as adverse and will not be used to derive a PoD. Since none of the other new studies report on adverse effects, including endocrine activity, that indicate a NOEL of lower than 25 mg/kg bw/day that was used in the SCCP opinion (2005). The SCCS, will use a PoD of 25 mg/kg bw/day for triclocarban based on a decrease in food consumption, body weights, and organ weights (*e.g.* liver, spleen) from a 2-year chronic feeding study in rats.

The human studies do not provide robust evidence of endocrine disruptive effects of triclocarban.

3.4.3.5 Endocrine activity of triclosan: *In vivo* animal data (Level 3)

Animal studies published after the previous SCCS Opinion on triclosan from 2011 are summarised in Table A1 in Annex A. The most relevant studies for defining a new NOAEL for triclosan are described in more detail below.

Female reproduction
The (anti)estrogenicity of triclosan was evaluated in the uterotrophic assay *(EPA's OPPTS 890.1600 guideline)* in 18-day old female Wistar rats (Montagnini *et al.* 2018). For three consecutive days from PND18-20, female rats were administered by gavage corn oil (negative control), estradiol valerate (positive control) or 0.8, 2.4 or 8 mg/kg of triclosan (n=6-7). For evaluation of the possible anti-estrogenicity of triclosan, the rats were given estradiol (negative control), estradiol valerate + tamoxifen citrate, estradiol valerate + 0.0, 2.4 or 8 mg/kg triclosan (n=6-7). After 24 hours of the final dose, the rats were examined for vaginal opening and weighed. Uterus was weighed. During the 3-day treatment period, general clinical observation was conducted. Triclosan had no effect on the uterus weight in the uterotrophic assay. NOAEL = 8 mg/kg bw/day.

Ref.: Montagnini 2018

Male reproduction
The (anti)androgenicity of triclosan was evaluated in the Hershberger assay *(*EPA's OPPTS 890.1400 guideline) in 52-day old male Wistar rats (Pernoncini *et al.* 2018). The triclosan dosages were based on the acceptable daily intake, in addition to 3 and 10-fold higher doses. Castrated males were administered by gavage corn oil (negative control), testosterone propionate (positive control) or 0.8, 2.4 or 8 mg/kg of triclosan (n=6). For evaluation of anti-androgenicity, rats were administered testosterone propionate, testosterone propionate and flutamide or 0.8, 2.4 or 8 mg/kg of triclosan in addition to testosterone propionate. The test items were given for 10 consecutive days. Twenty-four hours after the final dose (PND62), the body weight and weight of the ventral prostate, seminal vesicle, levator ani-bulbocavernosus muscles, paired Cowper's glands, glans penis, liver, paired kidneys and paired adrenals were recorded. During the 10-day treatment period, animals were observed daily for mortality, morbidity, and general signs of toxicity, such as changes in behaviour (e.g., agitation, lethargy, and hyperactivity), neurological changes (e.g., convulsions, tremors, muscle rigidity, and hyperreflexia), and autonomic signs (e.g., lacrimation, piloerection, pupil size, and unusual respiratory patterns). No statistical differences were observed in the weight of the organs (seminal vesicles, prostate, Cowper's glands, Levator anibulbocarvenosus muscle, glans penis, adrenals, liver, kidney) of the triclosan-treated

groups compared to the vehicle group. The results demonstrated that triclosan did not act as an endocrine disrupter, with no (anti)androgenic effect in the Hershberger assay. NOAEL = 8 mg/kg bw/day.

Ref.: Pernoncini 2018

3.4.3.6 Endocrine activity of triclosan: *In vivo* animal data (Level 4)

From SCCS/1414/11
Several studies show that triclosan can affect thyroid hormone homeostasis in the rat. The effective doses vary between studies, which are probably related to differences in exposure duration as well as sex, age and strain of rats. Overall, a NOEL of 9.4 mg/kg bw/day, and a LOEL of 18.75 mg/kg bw/day for decreases in total serum T4 (Stoker *et al.*, 2010) can be considered as valid estimates. The likely mode of action for this effect is increased clearance of T4 hormone. But the rat is a rather sensitive model for chemical induced changes in thyroid hormones compared to humans, due to a lack of T4 binding protein which results in a shorter T4 serum half-life. It is important to acknowledge major differences in the thyroid hormone physiology and regulation between rats and humans.

Ref.: Stoker 2010; SCCS 2011

Animal studies published after the previous SCCS opinion on triclosan from 2011 are summarized in Table A1 in Annex A. The most relevant studies for defining a new NOAEL for triclosan are described in more details below.

Female reproduction
Jung *et al.* (2012) used Sprague-Dawley rats for screening estrogenic activity of triclosan in the uteri of immature rats. From postnatal days (PNDs) 19 to 21, rats were treated daily with 17α-Ethinylestradiol (positive control; 1 mg/kg bw/day) and triclosan (7.5, 37.5, and 187.5 mg/kg bw/day) via oral gavage or with corn oil (5 ml/kg BW/day) as a vehicle control. Bodyweight, clinical signs, and abnormal behaviours were recorded daily throughout the experimental period. All animals were euthanized 24 h after the final treatment. Changes in uterine weights were recorded.
All doses of triclosan significantly increased uterine wet weight (no dose-response). In addition, the expressions of calbindin-D9k (CaBP-9k) and complement C3 (C3) were significantly induced by estrogen and triclosan in the uteri of immature rats, indicating that triclosan can induce their expression mediated by estrogenic activity. LOAEL = 7.5 mg/kg bw/day. Due to the short exposure period of only three days and the lack of a dose-response relationship with regard to uterine weight, Jung *et al.* (2012) is not used by the SCCS to derive a point of departure (PoD).

Ref.: Jung 2012

The purpose of the study by Louis *et al.* (2017) was to characterize the influence of triclosan on the reproductive and thyroid axes of the female Wistar rats using a chronic exposure regimen. Three weeks before the start of the experiment, the estrous cyclicity of the animals was assessed daily by vaginal lavage and vaginal cytology to identify females with regular cycles. The rats were then exposed by oral gavage to vehicle control (corn oil), ethinyl estradiol (1 µg/kg, positive control), or triclosan (2.35, 4.69, 9.375 or 37.5 mg/kg) for 8 months (n=8/group). Estrous cycles were assessed daily by vaginal lavage for the first 3 months of treatment and collected on alternating two-week cycles thereafter. Animals were also assessed weekly starting at 5 months of age for the presence of mammary tumors by palpitation. After approximately 8 months of daily triclosan administration, animals were necropsied between PND 346 and 349. Anterior pituitary, uteri, ovaries, adrenal glands, kidneys, and whole liver were weighed. Anterior pituitaries were used for hormone analysis (serum estradiol (E1, E2), progesterone, T3, total T4 estrone (E1), luteinizing hormone (LH) and TSH, pituitary LH). Uteri, ovaries, and trachea with attached thyroid lobes were used for histopathological analysis. The right lobe of the liver was used for RNA analysis.

Weight/morphology: All animals maintained a healthy appearance with no apparent abnormal clinical signs of toxicity or marked changes in body weight throughout the course of the study. Mean uterine weight was not significantly different between the different groups. Similarly mean pituitary, ovary, kidneys, adrenal glands, and whole liver weight were not markedly different between groups. No marked morphological differences between groups were observed. *Estrous cyclicity*: Although a divergent pattern of reproductive senescence appeared to emerge from 5 to 11 months of age between controls and estradiol-treated females, no significant difference in cyclicity was noted between. *Reproductive hormones*: None of the treated groups were significantly different from controls for progesterone and serum or pituitary LH. No marked differences were detected between persistent diestrus and persistent estrus groups for E2 and E1 or between control and treated groups. However, there was a significant difference between 4.69 and 37.5 mg/kg mean for E2 levels in the persistent diestrus group. Further, the anterior pituitary LH concentrations in triclosan-treated animals were not significantly different from controls at necropsy. *Thyroid function*: Levels of serum T3 and TSH were not markedly affected by triclosan. Serum concentrations of T4 were significantly decreased in females following 8 months of treatment with 9.375 or 37.5 mg/kg of triclosan compared to controls by approximately 17 and 35%, respectively. No marked effects on thyroid tissue weight and histology were observed. *Hepatic enzyme gene expression*: There was a dose-dependent 2.2-fold increase in gene expression of Cyp2b2 at 37.5 mg/kg triclosan, whereas Cyp3a23/3a1, Sult1c1/1c3, Sult1b1, and Ugt1a1, were not significantly different from control liver gene expression. NOAEL = 4.69 mg/kg bw/day.
Since the only effect of 8 months of daily treatment with triclosan was seen for T4 with no changes in T3 and TSH, as well as thyroid tissue weight and histology, estrous cyclicity and reproductive hormones (E1, E2, progesterone, LH), Louis *et al.* (2017) is not used by the SCCS to derive a PoD.

Ref.: Louis 2017

After 3–4 regular estrous cycles, female ICR mice were given triclosan orally at doses of 0 (corn oil), 1, 10 and 100 mg/kg bw/day for 50 days (Cao *et al.* 2018). In a second experiment, mice were given 10 mg bw/day of triclosan orally for 50 days and subcutaneous injections with 20 mg/kg/day of levothyroxine (L-T4) or intraperitoneal injection with 2 mg/kg quinpirole at the end of the exposure period. Urine was collected for triclosan analysis. The levels of serum estradiol, progesterone, LH and follicle-stimulating hormone (FSH) were measured on the day of diestrus (exp. 1). Ovaries (collected from mice at diestrus) were used for histological examination. Brains were used for immunohistochemical analysis of kisspeptin neurons.
Exposure to 10 or 100 mg/kg/day triclosan caused prolongation of diestrus and decrease in antral follicles and corpora lutea within 2 weeks. Triclosan treated mice showed decrease in the levels of LH, FSH and progesterone, and gonadotrophin-releasing hormone mRNA with the lack of LH surge and elevation of prolactin. Triclosan mice had lower kisspeptin immunoreactivity and kiss1 mRNA in anteroventral periventricular nucleus and arcuate nucleus. In addition, the serum thyroid hormones, T3 and T4, in triclosan mice were reduced with increases in levels of TSH and TRH. In triclosan treated mice, the treatment with L-T4 corrected the increases in prolactin, TSH and TRH. Furthermore, triclosan mice treated with L-T4 or quinpirole resumed regular estrous cycling, follicular development and ovulation. The authors concluded that these findings indicate that exposing adult female mice to triclosan (≥10 mg/kg) reduces thyroid hormones causing hyperprolactinemia that then suppresses hypothalamic kisspeptin expression, leading to deficits in reproductive endocrine and function. NOAEL = 1 mg/kg bw/day. LOAEL = 10 mg/kg bw/day.

Ref.: Cao 2018

Male reproduction

Lan *et al.* (2013) investigated triclosan-induced sperm toxicity and histopathological changes of reproductive organs in Sprague-Dawley rats (6 weeks old). Triclosan in corn oil was given intragastrically at doses of 0, 10, 50 and 200 mg/kg for 8 weeks (n=8/group). After the final treatment, all testes and epididymides were excised and weighed. The left testis and

epididymis were used for histopathological observations. The right testis and epididymis were used for sperm head counting and sperm morphology studies.
The absolute weights of testes and epididymides were not significantly affected by triclosan, but the body weight and weights of the ventral prostate glands were significantly decreased in the group treated with a high dose (200 mg/kg) compared with the control. Minor damage was observed in the cauda epididymis and the testis at the high dose of triclosan. The daily sperm production significantly decreased by 19.6% and 46.4% in the groups treated with 50 and 200 mg/kg triclosan compared to the control. Compared to the number of sperm in the control group, the groups treated with 50 mg/ kg and 200 mg/kg triclosan both showed elevated ratios of abnormal sperm heads and ratios of abnormal sperm tails. NOAEL = 10 mg/kg bw/day. LOAEL = 50 mg/kg bw/day.

Ref.: Lan 2013

Lactating mother rats (Rattus norvegicus) were given oral daily doses of 0, 3, and 5 mg/kg bw/day of triclosan from the day of delivery until 28 days, equivalent to their natural breastfeeding duration. At 28 days, the male pups of all three groups were sacrificed and their biochemical parameters evaluated. Testicular sperm content and daily sperm production (DSP)/g testis analysis, histopathological analysis of the testes, and gene expression analysis were performed. For the highest dose of triclosan, the pups' body weights were significantly reduced (>10%) than that of the control. The testis weight was significantly lower in the highest dose group (50%) compared to the control. Pups had a decreased number of OCT 3/4 positive germ cells and Leydig cells positive for 3βhydroxysteroid dehydrogenase (3βHSD) at both doses, and AR-positive germ cells at the highest dose compared to the control. The pups also had decreased mRNA levels for 3βHSD and OCT3/4 at both doses, and AR at the highest dose compared to the control. The daily sperm production was significantly reduced in both dose groups compared to the control (5% and 37% for low and high dose, respectively). According to the authors, germ cell maturation of the male pups and bodyweight were significantly influenced by the higher dose. NOAEL = 3.0 mg/kg bw/day.

