Office for Product Safety & Standards

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

Opinion on 4-Methylbenzylidene Camphor as a UV Filter in Cosmetic Products

1. Introduction

1.1. 4-Methylbenzylidene camphor (CAS No. 38102-62-4/36861-47-9) is currently included on the list of substances permitted for use up to a concentration of 4% as a UV filter within Annex VI (Entry 18) of the Cosmetic Products Regulation UK No 1223/2009 (as amended).[1]

1.2. 4-Methylbenzylidene camphor (also known as 4-MBC and referred to as this 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)[2]. Currently no EU harmonised or UK mandatory classification and labelling entries exists for 4-methylbenzylidene camphor (databases accessed November 2022). However, 4-MBC has been identified as a substance of very high concern (SVHC) within the EU with

[1] The UK Regulation currently consists of the Regulation UK No 1223/2009 as amended by SI 696/2019 Product Safety and Metrology (EU Exit) Regulations. The full consolidated UK text will be available in due course.

[2] The GB CLP Regulation No 1272/2008 as amended by The Chemicals (Health and Safety) and Genetically Modified Organisms (Contained Use) (Amendment etc.) (EU Exit) Regulations 2019. The full consolidated UK text will be available soon.

respect to endocrine disrupting properties relevant to human health, with adverse effects on the reproductive system (ECHA, 2021)[3].

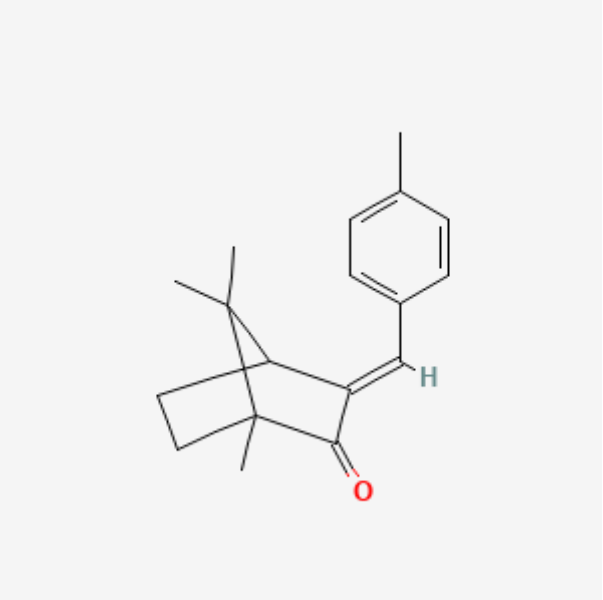

Figure 1: The chemical structure of 4-methylbenzylidene camphor (source: PubChem)

1.3. OPSS requested the data package to support the safety of 4-MBC from industry through a call for data. No additional data were received. The SAG-CS were, therefore, only able to review publicly available studies and reviews.

1.4. This Opinion is limited to the safety assessment of 4-MBC in dermal applications of sunscreen products and other cosmetic products (exposure scenarios via inhalation (i.e. aerosols and sprays) or the oral (i.e. lip care products) routes were not considered as Industry did not wish to continue using 4-MBC in products that may result in exposures through these routes.

2. Background

Intended function and uses of 4-MBC:

2.1. 4-MBC is a UV filter used in sunscreen products and other cosmetics up to a maximum concentration of 4%. 4-MBC is also used as a UV-filter for product protection (preservative function) in reported concentrations of 0.5% or lower.

2.2. 4-MBC is predominantly used as a UV-B filter and has an absorption maximum (λ_{max}) at 299 ± 2 nm.

2.3. The usage of 4-MBC in sunscreen products and other cosmetic products in the UK is following a downward trend. A survey of 377 products found that 4-MBC was used in 1.2% of products in 2010 in comparison to 25% of products in 2005 (Kerr, 2011).

[3] ECHA (2021), Agreement of the member state committee on the identification of '(±)-1,7,7-trimethyl-3-[(4-methylphenyl)methylene]bicyclo[2.2.1]heptan-2-one covering any of the individual isomers and/or combinations thereof (4-MBC)' as substances of very high concern.

2.4. The regulation of 4-MBC varies between other jurisdictions. 4-MBC is approved for usage in Canada by Health Canada at levels of 4% and below. It is not approved for use in the United States by the US Food and Drug Administration, and it is not permitted for use in Japan or Denmark, and will be prohibited as an ingredient in the EU from 1 May 2025.

3. Potential Endocrine Disrupting Properties

3.1. In 2021, the Danish Environmental Protection Agency (EPA) submitted an Annex XV proposal to the European Chemicals Agency (ECHA) to classify 4-MBC as a substance of very high concern (SVHC). Within this proposal, it was concluded that 4-MBC is an endocrine disruptor via T- and E- modalities (ECHA, 2021). The Scientific Committee on Consumer Safety (SCCS) concurred with the conclusions of the Annex XV proposal in their 2021 opinion, concluding that "*there is sufficient evidence that 4-MBC may act as an endocrine disruptor, and have effects on both the thyroid and estrogen systems. Effects on the androgen system are not so evident, as only in vitro evidence is available"* (SCCS, 2022).

