Australian Government
Department of Health, Disability and Ageing
Therapeutic Goods Administration

Safety review of 4-Methylbenzylidene Camphor (4-MBC)

July 2026

Contents

Glossary

Abbreviation	Explanation
4-MBC	4-Methylbenzylidene camphor
AICIS	Australian Industrial Chemicals Introduction Scheme
AR	Androgen receptor
ASEM	Australian sunscreen exposure model
AUC	Area under the time concentration curve
Cmax	Maximum concentration
DAa	Dermal absorption
E2	Estradiol
ECHA	European Chemicals Agency
EPA	Environmental protection agency
ER	Estrogen receptor
ERα	Estrogen receptor alpha
ERβ	Estrogen receptor beta
EU	European Union
FSH	Follicle-stimulating hormone
h	Hour
IC_{50}	Half maximal inhibitory concentration
IGF1	Insulin growth factor 1
LD_{50}	Median lethal dose
LH	Luteinizing hormone
MoS	Margin of safety
NOAEL	No observed adverse effect level
NOEL	No observed effect level
OECD	The Organisation for Economic Co-operation and Development
PBK	Physiologically based kinetic
PND	Post-natal day
PO	Orally
PR	Progesterone receptor
QSAR	Quantitative structure–activity relationship
SAG-CS	Scientific Advisory Group on Chemical Safety of Non-Food and Non-Medicinal Consumer Products
SCCNFP	Scientific Committee on Cosmetic Products and Non-food Products Intended for Consumers
SCCS	Scientific Committee on Consumer Safety
SD	Standard deviation
SED	Systemic exposure dose
SPF	Sun protection factor

Abbreviation	Explanation
T3	Triiodothyronine
T4	Thyroxine
TGA	Therapeutic Goods Administration
T_{max}	Time to maximum concentration
TSH	Thyroid-stimulating hormone
UV	Ultraviolet
UVB	Ultraviolet-B

Executive summary

We conducted a safety review of 4-Methylbenzylidene camphor (4-MBC), an active ingredient in therapeutic sunscreens.

This safety review was dependent on national and international safety assessment reports and peer reviewed publications investigating the safety and toxicokinetics of 4-MBC, where available.

However, based on the data considered in this safety review, the TGA recommends regulatory controls for 4-MBC to restrict its permitted concentration and use in therapeutic sunscreens.

The two main issues considered in this safety review were the evidence for the ability of 4-MBC to penetrate the skin to reach viable cells systemically and the potential toxicity exerted by 4-MBC.

Based on the data available, a Margin of Safety (MoS) was determined for 4-MBC using the Australian Sunscreen Exposure Model (ASEM) which underwent public consultation in 2024. A MoS of 100 or more is considered to be satisfactory for controlling for the risks to human health and safety from long-term use of an ingredient by the Australian population. The MoS was calculated based on the current maximum permitted concentration in therapeutic sunscreens (which are regulated as listed medicines).

However, it is important to note that the concentration of 4-MBC in products can be less than the maximum permitted amounts; and that some products contain a combination of active ingredients.

The ASEM has been used to calculate the highest estimated average daily sunscreen exposure modelled to account for use of therapeutic sunscreens applied long-term to the face and body by children and adults. The MoS using the highest estimated sunscreen exposure for application of a general sunscreen to the body, at the maximum permitted concentration, was less than 100. Hence, the ASEM was utilised to estimate alternative exposures based on specific parts of the body e.g. head, face and/or hands. In this case, the MoS was more than 100 and considered low-risk for long-term use when limited to the face and hands at concentrations between 16.5% and 3.8%, depending on the type of product and the directions for use (e.g. limited to face-only use).

The limitations of this review are:

1. The toxicological endpoints, (NOAELs), were collected from published international safety assessment reports and scientific literature. As full data sets, including all raw study data, were not available for independent corroboration of the findings from these reports and literature, this review was dependent on the veracity of the details provided in those reports and literature.

2. Consumer products other than sunscreens that contain the same active ingredient were not considered in this review.

3. The exposure to metabolites or impurities of the active ingredient has not been considered in this review.

Safety assessment

4-Methylbenzylidene camphor (4-MBC) is an organic camphor derivative used as an ultraviolet-B (UVB) filter in the 280–320 nm range in sunscreens products. Upon exposure to ultraviolet (UV) light, 4-MBC undergoes reversible *trans–cis* photoisomerization, dissipating the absorbed photon energy primarily as heat.

Summary of relevant toxicity findings

- *In vitro* studies using porcine skin estimated 4-MBC dermal absorption at 4.18 µg/cm² (corrected from 1.96 µg/cm² due to methodological limitations, +2 standard deviation [SD] adjustment) (24 hours [h]). Human volunteer studies (n = 4–6) reported absorption ranging from 1.3 to 4.75 µg/cm² (6 h). A dermal adsorption rate of 4.75 µg/cm^2 was used for calculation of the systemic exposure dose.

- 4-MBC had low acute toxicity oral toxicity in mice, rats and dogs, respectively (respective median lethal dose [LD_{50}] values 10000 mg/kg and >5000 mg/kg). 4-MBC had low acute dermal toxicity in rats with an LD_{50} of >2000 g/kg, with no deaths or clinical signs of toxicity or local irritation observed. Severe local irritation was observed in rats following repeat dermal dosing at 2000 mg/kg/day, a level far exceeding expected real-world exposure.
- 4-MBC showed no skin irritation, sensitisation, or photosensitisation in human studies. 4-MBC was not a skin or eye irritant in rabbits or a skin sensitiser in guinea pigs.
- In a 90-day repeated-dose toxicity study in rats following oral administration of 4-MBC, effects on the thyroid were observed. Findings included adverse effects on thyroid function (increased serum thyroid-stimulating hormone [TSH], triiodothyronine [T3] and thyroxine [T4] levels), increased organ weight and histopathological findings of thyroid hypertrophy and epithelial hyperplasia at doses of ≥50 mg/kg/day. Similar effects were observed in shorter rat studies, while dogs exhibited no overt toxicity but had elevated T3/T4 levels. A no observed adverse effect level (NOAEL) of 25 mg/kg/day was established in this study. Following dermal dosing in rats, no systemic endocrine effects were observed at doses up to 400 mg/kg/day.
- The genotoxic potential of 4-MBC was evaluated in a bacterial mutagenicity assay, a mammalian mutagenicity assay *in vitro*, and in an *in vitro* chromosomal aberration assay. 4-MBC was negative for mutagenicity in guideline compliant studies. 4-MBC was negative in an *in vitro* chromosomal aberration assay, however it is noted that this study was not compliant with current The Organisation for Economic Co-operation and Development (OECD) guidelines and therefore the results are considered inconclusive. No *in vivo* studies have been conducted with 4-MBC. quantitative structure–activity relationship (QSAR) analysis performed independently by the Australian Industrial Chemicals Introduction Scheme (AICIS) using a range of models. Based on a weight of evidence analysis of the available *in vitro* and *in silico* data, the TGA considers that 4-MBC is unlikely to pose a genotoxic hazard.
- There are no carcinogenicity studies available for 4-MBC.
- A NOAEL of 30 mg/kg/day was established in reproductive toxicity studies in rats following oral dosing. No effects on reproductive performance were observed. Similar effects on the thyroid as seen in repeat dose toxicity studies were reported in adult animals treated with 4-MBC and in offspring of treated dams with a NOAEL for developmental toxicity established at 50 mg/kg/day. In other studies, 4-MBC was shown to affect gene expression and protein levels of endocrine-related receptors and growth factors in the brain, prostate and uterus in the offspring of treated dams. Altered sexual behaviour was also observed in female offspring of treated dams. However methodological limitations affect the interpretation and reliability of these results.
- The Danish Environmental protection agency (EPA) concluded in 2021 that 4-MBC is an endocrine disruptor via T- and E- modalities. Based on these findings the Danish EPA have submitted an Annex XV proposal to the European Chemicals Agency (ECHA) to classify 4-MBC as a substance of very high concern. This conclusion was supported by the Scientific Committee on Consumer Safety (SCCS) in their 2021 Opinion, stating: "there is sufficient evidence that 4-MBC may act as an endocrine disruptor, and have effects on both the thyroid and estrogen systems".
- In their 2021 opinion, the SCCS upheld a NOAEL of 25 mg/kg/day for 4-MBC, based on a 90-day oral repeat-dose toxicity study in rats. The TGA concurs with the SCCS's assessment that this study provides the most reliable basis for determining the oral NOAEL for risk assessment and is protective of both findings observed in the thyroid gland and in reproductive toxicity studies.

The limitations of this review are:

- The toxicological endpoints (NOAELs) were collected from published international safety assessment reports and scientific literature. As full data sets, including all raw study data, were not available for independent corroboration of the findings from these reports and literature, this review was dependent on the veracity of the details provided in those reports and literature.

- Consumer products other than sunscreens that contain 4-MBC were not considered in this review.
- The exposure to metabolites or impurities of the active ingredient has not been considered in this review.

Systemic exposure dose

The Australian Sunscreen Exposure Model (ASEM)[1] provides the maximum estimated daily sunscreen exposure for all possible scenarios assuming: 673 mg/kg/day (Method 1 of model) or 336 cm^2/kg/day (Method 2 of model) based on the most sensitive population (toddlers). These values are then corrected based on compound specific factors (e.g. extent of dermal absorption + concentration in solution [Model 1] or dermal absorption as µg/cm^2 [Method 2]). A dermal absorption value of 4.75 µg/cm^2 was obtained in experiments in human volunteers using a formulation containing 5% 4-MBC applied at a rate of 5 mg/cm^2. This study reported the dermal absorption of 1.9% based on 250 µg pure 4-MBC applied and 4.75 µg absorbed.

The maximum concentration of 4-MBC in products currently permitted in Australian sunscreens is 4%. In the absence of specific information on linearity of absorption to allow a pro-rata correction for other concentrations of 4-MBC, we have employed method 1 of the ASEM, for the systemic exposure dose (SED) calculation to estimate the margin of safety (MoS) without applying a correction to the dermal absorption %.

Additionally, it was noted that the rate of application in the dermal absorption study was 5 mg/cm^2. As we have mentioned previously, in the ASEM consultation outcomes[2], an application rate of >2 mg/cm^2 (which is the recommended application rate to achieve the labelled sun protection factor [SPF] rating) can cause variability in the risk quantification between method 1 and 2. Hence, in the absence of specific information regarding impacts of dose deposition on the amount absorbed, calculations for SED and MoS assume an application rate of 2 mg/cm^2. Assuming an application rate of 2 mg/cm^2 the dermal absorption value has been adjusted to 4.75% (based on 100 µg pure 4-MBC applied and 4.75 µg absorbed).

A MoS of 100 or more is generally considered safe under the specified use conditions for controlling the risks to human health and safety from the long-term use of the active ingredient by the Australian population.