Ref.: Mandal 2020

Raj *et al.* (2021) studied the effects on the weights and histopathology of the epididymis and seminal vesicle, sperm indices (motility, viability, count and morphology), concentrations of epididymal sialic acid and seminal vesicular fructose. Swiss strain adult male mice were given 0, 40, 80, 160 of 320 mg/kg bw/day of triclosan orally on 42 consecutive days (n=12/group). Twenty-four hours after the last treatment, final body weights of the mice were recorded. Six animals from each group were used for the histological studies and sperm assessment while the other six were used for biochemical studies and determination of triclosan, accumulated in the accessory reproductive organs. At all doses compared to the control, triclosan induced significant reductions in the weights of the epididymis and seminal vesicle along with noticeable histopathological alterations in these organs. Further, triclosan caused significant reductions in the count, percentage of motile and viable spermatozoa while a significant increase in the percentage of abnormal spermatozoa in the epididymis. Concentrations of epididymal sialic acid and seminal vesicular fructose declined significantly in the treated mice. A significant increase was noticed in the concentration of triclosan, accumulated in the epididymis and seminal vesicle following triclosan exposure at the highest dose. LOAEL = 40 mg/kg bw/day.

Ref.: Raj 2021

Gestational glucose homeostasis and insulin sensitivity

In Hua *et al.* (2017), the influence of triclosan on glucose homeostasis and insulin sensitivity in gestational ICR mice (G-mice) were investigated. Triclosan was given orally at the doses of 0 (corn oil), 1, 4 or 8 mg/kg bw/day from GD5 to GD17 (n=10/group). Non-gestational mice (Ng-mice) of the same age received corn oil or triclosan (8 mg/kg/d) for 13 days as a control.

Serum total and free T4, total T3, estrogen and progesterone, as well as plasma glucose and insulin, were measured. Glucose tolerance test and insulin tolerance test were performed. The pancreas were weighed and used for insulin immune-staining. Total RNA was extracted from muscle and adipose tissues and used for reverse transcription quantitative PCR.
Exposure of G-mice to 8 mg/kg triclosan significantly increased the levels of fasting plasma glucose and serum insulin, and insulin content in pancreatic β-cells with reduced homeostasis model assessment (HOMA)-β index and increased HOMA-IR index. Exposure to triclosan (4 and 8 mg/kg) in G-mice caused decreases in the levels of serum total T4 and total T3 compared with control G-mice. Further, exposure to triclosan (8 mg/kg) in G-mice caused decreases in the levels of free T4 compared to control G-mice. Exposure to triclosan (8 mg/kg) in ng-mice caused decreases in the levels of serum total T4, total T3, and free T4 compared with control ng-mice. Levels of the reproductive hormones estrogen and progesteron were not altered. Although exposure to triclosan (8mg/kg) in ng-mice reduced thyroid hormones levels, it did not cause the insulin resistance or affect PPARγ and GLUT4 expression, and Akt phosphorylation. The authors concluded the findings indicate that the exposure of gestational mice to triclosan (≥8mg/kg) results in insulin resistance via thyroid hormones reduction.
Due to the short exposure period of only 13 days, Hua *et al.* (2017) is not used by the SCCS to derive a PoD.

Ref.: Hua 2017

3.4.3.7 Endocrine activity of triclosan: *In vivo* animal data (Level 5)

Reproduction
Female rats were evaluated for the reproductive effects of triclosan in a two-generation reproduction toxicity study *(based on OECD TG 416 and 426).* Female rats were treated daily by gavage with triclosan at the doses of 0.8, 2.4 and 8.0 mg/kg/day or corn oil (control group) over 10 weeks (F0) and over 14 weeks (F1) prior to mating and then throughout mating, gestation and lactation until weaning of F1 and F2 generation, respectively. Body weight and food consumption measurements, and estrous cycle, sexual behaviour, maternal behaviour and reproductive performance were evaluated. Tissues and organs (liver, kidneys, adrenals, ovaries and uterus) were weighed and used for histomorphological analysis. Offspring evaluations (F1 and F2 females) were performed for sexual, physical and neuromotor development.
Triclosan exposure compromised female sexual behaviour, decreased maternal food consumption and increased pup grooming in the 2.4 mg/kg/day triclosan group. Chronic triclosan exposure also decreased the perimetrium thickness of F0 females from triclosan in the 8.0 mg/kg/day group and growing follicle number of triclosan 2.4 mg/kg/day females from F1 generation. Despite some specific changes detected in the two-generation study, no impairment was observed in the uterotrophic assay (see section 3.4.3.4) and other important reproductive endpoints. The authors concluded that, in a weight of evidence evaluation, the results suggest that exposure to triclosan at low doses did not act as an endocrine disruptor in the female rat reproductive system. NOAEL = 8 mg/kg bw/day.

Ref.: Montagnini 2018

Pernoncini *et al.* (2018) evaluated the sexual behaviour, sperm motility, sperm viability, and testicular histomorphometry of triclosan in 49-day old male Wistar rats (OECD TG 416). Triclosan dosages were based on the acceptable daily intake, in addition to 3 and 10-fold higher doses. Male rats were administered by gavage corn oil (control) or 0.8, 2.4 or 8 mg/kg of triclosan (n=10/group). Test item was given daily from PND 49 till PND 140. No statistical difference was detected in the parameters of copulatory or sexual incentive motivation parameters, differences between the percentage of animals that displayed copulatory behaviour or the frequencies of ejaculations of the triclosan-treated groups compared to the control group. No statistical difference was observed in sperm morphology, viability, motility or concentration or in the sperm count, testicular volume, interstitial content volume,

seminiferous tubules volume or the diameter of seminiferous tubules. The results demonstrated that triclosan did not act as an endocrine disrupter, with no (anti)androgenic effect in the Hershberger assay (see section 3.4.3.4) and without interfering with the parameters evaluated in the reproductive toxicity study. NOAEL = 8 mg/kg bw/day.

Ref.: Pernoncini 2018

In a two-generation reproduction toxicity study in males based on OECD 416 and 426, female and male Wistar rats were treated daily by gavage with triclosan at doses of 0.8, 2.4, and 8.0 mg/kg/day or corn oil (control group) over 10 weeks (F0) and over 14 weeks (F1) before mating and then throughout mating, until weaning F2 generations, respectively (Montagnini *et al.* 2021). In F1 during premating, no mortality, morbidity, body and organ weight change, or general signs of toxicity such as changes in behaviour (agitation, lethargy, and hyperactivity), neurological changes (convulsions, tremors, muscle rigidity, and hyperreflexia), or autonomic signs (lacrimation, piloerection, and unusual respiratory patterns) were observed during the treatment period. Triclosan at 2.4 mg/kg bw/day in F1 males reduced the sperm viability (percentage of live sperm or mobile sperm) compared to the control animals, but no similar effects were observed at 8.0 mg/kg bw/day). No statistical differences were observed in the sperm count parameters. No changes in testicular histomorphometry were observed in F1 (testicular volume, interstitial content volume, seminiferous tubules volume, diameter of seminiferous tubules, and total length of seminiferous tubules). Triclosan did not affect sexual development in F1 and F2 generations (number of pups, sex ration, relative AGD, nipple retention). Further, no effects were seen for physical and neuromotor development or motor activity. NOAEL = 8 mg/kg bw/day.

Ref.: Montagnini 2021

SCCS comment on animal *in vivo* data for triclosan (Levels 3-5)
In SCCP (2009) a NOAEL of 12 mg/kg bw/day was used as the PoD (LOAEL = 40 mg/kg bw/day). The following studies support the selection of a new PoD for triclosan:

- 10 mg/kg bw/day: decrease in daily sperm production after 8 weeks of oral exposure of Sprague-Dawley rats (Lan *et al.*, 2015) (LOAEL: 50 mg/kg bw/day)
- 8 mg/kg bw/day: no effects on uterus weight, estrous cyclic endpoints in F0 or F1 at the highest dose tested in a two-generation study in Wistar rats (Montagnini *et al.*, 2018)
- 8 mg/kg bw/day: no effects in Hershberger assay and the reproductive toxicity study in Wistar rats at the highest dose tested (Pernoncini *et al.*, 2018)
- 8 mg/kg bw/day: no effects in males in a two-generation reproduction toxicity study at the highest dose tested (Montagnini *et al.*, 2021)
- 3 mg/kg bw/day: Effects on germ cell maturation and body weight in males (Mandal *et al.*, 2020) (LOAEL: 5 mg/kg bw/day) (Mandal *et al.*, 2020)
- 1 mg/kg bw/day: changes in thyroid hormones, reproductive hormones, length of estrous cycle/diestrus and number of antral follicles after 50 days of oral exposure of ICR mice (Cao *et al.*, 2018) (LOAEL: 10 mg/kg bw/day)

Data from studies in humans and rats provide no evidence for a bioaccumulation potential, whilst in mice retention of triclosan (and/or metabolites) appears to occur in liver. Therefore, the SCCS considers rat as a better model for adverse effects of triclosan than mice, and will use data from rat studies as the basis for deriving a PoD.

The study by Mandal *et al.* (2020) was not based on an OECD test guideline. In addition, the number of rats used for mating and allocation of females to the different dose groups, the number of males used from each litter and the number of males used for each of the outcomes are poorly reported. The SCCS will not use data from this study as the basis for deriving a PoD.

The four remaining rat studies, as well as the key study identified in SCCP (2009), provide evidence for a NOAEL between 8 and 12 mg/kg bw/day and a LOAEL of 40 mg/kg bw/day. Since Montagnini *et al.* (2018), Montagnini *et al.* (2021) and Pernoncini *et al.* (2018) are well-performed Level 3 and Level 5 rat studies that show consistent results using standardised test guidelines (uterotrophic and Hershberger assays, and two-generation reproductive toxicity studies, respectively), the SCCS considers a PoD based on NOAEL of 8 mg/kg bw/day to be appropriate for safety assessment of triclosan. A 20-day repeated dose toxicity study and an uterotrophic assay in rats (Stoker *et al.* 2010), where the authors derived a NOEL of 9.375 mg/kg bw/day and LOEL of 18.75 mg/kg bw/day based on reduction in T4 and estradiol serum levels, provide further support for a PoD based on NOAEL of 8 mg/kg bw/day.

3.4.3.8 Endocrine activity of triclosan: Human data

In 2009, the SCCP (SCCP/1192/08) evaluated data from five clinical studies and concluded that these studies showed no signs of overt toxicity in humans. In addition, based on consumer use information for triclosan-containing toothpaste, data indicate that triclosan can be used safely and with good tolerability at levels that also are found in personal care products.

Ref.: SCCP 2009

An overview on endocrine-related effects in human studies for triclosan published after SCCP (2009) is given in Table 3.

Exposure during pregnancy

Using a case-control study nested in the EDEN and PELAGIE mother–child cohorts (5200 pregnant women), Chevrier *et al.* (2012) examined whether prenatal exposure to triclosan was associated with occurrence of hypospadias and undescended testes. Cases of hypospadias (n = 21) and undescended testis (unilateral or bilateral, not in scrotum, n = 50) were identified during the first days after birth. No associations between triclosan levels in urine (<4 vs 4-51 and ≥51 nmol/L) and hypospadias or undescended testis were observed.

Ref.: Chevrier 2012

Geer *et al.* (2017) examined the relationship between human exposure triclosan and birth outcomes including birth weight, body length and head size, and gestational age at birth. Maternal third trimester urinary and umbilical cord blood plasma concentrations of triclosan were measured in 185 mothers and 34 paired singleton neonates.
Mean plasma level of triclocarban was 8.38 µg/L (min,max: 0.16, 127.6) and mean urinary level was 166.69 µg/L (min,max: 0.16, 11909). No associations were observed between triclosan and the birth outcomes.

Ref.: Geer 2017

Wei *et al.* (2017) investigated the potential impact of exposure to triclosan on fetal abnormalities (classified according to ICD-10 guidelines). Triclosan levels were measured in maternal and umbilical cord blood samples from 39 pregnant women diagnosed with fetal or post-birth. Controls were 52 pregnant women who gave birth to healthy neonates during the same period of time. Congenital malformations of the circulatory system, eye, ear, face, neck, urinary system and musculoskeletal system were among the most frequent abnormalities.
The detection rate of triclosan in maternal sera in fetal anomaly group was significantly higher than that in the control group (80.00% vs 53.80%). No significant differences in triclosan levels in maternal and cord serum were found between cases and controls (Case: 0.548 ± 1.355 ng/mL and 0.160 ± 0.293 ng/mL in maternal and cord serum, respectively; Controls: 0.649 ± 1.562 ng/mL and 0.245 ± 0.478 ng/mL in maternal and cord serum, respectively).

Ref.: Wei 2017

A randomized intervention of wash products with or without triclosan, including toothpaste, enrolled pregnant women from 20 weeks' gestation (Ley *et al.* 2017). Urinary triclosan, TSH, T4 and T3 were measured at enrolment, 36 weeks' gestation and/or post-delivery. Anthropometric measures at birth were ascertained from medical records. Of the participants, 78 and 76 mothers were assigned to the triclosan-containing and no-triclosan-containing product arms, respectively. Both intervention groups were provided commercially available wash products (liquid and bar soap, toothpaste, dishwashing liquid), and supplies were replenished every four months as needed. Triclosan-containing toothpaste was provided to households assigned to the triclosan arm only after the baby was born. At enrolment, triclosan levels were low and similar across arms (median: 6.8 pg/μL in both arms). Considering only post-triclosan randomization urine samples, median triclosan levels were seven-fold higher in the triclosan arm than in the no-triclosan arm (median: 19.0 pg/μL vs. 2.7 pg/μL, respectively, p=0.002). No differences were observed in any thyroid function measure at any time point or in any anthropometric measurement at birth between either exposure arms or lowest and highest urinary triclosan quartile groups. Thus, in this randomized intervention study, triclosan from wash products, primarily liquid and bar soaps, did not affect thyroid function measures during pregnancy or babies' anthropometric measures at delivery.

