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

4-Pentenal, 2,4-dimethyl-5-(4-methylphenyl)-, (4*E*)-

Assessment statement (CA09630)

22 August 2024

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AICIS assessment (CA09630)

Chemical in this assessment

Name	CAS registry number
4-Pentenal, 2,4-dimethyl-5-(4-methylphenyl)-, (4*E*)-	1226911-73-4

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:

- a fragrance component imported into Australia at up to 1 tonne per year
- imported at up to 85% concentration for local reformulation into finished cosmetic and household products
- imported or reformulated as a component of finished end-use cosmetic and household products at up to:
    - 0.3% concentration in spray deodorant
    - 0.6% concentration in fine fragrances
    - 0.5% concentration in leave-on cosmetic products
    - 6% concentration in rinse-off cosmetic products
    - 7% concentration in laundry and cleaning products and in air care products – continuous action
    - 20% concentration in candles

Summary of assessment

Summary of introduction, use and end use

The assessed chemical is a fragrance ingredient and will not be manufactured in Australia. It will be imported in tightly closed lacquered drums of varying sizes up to 180 kg. These drums will be either stored at the applicant's warehouse facilities or transported directly to the industrial facilities of customers for formulation of fragranced products.

The assessed chemical will be imported either at up to 85% concentration for reformulation into finished cosmetic and household products or as a fragrance component in finished end use cosmetic and household products. The proposed maximum use concentrations of the assessed chemical in various cosmetic and household products will be at up to 0.3% concentration in spray deodorant, up to 0.6% concentration in fine fragrances, up to 0.5%

concentration in leave-on cosmetic products, up to 6% concentration in rinse-off cosmetic products, up to 7% concentration in laundry and cleaning products and in air care products (continuous action), and at up to 20% concentration in candles.

Finished consumer products containing the assessed chemical at various concentrations will be packaged in containers suitable for retail sale.

Human health

Summary of health hazards

The submitted toxicological data on assessed chemical or analogues of assessed chemical, indicate that the assessed chemical is:

- likely to be of low acute oral toxicity
- irritating to the skin
- non irritating to the eyes
- a skin sensitiser
- not likely to cause systemic toxicity following repeated oral exposure (up to 300 mg/kg bw/day in rats)
- not considered to be genotoxic

No dermal or inhalation toxicity data were provided on the assessed chemical.

Hazard classifications relevant for worker health and safety

Based on the data provided by the applicant, the assessed chemical satisfies 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.

Health hazards	Hazard category	Hazard statement
Skin irritation	Category 2	H315: Causes skin irritation
Skin sensitisation	Category 1B	H317: May cause an allergic skin reaction

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 through the use of a wide range of cosmetic and household products (at up to 0.3% concentration in spray deodorant, up to 0.6% concentration in fine fragrances, up to 0.5% concentration in leave-on cosmetic products, up to 6% concentration in rinse-off cosmetic products, up to 7% concentration in air care products (continuous action), and at up to 20% concentration in candles). The principal route of exposure will be dermal, while ocular and inhalation exposures are also possible, particularly from air care products and from products applied by spray.

The assessed chemical is a skin irritant (Category 2) and skin sensitiser (Category 1B). Given the proposed low use concentrations of the assessed chemical in cosmetic and household

products and fine fragrances, skin irritation and skin sensitisation effects are not expected. Similarly, skin irritation and skin sensitisation effects are also not expected when the assessed chemical is used at up to 7% concentration in air care products and at up to 20% concentration in candles as there is no direct dermal contact. No inhalation toxicity data are provided for the assessed chemical. However, the assessed chemical is of low vapour pressure (0.132 Pa at 25 °C) and is not persistent in the environment and therefore, not expected to cause inhalation risk when using at up to 7% concentration in continuous action, electrical air fresheners.

The repeated dose toxicity potential of the assessed chemical was estimated by calculating the margin of exposure (MOE), using the worst-case exposure scenario from use of multiple products simultaneously by an individual. The total daily systemic exposure was estimated as 2.9813 mg/kg bw/day (see **Supporting information, Human Exposure Section**). Using a No Observed Adverse Effect Level (NOAEL) of 300 mg/kg bw/day for the assessed chemical, MOE of 101 was calculated. MOE greater than or equal to 100 is considered acceptable to account for intra- and inter-species differences. The MOE would be 123 excluding the laundry products (not applied to the skin deliberately and any accidental spillage is expected to be washed-off immediately). In addition, the MOE of 123 was derived for the worst-case systemic exposure scenario considering a dermal absorption rate of 100%.

Overall, no risks are identified for public health during this assessment that require specific risk management measures.

Workers

Potential exposure of workers to the assessed chemical at up to 85% concentration may occur during reformulation processes. Exposure to the assessed chemical in end use products (at up to 6% concentration) may occur in professions where the services provided involve the application of cosmetic and personal care products to clients (e.g., hairdressers and workers in beauty salons) or the use of household products in the cleaning industry.

The principal routes of exposure will be dermal and inhalation (spray products), while ocular exposure is also possible. Professionals may use personal protective equipment (PPE) to minimise repeated exposure, and good hygiene practices are expected to be in place. 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 end use products containing the assessed chemical at up to 6% concentration.

Given that risks of critical health effects (skin irritation, skin sensitisation) of the assessed chemical, control measures to minimise dermal exposure are required to manage the risks to workers (see **Means for managing risk section**). Control measures to minimise inhalation exposure may be also required to manage the risks to workers if aerosols or mists are formed during the blending process.