Values used to determine SED and MoS are shown below:

- Oral NOAEL = 25 mg/kg/day (based on a 90-day oral repeat-dose toxicity study in rats). This is the lowest NOAEL observed in repeat-dose toxicity studies and is protective of thyroid effects observed in rats and findings observed in reproductive toxicity studies.
- Oral bioavailability to adjust the NOAEL = in the absence of data a default value of 50% was applied.[3]
- Systemic NOAEL adjusted for oral bioavailability = 12.5 mg/kg/day
- Dermal absorption (DA_a) = 4.75 µg/cm^2
- $ASEM_{\text{highest estimated daily sunscreen exposure}}$ (Method 2) = 336 cm^2/kg/day
- Dermal absorption (DA_p) = 4.75%
- $ASEM_{\text{highest estimated daily sunscreen exposure}}$ (Method 1) = 673 mg/kg bw/day

[1] Australian sunscreen exposure model. https://www.tga.gov.au/resources/publication/corporate-reports/australian-sunscreen-exposure-model

[2] https://consultations.tga.gov.au/tga/proposed-model-for-assessing-sunscreen-ingredients/

[3] SAG-CS Opinion 18: 4-Methylbenzylidene Camphor as a UV Filter in Cosmetic Products (2025)

- Highest concentration permitted in Australian sunscreens (C) = 4%

Using the following equation, an **SED** of **1.28 mg/kg bw/day** was determined for 4-MBC:

$$SED = ASEM_{(\text{highest estimated daily sunscreen exposure})} \times DA_p \times C$$

A MoS of 9.7 was determined using the following equation, with the NOAEL being the systemic NOAEL adjusted for oral bioavailability:

$$SED = ASEM_{(\text{method 1})} \times DA_p \times C$$

$$= 673\ mg/kg\ bw/day\ \times 4.75\ \% \times 4\ \% = 1.28\ mg/kg\ bw/day$$

$$MoS = \frac{NOAEL\ (mg/kg\ bw/day)}{SED\ (mg/kg\ bw/day)} = \frac{12.5\ mg/kg\ bw/d}{0.51\ mg/kg\ bw/d} = \mathbf{9.7}$$

DA_p: Dermal Absorption, C: Concentration

Therefore, for a general sunscreen product, the acceptable concentration of 4-MBC would be **0.39%**, based on the MoS calculation below.

4-MBC concentration for an acceptable SED and MoS using the ASEM method 1 (%)

$$SED = ASEM_{(\text{method 1})} \times DA_p \times C$$

$$= 673\ mg/kg\ bw/day\ \times 4.75\ \% \times 0.39\ \% = 0.124\ mg/kg\ bw/day$$

$$MoS = \frac{NOAEL\ (mg/kg\ bw/day)}{SED\ (mg/kg\ bw/day)} = \frac{12.5\ mg/kg\ bw/d}{0.124\ mg/kg\ bw/d} = \mathbf{100}$$

Margin of safety for risk assessment

An MoS value of 100 accounts for 2 safety/uncertainty factors of 10 each (interspecies differences and human variability)[4]. It is noted that in their 2022 opinion[5], the SCCS reduced the usual 100-fold uncertainty factor used in safety assessments to 25 when considering acceptable exposure.

The SCCS notes the following:

"When comparing the human and rat toxicokinetic data, the area under time-concentration curve (AUC) and maximum concentration (C_{max}) values in humans are lower than in rat, supporting the reduction of the toxicokinetic factor from 4 to 1. The SCCS therefore agrees to reduce the toxicokinetic factor from 4 to 1 as proposed in the previous Opinion. The SCCS considers the use of a safety factor of 1 appropriate for interspecies differences in toxicokinetics, whereas in the absence of substance specific data, a safety factor of 2.5 to account for interspecies differences in toxicodynamics will be used for MoS calculation (i.e. overall safety factor for interspecies differences

[4] WHO (2005). Chemical-specific adjustment factors for interspecies differences and human variability: guidance document for use of data in dose/concentration-response assessment

[5] SCCS opinion on 4-Methylbenzylidene Camphor (4-MBC) SCCS/1640/21

is 2.5). Combined with a factor of 10 to account for intra-human toxicokinetic and toxicodynamic differences, this leads to an overall MoS of 25 that will be used for safety calculations."

The SCCS opinion was based on estimating the repeated dose plasma levels for 4-MBC and its metabolites in humans, based upon the available single dose plasma levels and the amounts still present after 24 hours, allowing accumulation to be calculated. Values in humans were then compared to the plasma levels of 4-MBC and its metabolites in the rat at the no observed effect level (NOEL) instead of the NOAEL value (worst case).

In contrast, the Scientific Advisory Group on Chemical Safety of Non-Food and Non-Medicinal Consumer Products (SAG-CS) notes in their opinion on 4-MBC, "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."

In consideration of the points raised by the SCCS and SAG-CS, the TGA concurs with the opinion of the SAG-CS, that there are no adequate data to justify a reduction of the standard margin of safety of 100 for 4-MBC.

Further consideration for 4-MBC

If the use of a sunscreen product containing 4-MBC is applied to specific parts of the body e.g. the face only, the resultant MoS may increase. As shown in the two tables below, using ASEM method 2 and the absolute dermal absorption value of 4.75 µg/cm^2 for the determination of MoS, for application of a 4-MBC containing sunscreen product twice a day for 240 days per year or 365 days per year, respectively, the estimates are satisfactory for adults under limited conditions. The ASEM assumes that if a specific application scenario is acceptable for toddlers, it is acceptable for all family members. However, under all assessed conditions, the MoS values were below 100 in toddlers.

Annual use of 4-MBC considered for 240 days/year based upon Scenario 1 of the ASEM and DAa of 4.75 µg/cm^2

Scenario*	Skin Surface Area (cm^2)	Body weight (kg)	Reapplications (no. per day)	Annual use (days/year)	SED (mg/kg/day)	MoS
Face only (Toddlers)	500	13	2	240	0.24	52
Face + Hands (Toddlers)	900	13	2	240	0.43	29
Adult Face only	675	107	2	240	0.04	329
Adult Face + Hands	1875	107	2	240	0.11	116

*95th percentile for SSA body parts and total body weight (For Adult: average of male and female adult values combined.

Annual use of 4-MBC considered for 365 days/years based upon Scenario 1 of the ASEM and DAa of 4.75 µg/cm^2

Scenario*	Skin Surface Area (cm^2)	Body weight (kg)	Reapplications (no. per day)	Annual use (days/year)	SED (mg/kg /day)	MoS
Face only (Toddlers)	500	13	2	365	0.37	34
Face + Hands (Toddlers)	900	13	2	365	0.66	19
Adult Face only	675	107	2	365	0.06	217
Adult Face + Hands	1875	107	2	365	0.16	76

*95th percentile for SSA body parts and total body weight (For Adult: average of male and female adult values combined)

The concentration of 4-MBC that is low-risk in sunscreen products, if applied to specific areas of the body.

Scenario*	Concentration (%) 240 d/yr	Concentration (%) 365 d/yr
Toddler Face only	2.6	1.71
Toddler Face + Hands	1.45	0.95
Adult Face only	16.5	10.8
Adult Face + Hands	5.8	3.8

*95th percentile for SSA body parts and total body weight (For Adult: average of male and female adult values combined).

Recommendations

A MoS less than 100 was calculated for 4-MBC using the ASEM. As a result, 4-MBC is not deemed to present a low risk to human health and safety when used at the highest maximum permitted concentration of 4% in therapeutic sunscreens.

To mitigate the risk from chronic exposure to 4-MBC in therapeutic sunscreens, it is recommended that 4-MBC is listed in the Poisons Standard. To manage the potential risks associated with 4-MBC it is recommended that the entry restrict the use of 4-MBC in therapeutic sunscreens, giving consideration to the following:

OPTION 1

- 4-MBC can be deemed low-risk and appropriate for use in general therapeutic sunscreens for daily use at a concentration up to 0.39%.

OPTION 2

- Specific use sunscreens are likely to be used differently by consumers, such as daily application year-round restricted to specific parts of the body, compared with the use pattern for general sunscreens which are applied to larger parts of the body. Calculations for 240 days/year (based

on ASEM scenario 1 for indoor workers) and 365 days/year exposure assumptions have been provided above.

4-MBC can be deemed low-risk and appropriate for use in specific therapeutic sunscreens for daily use when:

– Used by adults only;

– Limited to face-only or face and hand application, not to the whole body; and

– At a reduced maximum concentration (between 3.8% and 16.5% of the product), depending on the types of products that are currently marketed and their directions for use.

OR

4-MBC can be deemed low-risk and appropriate for use in general therapeutic sunscreens for daily use by the whole family when:

– Limited to face-only or face and hand application, not to the whole body; and

– At a reduced maximum concentration (between 0.95% and 2.6% of the product), depending on the types of products that are currently marketed and their directions for use.

4-MBC can be a common ingredient in other products such as cosmetic sunscreens. Consideration should be given to potential exposure of 4-MBC from other sources. Use of specific warning statements or directions for use, and/or product packaging limitations to ensure appropriate use.

It is important to note that therapeutic sunscreens listed on the Australian Register of Therapeutic Goods contain different concentrations of 4-MBC (up to a maximum of 4%) with claimed SPF rating of 50+.

Disclaimer

Skin cancer is a major health issue in Australia. The Australasian College of Dermatologists recommends that daily sun protection should be used in Australia, particularly during the spring and summer months, where the UV index is often 3 or higher for nearly the entire day. In addition, the Cancer Council recommends Australians use SPF50 or SPF50+, broad-spectrum, water-resistant sunscreen. Given the widely recognised public health importance of sunscreens, Australians should continue to use sunscreens along with other sun protective behaviours when the UV index is 3 or more. The 5 SunSmart S's - slip, slop, slap, seek, slide are protective measures include seeking shade, wearing a hat, wearing protective clothing and eyewear and using sunscreen. This approach clearly supports the benefits of optimal sunscreen use, benefits which are substantial, and balanced against any theoretical risks.

Main body of report

Introduction

4-methylbenzlidene camphor is an organic camphor derivative used as a UVB filter in the 280–320 nm range in sunscreens products. Currently in Australia, 4-MBC is included in the Therapeutic Goods (Permissible Ingredients) Determination (No. 2) 2025 as an active ingredient in sunscreen products for dermal application and it is not to be included in medicines intended for use in the eye. The concentration of the medicine must not be more than 4%. When used in primary sunscreen

products, the following warning statements are required on the label: 'Avoid prolonged exposure in the sun' (or words to this effect); and 'Wear protective clothing - hats and eyewear when exposed to the sun' (or words to this effect).

This report focusses on the safety of 4-MBC as a sunscreen active and is dependent on peer reviewed publications investigating the safety and pharmacokinetics of 4-MBC.

