Australian Government
Department of Health, Disability and Ageing
Australian Industrial Chemicals Introduction Scheme

Benzoic acid, 2-hydroxy-, 2-methylpentyl ester

Assessment statement (CA09686)

12 November 2025

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AICIS assessment (CA09686)

Chemical in this assessment

Name	CAS registry number
Benzoic acid, 2-hydroxy-, 2-methylpentyl ester	98969-19-8

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 Health Focus type.

Defined scope of assessment

The chemical has been assessed:

- as imported into Australia at up to 1 tonne per year
- as imported at up to 100% concentration for reformulation into finished end-use products
- as imported in finished end-use products as a component
- for end-use in personal care products (cosmetics) excluding lipsticks and oral care products, laundry and dishwashing products, cleaning and furniture care products, and air care products
- for end use at a concentration of
    - up to 0.1% in cosmetics if used by children below 10 years of age
    - up to 2% in leave-on cosmetics and fine fragrances when not used by children below 10 years of age
    - less than 3% in rinse-off cosmetics when not used by children below 10 years of age
    - up to 0.4% in deodorants
    - up to 3% in laundry and dishwashing products, cleaning and furniture care products, and air care products

Summary of assessment

Summary of introduction, use and end use

The assessed chemical will not be manufactured in Australia. It will be imported at up to 100% concentration for reformulation into end-use personal care products (cosmetics), laundry and dishwashing products, cleaning and furniture care products, and air care products. The chemical will be imported and distributed in tightly closed lacquered drums of varying sizes up to 180 kg. It will also be imported as a component in finished end use products. The

concentration of the assessed chemical will vary depending on end use product types to a maximum of 3%. The end use consumer products containing the assessed chemical will be packaged in containers suitable for retail distribution.

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 the skin and eyes
- unlikely to cause serious systemic health effects (other than developmental toxicity) following repeated exposure (up to 237 mg/kg bw/day for salicylic acid as tested in rats)
- not considered to be genotoxic

It is expected that the assessed chemical will hydrolyse into salicylic acid (CAS No 69-72-7) in physiological conditions. The toxicological information including the data on the metabolite salicylic acid indicates that the assessed chemical:

- is a skin sensitiser
- may cause adverse effects on foetus development

Based on the results of the adverse outcome pathway (AOP) assays and using the defined approach '2 out of 3' in the OECD Guideline (GL) 497, the chemical is a skin sensitiser. When tested at 20% concentration in a human repeat insult patch test (HRIPT) no skin reactions were observed during the induction or challenge phases on any subjects.

The assessed chemical has been tested in two guideline screening studies for reproductive and developmental toxicity studies (OECD TG 421 and OECD TG 422) in rats. In the OECD TG 422 study (Combined Repeated Dose Toxicity Study with the Reproduction/Developmental Toxicity Screening Test), when the assessed chemical was tested at 1,500, 3,750, and 7,500 ppm via the diet, the reproduction and developmental NOAEL could not be established. This is because the treatment related effects were observed at all dose levels, although the effects were statistically significant only at the highest dose level. In the OECD TG 421 study (Reproduction/Developmental Toxicity Screening Test), at up to 3,750 ppm (equivalent to 252 and 360 mg/kg/day for males and females, respectively) via the diet, no effects on reproductive or developmental toxicity were observed.

Studies following OECD TGs 421 or 422 do not normally include evaluations of foetus structural development, including skeletal and visceral malformations, which are key concern for salicylates. Salicylic acid and other salicylates caused adverse effects on foetus development in studies in 2 animal species (rat and monkey). In Wistar rats, the lowest developmental NOAEL was established at 75 mg/kg bw/day based on a non-guideline pre-natal developmental toxicity study similar to OECD TG 414. The main effects observed were increased incidences of neural tube defects (craniorachischisis), increased incidences of skeletal variations, decreased pup body weight, foetal growth retardation and increased foetal mortality in pups born from parental rats that were exposed to salicylic acid, sodium salicylate, methyl salicylate or acetyl salicylic acid (aspirin, a metabolic precursor of salicylic acid) during gestation. In monkeys, neural tube defects and kidney cysts were observed at 150 mg/kg bw/day for aspirin. Epidemiology studies from human medicinal use of aspirin, did not indicate an increased risk of birth defects (AICIS 2024).

No dermal or inhalation repeated dose toxicity data were submitted on the assessed chemical.

For further details of the health hazard information see **Supporting Information.**

Hazard classifications relevant for worker health and safety

Based on the available data, the assessed chemical satisfies the criteria for classification for human health according to the *Globally Harmonized System of Classification and Labelling of Chemicals* (GHS, UNECE 2017), as adopted for industrial chemicals in Australia.

Health hazards	Hazard category	Hazard statement
Skin Sensitisation	Skin Sens. 1	H317: May cause an allergic skin reaction
Reproductive Toxicity	Repr. 2	H361d: Suspected of damaging the unborn child

Summary of health risk

Public

There will be widespread and repeated exposure of the public to the assessed chemical at up to 3% concentration through the use of a wide range of personal care products (cosmetics excluding lipsticks and oral care products), and laundry and dishwashing products. The principal route of exposure will be dermal and inhalation, while incidental oral or ocular exposure is also possible. Inhalation exposure occurs particularly from the use of air care products and other products applied by spray.