Ref.: Ley 2017

Aker *et al.* (2018) investigated the association between triclosan and four plasma thyroid hormones in 439 pregnant women in a case-control study nested within a longitudinal birth cohort (USA). Urine and blood samples were collected from up to four visits during pregnancy Linear mixed models were constructed to take into account the repeated measures jointly, followed by multivariate linear regression models stratified by gestational age to explore potential windows of susceptibility. Decreased total T3 in relation to an IQR increase in triclosan was observed. While an IQR increase in triclosan was associated with a 7.7% increase in TSH. There were no significant associations between triclosan and any thyroid hormone in models stratified by gestational age.

Ref.: Aker 2018

Aker *et al.* (2019) examined the association between triclosan exposure with maternal reproductive and thyroid hormones in 602 pregnant women in Puerto Rico. Urinary triclocarban and serum hormones (estriol, progesterone, testosterone, sex-hormone-binding globulin (SHBG), corticotropin-releasing hormone (CRH), total T3, total T4, free T4 and TSH) were measured at two visits during pregnancy. Specific gravity-corrected urinary level of triclosan was 21.78 ± 8.72 μg/L (geometric mean and SD) for weeks 16-20 and 25.03 ± 327 μg/L for weeks 24-28. At 24–28 weeks gestation, there was a positive association between triclosan and estriol.

Ref.: Aker 2019

Arbuckle *et al.* (2018) studied the association between prenatal exposure to triclosan and anogenital distance (AGD) and the ratio between the length of the second and fourth fingers (2D:4D digit ratios). Triclosan was measured in single spot urine samples collected in the first trimester from the MIREC Study. Anogenital distance (n=394) at birth and 2D:4D digit ratios (n=420) at 6 months were measured in male and female infants. Maternal total (geometric mean: 10.83 μg/L; 95% CI: 8.69-13.51) or free triclosan levels (geometric mean: 0.07 μg/L; 95% CI: 0.05-0.08) were not significantly associated with any AGD metric or 2D:4D digit ratios in male or female infants.

Ref.: Arbuckle 2018

By using a prospective cohort (HOME study, USA), Braun *et al.* (2018) measured urinary triclosan up to three times in women between 16 weeks of pregnancy and delivery, and up to three times in children between age 1–3 years. Serum levels of TSH and total and free T4

and T3 in mothers at 16-weeks gestation (n=202), neonates at delivery (n =274), and children at age 3 years (n =153) were quantified. Average gestational urinary triclosan levels were higher than average childhood urinary triclosan levels (medians: 14 vs. 8.1 ng/mL). Triclosan was not associated with thyroid hormones during pregnancy. Higher gestational triclosan was associated with lower cord serum total T4. Childhood triclosan at age 1 year was positively associated with total T4 at age 3 years. No statistically significant associations were observed between triclosan and T3 and TSH. The authors concluded that their findings suggest that triclosan exposure may influence some features of neonatal and early child thyroid function.

Ref.: Braun 2018

Exposure in children

Wolff *et al.* (2010) investigated associations of concurrent exposures from triclosan with pubertal stages in a longitudinal study of 1151 girls from USA who were 6–8 years of age at enrolment. Associations between urinary triclosan at visit 1 (median: 14.7 µg/g creatinine; range: LOD-2535) and breast and pubic hair development (present or absent) one year later were examined. Triclosan had a suggestive inverse association with pubic hair development, but the trend was not monotonic, and the confidence intervals were similar for every quintile.

Ref.: Wolff 2010

Exposure in adults

Allmyr *et al.* (2009) investigated if an everyday exposure to triclosan via triclosan-containing toothpaste for 14 days in 12 adult humans caused an increase in plasma 4β-hydroxycholesterol, indicative of CYP3A4 induction, and/or alterations in thyroid hormonal status. The plasma triclosan concentrations increased from 0.009–0.81 ng/g to 26–296 ng/g (ranges) upon exposure, but there were no significant changes in plasma levels of either plasma 4β-hydroxycholesterol or thyroid hormones during the exposure. The authors concluded that this indicates that the normal use of triclosan-containing toothpaste is not likely to alter metabolism of drugs via CYP3A4 induction or cause adverse events because of thyroid disturbances in humans.

Ref.: Allmyr 2009

Smarr *et al.* (2017) aimed to prospectively assess couples' urinary concentrations of triclosan in the context of fecundity, measured as time to pregnancy (TTP) using a prospective cohort of 501 couples. Preconception urinary triclosan levels were measured. The urinary creatinine-level of triclosan in females was 16.8 µg/g (5.32–67.5; Median (IQR)) and males 16.2 µg/g (4.41–64.4). Overall, 347 (69%) couples became pregnant. No associations were observed with couple fecundity and triclosan.

Ref.: Smarr 2017

Preconception levels of triclosan were measured in spot urine samples from 501 male partners of couples planning to become pregnant (Smarr *et al.* 2018). The men also provided semen sample at baseline and one approximately one month later where a 24-hour semen quality analysis was performed. Triclosan (Median: 17.6 ng/mL; IQR: 4.42, 77.1) was significantly positively associated with sperm concentration and total sperm count, but not with any of the motility, morphometry or morphology parameters.

Ref.: Smarr 2018

SCCS comment for human data for triclosan

The human studies do not provide any strong evidence of endocrine disruptive effects of triclosan. There are inconsistent findings in regard to the effects of triclosan on thyroid hormones, as well as statistically non-significant associations between triclosan and birth outcomes.

Overall SCCS comment on endocrine activity

Triclocarban

In silico and *in vitro* studies provide evidence for a moderate estrogenic and androgenic potential of triclocarban. There is a further indication of a weak affinity for thyroid receptor.

The human studies do not provide strong evidence of endocrine disruptive effects of Triclocarban.

The SCCS has selected a PoD based on NOAEL of 25 mg/kg bw/day for triclocarban based on a 2-year chronic feeding study in rats (SCCP 2005).

Triclosan

Several studies have demonstrated estrogenic activity and anti-androgenic activity of triclosan, through both direct and indirect MoA, confirming the androgen- and estrogen-mediated activity of triclosan. There is also evidence of endocrine activity of triclosan from *in vivo* animal studies, whereas there are either no or inconsistent findings in human studies.

The SCCS has selected a PoD based on NOAEL of 8 mg/kg bw/day for triclosan from the reproductive toxicity assays in rats performed by Montagnini *et al.* (2018, 2021) and Pernoncini *et al.* (2018).

Table 3. Summary of human studies on triclosan
↑: positive association; ↔: no association; ↓: inverse association

Reference	N	Exposure period	Outcome measurement period	T4	T3	TSH	Estriol	Sperm		Fecundity	Birth outcome[2]	Foetal abnormality	Puberty[3]
								Conc/ count	Other[1]				
Ley 2017	154	P	NB	☐	☐	☐					☐		
Aker 2018	439	P	P	☐	↓	↑							
Aker 2019	602	P	P	☐	☐	☐	↑						
Braun 2018	153-274	P	P	☐	☐	☐							
		P	CB	↓	☐	☐							
		1 y	3 y	↑	☐	☐							
Chevrier 2012	71	P	NB								☐		
Arbuckle 2018	394-420	P	NB								☐		
Geer 2017	34	P	NB								☐		
Wei 2017	91	P	NB									☐	
Wollf 2011	1151	6-8 y	AD										☐
Allmyr 2009	12	A											
Smarr 2017	347	A								☐			
Smarr 2018	501	A						↑	☐				

[1] General characteristics: semen volume, straw distance, hypo-osmotic swollen; Motility measures: average path velocity, straight line velocity, curvilinear velocity, amplitude head displacement, beat cross frequency, straightness, linearity, percent motility; Sperm head measures: length, area, width, perimeter, elongation factor, acrosome area of head; Morphology measures: strict criteria, traditional normal, amorphous, round, pyriform, bicephalic, taper, megalo head, micro head, neck and midpiece abnormalities, coiled tail, other tail abnormalities, cytoplasmic droplet and immature sperm; Sperm chromatin stability measures: DNA fragmentation index, high DNA stainability
[2] Gestational age, anthropometry, anogenital distance, 2D:4D digit ratio, hypospadias
[3] Breast and pubic hair development
A: adult; AD: adolescent; CB; cord blood; Conc: concentration; NB: newborn; P: pregnancy; y: year

3.5 EXPOSURE ASSESSMENT

3.5.1 Exposure Assessment of Triclocarban

3.5.1.1 Exposure assessment of Triclocarban in adults

SED calculations were based on the use of triclocarban as an ingredient in rinse-off products (shower gel, hand wash soap, shampoo and hair conditonners) at a maximum concentration of 1.5% or on the use as a preservative at a maximum concentration of 0.2% and a dermal absorption of 8% (mean+SD: 6+2%) from Wester *et al.* (1985) (Table 4).

An overview on the aggregated SEDs for triclocarban as an ingredient in rinse-off products and when used as a preservative are shown in Table 4.

Table 4. SED calculations for triclocarban **in rinse-off products** at the maximum use level of 1.5%

Type of cosmetic product exposure	Product category	Relative Daily Exposure	Concentration Triclocarban C	Dermal absorption DAp	SED
		(mg/kg bw/d)	(%)	(%)	(µg/kg bw/d)
Rinse-off skin and hair cleansing products	Shower gel	2.79	1.5	8	3.348
	Hand wash soap	3.33	1.5	8	3.996
	Shampoo	1.51	1.5	8	1.812
	Hair conditionner	0.67	1.5	8	0.804
Aggregate exposure		8.3	1.5	8	9.96

Table 5. SED calculations for triclocarban used **as a preservative** at the maximum use level of 0.2%

Type of cosmetic product exposure	Product category	Relative Daily Exposure	Concentration Triclocarban C	Dermal/Oral absorption DAp	SED
		(mg/kg bw/d)	(%)	(%)	(µg/kg bw/d)
Rinse-off skin and hair cleansing products	Shower gel	2.79	0.2	8	0.4464
	Hand wash soap	3.33	0.2	8	0.5328
	Shampoo	1.51	0.2	8	0.2416
	Hair conditionner	0.67	0.2	8	0.1072
Leave-on skin and hair cleansing products	body lotion	123.2	0.2	8	19.712
	Face cream	24.14	0.2	8	3.8624
	Hand cream	32.1	0.2	8	5.136

	Deodorant non-spray	22.08	0.2	8	3.5328
	Hair styling	5.74	0.2	8	0.9184
Make-up products	Liquid foundation	7.9	0.2	8	1.264
	Make-up remover	8.33	0.2	8	1.3328
	Lipstick	0.9	0.2	100	1.8
	Eye make-up	0.33	0.2	8	0.0528
	Mascara	0.42	0.2	8	0.0672
	Eyeliner	0.08	0.2	8	0.0128
Oral care products	Toothpaste	2.16	0.2	100	4.32
	Mouthwash	32.54	0.2	100	65.08
Aggregate exposure		269			108.4192

[1] According to values in Table 5 of the SCCS notes of guidance (11th revision)
[2] SED = $E_{product}$*1000 (DA_p/100)*(C/100)
No dermal penetration applied to lipstick, toothpaste and mouthwash; SCCS default 100% absorption used.

Table 6. SED for aggregated exposures for triclocarban

Use	**Triclocarban content (%) C**	**SED[1] (µg/kg bw/d)**
As an ingredient in rinse-off products	1.5	10
As a preservative	0.2	108
As an ingredient in rinse-off products & as a preservative	**1.5 & 0.2**	**118**

3.5.1.2 Exposure assessment of triclocarban in children

As for adults, SED calculations were based on the use of triclocarban as an ingredient in rinse-off products (shower gel, hand wash soap, shampoo and hair conditonners) at a maximum concentration of 1.5% and on the use as a preservative at a maximum concentration of 0.2% and a dermal absorption of 8% (mean+SD: 6+2%) from Wester *et al.* (1985) (Table 7).

1. Dermal exposure

Daily exposure to triclocarban for the different age categories were based on data for daily exposures in adults and the body surface area of adults and children. *E.g.* the exposure to preservatives used in shower gel is considered to be 190 mg/day on a surface of 17 500 cm^2 for an adult. For an adolescent of *e.g.* 14-18 years of age with a total body surface area 17 000 cm^2, the daily exposure would then result in 190 mg/d *17 000 cm^2/17 500 cm^2 = 185 mg/day.

Table B1 in Annex B shows the calculated child application surface areas and daily exposure doses for the different age categories and product types included in the different exposure scenarios.

An overview on the aggregated SEDs for triclocarban as an ingredient in rinse-off products and when used as a preservative are shown in Table 7 and 8.

