Australian Government
Department of Health and Aged Care
Australian Industrial Chemicals Introduction Scheme

4*H*-1,3-Benzodioxin, hexahydro-4-methyl-2-(phenylmethyl)-

Assessment statement (CA09866)

9 April 2024

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AICIS assessment statement (CA09866)

Chemical in this assessment

Name	CAS registry number
4*H*-1,3-Benzodioxin, hexahydro-4-methyl-2-(phenylmethyl)-	1373821-23-8

Reason for the assessment

An application for an assessment certificate under section 31 of the *Industrial Chemicals Act 2019* (the Act).

Certificate Application type

AICIS received the application in a Very Low to Low Risk type.

Defined scope of assessment

The chemical has been assessed:

- as imported into Australia at up to 1 tonne/year
- as imported in fragrance formulations at up to 1% concentration for reformulation into end use cosmetic and household products in
  - continuous action air fresheners at up to 0.9% concentration
  - fine fragrances at up to 0.5% concentration
  - instant action air fresheners at up to 0.1% concentration
  - other cosmetic and household products at up to 0.02% concentration
- as imported in finished products for sale in:
  - continuous action air fresheners at up to 0.9% concentration
  - fine fragrances at up to 0.5% concentration
  - instant action air fresheners at up to 0.1% concentration
  - other cosmetic and household products at up to 0.02% concentration

Summary of assessment

Summary of introduction, use and end use

The assessed chemical will not be manufactured in Australia. It will be imported either in fragrance formulations at up to 1% concentration for reformulation into end use cosmetic and household products, or in finished cosmetic and household products at up to 0.9% concentration in continuous action air freshener, at up to 0.5% concentration in fine fragrances, at up to 0.1% concentration in instant action air fresheners, and at up to 0.02% concentration in other household products and leave-on and rinse-off cosmetic products.

The cosmetic and household end use products containing the assessed chemical are proposed to be used by professional workers and by members of the general public.

Human health

Summary of health hazards

The submitted toxicological data on the assessed chemical (see **Supporting information**) indicate that the assessed chemical is:

- of low acute oral toxicity (LD50 > 2,000 mg/kg bw in rats)
- not irritating to skin
- irritating to eyes (not meet GHS criteria for classification)
- not considered to cause point mutations
- not a skin sensitiser (a local lymph node assay showed SI values below 3 at up to 100% concentration, although the study authors classified the chemical as a Cat 1B skin sensitiser based on a EC1.4 value of 11.36%) (see **Supporting information**).

No data on inhalation toxicity and repeated dose toxicity were submitted.

Hazard classifications relevant for worker health and safety

Based on the data provided by the applicant, the assessed chemical does not satisfy the criteria for classification according to the *Globally Harmonized System of Classification and Labelling of Chemicals* (GHS) (UNECE 2017) for hazard classes relevant for worker health and safety as adopted for industrial chemicals in Australia.

Summary of health risk

Public

When introduced and used in the proposed manner, there will be widespread and repeated exposure of the public to the assessed chemical at up to 0.9% concentration through the use of a wide range of cosmetic and household products. The principal route of exposure will be dermal, while ocular and inhalation exposures, particularly from the use of air care products and other products applied by spray, are also possible.

The assessed chemical in neat form is expected to be irritating to the eyes. However, eye irritation is not expected to occur from use of the assessed chemical at the proposed low end use concentrations (up to 0.9%) in cosmetic and household products.

No inhalation toxicity data are provided for the assessed chemical. Due to low concentrations of the assessed chemical in the end use products, it is not expected to pose health risks from inhalation when the assessed chemical is used in the proposed manner.

No repeated dose toxicity data were provided on the assessed chemical. Based on the quantitative risk assessment (QRA) for the worst-case exposure scenario, consumers simultaneously using multiple cosmetics and household products may be systemically exposed to the assessed chemical at approximately 111 µg/kg bw/day through repeated or prolonged exposure (see **Supporting information** section). Considering the low systemic exposure level to the assessed chemical, health risks from repeated exposure to the public are not expected.

Overall, this assessment does not identify any risks to public health that would require specific risk management measures.

