Scientific Committee on Consumer Safety

SCCS

SCIENTIFIC ADVICE

on the safety of Diethylamino Hydroxybenzoyl Hexyl Benzoate – DHHB – S83

(CAS/EC No. 302776-68-7/443-860-6)

The SCCS adopted this document
by written procedure on 14 February 2025

ACKNOWLEDGMENTS

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

For the Preliminary Scientific Advice

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

SCCS external experts
Dr E. Benfenati
Dr N. Cabaton
Prof. E. Corsini
Dr Ch. Delmaar
Dr A. Koutsodimou
Dr M. Henriqueta D.L.G. Louro
Prof. W. Uter
Dr N. von Goetz

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

The SCCS concludes the following:

1. *Considering the recent concerns over the presence of DnHexP as a contaminant in the production of Diethylamino Hydroxybenzoyl Hexyl Benzoate (DHHB) used as a UV-filter in cosmetic products, as well as in view of technical and scientific progress and taking under consideration in particular the various health concerns, the SCCS is requested to identify the maximum safe level of DnHexP as a contaminant in DHHB preparations*

   Taking into account the health concerns associated with DnHexP, the SCCS calculated a maximum level of 0.026% (260 ppm) for this contaminant in the UV filter DHHB. This applies when DHHB is used up to 10% in cosmetic products and only if DnHexP is an unavoidable impurity.

2. *Does the SCCS have any further scientific concerns regarding the presence of DnHexP in DHHB as a UV-filter in cosmetic products?*

   The SCCS has noted available information showing that DnHexP was below the level of detection in several DHHB containing sunscreen products and DHHB sources. The SCCS has also noted the available information showing that the levels of DnHexP in DHHB can be lowered down to 1ppm. Therefore, the SCCS is of the opinion that this trace level (1 ppm) should be the target for the maximal level of DnHexP as an unavoidable trace impurity in DHHB.

Keywords: SCCS, scientific advice, Diethylamino Hydroxybenzoyl Hexyl Benzoate, DHHB, S83, Regulation 1223/2009, CAS/EC No. 302776-68-7/443-860-6

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

SCCS

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

Scientific Committee members

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

Contact

European Commission
Health and Food Safety
Directorate B: Public Health, Cancer and Health security
Unit B3: Health monitoring and cooperation, Health networks
L-2920 Luxembourg
SANTE-SCCS@ec.europa.eu

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2. MANDATE FROM THE EUROPEAN COMMISSION

Background

Diethylamino Hydroxybenzoyl Hexyl Benzoate (DHHB) (CAS/EC No. 302776-68-7/443-860-6) is the INCI name of the chemical compound 'benzoic acid, 2-[4-(diethylamino)-2-hydroxybenzoyl]-, hexylester' with reported functions in CosIng database as 'UV-filter', 'UV-absorber', and 'light stabiliser'.

DHHB has been authorised for use in cosmetic products as a UV-filter (entry 28 of Annex VI to the Cosmetics Regulation (EC) No. 1223/2009). It is an organic compound highly valued for its exceptional UV-absorbing properties (especially UVA radiation), excellent photostability and compatibility with other UV absorbers/filters and other cosmetic ingredients, serving, therefore, as a key component in many cosmetic formulations included but not limited to sunscreens, moisturizers, foundations, and other skincare and makeup products.

DHHB has been assessed by the SCCNFP in 2003 (SCCNFP/0650/03[1] and SCCNFP/0756/03[2]) and by SCCP in 2006 (SCCP/0996/06[3]) and in 2008 (SCCP/1166/08[4]). In the last SCCP Opinion of 2008, the scientific committee concluded on the safety of DHHB when used as a UV-filter in cosmetic products up to a maximum concentration of 10 % w/w.

In 2024, the German authorities informed the Commission services on the detection of the degradation product of a plasticizer in urine samples of children. In particular, 'mono-n-hexyl phthalate' (MnHexP) was detected in urine samples. MnHexP can be a metabolite from various phthalates, such as di-n-hexyl phthalate (DnHexP), decylhexyl phthalate or certain other mixed-chain phthalates, or can be directly taken up in the form of hexyl hydrogen phthalate.

Phthalates are chemical compounds that are mainly used as plasticisers in plastics to make them soft but are not firmly bound in them and can be released. As phthalates are produced and used in large quantities and in many applications, they can be detected almost ubiquitously in the environment (soil, water, air).

In particular, the assessment from the German Authorities illustrated that the presence MnHexP in urine samples could be from potential exposure to sunscreens. One of the phthalates that MnHexP could be produced from is DnHexP. Nevertheless, DnHexP is already prohibited in cosmetics (entry 1559 of Annex II to the Cosmetics Regulation), however, DnHexP could be a contaminant in the production process of an authorised UV-filter that is Diethylamino Hydroxy benzoyl Hexyl Benzoate (DHHB).

