SCIENTIFIC ADVISORY GROUP ON CHEMICAL SAFETY OF NON-FOOD AND NON-MEDICINAL CONSUMER PRODUCTS (SAG-CS)

Final Opinion on Butylated Hydroxytoluene in Cosmetic Products

1. Introduction

1.1. Butylated hydroxytoluene (2,6-di-tert-butyl-4-methylphenol, 2,6-di-tert-butyl-p-cresol; CAS No. 128-37-0) is not currently regulated under the Cosmetic Products Regulation UK No 1223/2009 (as amended).

1.2. Butylated hydroxytoluene (also known as BHT and referred to as such from here on) does not have any human health related harmonised classifications under the GB Classification, Labelling and Packaging (CLP) regulation No 1272/2008 (as amended). Currently no EU harmonised or GB mandatory classification and labelling entries exists for BHT (databases accessed November 2022). However, BHT is suspected of being an endocrine disruptor (MSCA France, 2017) and a targeted assessment of this is under development by the French authority - Ministry of Ecology, Sustainable Development and Energy (MEDDE).

1.3. In April 2022, OPSS released a call for data on the safety of cosmetic ingredients with suspected endocrine disrupting properties in which BHT was included.

1.4. Several responses have been submitted by industry applicants to OPSS to support the safe use of BHT in cosmetic products up to a maximum concentration of 0.1% in toothpaste, 0.001% in mouthwash products, 0.001% in leave-on oral care products, and 0.8% in all other cosmetic products. OPSS requested that the SAG-CS assess the safety of BHT intended to be used within cosmetic products.

2. Background

Intended function and uses of BHT

2.1. BHT is a synthetic antioxidant which may be added to cosmetic and care products to improve their stability and prevent oxidation. Typical use concentrations of BHT across a wide spectrum of cosmetic product types, dermally applied, and spray products are 0.0002 – 0.8%. Oral products typically utilise a lower concentration of a maximal 0.1% in toothpaste and 0.001% in mouthwashes.

2.2. BHT is additionally used as a food additive, often to supplement natural antioxidants. It is used to preserve and stabilise the flavour, colour, freshness and nutritional value of food.

3. Potential Endocrine Disrupting Properties

Data on endocrine disruption submitted and reviewed by the SAG-CS

3.1. *In vitro* assays did not result in clear evidence of endocrine activity (estrogen and androgen receptor binding, or with respect to thyroid and steroidogenesis modes of action) of BHT.

3.2. *In vivo* assays did not result in clear evidence of endocrine activity of BHT. With respect to endocrine-related adversity observed *in vivo*, while effects on the thyroid were reported, they were considered likely to be secondary to liver toxicity, rather than based on an endocrine mode of action. However, it is noted that an in-depth mode of action, biological plausibility and human-relevance analysis has not yet been conducted.

4. Previous Expert Group Opinions

4.1. Following their call for data on substances with potential endocrine disrupting properties in 2019, the Scientific Committee of Consumer Safety (SCCS) were mandated by the European Commission to perform a safety assessment for BHT considering the data received (SCCS, 2021).

4.2. Within this assessment, the SCCS (2021) calculated aggregate systemic exposure doses (SED) for oral products and dermal products. Within these calculations, a dermal absorption of 0.4% was used from a Eurofins study involving a 24-hour exposure period (Eurofins, 2020). A SED_{oral} of 0.00969 mg/kg bw/day was determined for combined use of toothpaste (0.1%), mouthwash (0.001%), and lipstick (0.8%). A SED_{dermal} of 0.00761 mg/kg bw/day was determined for combined use of the following products all containing 0.8% BHT: hydroalcoholic based fragrances, shower gel, hand wash soap, shampoo, hair conditioner, body lotion, face cream, hand cream,

deodorant non-spray, hair styling, liquid foundation, make-up remover, eye make-up, mascara and eyeliner. A total SED of 0.0173 mg/kg bw/day was determined. Notably, within calculations for the SED, the normalised exposure value to a product, $E_{product}$, was determined using the specific body weight of the persons involved in the studies by Hall *et al.* and not the default value of 60 kg (Hall *et al.*, 2007; Hall *et al*, 2011).

4.3. The SCCS (2021) performed Margin of Safety (MoS) calculations with a No Observed Adverse Effect Level (NOAEL) of 25 mg/kg bw/day for non-neoplastic effects (effects on litter size and pup body weight gain during the lactation period, in the reproduction segment of the study) from a 2 -generation study in rats. This NOAEL also covers the observed increase in hepatocellular adenomas and carcinomas. A MoS_{oral} of 2,580 was determined. A MoS_{dermal} of 3,285 was determined. A total aggregate MoS of 1445 was determined.