Overseas Regulatory history

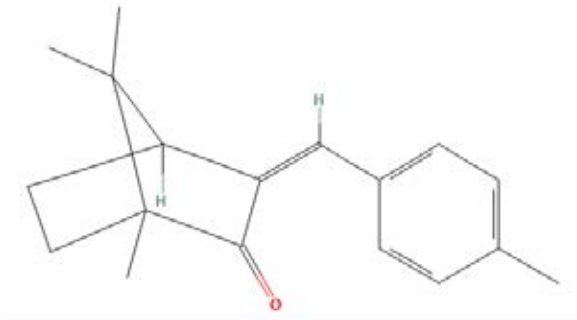
- 4-MBC is not registered in the US.[6]
- In the European Union (EU), 4-MBC in cosmetic products is being phased out, due to concerns about its potential as an endocrine disruptor. From 1 May 2025, products containing 4-MBC cannot be placed on the EU market, and from 1 May 2026, they cannot be sold within the EU. Additionally, 4-MBC has been removed from Annex VI of the EU Cosmetics Regulation, which lists approved UV filter.[7]
- 4-MBC is approved for use in Canada at concentrations up to 4%.[8]
- In the United Kingdom, new cosmetic products containing 4-MBC cannot be released into the market from 15 July 2026, and products containing 4-MBC cannot be sold from 15 January 2027.

Chemistry

The chemical properties of 4-MBC are shown below:

Chemical name	(3Z)-1,7,7-trimethyl-3-[(4-zethylphenyl) methylidene] bicyclo [2.2.1] heptan-2-one
CAS No.	36861-47-9
Form	Crystalline solid
Molecular weight	254.4 g/mol
Water solubility	1.08 ± mg/L at 20°C and pH 5-6 (practically insoluble in water)
Partition coefficient (Log PoW)	5.1 at 23°C
Boiling point	357°C at 101.3 kPa

Figure 1: Chemical structure of 4-MBC



[6] OTC Monograph Sunscreen Drug Products for Over-the-Counter Human Use; 2021

[7] Regulation - EU - 2024/996 - EN - EUR-Lex

[8] Primary Sunscreen Monograph

Data sources

This safety evaluation is based primarily on the following sources:

- Scientific Committee on Cosmetic Products and Non-food Products Intended for Consumers (SCCNFP) opinion published in 2004[9]
- Scientific Committee on Consumer Safety opinion published in 2006[10], 2008[11] and revised in 2021[5]
- ECHA — Member state committee support document for identification of 4-MBC as a substance of very high concern because of its endocrine disruption properties - adopted on 29 November 2021[12]
- Literature search in PubMed (search strategy detailed in Appendix)

Pharmacokinetics and toxicology

Pharmacokinetics

Percutaneous absorption

Dermal absorption of 4-MBC was assessed using female pig skin samples across eight experiments. The skin was exposed for 24 h to a concentration of 4% 4-MBC (178 µg/cm²) in a cosmetic sunscreen formulation. No 4-MBC was detected in the receptor fluid; however, supporting data for this finding were not provided. Full study reports were unavailable, and due to concerns regarding the methodology and lack of access to raw data, the SCCS[8] calculated a dermal absorption value assuming that a non-detectable amount of approximately 0.1 µg/cm² of the applied 4-MBC in the receptor fluid (or dermis) was consistent with the analytical data, (considering the assay's lowest limit of quantification of 0.1 µg/mL) and using 2 SDs. The dermal absorption was calculated as shown in the table below.

Table 1 Dermal absorption of 4-MBC in porcine skin samples.

	Mean	SD	Mean + 2SD
Epidermis	1.5 µg/cm^2	0.7 µg/cm^2	2.9
Dermis	0.46 µg/cm^2	0.36 µg/cm^2	1.18
Receptor fluid	Not detected	-	0.1
Dermal Absorption	1.96 µg/cm^2	-	4.18 µg/cm^2

Dermal absorption of 4-MBC has also been investigated in human volunteers. In the first study, six healthy male volunteers received a 5% ^{14}C-labelled 4-MBC in an oil-in-water formulation, applied at 1 g over 200 cm² of shaved forearm skin for 6 h without occlusion. After washing with soap and water, low recovery of radioactivity was observed, likely due to the poor water solubility of the compound. The authors estimated percutaneous absorption at 0.9% (2.25 µg/cm²), though an analysis by the SCCP suggested the value closer to 1.9% (**4.75 µg/cm²**) in humans and this dermal absorption value is used in the current evaluation. In a second study involving four subjects, the same method was

[9] SCCNFP opinion concerning 4-Methylbenzylidene Camphor
[10] SCCP opinion on 4-Methylbenzylidene Camphor SCCP/1042/06
[11] SCCP opinion on 4-Methylbenzylidene Camphor (4-MBC) SCCP/1184/08
[12] ECHA: Annex XV report

used as above, but rinsing was performed with xylene/ether, improving recovery to approximately 90%. Absorption was calculated at 0.53% ± 0.26 (1.3 µg/cm²). A third report combined data from the previous two studies and estimated average percutaneous absorption at 0.75% ± 0.21, equivalent to 1.9 µg/cm². However, due to inconsistencies between the reported figures and earlier data, this study was considered unreliable and excluded form evaluation. An overview of dermal absorption studies with 4-MBC is shown in the table below:

Table 2 Overview of the dermal absorption data for 4-MBC

Species	Exposure (h)	Experimental System	DAa (µg/cm^2)
Human	6	Healthy volunteers; n = 6	4.75
		Healthy volunteers; n = 4	1.3
Pig	24	*In vitro*, porcine skin samples	1.96
			4.18*

* = SCCP 2008 values (+2SD)

Toxicokinetics

The pharmacokinetics parameters of 4-MBC following single oral (rat) or dermal (comparative study in rat and human)[13] administration has been evaluated by SCCP in 2006[10] and 2008[11] and by Greis *et al.* (2022)[14].

In rats following single oral administration (Table 3), exposure (C_{max}) was greater in males than in females and the half-life was ~15 h, with time to maximum concentration (T_{max}) between 8 to 10 h post-dose. Exposure to 4-MBC, and its metabolites were dose proportional in rats following dermal application, with no significant sex differences observed (Table 4).

Table 3. Mean concentration of 4-MBC, metabolite 1 and metabolite 2 (pM) in rat plasma (*n*=3/sex/dose) following single oral administration of 4-MBC

Time (h)	25 mg/kg						250 mg/kg					
	4-MBC		M1		M2		4-MBC		M1		M2	
	♀	♂	♀	♂	♀	♂	♀	♂	♀	♀	♂	♂
0	-	-	-	-	-	-	-	-	-	-	-	-
3	22	17	-	-	21597	13743	123	69	-	-	99296	80903
6	30	11	-	-	18764	12376	147	131	-	-	115873	88850
9	37	3	-	-	19278	10354	217	81	-	-	123418	86821
24	20	-	-	-	15727	-	173	108	-	-	73087	22140
48	8	-	-	-	4510	-	32	124	-	-	29862	-
96	8	-	-	-	-	-	4	26	-	-	1308	-

M1 = metabolite 1; M2 = metabolite 2; 4-MBC = 4-methylbenzylidene camphor; - = not detected

[13] Schauer U.M., Völkel W., Heusener A., Colnot T., Broschard T.H., von Landenberg F. *et al.* (2006) Kinetics of 3-(4-methylbenzylidene)camphor in rats and humans after dermal application. *Toxicol. Appl. Pharmacol.* **216:** 339–346.

[14] Gries W *et al.* (2024) 3-(4′ -Methylbenzylidene)camphor (4-MBC) – Determination of 3-(4′ -carboxybenzylidene)camphor and 3-(4′ -carboxybenzylidene) hydroxycamphor in urine by UPLC-MS/MS. Biomonitoring Method – Translation of the German version from 2024. *MAK Collect Occup Health Saf.* 2024 Sep;9(3):Doc080 bi3686147e9_3or.pdf

Table 4. Mean concentration and $AUC_{0.5\text{-}96h}$ of 4-MBC, metabolite 1 and metabolite 2 in rat plasma following single dermal administration of 4-MBC (mean values; *n*=3/sex/dose)

Time (h)	Concentration (pM)											
	400 mg/kg ^						2000 mg/kg ^^					
	4-MBC		M1		M2		4-MBC		M1		M2	
	♀	♂	♀	♂	♀	♂	♀	♂	♀	♂	♀	♂
0.5	15	34	-	-	73	45	60	101	-	-	139	137
1	43	68	-	-	185	156	170	230	2	29	467	589
3	125	133	-	33	766	715	502	595	13	126	3060	2764
6	213	219	7	166	1683	1852	1032	932	72	734	7820	6067
24	211	233	44	1111	8162	5197	1181	1050	322	5590	35070	21514
48	82	96	153	3540	18838	10880	504	1035	792	17900	51761	36444
72	32	35	53	740	11489	3535	217	366	699	16600	42641	37500
96	-	-	16	423	5345	1844	51	83	697	4013	54542	13901
	AUC0.5-96h (nmol/mL *h)											
-	10.8	12.0	5.9	119.5	983.9	494.0	55.2	70.6	50.9	1046.2	3813.7	2579.0

M1 = metabolite 1; M2 = metabolite 2; 4-MBC = 4-methylbenzylidene camphor; ^= 4% 4-MBC/36cm^2; ^^= 20% 4-MBC/36cm^2,

Following repeated dermal administration in rats at doses of 0, 100, 400, and 2000 mg/kg/day, lower levels of 4-MBC were observed in rats after 90 days of exposure compared to single exposure, alongside the opposite trend seen for the metabolite 1 (M1) and metabolite 2 (M2). These results suggest enzyme induction following repeated dosing. The plasma concentrations of 4-MBC and its metabolites are presented in the table below.

Table 5 Concentration of 4-MBC and metabolite 1/2 in rats (*n* = 3) following repeated dermal administration

Dose (mg/kg/day)	Time point	$AUC_{0.25\text{-}24\ h}$ (pmol/mL·h)					
		4-MBC Female	4-MBC Male	M1 Female	M1 Male	M2 Female	M2 Male
100	Day 1	10741	11615	6884	18232	339778	145792
	Day 90/91	4635	2645	10652	45882	1085003	270198
400	Day 1	34928	16666	7680	21233	502911	210936
	Day 90/91	29535	21458	23270	110104	2520350	1007126
2000	Day 1	142255	124099	21627	53533	2573155	671095
	Day 90/91	No data					

h = hour; M1 = metabolite 1; M2 = metabolite 2; 4-MBC = 4-methylbenzylidene camphor

The kinetics of 4-MBC were studied in humans after a single dermal application of a sunscreen containing 4% 4-MBC. Sunscreen was applied to 90% of the body surface of six volunteers (3 males, 3 females), resulting in a mean dermal dose of 22.0 ± 1.3 mg/kg.[13] Peak plasma levels of 4-MBC were greater in females compared to males, despite dose normalisation to body surface area (Table 6). This suggests potential variations in absorption, possibly influenced by differences in fat distribution, although the underlying cause remains unclear; T_{max} was the same in both sexes (6 h). The half-life of

4-MBC following dermal administration was ~9 h, while the half-lives of metabolites M1 and M2 ranged from 20 to 31 h, and were generally longer in men compared to women.