The BfR assessed whether cosmetic products containing a potentially contaminated UV filter with DnHexP (as could be the case of DHHB) could pose a health risk to consumers and concluded that this is very unlikely (i.e., there is a sufficient margin of safety in the use of sunscreen products containing up to 10 % of a UV filter contaminated with up to 0.3 % DnHexP). However, the BfR noted that the removal of DnHexP in DHHB is technically possible (i.e., the presence of DnHexP is technically avoidable) but requires special manufacturing and purification processes to ensure the lowest possible presence of this phthalate and may vary depending on the manufacturer.

Given the possible health risks, the safe use of DHHB in cosmetic products should be re-evaluated by the SCCS in view of technical and scientific progress and the concerns raised about the presence of potential contaminants, highlighting the importance of purity of ingredients used in cosmetic formulations. The Commission, therefore, requests the SCCS to provide a scientific advice on the safety of DHHB in cosmetic products and the presence of DnHexP.

[1] https://ec.europa.eu/health/ph_risk/committees/sccp/documents/out223_en.pdf
[2] https://ec.europa.eu/health/ph_risk/committees/sccp/documents/out241_en.pdf
[3] https://ec.europa.eu/health/ph_risk/committees/04_sccp/docs/sccp_o_059.pdf
[4] https://ec.europa.eu/health/ph_risk/committees/04_sccp/docs/sccp_o_130.pdf

Terms of reference

1. Considering the recent concerns over the presence of DnHexP as a contaminant in the production of Diethylamino Hydroxybenzoyl Hexyl Benzoate (DHHB) used as a UV-filter in cosmetic products, as well as in view of technical and scientific progress and taking under consideration in particular the various health concerns, the SCCS is requested to identify the maximum safe level of DnHexP as a contaminant in DHHB preparations

2. Does the SCCS have any further scientific concerns regarding the presence of DnHexP in DHHB as a UV-filter in cosmetic products?

3. SCIENTIFIC ADVICE

Preamble

In view of the mandate, this scientific advice is focused on DnHexP (di-n-hexyl phthalate, CAS nr 84-75-3), which has been identified as an impurity in the UV filter DHHB. This is because no new information is available on DHHB, which has been already approved as an ingredient which can constitute up to 10% of a cosmetic product (SCCP/1166/08), and because the safety concern relates to the presence of DnHexP impurity.

3.1 CHEMICAL AND PHYSICAL SPECIFICATIONS

3.1.1 Chemical identity

3.1.1.1 Primary name and/or INCI name

Dihexyl phthalate
https://pubchem.ncbi.nlm.nih.gov/compound/Dihexyl-phthalate, consulted October 2024

3.1.1.2 Chemical names

IUPAC Name: dihexyl benzene-1,2-dicarboxylate, Computed by Lexichem TK 2.7.0 (PubChem release 2021.10.14)

3.1.1.3 Trade names and abbreviations

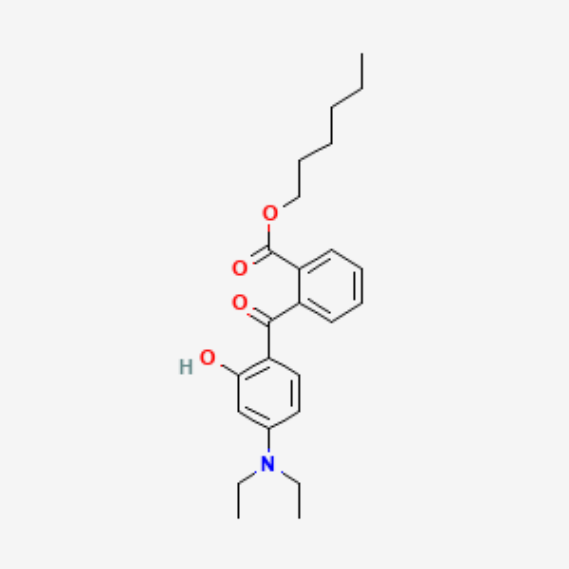
3.1.1.4 CAS / EC number

CAS Number: 84-75-3
EC Number: 201-559-5

From European Chemicals Agency (ECHA)

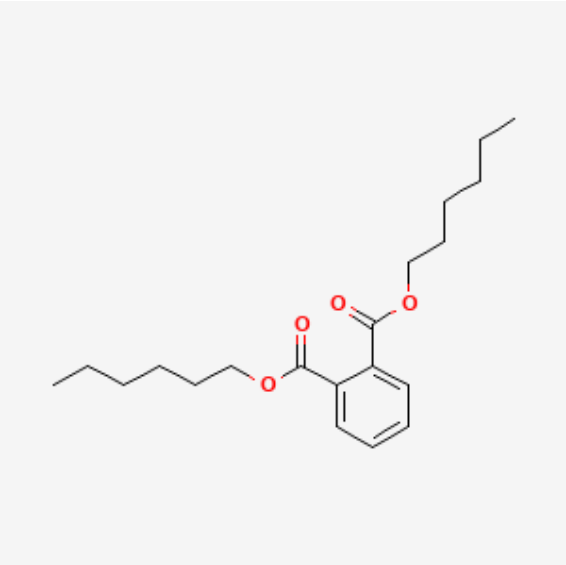
3.1.1.5 Structural formula

DHHB



From https://pubchem.ncbi.nlm.nih.gov/compound/10111431, consulted on 27th September 2024