Based on a typical use pattern of the consumer products containing the assessed chemical, the total daily systemic exposure of an adult user is estimated to be 0.71 mg/kg bw/day (see **Supporting information**), considering a dermal absorption of 13.4% as reported by EU Scientific Committee on Consumer Safety (SCCS 2023a) for the analogue chemical hexyl salicylate. The risk of the assessed chemical through daily use can be estimated by calculating the margin of exposure (MOE). Based on the lowest developmental NOAEL of 75 mg/kg bw/day for salicylic acid (molecular weight 138.12 g/mol) (see **Supporting information**), the NOAEL for the assessed chemical (molecular weight 222.28 g/mol) can be estimated as 120 mg/kg bw/day on a molar ratio basis. Therefore, an MOE of 169 can be derived for the chemical under the proposed consumer use scenarios. MOE greater than or equal to 100 is considered acceptable to account for intra- and inter-species differences. No risk of adverse developmental effects is expected upon daily normal use of the consumer products containing the assessed chemical at the assessed concentrations.

End use consumer products potentially available for use by children below 10 years of age will not contain the assessed chemical exceeding 0.1% concentration. This is below the concentration concluded to be safe by the EU SCCS (SCCS 2023a).

The assessed chemical is a skin sensitiser. In a Human Repeat Insult Patch Test (HRIPT, see **Supporting information**), the assessed chemical at 20% concentration was determined as not eliciting a sensitisation response. Consideration of the details of the submitted study allowed the derivation of an Acceptable Exposure Level (AEL) of 34.67 µg/cm^2/day for consumers using an overall safety factor of 100. Based on the quantitative risk assessment (QRA) calculations, this AEL was considered to be greater than or equal to each of the individual consumer exposure levels (CELs) for various personal care products (cosmetics) and laundry and dishwashing products with intended maximum use concentrations as

proposed in the application. Since the AEL is greater than or equal to CEL, induction of skin sensitisation associated with the use of the assessed chemical in a single consumer product at the assessed concentration is unlikely to occur. However, it is acknowledged that consumers may be exposed to multiple products containing the assessed chemical, and a quantitative assessment based on aggregate exposure has not been conducted.

Overall, there are no risks to the public identified in this assessment that require risk management.

Workers

Typically, industrial reformulation and filling processes will be automated and occur in fully enclosed systems. The end-use personal care products (cosmetics) and laundry and dishwashing products will be filled into various size containers suitable for retail distribution. Dermal, ocular and inhalation exposure (if aerosols or mists are formed) of workers to the assessed chemical in its neat form is possible during the operations. According to the applicant, worker exposure is expected to be minimised through the use of engineering controls and personal protective equipment (PPE) such as protective clothing, eye protection, impervious gloves, and appropriate respiratory protection. No health risk for reformulation workers is expected if control measures are in place.

Professional workers in cosmetic and cleaning businesses may experience exposure to the assessed chemical at up to 3% concentration mainly via dermal and inhalation routes during applications of the end use products containing the assessed chemical. These professional workers may wear PPE, including gloves, safety glasses, face masks and coveralls. If PPE is used, risk potential for such workers is expected to be of a similar or lesser extent than that of consumers using the same end use products containing the assessed chemical (see above **Public** section).

Environment

Summary of environmental hazard characteristics

According to the *Australian Environmental Criteria for Persistent, Bioaccumulative and/or Toxic Chemicals* (DCCEEW 2022) and based on the available data the assessed chemical is:

- Not persistent (not P)
- Not bioaccumulative (not B)
- Toxic (T)

Environmental hazard classification

The chemical satisfies the criteria for classification according to the *Globally Harmonized System of Classification and Labelling of Chemicals* (GHS) (UNECE 2017) as Acute Category 1 (H400) and Chronic Category 1 (H410) based on the toxicity data for aquatic organisms. Considerations were also made for the rapid biodegradation and bioaccumulation potential of the assessed chemical.

Environmental Hazard	Hazard Category	Hazard Statement
Hazardous to the aquatic environment (acute / short-term)	Aquatic Acute 1	H400: Very toxic to aquatic life

Hazardous to the aquatic environment (long-term)	Aquatic Chronic 1	H410: Very 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 will result in the release of the assessed chemical to sewers and to air.

The assessed chemical is readily biodegradable, not persistent and not bioaccumulative. The assessed chemical is toxic to aquatic organisms.

Although the assessed chemical is toxic, according to the *Australian Environmental Criteria for Persistent, Bioaccumulative and/or Toxic Chemicals* (DCCEEW 2022), 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 calculated 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

Recommendation to Safe Work Australia

It is recommended that Safe Work Australia (SWA) update the *Hazardous Chemical Information System* (HCIS) to include classifications relevant to work health and safety (see **Hazard classifications relevant for worker health and safety**).

Information relating to safe introduction and use

The information in this statement, including recommended hazard classifications, 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 dusts, mists or aerosols
- Use of safe work practices to
    - avoid contact with skin
    - avoid inhalation of vapours, mists or aerosols
- Use of personal protective equipment (PPE)
    - impervious gloves

    - protective clothing
    - respiratory protection where local ventilation may be inadequate

- The storage of the assessed chemical should be in accordance with the Safe Work Australia *Code of Practice for Managing Risks of Hazardous Chemicals in the Workplace* (SWA 2023) or relevant State or Territory Code of Practice.
- As the assessed chemical is a skin sensitiser, the control measures may need to be supplemented with health monitoring for any worker who is at significant risk of exposure to the chemical, if valid techniques are available to monitor the effect on the worker's health.
- A copy of the Safety Data Sheet (SDS) should be easily accessible to workers.