The potential for 4-MBC to interfere with drug metabolism was investigated by Qusa *et al.* (2024)[15]. In human liver microsomes, 4-MBC exhibited inhibitory activity only against CYP2C9, with a half maximal inhibitory concentration (IC_{50}) value reported as 14.76 µM. However, the basis for this IC_{50} determination is unclear, as the maximum tested concentration listed in the supplementary information was only 11.79 µM (Supplementary file1[16]). Across the tested concentration range (0.047–11.79 µM), no significant inhibition (≥50%) was observed for any of the evaluated enzymes or transporters. Based on the maximum *in vitro* concentration tested (11.79 µM), meaningful pharmacokinetic interactions are not expected following dermal administration of 4-MBC, as this level far exceeds the estimated plasma free C_{max} of 0.08 pM.[17] 4-MBC had no effects on uptake transporter assays employing transfected cell lines expressing organic anion transporter 3, organic cation transporter 2 and organic anion transporting polypeptide 1B1.

Table 6 Mean concentration (pM) of 4-MBC, metabolite 1 and metabolite 2 in human plasma and urine following single dermal administration of 4-MBC (*n* = 3/sex)

Plasma							Urine						
Time (h)	4-MBC		M1		M2		Time (h)	4-MBC		M1		M2	
	♀	♂	♀		♀	♂		♀	♂	♀	♂	♀	♂
0	-	-	–	-	-	-	0	-	-	-	11	-	7
0.5	23	17	-	-	-	-	8	-	-	1947	2197	523	687
1	14	60	-	-	15	5	16	-	-	3352	5196	827	1395
2	74	95	9	19	59	45	24	-	-	2417	3387	733	1290
4	98	161	30	13	121	109	32	-	-	2271	4551	542	696
6	100	200	38	45	136	184	40	-	-	1319	2115	242	259
8	97	186	37	58	124	206	48	-	-	1036	1096	292	334
12	87	152	47	70	129	211	56	-	-	946	1783	200	237
24	12	51	47	83	65	111	64	-	-	675	1012	161	108
36	-	21	15	15	38	46							
48	-	-	9	17	26	35	72	-	-	550	772	117	260
60	-	-	4	5	19	32							
72	-	-	3	12	15	25	80	-	-	473	1100	51	114
84	-	-	3	9	12	20	88	-	-	310	732	25	104
96	-	-	5	11	10	20	96	-	-	341	545	74	208

M1 = metabolite 1; M2 = metabolite 2; 4-MBC = 4-methylbenzylidene camphor; - = not detected

In both rats and humans, 4-MBC undergoes hydroxylation, forming 3-(4′-hydroxymethylbenzylidene) camphor, a benzyl alcohol intermediate leading to two major metabolites: M1 (3-(4-carboxybenzylidene)-6-hydroxycamphor; cx-MBC-OH) and M2 (3-(4-carboxybenzylidene)-camphor; cx-MBC) and their glucuronides. Following oral administration of 4-MBC, metabolite M1 was below the quantification limit in plasma. The parent drug was detected at relatively low levels — approximately 500-fold lower than the peak plasma concentrations of M2. Similarly low plasma 4-MBC were observed following dermal application, though both M1 and M2 metabolites were detected

[15] Qusa M., Qosa H. and Volpe D.A. (2024) Evaluation of In Vitro Metabolism- and Transporter-Based Drug Interactions with Sunscreen Active Ingredients. *Pharm. Res.* **41:** 1613–1620.

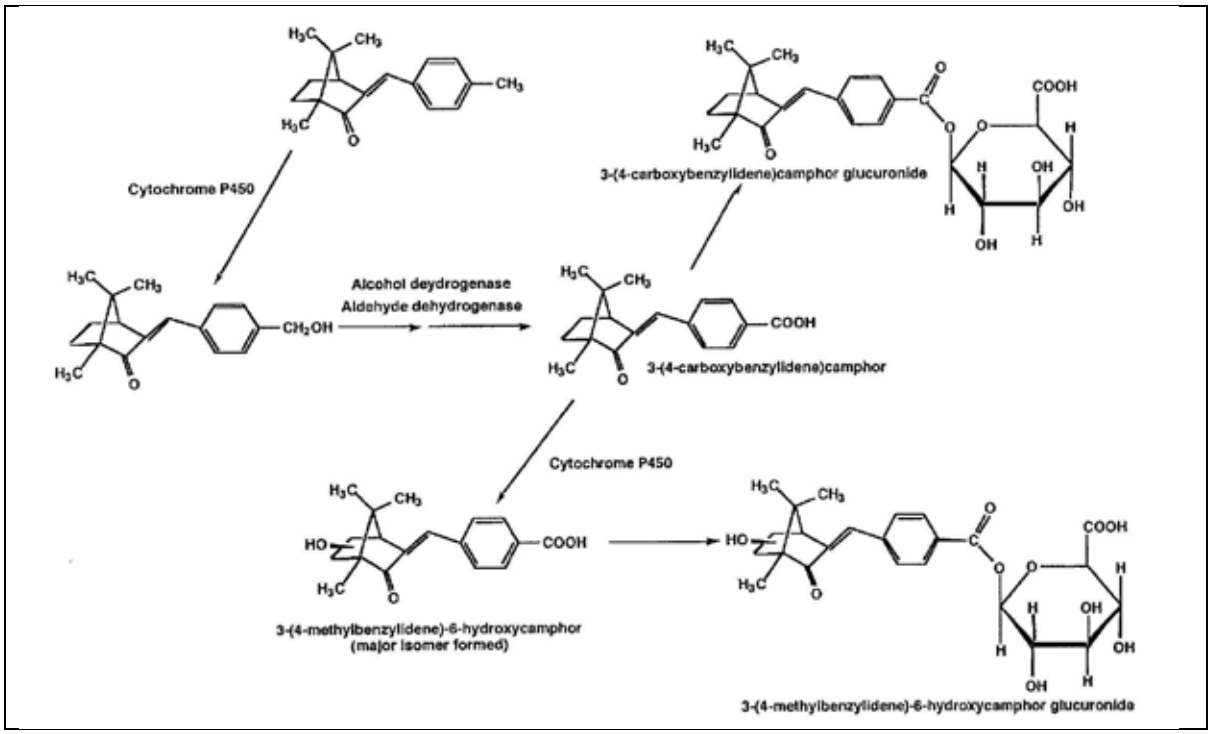
[16] 11095_2024_3746_MOESM1_ESM.pdf

[17] Based on C_{max} in male volunteers after a single dermal dose of 4-MBC and unbound plasma protein fraction of 0.04% (free C_{max} = 200 pM × 0.04%/100% = 0.08 pM)

in the circulation. The relatively low plasma levels of 4-MBC compared to M1 or M2 metabolites suggest that the orally administered drug undergoes extensive first-pass metabolism in the liver. Similar trend (levels of 4-MBC and M1 compared to M2 levels) observed in rats and humans following dermal application indicating a comparable metabolism between the two species.

The proposed metabolic pathway of 4-MBC is shown below:

Figure 2 Proposed metabolic pathway of 4-MBC in rat and human *(adopted from Schauer et al. 2006)*[18]



Urinary excretion was a minor elimination pathway for 4-MBC following oral administration, as the majority of the dose was recovered in faeces (Table 7). Although glucuronide conjugates of the two major 4-MBC metabolites were also detected in faecal samples, they were not quantified due to partial degradation during sample processing. Less than 1% of the applied dose of 4-MBC was recovered in urine of human volunteers following dermal administration. 4-MBC was not detected in human urine after dermal application, nor in rat urine following oral administration, suggesting limited renal elimination of the parent compound. Urinary metabolites were detected in part as glucuronide conjugates. The relatively slow urinary excretion and low recovery of 4-MBC metabolites in urine may be attributed to the enterohepatic recirculation of glucuronide conjugates.

Table 7 Mean (*n* = 3) recovery data of 4-MBC in excreta following oral administration

4-MBC	Female				Male			
	25 mg/kg		250 mg/kg		25 mg/kg		250 mg/kg	
	µM	% of dose	µM	% of dose	µM	% of dose	µM	% of dose
Applied	19	100	234	100	28	100	416	100
Urine	0.9	4.8	28	12	0.6	2.3	36	8.6

[18] Schauer U.M., Völkel W., Heusener A., Colnot T., Broschard T.H., von Landenberg F. *et al.* (2006) Kinetics of 3-(4-methylbenzylidene)camphor in rats and humans after dermal application. *Toxicol. Appl. Pharmacol.* **216:** 339–346.

4-MBC	Female				Male			
	25 mg/kg		250 mg/kg		25 mg/kg		250 mg/kg	
	µM	% of dose	µM	% of dose	µM	% of dose	µM	% of dose
Faeces	ND	ND	103	44	ND	ND	216	52
Total	-		131	56	-		252	61

ND = – not detected; 4-MBC = 4-methylbenzylidene camphor

Li *et al*. (2023)[19] employed a physiologically based kinetic (PBK) modelling integrating both *in vitro* and *in silico* data to characterise the pharmacokinetics of highly protein-bound UV filters, including 4-MBC. The novel *in vitro* data included blood partitioning assays using whole human blood to determine the blood-to-plasma concentration ratio (R_{bp} = 0.88), cross-filtration techniques to assess plasma protein binding and calculate the fraction unbound (F_{up} = 0.04%), and metabolic stability studies in primary human hepatocytes in suspension to estimate hepatic clearance (Cl = 30 µL/min/million cells – scaled to 216 l/h/kg liver). The skin permeability coefficient was calculated based on dermal absorption values adopted from Sasson *et al*. (2009)[20]. The model was validated against human dermal pharmacokinetic data from Schauer *et al*. (2006)[1813], showing agreement with observed plasma concentration profiles (see Figure 3 and Table 8 below).

Figure 3. Comparison between observed (dot, mean) and PBK simulated (solid curve, mean) plasma concentration time profiles in female (A) and male (B) human subjects after dermal application of a sunscreen formulation containing 4% 4-MBC (~22 mg/kg). The shaded area represents the 90th percentiles of human population simulation.