DnHexP



From https://pubchem.ncbi.nlm.nih.gov/compound/Dihexyl-phthalate, consulted on 2nd October 2024

3.1.1.6 Empirical formula

DnHexP: $C_{20}H_{30}O_4$,
Computed by PubChem 2.2 (PubChem release 2021.10.14)

From https://pubchem.ncbi.nlm.nih.gov/compound/Dihexyl-phthalate

3.1.2 Physical form

Di-n-hexyl phthalate is a yellow-brown oily viscous liquid with a slight aromatic odor.

From National Toxicology Program, Institute of Environmental Health Sciences, National Institutes of Health (NTP). 1992. Chemical Repository Database.

Clear oily liquid; [HSDB] Yellow-brown viscous liquid; [CAMEO] Clear colorless oily liquid; [MSDSonline]

Yellow-brown oily viscous liquid with a slight aromatic odor.

From Occupational Safety and Health Administration (OSHA)

3.1.3 Molecular weight

DnHexP: 334.4 g/mol - Computed by PubChem 2.2 (PubChem release 2021.1

From https://pubchem.ncbi.nlm.nih.gov/compound/Dihexyl-phthalate, October 2024

3.1.4 Purity, composition and substance codes

See section 3.4.10

3.1.5 Impurities / accompanying contaminants

See section 3.4.10

3.1.6 Solubility

DnHexP:
Phthalate esters are soluble to various extents in many common organic solvents and oils but have a relatively low solubility in water. /Phthalate esters/

From Nat'l Research Council Canada; Phthalate Esters in the Aquatic Environment p.16 (1980) NRCC No. 17583

In water: 0.05 mg/L at 25 °C

From Ellington JJ; J Chem Eng Data 44: 1414-8 (1999) https://doi.org/10.1021/je990149u

3.1.7 Partition coefficient (Log Pow)

log Kow = 6.82 (measured)

From Ellington JJ, Floyd TL; Octanol/water partition coefficients for eight phthalate esters. USEPA/600/S-96/006, Athens, GA: USEPA (National Exposure Research Lab) (1996)

3.1.8 Additional physical and chemical specifications

Color: Clear, oily liquid
From David RM *et al.*; Patty's Toxicology. (2007). NY, NY: John Wiley & Sons, Inc. Esters of Aromatic Mono-, Di, and Tri-carboxylic Acids, Aromatic Diacids and Di-, Tri-, Or Polyalcohols. On-line posting date: Apr 16, 2001.

Odour: Slightly aromatic

From Lewis, R.J. Sr.; Hawley's Condensed Chemical Dictionary 14th Edition. John Wiley & Sons, Inc. New York, NY 2001., p. 371

Melting point:
-57.8 °C (NTP, 1992)

From National Toxicology Program, 1992. Repository Database. North Carolina.

-58 °C
From David RM *et al.*; Patty's Toxicology. (2007), NY: John Wiley & Sons).

Boiling point:
350 °C at 735 mmHg (NTP, 1992)

From National Toxicology Program 1992. Chemical Repository Database. North Carolina.

- 210 °C at 5 mm Hg.

From Lide DR CRC Handbook of Chemistry and Physics 86T ed.

Flash point:
176.7 °C (NTP, 1992)

From National Toxicology Program 1992. Chemical Repository Database, North Carolina.

193.9 °C; 193 °C
From Lewis, R.J. Sr.; Hawley's Condensed Chemical Dictionary 15th ed.

Vapour pressure**:** 1.4 x 10^{-5} mm Hg at 25 °C

From Howard PH *et al.*; Environ Toxicol Chem 4: 653-61 (1985)

Density:
0.995 at 20 °C (NTP, 1992) - Less dense than water; will float

From National Toxicology Program 1992. Chemical Repository Database, North Carolina.

1.010-1.016 at 20 °C/20 °C.

From Lewis: Hawley's Condensed Chemical Dictionary 14th ed. John Wiley & Sons, Inc. New York, NY 2001., p. 371

UV/visible light absorption spectrum: UV: 297nm

From Sadtler Research Laboratories Spectral Collection), Lide, Milne (eds.). Handbook of Data on Organic Compounds. Volume I. 3rd ed.