Table 7. SED calculations for triclocarban in **rinse-off products** at the maximum use level of 1.5% for non–preservative use by age group

Product type	Age category (yrs)	Calculated child exposure	Concentration Triclocarban C	Dermal absorption DAp	SED [2]
		(mg/kg bw/d)	%	%	(µg/kg bw/d)
Shower gel					
Infants	0.5 -1	5.68	1.5	8	6.82
Toddlers	1-3	5.04	1.5	8	6.05
Children	3-10	3.90	1.5	8	4.68
Adolescents	10-14	3.23	1.5	8	3.87
Adolescents	14-18	2.94	1.5	8	3.52
Adults					
Hand soap					
Infants	0.5 -1	5.68	1.5	8	6.82
Toddlers	1-3	5.04	1.5	8	6.05
Children	3-10	4.33	1.5	8	5.19
Adolescents	10-14	3.46	1.5	8	4.15
Adolescents	14-18	3.10	1.5	8	3.72
Adults					
Shampoo					
Infants	0.5 -1	3.41	1.5	8	4.09
Toddlers	1-3	3.36	1.5	8	4.03
Children	3-10	2.16	1.5	8	2.60
Adolescents	10-14	1.84	1.5	8	2.21
Adolescents	14-18	1.79	1.5	8	2.15
Adults					
Hair conditioner					
Toddlers	1-3	0.84	1.5	8	1.01
Children	3-10	0.87	1.5	8	1.04
Adolescents	10-14	0.69	1.5	8	0.83
Adolescents	14-18	0.65	1.5	8	0.78
Adults					
Aggregated					
Infants	0.5 -1	14.77	1.5	8	**17.73**
Toddlers	1-3	14.29	1.5	8	**17.14**
Children	3-10	11.26	1.5	8	**13.51**
Adolescents	10-14	9.22	1.5	8	**11.06**
Adolescents	14-18	8.48	1.5	8	**10.18**
Adults					

[2] SED = $[E_{product}*1000*(DA_p/100)*(C/100)]/bw$

Table 8. SED calculations for triclocarban **used as a preservative** at the maximum use level of 0.2% by age groups and exposure scenarios.

Product type[1]	Age category (yrs)	Calculated child exposure	Concentration Triclocarban C	Dermal absorption DAp	SED [2]
		(mg/kg bw/d)	%	%	(µg/kg bw/d)
Shower gel					
Infants	0.5 -1	5.68	0.2	8	0.91
Toddlers	1-3	5.04	0.2	8	0.81
Children	3-10	3.90	0.2	8	0.62
Adolescents	10-14	3.23	0.2	8	0.52
Adolescents	14-18	2.94	0.2	8	0.47
Adults					
Hand soap					
Infants	0.5 -1	5.68	0.2	8	0.91
Toddlers	1-3	5.04	0.2	8	0.81
Children	3-10	4.33	0.2	8	0.69
Adolescents	10-14	3.46	0.2	8	0.55
Adolescents	14-18	3.10	0.2	8	0.50
Adults					
Shampoo					
Infants	0.5 -1	3.41	0.2	8	0.55
Toddlers	1-3	3.36	0.2	8	0.54
Children	3-10	2.16	0.2	8	0.35
Adolescents	10-14	1.84	0.2	8	0.29
Adolescents	14-18	1.79	0.2	8	0.29
Adults					
Hair conditioner					
Toddlers	1-3	0.84	0.2	8	0.13
Children	3-10	0.87	0.2	8	0.14
Adolescents	10-14	0.69	0.2	8	0.11
Adolescents	14-18	0.65	0.2	8	0.10
Adults					

Product type[1]	Age category (yrs)	Calculated child exposure	Concentration Triclocarban C	Dermal absorption DAp	SED [2]
		(mg/kg bw/d)	%	%	(µg/kg bw/d)
Body lotion					
Infants	0.5 -1	223.86	0.2	8	35.82
Toddlers	1-3	210.08	0.2	8	33.61
Children	3-10	168.40	0.2	8	26.94
Adolescents	10-14	133.87	0.2	8	21.42
Adolescents	14-18	123.98	0.2	8	19.84
Adults					
Face cream					
Infants	0.5 -1	44.32	0.2	8	7.09
Toddlers	1-3	41.18	0.2	8	6.59
Children	3-10	33.33	0.2	8	5.33
Adolescents	10-14	26.27	0.2	8	4.20
Adolescents	14-18	24.47	0.2	8	3.92
Adults					
Hand cream					
Infants	0.5 -1	61.36	0.2	8	9.82
Toddlers	1-3	57.98	0.2	8	9.28
Children	3-10	46.32	0.2	8	7.41
Adolescents	10-14	36.87	0.2	8	5.90
Adolescents	14-18	34.26	0.2	8	5.48
Adults					
Deodorant					
Children	3-10	32.47	0.2	8	5.19
Adolescents	10-14	25.58	0.2	8	4.09
Adolescents	14-18	23.82	0.2	8	3.81
Hair styling				8	
Children	3-10	8.66	0.2	8	1.39
Adolescents	10-14	6.91	0.2	8	1.11
Adolescents	14-18	6.36	0.2	8	1.02
Adults			0.2	8	0.00

Liquid foundation						
Adolescents	10-14	0.38	8.76	0.2	8	1.40
Adolescents	14-18	0.5	8.16	0.2	8	1.31
Adults						
Make-up remover						
Adolescents	10-14	0.37	8.53	0.2	8	1.36
Adolescents	14-18	0.49	7.99	0.2	8	1.28
Lipstick						
Adolescents	10-14	0.04	0.92	0.2	100	1.84
Adolescents	14-18	0.06	0.98	0.2	100	1.96
Adults						
Eye make-up						
Adolescents	10-14	0.01	0.23	0.2	8	0.04
Adolescents	14-18	0.02	0.33	0.2	8	0.05
Adults						
Mascara						
Adolescents	10-14	0.02	0.46	0.2	8	0.07
Adolescents	14-18	0.03	0.49	0.2	8	0.08
Adults				0.2	8	
Eyeliner				0.2	8	
Adolescents	10-14	0.01	0.23	0.2	8	0.04
Adolescents	14-18	0.01	0.16	0.2	8	0.03
Adults						
Aggregated						
Infants	0.5-1		344.32	0.2	8	55.09
Toddlers	1-3		323.53	0.2	8	51.76
Children	3-10		300.43	0.2	8	48.07
Adolescents	10-14		249.31	0.2	8	41.59
Adolescents	14-18		231.65	0.2	8	38.86

[1] See Table B1 in Annex B for calculations of daily exposures.
[2] SED = [$E_{product}$*1000 (DA_p/100)*(C/100)]/bw where C=0.2% and bodyweights are default values from EFSA 2012 (Infants: 8.8 kg; Toddlers: 11.9 kg; Children: 23.1 kg; Adolescents 10-14 yrs: 43.4 kg; Adolescents 14-18 yrs: 61.3 kg).

2. Oral exposure

Intakes for 1-6 years of age:

The use of toothpaste starts with first erupted teeth and occurs with a high percentage of dentifrice ingestion. Therefore, the amount of toothpaste to be used by children age 6 and under, as implemented for fluoride toothpastes, is generally set at a pea-size amount. The SCCNFP (2003) defined this as 0.25 grams when assessing the safety of fluoridated oral care products for children. Furthermore, a retention factor of 40% for children 7 months-8 years of age was explicitly stated to be "already an overestimate" when these exposure calculations were revisited (SCCP 2005). Taking the above intake values from product-use scenarios, and dividing by the EFSA default body weights (EFSA 2012b) for specific age ranges, the following conservative intakes in mg/kg/day are calculated in Table 10.

The use of mouthwash potentially starts at age 6 (it is generally recommended that children under 6 should not use mouthwash). The usage volume of 21.62 ml/day and retention factor of 10 % from SCCS's 2018 Notes of Guidance is used.

Table 9. SED calculation for triclocarban in oral products in children

Oral products	amount (g/use)	frequency (use/d)	retention factor RF	max conc TTC (%)	SED (mg/d)	kg (EFSA P50)	SED (µg/kg bw/d)
Toothpaste <1 year	0.25	2	0.4	0.2	0.4	8.8	45.45
Toothpaste, 1-3y years	0.25	2	0.4	0.2	0.40	11.9	33.61
Toothpaste, 3-10 years	0.25	2	0.4	0.2	0.40	23.1	17.32
Toothpaste, 10-14 years	2.75	1	0.05	0.2	0.28	43.4	6.34
Toothpaste, 14-18 years	2.75	1	0.05	0.2	0.28	61.3	4.49
mouthwash, 6-10 years	21.62	1	0.1	0.2	4.32	21.7	199.26
mouthwash, 10-14 years	21.62	1	0.1	0.2	4.32	42	102.95
mouthwash, 14-18 years	21.62	1	0.1	0.2	4.32	60	72.07
Agg toothpaste and mouthwash, 6-10 years							**216.58**
Agg toothpaste and mouthwash, 10-14 years							**109.29**
Agg toothpaste and mouthwash, SCCS, 14-18 years							**76.55**

3. Dermal + oral exposure

Aggregated exposure in children including oral exposure:

Table 10. SED for aggregated exposures for triclocarban in children

Age categories		Dermal TCC as a preservative (µg/kg bw/d)	Dermal TCC in rinse -off products (µg/kg bw/d)	Oral * (µg/kg bw/d)	Aggregated (µg/kg bw/d)
Infants	0.5 -1	55.09	17.73	45.45	118.27
Toddlers	1-3	51.76	17.14	33.61	102.51
Children	3-6	48.07	13.51	17.32	78.90
Children	6-10	48.07	13.51	17.32	78.90
Adolescents	10-14	41.59	11.06	6.34	58.99
Adolescents	14-18	38.86	10.18	4.49	53.53

*: without use of mouthwash from 6 years

3.5.2 Exposure Assessment of Triclosan

In the case of triclosan, SED for both oral and dermal exposure were calculated. SED calculations were based on the maximally allowed triclosan concentrations. Triclosan can be used in nail products for cleaning the fingernails and toenails before the application of artificial nail systems. The SCCS considers the consumer exposure from such products to be negligible and therefore not included in the exposure assessment.

For the purpose of SED calculations for oral formulations (toothpaste, mouthwash), an oral availability of 100% was assumed.

3.5.2.1 Exposure assessment of triclosan in adults

Table 10 shows the results for the SED calculations for oral products in adults.

Table 10. SED calculation for triclosan in oral products

Description	Parameter	Toothpaste	Mouthwash	Unit
Calculated relative daily exposure	$E_{product}$	2.16	32.54	mg/kg bw/d
Triclosan content	C	0.3	0.2	%
Oral bioavailability		100	100	%
SED_{oral}	$E_{product}$*(C/100)*(Fret/100)	**0.00648**	**0.0651**	**mg/kg bw/d**

[1] Potential amount available for oral exposure
No dermal penetration applied to toothpaste and mouthwash; SCCS default 100% absorption used.

For dermal formulations, SED calculations were based on percutaneous absorption data from *in vitro* human studies (Table 1). SED calculations for individual personal-care products containing triclosan were carried out based on dermal absorption values (µg/cm^2) from *in vitro* percutaneous absorption studies conducted with deodorant and w/o formulations containing 0.2% triclosan and dilute soap solution formulation containing 0.02% triclosan. In each calculation for dermal products, an extrapolated value for flux (µg/cm^2 absorption) was used, based on the assumption that skin penetration is by passive diffusion, such that flux would be proportional to the concentration of triclosan applied to the skin. For hand soap and body soap, the conversion of the µg/cm^2 dermal absorption value to a current-use value for amount of triclosan in the product type assumed a 10-fold dilution of 0.3% triclosan. For both soaps, a retention factor was not used due to the inclusion of a rinse-off step in the relevant *in vitro* percutaneous absorption study. Tables 11-12 show the results for the SED calculations for dermal products.

An overview on the SED values for individual products and aggregated exposures for triclosan are shown in Table 13.

Table 11. SED Calculation for triclosan in leave-on products

Description	Parameter	Deodorant stick	Body lotion	Face powder	Blemish concealer	Unit
Dermal absorption based on 0.2% triclosan[1]	DA_a	0.303	0.420	0.420	0.420	µg/cm²
Triclosan content	C	0.3	0.3	0.3	0.3	%
Calculated dermal absorption based on triclosan content[2]	Calculated DA_a	0.455	0.630	0.630	0.630	µg/cm²
Skin surface area	SSA	200	15 670	565	57	cm²
Dermal absorption per application	DA_a*SSA* 0.001	0.091	9.8721	0.35595	0.03591	mg
Frequency of application	F	2	2.28	1	1	Appl/d
Default bodyweight	bw	60	60	60	60	kg
SED_{dermal}	**DA_a*SSA* 0.001*F/bw**	**0.00303**	**0.37514**	**0.00593**	**0.00060**	**mg/kg bw/d**

[1] Dermal absorption values based on *in vitro* data using 0.2% in deodorant formulation (for deodorant stick) and 0.2% water/oil emulsion (for body lotion, face powder, and stick concealer).
[2] Calculated DA_p = (Absorption from 0.2% triclosan applied in the relevant *in vitro* study) x (triclosan content for the product/0.2%) = Absorption from 0.3% triclosan. This assumes that skin penetration is by passive diffusion, such that flux would be proportional to the concentration of triclosan applied to the skin.