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:

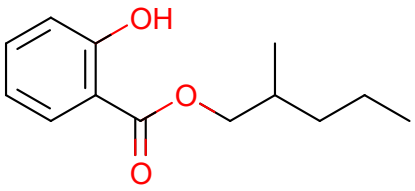
1. Obligations to report additional information about hazards under s 100 of the *Industrial Chemicals Act 2019* apply.
2. You should be aware of your obligations under environmental, workplace health and safety and poisons legislation as adopted by the relevant state or territory.

Supporting information

Chemical identity

CAS number	98969-19-8
CAS name	Benzoic acid, 2-hydroxy-, 2-methylpentyl ester
Molecular formula	$C_{13}H_{18}O_3$
Associated names	2-Methylpentyl 2-hydroxybenzoate 2-Methylpentyl salicylate
Molecular weight (g/mol)	222.28
SMILES (canonical)	O=C(OCC(C)CCC)C=1C=CC=CC1O

Representative structure



Additional chemical identity information

The assessed chemical is a racemate and has a degree of purity of greater than or equal to 95%.

Relevant physical and chemical properties

Physical form	Colourless liquid
Melting point	< - 83.7 °C
Boiling point	289.3 °C at 102.4 kPa
Density	1.04×10^3 kg/m^3 at 20.0 °C
Vapour pressure	2.8×10^{-4} kPa at 20 °C or 4.7×10^{-4} kPa at 25 °C
Flash point	141 °C
Auto-ignition temperature	370 °C at 101.2 and 101.9 kPa
Water solubility	1.59 mg/L at 20 °C
Ionisable in the environment	Not significant (< 10% ionisation)
pK_a	9.82 at 20 °C

log K_{OW}	5.6 at 35 °C
Log K_{OC}	4.124 (calc.)

Regulatory status of salicylic acid

Canada

Salicylic acid is listed in the *List of Ingredients that are Restricted for Use in Cosmetic Products* as permitted to be used at a maximum concentration of 2% (Canada 2025).

European Union

Cosmetics Directive Annex III *List of Restricted Substances* restricts salicylic acid to:

- 3.0% for rinse off hair products
- 2.0% for cosmetic products other than rinse off hair products, except body lotion, eye shadow, mascara, eyeliner, lipstick and roll-on deodorant
- 0.5% for body lotion, eye shadow, mascara, eyeliner, lipstick and roll-on deodorant.

Cosmetics Directive Annex VI *List of Preservatives Allowed* restricts salicylic acid and its salts to 0.5 % maximum for use as preservatives. Salicylic acid is:

- not to be used in preparations for children under 3 years of age
- not to be used in applications that may lead to exposure of the end-user's lungs by inhalation
- not to be used in oral products.

The EU SCCS (SCCS 2025) assessed the safety of exposure to salicylic acid for children of the age group between 3 and 10 years old and concluded that salicylic acid is not considered safe for this age group when used at 0.5%, due to concerns regarding aggregate exposure.

The EU SCCS concluded that use of salicylic acid in rinse-off products at up to 0.5%, leave-on products up to 0.15% and oral care products up to 0.1% is safe for children 3-10 years old.

Australia

Salicylic acid in preparations for dermal use except in preparations containing 40% or less is listed in the *Poisons Standard* (the SUSMP) as Schedule 3 and sodium salicylate in preparations for internal use for the treatment of animals is listed in the SUSMP as Schedule 4.

Schedule 3 chemicals are labelled with “pharmacist only medicine” and are described as “substances, the safe use of which requires professional advice but which should be available to the public from a pharmacist without a prescription.”

Schedule 4 chemicals are labelled with “prescription only medicine or prescription animal remedy” and are described as “substances, the use or supply of which should be by or on the order of persons permitted by State or Territory legislation to prescribe and should be available from a pharmacist on prescription.”

Human exposure

Public

Data on typical use patterns of 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 tables. For the purposes of exposure assessment, Australian use patterns for the various product categories are assumed to be similar to those in Europe. A combined average body weight (BW) for males and females of 60 kg is used for the calculations.

Dermal exposure

EU SCCS has reported a dermal absorption rate (DA) of 13.4% for hexyl salicylate that is a close analogue of the assessed chemical (SCCS 2023a). Given the structural similarity, it is reasonable to use this DA for the purposes of calculating the daily systemic exposure of the chemical.

Personal care products (cosmetics)

Product type	Amount (mg/day)	C (%)	RF	Daily systemic exposure (mg/kg bw/day)
Body lotion	7,820	2	1	0.3493
Face cream	1,540	2	1	0.0688
Hand cream	2,160	2	1	0.0965
Fine fragrances	750	2	1	0.0335
Deodorant (non-spray)	1,500	0.4	1	0.0134
Shampoo	10,460	3	0.01	0.0070
Conditioner	3,920	3	0.01	0.0026
Shower gel	18,670	3	0.01	0.0125
Hand wash soap	20,000	3	0.01	0.0134
Hair styling products	4,000	2	0.1	0.0179
Total				0.6149

C = maximum intended concentration of assessed chemical; RF = retention factor
Daily systemic exposure = (Amount × C × RF × DA)/BW; DA = 13.4%; BW = 60 kg

Laundry products - from wearing clothes

Product type	Amount (g/use)	C (%)	Product Retained (PR) (%)	Percent Transfer (PT) (%)	Daily systemic exposure (mg/kg bw/day)
Laundry liquid	230	3	0.95	10	0.0146

