Scientific Committee on Consumer Safety

SCCS

OPINION on
Butylparaben
(CAS No. 94-26-8, EC No. 202-318-7)

Children exposure

The SCCS adopted this document
by written procedure on 10 January 2025

ACKNOWLEDGMENTS

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

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1. ABSTRACT

The SCCS concludes the following:

1. *In light of the data provided and taking under consideration the conclusions of the SCCS/1651/23 Opinion on children exposure, does the SCCS consider Butylparaben safe for children, when used as a preservative up to a maximum concentration of 0.14 %?*

   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 the use of Butylparaben as preservative at a maximum concentration of 0.14 % (as acid) in all cosmetic products included in this exposure assessment is not safe for children between 0.5-1 years, 1-3 years, 3-6 years and 6-10 years when used in combination. With the exception of body lotion, it is safe in single dermal and oral product categories, when used only in the respective product category.

2. *Alternatively, what is, according to the SCCS, the maximum concentration of Butylparaben that is considered safe for the age groups of children considered in this opinion"?*

   In the SCCS's opinion, to be safe for all the childrens' age groups that were considered, the maximum concentration of Butylparaben in final products should not exceed 0.028% (as acid). However, the necessity of a reduction in Butylparaben concentration could be reassessed when a well-carried out dermal absorption study and better exposure studies specifically tailored to EU children become available.

3. *Does the SCCS have any further scientific concerns regarding the use of Butylparaben in cosmetic products and children's exposure?*

   This Opinion is not applicable to any sprayable product (including mouth spray) that may lead to exposure of end-user's lungs by inhalation.

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

Keywords: SCCS, scientific opinion, Butylparaben, preservative, Regulation 1223/2009, CAS No. 94-26-8, EC No. 202-318-7, children exposure

Opinion to be cited as: SCCS (Scientific Committee on Consumer Safety), Opinion on Butylparaben (CAS No. 94-26-8, EC No. 202-318-7) – children exposure, preliminary version of 10 January 2025, SCCS/1674/25

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SCCS

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

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2. MANDATE FROM THE EUROPEAN COMMISSION

Background

The ingredient Butylparaben (CAS No. 94-26-8, EC No. 202-318-7) with the chemical name 'Butyl 4-hydroxybenzoate' is currently regulated as a preservative (Annex V, entry 12a) in a concentration up to 0.14 % (as acid) when used on its own or for the sum of its combined use with propyl paraben and its salts (Annex V, entry 12a, column g).

Butylparaben has been subject to different safety evaluations by the SCCP in 2005 (SCCP/0874/05)[1], 2006 (SCCP/1017/06)[2] and 2008 (SCCP/1183/08)[3] and by the SCCS in 2010 (SCCS/1348/10)[4], 2011 (SCCS/1446/11)[5] and 2013 (SCCS/1514/13)[6].
In 2023, the SCCS re-assessed the safety of Butylparaben in view of its potential endocrine effects following a call for data where stakeholders submitted scientific evidence to demonstrate the safety of Butylparaben in cosmetic products. In the SCCS/1651/23[7] Opinion, the scientific committee confirmed the safety of Butylparaben as a preservative in cosmetic products at concentrations of up to 0.14% (expressed as acid). Nevertheless, the experts noted that *'In the absence of exposure data specific for children to Butylparaben in cosmetic products, potential safety concerns cannot be excluded.'*.

In March 2024, the Commission services received additional information from industry to defend the use of Butylparaben in cosmetic products used in children[8]. This submission is based on the product categories used in different age groups of children as they appear in *Table A.7.2* of the 12th edition of the SCCS Notes of Guidance[9]. The Commission, therefore, requests the SCCS to carry out a safety assessment on Butylparaben in view of the new information provided.

Terms of reference

1. *In light of the data provided and taking under consideration the conclusions of the SCCS/1651/23 Opinion on children exposure, does the SCCS consider Butylparaben safe for children , when used as a preservative up to a maximum concentration of 0.14 %?*
2. *Alternatively, what is, according to the SCCS, the maximum concentration of Butylparaben that is considered safe for the age groups of children considered in this opinion?*
3. *Does the SCCS have any further scientific concerns regarding the use of Butylparaben in cosmetic products and children's exposure?*

[1] https://ec.europa.eu/health/ph_risk/committees/04_sccp/docs/sccp_o_00d.pdf and https://ec.europa.eu/health/ph_risk/committees/04_sccp/docs/sccp_o_019.pdf
[2] https://ec.europa.eu/health/ph_risk/committees/04_sccp/docs/sccp_o_074.pdf
[3] https://ec.europa.eu/health/ph_risk/committees/04_sccp/docs/sccp_o_138.pdf
[4] https://ec.europa.eu/health/scientific_committees/consumer_safety/docs/sccs_o_041.pdf
[5] https://ec.europa.eu/health/scientific_committees/consumer_safety/docs/sccs_o_069.pdf
[6] https://ec.europa.eu/health/scientific_committees/consumer_safety/docs/sccs_o_132.pdf
[7] https://health.ec.europa.eu/publications/butylparaben-cas-no-94-26-8-ec-no-202-318-7_en
[8] covering infants (6-12 months), toddlers (1-3 years) and children (3-10 years)
[9] https://health.ec.europa.eu/latest-updates/sccs-notes-guidance-testing-cosmetic-ingredients-and-their-safety-evaluation-12th-revision-2023-05-16_en

3. OPINION

3.1 CHEMICAL AND PHYSICAL SPECIFICATIONS

3.1.1 Chemical identity

3.1.1.1 Primary name and/or INCI name

Butylparaben

3.1.1.2 Chemical names

IUPAC: Butyl p-hydroxybenzoate

EC name: Butyl 4-hydroxybenzoate

(ECHA Brief Profile Butyl 4-hyroxybenzoate, 2022)

3.1.1.3 Trade names and abbreviations

Depository supplied synonyms: (n-)Butyl paraben, Butyl parahydroxybenzoate; 4-Hydroxybenzoic acid n-butyl ester

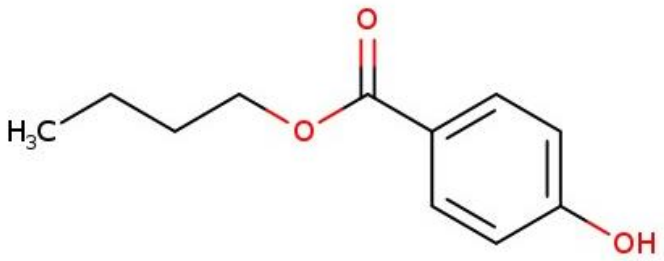
Additional depository supplied synonyms can be found at the link provided below:

PubChem:
https://pubchem.ncbi.nlm.nih.gov/compound/Butylparaben#section=Depositor-Supplied-Synonyms

3.1.1.4 CAS / EC number

CAS No. 94-26-8, EC No. 202-318-7

3.1.1.5 Structural formula



3.1.1.6 Empirical formula

$C_{11}H_{14}O_3$

3.1.2 Physical form

Solid: white particulate/powder
(ECHA Brief Profile Butyl 4-hyroxybenzoate, 2022)

3.1.3 Molecular weight

194.2286 g/mol (ChemIDplus)

3.1.4 Purity, composition and substance codes

>99% (PubChem)

SCCS comment
The analytical methods used for the determination of purity of the test substance should be provided, according to the SCCS Notes of Guidance.

3.1.5 Impurities / accompanying contaminants

SCCS comment
Data on impurities of the test substance must be provided. The analytical methods used for the determination of impurities, along with the results of these studies, should be provided, according to the SCCS Notes of Guidance.

3.1.6 Solubility

In water: 207 mg/L at 20°C (pH not specified)
(Yalkowsky & He 2003)

Freely soluble in acetone, ethanol, ether, chloroform, propylene glycol.
Very slightly soluble in glycerin.
(PubChem)

3.1.7 Partition coefficient (Log Pow)

Computed Log P_{ow} =3.57 (pH and temperature not reported)
(Hansch *et al.* 1995)

3.1.8 Additional physical and chemical specifications

Boiling point (°C): 369°C at 77 mmHg (ChemSpider)
330 – 337 °C at 102.4 kPa
(ECHA Brief Profile Butyl 4-hyroxybenzoate, 2022)
Melting point (°C): 68-69°C
(PubChem)

Vapour pressure: 0.002 Pa at 20°C, 0.005 Pa at 25°C, 0.113 Pa at 50°C

(ECHA Brief Profile Butyl 4-hyroxybenzoate, 2022)

2.51x10-4 mm Hg at 25 °C. With very feint phenolic odour

(PubChem)

pKa: 8.47

(PubChem)

Density: 1.2365 g/cm3 at 20.0 °C

(ECHA Brief Profile Butyl 4-hyroxybenzoate, 2022)

Surface tension: ca. 44.5 mN/m at 20 °C at 90% of the saturation

(ECHA Brief Profile Butyl 4-hyroxybenzoate, 2022)

3.1.9 Homogeneity and Stability

Stable in air and does not hydrolyse in hot or cold water or in acidic conditions. Above pH 7, considerable hydrolysis occurs. Shelf life 24 months or longer if stored properly.

(PubChem)

3.2 TOXICOKINETICS

3.2.1 Dermal / percutaneous absorption

Taken from the discussion of SCCS/1651/23:

No available *in vitro* dermal absorption study has been done according to the SCCS Notes of Guidance (SCCS/1628/21), although one has been requested on several occasions. The SCCS is of the opinion that a value of 3%, proposed by the Applicant is not acceptable.

3.2.2 Other studies on toxicokinetics

Taken from the discussion of SCCS/1651/23:

- The remarks, made earlier with respect to the dermal exposure of newborns and infants up to 6 months of age and the possibility of exposure to a higher internal dose and potential differences in the half-life of the unmetabolised parabens compared to adults, have not been taken up in the newly submitted data. Additional toxicokinetic data (Mathews *et al.* 2013; Campbell *et al.* 2015; Moos *et al.* 2016) were submitted and reviewed, but these did not bring new data with respect to the above-mentioned young age groups.

- An overview of the oral *in vitro* and *in vivo* toxicokinetic studies showed mainly qualitative data, indicating high oral absorption, extensive clearance and major excretion via the urine and a number of common metabolites in rat and human urine. The main difference in metabolism was described as the appearance of a new metabolite (3OH-n-Butylparaben) in humans and a greater amount of glycine conjugation.
The available dermal toxicokinetic studies (Aubert *et al.* 2009 and Janjua *et al.* 2008) were discussed in previous SCCS Opinion (SCCS/1514/13). The *in vivo* rat study of Mathews *et al.* 2013 was used in the argumentation for a dermal absorption value of 3%, which is not accepted.