3.1.9 Homogeneity and Stability

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3.2 TOXICOKINETICS

3.2.1 Dermal / percutaneous absorption

The SCCP estimated that the dermal absorption of different phthalates is maximally 5% (SCCP/ 2007).
In a recent publication a dermal absorption fraction of 0.05 (i.e. 5%) was assumed for DnHexP (Pirow *et al.*, 2024). The authors based this on (i) the cumulative dermal absorption of 18% over 7 days following the application of ^{14}C -labelled DnHexP under occlusive conditions in rats (Elsisi *et al.,* 1989), and (ii) on the fact that rat skin is approximately four times more permeable than human skin (Pakalin *et al.,* 2008; SCCP 2007).

In the abovementioned study by Elsisi *et al.* (1989), the dermal absorption of several (radiolabelled) phthalates was estimated by measuring the percentage excreted in the faeces and urine after a single dosing on the dorsal skin of rats (5-8 mg/cm^2, number of animals not stated). The cumulative % dose measured for DnHexP in urine and faeces was about 2% after 24 hours and about 18% after 7 days. The total recovery of the radioactivity was 78%, where a recovery of 55% was noted from the skin area of application (Ref: Elsisi *et al.*, 1989).

This study, however, has not been conducted according to SCCS Notes of Guidance (SCCS/1647/22). In the absence of studies that conform to the SCCS's Notes of Guidance, a default dermal absorption value of 50% will be used in this Scientific Advice.

3.2.2 Other studies on toxicokinetics

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3.3 EXPOSURE ASSESSMENT

3.3.1 Function and uses

DnHxP is prohibited in cosmetics according to entry 1559 of Annex II to the Cosmetics Regulation. It has a CLP classification Repr 1B.

3.3.2 Calculation of SED/LED

See 3.5: Safety evaluation

3.4 TOXICOLOGICAL EVALUATION

While the general toxicity (outside the reproductive hazard) of the group of phthalates to which DnHexP belongs is considered low, their reproductive hazard has been well established. The primary concern regarding DnHexP is the influence on testosterone production in the fetal testis, leading to alterations in male offspring. Accordingly, it has been classified under CLP regulation as Repr 1B.
Therefore, the SCCS will for this Scientific Advice focus its evaluation on the reproductive toxicity of DnHexP as the most relevant effect.
As part of a risk assessment, Pirow *et al.* (2024, supplemental information) conducted a literature search on *in vivo* animal studies with at least three doses of DnHexP addressing the reproductive hazard of DnHexP in order to identify a PoD. Of the 19 studies, the publication by Saillenfait (2013) was considered to be the most robust, reporting a NOAEL of 5 mg/kg bw/d.
The studies were also examined by the SCCS and are summarised below.

1. Prenatal developmental toxicity study in rats

The study evaluated the dose–response relationship for the effects of DnHexP on the synthesis and production of testosterone in the fetal rat testis. Pregnant Sprague–Dawley rats were administered the vehicle (olive oil) and either DnHexP (5 to 625 mg kg^{-1} per day) or diethylhexyl phthalate (DEHP) (50 or 625 mg kg^{-1} per day), by gavage, from gestation day (GD) 12 to 19. Fetal testes were assessed on GD 19. DnHexP reduced ex vivo testosterone production and down-regulated the expression of several genes required for cholesterol transport and steroid synthesis (i.e. SR-B1, StAR, P450scc, 3bHSD and P450c17). These inhibitions were dose dependent. A no-effect level was established at 5 mg kg^{-1} per day and a lowest-effect level at 20 mg kg^{-1} per day. mRNA levels of SR-B1, StAR, P450scc and 3bHSD were not similarly decreased in the adrenals. The authors concluded that DnHexP shares the same mode of action as DEHP in disrupting fetal testicular androgen synthesis. Alterations in testosterone production and in key steroidogenic gene expressions were apparent at lower doses than those causing postnatal reproductive malformations after gestational exposure during the critical period of male sexual differentiation.
(Ref: Saillenfait 2013)

SCCS comment
The SCCS noted a NOAEL of 5 mg/kg bw/d based on the reduced testosterone production *ex vivo.* The SCCS will base its conclusions on this NOAEL because of the good quality of this study and because it is the lowest compared to those that could be estimated from other studies on this critical endpoint.

2. Developmental toxic potential of di-n-hexyl phthalate (DnHexP) and dicyclohexyl phthalate (DCHP) in rats

Pregnant Sprague–Dawley rats were exposed to DnHP or DCHP at doses of 0 (olive oil), 250, 500 and 750 mg kg^{-1} per day, by gavage, on gestational days (GD) 6–20. Maternal food consumption and body weight gain were significantly reduced at 750 mg kg^{-1} per day of DnHP and at the two high doses of DCHP. Slight changes in liver weight associated with peroxisomal enzyme induction were seen in dams treated with DnHP or DCHP. DnHP caused dose related developmental toxic effects, including marked embryo mortality at 750 mg kg^{-1} per day, and presence of malformations (mainly cleft palate, eye defects and axial skeleton abnormalities) and significant decreases in fetal weight at 500 and 750 mg kg^{-1} per day. A significant delay of ossification and increase in the incidence of skeletal variants (e.g. supernumerary lumbar