Table 12. SED Calculation for triclosan in rinse-off products (hand soap and shower gel)

Description	Parameter	Hand soap	Shower gel	Unit
Dermal absorption based on 0.02% triclosan[1]	DA_a	0.0306	0.0306	µg/cm²
Triclosan content	C	0.03	0.03	%
Calculated dermal absorption based on triclosan content[2]	Calculated DA_a	0.046	0.046	µg/cm²
Skin surface area	SSA	860	17 500	cm²
Dermal absorption per application	DA_a*SSA*0.001	0.03956	0.80500	mg
Frequency of application	F	10	1.43	Appl/d
Default bodyweight	bw	60	60	kg
SED_{dermal}	**DA_a*SSA*0.001*F/bw**	**0.00659**	**0.01919**	**mg/kg bw/d**

[1] Dermal absorption value based on *in vitro* data using 0.02% soap solution.
[2] Calculated DA_p = (Absorption from 0.02% triclosan applied in the relevant *in vitro* study) x (0.03%/0.02%) = Absorption from 0.03% triclosan solution. This assumes that 1) a 10x dilute solution of 0.3% triclosan is applied and 2) skin penetration is by passive diffusion, such that flux would be proportional to the concentration of triclosan applied to the skin.

Table 13. Summary of individual and aggregated SEDs for triclosan in adults

Product type	**SED_{oral} or SED_{dermal} (mg/kg bw/d)**
Toothpaste	0.00648
Mouthwash	0.0651
Deodorant stick	0.00303
Body lotion	0.37514
Face powder	0.00593
Blemish concealer	0.00060
Hand soap	0.00659
Shower gel	0.01919
All products	**0.48206**

3.5.2.2 Exposure assessment of triclosan in children

The use of toothpaste starts with first erupted teeth and occurs with a high percentage of dentifrice ingestion. Therefore, the amount of toothpaste to be used by children aged 6 years and under, as implemented for fluoride toothpastes, is generally set at a pea-size amount. The SCCNFP (2003) defined this as 0.25 grams when assessing the safety of fluoridated oral care products for children. In general, children up to 6 years of age are expected to ingest more toothpaste than adults. A retention factor of 0.4 for infants, toddlers and children aged 3-6 years were used for the SED calculations. Whereas SED was calculated using a retention factor of 0.1 for children aged 6-10 years. Since the use of mouthwash is not recommended for children up to 6 years of age, mouthwash was not included in the SED calculation for infants, toddlers and children aged 3-6 years. Table 14 shows the results for the SED calculations for oral products by age categories.

For dermal formulations, SED calculations were based on the same percutaneous absorption data as for adults. As for triclocarban, extrapolation of surface area and daily exposure were made for children on the basis of the body surface area. Tables in Annex B shows the calculated child application surface areas and daily exposure doses for the different age categories and exposure scenarios.

Tables 14-16 show the results for the SED calculations for oral products and dermal leave-on and rinse-off products, respectively.

An overview on the SED values for individual products and aggregated exposures for triclosan are shown in Table 17.

Table 14. SED calculation for triclosan in oral products by age categories

Age category	**Age (yrs)**	**Calculated daily exposure (mg/d) q_x**	**Retention factor[1] F_{ret}**	**Body weight[2] (kg) bw**	**Calculated relative daily exposure[3] (mg/kg bw/d) $E_{product}$**	**Triclosan content (%) C**	**Oral bioavailability[4] (%)**	**SED[5] (mg/kg bw/d)**
Toothpaste								
Infant	0.5-1	500	0.4	8.8	22.73	0.3	100	0.06819
Toddler	1-3	500	0.4	11.9	16.81	0.3	100	0.05043
Children	3-6	500	0.4	23.1	8.66	0.3	100	0.02598
Children	6-10	2 750	0.05	23.1	5.95	0.3	100	0.01785

Adolescents	10-14	2 750	0.05	43.4	3.17	0.3	100	0.00951
Adolescents	14-18	2 750	0.05	61.3	2.24	0.3	100	0.00672
Mouthwash[6]								
Children	6-10	21 600	0.1	23.1	93.51	0.2	100	0.18702
Adolescents	10-14	21 600	0.1	43.4	49.77	0.2	100	0.09954
Adolescents	14-18	21 600	0.1	61.3	35.24	0.2	100	0.07048

[1] Due to not sufficiently developed swallowing reflexes in children up to 6 years of age, a retention factor of 0.4 was used for children under age 6 years
[2] Default values from EFSA 2012
[3] $E_{product}=q_x*F_{ret}/bw$
[4] Potential amount available for oral exposure
[5] $SED=E_{product}*(C/100)*(\text{oral bioavailability}/100)$
[6] Since the use of mouthwash is not recommended for children under age 6 years, SED calculations were not made for children younger than 6 years of age.

Table 15. SED Calculation for triclosan in leave-on products by age and exposure scenarios

Age category	Age (yrs)	Calculated dermal absorption[1] (μg/cm²) DA_a	Calculated skin surface area[2] (cm²) SSA	Dermal absorption/application[3] (mg) DA_a/F	Frequency of application F	Body weight (kg)[4] bw	SED[5] (mg/kg bw/d)
Deodorant							
Children	3-10	0.455	99	0.04524	2	23.1	0.00392
Adolescents	10-14	0.455	149	0.06760	2	43.4	0.00312
Adolescents	14-18	0.455	194	0.08840	2	61.3	0.00288
Body lotion							
Infants	0.5-1	0.63	3 940	2.48	2.28	8.8	0.64255
Toddler	1-3	0.63	5 014	3.16	2.28	11.9	0.60545
Children	3-10	0.63	7 790	4.91	2.28	23.1	0.48462
Adolescents	10-14	0.63	11 641	7.33	2.28	43.4	0.38508
Adolescents	14-18	0.63	15 222	9.59	2.28	61.3	0.35669
Face powder							
Adolescents	14-18	0.63	549	0.34578	1	61.3	0.00564
Blemish concealer							
Adolescents	14-18	0.63	55	0.03488	1	61.3	0.00057

[1] DA_a = (Absorption from 0.2% triclosan applied in the relevant *in vitro* study) x (triclosan content for the product/0.2%) = Absorption from 0.3% triclosan. This assumes that skin penetration is by passive diffusion, such that flux would be proportional to the concentration of triclosan applied to the skin.

[2] See Tables B2-B3 in Annex B for calculation of child skin surface areas.

[3] DA_a/F = DAa*SSA/1000

[4] Default values from EFSA 2012

[5] SED = [(DA_a/F) * F]/bw

Table 16. SED Calculation for triclosan in rinse-off products by age

Age category	Age (yrs)	Calculated dermal absorption[1] (%) DA_a	Child body surface area for application[2] (cm^2) SSA	Calculated skin surface area[3] (cm^2)	Dermal absorption/ application[4] (mg) DA_a/F	Frequency of application F	Body weight[5] (kg) bw	SED[6] (mg/kg bw/d)
Shower gel								
Infants	0.5-1	0.046	4 400		0.20240	1.43	8.8	0.03289
Toddler	1-3	0.046	5 600		0.25760	1.43	11.9	0.03096
Children	3-10	0.046	8 700		0.40020	1.43	23.1	0.02477
Adolescents	10-14	0.046	13 000		0.59800	1.43	43.4	0.01970
Adolescents	14-18	0.046	17 000		0.78200	1.43	61.3	0.01824
Hand soap								
Infants	0.5-1	0.046		216	0.00995	10	8.8	0.01131
Toddler	1-3	0.046		275	0.01266	10	11.9	0.01064
Children	3-10	0.046		428	0.01967	10	23.1	0.00852
Adolescents	10-14	0.046		639	0.02939	10	43.4	0.00677
Adolescents	14-18	0.046		835	0.03843	10	61.3	0.00627

[1] DA_a = (Absorption from 0.02% triclosan applied in the relevant *in vitro* study) x (0.03%/0.02%) = Absorption from 0.03% triclosan solution. This assumes that 1) a 10x dilute solution of 0.3% triclosan is applied and 2) skin penetration is by passive diffusion, such that flux would be proportional to the concentration of triclosan applied to the skin.

[2] Values from Sharkey *et al.* 2001

[3] See Table B3 in Annex B for calculation of child surface area for hand soap.

[4] DA_a/F = DAa*SSA/1000

[5] Default values from EFSA 2012

[6] SED = $[(DA_a/F) * F]/bw$

Table 17. SED (mg/kg bw/day) for aggregated exposures for triclosan by age group

		Oral products	Dermal products	All products
Age category	**Age (yrs)**	**SED_{oral}**	**SED_{dermal}**	**SED total**
Infants	0.5-1	0.06819	0.68675	0.75494
Toddler	1-3	0.05043	0.64705	0.69748
Children	3-6	0.02598	0.52183	0.54781
Children	6-10	0.20487	0.52183	0.72670
Adolescents	10-14	0.10905	0.41467	0.52372
Adolescents	14-18	0.07720	0.39029	0.46749

3.6 SAFETY EVALUATION

3.6.1 SAFETY EVALUATION OF TRICLOCARBAN

A NOAEL of 25 mg/kg bw/day was selected from a 2-year chronic feeding study in rats. The information on absorption after oral administration, *i.e.* 27%, was used to calculate an adjusted NOAEL of 6.75 mg/kg bw/day (25 mg/kg bw/day x 27% = 6.75 mg/kg bw/day).

3.6.1.1 Safety evaluation of triclocarban in adults

MoS calculations for the use of triclocarban as an ingredient in the rinse-off products and as a preservative for adults are shown in Table 18 and Table 19, respectively.

Table 18. MoS calculations for triclocarban when used as an ingredient in rinse-off products

Type of cosmetic product exposure	Product category	SED	NOAEL	Oral Bioavailability	NOAEL Adj	MOS
		(µg/kg bw/d)	(mg/kg bw/d	(%)	(µg/kg bw/d)	
Rinse-off skin and hair cleansing products	Shower gel	3.348	25	27	6750	2016
	Hand wash soap	3.996	25	27	6750	1689
	Shampoo	1.812	25	27	6750	3725
	Hair conditionner	0.804	25	27	6750	8396
Aggregate exposure		9.96	25	27	6750	678

The Margin of Safety (MoS) for exposure to triclocarban used in rinse-off products (1.5%) is above 100 for each individual product category, as well as for the aggregated product categories.

Table 19. MoS calculations for triclocarban when used as a preservative (0.2%)

Type of cosmetic product exposure	Product category	SED	NOAEL	Oral Bioavailability	NOAEL Adj	MOS
		(µg/kg bw/d)	(mg/kg bw/d)	(%)	(µg/kg bw/d)	
Rinse-off skin and hair cleansing products	Shower gel	0.4464	25	27	6750	15121
	Hand wash soap	0.5328	25	27	6750	12669
	Shampoo	0.2416	25	27	6750	27939
	Hair conditionner	0.1072	25	27	6750	62966
Leave-on skin and hair cleansing products	body lotion	19.712	25	27	6750	342
	Face cream	3.8624	25	27	6750	1748
	Hand cream	5.136	25	27	6750	1314
	Deodorant non-spray	3.5328	25	27	6750	1911
	Hair styling	0.9184	25	27	6750	7350
Make-up products	Liquid foundation	1.264	25	27	6750	5340
	Make-up remover	1.3328	25	27	6750	5065
	Lipstick	1.8	25	27	6750	3750
	Eye make-up	0.0528	25	27	6750	127841
	Mascara	0.0672	25	27	6750	100446
	Eyeliner	0.0128	25	27	6750	527344
Oral care products	Toothpaste	4.32	25	27	6750	1563
	Mouthwash	65.08	25	27	6750	104
Aggregate exposure		108.4192	25	27	6750	62

The Margin of Safety (MoS) for exposure to triclocarban used as a preservative (0.2%) is above 100 for each individual product category, but when aggregated the MOS is below 100, mainly due to exposure through mouthwash.

Aggregated exposure to triclocarban as an ingredient in rinse-off products and when used as a preservative is shown in Table 20.

Table 20. MoS calculations for aggregated exposure of triclocarban when used together as an ingredient at 1.5% in rinse off products and at 0.2% as a preservative

Products categories	SED[1]	NOAEL	Oral Bioavailability	NOAEL Adj	MOS
	(µg/kg bw/d)	(mg/kg bw/d)	(%)	(µg/kg bw/d)	
rinse off products	10	25	27	6750	675
preservative	108.4	25	27	6750	62
aggregated	118.4	25	27	6750	57

Combined exposures of triclocarban in rinse off products when used as a cosmetic ingredient at 1.5%, and/or at 0.2% as a preservative result in a MoS below 100.

3.6.1.2 Safety evaluation of triclocarban in children

MoS calculations for the use of triclocarban as an ingredient in the rinse-off products and as a preservative for children in different age groups are shown in Table 21 and Table 22, respectively.

Aggregated exposure to triclocarban as an ingredient in rinse-off products and when used as a preservative is shown in Table 23.

Table 21. MoS calculations for triclocarban by age categories when used as an ingredient in rinse-off products (1.5%)

Product type[1]	Age category (yrs)	SED [7] (µg/kg bw/d)	NOAEL Adj (µg/kg bw/d)	MOS
Shower gel				
Infants	0.5 -1	6.82	6750	990
Toddlers	1-3	6.05	6750	1116
Children	3-10	4.68	6750	1444
Adolescents	10-14	3.87	6750	1744
Adolescents	14-18	3.52	6750	1916
Adults				
Hand soap				
Infants	0.5 -1	6.82	6750	990
Toddlers	1-3	6.05	6750	1116
Children	3-10	5.19	6750	1299
Adolescents	10-14	4.15	6750	1628
Adolescents	14-18	3.72	6750	1815
Adults				
Shampoo				
Infants	0.5 -1	4.09	6750	1650
Toddlers	1-3	4.03	6750	1673
Children	3-10	2.60	6750	2599
Adolescents	10-14	2.21	6750	3052
Adolescents	14-18	2.15	6750	3135
Adults				
Hair conditioner				
Toddlers	1-3	1.01	6750	6694
Children	3-10	1.04	6750	6497
Adolescents	10-14	0.83	6750	8138
Adolescents	14-18	0.78	6750	8620
Adults				
Aggregated				
Infants	0.5 -1	17.73	6750	381
Toddlers	1-3	17.14	6750	394
Children	03-oct	13.51	6750	500
Adolescents	10-14	11.06	6750	610
Adolescents	14-18	10.18	6750	663
Adults				

Exposure to triclocarban used in rinse-off products (1.5%) result in a MoS above 100 for each individual product category as well as for the aggregated product categories.