Intravenous toxicokinetic studies (Mathews *et al.* 2013) showed, as also seen for the oral, subcutaneous and dermal routes, a rapid clearance and excretion, and the same broad spectrum of metabolites.

The SCCS came to the conclusion that, given the problems identified and the absence of a quality *in vitro/in vivo* dermal absorption study in humans, **the dermal absorption for Butylparaben for the calculation of the SED will be the default value of 50%.**

3.3 EXPOSURE ASSESSMENT

3.3.1 Function and uses

Butylparaben has been used widely and safely as a preservative in cosmetics and pharmaceutical preparations around the world for more than 70 years.

3.3.1.1 Cosmetics use

The use of Butylparaben as a preservative in cosmetics is regulated in Annex V to Regulation EC N°1223/2009. The latest update to Annex V relating to the co-use of Butylparaben and/or Propylparaben was published on 5 August 2019.
https://ec.europa.eu/growth/tools-databases/cosing/pdf/COSING_Annex%20V_v2.pdf
Butylparaben can maximally be used in any cosmetic product up to 0.14% (alone, as acid) or up to a combined maximum of 0.14% (as acid) as the sum of the individual concentrations of Butylparaben, Propylparaben and their salts, when used together as a mixture of ingredients in the same product. The maximum total paraben concentration in the context of combined paraben use with those paraben ingredients listed in entry 12 (Methyl-, Ethylparaben and their salts) is 0.8% (as acid), but Butylparaben in that mixture must not exceed 0.14% (as acid).
Given the concentration in the regulation is cited 'as acid', molecular weight conversions are needed to convert this value to the % inclusion level of Butylparaben ester as follows:

- Molecular weight of p-hydroxybenzoic acid is 138.111 g/mol
- Molecular weight of Butylparaben is 194.23 g/mol
- The maximum value of Butylparaben ester is 0.14% x (194.23/138.111) = 0.197%

Therefore, technically, the current regulatory restriction translates to a maximum concentration of 0.197% Butylparaben ester in all cosmetic product types, except leave-on products for the nappy area in children under the age of 3 years, which is not allowed.

3.3.1.2 Food use

Under US FDA regulation, Butylparaben is generally recognised as safe (GRAS) when used as a chemical preservative in foods, with a use limit of 0.1%. Butylparaben is not approved for use as an additive or preservative in EU foods (EFSA 2004; Directive 2006/52/EC). In EFSA (2004) the opinion was given that there was not sufficient data to set an acceptable daily intake (ADI). There is a lack of interest in the use of Butylparaben as a preservative in foods and it has not been formally approved for use.

3.3.1.3 Pharmaceutical use

Butylparaben is rarely used in Europe as a preservative of choice in pharmaceutical products (EMA 2015). RIVM (2018) found that in the Netherlands only 9 medicinal products containing Butylparaben could be found on the market and there was no cause for concern regarding its use.

3.3.2 Calculation of SED/LED in children

According to the Applicant, there is increasing discussion on children's exposure to products. The OECD published a report in 2019 in which it states '*Children exhibit specific habits and practices that may result in exposure scenarios not considered for other population groups. In addition, there are physiological differences between children and adults, affecting the exposure assessment methodologies. Presently, there is often no structured and harmonised approach for determining when to include a separate children's exposure assessment within risk assessments for chemicals in products*.' A decision tree was provided in the OECD report that acts as a prompt for when a specific children's exposure is necessary, but this still explains that a bespoke approach is needed case by case.

Two main factors that can be considered for cosmetics are smaller surface areas and lower body weights for children as compared to adults, and differences in behaviour that may lead to increased exposure e.g. higher ingestion from swallowing toothpaste and mouthwash.

According to the Applicant, it has been a long-standing view of the SCCS in the Notes of Guidance, and within industry practices, that there is usually no need for a separate cosmetics safety evaluation for systemic toxicity in children via the dermal route. The approach to aggregated dermal exposure assessment for adults and the associated uncertainty factors applied have always implicitly been regarded as also covering children's use of the same products. A MoS of 100 is generally accepted as safe, incorporating an inter-individual safety factor of 10 accounting for human variability in physiologies, thereby covering different age groups including children.

The risk factors for children compared to adults are cited in the SCCS 12th Notes of Guidance as:

(i) Differences in surface area/body weight ratio between children and adults
(ii) Toxicokinetic parameters
(iii) In-use conditions of topical products
(iv) The nappy area
(v) Susceptibility against microorganisms

For the purposes of this case study on Butylparaben for infants, toddlers and children, the risk factors (i), (ii) and (iii) are pertinent.

SCCS comment

The SCCS is currently developing a position on children's exposure, in light of new data regarding endocrine activity, and new exposure data that makes it possible to further refine aggregate exposure assessments. This will be updated in the next revision of the SCCS Notes of Guidance.

3.3.2.1 Differences in surface area/body weight ratio between children and adults

According to the Applicant, as explained in the SCCS 12th Notes of Guidance (page 112), skin surface area/body weight ratios are different between children and adults: "the ratio between the skin surface area/body weight of children and adults changes from 0 to 10 years and is 2.3 at birth, 1.8 at 6 months, 1.6 at 12 months, 1.5 at 5 years, 1.3 at 10 years (Renwick 1998). The ratio between the skin surface area/body weight children of 0 to 1 year of age and that of adults is at maximum 2.3. A factor of 3.2 is generally applied by the WHO and also covers variability in human kinetics (see Section 3-5.1.3). Consequently, the inter-individual variation in skin surface area/body weight is covered by the generally accepted default [margin of safety] value of 100 for intact skin". Also, as reiterated in the 12th notes of guidance "the SCCS is of the opinion that there is no need for an additional UF for children when intact skin is present (SCCNFP/0557/02)".

Therefore, the standard way of performing Tier 1 deterministic and Tier 2 probabilistic aggregate exposure calculations for adults are designed to be conservative in adding the intakes from 17 product types (15 dermally applied and 2 oral care products) with the assumptions that all products contain the ingredient in question and all products are used on the same day. When a MoS of 100 is obtained from the approach for adults, the long-standing implicit assumption as explained above is that children's potential for exposure, based on skin surface area and body weight differences alone, has also been covered off. Any products targeted and marketed specifically for children have typically been assessed specifically for children, such as specific children's oral care products, where there may be the potential for greater foreseeable and 'accidental' ingestion than in adults, for example.

The values for skin surface area/body weight ratios from Renwick (1998) and WHO (1994) are based on relatively old body weight and skin surface area data and provide a simple way of scaling adult to children's exposure. According to the Applicant, more up to date information on children's body weight and surface areas according to age are available from authoritative sources.

i) Body weight data
SCCS 12th Notes of Guidance (p115) states "Default values for body weights of different age groups have been published by the European Food Safety Authority (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)", thereby inferring that these mean body weights are appropriate also to use in cosmetic safety evaluations for the European population. However, using these body weight values to convert external applied product/ingredient dose (g/day) to mg/kg/day is applied alongside information about skin surface area of children relative to adults. In the absence of data specifically on children's g/day product use, a scaling approach is considered applying body weight and skin surface area data to mg/day product use amounts/external applied dose from adult data.

ii) Skin surface area data
There are data on adult skin surface area for different body parts and the whole body (Table 4 in the SCCS 12th Notes of Guidance); from Bremmer *et al*. 2006 a and b). The SCCS cite in the footnote to this table the US EPA exposure factors handbook from 1997, but it has been noted on p99 that the most recent US EPA exposure factors handbook is from 2011 (US EPA 2011). No information on skin surface area datasets to use for children are specifically provided in Appendix 7 of the new guidance for children's exposure assessment in the SCCS 12th Notes of Guidance. There are a number of sources that include a review of children's skin surface area information.

The Nordic Council of Ministers produced a report in 2022 from the Nordic Exposure Group Project, reviewing the most recent sources of evidence for physiological parameters, including data for children's body surface area, by age and by body part. In agreement

with the Nordic Council of Ministers Report (2022), the Applicant proposed here that the most relevant data to use for children's skin surface area is from the RIVM (2014) factsheet on consumer exposure values to use in safety assessment (Table 3).

Table 1: Default values of the surface area of the total body and different parts of the body for male and female adults (from RIVM 2014).

	Men		Women		Adults[c]		Q-factor
Surface area	m^2	%	m^2	%	m^2	%	
Total							
Deterministic[a]	1.97		1.73		1.82		4
Probabilistic[b]							
GM	2.09		1.84		1.96		4
CV	1.09		1.09		1.11		
Head	0.13	6.8	0.12	6.7	0.12	6.75	3
Trunk	0.75	38.3	0.60	34.4	0.66	36.35	3
Arms	0.30	15	0.24	13.7	0.26	14.35	3
Hands	0.10	5.2	0.08	4.9	0.09	5.05	3
Legs	0.65	32.8	0.56	32.1	0.59	32.45	3
Feet	0.13	6.7	0.12	6.8	0.12	6.75	3

[a] Deterministic default value is 25th percentile
[b] Body weight distribution for probabilistic calculations (GM: Geometrical Mean and CV: Coefficient of Variation)
[c] For percentage of adults, the average of men and women is assumed

Table 2: Deterministic default values of the skin surface of children of different ages for total body and by body part (from RIVM 2014).