4. Previous Expert Group Opinions

4.1. The Scientific Committee on Cosmetic and Non-Food Products (SCCNFP) first assessed the safety of 4-MBC in 1998 and concluded that a maximum use concentration of 4% was justified owing to a calculated Margin of Safety (MoS) of 110 (SCCNFP, 1998).

4.2. In 2001, the SCCNFP reviewed the potential estrogenic effects of 4-MBC. A No Observed Effect Level (NOEL) of 66 mg/kg bw/day was determined in an uterotrophic assay in rats. In combination with a calculated Systemic Exposure Dose (SED) of 0.23 mg/kg bw/day, a 'screening MoS' was determined at 289, which was deemed acceptable (Schlumpf, 2001; SCCNFP, 2001). The SCCNFP noted that the study from which the NOEL was derived was not long-term (chronic), and a 2-generation reproductive toxicity study would better be able to generate a 'real' NOEL value necessary for calculation of a reproductive toxicity MoS (SCCNFP, 2001).

4.3. The safety of 4-MBC for use in sunscreen products was additionally assessed by the SCCNFP in 2004 with particular regard to data submitted by industry relating to changes in thyroid hormone profile and thyroid morphology. The SCCNFP concluded that current use of 4-MBC in sunscreen products posed a reason for concern owing to the very low MoS that could be derived. The SCCNFP requested further data for review as a matter of urgency (SCCNFP, 2004).

4.4. Following subsequent submission of data, the Scientific Committee on Consumer Products (SCCP) concluded that the majority of the questions and requirements raised by the SCCNFP in their 2004 opinion had not been addressed and that, at the time, the safe use of 4-MBC at a maximum concentration of 4% in sunscreens and other cosmetic products could not be established (SCCP, 2006).

4.5. Following submission of further data, the SCCP reviewed their 2006 opinion in 2008. A MoS of 42.5 was calculated from a NOAEL of 25 mg/kg bw/day based on thyroid effects in the rat, and an *in vitro* dermal absorption value of 1.96 µg/cm^2. The SCCP found it was justified to reduce the interspecies toxicokinetic factor from 4 to 1, allowing a minimum MoS of 25. Hence the SCCP concluded that 4-MBC can be considered safe for use in finished cosmetic products (whole body application) at a concentration of up to 4%. Notably this conclusion applies only to dermal application and does not cover inhalation (e.g. propellant sunscreens) or oral (e.g. lip-care products) routes of exposure (SCCP, 2008).

4.6. In 2021, the SCCS were mandated to form an opinion on the safety of 4-MBC considering concerns relating to potential endocrine disrupting properties. The SCCS were not able to conclude on the safety of 4-MBC due to insufficient genotoxicity data. Further, the SCCS concluded that there is sufficient evidence that 4-MBC may have endocrine disrupting effects on both the thyroid and estrogenic systems. The SCCS noted that, even excluding the genotoxic potential, the systemic exposure dose for 4-MBC is approximately four times higher than previously established, resulting in a MoS lowered to the point that a maximum concentration of 4% in cosmetic products would no longer be considered safe (SCCS, 2022).

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

5.1. At their April and November 2022 meetings, the SAG-CS discussed a paper which focussed on the safety evidence and risks posed to health by 4-MBC when used as a UV filter in cosmetic products. Members identified several areas where more data would be required in order to undertake a full risk assessment on 4-MBC. Subsequently, OPSS published a call for data on 14th August 2023 with a deadline of 15th December 2023 requesting further data from industry to support the safety assessment of this ingredient. No data were forthcoming.

5.2. Members identified several published methods for the chemical characterisation of 4-MBC. One method utilises liquid chromatography tandem mass spectrometry (LC-MS-MS) (Rodil et al, 2008) and other more routine LC-UV and GC-MS methods (Kim et al, 2021; Zhang et al 2021; Lü et al, 2021)

5.3. Members reported that degradation of 4-MBC through exposure to UV radiation may produce substances (through hydroxylation, chlorine substitution, oxidation and demethylation) that are toxic but agreed that such a degradation pathway is not expected to operate in routine cosmetic usage and therefore such toxicity is not deemed relevant for human exposure.