ribs) also appeared at 250 mg kg^{-1} per day. DCHP produced fetal growth retardation at 750 mg kg^{-1} per day, as evidenced by significant reduction of fetal weight. DnHP and DCHP induced a significant and dose-related decrease in the anogenital distance of male fetuses at all doses, and there was a significant increase in the incidence of male fetuses with undescended testis at 500 and 750 mg kg^{-1} per day of DnHP. In conclusion, DnHP showed clear embryo lethality and teratogenicity, but not DCHP. There was evidence that both phthalates could alter the development of the male reproductive system after in utero exposure, DnHP being much more potent than DCHP.
The authors stated that a NOAEL could not be derived from this study, while the lowest observable adverse effect was judged to be 250 mg/kg bw/d.

(Ref: Saillenfait 2009)

3. Study on Leydig cell hyperplasia

DnHexP (in the publication abbreviated as DNHP) in doses of 0, 10, 100, and 1000 mg/kg was administered via gavage to 35-day-old male Sprague-Dawley rats for 21 days. Serum levels of testosterone, luteinizing hormone, follicle-stimulating hormone, Leydig cell number, the expression of Leydig and Sertoli cell genes and proteins were investigated. DNHP significantly increased serum testosterone levels at 10 mg/kg but lowered its level at 1000 mg/kg. DnHexP significantly increased luteinizing hormone levels at 1000 mg/kg without affecting follicle-stimulating hormone levels. DnHexP increased Leydig cell number at all doses but downregulated the expression of Lhcgr, Hsd3b1, Hsd17b3, and Hsd11b1 in Leydig cell per se at 1000 mg/kg. DNHP elevated phosphorylation of ERK1/2 and GSK-3β at 10 mg/kg but decreased SIRT1 and PGC-1α levels at 1000 mg/kg. In conclusion, DNHP exposure caused Leydig cell hyperplasia possibly via stimulating phosphorylation of ERK1/2 and GSK-3β signaling pathways.

(Ref: Ye 2020)

4. Short-term *In Vivo* Screen Using Fetal Testosterone Production

The study was designed to develop and validate a short-term *in vivo* protocol (so-called Fetal Phthalate Screen (FPS)) to detect phthalate esters (PEs) and other chemicals that disrupt fetal testosterone synthesis and testis gene expression in rats. The authors propose that the FPS can be used to screen chemicals that produce adverse developmental outcomes via disruption of the androgen synthesis pathway more rapidly and efficiently, and with fewer animals than a postnatal one-generation study. Pregnant rats were dosed from gestational day (GD) 14 to 18 at one dose level with one of 27 chemicals including DnHexP. Ex vivo testis testosterone production (T Prod) was measured on GD 18. Dose-response studies also were conducted to determine their relative potencies. CD-1 mice were also exposed to varying dose levels of Dipentylphthalate (DPeP) from GD 13 to 17 to determine if DPeP reduced T Prod in this species since there is a discrepancy among the results of in utero studies of PEs in mice.

Compared to the known male reproductive effects of the PEs in rats the FPS correctly identified all known "positives" and "negatives" tested.

The study does not report a NOAEL, but from one of the graphic presentations showing an effect on testis testosterone production, a NOAEL of 10 mg kg bw/d could be deduced.

(Ref: Furr 2014)

5. Biochemical and histopathological studies in rats on prenatal / in utero exposure to DnHexP

In a series of experiments in rats from the same research group (Aydemir, 2023; Barlas, 2020; Aydogan Ahbab, 2013, 2015 and 2017; Dogan Ahb, 2014), the effects of DnHexP on various fertility/reproductive toxicity parameters were investigated. All experiments used the same doses of 0, 20, 100, and 500 mg/kg bw/day on gestational day 6 - 19. Besides clinical serum and hematological parameters, decreased anogenital distance (AGD), decreased weight of the male reproductive organs and histopathological findings in the testes, prostate, epididymis and an increased number of abnormal sperm in the male offspring were observed. While a LOAEL of 20 mg/kg bw/day could be derived, a NOAEL was not established.
In a recent publication with literature review (Pirow, 2024, Supplement) reservations were expressed regarding the reliability of the studies from this research group.

3.4.1 Repeated dose toxicity

See section 3.4 above

3.4.2 Reproductive toxicity

See section 3.4 above

3.4.3 Mutagenicity / genotoxicity

No mutagenicity/genotoxicity studies are available. DnHexP shares the same mechanism of action with DEHP. EFSA (2019) considered DEHP along with Benzylbutylphthalate (BBB) and Di-n-Butylphthalate (DBP). In agreement with the ECHA assessment (ECHA, 2017), the EFSA Panel (EFSA, 2019) noted that the overall evidence from *in vitro* and *in vivo* data on mutagenicity or chromosomal damage for DBP, BBP and DEHP does not give indication of a concern for genotoxicity. This is supported by the absence of genotoxic potential of the batches of DHHB as noted in the previous SCCS Opinion (SCCP/1166/08).