Workers

Reformulation workers may be incidentally exposed to the assessed chemical at up to 1% concentration during reformulation processes mainly via the dermal route, while ocular and inhalation exposures are also possible. The assessed chemical in neat form is irritating to eyes. However, eye irritation effects are not expected to occur during handling of the assessed chemical at up to 1% concentration for reformulation. To mitigate any risks to reformulation workers from repeated exposure, control measures would be required (see **Means for managing risk**) to minimise the exposure. It is anticipated by the applicant that engineering controls such as enclosed and automated processes and local ventilation will be implemented where possible. Use of appropriate personal protective equipment (PPE) such as safety glasses, impervious chemical resistant gloves, protective clothing and respiratory protection will reduce worker exposure.

Professional workers in cleaning or cosmetic businesses may experience exposure via dermal, inhalation and accidental ocular exposure to the assessed chemical during the use of cleaning or cosmetic products containing the assessed chemical at up to 0.5% concentration. The professional workers may wear some PPE (including gloves, coveralls, safety glasses or face masks) to reduce exposure. If PPE is used, exposure of such workers is expected to be of a similar or lesser extent than that experienced by consumers using the same end use products containing the assessed chemical, requiring no specific risk management measures for these workers.

Environment

Summary of environmental hazard characteristics

According to domestic environmental hazard thresholds and based on the available data the chemical is:

- Persistent (P)
- Not Bioaccumulative (Not B)
- Not Toxic (Not T)

Environmental hazard classification

The assessed chemical satisfies the criteria for classification according to the GHS (UNECE 2017) as Acute Category 2 (H401) and Chronic Category 2 (H411) based on the toxicity data for aquatic organisms. Considerations were also made for the degradation and bioaccumulation potential of the assessed chemical.

Environmental Hazard	Hazard Category	Hazard Statement
Hazardous to the aquatic environment (acute / short-term)	Aquatic Acute 2	H401: Toxic to aquatic life
Hazardous to the aquatic environment (long-term)	Aquatic Chronic 2	H411: Toxic to aquatic life with long-lasting effects

Summary of environmental risk

The assessed chemical will be introduced as a fragrance ingredient for use in a variety of products. These uses may result in the release of the assessed chemical to sewers and to air.

The assessed chemical is not readily degradable and is persistent. The assessed chemical does not have the potential for bioaccumulation and is not expected to cause toxic effects in aquatic organisms according to the Australian Environmental Criteria for Persistent, Bioaccumulative and/or Toxic Chemicals (DCCEEW, 2022).

Although the assessed chemical is persistent, it does not meet all three PBT criteria. It is unlikely to have unpredictable long-term effects and its risk may be estimated by the risk quotient method (RQ = PEC ÷ PNEC). Based on the expected RQ values < 1 for the river and ocean compartments, it is expected that the environmental risk from the introduction of the assessed chemical can be managed.

Means for managing risk

Workers

Information relating to safe introduction and use

The information in this statement should be used by a person conducting a business or undertaking at a workplace (such as an employer) to determine the appropriate controls under the relevant jurisdiction Work Health and Safety laws.

The following control measures could be implemented to manage the risk arising from exposure to the assessed chemical during reformulation:

- Use of engineering controls such as
  - Enclosed and automated systems where possible
  - Adequate workplace ventilation to avoid accumulation of vapours, mists or aerosols

- Use of safe work practices to
  - Avoid contact with skin and eyes
  - Avoid inhalation of vapours, mists or aerosols

- Workers should wear the following personal protective equipment (PPE)
  - Impervious gloves
  - Protective clothing
  - Respiratory protection where local ventilation may be inadequate

Conclusions

The Executive Director is satisfied that the risks to human health or the environment associated with the introduction and use of the industrial chemical can be managed.

Note:

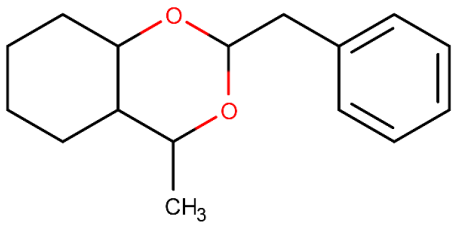
1. Obligations to report additional information about hazards under s 100 of the *Industrial Chemicals Act 2019* apply.
2. You should be aware of your obligations under environmental, workplace health and safety and poisons legislation as adopted by the relevant state or territory.

Supporting information

Chemical identity

Chemical name	4*H*-1,3-Benzodioxin, hexahydro-4-methyl-2-(phenylmethyl)-
CAS Number	1373821-23-8
Synonyms	Hexahydro-4-methyl-2-(phenylmethyl)-4*H*-1,3-benzodioxin
Molecular formula	$C_{16}H_{22}O_2$
Molecular weight (g/mol)	246.35
SMILES (canonical)	O1C(OC2CCCCC2C1C)CC=3C=CC=CC3

Structural formula



Chemical description

The assessed chemical is a mixture of stereoisomers with a combined purity of greater than or equal to 97%.