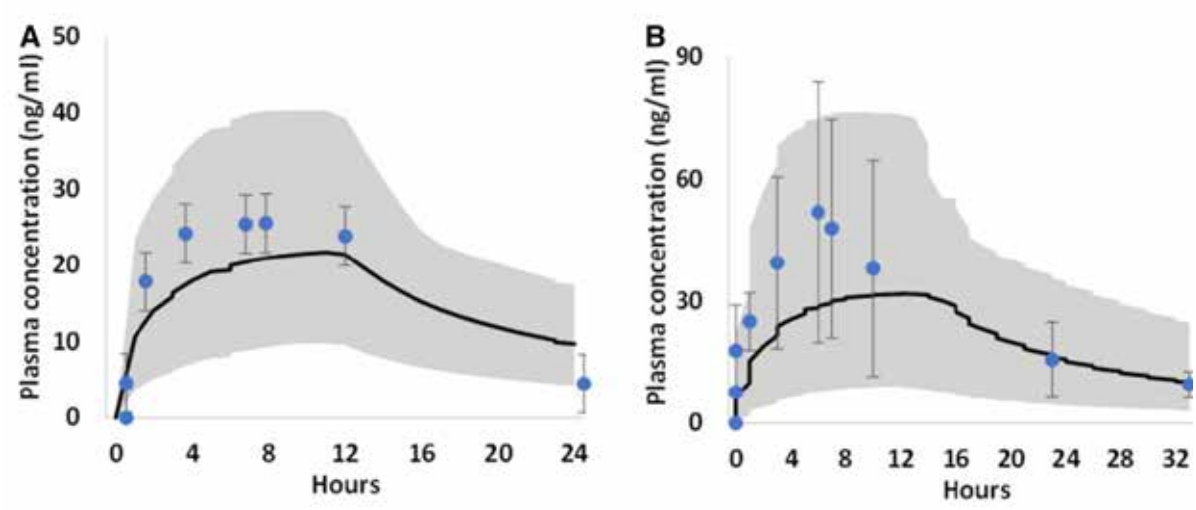


Table 8 Simulated and observed plasma concentrations of 4-MBC (C_{max} and AUC_{0-t}) in humans

Dose (mg/kg)	Sex	C_{max} (ng/mL)		AUC_{0-t} (ng·h/mL)	
		Observed	Predicted	Observed	Predicted
22	Female	25.5 [0.1 µM]	21.7 [0.085 µM]	485.6	373.8

[19] Li H., Bunglawala F., Hewitt N.J., Pendlington R., Cubberley R., Nicol B. *et al.* (2023) ADME characterization and PBK model development of 3 highly protein-bound UV filters through topical application. *Toxicol. Sci.* **196:** 1–15.

[20] Sasson, C.S., Sato, M.E., da Silva Beletti, K., Mota, F.C., and Piaceski, A.D. (2009). Influence of cosmetics vehicles on 4-methylbenzylidene-camphor's skin penetration, in vitro. Brazilian Archives of Biology and Technology *52*, 299–303.

Dose (mg/kg)	Sex	C_{max} (ng/mL)		AUC_{0-t} (ng·h/mL)	
		Observed	Predicted	Observed	Predicted
	Male	51.9 [0.2 µM]	31.8 [0.125 µM]	987.9	583.5

C_{max} = maximum concentration; AUC_{0-t} = area under time concentration curve from 0 to t; t = 24 h female, 36 h male; all data presented as geometric mean

Table 9 Human tissue: simulated plasma partition coefficient

Tissue	Coefficient
Adipose	2.18
Brain	1.52
Heart	0.66
Kidney	0.81
Liver	1.08
Lung	0.49
Muscle	0.81
Red Marrow	1.46
Rest of Body	0.83
Skin	0.89
Yellow Marrow	2.18

Overall, PBK modelling in humans underestimated the observed C_{max} and AUC for 4-MBC.

In summary, the limited and fragmented pharmacokinetic data suggest a broadly similar pharmacokinetic profile of 4-MBC in rats and humans.

Toxicology

Acute toxicity

Based on available date, 4-MBC has low acute oral toxicity. Oral LD_{50} values were 10000 mg/kg in mice and rats and > 5000 mg/kg in dogs. 4-MBC had low acute dermal toxicity in rats with an LD_{50} of > 2000 g/kg, with no deaths or clinical signs of toxicity or local irritation observed. The acute inhalational toxicity of 4-MBC has not been examined.

Repeat-dose toxicity

The nonclinical assessment of 4-MBC conducted by the SCCP in 2004 comprised two pilot studies in rats (up to 28 days, with oral doses up to 1000 mg/kg/day; *n* = 10 per sex per dose) and two studies in beagle dogs: a 14-day oral tolerability study with escalating doses (up to 2500 mg/kg on day 4, followed by 500 mg/kg/day from days 5–14; *n* = 1 per sex per dose), and a 3-week oral toxicity study incorporating a wash-out phase (up to 500 mg/kg/day; *n* = 2 per sex per dose). The authors concluded that no treatment-related effects were observed in dogs, although total T3 and total T4 levels tended to be consistently higher post-exposure compared to pre-dose values. Histopathology was not examined. A NOAEL could not be determined in these pilot studies

Rats exhibited notable endocrine and organ weight changes. Serum TSH levels were elevated in the 300 mg/kg/day group—1.9-fold in females and 7.5-fold in males relative to controls. At 1000 mg/kg/day, serum T3 levels increased by up to 196%, while serum T4 levels decreased by ~70% in both sexes. Additionally, the relative weight of the prostate was significantly reduced at all examined dose levels, with decreases of 82% and 75% at 30 and 300 mg/kg/day, respectively; data for the 1000 mg/kg/day group was not reported.

In a pivotal 90-day oral toxicity study in rats at doses of 0, 25, 50, 125 and 312 mg/kg/day, conducted in 2 parts, adverse effects on thyroid function were observed and a statistically significant increase in serum T3 levels (exact fold change not reported) was noted at doses of ≥ 50 mg/kg/day. Additionally, a dose-dependent increase in serum TSH was observed in both sexes (≥ 50 mg/kg/day), reaching up to 3.5-fold compared to controls. T4 levels were elevated in males and females at 312 mg/kg/day (up to 46% *cf.* controls). Histopathological examination revealed dose-related thyroid hypertrophy and epithelial hyperplasia in most animals at 50 mg/kg/day. These findings correlated with increased thyroid weights at doses of 125 and 312 mg/kg/day across sexes. Statistically significant increases in liver weight were observed in females at 125 mg/kg/day and males at 312 mg/kg/day. Spleen weights were also increased in both sexes, while a reduction in prostate weight was noted in males at the highest dose. An oral NOAEL was established at 25 mg/kg/day. The TGA agrees with the ECHA conclusion that "*The study provides strong evidence of adverse effects on thyroid hormone signalling as well as on prostate weight, after prolonged adult exposure to 4-MBC*."

In a dermal repeated dose toxicity study conducted over 90 days in rats, 4-MBC was applied topically to a 25 cm^2 area of shaved skin at doses of 0 (control), 100, 400, or 2000 mg/kg/day (*n* = 19–24/sex/dose) using a daily 6-hour semi-occlusive exposure. No systemic signs of toxicity were observed; however, dose-dependent local skin reactions were observed. The highest dose group (2000 mg/kg/day) exhibited severe dermal effects—including erythema, scaling, scabbing, epidermal lesions, oedema, necrosis, and discharge—leading to early termination on Day 15, while the 400 mg/kg/day group showed no treatment-related pathological findings. Histopathological analysis revealed no changes in thyroid tissue, and serum levels of TSH, total T3, and total T4 remained unaffected in the lower dose groups. 4-MBC was absorbed and metabolised into its two major metabolites after dermal application in a dose-dependent manner. The study was deemed high quality and reliable without restrictions by ECHA, with a dermal NOAEL established at 400 mg/kg/day.

Genotoxicity and carcinogenicity

The genotoxic potential of 4-MBC was evaluated by the SCCNFP in 2004[9] in a bacterial mutagenicity assay (Ames test), a mammalian mutagenicity assay *in vitro*, and in an *in vitro* chromosomal aberration study in Chinese hamster V79 cells. No *in vivo* studies were conducted.

In a GLP-compliant Ames test, there was no evidence of mutagenicity, either with or without metabolic activation. In contrast, Zhang *et al*. (2021)[21] investigated the mutagenic potential of 4-MBC at concentrations up to 2500 µg/plate. The compound exhibited mutagenicity in *S. typhimurium* strains TA97, TA98, and TA102, both with and without metabolic activation. However, no mutagenic effects were observed in strain TA100 under the same conditions. Neither positive controls nor *E. coli* strains were included in the study, which limits the interpretability of the results and therefore the regulatory value of this study is limited.

In a mammalian gene mutation study using Chinese hamster V79 cells, no relevant or reproducible increase in mutant colony numbers per 1 million cells was observed, with or without metabolic activation. Based on these results, 4-MBC was considered non-mutagenic in this study.

An *in vitro* chromosomal aberration study was also conducted in Chinese hamster V79 cells under GLP conditions, with and without metabolic activation. Cytotoxicity was observed at 36 µg/mL in cultures without S9. A slight increase in the percentage of chromosomal aberrations was noted after 7

[21] Zhang J., Pei Z.T., Zhao Y.N., Zhang M., Zhang L.L., Wang W.Q. *et al.* (2021) Mutagenicity evaluation to UV filters of benzophenone-6, benzophenone-8, and 4-methylbenzylidene camphor by Ames test. *PLoS One* **16:** e0255504.

and 28 h of exposure at the highest dose in the presence of S9 mix. This finding was not concentration dependant, and the study was evaluated as negative. When re-evaluated by the SCCS in 2022[5], the study was considered inconclusive, as it did not meet the acceptance criteria outlined in the current OECD Test Guideline 473 (adopted in 2016). Specifically, the study used only a 4 h exposure with and without S9 metabolic activation. This deviates from the current recommendation, which requires both a 4-hour exposure (±S9) and a 24-hour exposure without S9. In the absence of further information, the SCCS[5] were not able to make a conclusion on the genotoxicity potential of 4-MBC. This conclusion was supported by SAG-CS in their opinion on 4-MBC[3].

In silico QSAR analysis for 4-MBC was performed independently by AICIS in May 2026 using OASIS-TIMES (v2.31.2), DEREK Nexus (v6.3.0) and Danish QSAR battery (v1.0) models (Appendix). 4-MBC was predicted to be negative for chromosome aberration by the Danish QSAR battery model. An equivocal result for the alerting group 309 alpha,beta-unsaturated ketone was detected using DEREK Nexus. The alert description states that “in general, the class does not show activity *in vivo*”. Predictions using OASIS TIMES were outside the applicability domain of the model. Based on a weight of evidence analysis of the available *in vitro* and *in silico* data, the TGA considers that 4-MBC is unlikely to pose a genotoxic hazard.

4-MBC (doses not specified in SCCNFP report) did not induce photomutagenic effects in *S. typhimurium* strains TA 102 and TA 1537 or in *E. coli* under UVA/UVB exposure. 4-MBC (1-6.6 µg/mL) was not photoclastogenic in CHO-K5 cells exposed to UVA/UVB light in an appropriately validated assay.

There are no carcinogenicity studies available for 4-MBC.

Reproductive and developmental toxicity

In 2006[10], the SCCP evaluated the effects of 4-MBC on reproductive function based on two *in vivo* studies in rats and one study using fertilised hen eggs. A separate study in rabbits, involving doses up to 100 mg/kg/day, was disregarded due to methodological limitations—specifically, the unusually low number of test animals and the use of an unsuitable vehicle.

In fertilised hen eggs, no toxic or teratogenic effects were observed in surviving chicks hatched from eggs (*n* = 20/dose) injected with up to 10 mg/egg of 4-MBC on either the first or fifth day of incubation. A no-effect level of 0.1 mg/egg was identified for both injection timings.