Age		Body surface area (m^2)		Surface area of parts of the body												
Mon-ths	years	Default	Q-factor	Head (incl. neck)		Trunk (excl. neck)		Arms (excl. hands)		Hands		Legs		Feet		Q-factor
				(%)	(m2)	(%)	(m2)	(%)	(m2)	(%)	(m2)	(%)	(m2)	(%)	(m2)	
0-1[a]		0.20	4	18.2	0.036	35.7	0.071	13.7	0.027	5.3	0.011	20.6	0.040	6.5	0.013	3
1-3[a]		0.28	4	18.2	0.051	35.7	0.100	13.7	0.038	5.3	0.015	20.6	0.058	6.5	0.018	3
3-6[a]		0.34	4	18.2	0.062	35.7	0.121	13.7	0.047	5.3	0.018	20.6	0.070	6.5	0.022	3
6-12[a]		0.41	4	18.2	0.075	35.7	0.146	13.7	0.056	5.3	0.022	20.6	0.084	6.5	0.027	3
	1-2[a]	0.47	4	16.5	0.078	35.5	0.167	13	0.061	5.7	0.027	23.1	0.109	6.3	0.030	3
	2-3[b]	0.57	4	12.3	0.070	37.2	0.212	14.4	0.082	4.7	0.027	25.3	0.144	6.3	0.036	3
	3-6[c]	0.69	4	12.0	0.082	37.3	0.257	14.2	0.098	4.8	0.033	25.5	0.176	6.3	0.044	3
	2-6[b]	0.63	4	12.3	0.077	37.2	0.234	14.4	0.090	4.7	0.029	25.3	0.159	6.3	0.039	3
	6-11[d]	0.93	4	10.2	0.094	36.9	0.343	14	0.130	4.9	0.046	27.5	0.256	6.7	0.062	3
	11-16[e]	1.40	4	7.4	0.105	36.9	0.517	14.1	0.198	4.6	0.064	30.1	0.421	6.8	0.095	3
	16-18[f]	1.68	4	6.2	0.104	38.6	0.648	14.7	0.246	4.5	0.075	29.9	0.501	6.4	0.108	3

[a] Mean per cent of total surface area from (US-EPA 2011). Note that head includes neck.
[b] Mean per cent of total surface area of 2–year-old boys and girls (Boniol et al. 2008)
[c] Average per cent of total surface area of 2 and 4-year-old boys and girls (Boniol et al. 2008)
[d] Mean per cent of total surface area of 6-year-old boys and girls (Boniol et al. 2008)
[e] Average per cent of total surface area of 10 and 12-year-old boys and girls (Boniol et al. 2008)
[f] Mean per cent of total surface area of 16-year-old boys and girls (Boniol et al. 2008)

Table 3: Skin Surface Area data (mean in cm^2) from RIVM (2014) as recommended for use by the Nordic Council of Ministers (2022) and Adult:Child ratios to use in exposure assessment calculations for children.

Body part	6-12 mth	1-3 years	3-6 years	6-11 years	3-11 years	Adult
Total body surface	4100	5200*	6900	9300	8100	18200
Head/Face	750	780$	820	940	880	1200
Hands	220	270*	330	460	395	900
Ratios Adult: Child						
Total body surface	4.4	3.5	2.6	2.0	2.2	-
Head/Face	1.6	1.5	1.5	1.3	1.4	-
Hands	4.1	3.3	2.7	2.0	2.3	-

*An average of data for 1-2, and 2-3 years from Table 2 above. $The higher of the two values for 1-2, and 2-3 years from Table 2 above, to be conservative.

SCCS comment

In the dossier, the Applicant has not explained how the surface area for children 3-10 years has been derived. From number checking, the SCCS assumes that it has been calculated by averaging the averages of the age groups 3-6 and 6-11, which is appropriate for similar sample sizes of the averaged groups.

Boniol *et al.* (2008) used anthropometric data on US children from 1977, which were processed in a computer human model to generate the surface areas. However, since anthropometrics of US children and European children may be different and since the US data are quite old, data on European children would be preferable. Furthermore, with 3D-scanning it is possible to determine actual surface areas directly (Yu *et al*. 2003; Schloesser *et al*. 2011), which presumably provides more accurate values.

However, when comparing the amounts derived from the SSA approach with measured data from Ficheux *et al*. 2016, Ficheux and Roudot 2017 and Garcia-Hidalgo *et al*. 2017 for children in France and Switzerland, respectively, the SSA approach amounts tend to be too low. Therefore, whenever adequate measured data are available, the SCCS will use the measured data as explained in Chapter 3.3.2.4.

3.3.2.2 Toxicokinetics

According to the Applicant, for a safety assessment in children, a specific toxicokinetic evaluation only needs to be considered if there is reasonable evidence that there are exceptional substance-specific differences in ADME parameters which may result in extreme differences in toxicity in children vs adults. On the basis of the available multigeneration study including plasma data in pups during gestation and lactation (Roberts *et al*. 2016 published paper from an NTP study with live phase in 2012), this is not expected to be the case for Butylparaben. There is no known evidence to suggest the ADME properties are different between adults and children, with ubiquitous esterase enzymes in the body being the major metabolising enzymes of parabens. Therefore, the toxicokinetic and toxicodynamic factors already accounted for in the required margin of safety of 100 will fully cover potential inter-individual differences between adults and children.

3.3.2.3 In use conditions of topical products

In 2023, the SCCS 12th Notes of Guidance was published and includes a new Appendix 7 offering advice on the types of general cosmetic products that can be used by children of different age groups (see Table 4).

Table 4: Cosmetic products considered by SCCS for safety assessment in children of different age groups (according to Table A.7.2 in SCCS/1647/22).

	Children between 0.5 and 1 year	**Children between 1 and 3 years**	**Children between 3 and 6 years**	**Children between 6 and 10 years**
Dermal products	Shower gel Hand soap Shampoo Body lotion Face cream Hand cream	Shower gel Hand soap Shampoo Body lotion Face cream Hand cream Hair conditioner	Shower gel Hand soap Shampoo Body lotion Face cream Hand cream Hair conditioner	Shower gel Hand soap Shampoo Body lotion Face cream Hand cream Hair conditioner
Oral products	Toothpaste (RF 40%)	Toothpaste (RF 40%)	Toothpaste (RF 40%)	Toothpaste (RF 5%) Mouthwash (RF 10%)

According to the Applicant, it is noted in this table that infants, toddlers and children between 6 months and 18 years can use toothpaste, and 6 months to 6 year-old are likely to retain and inadvertently ingest more (40%) than is assumed for older children, adolescents and adults. Similarly, 6-10 year-old children use toothpaste and mouthwash and are assumed to retain and ingest 5% and 10%, respectively. For this reason, it is useful to consider 3-6 and 6-10 years separately in overall safety evaluation of dermal and oral care products. The dermal product aggregation of seven products is the same for 3-10 year-old; the differential oral care product calculations will be added for 3-6 years (plus toothpaste), and 6-10 years (plus toothpaste and mouthwash), respectively.

When looking at aggregated exposure it should be noted that in the SCCS 12th NoG p31, "$E_{product}$ for the oral care products is used for calculating the dermal exposure (via mucosa) and not oral (ingestion) exposure per se. Oral exposure (ingestion), if applicable, needs to be calculated separately." A single calculation as aggregated here, covers for the retention of oral care products and includes 100% absorption factor, therefore dermal and oral routes are covered in the single oral care calculations provided.

There are no specific habits and practices data on the actual product amounts g/day used by infants, toddlers and children of each of these product types. Appendix 7 of the SCCS 12th Notes of Guidance proposes a simple scaling approach to modify product amounts for children from adult use g/day levels, using shower gel as an example:
"*Exposure data for children could also be deduced from the daily exposure data for adults taking into consideration 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 5001 cm^2 for an adult (Table 4 in 3-3.4.2.1). For a toddler of 1-3 years of age with a total body surface area of 5 600 cm^2, the daily exposure to preservatives would then result in 190 mg/d X 5 600 cm^2/17 500 cm^2 = 61 mg/day*."

This principle in the example cited is followed by the Applicant in the case study for Butylparaben for infants, toddlers and children.

3.3.2.4 Exposure scenarios

The Applicant presented several aggregate exposure scenarios:

TIER 1 - Deterministic approach for the dermal and oral care products

The Applicant used a skin absorption value of 3.7% and 50% for:

- Scenario A: using maximum % inclusion level of 0.197% for Butylparaben ester in all product categories, covering a highly worst-case aggregate exposure calculation
- Scenario B: using P90 % (w/w) use levels of Butylparaben from Cosmetics Europe 2016 survey

TIER 2 - Probabilistic approach using the Crème Global model for the dermal and oral care products

As input parameters cannot be changed specifically for children in this model, the aggregation of 17 product types as per SCCS/1647/22, with the inclusion of body weights and habits and practices data for adult populations were used by the Applicant. Crème global modelling thus already includes toothpaste and mouthwash products with adult retention factors. The Applicant used a skin absorption value of 3.7% in the modelling.

- Scenario A: using maximum % inclusion level of 0.197% for Butylparaben ester in all product categories
- Scenario B: using P90 % (w/w) use levels of Butylparaben from Cosmetics Europe 2016 survey

TIER 2 - Probabilistic approach using the PACEM webtool

This model included adult population body weights and habits practices data. As total adult exposure, the P95 output of the exposed population is used. The Applicant used a skin absorption value of 3.7% and 50% in the modelling.

Tier 2a - For the 7 dermal products only

- Scenario A: using maximum % inclusion level of 0.197% for Butylparaben ester in all product categories
- Scenario B: using P90 % (w/w) use levels of Butylparaben from Cosmetics Europe 2016 survey

Tier 2b - For the 7 dermal products plus 2 oral care products

- Scenario A: using maximum % inclusion level of 0.197% for Butylparaben ester in all product categories
- Scenario B: using P90 % (w/w) use levels of Butylparaben from Cosmetics Europe 2016 survey

SCCS comment

As explained in the Notes of Guidance SCCS/1647/22, the SCCS accepts only the use of maximum-allowed weight concentrations for the calculation of exposure estimates and will therefore not use Scenario B calculations.

In the absence of appropriate quantitative data for the dermal absorption of Butylparaben, a 50% default value is used. Consequently, calculations will be based exclusively on the assumption of 50% dermal absorption rate. As the Crème Global exposure modelling only used a dermal absorption rate of 3.7%, the Tier 2 probabilistic approach using the Crème Global model is no longer be considered valid.

TIER 1 - Deterministic calculations of the SED for dermal and oral care products

A. Dermal exposure

Case study provided by the Applicant for children aged 3-10 years (scenario A):
As per the selection of products to be aggregated according to Appendix 7 in the SCCS 12th Notes of Guidance (2023)(Table 4), face cream, hand cream, body lotion, handwash soap, shower gel, hair conditioner and shampoo are included in the Tier 1 Scenario A deterministic children's dermal exposure assessment for regulatory maximum % w/w use levels of Butylparaben in Table 5.
The daily amounts of product use in g/day for each product in adults has been used as the starting point. The SSA ratios for Adult:Child from Table 3 above have been applied to reduce the g/day product use proportionate to a smaller skin surface area in children age 3-10 years. The retention factors for dermal exposure are assumed to be the same as in adults.
The $E_{product}$ calculated in mg/kg/day is calculated using the default body weight of 23.1 kg for children aged 3-10 years.
In this Tier 1 Scenario A assessment, the regulatory maximum of 0.197%w/w use levels of Butylparaben as ester (equivalent to 0.14% as acid) has been applied to all product categories (Table 5) for children aged 3-10 years and yields a systemic exposure dose (SED) for children of 250 µg/kg/day using default 50% skin absorption for the seven dermally applied products according to SCCS 12th Notes of Guidance (2023).