Relevant physical and chemical properties

Physical form	Pale yellow translucent liquid
Melting point	-53.6 °C
Boiling point	324.2 °C
Density	1,048.9 kg/m^3 at 20 °C
Vapour pressure	0.295 Pa at 25 °C (QSAR prediction[#])
Water solubility	30.3 mg/L at 20°C (Exp.)
Ionisable in the environment	No
pK_a	N/A
log K_{ow}	3.65 at 20°C (Exp.)

Log K_{oc}	3.46 (Calc.)
Flash point	162 °C
Autoignition temperature	401 °C

[#] Calculated value from iSafeRat® High Accuracy QSAR for Vapour Pressure: v1.5

Human exposure

Public

Dermal exposure

Data on typical use patterns of cosmetic products (SCCS 2012; Cadby et al. 2002; ACI 2010; Loretz et al. 2006) in which the assessed chemical may be used are shown in the following table. A dermal absorption (DA) rate of 100% was used as a worst-case scenario along with a combined average body weight (BW) for males and females of 60 kg for calculation purposes.

Product type	Amount (mg/day)	C (%)	RF	Daily systemic exposure (µg/kg bw/day)
Body lotion	7,820	0.02	1	26
Face cream	1,540	0.02	1	5
Hand cream	2,160	0.02	1	7
Fine fragrances	750	0.5	1	63
Deodorant (non-spray)	1,500	0.02	1	5
Shampoo	10,460	0.02	0.01	0
Conditioner	3,920	0.02	0.01	0
Shower gel	18,670	0.02	0.01	1
Hand wash soap	20,000	0.02	0.01	1
Hair styling products	4,000	0.02	0.1	1
Total				**109**

C = maximum intended concentration of assessed chemical; RF = retention factor
Daily systemic exposure = (Amount × C × RF × DA)/BW

Dermal exposure from using household cleaning products and wearing clothes will result in additional 1 µg/kg bw/day systemic exposure, considering low concentrations and retention factors for these products.

Inhalation exposure

Hairspray was taken as a worst-case scenario example for the inhalation exposure assessment. A 2-zone approach was used (Steiling et al. 2014; Rothe et al. 2011; Earnest Jr. 2009). An adult inhalation rate of 20 m^3/day (enHealth 2012) was used and it was conservatively assumed that the fraction of the assessed chemical inhaled is 50%.

Amount of hairspray applied	9.89	g/day
Maximum intended concentration of the chemical	0.02	%
Inhalation rate of the user	20	m^3/day
Exposure duration in zone 1	1	minutes
Exposure duration in zone 2	20	minutes
Fraction inhaled by the user	50	%
Volume of zone 1	1	m^3
Volume of zone 2	10	m^3
Daily systemic exposure	**1**	µg/kg bw/day

C = maximum intended concentration of assessed chemical
Total daily systemic exposure = Daily systemic exposure in zone 1 [(amount × C × inhalation rate × exposure duration (zone 1) × fraction inhaled)/(volume (zone 1) × body weight)] + Daily systemic exposure in zone 2 [(amount × C × inhalation rate × exposure duration (zone 2) × fraction inhaled)/(volume (zone 2) × body weight)]

It is acknowledged that inhalation exposure to the assessed chemical from use of other cosmetic and household products may also occur.

Overall, the worst-case scenario estimation is for a person who is a simultaneous user of all products listed in the above tables that contain the assessed chemical at the maximum intended concentrations specified in various product types. This would result in a combined internal dose of 111 µg/kg bw/day (= 0.111 mg/kg bw/day) for the assessed chemical. This low level of worst-case systemic exposure is unlikely to pose health risk to the public with repeated use of products containing the assessed chemical.

Health hazard information

Acute toxicity

Oral

In an acute oral toxicity study (OECD TG 423), 6 female Sprague Dawley (SD) rats were administered a single dose of the assessed chemical at 2,000 mg/kg bw. No mortalities or macroscopic findings were observed in any treated animals. Clinical signs in treated animals included a decrease in spontaneous activity (2/6) at the 3-hour observation, which persisted until the 4-hour observation. No clinical signs were noted at the 24-hour observation. Body weight gain appeared normal. The median lethal dose (LD50) was determined to be greater than 2,000 mg/kg bw indicating the assessed chemical is of low acute oral toxicity.