3.4.4 Carcinogenicity

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3.4.5 Photo-induced toxicity

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3.4.6 Human data

A recent publication (Pirow, 2024) presented an exposure estimation and assessment of health risks of DnHexP. The authors performed an exposure assessment for the hypothetical case that consumers would use a sunscreen containing 10% of a UV filter which in turn would be contaminated with 0.3% DnHexP. The DnHexP concentration in such a sunscreen would consequently be 0.03%, i.e. 300 mg/kg. The authors estimated the systemic exposure dose

(SED) as 4.5 µg/kg bw/day for adults. For young children (0–3 years), they estimated an SED of 14.6 µg/kg bw/ day. The SED values for this hypothetical contamination of sunscreen would correspond to the fraction of the provisional TDI of 7.1% (adults) and 23.3% (children).
The authors also made a calculation for a contamination with DnHexP of 16 mg/kg assumed for the cosmetic products sunscreen, lip balm and pump spray, based on the maximum value reported for 57 samples of sunscreen products from 2020 to 2023 (CVUA Karlsruhe, 2024). The dermal exposure of adults and young children to this DnHexP level in sunscreen resulted in an SED of 0.24 and 0.78 µg/kg bw/day, respectively. For the oral exposure of adults following the application of lip balm, an ingested amount of 57 mg/day and an oral absorption fraction of 1 were assumed. The authors calculated an SED of 0.015 µg/kg bw/day. For a 3-year-old child with a body weight of 10 kg, by assuming the same ingested amount as for adults, the SED resulting from lip balm exposure was estimated at 0.091 µg/kg bw/day.
(Ref: Pirow, 2024)

3.4.7 Special investigations

In a report from the German authorities 57 sunscreen cosmetic products that were on the market in the years 2020 – 2023 were analysed (CVUA Karlsruhe, 2024). Of these products, 40 contained DHHB; in 21 of these the impurity DnHexP was present. In the other 19 DHHB containing products, DnHexP could not be detected at levels below 0.2 mg/kg (0.2 ppm).
In the 17 samples without DHHB, the presence of DnHexP could not be detected.

According to an entry in the patent register (WIPO, 2023) it is possible by the described inventive methods to obtain a DnHexP content in DHHB of (more preferred) less than 5 ppm and (most preferred) less than 1 ppm.

The SCCS had also access to personal communication with analytical results of DHHB from four different sources, which show that the content of DHHB can be as low as <1 mg/kg (1 ppm).

SCCS comment
Based on the findings by the German authorities, a patent application and a technical-analytical report, the SCCS concludes that it is technically possible to produce DHHB in which DnHexP is absent or not higher than 1 ppm.

3.5 SAFETY EVALUATION (INCLUDING CALCULATION OF THE MOS)

Back-calculations for dermal exposure of the maximum safe levels of DnHexP from the SED derived from the (adjusted) NOAEL* = 2.5 mg/kg bw/d

*) adjusted for 50% oral absorption (EFSA 2019)

For childrens' body weights, the SCCS used the 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. 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. For the 10 – 14 years age group, a body weight of 43.4 kg was used. 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 were taken from the SCCS Notes of Guidance 12th revision (SCCS/1647/22).

In the absence of better exposure data for children in the EU, the SCCS will rely on the currently available children-specific data where possible (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). Where needed, refinement for specific age categories was performed based on the skin surface areas and bodyweights as explained above (SSA/BW scaling approach).

In Table 1 the SCCS has, for the respective age categories, back-calculated the fractions of DnHexP that can be considered safe, based on a SED of 0.025 mg/kg bw/d for DnHexP.

In the absence of data that are specific for DnHexP and in view of EFSA's considerations regarding the oral availability of phthalates (EFSA, 2019), the SCCS has applied a 50% adjustment to the NOAEL.

Thus, the maximum SED that can be considered safe is derived from a MoS = 100, i.e. 0.01 X NOAEL(adj) = 0.025 mg/kg bw/d.

This safe SED = Amount applied on skin in mg **X** %DHHB **X** %DnHexP in DHHB **X** %DermAbs)**/**Bodyweight

Following this, the maximum safe fraction of DnHexP in DHHB is:
0.025 mg/kg bw/d divided by [product amount applied in mg/kg bw/d x fraction DHHB allowed in product x fraction DermAbs]

For the product amount, the SCCS has used a (conservative) deterministic approach.