In Wistar rats (*n* = 25/ dose) treated with 4-MBC (0, 10, 30, 100 mg/kg/day orally [PO]) over gestation day 6 to 16, reduced ossification of the sternum in pubs of both sexes was observed from doses of 30 mg/kg/day. Additionally, delayed ossification of extremities was observed in male fetuses at 100 mg/kg/day. A dose-dependent increase in rudimentary lumbar ribs was noted across both sexes. No teratogenic effects were observed. While maternal stress was suggested as a contributing factor, the initial NOAEL for embryofetal development was determined to be 10 mg/kg/day PO. However, the SCCP's revision of the original study in 2008[11] and 2022[5], concluded that the observed effects lacked statistical significance and were not clearly attributable to the test substance. As a result, the findings were considered secondary to maternal stress, and the NOAEL for both maternal and embryofetal toxicity was revised to 30 mg/kg/day PO.

In a one generation reproductive toxicity study, female rats were treated with 4-MBC (0, 12.5, 25, 50 mg/kg/day PO) for 28-day during the premating period, and during mating, gestation, and lactation (84 days of exposure)[9,12]. Male rats (F_0) and offspring (F_1) were not directly exposed. There were no treatment related findings on reproductive endpoints in treated dams. Necropsy of dams on post-natal day (PND) 22 revealed no significant histopathological changes. While thyroid weights increased by up to 19% in dams at 50 mg/kg/day and uterus weights showed a slight dose-dependent increase (~8%), these changes were not statistically significant. T3, TSH, and prolactin levels were within historical control ranges. Follicle-stimulating hormone (FSH) levels in dams at 50 mg/kg/day increased by 3.6-fold compared to controls, while luteinizing hormone (LH) levels were elevated by 16- and 34-fold at doses of 12.5 and 25 mg/kg/day, respectively. However, due to high inter-animal variability, these differences were not statistically significant. F_1 offspring showed a minor delay in vaginal opening in treatment groups, with no changes in male developmental milestones (testes descent,

preputial separation). Water maze testing revealed no cognitive deficits, though interpretation was limited by binary scoring and lack of sex-specific analysis. At PND22, male organ weights showed no statistically significant changes, although thyroid weights exhibited a dose-related increase of up to 33%, despite only a minimal increase in body weight, and seminal vesicle body relative weights showed a non-significant decrease (-16%) in males at 50 mg/kg/day. Male reproductive organs were unaffected. Significant increases in ovary weights (~25%) were observed in females at doses of 25 and 50 mg/kg/day, whereas uterus weights were significantly reduced (−39%) at 50 mg/kg/day. These effects were generally reversible, and by PND55, no treatment-related changes were detected in reproductive or thyroid organs in either sex. No treatment-related histopathological changes were reported. At PND55, TSH and T3 levels were slightly but significantly reduced in males (−16%) at 50 mg/kg/day, while changes in females were minor and not statistically significant. There were no treatment-related effects on T4 and female reproductive hormones (estradiol [E2], LH, prolactin). FSH levels declined by 61% in females at 50 mg/kg/day, though the change was not statistically significant due to individual animal variability. In males, FSH (-27% and -56% at 25 and 50 mg/kg/day, respectively) and LH levels (-20 – 34%) decreased in a dose-dependent manner, with FSH reaching statistical significance at 50 mg/kg/day but were considered incidental. ECHA noted that the relatively low maximum dose tested, and certain methodological limitations prevented definitive conclusions regarding the endocrine-disrupting potential of 4-MBC. The SCCP established a NOAEL of 50 mg/kg/day PO for systemic toxicity in dams and developmental toxicity, a position supported by the TGA, which agreed that the observed findings were generally reversible and lacked histopathological correlates.

In a series of modified one-generation reproductive and developmental toxicity studies, Long Evans rats, were treated with 4-MBC in at doses of 0.01, 0.1, 0.33 and 0.66 g/kg chow (equivalent to 0.7, 7, 24 and 47 mg/kg/day) for 28 days prior to mating, with females also treated during gestation and lactation. F_1 offspring were treated into adulthood. Results were reported in four publications by Durrer *et al*. (2005[22], 2007[23]) and Maerkel *et al.* (2005[24], 2007[25]). It is unclear whether the publications report endpoints from the same animal experiment or present findings from independent studies. This ambiguity represents a significant limitation, reducing the reliability of the evidence and for the purposes of this assessment, the publications have been treated as a single animal study. The key findings have been consolidated into the table below.

[22] Durrer S, Maerkel K, Schlumpf M, Lichtensteiger W. Estrogen target gene regulation and coactivator expression in rat uterus after developmental exposure to the ultraviolet filter 4-methylbenzylidene camphor. Endocrinology. 2005;146(5):2130-2139.

[23] Durrer S, Ehnes C, Fuetsch M, Maerkel K, Schlumpf M, and Lichten-steiger W. Estrogen Sensitivity of Target Genes and Expression of Nu-clear Receptor Co- Regulators in Rat Prostate after Pre- and Postnatal Expo-sure to the Ultraviolet Filter 4-Methylbenzylidene Camphor. Environmental Health Perspectives. 2007; 115:42-50.

[24] Maerkel K, Lichtensteiger W, Durrer S, Conscience M, and Schlumpf M. Sex- and region-specific alterations of progesterone receptor mRNA levels and estrogen sensitivity in rat brain following developmental exposure to the estrogenic UV filter 4-methylbenzylidene camphor. Environmental Toxicology and Pharmacology. 2005; 19:761-765.

[25] Maerkel K, Durrer S, Henseler M, Schlumpf M, and Lichtensteiger W. Sexually dimorphic gene regulation in brain as a target for endocrine disrupters: Developmental exposure of rats to 4- methylbenzylidene camphor. Toxicology and Applied Pharmacology. 2007. 218:152-165.

Table 10 The effect of 4-MBC on F_1 rats following pre- and postnatal exposure

Rat (Long Evans) (F_0 – 5- to 6-week-old) ♂ and ♀ were treated for 10 weeks before mating; treatment continued throughout pregnancy and in the F_1 offspring until adulthood, F_1 animals were terminated on week 12 (*n* = 6-9/dose) **Estrogen challenge** (*n* = 8/treatment): F_1 animals were gonadectomized on week 10 and following 2-week recovery (week 12) were injected (SC) with E2 (estradiol-17β; 10, 50 µg /kg) and euthanised after 6 h. **Dose:** 0.01, 0.1, 0.33 and 0.66 g/kg chow equivalent to 0.7, 7, 24, 47 mg/kg/day (LD, MD1, MD2, HD respectively) Changes are presented relative to controls	
Source	Major Findings in F_1 offspring
Durrer *et al*., 2005	Body weight (♀): No treatment related effects Uterine weight (body relative): ↓ at MD2 (by ~12%, no effect at HD) Uterine mRNA expression: ↓ progesterone receptor (PR) (by up to ~50%) and ERα (by ~25 %) ≥ MD2 Uterine protein levels: ↓ Estrogen receptor alpha (Erα) at HD (by ~50%) Estrogen sensitivity test in ovariectomised ♀ (HD not assessed) ↓ Insulin growth factor 1 (IGF-1) and androgen receptor (AR) mRNA change at MD2 in response to E2 injection
Durrer *et al*., 2007	Puberty endpoints (♂ ≥ PND41, ♀ ≥ PND30) Body weight at puberty onset ↓ (up to ~9%) in ≥ MD1♀ (LD not assessed) Delayed preputial separation (PND) ≥ MD1♂ (dose dependent, by up to ~3 days in HD; LD not assessed) Reproductive Organs ↓ VP weight (body relative) ≥ MD1♂ (by up to ~33%) ↑ Testis weight (~8%) in HD♂ ↓ Epididymis weight (by 12%) in HD♂ ↓ AR and IGF-1 mRNA (up to ~25%) in DP ≥ MD2♂ ↓ Estrogen receptor beta (Erβ) mRNA (up to 25%) in VP and DP at ≥ MD2♂ ↓ AR protein (by up to ~60%) in DP and VP in MD1 and MD2 (HD no assessed) ↓ Erα protein in DP (by up to ~90%) in MD1 and MD1 (no effect in VP; HD not assessed) Estrogen sensitivity test in castrated ♂ (HD not assessed) ↓ IGF-1 and AR mRNA change in VP in response to E2 injection in MD1 and MD1
Maerkel *et al*., 2005	Brain gene expression (HD not assessed) ↓ PR in VMH in ♀ at ≥ MD1 (~2-fold) ↑ PR in MPO in ♂ at ≥ MD1 (up to ~60%) Brain gene expression following estrogen sensitivity test in gonadectomised ♂ and ♀ (HD not assessed) ↑ PR mRNA in ♂ VMH at ≥ MD1 (by up to ~75%)

Rat (Long Evans) (F_0 – 5- to 6-week-old) ♂ and ♀ were treated for 10 weeks before mating; treatment continued throughout pregnancy and in the F_1 offspring until adulthood, F_1 animals were terminated on week 12 (*n* = 6-9/dose) **Estrogen challenge** (*n* = 8/treatment): F_1 animals were gonadectomized on week 10 and following 2-week recovery (week 12) were injected (SC) with E2 (estradiol-17β; 10, 50 µg /kg) and euthanised after 6 h. **Dose:** 0.01, 0.1, 0.33 and 0.66 g/kg chow equivalent to 0.7, 7, 24, 47 mg/kg/day (LD, MD1, MD2, HD respectively) Changes are presented relative to controls	
Maerkel *et al*., 2007	Thyroid Effects: ↑ Thyroid weights (body relative): ≥ MD1♂ and ≥ MD2♀ (dose dependent, by up to ~30%) ↑ Serum TSH in HD♀ ↑ Serum T3 in ≥ MD2♀ Brain gene expression ↓ ERα in VMH in ♂ and ♀ at ≥ MD1 ↓ PR in VHM in ♀ at ≥ MD1 (up to ~2-fold) ↑ PR in MPO in ♂ at ≥ MD1 (up to ~60%) Brain gene expression following estrogen sensitivity test in gonadectomised ♂ and ♀ (HD not assessed) ↑ repression of PPE mRNA in ♂ VMH and MPO at MD2

PR = progesterone receptor; IGF-1 = Insulin-like growth factor; PPE = preproenkephalin; VP =ventral prostate; DP = dorsolateral prostate; MPO = medial preoptic area; VHM = ventromedial hypothalamic nucleus

Key findings in F_1 offspring included dose-dependent delays in male puberty onset, altered uterine and prostate weights, and significant changes in gene and protein expression related to sex hormones (ERα, ERβ, PR, AR) and IGF-1 (from 7 mg/kg/day). Thyroid effects were observed at 24 mg/kg/day, with increased thyroid weights and altered T3/TSH levels. Brain gene expression changes were sex- and region-specific, highlighting potential neuroendocrine activity modulation. The reliability of these findings was impaired by the absence of histopathological evaluations. Nevertheless, the overall evidence indicates that exposure to 4-MBC may induce differential changes in several genes associated with the sex hormone axis in both male and female offspring. This extended one generation reproductive toxicity study was excluded from the final assessment by the SCCP, concluding that while 4-MBC induced molecular changes in reproductive organs, these effects were inconsistent and not clearly associated with adverse reproductive outcomes. However, the ECHA relied on this data in their assessment of the potential endocrine-disrupting effects of 4-MBC.