Table 22. MoS calculations for triclocarban by age categories when used as a preservative (0.2%) for different exposure scenarios.

Product type[1]	Age category (yrs)	SED [7] (µg/kg bw/d)	NOAEL Adj (µg/kg bw/d)	MOS
Shower gel				
Infants	0.5 -1	0.91	6750	**7425**
Toddlers	1-3	0.81	6750	**8367**
Children	3-10	0.62	6750	**10828**
Adolescents	10-14	0.52	6750	**13078**
Adolescents	14-18	0.47	6750	**14367**
Adults				
Hand soap				
Infants	0.5 -1	0.91	6750	**7425**
Toddlers	1-3	0.81	6750	**8367**
Children	3-10	0.69	6750	**9745**
Adolescents	10-14	0.55	6750	**12206**
Adolescents	14-18	0.50	6750	**13611**
Adults				
Shampoo				
Infants	0.5 -1	0.55	6750	**12375**
Toddlers	1-3	0.54	6750	**12551**
Children	3-10	0.35	6750	**19491**
Adolescents	10-14	0.29	6750	**22887**
Adolescents	14-18	0.29	6750	**23510**
Adults				

Hair conditioner				
Toddlers	1-3	0.13	6750	**50203**
Children	3-10	0.14	6750	**48727**
Adolescents	10-14	0.11	6750	**61031**
Adolescents	14-18	0.10	6750	**64652**
Adults				
Body lotion				
Infants	0.5 -1	35.82	6750	**188**
Toddlers	1-3	33.61	6750	**201**
Children	3-10	26.94	6750	**251**
Adolescents	10-14	21.42	6750	**315**
Adolescents	14-18	19.84	6750	**340**
Adults				
Face cream				
Infants	0.5 -1	7.09	6750	**952**
Toddlers	1-3	6.59	6750	**1025**
Children	3-10	5.33	6750	**1266**
Adolescents	10-14	4.20	6750	**1606**
Adolescents	14-18	3.92	6750	**1724**
Adults				
Hand cream				
Infants	0.5 -1	9.82	6750	**688**
Toddlers	1-3	9.28	6750	**728**
Children	3-10	7.41	6750	**911**
Adolescents	10-14	5.90	6750	**1144**
Adolescents	14-18	5.48	6750	**1231**
Adults				
Deodorant				
Children	3-10	5.19	6750	**1299**
Adolescents	10-14	4.09	6750	**1649**
Adolescents	14-18	3.81	6750	**1771**
Hair styling				
Children	3-10	1.39	6750	**4873**
Adolescents	10-14	1.11	6750	**6103**
Adolescents	14-18	1.02	6750	**6631**
Adults				
Liquid foundation				
Adolescents	10-14	1.40	6750	**4818**
Adolescents	14-18	1.31	6750	**5172**
Adults				

Make-up remover				
Adolescents	10-14	1.36	6750	**4948**
Adolescents	14-18	1.28	6750	**5278**
Lipstick				
Adolescents	10-14	1.84	6750	**3662**
Adolescents	14-18	1.96	6750	**3448**
Adults				
Eye make-up				
Adolescents	10-14	0.04	6750	**183094**
Adolescents	14-18	0.05	6750	**129305**
Adults				
Mascara				
Adolescents	10-14	0.07	6750	**91547**
Adolescents	14-18	0.08	6750	**86203**
Adults				
Eyeliner				
Adolescents	10-14	0.04	6750	**183094**
Adolescents	14-18	0.03	6750	**258609**
Adults				
Aggregated				
Infants	0.5 -1	55.09	6750	**123**
Toddlers	1-3	51.76	6750	**130**
Children	3-10	48.07	6750	**140**
Adolescents	10-14	41.59	6750	**162**
Adolescents	14-18	38.86	6750	**174**
Adults				

Exposure to triclocarban used as a preservative (0.2%) result in a MoS above 100 for each individual product category as well as for the aggregated product categories.

Table 23. MoS calculations for triclocarban by age categories when used as a preservative in oral products only.

Oral products	SED (µg/kg bw/d)	NOAEL Adj (µg/kg bw/d)	MOS
Toothpaste <1 year	45.45	**6750**	**149**
Toothpaste, 1-3y years	33.61	**6750**	**201**
Toothpaste, 3-10 years	17.32	**6750**	**390**
Toothpaste, 10-14 years	6.34	**6750**	**1065**
Toothpaste, 14-18 years	4.49	**6750**	**1505**
mouthwash, 6-10 years	199.26	**6750**	**34**
mouthwash, 10-14 years	102.95	**6750**	**66**
mouthwash, 14-18 years	72.07	**6750**	**94**
Agg toothpaste and mouthwash, 6-10 years	**216.58**	**6750**	**31**
Agg toothpaste and mouthwash, 10-14 years	**109.29**	**6750**	**62**
Agg toothpaste and mouthwash, SCCS, 14-18 years	**76.55**	**6750**	**88**

Exposure to triclocarban used as a preservative (0.2%) in oral care products result in a MoS above 100 for toothpaste for all age categories. However, the MoS is < 100 for mouth wash for children of all age categories.

Table 24. MoS calculations for triclocarban by age categories when used as a preservative (0.2%) and in rinse off products (1.5%), mouthwash use excluded.

Age categories		Dermal TCC as a preservative (µg/kg bw/d)	Dermal TCC in rinse -off products (µg/kg bw/d)	Oral * (µg/kg bw/d)	Aggregated (µg/kg bw/d)	NOAEL Adj (µg/kg bw/d)	MOS
Infants	0.5 -1	55.09	17.73	45.45	118.27	**6750**	**57**
Toddlers	1-3	51.76	17.14	33.61	102.51	**6750**	**66**
Children	3-6	48.07	13.51	17.32	78.90	**6750**	**86**
Children	6-10	48.07	13.51	17.32	78.90	**6750**	**86**
Adolescents	10-14	41.59	11.06	6.34	58.99	**6750**	**114**
Adolescents	14-18	38.86	10.18	4.49	53.53	**6750**	**126**

* Without mouth wash

Aggregated exposure to triclocarban used as a preservative (0.2%) and in rinse–off products (1.5%) result in a MoS below 100 for children below the age of 10 years.

3.6.2 SAFETY EVALUATION OF TRICLOSAN

A NOAEL of 8 mg/kg bw/day based on the highest dose tested in the studies by Montagnini *et al.* (2018, 2020) and Pernoncini *et al.* (2018) is used for the calculation of MoS. An oral availability of 100% was assumed, and thus no adjustments to the NOAEL were performed.

3.6.2.1 Safety evaluation of triclosan in adult

MoS calculations for separate product types and aggregated exposures are shown in Table 24. Since body lotions contribute significantly to the SED for aggregated exposures, MoS for aggregated exposures not including body lotion is also calculated.

Table 24. Calculation of total SED for aggregated exposures of triclosan

Product type	Triclosan content (%)	SED_{oral} or SED_{dermal} (mg/kg bw/d)	NOAEL (mg/kg bw/d)	MoS
Toothpaste	0.3	0.00648	8	1234
Mouthwash	0.2	0.0651	8	1 23
Deodorant stick	0.3	0.00303	8	2 640
Body lotion	0.3	0.37514	8	21
Face powder	0.3	0.00593	8	1 349
Blemish concealer	0.3	0.00060	8	13 333
Hand soap	0.03	0.00659	8	1 214
Shower gel	0.03	0.01919	8	417
Aggregated exposure		**0.48206**	8	**17**
Aggregated exposure not including body lotion		**0.107**	8	**75**

With the exception of body lotion, each separate product type has a MoS above 100. Aggregated exposure to triclosan results in a MoS lower than 100 due to the contribution of triclosan in body lotions and mouthwash.

3.6.2.2 Safety evaluation of triclosan in children

MoS calculations for separate product types and aggregated exposures for each product category are shown in Tables 25-27. MoS calculations for aggregated exposure for all product types by age are shown in Table 28.

Table 25. SED calculation for triclosan in oral products by age categories

Age category	Age (yrs)	Triclosan content (%)	SED_{dermal} (mg/kg bw/d)	NOAEL (mg/kg bw/d)	MoS
Toothpaste					
Infants	0.5-1	0.3	0.06819	8	117
Toddler	1-3	0.3	0.05043	8	159
Children	3-6	0.3	0.02598	8	308
Children	6-10	0.3	0.01785	8	448
Adolescents	10-14	0.3	0.00951	8	841
Adolescents	14-18	0.3	0.00672	8	1 190
Mouthwash					
Children	6-10	0.2	0.18702	8	43
Adolescents	10-14	0.2	0.09954	8	80
Adolescents	14-18	0.2	0.07048	8	114
Aggregated exposure					
Infants	0.5-1	0.3	0.06819	8	117
Toddler	1-3	0.3	0.05043	8	159
Children[1]	3-6	0.3	0.02598	8	308
Children[2]	6-10	0.3/0.2	0.20487	8	39
Adolescents	10-14	0.3/0.2	0.10905	8	73
Adolescents	14-18	0.3/0.2	0.07720	8	104

[1]Retention factor for toothpaste: 0.4; Mouthwash not included
[2]Retention factor for toothpaste: 0.05; Mouthwash included

Table 26. MoS calculation for triclosan in leave-on products by age categories and exposure scenarios

Age category	Age (yrs)	Triclosan content (%)	SED_{dermal} (mg/kg bw/d)	NOAEL (mg/kg bw/d)	MoS
Deodorant					
Children	3-10	0.3	0.00392	8	2 041
Adolescents	10-14	0.3	0.00312	8	2 564
Adolescents	14-18	0.3	0.00288	8	2 778
Body lotion					
Infants	0.5-1	0.3	0.64255	8	12
Toddler	1-3	0.3	0.60545	8	13
Children	3-10	0.3	0.48462	8	17
Adolescents	10-14	0.3	0.38508	8	21
Adolescents	14-18	0.3	0.35669	8	22
Face powder					
Adolescents	14-18	0.3	0.00564	8	1 418
Blemish concealer					
Adolescents	14-18	0.3	0.00057	8	14 035
Aggregated exposure					
Infants	0.5-1	0.3	0.64255	8	12
Toddler	1-3	0.3	0.60545	8	13
Children	3-10	0.3	0.48854	8	16
Adolescents	10-14	0.3	0.38820	8	21
Adolescents	14-18	0.3	0.36578	8	22
Aggregated exposure without body lotion					
Infants	0.5-1	0.3	-	8	-
Toddler	1-3	0.3	-	8	-
Children	3-10	0.3	0.00392	8	2 041
Adolescents	10-14	0.3	0.00312	8	2 564
Adolescents	14-18	0.3	0.00909	8	880

Table 27. SED Calculation for triclosan in rinse-off products by age categories

Age category	Age (yrs)	Triclosan content (%)	SED_{dermal} (mg/kg bw/d)	NOAEL (mg/kg bw/d)	MoS
Shower gel					
Infants	0.5-1	0.03	0.03289	8	243
Toddler	1-3	0.03	0.03096	8	258
Children	3-10	0.03	0.02477	8	323
Adolescents	10-14	0.03	0.01970	8	406
Adolescents	14-18	0.03	0.01824	8	439
Hand soap					
Infants	0.5-1	0.03	0.01131	8	707
Toddler	1-3	0.03	0.01064	8	752
Children	3-10	0.03	0.00852	8	939
Adolescents	10-14	0.03	0.00677	8	1 182
Adolescents	14-18	0.03	0.00627	8	1 276
Aggregated exposure					
Infants	0.5-1	0.03	0.04420	8	181
Toddler	1-3	0.03	0.04160	8	192
Children	3-10	0.03	0.03329	8	240
Adolescents	10-14	0.03	0.02647	8	302
Adolescents	14-18	0.03	0.02451	8	326

Table 28. Calculation of MoS for aggregated exposures of triclosan by age categories

Age category	Age (yrs)	SED_{oral}	SED_{dermal}	SED_{total}	NOAEL	MoS_{oral}	MoS_{dermal}	MoS_{total}
		mg/kg bw/d						
Infants	0.5-1	0.06819	0.68675	0.75494	8	117	12	11
Toddler	1-3	0.05043	0.64705	0.69748	8	159	12	11
Children[1]	3-6	0.02598	0.52183	0.54781	8	308	15	15
Children[2]	6-10	0.20487	0.52183	0.72670	8	39	15	11
Adolescents	10-14	0.10905	0.41467	0.52372	8	73	19	15
Adolescents	14-18	0.07720	0.39029	0.46749	8	104	20	17
Aggregated exposure not including body lotion								
Infants	0.5-1	0.06819	0.04420	0.11239	8	117	181	71
Toddler	1-3	0.05043	0.04160	0.09203	8	159	192	87
Children[1]	3-6	0.02598	0.03721	0.06319	8	308	215	127
Children[2]	6-10	0.20487	0.03721	0.24208	8	39	215	33
Adolescents	10-14	0.10905	0.02959	0.13864	8	73	270	58
Adolescents	14-18	0.07720	0.03360	0.11080	8	104	238	72

[1]Retention factor for toothpaste: 0.4; Mouthwash not included
[2]Retention factor for toothpaste: 0.05; Mouthwash included

Regarding toothpaste, MoS is above 100 for all age categories. MoS is below 100 for mouthwash for children aged 6-10 and adolescents aged 10-14 when used individually or in combination with toothpaste. MoS is above 100 for mouthwash for adolescents aged -10 when used individually or in combination with toothpaste.