Product type	Amount (g/use)	C (%)	Product Retained (PR) (%)	Percent Transfer (PT) (%)	Daily systemic exposure (mg/kg bw/day)
Fabric softener	90	3	0.95	10	0.0057
Total					0.0203

C = maximum intended concentration of assessed chemical
Daily systemic exposure = (Amount × C × PR × PT × DA)/BW; DA = 13.4%; BW = 60 kg

Laundry, dishwashing and cleaning products

Product type	Frequency (use/day)	C (%)	Contact area (cm^2)	Product use C (g/cm^3)	Film thickness (cm)	Time scale factor	Daily systemic exposure (mg/kg bw/day)
Laundry liquid	1.43	3	1,980	0.01	0.01	0.007	0.0001
Dishwashing liquid	3	3	1,980	0.009	0.01	0.03	0.0011
All-purpose cleaner	1	3	1,980	1	0.01	0.007	0.0093
Total							0.0105

C = maximum intended concentration of assessed chemical
Daily systemic exposure = (Frequency × C × Contact area × Product Use Concentration × Film Thickness on skin × Time Scale Factor × DA)/BW; DA = 13.4%; BW = 60 kg

Inhalation exposure

Hairspray was taken as a worst-case scenario example for inhalation exposure assessment. A 2-zone approach was applied (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%.

It is acknowledged that inhalation exposure to the assessed chemical from use of other personal care or cleaning products (in addition to hair spray) may occur. However, it is considered that the combination of the conservative hair spray inhalation exposure assessment parameters, and the aggregate exposure from use of the dermally applicable products, is sufficiently protective to cover additional inhalation exposure to the assessed chemical from use of other spray products with lower exposure.

Hair spray

Amount of hairspray applied	9.89	g/day
Maximum intended concentration of the chemical	2	%
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	0.0687	mg/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) × BW)] + Daily systemic exposure in zone 2 [(amount × C × inhalation rate × exposure duration (zone 2) × fraction inhaled)/(volume (zone 2) × BW)]; BW = 60 kg

The worst-case scenario estimation using the above assumptions is for a person who is a simultaneous user of all products listed in the tables that contain the assessed chemical at the maximum intended concentrations specified in various product types. This would result in a combined daily systemic exposure of 0.71 mg/kg bw/day for the assessed chemical, accounting for both dermal and inhalation routes. This value is used in this assessment for QRA purposes to calculate the MOE for the assessed chemical (see **Summary of health risk**).

According to the information submitted by the applicant, the assessed chemical is not expected to be used in lipsticks and oral care (including toothpaste and mouthwash) products. The chemical is also not expected to be used at a concentration exceeding 0.1% in all products that may be potentially used by children below 10 years.

Health hazard information

The chemical is expected to be readily metabolised to salicylic acid (CAS No 69-72-7) (see below). Therefore, conclusions on systemic toxicity were further supported by data on salicylic acid.

Toxicokinetics

No specific toxicokinetic data are available for the assessed chemical.

Given the low molecular weight (222.28 g/mol) of the assessed chemical, there is potential for it to cross biological membranes, including the skin. However, the partition coefficient (log K_{OW} = 5.6 at 35 °C) implies low water solubility of the chemical to be absorbed through biological membranes. An *in vitro* human skin absorption study according to OECD TG 428 is available on hexyl salicylate that is a close analogue of the assessed chemical. A total measure absorption value of 4.47% was determined in this study. Based on application of a correction factor to allow for exposure conditions, EU SCCS reported a DA of 13.4% (SCCS 2023a).

It is known that n-alkyl salicylates are systemically converted to salicylic acid as the main metabolite by skin esterases and liver enzymes (SCCS 2023a). In the OECD TG 428 study described above, hydrolysis of hexyl salicylate to salicylic acid was almost complete when applying a dose of 0.1% concentration at 10 µl/cm^2 to skin (SCCS 2023a). Therefore it is expected that the assessed chemical will hydrolyse into 1-pentanol, 2-methyl- (CAS No 105-30-6) and salicylic acid (CAS No 69-72-7) in physiological conditions.

Acute toxicity

Oral

In an acute oral toxicity study (OECD TG 420), the assessed chemical was administered by oral gavage to one group of four female Wistar Han rats at 2,000 mg/kg bw. All animals survived to the end of the 14-day study period. There were hunched posture and piloerection in all animals between days 1 and 3. All effects fully reversed by day 4. The mean body weight gain shown by the females over the study period was considered to be normal. No macroscopic findings were recorded at necropsy. The acute oral LD50 value for the assessed chemical was determined to be > 2,000 mg/kg bw.

No acute dermal or inhalation toxicity data were submitted for the assessed chemical.

Corrosion/Irritation

Skin irritation

The assessed chemical was determined not to be irritating to skin in an *in vitro* skin irritation test using reconstructed human epidermis tissue model (EPISKIN Small) (OECD TG 439). The undiluted assessed chemical (25 µL each) was applied to the tissues for a 15-minute exposure followed by a 42-hour post-exposure incubation. The relative mean viability of the treated tissues, as compared to the negative controls, was 82% (above the threshold for irritancy of ≤ 50%). Under the conditions of the study and according to the test guideline, the assessed chemical was not considered to be irritating to the skin.