A further study investigated the effects of pre- and post-natal exposure to 4-MBC (7 and 24 mg/kg/day PO) on female sexual behaviour in Long Evans rats[26]. Males and females were treated for 10 weeks before mating; with treatment continued throughout pregnancy in females and in the F_1 offspring. In F_1 females (male offspring were not investigated), decreased preceptive behaviour and lordosis (reflexive body positioning crucial to reproductive behaviour) were observed at both dose levels. No treatment-related effects were observed on the oestrous cycle. These genetic alterations appear to result in aberrant sexual behaviour in female offspring, indicating potential effects on neuroendocrine pathways essential for postnatal development and reproductive function. While the TGA considers

[26] Faass O., Schlumpf M., Reolon S., Henseler M., Maerkel K., Durrer S. *et al.* (2009) Female sexual behavior, estrous cycle and gene expression in sexually dimorphic brain regions after pre- and postnatal exposure to endocrine active UV filters. *Neurotoxicology* **30:** 249–260.

these observations biologically relevant, a number of study limitations, including the absence of male cohort data, limited number of endpoints examined, and a limited dose range, reduce interpretation and reliability of the data. Consequently, the study is not considered adequate to establish a NOAEL.

Human breast milk samples collected from Swiss mothers between 2004 and 2006 contained detectable levels of 4-MBC, with a mean concentration of 22.1 ng/g lipid. These levels were approximately 4- to 10-fold lower than those measured in milk extracted from the stomach of rat pups on PND6, whose mothers received 4-MBC at 0.7 or 7 mg/kg/day PO[27].

Potential for endocrine activity modulation

This section summarises ECHA's assessment of the potential endocrine activity of 4-MBC. Although there is considerable overlap with SCCP data, particularly from *in vivo* studies, the primary focus of this analysis is on endocrine effects, with findings integrated and discussed in this context. The ECHA assessed all studies using the Klimisch scoring system (scores 1–4), which assesses the reliability of toxicological data. Unless stated otherwise, only statistically significant findings from studies with a Klimisch score of 1 (reliable without restriction) or 2 (reliable with restrictions) are discussed. The key lines of evidence considered in this assessment are outlined below.

ECHA lines of evidence for endocrine activity and adverse effects *via* thyroid modality

- *Receptor Activity and Gene Expression***:** Although endpoint consistency across *in vitro* studies was limited, available evidence indicates that 4-MBC can function as both an agonist and antagonist at thyroid hormone receptors. 4-MBC may also upregulate deiodinase gene expression (DIO1), suggesting potential modulation of thyroid hormone metabolism.
- *Thyroid Hormone Alterations in Rodents***:** Oral exposure studies in rodents consistently reported elevated TSH and T3 levels. At higher doses (≥ 230 mg/kg/day), T4 levels tended to decrease, while lower doses (≤ 50 mg/kg/day) showed no significant effect on T4. In contrast, dermal exposure in rats and humans) did not significantly alter thyroid hormone levels.
- *Thyroid Gland Morphology and Histopathology:* Only one oral study investigating adult (PND55) rats exposed perinatally (up to 50 mg/kg/day) displayed no effect on thyroid gland. Other rat studies with 4-MBC, assessing thyroid endpoints reported increases in thyroid weight at doses ≥ 24 mg/kg/day, often accompanied by adverse histopathological changes. In addition, 4-MBC (12.5, 25, 50 mg/kg/day PO) led to a 19% increase in thyroid weight in dams (assessed on PND22 after 84 days of total exposure) and in a 33% increase in male offspring on PND22 *cf.* controls. However, due to high variability, the changes were not statistically significant. In contrast, no effects on the thyroid gland were observed following dermal exposure in rats (90 days study with 4-MBC up to 400 mg/kg/day)[28]. Similarly, no significant thyroid histopathology was noted in dogs. However, the limited sample size (*n* = 1–2 per sex per dose) in dog studies constrains the reliability of these finding.[29]
- Neurodevelopment: No effects on learning and memory were observed in male or female rat offspring, born to dams treated with 4-MBC (up to 50 mg/kg/day PO). However relevant endpoints were assessed in only one study, which had several methodological limitations: the high dose was relatively low, the group size was small (*n* = 10), and the behavioural assessment method lacked sensitivity. The ECHA concluded that the design of this study was not robust enough to exclude potential impact on neurodevelopment.

ECHA lines of evidence for endocrine activity *via* estrogen and other modalities

In vitro

[27] Sunscreens: are they beneficial for health? An overview of endocrine disrupting properties of UV-filters - Krause - 2012 - International Journal of Andrology - Wiley Online Library

[28] Due to dermal toxicity 2000 mg/kg/day cohort has been terminated after 11 days.

[29] For dosing details, refer to the repeated-dose toxicity section, which includes a 14-day oral tolerability study and a 21-day oral toxicity study incorporating a wash-out phase.

- *Estrogen Receptor*: 4-MBC led to increased proliferation of MCF-7 human breast cancer cells in E-screen assays indicating estrogenic response. Several *in vitro* systems—including the Yeast Estrogen Screen (YES) and hERα assays—demonstrated estrogen receptor (ER) activation. The majority of studies concluded that 4-MBC acts as an ER agonist, though with relatively weak potency. Findings on ER antagonism were equivocal: two of four studies reported clear antagonistic effects, while the remaining two observed no effects. ER binding data was inconclusive, with one study showing binding, another reporting ambiguous results, and a third finding no binding activity.
- Androgen Receptor: AR antagonism was consistently observed, with four out of five in *vitro* studies manifesting antagonistic effects. No AR agonistic activity was reported.
- *Progesterone Receptor*: In total, three studies have shown that exposure to 4-MBC has potential to mimic the effects of progesterone in human sperm cells, triggering Ca^{2+} influx *via* the CatSper channel. Although these studies demonstrated a consistent pattern of physiological responses, it remains uncertain whether the observed effects were indicative of endocrine activity. Data on PR activation was inconsistent, with two available studies yielding conflicting results i.e. pronounced antagonistic effects were observed in the PR CALUX assay, while *SULT1E1* mRNA expression was not affected in human adenocarcinoma cell line (Ishikawa cells) indicating no anti-progestogenic activity.

In vivo

- *Uterotrophic effects*: Immature female rats (PND21–26) exhibited increased uterine weights following exposure to 4-MBC *via* dermal (≥ 37 mg/kg/day, estimated dose) or oral route (≥ 119 mg/kg/day; in feed). In adult animals treated with 4-MBC (≥ 500 mg/kg/day subcutaneously), increased uterine weight (~30%) was observed. Similarly, dose-dependent increases in uterine weight (up to 90% compared to controls) were observed following oral dosing at 500 and 800 mg/kg/day. Interestingly, in immature female rats, uterotrophic effects were observed only in younger animals (PND19–21) (1000 mg/kg/day subcutaneously), with no increases in uterine weight reported in older animals (PND21–23).
- *Gene Expression*: In rats fed a 4-MBC supplemented diet during perinatal and adult stages (≥ 7 mg/kg/day), sexually dimorphic alterations in ERα and PR expression were observed in the brain. Additionally, estrogen target gene responsiveness was altered following E2 injection in adult gonadectomised offspring. Changes in estrogen-regulated gene expression were also noted in the uterus and prostate.
- *Gonadotropin Regulation*: In adult rats, exposure to 4-MBC led to decreased levels LH and FSH. Similar hormonal alterations were observed in offspring exposed during the perinatal period; however, the reliability of these findings was limited. A human study involving dermal exposure to 4-MBC (2 mg/cm² of a 10% formulation applied over four consecutive days; *n* = 15 ♂ and 17 postmenopausal ♀) reported no significant changes in gonadotropin levels.

ECHA lines of evidence for estrogen and EAS mediated adverse effects in rat studies

- *Sexual behaviour* in adult female rat offspring was altered in a dose-related manner following exposure to 4-MBC (in feed) from perinatal stages. The observed effects included reductions in proceptive and receptive behaviours, along with increased rejection behaviours toward males. These changes were observed at doses ≥ 7 mg/kg/day and were reported across individual assessments (*n* = 12–14) as well as litter-based evaluations (*n* = 6–7).
- No statistically significant changes or dose-dependent relationships were observed in rat studies (up to 50 mg/kg/day PO) classified as reliable with respect to vaginal opening, oestrous cycling, or anogenital distance (AGD). Similarly, the number of implantations, corpora lutea, and post-implantation losses were unaffected by the treatment. Reduced ovary weight was observed in one study at 1000 mg/kg/day PO. Uterotrophic effects, while not strictly adverse, are discussed above.
- Decreased prostate weight was observed in several studies at doses ≥ 30 mg/kg/day in adult animals. In animals exposed both perinatally and during adulthood (7, 24, or 47 mg/kg/day via feed), delayed male puberty was noted across all exposure groups in a dose-dependent

manner. Preputial separation was delayed by ~ 3 days in the HD cohort. In adult male offspring, both absolute and relative prostate weights were reduced in all groups. Although no statistically significant effects were reported, testis weight was increased in the MD and HD groups. Epididymis and seminal vesicle weights were reduced in the HD cohort; however, these changes were not statistically significant.

Based on the available *in vitro* and *in vivo* evidence as well as the mode of action and biological plausibility analysis, ECHA concluded that there is strong indication that oral exposure to 4-MBC may disrupt thyroid hormone production. This disruption is likely to increase secretion of TSH, which in turn may cause adverse effects on the thyroid gland, including increased weight and histopathological changes. Furthermore, due to its interference with the thyroid hormone system, 4-MBC has the potential to impact neural development. Although no effects on learning and memory have been observed in rat offspring, a single *in vivo* study was considered inconclusive and thus insufficient to unequivocally rule out neurodevelopmental impact. Disruption of thyroid hormones during critical developmental windows may have long-term consequences, and the complexity of thyroid-related responses makes it difficult to fully characterize these effects. Furthermore, the report concluded that estrogen receptor activation by 4-MBC may lead to adverse effects on the reproductive system, specifically altered female sexual behaviour and reduced prostate weight in males. This conclusion was considered biologically plausible and supported by *in vitro* and *in vivo* evidence. The mode of action of 4-MBC was consistent with endocrine effects mediated through the EATS pathways (Estrogen, Androgen, Thyroid, and Steroidogenesis). Since most of the studies were conducted in rats, a higher sensitivity to 4-MBC in this species cannot be excluded. However, in the absence of data indicating that these endocrine modes of action are not relevant to humans, ECHA assumed human relevance by default. **No definitive safe limits for 4-MBC in the context of endocrine effects have been established by the ECHA. The TGA agrees with ECHA's opinion on the endocrine activity modulation properties of 4-MBC**.