4.4. As a result of the above MoS calculations, the SCCS (2021) concluded that *"…BHT is safe as an ingredient up to a maximum concentration of 0.001% in mouthwash and 0.1% in toothpaste…BHT is safe as an ingredient up to a maximum concentration of 0.8% in other leave-on and rinse-off products…BHT is also considered safe for a combined use of mouthwash at a concentration of 0.001%, toothpaste at a concentration of 0.1% and other leave-on and rinse-off products at the concentration of 0.8%."*.

5. Discussion by the Scientific Advisory Group on Chemical Safety of Non-Food and Non-Medicinal Consumer Products (SAG-CS)

5.1. At their September and November 2022 meetings, the SAG-CS discussed the safety of BHT used within cosmetic products.

5.2. Members discussed the current uses of BHT and reported that it is a permitted food additive in oils, fats and chewing gum. For oils, butylated hydroxytoluene is allowed up to a level of 100 mg/kg (UK SI, 2007).

5.3. Members commented on the availability of validated analytical methods for determination of BHT in cosmetic formulations within the regulatory community. Members noted that analytical methods are available for determination of BHT in food materials. These methods are based upon gas chromatography (GC). As BHT is a lipid-based additive in food, members commented that such analytical methods may be readily transferable to cosmetic products.

5.4. Members noted that exposure to BHT is likely to occur predominantly via the oral route and commented on other advisory groups' conclusions (EFSA, 2012) that suggested that such exposure is unlikely to cause adverse health effects

as the Acceptable Daily Intake (ADI; 0.25 mg/kg bw/day) was not largely exceeded (95th percentile above ADI).

5.5. Members commented that BHT was not acutely toxic via the oral or dermal routes of exposure. Members noted that dermal absorption of BHT was low. A dermal absorption value of 0.4% (Eurofins, 2020) was concluded from the available data, for use in the safety assessment.

5.6. Members noted that BHT is slightly irritating to the skin based on studies on skin and eyes of rabbits. However, members noted that, considering the low concentrations used in formulated products, BHT is not a skin or eye irritant when used in cosmetic products. BHT is also not skin sensitising in humans at the concentrations used in cosmetic products.

5.7. Members commented that a large number of *in vitro* and *in vivo* genotoxicity studies had been undertaken covering all three genetic endpoints (gene mutations, structural and numerical chromosome aberrations). The vast majority of studies were negative. Some positive results were observed[1], however, the suggested mechanism of genotoxicity (pro-oxidative chemistry, giving rise to the formation of quinones and reactive oxygen species) is considered to have a threshold. Consequently, members agreed that genotoxicity is not considered to be a concern for BHT at the concentrations likely to result from exposure to the cosmetic products discussed.

5.8. Members agreed the NOAEL of 25 mg/kg bw/day (based on reproductive and developmental effects in the two-generation study in rats; Olsen *et al.,* 1986 and JECFA, 1996) was appropriate to derive the Point of Departure (PoD) for use in the human health safety assessment, and that this resulted in a sufficiently protective Margin of Safety (MoS) in each outlined scenario. The key inputs used to calculate the systemic exposure dose (SED) and MoS for BHT are presented below (Table 1).

5.9. Members discussed the major metabolites of BHT and their potential effects.

5.10. Members discussed the limited available data regarding endocrine effects and, while noting some positive study results exist, considering the weight of evidence available, members did not consider BHT to be endocrine active.

[1] One *in vitro* study concluded BHT was a weak mutagen (Patterson *et al.*, 1987) and two *in vitro* studies resulted in some genotoxicity at cytotoxic concentrations only (Grillo and Dulout, 1995; McGregor *et al.*, 1988).

Table 1. Key inputs, SED and MoS for BHT. Detailed safety assessment calculations for individual product types and aggregate exposure are included in the Appendix.

	Toothpaste	Mouthwash	Lip salve / lipstick	Leave-on oral care products	Total oral exposure	Total dermal exposure[1]	Total aggregate exposure	Reference
Dermal absorption value (%)	Not applicable	Not applicable	Not applicable	Not applicable	Not applicable	0.4	0.4	Cosmetics Europe, 2020
Calculated relative daily exposure[2] (mg/kg bw/day)	2.16	32.54	0.90	43.29	78.9	237.9	316.8	SCCS Notes of Guidance, 2021
Concentration BHT in the product (%)	0.1	0.001	0.8	0.001	0.001-0.8	0.8	0.001-0.8	
Body weight (kg)	60	60	60	60	60	60	60	SCCS Notes of Guidance, 2021
Oral absorption value (%)	100	100	100	100	100	100	100	EFSA, 2012
SED (mg/kg bw/day)	0.00217	0.00033	0.00720	0.00043	0.01012	0.00761	0.01774	
PoD systemic[3] (mg/kg bw/day)	25	25	25	25	25	25	25	Olsen *et al.,* 1986 and