Table 1

Age	Body weight (kg)	Body surface (cm^2)	Amount applied in mg/kg bw/per day		Amount DHHB applied in mg/kg bw/d (max 10% allowed in cosmetic products)	Max SED of DnHexP (mg/kg bw/d) considered safe *)	Derived max level DnHexP impurity in DHHB **)
6-12 months	8.7	4400	Sunscreen	829.4 [2]		0.025	
			Hand cream	62.4 [3]			
			Body lotion	839 [4]			
			Face cream	44.5 [3]			
					177.5		0.03% (300 ppm)
			Total	1775			
1-3 yrs	11.6	5600	Sunscreen	791.7 [2]		0.025	
			Hand cream	59.6 [3]			
			Body lotion	981 [4]			
			Face cream	42.5 [3]			
					187.5		0.026% (260 ppm)
			Total	1875			
3-6 yrs	14	6200	Sunscreen	726.3 [2]		0.025	
			Hand cream	54.7 [3]			
			Body lotion	620 [5]			
			Face cream	39 [3]			
					144		0.034% (340 ppm)
			Total	1440			
6-10 yrs	21.7	8500	Sunscreen	642.4 [2]		0.025	
			Hand cream	48.4 [3]			
			Body lotion	409 [5]			
			Face cream	34.5 [3]			
					113.4		0.044 % (440 ppm)
			Total	1134			
10-14 yrs	43.4	14000	Sunscreen	521.1 [6]		0.025	
			Hand cream	49.7 [7]			
			Body lotion	180.2 [7]			
			Face cream	35.5 [7]			
					78.7		0.063% (630 ppm)
			Total	787			
Adults	60	17500	Sunscreen	300 [1]			

		Hand cream	32.7 [1]	0.025	
		Body lotion	123.2 [1]		
		Face cream	24.1 [1]		
				48	0.1 % (1000 ppm)
		Total	480		

*) Derived from NOAEL(adj)=2.5 mg/kg bw/d and MoS=100
**) Only applicable if the presence of DnHexP in DHHB is unavoidable. Back-calculated from the max acceptable SED=0.025, from the applied amount of DHHB and from the dermal absorption.

1) from the Notes of Guidance
2) SSA/BW scaling approach, using Gomez-Berrada (2017) Table 5
3) SSA/BW scaling
4) Ficheux and Roudot 2017, Crème hydratante corps for 0.5-3 yrs
5) Garcia-Hidalgo *et al*. 2017 body lotion for 3-10 yrs: 0.4 application/day based on the most probable frequency for both sexes of 2-3 times per week for 3-10 years age group
6) Gomez-Berrada 2017
7) Scaled to BW

Systemic exposure from *oral* exposure

From the application of 57 mg/day lip care products (SCCS, Notes of Guidance) a conservative estimate of ingestion of this amount can be derived. From the maximally safe concentration as calculated above for sunscreen application for adults (0.1% in DHHB), this would (after taking into account 50% oral availability) for an adult add only 0.05 µg/kg bw/d to the systemic exposure of DnHexP. If children would apply and ingest the same amounts, this would imply an addition for the respective age categories of 0.33, 0.23, 0.18, 0.14 and 0.07 µg/kg bw/d of DnHexP to the systemic exposure.

Systemic exposure from *inhalation*

From the application of 1540 mg/day pump spray products for the face (SCCS, Notes of Guidance) a conservative estimate of inhalation of his amount can be derived. From the maximally safe concentration in adults as calculated above for sunscreen application (Table 1: 0.1% in DHHB), and an airborne fraction of 0.2 this would for an adult imply that 0.5 µg/kg bw/day would be available for inhalation. This means that at the most 0.5 µg/kg bw/d DnHexP would be added to the systemic exposure.
When for children the same amounts of facial pump spray usage would be assumed, then the addition to the systemic exposure would for the respective age categories be less than 3.5, 2.6, 2.2, 1.7 and 0.9 µg/kg bw/day.

From the application of whole-body propellant-based spray and pump spray which would contain 0.1% DnHexP in the maximally allowed fraction of 10% in a sunscreen, the calculations in Table 2 (Annex I) indicate that this would result for adults in a systemic exposure of 1.75 µg/kg bw/d. In the absence of an agreed framework for inhalation exposure by children, the SCCS will assume that for these age groups the systemic exposure is not substantially different.

Maximum concentration considered as safe

In view of the marginal addition of oral exposure from lip products and inhalation exposure from facial and whole-body sprays to the systemic exposure, the SCCS will base the maximally safe fractions on the maximum calculated fractions of DnHexP as established in a deterministic conservative approach for dermally applied products in Table 1 above.

This implies that for a safe level for all age categories, the fraction of DnHexP in DHHB when used as sunscreen ingredient should not exceed 0.026% (260 ppm), only if DnHexP is an unavoidable impurity.

3.6 DISCUSSION

Exposure

Dermal
The SCCS has made a back-calculation from a systemic exposure dose (SED) based on the dermal exposure and adjusted NOAEL of 2.5 mg/kg bw/d for DnHexP. In the absence of data that are specific for DnHexP, the SCCS has used a 50% adjustment of the NOAEL based on EFSA's considerations regarding the oral availability of phthalates (EFSA, 2019). Allowing for the MoS to be at least 100, a maximum concentration of DnHexP in the parent ingredient DHHB (considering a maximally permitted concentration of 10% DHHB in cosmetic products) could be derived.
For these calculations, the SCCS has used the default dermal absorption percentage of 50%.