The SCCS[5], concurred with the ECHA opinion that there is sufficient evidence indicating that 4-MBC may act as an endocrine disruptor, potentially affecting both the thyroid and estrogen systems. The SCCS noted that thyroid effects generally occurred at oral exposure levels of ≥50 mg/kg/day, while for dermal exposure, thyroid effects were observed at doses >400 mg/kg/day. In addition, the SCCS noted that the observed effects on the estrogen system generally occurred at exposure levels ≥ 100 mg/kg/day. **The SCCS upheld a NOAEL of 25 mg/kg/day for 4-MBC, based on a 90-day oral repeat-dose toxicity study in rats. The TGA concurs with the SCCS's assessment that this study provides the most reliable basis for determining the oral NOAEL for and is protective of both findings observed in the thyroid gland and in reproductive toxicity studies.**

Local tolerance

In humans 4-MBC was not a skin irritant in three separate studies of up to 10 subjects. While study details are limited, no skin irritation or discomfort was observed following 24 h exposure. 4-MBC was not a skin sensitiser in humans treated with 5% 4-MBC for 3 weeks (3 applications/week) followed by application to a new area 8-10 days later. 4-MBC was negative in photosensitisation studies in human subjects.

4-MBC was not a skin or eye irritant in rabbits or a skin sensitiser in guinea pigs.

Appendix

Table 11 Literature Search Strategy (March 2025)

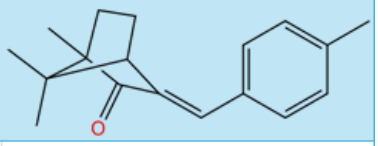
Embase, Ovid MEDLINE(R)		
#	Search Statement	Results
1	exp drug carcinogenicity/	941
2	exp carcinogenicity/	41543
3	exp carcinogen/	307159
4	exp Carcinogens/	307159
5	exp Carcinogenicity Tests/	9906
6	exp Mutagens/	117020
7	exp mutagenicity tests/	68568
8	exp genotoxicity/	43120
9	exp Neoplasms/	1E+07
10	((Dermal or systemic) adj2 carcinog*).mp. [mp=ti, ab, hw, tn, ot, dm, mf, dv, kf, fx, dq, bt, nm, ox, px, rx, ui, sy, ux, mx]	467
11	Carcinog*.mp. [mp=ti, ab, hw, tn, ot, dm, mf, dv, kf, fx, dq, bt, nm, ox, px, rx, ui, sy, ux, mx]	678781
12	1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9 or 10 or 11	1.1E+07
13	exp drug toxicity/	310590
14	exp reproductive toxicity/	15628
15	exp toxicity/	845091
16	exp toxicity testing/	94903
17	exp acute toxicity/	30473
18	exp developmental toxicity/	5575
19	exp Toxicity Tests/	215304
20	exp Toxicology/	100048
21	exp teratogens/	63988
22	exp teratogen/	63988
23	exp teratogenesis/	12961
24	exp teratogenicity/	18798
25	((Development* or reproduct*) adj3 toxic*).mp. [mp=ti, ab, hw, tn, ot, dm, mf, dv, kf, fx, dq, bt, nm, ox, px, rx, ui, sy, ux, mx]	51629
26	13 or 14 or 15 or 16 or 17 or 18 or 19 or 20 or 21 or 22 or 23 or 24 or 25	1322323
27	exp toxicokinetics/	14697
28	Toxicokinetic*.mp. [mp=ti, ab, hw, tn, ot, dm, mf, dv, kf, fx, dq, bt, nm, ox, px, rx, ui, sy, ux, mx]	22163
29	27 or 28	22163

Embase, Ovid MEDLINE(R)		
30	exp endocrine function/	594626
31	exp endocrine disease/	3928106
32	exp endocrine system/	1373360
33	exp Endocrine Disruptors/	23961
34	(("long term" or endocrin*) adj3 effect*).mp. [mp=ti, ab, hw, tn, ot, dm, mf, dv, kf, fx, dq, bt, nm, ox, px, rx, ui, sy, ux, mx]	265732
35	30 or 31 or 32 or 33 or 34	5400118
36	exp contact dermatitis/	89789
37	exp skin allergy/	27924
38	exp skin toxicity/	26996
39	exp skin irritation/	22259
40	exp skin sensitization/	7750
41	exp sensitization/	89410
42	exp photodermatosis/	13524
43	exp application site reaction/	6171
44	exp application site inflammation/	103
45	exp Skin Irritancy Tests/	95705
46	exp Skin Tests/	146536
47	exp skin pruritus/	5388
48	exp pruritus/	148820
49	exp allergic rash/	504
50	exp contact allergy/	9040
51	exp contact dermatitis/	89789
52	exp drug hypersensitivity/	142771
53	exp allergy/	694213
54	exp Hypersensitivity/	1214220
55	exp Allergens/	130495
56	((dermal or skin) adj3 (sensiti* or irritat*)).mp. [mp=ti, ab, hw, tn, ot, dm, mf, dv, kf, fx, dq, bt, nm, ox, px, rx, ui, sy, ux, mx]	51107
57	36 or 37 or 38 or 39 or 40 or 41 or 42 or 43 or 44 or 45 or 46 or 47 or 48 or 49 or 50 or 51 or 52 or 53 or 54 or 55 or 56	1650945
58	exp phototoxicity/	11313
59	exp photoallergy/	3796
60	(phototox* or photoalle*).mp. [mp=ti, ab, hw, tn, ot, dm, mf, dv, kf, fx, dq, bt, nm, ox, px, rx, ui, sy, ux, mx]	24697
61	58 or 59 or 60	24697

Embase, Ovid MEDLINE(R)		
62	exp drug bioavailability/	84500
63	exp bioavailability/	196194
64	exp drug absorption/	96472
65	exp pharmacokinetics/	1239731
66	exp Skin Absorption/	21869
67	exp Biological Availability/	196194
68	exp Absorption, Physiological/	170590
69	(absorp* or absorb*).mp. [mp=ti, ab, hw, tn, ot, dm, mf, dv, kf, fx, dq, bt, nm, ox, px, rx, ui, sy, ux, mx]	1338098
70	(penetration or penetrate or permeability).mp. [mp=ti, ab, hw, tn, ot, dm, mf, dv, kf, fx, dq, bt, nm, ox, px, rx, ui, sy, ux, mx]	711181
71	(penetration or penetrate or permeability).mp. [mp=ti, ab, hw, tn, ot, dm, mf, dv, kf, fx, dq, bt, nm, ox, px, rx, ui, sy, ux, mx]	711181
72	bioavail*.mp. [mp=ti, ab, hw, tn, ot, dm, mf, dv, kf, fx, dq, bt, nm, ox, px, rx, ui, sy, ux, mx]	312411
73	62 or 63 or 64 or 65 or 66 or 67 or 68 or 69 or 70 or 71 or 72	3045845
74	(safe or safety or "side effect" or "side effects" or adverse).mp. or exp adverse drug reaction/ or exp drug-related side effects/ or exp drug safety/ or toxic*.mp. or hazard*.mp.	1.1E+07
75	4-Methylbenzylidene camphor.mp. or exp "3 (4 methylbenzylidene)camphor"/	705
76	36861 47 9.rn.	363
77	"(3Z)-1,7,7-trimethyl-3-[(4-methylphenyl)methylidene]bicyclo[2.2.1]heptan-2-one".af.	0
78	Enzacamene.af.	131
79	"3-(4-Methylbenzylidene)camphor".af.	511
80	"3-(4'-Methylbenzylidene)camphor".af.	511
81	"4-MBC cpd".af.	0
82	"4-MBC".af.	337
83	"(3Z)-1,7,7-trimethyl-3-[(4-methylphenyl)methylidene]bicyclo[2.2.1]heptan-2-one".af.	0
84	"1,7,7-Trimethyl-3-(4-methylbenzylidene)bicyclo[2.2.1]heptan-2-one".af.	0
85	"1,7,7-trimethyl-3-[(4-methylphenyl)methylene]bicyclo[2.2.1]heptan-2-one".af.	0
86	"Bicyclo[2.2.1]heptan-2-one, 1,7,7-trimethyl-3-[(4-methylphenyl)methylene]".af.	0
87	"(±)-1,7,7-trimethyl-3-[(4-methylphenyl)methylene]bicyclo[2.2.1]heptan-2-one".af.	0
88	"3-(4-Methylbenzylidene) bornan-2-one".af.	1
89	"1,7,7-Trimethyl-3-(4-methylbenzylidene)-norbornan-2-one".af.	0

Embase, Ovid MEDLINE(R)		
90	75 or 76 or 77 or 78 or 79 or 80 or 81 or 82 or 83 or 84 or 85 or 86 or 87 or 88 or 89	803
91	12 and 90	81
92	26 and 90	144
93	29 and 90	9
94	35 and 90	166
95	57 and 90	116
96	61 and 90	60
97	73 and 90	179
98	74 and 90	397
99	91 or 92 or 93 or 94 or 95 or 96 or 97 or 98	571
100	limit 99 to english language	539
101	limit 100 to yr="2010 -Current"	376
102	remove duplicates from 101	253

Table 12 QSAR analysis of 4-MBC:

Data type	Assay	4-MBC (36861-47-9)
Structure	NA	
in vitro data	Chromosome aberration in vitro	negative[1]
OASIS TIMES (v2.31.2)	Chromosome aberration in vitro	negative out of applicatbility domain
DEREK Nexus (v6.3.0)[4]	Chromosome aberration in vitro	equivocal alert[3]
Danish QSAR battery (v1.0)	Chromosome aberration in vitro	negative
in vivo data	Micronucleus in vivo	N/A
OASIS TIMES (v2.31.2)	Micronucleus in vivo	negative out of domain
DEREK Nexus (v6.3.0)[5]	Chromosome damage in vivo	no alert
Danish QSAR battery (v1.0)[6]	Micronucleus in vivo	negative
Footnotes		

1) Non guideline testing conditions unclear. Test reported as being evaluated as negative in 2004 SCCNFP opinion. SCCS re-evaluation in 2021 concluded study was inconclusive due to deviations from OECD TG 473 (original study not reviewed)

2) chromosome aberration assay in Chinese hamster ovary cells reported to be compliant with OECD TG 473 positive in presence of activation in a dose of 25 µg/ml at 24h (original study not reviewed)

3) 309 alpha,beta-Unsaturated ketone. The alert description for 309 alpha,beta-Unsaturated ketone states-"in general, the class does not show activity in vivo

4) The metabolites of 4-MBC were predicted using Meteor Nexus (v3.2.0). Some predicted metabolites and metabolites identified by SCCS had the same equivocal alert for in vitro chromosome aberrations as 4-MBC. No other alerts were fired.

5) Non-guideline micronucleus test in Oncins France 1 (OF-1) mice. Negative - No significant increases in micronucleated polychromatic erythrocytes were observed at 24, 48 and 72 hours after intraperitoneal (i.p.) administration of 700 or 1400 mg/kg in males or 800 or 1600 mg/kg in females. (original study not reviewed)

6) The Danish QSAR battery prediction includes predictions from 3 statistical models. These models are Leadscope, MultiCase and SciQSAR. The identity of the chemicals in these training sets is not publicly available. Results from these models do not provide information on potential mechanisms of toxicity.

Version history

Version	Description of change	Author	Effective date
V1.0	Original publication	TGA	July 2026

Therapeutic Goods Administration

PO Box 100 Woden ACT 2606 Australia
Email: info@tga.gov.au Phone: 1800 020 653 Fax: 02 6203 1605
Web: tga.gov.au