								JECFA, 1996
MoS	**11,547**	**76,828**	**3,472**	**57,750**	**2,470**	**3,284**	**1,410**	

SED – systemic exposure dose
PoD – point of departure
MoS – margin of safety
1 – Exposure to fragrances, leave-on, rinse-off and face make-up products. Includes: Hydroalcoholic-based fragrances, shower gel, hair shampoo and conditioner, hand wash soap, body lotion, face cream, hand cream, deodorant (spray and non-spray), hair styling products, liquid foundation, make-up remover and make-up (eye shadow, mascara and eyeliner).
2 - The specific body weight of the persons involved in the study is used and not the default value of 60 kg.
3 - The oral absorption value is taken into account (in this case the default value of 100%) when converting the PoD from the available database (i.e. lowest NOAEL) to a PoD systemic.
NOTE: SED values stated are rounded. Calculation of the MoS used unrounded numbers and therefore sometimes resulted in different final MoS values compared to those the rounded figures would lead to.

6. Conclusions

Members were satisfied that there was sufficient evidence to form an opinion at this stage.

Members agreed that there would be no appreciable increase in health risk following the addition of BHT in the following scenarios:

- *Hydroalcoholic-based fragrances (spray and non-spray): 0.8%*
- *Rinse-off skin and hair cleansing products; shower gel, hair conditioner, shampoo, hand wash soap: 0.8%*
- *Leave-on skin and hair products; body lotion (spray and non-spray), face cream, hand cream, deodorant (spray and non-spray), hair styling products (spray and non-spray): 0.8%*
- *Face make-up products; liquid foundation, lipstick / lip salve, make-up remover, eye-make up, mascara, eyeliner: 0.8%*
- *Oral care products 1) toothpaste: 0.1% 2) mouthwash: 0.001% 3) topical leave-on oral care product: 0.001%.*

Based on the (limited) available data, members did not consider BHT to show evidence for endocrine activity.

Members stated that BHT use in products may need to be further reviewed with respect to aggregated exposure from other sources, including foods.

Scientific Advisory Group on Chemical Safety of Non-Food and Non-Medicinal Consumer Products

February 2023

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The Miscellaneous Food Additives and the Sweeteners in Food (Amendment) (England) Regulations 2007. UK SI 2007 No. 1778, Schedule 2 https://www.legislation.gov.uk/uksi/2007/1778/schedule/2/made

Appendix – Safety Assessment Calculations

These calculations followed the SCCS NoG (2021) principles and calculations for dermal and oral exposure. The equations used were as follows:

SED_{oral}	**=**	**Calculated relative daily exposure (mg/kg bw/day)**	**x**	**Concentration BHT (%)**	**x**	**Oral absorption (%)**

OR

SED_{dermal}	**=**	**Calculated relative daily exposure (mg/kg bw/day)**	**x**	**Concentration BHT (%)**	**x**	**Dermal absorption (%)**

Where:

- The calculated relative daily exposure is taken from the SCCS NoG (2021) Tables 3A, 3B and 5.
- The default oral absorption (or bioavailability) value of 100% is used in the absence of substance specific data.
- The dermal absorption value of 0.4% is used, based on substance specific data.

$PoD_{systemic}$ = NOAEL x Oral bioavailability

Where:

- The NOAEL of 25 mg/kg bw/day is used, based on reproductive and developmental effects in the two-generation study in rats (Olsen *et al.*, 1986 and JECFA, 1996).
- The default oral absorption (or bioavailability) value of 100% is used in the absence of substance specific data.