Oral: The SCCS has calculated the systemic exposure doses that would result from ingestion of lip care products while applying the maximum levels calculated for the dermal exposure as explained above.
Inhalation: Similarly, the SCCS has calculated the SED resulting from inhalation exposure.

The calculated amounts indicate that the additional systemic exposure from ingestion and inhalation are negligible in view of the estimated dermal exposure from sunscreen use. In view of this marginal addition of oral exposure from lip products and inhalation exposure from facial and whole-body sprays to the systemic exposure, the SCCS will base the maximally safe fractions on the calculated maximum fractions of DnHexP as established for dermally applied sunscreen in Table 1 above.
From these back-calculated maximum safe concentrations (Table 1), the SCCS identified as maximum safe level the value for children, being the most sensitive age category, at 0.026% (260 ppm) DnHexP in the parent compound DHHB.

Toxicological Evaluation

The reproductive hazard of phthalates is well established. The primary concern regarding DnHexP is the testosterone production in the foetal testis, leading to alterations in male offspring. Accordingly, ECHA has identified DnHexP as a substance of very high concern because of its CMR properties, in particular as being toxic for reproduction (ECHA, 2013).
From a well-conducted prenatal developmental study in rats (Saillenfait 2013), a NOAEL of 5 mg/kg bw/d can be derived.
According to EFSA (2019), the conclusions on human health hazard assessment highlight that even though reproductive toxicity is selected as the most relevant effect, there are indications that exposure to the phthalates DEHP, DBP, BBP and DIBP could lead to immunological disorders (allergy, asthma and eczema) possibly at levels lower than reproductive toxicity. The effects on other endpoints such as metabolism and neurodevelopment have not been elucidated yet.

4. CONCLUSION

1. *Considering the recent concerns over the presence of DnHexP as a contaminant in the production of Diethylamino Hydroxybenzoyl Hexyl Benzoate (DHHB) used as a UV-filter in cosmetic products, as well as in view of technical and scientific progress and taking under consideration in particular the various health concerns, the SCCS is requested to identify the maximum safe level of DnHexP as a contaminant in DHHB preparations*

Considering the health concerns associated with DnHexP, the SCCS calculated a maximum safe level of 0.026% (260 ppm) for this contaminant in the UV filter DHHB. This applies when DHHB is used up to 10% in cosmetic products and only if DnHexP is an unavoidable impurity.

2. *Does the SCCS have any further scientific concerns regarding the presence of DnHexP in DHHB as a UV-filter in cosmetic products?*

The SCCS has noted available information showing that DnHexP was below the level of detection in several DHHB containing sunscreen products and DHHB sources. The SCCS has also noted the available information showing that the levels of DnHexP in DHHB can be lowered down to 1ppm. Therefore, the SCCS is of the opinion that this trace level (1 ppm) should be the target for the maximal level of DnHexP as an unavoidable trace impurity in DHHB.

5. MINORITY OPINION

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6. REFERENCES

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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 – 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 – from page 158

ANNEX I

Table 2

Systemic exposure calculations for *adults* after inhalation exposure to a maximally safe concentration of 0.1% DnHexP in DHHB (see Table 1) i.e. the maximally safe concentration of 0.001% in the non-propellant part of the sunscreen spray product.

	Parameter	Propellant spray	Pump spray	Unit
Amount by application[1]	A	15000	9000	mg/application
Fraction of DnHexP in non-propellant	C	0.001	0.001	(w/w)
Proportion of non-propellant in formulation	P	0.6	1	-
Airborne Fraction[2]	AF	1	0.2	-
Potential amount to be inhaled	EA = (A*C*P*AF)	9	1.8	mg
First step: near field $1m^3$	V1	1000	1000	L
Breathing rate	BR	13	13	L/min
2 min in the near field	t1	2	2	min
Potential amount inhaled during t1	IA1 = (EA/V1*BR*t1)	0.234	0.047	mg
Second step: far field $10m^3$	V2	10000	10000	L
Breathing rate	BR	13	13	L/min
10 min in far-field	t2	10	10	min
Potential amount inhaled during t2	IA2 = (EA/V2*BR*t2)	0.117	0.023	mg
Substance availability fraction [2]	G	0.75	0.75	-
Respirable fraction	RF	0.2	0.01	-
Frequency of application	F	2	2	Per day
Default body weight adult	BW	60	60	kg
SED(inhal) adult	(IA1 + IA2) *G*RF*F/BW	1.75	0.017	µg/kg bw/d

[1] Adjusted for the proportion of propellant to achieve a final 'on body' amount of 9000 mg
[2] According to the SCCS Notes of Guidance