Corrosion/Irritation

Skin irritation

The assessed chemical was tested for skin irritation using 3 male albino New Zealand rabbits (OECD TG 404). A single 4-hour, semi-occluded application of the undiluted test substance to the intact skin of the rabbits produced no erythema or oedema at the 1-hour, 24-hour, 48-hour or 72-hour observations. Under the conditions of this study, the assessed chemical is considered not irritating to skin.

Eye irritation

The assessed chemical was tested for eye irritation using 3 male albino New Zealand rabbits (OECD TG 405). A single application of the undiluted test substance to one eye of each rabbit produced no iridial or corneal effects. Slight to severe conjunctival irritation (mean individual scores of 3, 2.3 and 2.3) was observed in the treated eye of all animals 1 hour after treatment. The mean conjunctival redness scores at 24, 48 and 72 hours were 1.7, 1.3 and 0.7, respectively. The mean conjunctival oedema scores at 24, 48 and 72 hours were 1.3, 0.3, 0.3, respectively. All treated eyes appeared normal at the Day 21 observation. Under the conditions of this study, the assessed chemical was irritating to the eyes but does not meet the GHS criteria for classification.

Sensitisation

Skin sensitisation

The skin sensitisation potential of the assessed chemical was assessed using a local lymph node assay (LLNA) in mice (OECD TG 429). Three groups (4 female CBA/J mice/group) were treated by daily application of 25 µL of the assessed chemical at concentrations of 5%, 10%, 25%, 50% or 100% using acetone/olive oil 4:1 as vehicle to the dorsal surface of each ear for 3 consecutive days.

There were no signs of systemic toxicity and body weights were comparable to controls. Slight dryness of the treated site was observed at Day 6 observation in the group treated with 50% (1/4) and 100% (4/4) of the assessed chemical. The stimulation index (SI) at the 5%, 10%, 25%, 50% and 100% concentrations were 0.84, 1.37, 1.70, 2.21 and 2.98, respectively. The theoretical concentration of the test substance resulting in a SI value of 1.4 (EC1.4 value) was calculated (by linear interpolation) to be 11.36%. Based on the results of this study, the study

authors have classified the assessed chemical for skin sensitisation Cat 1B (H317: May cause an allergic skin reaction). However, the results do not meet the GHS criteria for classification as the SI values were below 3 at up to 100% concentration, although there was a dose response.

Genotoxicity

The assessed chemical was found to be non mutagenic in a bacterial reverse mutation assay using *Salmonella typhimurium* strains TA98, TA100, TA1535 and TA1537 and *Escherichia coli* strain WP2(pKM101) in both the presence and absence of metabolic activation (OECD TG 471).

Environmental exposure

The assessed chemical will be imported into Australia for use as a fragrance in end use products, or as a component of fragrance formulations for reformulation into end use products. Reformulation and repackaging will occur in both closed and open processes. Significant releases of the assessed chemical to the environment are not expected during reformulation, transport or storage.

The assessed chemical will be included in a wide range of products, resulting in a variety of potential exposure scenarios.

Consumer and professional end use of the assessed chemical in cosmetic and household products is expected to result in the release of the assessed chemical “down the drain” and into the sewers. Consequently, the assessed chemical will be treated at sewage treatment plants (STPs) before release to surface waters.

Use of the assessed chemical in air care products will result in direct release of the assessed chemical into the air compartment.

Environmental fate

Partitioning

The partitioning of the assessed chemical was not determined. The chemical is treated as if it is mobile in the environment as a worst-case scenario.

Degradation

Degradation studies in water indicate that the assessed chemical is not readily biodegradable. A supplied OECD 301D biodegradation study for the assessed chemical demonstrated 23% degradation of the assessed chemical over 28 days and 27% degradation at 60 days. In another OECD 301D biodegradation study, the degradation of the assessed chemical at 28 days was 17.15%. In both studies, the assessed chemical did not satisfy the 10-day-window criterion for degradation.

Bioaccumulation

Based on its log K_{OW} value, the assessed chemical does not have the potential to bioaccumulate.

No bioaccumulation information was provided for the assessed chemical. The experimental partition coefficient of the assessed chemical (log K_{OW} = 3.65) is below the domestic bioaccumulation threshold of log K_{OW} = 4.2 (EPHC, 2009).