5.4. Members did not have access to the full data package from the industry consortium even though a request for the data was made by the OPSS. Therefore Members had to draw conclusions based on derived data presented in the published opinions on 4-MBC (SCCNFP, 1998; SCCNFP 2001,

SCCNFP 2004; SCCP 2006; SCCP 2008; SCCS, 2022). Members discussed the data available for dermal absorption and identified a dermal absorption value of 4.18 µg/cm^2 (equivalent to 2.35%) as appropriate for use in the safety assessment. Members discussed the toxicokinetic data available with respect to identifying an oral absorption value and agreed that these data were inadequate to allow divergence from the standard 50% default value. Members discussed the limited toxicokinetic data available with respect to the proposal to reduce the toxicokinetic factor from 4 (standard) to 1 and consequently reduce the Margin of Safety (MoS) from 100 (standard) to 25 as discussed by the SCCP in 2008. The SAG-CS considered the Opinion provided by the SCCS in 2022 where there were concerns around the safe use of 4-MBC in sunscreen products relating to potential endocrine disrupting properties and insufficient genotoxicity data. Based on the limited data presented in the SCCS Opinion (2022) the SAG-CS agreed that they did not have adequate data to justify a deviation from the standard margin of safety of 100 for 4-MBC. Therefore, any calculations should use the standard MoS of 100 and not the reduced MoS of 25 as proposed by industry.

5.5. Members discussed the data available with respect to the lowest NOAEL for derivation of a point of departure (PoD) for the safety assessment. A 90-day dermal study in rats was available to the SCCS (Hofmann et al, 1984). The SCCS were able to derive a NOAEL for local effects from this study, however, a NOAEL for systemic effects could not reliably be derived. The lowest NOAEL for systemic effects was identified in the 90-day oral study in rats, as 25 mg/kg bw/day; and the SCCS determined that this was the most appropriate NOAEL to use in the safety assessment of systemic effects. The SAG-CS did not attempt to derive a point of departure for 4-MBC given the potential for genotoxicity and endocrine disruption as they did not have the full data package available.

5.6. Members stated that there was evidence to show that 4-MBC demonstrated endocrine activity in *in vitro* studies. A number of studies *in vivo* presented more varied results. Members considered the reproductive and developmental data together with effects noted on thyroid function and physiology. On the balance of this evidence, members considered that this substance should be regarded as a reproductive and developmental toxicant, likely to be acting *via* endocrine mechanisms. This would mean that 4-MBC should be regarded as an endocrine disruptor in the intact organism according to the WHO definition[4].

5.7. Overall, the limited available data reviewed by the SAG-CS suggested that 4-MBC may exhibit effects on the male and female rat endocrine system and exhibit potential for endocrine effects at the thyroid and pituitary axes. Overall, members agreed that 4-MBC exhibits endocrine disrupting properties *via* the

[4] WHO/IPCS (2002) definition, an endocrine disruptor is *'an exogenous substance or mixture that alters function(s) of the endocrine system and consequently causes adverse health effects in an intact organism, or its progeny, or (sub) populations'*

oral route with limited data to suggest effects on the thyroid via the dermal route in rodent 90 day studies.

5.8. Members did not have access to the full database of studies, and they were unable to draw firm conclusions from the available data. The confidence of members in the robustness of the reproductive and developmental toxicity database was extremely low. Members noted a lack of dose-response relationship in many studies and inconsistences in the study design as indicated by the study summaries available.

5.9. Members noted that the information provided on genotoxicity studies, using older protocols that have since been updated, comprised only of an Ames test and a chromosomal aberration test (both conducted in the 1980s). One additional mammalian cell gene mutation test from 2017 was brought to the attention of the Members. The number of genetic endpoints covered are limited and only gene mutations have been reliably addressed by the available data. To address this data gap, guidance from the Committee on Mutagenicity of Chemicals in Food, Consumer Products and the Environment (COM) on 'a strategy for test of chemicals for genotoxicity' (COM, 2021)[5] should be followed. Members agreed that genotoxicity potential could not be excluded based upon an insufficient amount and quality of available data.

6. Conclusions

Members did not have access to the full industry data package for 4-MBC even though this had been requested by the OPSS.

In the absence of data from industry and an incomplete data package it was necessary to draw conclusions from the published opinions from other authoritative bodies such as the SCCS. Members noted that the SCCS was unable to derive a safe level for 4-MBC in cosmetics.

The Members agreed that 4-methylbenzylidene camphor exhibits endocrine disrupting properties in in vivo studies

The Members noted concerns with regard to the safety of 4-MBC including the lack of a robust genotoxicity and reproductive/developmental toxicity package and concerns with regard to endocrine disruption properties.

The Members were not able to derive a safe level for use of 4-methylbenzylidene camphor in cosmetics.

Given the limited data package available for review, and potential concerns for genotoxicity and endocrine disruption, the SAG-CS could not conclude that 4-MBC is safe for use in sunscreen products and other cosmetic products.

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

[5] https://www.gov.uk/government/publications/a-strategy-for-testing-of-chemicals-for-genotoxicity

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