MoS = $PoD_{systemic}$ / SED_{oral} OR MoS = $PoD_{systemic}$ / SED_{dermal}

Therefore, for oral exposure to oral care products and lip salve/lipstick

For toothpaste:	SED_{oral} = 2.16 x 0.1% x 100% = 0.00216 $PoD_{systemic}$ = 25 x 100% = 25 MoS = 25 / 0.00216 = 11,574				
For mouthwash:	SED_{oral} = 32.54 x 0.001% x 100% = 0.00033 $PoD_{systemic}$ = 25 x 100% = 25 MoS = 25 / 0.00033 = 76,829				
For lipstick / lip salve	SED_{oral} = 0.90 x 0.8% x 0.4% = 0.00720 $PoD_{systemic}$ = 25 x 100% = 25 MoS = 25 / 0.00720 = 3,472				
For topical leave-on oral care products:	Calculated relative daily exposure (mg/kg bw/day)	=	Relative daily amount applied (mg/kg bw/day) (Taken from the SCCS NoG (2021) Table 3A; for toothpaste)	x	Retention factor
	Calculated relative daily exposure (mg/kg bw/day)	=	43.29 x 1.00 = 43.29		
	SED_{oral} = 43.29 x 0.001% x 100% = 0.00043 $PoD_{systemic}$ = 25 x 100% = 25 MoS = 25 / 0.00043 = 57,750				
Total	**SED_{oral} =** 0.00216 + 0.00033 + 0.00720 + 0.00043 = **0.01012** $PoD_{systemic}$ = 25 x 100% = 25 **MoS =** 25 / 0.01012 = **2,471**				
NOTE: SED values stated are rounded. Calculation of the MoS used unrounded numbers and therefore sometimes resulted in different final MoS values compared to those the rounded figures would lead to.					

For dermal exposure to hydroalcoholic-based fragrances, rinse-off, leave-on and face make-up products.

Hydroalcoholic-based fragrances	SEDdermal = 4.67 x 0.8% x 0.4% = 0.00015 PoDsystemic = 25 x 100% = 25 MoS = 25 / 0.00015 = 167,291
Shower gel	SED_{dermal} = 2.79 x 0.8% x 0.4% = 0.00009 $PoD_{systemic}$ = 25 x 100% = 25 MoS = 25 / 0.00009 = 280,018
Hair conditioner	SED_{dermal} = 0.67 x 0.8% x 0.4% = 0.00002 $PoD_{systemic}$ = 25 x 100% = 25 MoS = 25 / 0.00002 = 1,166,045
Hair shampoo	SED_{dermal} = 1.51 x 0.8% x 0.4% = 0.00005 $PoD_{systemic}$ = 25 x 100% = 25 MoS = 25 / 0.00005 = 517,384
Hand wash soap	SED_{dermal} = 3.33 x 0.8% x 0.4% = 0.00011 $PoD_{systemic}$ = 25 x 100% = 25 MoS = 25 / 0.00011 = 234,610
Body lotion	SED_{dermal} = 123.20 x 0.8% x 0.4% = 0.00394 $PoD_{systemic}$ = 25 x 100% = 25 MoS = 25 / 0.00394 = 6,341
Face cream	SED_{dermal} = 24.14 x 0.8% x 0.4% = 0.00077 $PoD_{systemic}$ = 25 x 100% = 25 MoS = 25 / 0.00077 = 32,363
Hand cream	SED_{dermal} = 32.70 x 0.8% x 0.4% = 0.00105 $PoD_{systemic}$ = 25 x 100% = 25 MoS = 25 / 0.00105 = 23,891
Deodorant (spray and non-spray)	SED_{dermal} = 22.08 (worst-case, non-spray used) x 0.8% x 0.4% = 0.00071 $PoD_{systemic}$ = 25 x 100% = 25 MoS = 25 / 0.00071 = 35,383
Hair styling products	SED_{dermal} = 5.74 x 0.8% x 0.4% = 0.00018 $PoD_{systemic}$ = 25 x 100% = 25 MoS = 25 / 0.00018 = 136,106
Liquid foundation	SED_{dermal} = 7.90 x 0.8% x 0.4% = 0.00025 $PoD_{systemic}$ = 25 x 100% = 25 MoS = 25 / 0.00025 = 98,892
Make-up remover	SED_{dermal} = 8.33 x 0.8% x 0.4% = 0.00027 $PoD_{systemic}$ = 25 x 100% = 25 MoS = 25 / 0.00027 = 93,788
Make-up (eye shadow, mascara and eyeliner)	SED_{dermal} = (0.33 + 0.42 + 0.08) x 0.8% x 0.4% = 0.00003 $PoD_{systemic}$ = 25 x 100% = 25 MoS = 25 / 0.00003 = 941,265

Total	**SED_{dermal} = 0.00761** $PoD_{systemic}$ = 25 x 100% = 25 **MoS =** 25 / 0.00761 = **3,284**
NOTE: SED values stated are rounded. Calculation of the MoS used unrounded numbers and therefore sometimes resulted in different final MoS values compared to those the rounded figures would lead to.	

For total aggregate oral and dermal exposure

Total	**SED =** 0.01012 + 0.00761 = **0.01773** $PoD_{systemic}$ = 25 x 100% = 25 **MoS =** 25 / 0.01773 = **1,410**