Eye irritation

The eye irritation potential of the assessed chemical was tested in an Isolated Chicken Eye test (OECD TG 438) by application of 30 µL undiluted chemical onto the centre of the cornea for 10 minutes. There was no significant corneal swelling (mean score = -3.3%) during the 4-hour observation on the treated eyes. No cornea opacity (mean score = 0) was noted. There was also no fluorescein retention (mean score = 0). No other morphological effect was observed. The assessed chemical was considered non-irritating to the eyes under the conditions of the test and according to the test guideline.

Sensitisation

Skin sensitisation

One direct peptide reactivity assay (DPRA, OECD TG442C), one ARE-Nrf2 luciferase assay (KeratinoSens, OECD TG 442D) and one genomic allergen rapid detection (GARD, OECD TG 442E) were provided by the applicant to evaluate the skin sensitisation potential of the assessed chemical. These tests were part of Integrated Approach to Testing and Assessment (IATA) which address specific key events of the Adverse Outcome Pathway (AOP) leading to development of skin sensitisation (OECD GL 497). The DPRA aimed to address the first key event (KE1, molecular initiation) of the AOP and the KeratinoSens aimed to address the second key event (KE2, keratinocyte activation) of the AOP. The assessed chemical tested positive in the KE1 and negative in the KE2.

The skin sensitisation potential of the assessed chemical was further tested in a GARD *in vitro* skin sensitisation assay, which addressed the third key event (KE3, dendritic cell activation) for binary prediction (OECD TG 442E). The assessed chemical returned positive results.

Based on the results of the AOP key event assays and using the "2 out of 3" approach of the OECD GL 497, the assessed chemical is a Cat 1 skin sensitiser warranting hazard classification under the GHS.

The skin sensitising potential of the assessed chemical at 30% concentration was evaluated in a human repeat insult patch test (HRIPT) with 98 subjects. The assessed chemical was dissolved in ethanol:diethyl phthalate (1:3) at 30% concentration. During the induction phase, the dissolved assessed chemical was applied using occlusive patch to the upper back of each subject for 24 hours. Patches were applied to the same site for a total of 9 applications. After a 2-week rest period, each subject was challenged with the assessed chemical at a virgin site for 24 hours and the skin reactions were scored over a period of 3 days. In the induction phase, one subject showed faint and minimal erythema on the treatment site on day 6. In the challenge phase, one subject showed faint and minimal erythema skin reaction to the first challenge at 24 hours. Another subject showed erythema to the second challenge at 48 hours. Therefore, skin sensitisation potential for the assessed chemical at 30% concentration cannot be ruled out.

The assessed chemical at 20% concentration was further evaluated in another HRIPT with 117 subjects using the same procedures. No skin reactions were observed during the induction or challenge phases on any subjects, indicating that the assessed chemical at 20% concentration does not demonstrate a potential for eliciting skin irritation or sensitisation under the test conditions. The results of this HRIPT are used for QRA purposes in this assessment to calculate AEL for the assessed chemical (see **Summary of health risk**).

Repeat dose toxicity

No repeated dose dermal or inhalation toxicity data on the assessed chemical were submitted.

A Reproduction/Developmental Toxicity Screening Test (OECD TG 421) via oral route was provided. In the test, the assessed chemical was administered to Crl:WI(Han) rats (10/sex/group) in diet at dose levels of 0, 500, 1,500 and 3,750 ppm for a minimum of 28 days. Males were treated for at least 2 weeks prior to mating and during the mating period. Females were treated for at least 2 weeks prior to mating, the variable time to conception, the duration of pregnancy and at least 13 days after delivery up to the day of scheduled necropsy.

There was no animal mortality nor treatment related clinical signs in daily clinical observations. Although there were some changes on body weight and body weight gain in males and females at 500 and 1,500 ppm, food consumption for these 2 groups was similar to the control group. There were also no treatment related gross or microscopic changes and alterations in organ weights. However, mean serum levels of total thyroxine (T4) decreased in males treated at 1,500 and 3,750 ppm (0.73 and 0.27-fold of the control respectively).

Under the conditions of the study, the NOAEL for repeated dose oral toxicity was considered to be 3,750 ppm (equivalent to 252 and 360 mg/kg/day for males and females respectively), based on no adverse effects noted at and below this dose level.

In a Combined Repeated Dose Toxicity Study With The Reproduction/Developmental Toxicity Screening Test (OECD TG 422), the assessed chemical was administered to Crl:WI(Han) rats (10/sex/group) in the diet at dose levels of 0 (with additional recovery group), 1,500, 3,750 and

7,500 (with additional recovery group) ppm for a minimum of 28 days, followed by a 14-day recovery.

Males were treated for 29-30 days, including a minimum of 14 days prior to mating and the duration of the mating period. Females were treated for 51-56 days, including 14 days prior to mating, period for conception and pregnancy, and at least 14 days after delivery up to the day of scheduled necropsy. Females that failed to deliver were treated for 42-44 days. Females that had a total litter loss were treated for 41-42 days.

No mortality happened during the study.

In males treated at 7,500 ppm, body weight stasis was seen in the first week of the treatment, followed by a decreased body weight gain in the following 3 weeks. At the end of the treatment, mean body weight of the group was 0.88-fold of the control. In the subsequent 14-day recovery, mean body weight recovered to 0.93-fold of the control.

In females treated at 7,500 ppm, decreased body weight gain was seen from day 4 post-coitum onwards, resulting in a mean body weight 0.81-fold of the control at the end of the gestation. This body weight gain decrease was associated with reduced food consumption. Potential treatment related effects on body weight and food consumption during lactation could not be assessed since only one lactating female with a single pup was present in the 7,500 ppm group. After the 14-day recovery period, the mean body weight of the recovery group treated at this level was 0.97-fold of the control, indicating a recovery.