A Tier 1 Scenario A deterministic exposure assessment for adults, as reported in SCCS Opinion (2023) generated an SED of about 300 µg/kg/day (17 dermal and oral care products aggregated using 50% skin absorption value). Indeed, it resulted in a MoS below 100 but also the SCCS identified it as a highly conservative scenario and selected the more realistic Tier 1 probabilistic exposure assessment for the final MoS calculation.
Thus, disregarding exaggerated worst-case exposure assessments, a scaling approach using BW and SSA data in principle corroborates the long-standing implicit understanding that an adult aggregated exposure assessment already generates an exposure estimate that is sufficiently protective to assure the safety of infants, toddlers and children.
Overall, the factors that are applied to account for the differences in both skin surface area and body weight between adults and children, cancel each other out. This always results in a similar SED estimate for adults and children aged 3-10 years after dermal exposure.
In practice, considering the difference in skin surface area between adults and children, for example, 18200 cm^2 (adults)/8100 cm^2 (3-10 children average) = 2.2, one divides the adult product use g/day by this factor. In considering the body weight difference (e.g., adult default 60kg/3-10-year-old child 23.1kg) ratio of approx. 2.6, one effectively multiplies the adult g/day product use values.
Impacts on the SED estimate may come with differential use of oral care products for which accidental ingestion is potentially greater in young children. But this is factored in as a separate calculation, as advised in the SCCS Notes of Guidance, and has routinely been the case where this has been applicable.

Table 5: Butylparaben exposure for children aged 3-10 years – 7 products applied dermally (Tier 1 Scenario A).

Tier 1 Scenario A Max regulatory %w/w Levels Deterministic Systemic Exposure Dose estimation							23.1	Default Body Weight (kg) (for children Aged 3-10 years: EFSA, 2012)		
							50%	**Default dermal absorption as per SCCS Opinion 2023**		
		Product Exposure					Ingredient exposure			
Category of Product	**Product type - Exposure from DERMALLY applied products**	**Daily amount (DA) of product use (g/d)*** (SCCS 12th NoG 2023)	**Skin Surface Area (SSA) Ratio (Adult:child)#**	**Daily amount of product use (Age 3-10 years) (g/d) Scaled by SSA ratio**	**Retention factor for dermal exposure**	**Eproduct by body weight per product (mg/kg/d)**	**Maximum use (w/w%) in the finished product**	**% absorbed dermally**	**Calculated SED per product (µg/kg/d)**	**MOS calculation** (NOAEL 325000 µg/kg/day)
Leave-on products	Face cream	1.540	1.4	1.100	1	47.62	0.197	50	46.9	6929
	Hand cream	2.160	2.3	0.939	1	40.65	0.197	50	40.0	8116
	Body lotion	7.820	2.2	3.555	1	153.88	0.197	50	151.6	2144
Rinse-off skin & hair cleansing products	Hand wash soap	20.000	2.3	8.696	0.01	3.76	0.197	50	3.7	87651
	Shower gel	18.670	2.2	8.486	0.01	3.67	0.197	50	3.6	89813
	Hair conditioner	3.920	1.4	2.800	0.01	1.21	0.197	50	1.2	272208
	Shampoo	10.460	1.4	7.471	0.01	3.23	0.197	50	3.2	102013
	TOTAL								**250.2**	**1299**

*Adult values as per used in SCCS 12th Notes of Guidance 2023; #Ratios based on using adult and children SSA data from RIVM (2014)

The Applicant provided similar calculations for infants (0.5–1 year) and toddlers (1-3 years) where body weight, skin surface area and dermal product types differ in the calculations, as shown in Tables 6 and 7, respectively:

Table 6: Butylparaben exposure for infants aged 0.5-1 year – 6 products applied dermally (Tier 1 Scenario A).

Tier 1 Scenario A Max regulatory %w/w Levels Deterministic Systemic Exposure Dose estimation							8.8	Default Body Weight (kg) (for Infants Aged 6-12 months: EFSA, 2012)		
							50%	**Default dermal absorption as per SCCS Opinion 2023**		
		Product Exposure					Ingredient exposure			
Category of Product	**Product type - Exposure from DERMALLY applied products**	**Daily amount (DA) of product use (g/d)*** (SCCS 12th NoG 2023)	**Skin Surface Area (SSA) Ratio (Adult:child)#**	**Daily amount of product use (Age 6-12mth) (g/d) Scaled by SSA ratio**	**Retention factor for dermal exposure**	**Eproduct by body weight per product (mg/kg/d)**	**Maximum use (w/w%) in the finished product**	**% absorbed dermally**	**Calculated SED per product (µg/kg/d)**	**MOS calculation** (NOAEL 325000 µg/kg/day)
Leave-on products	Face cream	1.540	1.6	0.963	1	109.38	0.197	50	107.7	3017
	Hand cream	2.160	4.1	0.527	1	59.87	0.197	50	59.0	5511
	Body lotion	7.820	4.4	1.777	1	201.96	0.197	50	198.9	1634
Rinse-off skin & hair cleansing	Hand wash soap	20.000	4.1	4.878	0.01	5.54	0.197	50	5.5	59523
	Shower gel	18.670	4.4	4.243	0.01	4.82	0.197	50	4.7	68429
	Shampoo	10.460	1.6	6.538	0.01	7.43	0.197	50	7.3	44414
	TOTAL								**383.2**	**848**

*Adult values as per used in SCCS 12th Notes of Guidance 2023; #Ratios based on using adult and children SSA data from RIVM (2014)

Table 7: Butylparaben exposure for children aged 1-3 years – 7 products applied dermally (Tier 1 Scenario A).

Tier 1 Scenario A Max regulatory %w/w Levels Deterministic Systemic Exposure Dose estimation							11.9	Default Body Weight (kg) (for Toddlers Aged 1-3 years: EFSA, 2012)		
							50%	**Default dermal absorption as per SCCS Opinion 2023**		
		Product Exposure					Ingredient exposure			
Category of Product	**Product type - Exposure from DERMALLY applied products**	**Daily amount (DA) of product use (g/d)*** (SCCS 12th NoG 2023)	**Skin Surface Area (SSA) Ratio (Adult:child)#**	**Daily amount of product use (Age 1-3 years) (g/d) Scaled by SSA ratio**	**Retention factor for dermal exposure**	**Eproduct by body weight per product (mg/kg/d)**	**Maximum use (w/w%) in the finished product**	**% absorbed dermally**	**Calculated SED per product (µg/kg/d)**	**MOS calculation** (NOAEL 325000 µg/kg/day)
Leave-on products	Face cream	1.540	1.5	1.027	1	86.27	0.197	50	85.0	3824
	Hand cream	2.160	3.3	0.655	1	55.00	0.197	50	54.2	5999
	Body lotion	7.820	3.5	2.234	1	187.76	0.197	50	184.9	1757
Rinse-off skin & hair cleansing products	Hand wash soap	20.000	3.3	6.061	0.01	5.09	0.197	50	5.0	64786
	Shower gel	18.670	3.5	5.334	0.01	4.48	0.197	50	4.4	73607
	Hair conditioner	3.920	1.5	2.613	0.01	2.20	0.197	50	2.2	150245
	Shampoo	10.460	1.5	6.973	0.01	5.86	0.197	50	5.8	56306
	TOTAL								**341.5**	**952**

*Adult values as per used in SCCS 12th Notes of Guidance 2023; #Ratios based on using adult and children SSA data from RIVM (2014)

SCCS comment

Regarding body weight, the SCCS will use the more conservative median (P50) values from EFSA (2012), which are 8.7 kg, 11.6 kg and 21.7 kg for the 0.5-1 year, 1-3 years and 6-10 years age groups, respectively. While the Applicant uses the same body weight value for both the 3-6 years and 6-10 years age groups, the SCCS recommends applying the more conservative EFSA P5 value of 14.0 kg (for children 3-10 years) for the 3-6 years age group. The SCCS has recalculated (see Table 8) the SED_{dermal} values following the SSA/BW scaling approach based on the body weights as specified above. Corresponding estimates of children's body surface areas were derived from these body weight values by following an approach as outlined in Sharkey *et al.* 2001. This same approach was applied in the scientific advice on Triclocarban and Triclosan (SCCS/1643/22) and Methyl Salicylate (SCCS/1654/23), and the most recent Opinion on Hexyl Salicylate (SCCS/1668/24). Adult data is taken from the SCCS Notes of Guidance 12th revision (SCCS/1647/22).

Table 8: SCCS calculations of SED_{dermal} for Butylparaben using the SSA/BW scaling approach for infants (0.5-1 year), toddlers (1-3 years), children (age 3-6 years), and children (age 6-10 years) per product type (Tier 1 Scenario A).

Product type	Body weight[1] (kg)	Skin surface area[2] (cm^2)	Daily exposure[3] (g/day)	Daily exposure (mg/kg bw/day)	Substance concentration (%)	Dermal absorption DAp (%)	SED_{dermal} (µg/kg bw/day)
SHOWER GEL							
Adults	*60*	*17500*	*0.19*				
Infants 0.5 - 1 yr	8.7	4400	0.05	5.49	0.197	50	5.41
Toddlers 1 - 3 yrs	11.6	5600	0.06	5.24	0.197	50	5.16
Children 3 – 6 yrs	14	6200	0.07	4.81	0.197	50	4.74
Children 6 – 10 yrs	21.7	8500	0.09	4.25	0.197	50	4.19
HAND SOAP							
Adults	*60*	*860*	*0.20*				
Infants 0.5 - 1 yr	8.7	216	0.05	5.78	0.197	50	5.69
Toddlers 1 - 3 yrs	11.6	275	0.06	5.52	0.197	50	5.43
Children 3 – 6 yrs	14	305	0.07	5.06	0.197	50	4.99
Children 6 – 10 yrs	21.7	418	0.10	4.48	0.197	50	4.41
SHAMPOO							
Adults	*60*	*1440*	*0.11*				
Infants 0.5 - 1 yr	8.7	362	0.03	3.18	0.197	50	3.13
Toddlers 1 - 3 yrs	11.6	461	0.04	3.03	0.197	50	2.99
Children 3 – 6 yrs	14	510	0.04	2.78	0.197	50	2.74
Children 6 – 10 yrs	21.7	699	0.05	2.46	0.197	50	2.43
HAIR CONDITIONER							
Adults	*60*	*1440*	*0.04*				
Infants 0.5 - 1 yr	8.7	-	-	-	-	-	-
Toddlers 1 - 3 yrs	11.6	461	0.01	1.10	0.197	50	1.09
Children 3 – 6 yrs	14	510	0.01	1.01	0.197	50	1.00
Children 6 – 10 yrs	21.7	699	0.02	0.90	0.197	50	0.88