Regarding the leave-on products, MoS was above 100 for individual use of deodorant, face powder and blemish concealer for the included age categories, whereas MoS was below 100 for body lotion in all age categories. MoS for combined use of all four leave-on product types is below 100 for all age categories, while the MoS is above 100 for combined used of deodorant, face powder and blemish concealer for the included age categories.

For all age categories, MoS is above 100 for the rinse-off products shower gel and hand soap when used individually or in combination.

MoS is below 100 in all age categories for the combined use of all the included product types. When excluding body lotion, MoS is above 100 for children aged 3-6 years only, whereas MoS is below 100 for the other age categories.

3.7 DISCUSSION

Triclocarban
The SCCS has noted that triclocarban is a weak skin irritant but not an eye irritant. Data show no evidence of skin sensitisation or photoallergenicity.

Triclocarban has been found to have a low acute oral, dermal and intraperitoneal toxicity.

The SCCS considers that the reproductive effects observed in Costa *et al.* studies (2020a and 2020b) cannot be regarded as adverse and will not be used to derive a PoD. Since none of the other new studies report on adverse effects, including endocrine activity, that indicate a NOEL of lower than 25 mg/kg bw/day that was used in the SCCP opinion (2005). The SCCS, will use a PoD of 25 mg/kg bw/day for triclocarban based on a decrease in food consumption, body weights, and organ weights (*e.g.* liver, spleen) from a 2-year chronic feeding study in rats.
In a 2-year chronic feeding study in rats (at doses of 25, 75, and 250 mg/kg bw/d), a decrease in food consumption, body weights, and organ weights *(e.g.,* liver, spleen) were observed in the mid-dose group of 75 mg/kg bw/d. The SCCS selected a PoD of 25 mg/kg bw/day for safety assessment of triclocarban.

Triclocarban was not found to be mutagenic or carcinogenic.

In silico and *in vitro* studies provide evidence for a moderate estrogenic and androgenic potential of triclocarban, with further indication of a weak affinity for thyroid receptor. There is also evidence of endocrine activity of triclocarban from *in vivo* animal studies. The human studies do not provide robust evidence of endocrine disruptive effects of triclocarban.

Triclosan
Triclosan at a concentration of 0.3% is not a skin or oral mucosal irritant, whereas at 1 to 10% concentrations it produced slight, reversible irritation in the rabbit eye. Triclosan has a low sensitisation potential in humans. Possible photocontact allergy has been rarely reported.

Triclosan is not acutely toxic via the oral route of administration (LD50 > 5 000 mg/kg body weight in dogs). Four rat studies give evidence for a NOAEL between 8 and 12 mg/kg bw/day (Lan, 2015; Montagnini 2018, 2021; Pernoncini 2018). Since Montagnini *et al.* (2018), Montagnini *et al.* (2021) and Pernoncini *et al.* (2018) are well-performed Level 3 and Level 5 rat studies that show consistent results using standardised test guidelines (uterotrophic and

Hershberger assays, and two-generation reproductive toxicity studies, respectively), the SCCS considers a PoD of 8 mg/kg bw/day to be appropriate for safety assessment of triclosan. A 20-day repeated dose toxicity study and an uterotrophic assay in rats (Stoker *et al.* 2010), where the authors derived a NOEL of 9.375 mg/kg bw/day and LOEL of 18.75 mg/kg bw/day based on reduction in T4 and estradiol serum levels, provide further support for a PoD of 8 mg/kg bw/day.

Triclosan was not found to be mutagenic or carcinogenic. However, it should be noted that triclosan is a peroxisome proliferator in mice liver.

Several studies have demonstrated estrogenic and an anti-androgenic activity of triclosan, through both direct and indirect MoA, confirming the androgen- and estrogen-mediated activity of triclosan. There is also evidence of endocrine activity of triclosan from *in vivo* animal studies. The human studies do not provide any strong evidence of endocrine disruptive effects of triclosan. There are inconsistent findings in regard to the effects of triclosan on the thyroid hormones, as well as statistically non-significant associations between triclosan and birth outcomes.

Environment

This Opinion did not assess the potential impact of triclocarban and triclosan on the environment.

4. CONCLUSION

In light of the information submitted via the call for data, the currently available scientific literature, relevant in silico tools and SCCS' expert judgement and taking under consideration in particular the concerns related to potential endocrine disrupting properties, the SCCS is requested:

1. *To identify and justify specific concerns regarding the safe use of triclocarban and triclosan in cosmetic products*

Based on the safety assessment carried out in consideration of all available information, including the potential endocrine effects, the SCCS is of the opinion that:

For Triclocarban

- The use of triclocarban as a preservative in **dermally applied cosmetic product** is safe up to a maximum concentration of 0.2% for both children (0.5-18 years) and adults, when used individually or in combination.
- In addition to the preservative function, the use of triclocarban is also safe up to a maximum concentration of 1.5% **in rinse-off product** when used individually or in combination for both children (0.5-18 years) and adults.
- However, the use of triclocarban to a maximum concentration of 0.2% **in mouthwash** is not safe for adults and children and in toothpaste is not safe for for children below 6 years old.
- This assessment does not include exposure of babies through wipes.

For Triclosan

- The use of Triclosan as a preservative at the concentrations reported in entry 25 of Annex V in **dermally applied cosmetic product** is safe except for body lotions, when used individually or in combination, for both adults and children (0.5-18 years).
- The use of Triclosan as a preservative **in toothpaste** is safe at the concentration of 0.3% when used individually for both adults and children (0.5-18 years) but it is not safe when used in combinations for children below 3 years old.
- For adults, the use of Triclosan as a preservative **in mouthwash** is safe at the concentration of 0.2% when used individually but not when used in combination. For *To highlight if there is a potential risk for human health from the use of triclocarban and triclosan in cosmetic products.*

The SCCS is not aware of the use of triclocarban and triclosan together in a single product, and, therefore, this has not been assessed.

5. MINORITY OPINION

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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

9. ANNEXES

ANNEX A

Table A. Summary of *in vivo* animal data on triclosan

Reference	Year	Species	Method	Results	Comments	NOAEL/LOAEL (mg/kg bw/d)
Jung *et al.*	2012	Immature female Sprague-Dawley rats	Oral gavage, PND19-21 Doses: 7.5, 37.5, and 187.5 mg/kg bw/d EE (positive control): 1 mg/kg bw/d n = 8/group	All doses of triclosan significantly increased uterine wet weight (none dose-response). In addition, the expressions of calbindin-D9k (CaBP-9k) and complement C3 (C3) were significantly induced by triclosan.		LOAEL = 7.5

Reference	Year	Species	Method	Results	Comments	NOAEL/LOAEL (mg/kg bw/d)
Paul *et al.*	2012	Female Long-Evans Rats	Oral gavage, GD6 - PND21 Doses: 10, 30, 100, 300 mg/kg/d Assigned to this order of doses n = 21, 12, 22, 22 + 11 animals/group for GD21 sacrifice	↓ T4 in GD20 dams at 300 ↓ T4 in PND22 dams at 100 and 300 ↓ T4 in GD20 and PND4 offspring at 300 ↔ T4 in PND14 and PND21 offspring ↑ hepatic PROD activity in PND4 pups and PND22 dams at 300 ↑ UGT activity in PND22 dams at 300 ↑ Cyp2b and Cyp3a expression in dams (minor) ↔ T3 and TSH ↔ dam liver weight	T4 reductions with concomitant increased PROD and UGT activity suggest that up-regulated hepatic catabolism may contribute to triclosan-induced hypothyroxinemia during development. Exposure conveyed from dams to offspring diminishes over the lactation period.	Dams: NOEL = 30 (PND22) BMDL = 25.2 (GD20)

Reference	Year	Species	Method	Results	Comments	NOAEL/LOAEL (mg/kg bw/d)
Axelstad *et al.*	2013	Wistar rat	Developmental toxicity study with gavage exposure of dams GD7-PND21 Doses: 75, 150 and 300 mg/kg n=10 Study with direct pups dosing PND3-16 at doses of 50 & 150 mg/kg (n=2)	Dams: ↓ T4 on GD15 and PND16 at all doses ↔ thyroid weight Offspring PND16: ↔ T4, thyroid gland histology ↓ T4 in directly exposed pups PND16 at both doses Female offspring: ↔ AGD, nipple retention, reproductive organs Male offspring: ↔ AGD, nipple retention, prostate weight	T3 and TSH not measured	LOAEL =75
Lan *et al.*	2015	Male Sprague-Dawley rats	Intragastric exposure of adult rats for 8 weeks Doses: 0, 10, 50 and 200 mg/kg n = 8/group	↓ ventral prostate 200 ↓daily sperm production at 50-200 changes to sperm morphology and epididymal histopathology at 200		NOAEL = 10
Feng *et al.*	2016	Female Sprague-Dawley rats	Exposure of pregnant rat dams from GD6 to GD20 Doses: 30, 100, 300 and 600 mg/kg bw/d	↓ uterine weight at 600 ↓ progesterone at all doses ↓ estradiol,	No investigations of effects in pups	LOAEL = 30 (progesterone)

Reference	Year	Species	Method	Results	Comments	NOAEL/LOAEL (mg/kg bw/d)
			n = 10, n=6 in most assays	prolactin at 100-600 ↓ testosterone at 300-600 ↓ hCG at all doses (flat response) ↔ LH, FSH ↑ mRNA of placental steroid metabolising enzymes: UGT1A1, Sult1E1, steroid 5alphareductase 1 and 2 at 100-300 (600 not tested) ↑progesterone receptor, estrogen receptor-alpha and androgen-receptor at 100-300 (600 not tested)		

Reference	Year	Species	Method	Results	Comments	NOAEL/LOAEL (mg/kg bw/d)
Hua *et al.*	2017	ICR mice	Gestational and non-gestational female mice Exposure from GD5-GD17 Doses: 1, 4, 8 mg/kg bw/d (gestational), 8 mg/kg bw/d (non-gestational) n=10	Gestational mice ↓ T3, T4 at 4 and 8 ↓ free T4 at 8 ↔ estrogen, progesteron ↔ body weight Non-gestational mice: ↓ T3, T4, free T4 at 8		NOAEL =1
Louis *et al.*	2017	Female Wistar rats	8-months oral gavage exposure of female rats Doses: 2.35, 4.69, 9.375, 37.5 mg/kg/day of triclosan or 1 ug/kg/day of EE n= 13-15/group, n=6 for EE	↓ T4 at 9.375 and 37.5 mg/kg ↔ T3, TSH, thyroid weight, histology (follicle height, colloid volume) ↑ cyp2b2 gene expression in liver at 37.5 mg/kg ↔ Cyp3a23, Sult1c1/1c3, Sult1b1, Ugta1 ↔ estrous cyclicity or senescence		NOAEL= 4.69

Reference	Year	Species	Method	Results	Comments	NOAEL/LOAEL (mg/kg bw/d)
Cao *et al.*	2018	Female ICR mice	12 week old female mice exposed for 50 days Doses: 1, 10, 100 mg/kg/d	↓ T3, T4 at 10 and 100 ↑ TSH, TRH at 10 and 100 ↓ FSH, LH, progesteron, *Gnrh m*RNA with the lack of LH-surge and ↑ prolactin ↑ length off estrous cycle and diestrus at 10 and 100 ↓ number of antral follicles and corpora lutea at 10 and 100 ↓ kisspeptin immunoreactivity and kiss1 mRNA in anteroventral periventricular nucleus Levothyroxine rescues estrous cycling, follicular development and ovulation		NOAEL = 1
Ena *et al.*	2018	Male Sprague-Dawley rats	60-day oral gavage exposure of prepubertal male rats Doses: 0.25, 25, 250 and 750 mg/kg bw/d n = 6	↓ weight of liver, kidney, testes, adrenal glands at 750 ↑ CYP2B1, RXR/PPAR, malondialdehyde at 250-750		LOAEL = 250 (sperm production)

Reference	Year	Species	Method	Results	Comments	NOAEL/LOAEL (mg/kg bw/d)
				↓ daily sperm production at 250-750 ↓ AR protein expression at 25		
Farmer *et al.*	2018	Male, castrated rat	Hershberger assay, oral gavage for 10 days Doses: 50, 200 mg/kg n=5-7/group	↓ T4 at 200 ↓ T4 at both doses in presence of testosterone proprionate ↔ weight of thyroid and liver, male tissue weights	No effect on androgen synthesis or activity	LOAEL = 50 (thyroid effects) NOAEL = 200 (male reproduction)
Ha *et al.*	2018	Male Sprague-Dawley rats	31 days gavage exposure to male rats Doses: 0, 50, 100, 200 mg/kg/day n = 6/group	↓ relative testis weight at 100-200 ↓ relative epididymis weight at 200 histopathologic alterations in testis at 100-200 ↓ LH at all doses ↓ Testosterone at 100-200 ↓ steroidogenic proteins at 100-200: SRB1, StAR, 3ß-HSD, P450c17 ↓ mRNA: LHR at all doses, AR at 200 ↑ miR-142 and		LOAEL = 100 mg/kg