There were statistically significant treatment related changes in clinical biochemistry at the end of the treatment. These included the followings.

- Total bilirubin concentrations decreased in males and females (recovery group) (0.61 and 0.68-fold respectively) at 7,500 ppm.
- Creatinine concentration increased in males at 7,500 ppm (1.21-fold).
- Serum levels of total T4 decreased at 3,750 and 7,500 ppm in males (0.60 and 0.19-fold) and females (0.55 and 0.23-fold). However, in males (recovery group) at 7,500 ppm, no difference was shown after the 14-day recovery. In females (recovery group) at 7,500 ppm, serum T4 level rather increased after the 14-day recovery (1.52-fold).
- Thyroid stimulating hormone (TSH) levels decreased in males at all dose levels (0.81, 0.70 and 0.81-fold at 1,500, 3,750 and 7,500 ppm respectively) and in females (recovery group) at 7,500 ppm (0.72-fold). However, TSH increased in females at 3,750 ppm (1.83-fold). After the 14-day recovery, TSH levels increased in the recovery males (1.72-fold) but decreased in females (0.77-fold).

A treatment related macroscopic finding was noted at 7,500 ppm in a single female, consisting of an enlarged spleen and correlating to extramedullary haematopoiesis. Possible treatment related decreases in thymus weights (absolute and relative to body weights) and increases in liver weights (relative to body weights) were observed in males at 7,500 ppm.

No NOAEL of repeated dose toxicity was established in this study as various effects were seen at all treatment levels.

In addition to the above studies, a 28-day dietary study on salicylic acid in rat reported a No Observed Effect Level (NOEL) of 237 mg/kg bw/day, the highest dose tested. A chronic oral toxicity study on aspirin in rats at a dose of 200 mg/kg bw/day for 200 days showed no treatment related effects (NICNAS 2013).

Observation in humans

Human data showed that oral doses of aspirin at 100 mg/kg bw or higher can induce salicylism or salicylic acid intoxication with symptoms occurring at plasma level of 35 mg/100 mL or higher (NICNAS 2013). Toxic effects have also been reported after topical application of salicylic acid to extensive areas of the body with diseased skin. Children are more sensitive than adults to develop salicylism after the treatment (SCCS 2023b).

Genotoxicity

The assessed chemical was not mutagenic in the bacterial Reverse Mutation Assay (Ames Test) when tested in *Salmonella typhimurium* strains TA98, TA100, TA1535, TA1537 and *Escherichia coli* strain WP2uvrA (pKM101) with or without metabolic activation (OECD TG 471). No significant increases in the frequency of revertant colonies were recorded for any of the bacterial strains at any tested concentrations (0, 1.6, 5, 16, 50, 160, 500, 1,600 and 5,000 µg/plate) in the absence or presence of S9-mix.

The assessed chemical was further tested for its clastogenic and aneugenic potential in an *in vitro* mammalian micronucleus test using TK6 human lymphoblastoid cells (OECD TG 487). Three experiments were conducted, 3-hour exposure without S9-mix (experiment 1), 3-hour exposure with S9-mix (experiment 2), and 24-hour exposure without S9-mix (experiment 3), at a concentration range of 4.567 to 2,000 µg/mL. Under the conditions of this study, the assessed chemical did not induce any statistically significant increase in number of cells with micronuclei, indicating that the assessed chemical was neither clastogenic nor aneugenic.

The assessed chemical is not likely to be genotoxic.

Reproductive and development toxicity

Salicylic acid and other salicylates caused adverse effects on foetus development in studies in 2 animal species (rat and monkey). In Wistar rats, the lowest developmental NOAEL was established at 75 mg/kg bw/day based on a non-guideline pre-natal developmental toxicity study similar to OECD TG 414. Based on information on the metabolite salicylic acid, the assessed chemical may cause adverse developmental effects warranting classification, and effects on fertility at high doses cannot be ruled out.

Assessed chemical

In the above-mentioned OECD TG 421 study (see **Repeat dose toxicity** above), there were 2/10 pairings at 1,500 ppm with no offspring. No abnormalities were seen in the reproductive organs of these males or females that could explain the lack of offspring. Stage dependent qualitative evaluation of spermatogenesis in the testes did not indicate any abnormality.

For reproduction, length and regularity of the oestrous cycle, mating index, precoital time, number of implantation sites and fertility index were not affected by the treatment.

Gestation index was not affected and all pregnant females had live offspring. There were no signs of difficult or prolonged parturition among the pregnant females. There were no signs of abortion or premature birth. Viability indices of offspring and lactation indices were not affected by the treatment. Post-implantation survival indices were 88%, 93%, 92% and 88% for 0, 500, 1,500 and 3,750 ppm groups respectively. Litter sizes were 11.5, 11.9, 11.5 and 10.9 living pups/litter for 0, 500, 1,500 and 3,750 ppm groups.

Among the pups, there were no treatment related clinical signs and there were no changes in body weight, anogenital distance, areola/nipple retention, clinical biochemistry, macroscopic finding and sex ratio.

The NOAEL was established at 3,750 ppm (equivalent to 252 and 360 mg/kg/day for males and females respectively) in this study for reproductive and development toxicity based on no adverse effects observed at any dose level.