BODY LOTION							
Adults	*60*	*15670*	*7.82*				
Infants 0.5 - 1 yr	8.7	3940	1.97	226	0.197	50	223
Toddlers 1 - 3 yrs	11.6	5014	2.50	216	0.197	50	213
Children 3 – 6 yrs	14	5552	2.77	198	0.197	50	195
Children 6 – 10 yrs	21.7	7611	3.80	175	0.197	50	172
FACE CREAM							
Adults	*60*	*565*	*1.54*				
Infants 0.5 - 1 yr	8.7	142	0.39	44.5	0.197	50	43.8
Toddlers 1 - 3 yrs	11.6	181	0.49	42.5	0.197	50	41.9
Children 3 – 6 yrs	14	200	0.55	39.0	0.197	50	39.0
Children 6 – 10 yrs	21.7	274	0.75	34.5	0.197	50	34.0
HAND CREAM							
Adults	*60*	*860*	*2.16*				
Infants 0.5 - 1 yr	8.7	216	0.54	62.4	0.197	50	61.5
Toddlers 1 - 3 yrs	11.6	275	0.69	59.6	0.197	50	58.7
Children 3 – 6 yrs	14	305	0.77	54.7	0.197	50	53.8
Children 6 – 10 yrs	21.7	418	1.05	48.4	0.197	50	47.6

[1]P50 body weight value from EFSA for 0.5-1 year, 1-3 years and 6-10 years age groups; P5 body weight value for children 3-10 years from EFSA 2012 for 3-6 years age group
[2]Child body surface area values are based on Sharkey *et al*. 2001; other child surface areas for application are calculated as follows: (surface area for application for adults * child body surface area) / adult body surface area
[3]Default values for adults from SCCS Notes of Guidance 12th revision (SCCS/1647/22); child daily exposure values are calculated as follows: (mg/day for adults * body surface area for age category) / surface area for adults (SCCS/1466/11)

In addition, the SCCS has reviewed the SSA/BW scaling approach against available children-specific data (probabilistic assessment based on questionnaire/interview data on use frequency, body weight and amount) from France (Ficheux *et al*. 2016, Ficheux and Roudot 2017) and Switzerland (Garcia-Hidalgo *et al*. 2017) and found that the use amounts extrapolated by the skin surface area-body weight approach consistently results in smaller exposure estimates for children compared to the data reported in these studies. Therefore, in the absence of better exposure data for EU children, the SCCS will rely on the currently available children-specific data where possible, and on the SSA/BW scaling approach (with corrections for body weight as recalculated in Table 8) where those are lacking (Table 9).

Table 9: SCCS calculations of deterministic SED for Butylparaben for infants (0.5-1 year), toddlers (1-3 years), children (age 3-6 years), and children (age 6-10 years) per product type (Tier 1 Scenario A).

Product type	Data source used for SED derivation	Daily exposure SSA/BW approach (mg/kg bw/day)	Daily exposure experimental (mg/kg bw/day)	Substance concentration (%)	Dermal absorption DAp (%)	SED_{dermal} (µg/kg bw/day)
SHOWER GEL						
Infants 0.5 - 1 yr	Ficheux and Roudot 2017, gel douche for all age groups	5.49	**7.40**	0.197	50	7.29
Toddlers 1 - 3 yrs		5.24	**9.37**	0.197	50	9.23
Children 3 – 6 yrs		4.81	**5.33**	0.197	50	5.25
Children 6 – 10 yrs		4.25	**5.33**	0.197	50	5.25
HAND SOAP						
Infants 0.5 - 1 yr	Ficheux and Roudot 2017, gel douche for all age groups	5.78	**7.40**	0.197	50	7.29
Toddlers 1 - 3 yrs		5.52	**9.37**	0.197	50	9.23
Children 3 – 6 yrs		5.06	**5.33**	0.197	50	5.25
Children 6 – 10 yrs		4.48	**5.33**	0.197	50	5.25
SHAMPOO						
Infants 0.5 - 1 yr	Ficheux and Roudot 2017, shampoing for all age groups	3.18	**4.79**	0.197	50	4.72
Toddlers 1 - 3 yrs		3.03	**4.52**	0.197	50	4.45
Children 3 – 6 yrs		2.78	**3.23**	0.197	50	3.18
Children 6 – 10 yrs		2.46	**3.23**	0.197	50	3.18
HAIR CONDITIONER						
Infants 0.5 - 1 yr	Ficheux and Roudot 2017, shampoing*	-	-	0.197	50	-
Toddlers 1 - 3 yrs		1.10	**4.52**	0.197	50	4.45
Children 3 – 6 yrs		1.01	**3.23**	0.197	50	3.18
Children 6 – 10 yrs		0.90	**3.23**	0.197	50	3.18
BODY LOTION	Ficheux and Roudot 2017, Crème hydratante corps for 0.5-3 yrs; Garcia-Hidalgo *et al*. 2017 body lotion for 3-10 yrs[$]					
Infants 0.5 - 1 yr		226	**839**	0.197	50	827
Toddlers 1 - 3 yrs		216	**981**	0.197	50	966
Children 3 – 6 yrs		198	**620**	0.197	50	611
Children 6 – 10 yrs		175	**409**	0.197	50	403
FACE CREAM						
Infants 0.5 - 1 yr	SSA/BW scaling approach for all age groups	**44.5**	n.a.	0.197	50	43.8
Toddlers 1 - 3 yrs		**42.5**	n.a.	0.197	50	41.8
Children 3 – 6 yrs		**39.0**	n.a.	0.197	50	38.4
Children 6 – 10 yrs		**34.5**	n.a.	0.197	50	34.0
HAND CREAM						
Infants 0.5 - 1 yr	SSA/BW scaling approach for all age groups	**62.4**	n.a.	0.197	50	61.5
Toddlers 1 - 3 yrs		**59.6**	n.a.	0.197	50	58.7
Children 3 – 6 yrs		**54.7**	n.a.	0.197	50	53.8

Children 6 – 10 yrs		**48.4**	n.a.	0.197	50	47.6
AGGREGATE DERMAL						
Infants 0.5 - 1 yr						**952**
Toddlers 1 - 3 yrs						**1094**
Children 3 – 6 yrs						**720**
Children 6 – 10 yrs						**502**

*Garcia-Hidalgo *et al*. 2017 data suggest that use of shampoo and conditioner is comparable for children
[$]calculated by multiplying the P95 for amount per application of female toddler (0-5 year) or children (6-10 years), respectively, by the most probable frequency of application (0.4, i.e. 2-3 times a week for both age groups)
n.a.: not available; SSA: skin surface area; BW: body weight

B. Oral exposure

The SCCS in Appendix 7 Table A.7.2 in the Notes of Guidance (SCCS/1647/22), differentiate between 3-6 years and 6-10 years in the inclusion of mouthwash products in the older age group, as mouthwash is not recommended for use below the age of 6 years. In the absence of any specific ADME data, there is a highly conservative assumption that 100% of the retained 40% applied dose could in theory be absorbed across the gut (including oral mucosa) and enter the systemic circulation.

Intake levels of children from use of toothpaste

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 (SCCNFP/0653/03) 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 is recommended by SCCS in a conservative approach (SCCS/1643/22).
Therefore, it was considered to be appropriately conservative to assume that children of this age use a pea-sized amount (0.25 g) of toothpaste twice a day with a retention factor (RF) of 40% (SCCP/0851/04). Above 8 years, the retention factor used is 5%. The oral bioavailability for children is considered to be 100%, as for adults. Tables 10, 11, 12 and 13 show the intake of Butylparaben in mg/person/day for any potential use in toothpaste for the 0.5-1 year, 1-3 years, 3-6 years and 6-10 years age groups.

Table 10: Calculation of intake levels from use of toothpaste in children aged 0.5-1 year (Tier 1 Scenario A).

6-12 months of age: Toothpaste			
Max Ingredient Concentration	IC	0.197	%
Amount used	A	0.25	g/use
Frequency	FQ	2	uses/day
Retention Factor	RF	40	%
Conversion Factor	CF	1000	mg/g
Systemic Exposure (mg/person/day) =		(IC)(A)(FQ)(RF)(CF)	
Systemic Exposure (mg/person/day) =		0.197/100 (0.25 g/use) (2 uses/day) (40)/100 (1000 mg/g)	
Intake (mg/person/day) =		**0.394**	
Intake (mg/kg/day)*		**0.045**	

*Assuming the default body weight of 8.8 kg for infants age 6-12 months (EFSA, 2012).

Table 11: Calculation of intake levels from use of toothpaste in children aged 1-3 years (Tier 1 Scenario A).

1-3 years of age: Toothpaste			
Max Ingredient Concentration	IC	0.197	%
Amount used	A	0.25	g/use
Frequency	FQ	2	uses/day
Retention Factor	RF	40	%
Conversion Factor	CF	1000	mg/g
Systemic Exposure (mg/person/day) =		(IC)(A)(FQ)(RF)(CF)	
Systemic Exposure (mg/person/day) =		0.197/100 (0.25 g/use) (2 uses/day) (40)/100 (1000 mg/g)	
Intake (mg/person/day) =		**0.394**	
Intake (mg/kg/day)*		**0.033**	

*Assuming the default body weight of 11.9 kg for toddlers aged 1-3y (EFSA, 2012).

Table 12: Calculation of intake levels from use of toothpaste in children aged 3-6 years (Tier 1 Scenario A).

3-6 years of age: Toothpaste			
Max Ingredient Concentration	IC	0.197	%
Amount used	A	0.25	g/use
Frequency	FQ	2	uses/day
Retention Factor	RF	40	%
Conversion Factor	CF	1000	mg/g
Systemic Exposure (mg/person/day) =		(IC)(A)(FQ)(RF)(CF)	
Systemic Exposure (mg/person/day) =		0.197/100 (0.25 g/use) (2 uses/day) (40)/100 (1000 mg/g)	
Intake (mg/person/day) =		**0.394**	
Intake (mg/kg/day)*		**0.017**	

*Assuming the default body weight of 23.1 kg for children aged 3-10y (EFSA, 2012).

Table 13: Calculation of intake levels from use of toothpaste in children aged 6-10 years (Tier 1 Scenario A).