Reference	Year	Species	Method	Results	Comments	NOAEL/LOAEL (mg/kg bw/d)
				miR-6321 in testis at 100-200		
Montagnini *et al.*	2018	Female, Wistar rats	Uterotrophic assay 0.8, 2.4 and 8 mg/kg n = 6-7 0.3 mg/kg estradiol valerate as positive control For anti-estrogenicity all triclosan doses were also combined with estradiol valerate 2-gen study 10 weeks (F0) and 14-week exposure (F1) Doses: 0.8, 2.4 and 8 mg/kg F0 n = 15-17 F1 n = 12-16 Behavior n = 10	Females: ↔ uterus weight in uterotrophic assay Dams & Offspring: ↔ estrous cyclicity endpoints in F0 or F1 ↔ organ weights in F0 or F1 females: uterus, ovary, liver - ↓ perimetrium thickness in F0 at 8 ↔ relative AGD (F1 and F2 female pups), vaginal opening and first estrus (F1) ↓ growing follicle number in F1 at 2.4		NOAEL = 8
Pernoncini *et al.*	2018	Male wistar rats	Gavage of 49 day old rats from PND 49-PND140 Doses: 0.8, 2.4 and 8.0 mg/kg n = 10/group Hershberger assay in 52 day old rats Doses at ADI and 3 and 10-fold higher: 0, 0.8, 2.4 and 8.0 mg/kg and the same	↔ reproductive parameters: *e.g.* reproductive organ weights, sperm morphology, sperm counts, testicular		NOAEL = 8

Reference	Year	Species	Method	Results	Comments	NOAEL/LOAEL (mg/kg bw/d)
			doses + 0.4 mg/kg testosterone propionate Positive control testosterone propionate n = 6/group	histomorphometry ↔ Hershberger assay: bw and reproductive organ weights		

Reference	Year	Species	Method	Results	Comments	NOAEL/LOAEL (mg/kg bw/d)
Zhang *et al.*	2018	Male Sprague-Dawley rats	31 days gavage exposure of 23 day old male rats Doses: 50, 100, 200 mg/kg bw/day n=6	↓ T3 and T4 at all doses ↔ TSH Histopathologic changes of thyroid ↑ Relative liver weight (%) at 200 ↑ hepatic enzymes (Ugt2b1, CYP2b1 at all doses, CYP1a1, CYP3a1 and Sult1c1 at 100 and 200, CYP1a2 at 200)		LOAEL= 50
Tabari *et al.*	2019	Adult NMRI mice	Adult male NMRI mice given oral gavage for 14 days Doses: 1000, 2000 and 4000 mg/kg bw/day n=8	↓ total distance movement, grip strength at 4000 ↓ open arms spent time, central to peripheral zone spent time, closed arms entry, latency to fall at all doses Adverse H&E stain on brain	Very high doses tested	LOAEL = 1000

Reference	Year	Species	Method	Results	Comments	NOAEL/LOAEL (mg/kg bw/d)
Mandal *et al.*	2020	Male rats (*Rattus norvegicus*)	Lactating mothers given oral doses from PND1-28 Doses: 3 and 5 mg/kg bw/day	↓ testis weight at 5 ↓ no. of OCT ¾ germ cells and mRNA levels at 3 and 5 ↓ no. of 3βHSD positive Leydig cells and mRNA levels at 3 and 5 ↓ no. of AR-positive germ cells and mRNA levels at 5 ↓ daily sperm production at 5		NOAEL = 5
Raj *et al.*	2021	Male Swiss rats	Adult rats given oral doses on 42 consecutive days Doses: 40, 80, 160 and 320 mg/kg bw/day N=12/group	↓ weights of epididymis and seminal vesicle at all doses ↓ spermatozoa count, percentage motile and viable spermatozoa at all doses Accumulation of triclosan in eoididymis and seminal vesicle at 320		LOAEL = 40

Reference	Year	Species	Method	Results	Comments	NOAEL/LOAEL (mg/kg bw/d)
Montagnini *et al.*	2021	Male Wistar rats	Two-generation reproduction study (based on OECD 416 and 426) 10 weeks (F0) and 14-week exposure (F1) Doses: 0.8, 2.4 and 8 mg/kg F0 n = 15-17 F1 n = 8-10	F1: ↔ AGD, organ weights, plasma testosterone ↓ sperm viability (percentage of live sperm or mobile sperm) at 2.4 ↔ sperm count parameters ↔ testicular histomorphometry F2: ↔ AGD, nipple retention		NOAEL = 8

ADI: Acceptable daily intake; AGD: Anogenital distance; AR: Androgen receptor; BMD: Bencjmark dose: BMDL: Lower bound of the BMD confidence interval; Cyp: Cytochorme P450 ; EE: 17α-Ethinylestradiol; FSH: Follicle-stimulating hormone; GD: Gestational day; Gnrh:Gonadotropinn-releasing hormone ; hCG: Human chorionic gonadotropin; H&E: Hematoxylin and eosin; HSD: Hydroxysteroid dehydrogenase; LH: Luteinising hormone; LHR: Luteinising hormone receptor; LOAEL: Lowest observed adverse effect level; miR: MicroRNA gene; NOAEL: No observed adverse effect level; NOEL: No observed effect level; PND: Postnatal day; PPAR: Peroxisome proliferator-activated receptor; PROD: Pentoxyresorufin O-dealkylase; RXR: Retinoid X receptor; SRB: Scavenger receptor type B; StAR: Steroidogenic acute regulatory protein; Sult: Sulfotransferase; T3: Triiodothyronine; T4: Thyroxine ; TSH: Thyroid-stimulating hormone; UGT: Uridine 5'-diphospho-glucuronosyltransferase.

ANNEX B

Table B1. Calculations of exposure to triclocarban as an ingredient in rinse-off products and as a preservative by age groups used in SED calculations for triclocarban.

Product type[1]	Age category (yrs)	Mean bodyweight[2] (kg)	Child body surface area[3] (cm^2)	Adult surface area for application[4] (cm^2)	Calculated child surface area for application[5] (cm^2)	Adult daily exposure[4] (g/d)	Calculated child exposure[6] g/d)
Shower gel							
Infants	0.5-1	8.8	4 400			0.19	0.05
Toddlers	1-3	11.9	5 600			0.19	0.06
Children	3-10	23.1	8 700			0.19	0.09
Adolescents	10-14	43.4	13 000			0.19	0.14
Adolescents	14-18	61.3	17 000			0.19	0.18
Hand soap							
Infants	0.5-1	8.8		860	216	0.2	0.05
Toddlers	1-3	11.9		860	275	0.2	0.06
Children	3-10	23.1		860	428	0.2	0.1
Adolescents	10-14	43.4		860	639	0.2	0.15
Adolescents	14-18	61.3		860	835	0.2	0.19
Shampoo							
Infants	0.5-1	8.8		1 440	362	0.11	0.03
Toddlers	1-3	11.9		1 440	461	0.11	0.04
Children	3-10	23.1		1 440	716	0.11	0.05
Adolescents	10-14	43.4		1 440	1 070	0.11	0.08
Adolescents	14-18	61.3		1 440	1 399	0.11	0.11
Hair conditioner							
Toddlers	1-3	11.9		1 440	461	0.04	0.01
Children	3-10	23.1		1 440	716	0.04	0.02
Adolescents	10-14	43.4		1 440	1 070	0.04	0.03
Adolescents	14-18	61.3		1 440	1 399	0.04	0.04
Body lotion							
Infants	0.5-1	8.8		15 670	3 940	7.82	1.97
Toddlers	1-3	11.9		15 670	5 014	7.82	2.50
Children	3-10	23.1		15 670	7 790	7.82	3.89
Adolescents	10-14	43.4		15 670	11 641	7.82	5.81
Adolescents	14-18	61.3		15 670	15 222	7.82	7.60
Face cream							
Infants	0.5-1	8.8		565	142	1.54	0.39
Toddlers	1-3	11.9		565	181	1.54	0.49
Children	3-10	23.1		565	281	1.54	0.77
Adolescents	10-14	43.4		565	420	1.54	1.14
Adolescents	14-18	61.3		565	549	1.54	1.50
Hand cream							
Infants	0.5-1	8.8		860	216	2.16	0.54
Toddlers	1-3	11.9		860	275	2.16	0.69
Children	3-10	23.1		860	428	2.16	1.07
Adolescents	10-14	43.4		860	639	2.16	1.60
Adolescents	14-18	61.3		860	835	2.16	2.10
Deodorant							
Children	3-10	23.1		200	99	1.5	0.75
Adolescents	10-14	43.4		200	149	1.5	1.11
Adolescents	14-18	61.3		200	194	1.5	1.46
Hair styling							
Children	3-10	23.1		1 010	502	0.4	0.20
Adolescents	10-14	43.4		1 010	750	0.4	0.30
Adolescents	14-18	61.3		1 010	981	0.4	0.39
Liquid foundation							
Adolescents	10-14	43.4		565	420	0.51	0.38
Adolescents	14-18	61.3		565	549	0.51	0.5

Product type[1]	Age category (yrs)	Mean bodyweight[2] (kg)	Child body surface area[3] (cm²)	Adult surface area for application[4] (cm²)	Calculated child surface area for application[5] (cm²)	Adult daily exposure[4] (g/d)	Calculated child exposure[6] g/d)
Make-up remover							
Adolescents	10-14	43.4		565	420	0.5	0.37
Adolescents	14-18	61.3		565	549	0.5	0.49
Lipstick							
Adolescents	10-14	43.4		4.8	3.57	0.06	0.04
Adolescents	14-18	61.3		4.8	4.66	0.06	0.06
Eye make-up							
Adolescents	10-14	43.4		24	17.83	0.02	0.01
Adolescents	14-18	61.3		24	23.31	0.02	0.02
Mascara							
Adolescents	10-14	43.4		1.6	1.19	0.03	0.02
Adolescents	14-18	61.3		1.6	1.55	0.03	0.03
Eyeliner							
Adolescents	10-14	43.4		3.2	2.38	0.01	0.01
Adolescents	14-18	61.3		3.2	3.11	0.01	0.01

[1] Calculation of daily exposure to toothpaste and mouthwash are shown in Table 14.
[2] Default values from EFSA 2012.
[3] Values from Sharkey *et al.* 2001.
[4] Default values from SCCS Notes of Guidance 11th version (SCCS/1628/21).
[5] Calculated child surface area for application = (surface area for application for adults * child body surface area)/adult body surface area.
[6] Calculated child daily exposure = (mg/d for adults * body surface are for age category)/ surface area for adults. SCCS 2011 (SCCS/1446/11).

Table B2. Calculations of surface area for application for leave-on products by age groups used in SED calculations for triclosan.

Age category	Age (yrs)	Mean bodyweight[1] (kg)	Child body surface area[2] (cm²)	Adult surface area for application[3] (cm²)	Calculated child surface area for application[4] (cm²)
Deodorant					
Children	3-10	23.1	8 700	200	99
Adolescents	10-14	43.4	13 000	200	149
Adolescents	14-18	61.3	17 000	200	194
Body lotion					
Infants	0.5-1	8.8	4 400	15 670	3 940
Toddlers	1-3	11.9	5 600	15 670	5 014
Children	3-10	23.1	8 700	15 670	7 790
Adolescents	10-14	43.4	13 000	15 670	11 641
Adolescents	14-18	61.3	17 000	15 670	15 222
Face powder					
Adolescents	14-18	61.3	17 000	565	549
Blemish concealer					

Adolescents	14-18	61.3	17 000	57	55

[1] Default values from EFSA 2012

[2] Values from Sharkey *et al.* 2001

[3] Default values from SCCS Notes of Guidance 11th version (SCCS/1628/21)

[4] Child calculated surface area for application = (surface area for application for adults * child body surface area)/adult body surface area

Table B3. Calculations of surface area for application of hand soap by age groups used for SED calculations of triclosan.

Age category	**Age (yrs)**	**Mean bodyweight[1] (kg)**	**Child body surface area[2] (cm²)**	**Adult surface area for application[3] (cm²)**	**Calculated child surface area for application[4] (cm2)**	**Adult daily exposure[3] (g/d)**	**Calculated child exposure[5] g/d)**
Infants	0.5-1	8.8	4 400	860	216	0.2	0.05
Toddlers	1-3	11.9	5 600	860	275	0.2	0.06
Children	3-10	23.1	8 700	860	428	0.2	0.1
Adolescents	10-14	43.4	13 000	860	639	0.2	0.15
Adolescents	14-18	61.3	17 000	860	835	0.2	0.19

[1] Default values from EFSA 2012

[2] Values from Sharkey *et al.* 2001

[3] Default values from SCCS Notes of Guidance 11th version (SCCS/1628/21)

[4] Child calculated surface area for application = (surface area for application for adults * child body surface area)/adult body surface area