In the OECD TG 422 study provided (see **Repeat dose toxicity** above), since several treated females at various levels were not pregnant, did not deliver, were sacrificed on lactation day 1, or had total litter loss, reproductive and developmental data were only available from limited numbers of dams.

The gestation indices were 78%, 100% and 10% for 1,500, 3,750 and 7,500 ppm groups when compared to the control group. In the 7,500 ppm group, gestation index was markedly decreased. Only 3/10 pregnant females delivered with 2 of them having total litter losses. The remaining female delivered only 1 single live pup. The gestation index at 1,500 ppm was also below the historical control data and was caused by total litter losses from 2 females on lactation day 1. This was considered to be related to the treatment as clear decreases in gestation indices were observed at 1,500 and 7,500 ppm although not 3,750 ppm. For one particular female at 7,500 ppm, which only delivered 1 single live pup, a gestation period of 23 days was noted while all other females with normal litters had 21-22 days.

No signs of difficult or prolonged parturition were observed among the pregnant females at up to 3,750 ppm. A toxicological evaluation at 7,500 ppm could not be conducted as data were only available from 3 females.

Decreased implantation sites (not statistically significant) were recorded in females at 7,500 and 1,500 ppm (10.1 and10.6 respectively when compared to 13.2 in the control group). Post-implantation survival indices were 83%, 88% and 1% for 1,500, 3,750 and 7,500 ppm groups respectively while the survival index of the control group was 94%. It was markedly reduced at 7,500 ppm treatment level. For the single female in the group that delivered only a single live pup, 12 uterine implantations were counted at necropsy. At 1,500 ppm, post-implantation survival index was reduced to the low limit of the historical control data. A trend towards a lower post-implantation survival index was also seen at 3,750 ppm. These findings were considered to be related to the treatment.

For 2 females in the 7,500 ppm group with total litter losses, dead pups were found during delivery, but the complete litter was cannibalised before the first litter check could be performed. For 1 female in the 1,500 ppm group, blood was observed in the cage with pups missing also indicating potential cannibalisation.

The live birth indices (the number of live offspring on Day 1 after littering compared to the total number of offspring born) were 94% and 99% for the 1,500 and 3,750 ppm groups when compared with the control group. The 7,500 ppm group only had 1 live pup. The decreases of live birth indices were considered to be related to the treatment.

For the live pups, clinical signs, body weight, sex ratio, anogenital distance, areola/nipple retention, serum T4 level and macroscopic findings were not affected by the treatment up to 3,750 ppm. These parameters in the 7,500 ppm group could not be adequately measured as only 1 live pup was available for analysis.

Based on the above results, treatment related reproductive and developmental effects of the assessed chemical were clearly seen. No NOAEL could be established based on the study as various effects were observed at all dose levels tested.

Salicylic acid

Salicylic acid showed 26% and 100% foetal mortality at 150 and 300 mg/kg bw/day in rats in a developmental toxicity study similar to OECD TG 414. Various other teratogenic effects, including external, internal and skeletal anomalies in offspring were observed. Based on the above evidence, the study authors established a NOAEL of 150 mg/kg bw/day for maternal toxicity and 75 mg/kg bw/day for developmental toxicity (AICIS 2024).

In several non-guideline developmental toxicity studies on salicylic acid conducted in rats and monkeys, various adverse developmental effects, including skeletal malformation, neural tube defects (craniorachischisis), growth retardation and foetal mortalities, were observed. The adverse effects on development caused by salicylic acid are supported by data on chemicals that metabolise to salicylic acid including methyl salicylate and aspirin. However, there were no developmental effects observed in rabbits for salicylic acid. Extensive human data on aspirin did not reveal evidence to support an increased risk of birth defects (AICIS 2024).

Overall, based on metabolism to salicylic acid, the assessed chemical is considered to be a developmental toxicant, warranting classification under GHS (Reproductive Toxicity Category 2, H361: suspected of damaging the unborn child).

Carcinogenicity

The metabolite salicylic acid is not expected to be carcinogenic (NICNAS 2013).

Endocrine effects

There are indications from the literature that the metabolite salicylic acid may have endocrine modulating properties, however, there are no *in vivo* or *in vitro* studies available that have explicitly examined the potential endocrine mode of action. The current available data do not provide evidence of an adverse effect from an endocrine mode of action (AICIS 2024).

Environmental exposure

The assessed chemical will be imported into Australia in its pure form and as a component in a fragrance formula or as a component of finished personal care and household products. Significant releases of the assessed chemical to the environment are not expected during transport or storage.

The assessed chemical is a fragrance ingredient to be included in a range of products, resulting in a variety of potential exposure scenarios.

Consumer and professional end-use of the assessed chemical in cosmetic products, washing products and cleaning products are 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 freshener products will result in the direct release of the assessed chemical into the air compartment.

Environmental fate

Partitioning

The assessed chemical is slightly water soluble (water solubility = 1.59 mg/L at 20 °C), moderately volatile (vapour pressure = 2.8×10^{-4} kPa at 20 °C or 4.7×10^{-4} kPa at 25 °C) and has a high calculated log K_{OC} value (log K_{OC} = 4.124). When the chemical is released to water, a considerable proportion of the chemical is expected to evaporate and partition to air. The remainder of the assessed chemical is not expected to stay in water and will partition to, and be immobile, in sediments.

The assessed chemical is not expected to partition out of the air compartment when released to air.