6-10 years of age: Toothpaste			
Max Ingredient Concentration	IC	0.197	%
Amount used	A	2.75	g/day
Retention Factor	RF	5	%
Conversion Factor	CF	1000	mg/g
Systemic Exposure (mg/person/day) =		(IC)(A)(RF)(CF)	
Systemic Exposure (mg/person/day) =		0.197/100 (2.75 g/day) (5)/100 (1000 mg/g)	
Intake (mg/person/day) =		**0.271**	
Intake (mg/kg/day)*		**0.012**	

*Assuming the default body weight of 23.1 kg for children aged 3-10y (EFSA, 2012)

SCCS comment

Taking into account new data on toothpaste use, published by Gomez-Berrada *et al*. 2018, Garcia-Hidalgo *et al.* 2017 and Adé *et al.* 2024, the SCCS recommends the following amounts of toothpaste for calculating oral exposure of children: 1.92 g/day for babies (0-3 years) and children 3-6 years old, and 2.63 g/day for children 6-10 years old. These represent the P95 values reported by Gomez-Berrada *et al.* 2018 for samples of N=96 children 2-6 years old and N=73 children 7-12 years old, respectively, which were assessed by weighing the toothpaste tubes before and after use. The data from Garcia-Hidalgo *et al.* 2017 on a smaller sample, assessed by means of a survey using pictures to show the

amounts, are similar and show that the findings are not specific for French children. A study by Adé *et al.* 2024 on Swiss preschool children also supports the use of higher amount values than the 0.25 g/application mentioned in the SCCS Notes of Guidance, which were based on SCCNFP/0653/03 (recommendation for parents for toothpaste use). However, no P95 values are available from this study.

The default values for retention rate (40% for 0-6 years; 5% for 6-10 years) remain unchanged.

The SCCS has recalculated the intake levels from the use of toothpaste, considering also the different body weight values for the different age groups (Table 14).

Table 14: SCCS calculation of intake levels of children of different age groups from the use of toothpaste assuming the maximum use levels of Butylparaben (Tier 1 Scenario A).

Age category	Amount used[2] (g/day)	Retention factor[3]	Oral bio-availability [3](%)	Systemic exposure (mg/person/day)	Body weight[4] (kg)	Relative daily exposure (mg/kg bw/day)	Substance concentration (%)	SED_{oral} (µg/kg bw/day)
Infants 0.5-1 yr[1]	1.92	0.4	100	768	8.7	88.3	0.197	174
Toddlers 1-3 yrs	1.92	0.4	100	768	11.6	66.2	0.197	130
Children 3-6 yrs	1.92	0.4	100	768	14	54.9	0.197	108
Children 6-10 yrs	2.63	0.05	100	132	21.7	6.06	0.197	12

[1]the use of toothpaste starts after the growth of the first teeth
[2]Based on P95 values from Gomez-Berrada *et al*. 2018
[3]From SCCS Notes of Guidance 12th revision (SCCS/1647/22)
[4]P50 body weight value from EFSA for 0.5-1 year, 1-3 years and 6-10 years age groups; P5 body weight value for children 3-10 years from EFSA 2012 for 3-6 years age group

Intake levels of children of 6-10 years of age from use of mouthwash

The use of mouthwash can start at age 6 (it is generally recommended that children under 6 should not use mouthwash) (www.ada.org; Zuanon 2005). The usage volume for adults of 21.62 ml/day and retention factor of 10 % from SCCS's 2023 Notes of Guidance SCCS/1647/22 is used. This is appropriate, considering published literature on the ingestion of mouthwash by 6 year-old children, with a reported 8 % retention (Zuanon, 2005). It was assumed that 1 ml mouthwash is roughly equivalent to 1 g.

Table 15: Calculation of intake levels from use of mouthwash in children aged 6-10 years (Tier 1 scenario A).

6 years of age to 10: Mouthwash			
Max Ingredient Concentration	IC	0.197	%
Amount used	A	21.62	g/day
Retention Factor	RF	10	%
Conversion Factor	CF	1000	mg/g
Systemic Exposure (mg/person/day) =		(IC)(A)(RF)(CF)	
Systemic Exposure (mg/person/day) =		0.197/100 (21.62 g/day) (10)/100 (1000 mg/g)	
Intake (mg/person/day) =		**4.259**	
Intake (mg/kg/day)*		**0.184**	

*Assuming the default body weight of 23.1 kg for children aged 3-10y (EFSA, 2012)

SCCS comment

The SCCS has recalculated the intake levels from the use of mouthwash, considering a P50 body weight of 21.7 kg for the 6–10 year age group (Table 16).

Table 16: SCCS calculation of intake levels of children of 6-10 years of age from the use of mouthwash assuming the maximum use levels of Butylparaben (Tier 1 Scenario A).

Age category	**Amount used[1] (g/use)**	**Frequency[1] (uses/day)**	**Retention factor[1]**	**Oral bio-availability[1] (%)**	**Systemic exposure (mg/person/day)**	**Body weight[2] (kg)**	**Relative daily exposure (mg/kg bw/day)**	**Substance concentration (%)**	**SED (µg/kg bw/day)**
Children 6-10 yrs	21.62	1	0.1	100	2162	21.7	99.6	0.197	196

[1]from SCCS Notes of Guidance 12th revision (SCCS/1647/22) and assuming that 1 ml mouthwash is equivalent to 1 g
[2]P50 body weight value from EFSA 2012

The total oral intake for children aged between 6-10 years is 12 µg/kg bw/day from toothpaste + 196 µg/kg bw/day from mouthwash = 208 µg/kg bw/day.

C. Aggregated dermal + oral exposure

Table 17 gives an overview of the deterministic aggregated dermal and oral exposure for Butylparaben for children of different age groups.

Table 17: Deterministic aggregated exposure for Butylparaben for children of different age groups assuming the maximum use levels of Butylparaben (Tier 1 Scenario A).

Age category	SED_{dermal} (µg/kg bw/day)	SED_{oral} (µg/kg bw/day)	$SED_{aggregated}$ (µg/kg bw/day)
Infants 0.5-1 yr	952	174	1126
Toddlers 1-3 yrs	1094	130	1224
Children 3-6 yrs	720	108	828
Children 6-10 yrs	502	208	710

TIER 2 - Probabilistic calculations of the SED using the PACEM webtool (run on 6 January 2024)

A web-based aggregate exposure modelling tool is available from RIVM as of 2023 at https://www.rivm.nl/en/consumer-exposure-to-chemical-substances/exposure-models/Pacem
N.B. the model included adult population body weight and habits and practices data. This tool was used to tailor an aggregation specifically for the 7 dermal products only (Tier 2a), as well as for the 7 dermal products plus 2 oral care products (Tier 2b). The Applicant performed the modelling using both maximum regulatory concentrations (scenario A) and using P90 % (w/w) use levels of Butylparaben from Cosmetics Europe 2016 survey (scenario B), with 3.7% and 50% dermal absorption rates. The reports from the PACEM webtool are provided in Appendices of the Applicant's dossier, with an example provided below. However, as previously stated, the SCCS does not use Scenario B for exposure calculations and only considers output data based on 50% dermal absorption in this Opinion.

Tier 2a – For the 7 dermal products only (scenario A) – all children age groups

Table 18: PACEM input/output values for probabilistic exposure calculation with 7 dermal products for adults.

Product exposure settings

	Concentration data		Exposure fractions (g/g substance used)		
Selected Products	% Products with substance	Concentration in product (%)	Inhalation	Dermal	Oral
Body lotion	100	0.197	0	1	0
Face moisturiser	100	0.197	0	1	0
Hand cream	100	0.197	0	1	0
Liquid soap	100	0.197	0	0.01	0
Rinse-off conditioner	100	0.197	0	0.01	0
Shampoo	100	0.197	0	0.01	0
Shower gel	100	0.197	0	0.01	0

Absorption fractions

Absorption fraction inhalation	0
Absorption fraction dermal	0.5
Absorption fraction oral	0

Simulation settings

Random seed	random number
Number of samples	100
Description	

Analysis results

Systemic dose per route

Percentile	25	50	75	90	95	99
Inhalation	0	0	0	0	0	0
Dermal	8.93×10^{-4}	2.21×10^{-3}	1.09×10^{-2}	2.38×10^{-2}	3.68×10^{-2}	8.06×10^{-2}
Oral	0	0	0	0	0	0
Total	8.93×10^{-4}	2.21×10^{-3}	1.09×10^{-2}	2.38×10^{-2}	3.68×10^{-2}	8.06×10^{-2}

Percentiles of systemic dose per route (mg/kg bw)

Due to the lack of specific habits and practices data for dermal cosmetic product use in infants, toddlers and children, the Applicant used a scaling approach to adapt the probabilistic exposure assessments for adults to children of the different age groups, as follows:

Total exposure (Exposed Population, p95) (Max % use levels in regulation, 50% dermal absorption) = 0.037 mg/kg bw/day.

Scaling these PACEM values for children:

- *0.5-1 year:*
  Total exposure (Exposed Population, p95) (Max % use levels in regulation, 50% dermal absorption) = 0.037 mg/kg bw/day

  Multiplied by 60kg (default adult bw) and divided by 8.8kg (child bw) = 0.252 mg/kg bw/day Assuming the same g/day product use as adults.
  Accounting for smaller SSA reducing product use, divide by 2 = 0.126 mg/kg bw/day.

- *1-3 years:*
  Total exposure (Exposed Population, p95) (Max % use levels in regulation, 50% dermal absorption) = 0.037 mg/kg bw/day

  Multiplied by 60kg (default adult bw) and divided by 11.9kg (child bw) = 0.187 mg/kg bw/day Assuming the same g/day product use as adults.
  Accounting for smaller SSA reducing product use, divide by 2 = 0.093 mg/kg bw/day.

- *3-10 years:*
  Total exposure (Exposed Population, p95) (Max % use levels in regulation, 50% dermal absorption) = 0.037 mg/kg bw/day

  Multiplied by 60kg (default adult bw) and divided by 23.1kg (child bw) = 0.096 mg/kg bw/day Assuming the same g/day product use as adults.
  Accounting for smaller SSA reducing product use, divide by 2 = 0.048 mg/kg bw/day.

SCCS comment

Given that the scaling was based on the same adult P95 PACEM output for all age groups, the 0.5-1 year age group also included hair conditioner as a dermal product, which deviates from the SCCS Notes of Guidance but can be considered a conservative approach.

The Applicant did not differentiate in skin surface area Adult:Child ratios for children of different age groups in the calculations, and used 23.1 kg as the default body weight for both the 3-6 years and 6-10 years age groups.