Predicted environmental concentration (PEC)

A predicted environmental concentration (PEC) for Australian waters was calculated assuming the maximum allowable introduction volume for environmental exposure band 2 (1,000 kg/annum) with a release reduction factor of 1 for down-the-drain style end use scenarios. Correspondingly, 100% of the introduction volume is released into sewage treatment plants (STP) over 365 days per annum. The extent to which the assessed chemical is removed from the effluent in STP processes was not calculated as a worst-case scenario.

This calculated value is conservative as not all uses of the assessed chemical are expected to result in release to STP.

The calculation of the PEC is detailed in the table below:

Total Annual Import Volume	1,000	kg/year
Proportion expected to be released to sewer	100%	
Annual quantity of chemical released to sewer	1,000	kg/year
Days per year where release occurs	365	days/year
Daily chemical release	2.74	kg/day
Water use	200	L/person/day
Population of Australia	25.423	Million
Removal within STP	0%	Mitigation
Daily effluent production	5,085	ML/day
Dilution Factor – River	1	
Dilution Factor – Ocean	10	
PEC – River	0.54	µg/L
PEC – Ocean	0.05	µg/L

Environmental effects

Effects on aquatic Life

Acute toxicity

The following median lethal concentration (LC50) and median effective concentration (EC50) values for model organisms across three trophic levels were provided by the applicant:

Taxon	Endpoint	Method
Fish	96 h LC50 = 5.7 mg/L	*Danio rerio* (Zebra fish) OECD TG 203 Static conditions Nominal concentration
Invertebrate	48 h EC50 = 6.4 mg/L	*Daphnia magna* (Water flea) Immobility/other effect iSafeRat, HA – QSAR v1.9, Ecotox module Calculated concentration
Algae	72 h ErC50 = 5.7 mg/L (Calc.)	*Desmodesmus subspicatus* (Green algae) Growth rate iSafeRat, HA – QSAR v1.9, Ecotox module Calculated concentration

Chronic toxicity

The following no-observed-effect concentrations (NOEC) values for model organisms were provided by the applicant:

Taxon	Endpoint	Method
Invertebrate	21 d EC10 = 1 mg/L (reproduction)	*Daphnia magna* (Water flea) Immobility/reproduction OECD 211 Semi-static conditions, Geometric Mean measured concentration
Algae	72 h NOErC = 2 mg/L	*Desmodesmus subspicatus* (Green algae) Growth rate iSafeRat, HA – QSAR v1.9, Ecotox module Calculated concentration

Predicted no-effect concentration (PNEC)

The predicted no-effect concentration is expected to be greater than 0.54 µg/L.

The available standard acute ecotoxicity endpoints for this chemical are greater than 0.54 mg/L. With a conservative assessment factor of 1,000, the lowest calculable PNEC is > 0.54 µg/L.

Categorisation of environmental hazard

The categorisation of the environmental hazards of the assessed chemical according to the Australian Environmental Criteria for Persistent, Bioaccumulative and/or Toxic Chemicals (DCCEEW, 2022) is presented below:

Persistence

Persistent (P). Based on a measured degradation study, the assessed chemical is categorised as Persistent.

Bioaccumulation

Not Bioaccumulative (Not B). Based on low measured log k_{ow} value (3.65), the assessed chemical is categorised as Not Bioaccumulative.

Toxicity

Not Toxic (Not T). Based on available acute ecotoxicity values above 1 mg/L and chronic ecotoxicity values above 0.1 mg/L, the assessed chemical is categorised as Not Toxic.

Environmental risk characterisation

Although the assessed chemical is persistent, it does not meet all three PBT criteria. It is hence unlikely to have unpredictable long-term effects (EPHC 2009). An estimate of risk may therefore be determined using the risk quotient method.

Compartment	PEC	PNEC	RQ
River	< 0.54 µg/L	> 0.54 µg/L	< 1
Ocean	< 0.05 µg/L	> 0.54 µg/L	< 0.1

The risk quotient for the aquatic compartment is expected to be less than 1. This is based on a conservative PEC, assuming 100% release of 1 tonne/annum to STPs and no removal from the aqueous stream during STP processes, and a conservative PNEC based on an assessment factor of 1,000 and acute aquatic toxicity endpoints for the chemical that each exceed 0.54 mg/L.

Therefore, based on the expected RQ < 1 the assessed chemical is not expected to pose a significant risk to the environment. As such, the environmental risks associated with the assessed chemical can be managed.

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