Degradation

Based on its measured degradation in water and predicted degradation in air, the assessed chemical is not persistent.

The half-life of the assessed chemical in air is calculated to be 0.576 day (6.907 hours), based on reactions with hydroxyl radicals (US EPA 2012; calculated using AOPWIN v1.92). As its calculated half-life in air is below the domestic threshold value of 2 days, the assessed chemical is not expected to persist in the air compartment.

Degradation studies in water indicate that the assessed chemical is readily biodegradable. A supplied OECD TG 301F biodegradation study for the assessed chemical demonstrated 81% degradation of the assessed chemical over 28 days and satisfied the 10-day-window criterion.

Bioaccumulation

Based on the weight of evidence, the assessed chemical is considered not bioaccumulative.

The experimental partition coefficient of the assessed chemical is log K_{OW} = 5.6, which is above the domestic bioaccumulation threshold value of log K_{OW} = 4.2. However, the calculated BCF value, using CATALOGIC v.5.15.2 model (LMC 2015) for the assessed chemical (Modelled BCF = 85.11) is below the domestic bioaccumulation threshold of 2,000 L/kg (EPHC 2009). The assessed chemical falls within the log $K_{OW,}$ water solubility and molecular weight applicability domains of the model. As the assessed chemical also meets the criteria for being readily biodegradable, the chemical is considered to be not bioaccumulative based on the weight of evidence.

Predicted environmental concentration (PEC)

A predicted environmental concentration (PEC) for Australian waters was calculated assuming 100% of the introduction volume is released into sewage treatment plants (STP) over 365 days per annum. The extent to which the assessed substance is removed from the effluent in STP processes is based on its physicochemical properties, modelled by SimpleTreat 3.0 (Struijs 1996). Based on the low water solubility, moderate volatility, high log K_{OW} and ready biodegradability, a large portion of the assessed chemical is expected to be removed by adsorption to biosolids, or through degradation and volatilisation during STP treatment. Total removal during STP treatment is estimated to be 94%. Therefore, 6% of the total introduction volume is estimated to be released to the aquatic environment.

The calculation of the PEC (Struijs 1996; EPHC 2009) 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	200.0	L/person/day
Population of Australia	25.423	Million
Removal within STP	94%	Mitigation
Daily effluent production	5,085	ML/day
Dilution Factor - River	1.0	
Dilution Factor - Ocean	10.0	
PEC - River	0.03	µg/L
PEC - Ocean	0.003	µg/L

Environmental effects

Effects on aquatic life

Acute toxicity

The following measured median lethal concentration (LC50) and median effective concentration (EC50) values for model organisms were supplied by the applicant:

Taxon	Endpoint	Method
Fish	96 h LC50 > 0.854 mg/L	*Gobiocypris rarus* (Rare minnow) Mortality OECD TG 203 Semi-static conditions Geometric mean of measured concentration
Invertebrate	48 h EC50 = 0.4 mg/L	*Daphnia magna* (Water flea) Immobility OECD TG 202 Semi-static conditions Arithmetic mean of measured concentration

Taxon	Endpoint	Method
Algae	72 h E_rC50 = 0.93 mg/L	*Pseudokirchneriella subcapitata* (Green algae) Growth rate OECD TG 201 Static conditions Time Weighted Average (TWA) of measured concentration

Chronic toxicity

The following measured No Observed Effect concentration (NOEC) value for a model organism was supplied by the applicant:

Taxon	Endpoint	Method
Algae	72 h NOEC = 0.22 mg/L	*Pseudokirchneriella subcapitata* (Green Algae) Growth rate OECD TG 201 Static conditions Time Weighted Average (TWA) of measured concentration

Endocrine effects

While there is some evidence that the metabolite of the assessed chemical, salicylic acid, interacts with the thyroid and glucocorticoid endocrine systems at high doses, there is currently insufficient evidence to suggest harmful effects in the environment (AICIS 2024).

Predicted no-effect concentration (PNEC)

A predicted no-effect concentration (PNEC) of 4 µg/L was calculated for the assessed chemical in the aquatic environment. This value was derived using the most conservative endpoint value for *Daphnia magna* (0.4 mg/L). An assessment factor of 100 was applied to this endpoint as acute toxicity data was available for three trophic levels and chronic toxicity data was incomplete (EPHC 2009). The acute endpoint was selected, over the algal chronic endpoint, in the absence of additional chronic endpoints to support the algal growth rate NOEC (ECHA 2008).

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

Not Persistent (Not P). Based on the measured degradation under screening test conditions, the assessed chemical is categorised as Not Persistent.

Bioaccumulation

Not Bioaccumulative (Not B). Based on weight of evidence, the assessed chemical is categorised as not Bioaccumulative.

Toxicity

Toxic (T). Based on the measured ecotoxicity values below 1 mg/L, the assessed chemical is categorised as Toxic.

Environmental risk characterisation

Although the assessed chemical is toxic, 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.

Based on the PEC and PNEC values determined above, Risk Quotients (RQ = PEC ÷ PNEC) have been calculated for release of the assessed chemical to water:

Compartment	PEC (µg/L)	PNEC (µg/L)	RQ
River	0.03	4	0.008
Ocean	0.003	4	0.001

For the river and ocean compartments, an RQ less than 1 indicates that introduction of the assessed chemical, in line with the terms outlined in this assessment certificate, is not expected to pose a significant risk to the environment. As such, the risk from the assessed chemical can be managed, based on consideration of the environmental hazard characteristics and estimated releases.

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