However, since the probabilistic calculations are based on surface area extrapolated use amounts only, which for some products are considerably lower than experimental values determined by Ficheux and Roudot 2017, the SCCS does not accept the probabilistic calculations.

Tier 2b – For the 7 dermal products plus 2 oral care products for children aged 3-10 years (scenario A)

Table 19: PACEM input/output values for probabilistic exposure calculation with 7 dermal and 2 oral care products for adults.

Product exposure settings

	Concentration data		Exposure fractions (g/g substance used)		
Selected Products	% Products with substance	Concentration in product (%)	Inhalation	Dermal	Oral
Body lotion	100	0.197	0	1	0
Face moisturiser	100	0.197	0	1	0
Hand cream	100	0.197	0	1	0
Liquid soap	100	0.197	0	0.01	0
Mouthwash	100	0.197	0	0	0.1
Rinse-off conditioner	100	0.197	0	0.01	0
Shampoo	100	0.197	0	0.01	0
Shower gel	100	0.197	0	0.01	0
Toothpaste	100	0.197	0	0	0.05

Absorption fractions

Absorption fraction inhalation	0
Absorption fraction dermal	0.5
Absorption fraction oral	1

Simulation settings

Random seed	random number
Number of samples	100
Description	

Analysis results

Systemic dose per route

Percentile	25	50	75	90	95	99
Inhalation	0	0	0	0	0	0
Dermal	8.27×10^{-4}	2.10×10^{-3}	1.05×10^{-2}	2.33×10^{-2}	3.62×10^{-2}	7.96×10^{-2}
Oral	1.37×10^{-3}	2.55×10^{-3}	1.20×10^{-2}	3.64×10^{-2}	5.29×10^{-2}	8.07×10^{-2}
Total	3.18×10^{-3}	9.06×10^{-3}	2.64×10^{-2}	5.32×10^{-2}	7.28×10^{-2}	1.20×10^{-1}

Percentiles of systemic dose per route (mg/kg bw)

Total exposure (Exposed Population, p95) (Max % use levels in regulation, 50% dermal absorption) = 0.073 mg/kg bw/day.

Scaling these PACEM values for children of 3-10 years:

Total exposure (Exposed Population, p95) (Max % use levels in regulation, 50% dermal absorption) = 0.073 mg/kg bw/day.
Multiplied by 60kg (default adult bw) and divided by 23.1kg (child bw) = 0.189 mg/kg bw/day Assuming the same g/day product use as adults.
Accounting for smaller SSA reducing product use, divide by 2 = 0.095 mg/kg bw/day.

SCCS comment
Given that the scaling was based on the same adult P95 PACEM output for children between 3-6 and 6-10 years, the 3-6 years age group also included mouthwash as an oral care product, which deviates from the SCCS Notes of Guidance but is considered a conservative approach. However, a retention factor of 5% was used for toothpaste, whereas the default value for children under 6 is 40%.

However, since the probabilistic calculations are based on surface area extrapolated use amounts only, which for some products are considerably lower than experimental values determined by Ficheux and Roudot 2017, the SCCS does not accept the probabilistic calculations.

SCCS conclusion
For all age groups of children considered in this Opinion, SCCS agrees to use the Tier 1 deterministic approach for MoS calculations based on the maximum use levels of Butylparaben (Scenario A), and relying on the currently available children-specific data where possible, and on the skin surface area-body weight-extrapolation approach from adult data (with corrections for body weight values from EFSA (2012)) where those are lacking.

3.4. TOXICOLOGICAL EVALUATION

As this Opinion only addresses exposure considerations for children, the toxicological evaluation relies on the previous opinion on Butylparaben.

Taken from the discussion of SCCS/1651/23:

Irritation and corrosivity
Considering that Butylparaben ester is used in cosmetic products only at concentrations up to 0.197%, the SCCS is of the opinion that there is no risk of skin irritation for the consumer.

Skin sensitisation
Butylparaben is not sensitising in animals and has in humans only a mild sensitising potential.

Acute toxicity
The SCCS is of the opinion that Butylparaben has no acute toxicity.

Repeated dose toxicity
The SCCS agrees with the Applicant that the target organ is the liver and the NOAEL from repeated dose toxicity study is 325 mg/kg bw/d.

Reproductive toxicity
The SCCS has carefully considered and agrees with the Applicant's argumentation with respect to the available *in vivo* reproductive and developmental studies to determine a NOAEL value of 325 mg/kg bw/d.

Mutagenicity / genotoxicity

The SCCS did not agree with the Applicant's conclusions of 'no mutagenicity' and 'no genotoxicity' because an Ames test according to OECD 471 recommended bacterial strain combination was not included and a valid *in vitro* micronucleus/ chromosomal aberration study was not provided. Both tests were subsequently requested (in the presence and absence of S9) and were delivered.

The SCCS carried out a systematic literature search with respect to mutagenicity/ genotoxicity assays of Butylparaben (see SCCS/1651/23 Appendix 2).

Based on the analysis of all available data of genotoxicity and mutagenicity of Butylparaben, the SCCS is of the opinion that Butylparaben has no mutagenic/genotoxic potential.

Carcinogenicity

The SCCS carried out an analysis of the data available in the scientific literature with respect to potential carcinogenicity of Butylparaben (see SCCS/1651/23 Appendix 2, summary Table 2.7). Because the available evidence shows that Butylparaben is not mutagenic/genotoxic (see SCCS/1651/23 Appendix 2, Tables 2.1 -2.6), and that there are no indications of carcinogenicity in the available literature (see SCCS/1651/23 Appendix 2, Table 2.7), the SCCS considers that further testing for carcinogenicity is not necessary.

Photo-induced toxicity

Butylparaben is not phototoxic.

Human data

Health Canada have drawn upon human biomonitoring (HBM) data to calculate estimated daily intakes in their draft safety evaluation for Butylparaben (Health Canada 2020). These data suggest that real life exposures would fall in the range 0.18 – 4.4 µg/kg bw/day.

Special investigation

Butylparaben displays endocrine activity as shown in a number of *in vitro* and *in vivo* assays (see SCCS/1651/23 Appendix 1, Tables 1.1 and 1.2). The PoD for calculating the MoS is taken from the oral rat study by Boberg *et al.* (2016) and is represented by a $BMDL_5$ value of 24.50 mg/kg bw/day.

3.5 SAFETY EVALUATION (INCLUDING CALCULATION OF THE MoS)

As point of departure for the risk assessment, the $BMDL_5$ of 24.5 mg/kg bw/day, derived from the oral study by Boberg *et al.* (2016) is used. As Butylparaben is well absorbed after oral exposure, no correction for oral bioavailability is used. In the absence of a well-carried out dermal absorption study, a default absorption rate of 50% is applied. Following MoS values for individual dermal and oral products, as well as aggregated exposure for children of different age groups, assuming the 0.14% (as acid) maximum use levels of Butylparaben (scenario A), can be calculated based on the Tier 1 deterministic approach:

- Dermal products

Table 20: MoS calculations for the dermally applied products used individually and combined in children of different age groups, assuming the maximum use levels of Butylparaben (scenario A).

Product type	SED_{dermal} (µg/kg bw/day)	$BMDL_5$ (mg/kg bw/day)	MoS
SHOWER GEL			
Infants 0.5 - 1 yr	7.29	24.5	**3360**
Toddlers 1 - 3 yrs	9.23	24.5	**2654**
Children 3 – 6 yrs	5.25	24.5	**4667**
Children 6 – 10 yrs	5.25	24.5	**4667**
HAND SOAP			
Infants 0.5 - 1 yr	7.29	24.5	**3360**
Toddlers 1 - 3 yrs	9.23	24.5	**2654**
Children 3 – 6 yrs	5.25	24.5	**4667**
Children 6 – 10 yrs	5.25	24.5	**4667**
SHAMPOO			
Infants 0.5 - 1 yr	4.72	24.5	**5191**
Toddlers 1 - 3 yrs	4.45	24.5	**5506**
Children 3 – 6 yrs	3.18	24.5	**7704**
Children 6 – 10 yrs	3.18	24.5	**7704**
HAIR CONDITIONER			
Infants 0.5 - 1 yr	-	-	**-**
Toddlers 1 - 3 yrs	4.45	24.5	**5506**
Children 3 – 6 yrs	3.18	24.5	**7704**
Children 6 – 10 yrs	3.18	24.5	**7704**
BODY LOTION			
Infants 0.5 - 1 yr	827	24.5	**30**
Toddlers 1 - 3 yrs	966	24.5	**25**
Children 3 – 6 yrs	611	24.5	**40**
Children 6 – 10 yrs	403	24.5	**61**
FACE CREAM			
Infants 0.5 - 1 yr	43.8	24.5	**559**
Toddlers 1 - 3 yrs	41.8	24.5	**586**
Children 3 – 6 yrs	38.4	24.5	**638**
Children 6 – 10 yrs	34.0	24.5	**790**
HAND CREAM			
Infants 0.5 - 1 yr	61.5	24.5	**398**
Toddlers 1 - 3 yrs	58.7	24.5	**417**

Children 3 – 6 yrs	53.8	24.5	**455**
Children 6 – 10 yrs	47.6	24.5	**515**
AGGREGATE DERMAL			
Infants 0.5 - 1 yr	952	24.5	**26**
Toddlers 1 - 3 yrs	1094	24.5	**22**
Children 3 – 6 yrs	720	24.5	**34**
Children 6 – 10 yrs	502	24.5	**49**

- Oral products

Table 21: MoS calculations for oral products (toothpaste and mouthwash) used individually and combined in children of different age groups, assuming the maximum use levels of Butylparaben (scenario A).

Product type	SED_{oral} (µg/kg bw/day)	$BMDL_5$ (mg/kg bw/day)	MoS
TOOTHPASTE			
Infants 0.5 - 1 yr	174	24.5	**141**
Toddlers 1 - 3 yrs	130	24.5	**189**
Children 3 – 6 yrs	108	24.5	**227**
Children 6 – 10 yrs	12	24.5	**2042**
MOUTHWASH			
Infants 0.5 - 1 yr	-	24.5	**-**
Toddlers 1 - 3 yrs	-	24.5	**-**
Children 3 – 6 yrs	-	24.5	**-**
Children 6 – 10 yrs	196	24.5	**125**
AGGREGATE ORAL			
Infants 0.5 - 1 yr	174	24.5	**141**
Toddlers 1 - 3 yrs	130	24.5	**189**
Children 3 – 6 yrs	108	24.5	**227**
Children 6 – 10 yrs	208	24.5	**118**

- Aggregated dermal + oral exposure

Table 22: MoS calculations for aggregated exposure to the dermally applied and oral products in children of different age groups, assuming the maximum use levels of Butylparaben (scenario A).

Age category	$SED_{aggregated}$ (µg/kg bw/day)	$BMDL_5$ (mg/kg bw/day)	MoS
Infants 0.5-1 yr	1126	24.5	**22**
Toddlers 1-3 yrs	1224	24.5	**20**
Children 3-6 yrs	828	24.5	**30**
Children 6-10 yrs	710	24.5	**35**

SCCS conclusion

Butylparaben is considered not safe for systemic health effects at the presented use concentration for infants (0.5-1 year), toddlers (1-3 years), and children aged 3-6 and 6-10 years when used individually in body lotion or in combination with other included dermal and/or oral product types. To be safe for all children age groups considered, the maximum concentration of Butylparaben in body lotion should not exceed 0.035% (as acid) and 0.028% (as acid) when used in combination. However, the necessity of a reduction in Butylparaben concentration could be reassessed when a well-carried out dermal absorption study and better exposure studies specifically tailored to EU children become available.

3.6 DISCUSSION

Physicochemical properties

The analytical methods used for the determination of the purity of the test substance should be provided, according to the SCCS Notes of Guidance.

Toxicokinetics

- No available *in vitro* dermal absorption study has been done according to the SCCS Notes of Guidance (SCCS/1628/21), although one has been requested on several occasions. The SCCS is of the opinion that a value of 3%, proposed by the Applicant is not acceptable.
- The SCCS came to the conclusion that, given the problems identified and the absence of a quality *in vitro/in vivo* dermal absorption study in humans, the dermal absorption for Butylparaben for the calculation of the SED will be the default value of 50%.

Exposure

For the calculation of the SED, the Applicant has provided Tier 1 (deterministic) and Tier 2 (probabilistic using the Crème Global model and PACEM webtool) assessments for infants (0.5-1 year), toddlers (1-3 years) and children (3-6 and 6-10 years) based on surface area-body weight-extrapolation from adult data, for two different exposure scenarios:

- Scenario A using maximum % inclusion level of 0.197% for Butylparaben ester in all product categories
- Scenario B using P90 % (w/w) use levels of Butylparaben from Cosmetics Europe 2016 survey. As the latter data have not been evaluated by the SCCS, these will not be used in this Opinion.

In the absence of appropriate quantitative data for the dermal absorption of Butylparaben, a 50% default value is used. As the Crème Global exposure modelling only used a dermal absorption rate of 3.7%, the Tier 2 probabilistic approach using the Créme Global model was therefore not further considered.

The SCCS has performed calculations for the Tier 1 deterministic scaling approach against the available children-specific data from France (Ficheux *et al*. 2016, Ficheux and Roudot 2017) and Switzerland (Gracia-Hidalgo *et al*. 2017) and found that the use amounts extrapolated by the surface area-body weight approach consistently underestimate the use amounts in children reported in these publications. Therefore, for product categories where children-specific data are available, the SCCS considers that these should be used for the exposure assessment. For other product categories the surface area-body weight approach could be used. In the latter case, the SCCS has used the more conservative median (P50) body weight values from EFSA (2012), which are 8.7 kg, 11.6 kg and 21.7 kg for the 0.5-1 year, 1-3 years and 6-10 years age groups, respectively. While the Applicant uses the same body weight value for both the 3-6 years and 6-10 years age groups, the SCCS recommends applying the more conservative EFSA P5 value of 14.0 kg (for children 3-10 years) for the 3-6 years age group. Corresponding estimates of children's body surface areas were derived from these body weight values, by following an approach as outlined in Sharkey *et al.* 2001. This same approach was applied in the scientific advice on Triclocarban and Triclosan (SCCS/1643/22) and Methyl Salicylate (SCCS/1654/23), and the most recent Opinion on Hexyl Salicylate (SCCS/1668/24). Adult data is taken from the SCCS Notes of Guidance 12th revision (SCCS/1647/22).

Since the probabilistic calculations based on the PACEM outputs are based on surface area extrapolated use amounts only, that for some products are considerably lower than experimental values determined by Ficheux and Roudot (2017), the SCCS does not accept the probabilistic calculations. Hence, in this Opinion, the Tier 1 deterministic approach has been considered based on the maximum use levels of Butylparaben (Scenario A) and relying on the currently available children-specific data where possible, and on the skin surface area-body weight-extrapolation approach from adult data (with corrections for body weight values from EFSA (2012)) where those are lacking.

Using this approach, the following aggregate SED_{dermal} values are obtained: 952 µg/kg bw/day for infants (0.5-1 year), 1094 µg/kg bw/day for toddlers (1-3 years), 720 µg/kg bw/day for children (3-6 years), and 502 µg/kg bw/day for children (6-10 years).

Regarding oral exposure, data on toothpaste use from Garcia-Hidalgo *et al.* (2017) and Gomez-Berrada *et al*. (2018) show that 0.25 g/use is an underestimation of toothpaste use for children. Therefore, the SCCS has recalculated the oral exposure to Butylparaben in toothpaste, using 1.92 g/day for babies (0-3 years) and children aged 3-6 years, and 2.63 g/day for children aged 6-10 years, while also taking into account the different EFSA body weight values for these age groups and applying retention factors of 40% for 0.5-6 year and 5% for 6-10 year old children. This yields the following SED_{oral} values for the use of toothpaste: 174 µg/kg bw/day for infants (0.5-1 year), 130 µg/kg bw/day for toddlers (1-3 years), 108 µg/kg bw/day for children (3-6 years), 12 µg/kg bw/day for children (6-10 years).

Adjusting the Applicant’s mouthwash exposure calculation for the age group 6-10 years with the median body weight value from EFSA (2012), yields an oral exposure of 196 µg/kg bw/day from mouthwash, which results in an aggregate oral exposure for 6-10 year old of 208 µg/kg bw/day.

Aggregation of dermal and oral exposure then yields $SED_{aggregated}$ values of 1126 µg/kg bw/day for infants (0.5-1 year), 1224 µg/kg bw/day for toddlers (1-3 years), 828 µg/kg bw/day for children (3-6 years), 710 µg/kg bw/day for children (6-10 years).

Toxicological Evaluation

Irritation and corrosivity
Considering that Butylparaben ester is used in cosmetic products only at concentrations up to 0.197%, the SCCS is of the opinion that there is no risk of skin irritation for the consumer.

Skin sensitisation
Butylparaben is not sensitising in animals and has in humans only a mild sensitising potential.

Acute toxicity
The SCCS is of the opinion that Butylparaben has no acute toxicity.

Repeated dose toxicity

The SCCS agrees with the Applicant that the target organ is the liver and the NOAEL from repeated dose toxicity study is 325 mg/kg bw/day.

Reproductive toxicity
The SCCS has carefully considered and agrees with the Applicant's argumentation with respect to the available *in vivo* reproductive and developmental studies to determine a NOAEL value of 325 mg/kg bw/day.

Mutagenicity / genotoxicity
The SCCS did not agree with the Applicant's conclusions of 'no mutagenicity' and 'no genotoxicity' because an Ames test according to OECD 471 recommended bacterial strain combination was not included and a valid *in vitro* micronucleus/ chromosomal aberration study was not provided. Both tests were subsequently requested (in the presence and absence of S9) and were delivered.
The SCCS carried out a systematic literature search with respect to mutagenicity/ genotoxicity assays of Butylparaben (see SCCS/1651/23 Appendix 2).
Based on the analysis of all available data of genotoxicity and mutagenicity of Butylparaben, the SCCS is of the opinion that Butylparaben has no mutagenic/genotoxic potential.

Carcinogenicity
The SCCS carried out an analysis of the data available in the scientific literature with respect to potential carcinogenicity of Butylparaben (see SCCS/1651/23 Appendix 2, summary Table 2.7). Because the available evidence shows that Butylparaben is not mutagenic/genotoxic (see SCCS/1651/23 Appendix 2, Tables 2.1 -2.6), and that there are no indications of carcinogenicity in the available literature (see SCCS/1651/23 Appendix2, Table 2.7), the SCCS considers that further testing for carcinogenicity is not necessary.

Photo-induced toxicity
Butylparaben is not phototoxic.

Human data
Health Canada have drawn upon human biomonitoring (HBM) data to calculate estimated daily intakes in their draft safety evaluation for Butylparaben (Health Canada 2020). These data suggest that real life exposures would fall in the range 0.18 – 4.4 µg/kg bw/day.

Special investigation
Butylparaben displays endocrine activity as shown in a number of *in vitro* and *in vivo* assays (see SCCS/1651/23 Appendix 1, Tables 1.1 and 1.2). The PoD for calculating the MoS is taken from the oral rat study by Boberg *et al.* (2016) and is represented by a $BMDL_5$ value of 24.50 mg/kg bw/day.

4. CONCLUSION

1. *In light of the data provided and taking under consideration the conclusions of the SCCS/1651/23 Opinion on children exposure, does the SCCS consider Butylparaben safe for children, when used as a preservative up to a maximum concentration of 0.14 %?*

   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 the use of Butylparaben as preservative at a maximum concentration of 0.14 % (as acid) in all cosmetic products included in this exposure assessment is not safe for children between 0.5-1 years, 1-3 years, 3-6 years and 6-10 years when used in combination. With the exception of body lotion, it is safe in single dermal and oral product categories, when used only in the respective product category.

2. *Alternatively, what is, according to the SCCS, the maximum concentration of Butylparaben that is considered safe for the age groups of children considered in this opinion"?*

   In the SCCS's opinion, to be safe for all the childrens' age groups that were considered, the maximum concentration of Butylparaben in final products should not exceed 0.028% (as acid). However, the necessity of a reduction in Butylparaben concentration could be reassessed when a well-carried out dermal absorption study and better exposure studies specifically tailored to EU children become available.

3. *Does the SCCS have any further scientific concerns regarding the use of Butylparaben in cosmetic products and children's exposure?*

   This Opinion is not applicable to any sprayable product (including mouth spray) that may lead to exposure of end-user's lungs by inhalation.

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

5. MINORITY OPINION

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7. GLOSSARY OF TERMS

See SCCS/1647/22, 12th Revision of the SCCS Notes of Guidance for the Testing of Cosmetic Ingredients and their Safety Evaluation – Appendix 15 - from page 158

8. LIST OF ABBREVIATIONS

See SCCS/1647/22, 12th Revision of the SCCS Notes of Guidance for the Testing of Cosmetic Ingredients and their Safety Evaluation – Appendix 15 - from page 158