Environment

Summary of environmental hazard characteristics

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

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

Environmental hazard classification

The assessed chemical satisfies the criteria for classification according to the *Globally Harmonized System of Classification and Labelling of Chemicals* (GHS) (UNECE 2017) as Acute Category 2 (H401) and Chronic Category 3 (H412) based on the toxicity data for aquatic invertebrates and green algae, respectively. Considerations were also made for the rapid biodegradation 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 3	H412: Harmful 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. This use may result in the release of the assessed chemical to sewers and to air.

The assessed chemical is readily degradable and is not persistent. The assessed chemical has low potential to bioaccumulate and is not toxic to aquatic organisms according to domestic threshold values.

The assessed introduction does not meet any of the 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 the 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 activities:

- Use of engineering controls such as

    - Enclosed and automated systems
    - Adequate workplace ventilation to avoid accumulation of vapours, 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

- As the assessed chemical is a skin sensitiser and respiratory sensitisation cannot be ruled out, 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:

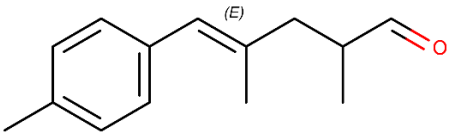
1. Obligations to report additional information about hazards under s 100 of the *Industrial Chemicals Act 2019* apply.
2. You should be aware of your obligations under environmental, workplace health and safety and poisons legislation as adopted by the relevant state or territory.

Supporting information

Chemical identity

Chemical name	4-Pentenal, 2,4-dimethyl-5-(4-methylphenyl)-, (4*E*)-
CAS No.	1226911-73-4
Molecular formula*	$C_{14}H_{18}O$
Molecular weight (g/mol)*	202.29
SMILES (isomeric)*	C(=C(/CC(C=O)C)\C)\C1=CC=C(C)C=C1

Structural formula*



Chemical description

The assessed chemical is a racemate of the 2R- and 2S- stereoisomers with a purity of greater than or equal to 75% and less than or equal to 85%.

Relevant physical and chemical properties

Physical form	Colourless liquid
Melting/Freezing point	< -20 °C[#]
Boiling point	294.5 ± 0.5 °C*
Density	968.5 kg/m^3 at 20.0 ± 0.5 °C*
Vapour pressure	0.132 Pa at 25 °C*
Flash point	135 ± 2 °C*
Auto-ignition temperature	252 °C[#]
Water solubility	24.67 mg/L at 25 °C[#]
Ionisable in the environment?	No
log K_{ow}	3.67 at 30 °C*

* chemical purity 78.2%; [#] chemical purity 98.6%

Human exposure

Workers

Reformulation

Typically, reformulation processes may incorporate blending operations that are automated and occur in a fully enclosed/contained environment with local exhaust ventilation, followed by manual or automated filling using sealed delivery systems into containers of various sizes. Dermal, ocular and inhalation exposure (if aerosols or mists are formed) of workers to the assessed chemical at up to 85% concentration is possible during weighing and transfer stages, blending, quality control analysis and cleaning, and during maintenance of equipment. However, the exposure is expected to be minimised through the use of mechanical ventilation and/or enclosed systems, and through the use of PPE (such as protective clothing, eye protection, impervious gloves, and appropriate respiratory protection) by workers.

Professional End Use

Exposure to the assessed chemical in end use products at up to 6% concentration may occur in professions where the services provided involve the application of cosmetic and personal care products to clients (e.g., hairdressers and workers in beauty salons) or the use of household products in the cleaning industry. These products, depending on their nature, could be applied in a number of ways, such as by hand, using an applicator or sprayed. The principal route of exposure will be dermal and inhalation (for air care products and spray products), while ocular exposure is also possible. Professionals may use PPE to minimise repeated exposure, and good hygiene practices are expected to be in place. 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 end use products containing at up to 6% of the assessed chemical.

Public

There will be widespread and repeated exposure of the public to the assessed chemical (at up to 0.3% concentration in spray deodorant, up to 0.6% concentration in fine fragrances, up to 0.5% concentration in leave-on cosmetic products, up to 6% concentration in rinse-off cosmetic products, up to 7% concentration in air care products (continuous action), and at up to 20% concentration in candles) through the use of various cosmetic and household products. The principal route of exposure will be dermal, while ocular and/or inhalation exposures are also possible, particularly if the products are applied by spray or when used in air fresheners.

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. Given the low molecular weight (268.39 g/mol) of the assessed chemical, there is potential for it to cross biological membranes, including the skin. However, the partition coefficient (log P_{ow} = 3.53 - 3.67 at 30 °C) implies low water solubility of the chemical (24.67 mg/L at 25°C) to absorb through biological membranes. A worst-case dermal absorption (DA) rate of 100% was used along with average lifetime bodyweight for males and females combined (BW) of 60 kg (enHealth 2012) for calculation purposes. 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%.

The following tables provide information on exposure estimates obtained using the above parameters.

Product type	Amount (mg/day)	C (%)	RF	Daily systemic exposure (mg/kg bw/day)
Body lotion	7,820	0.5	1	0.6517
Face cream	1,540	0.5	1	0.1283
Hand cream	2,160	0.5	1	0.1800
Fine fragrances	750	0.60	1	0.075
Deodorant (non-spray)	1,500	0.3	1	0.0750
Deodorant (spray)	1,430	0.3	1	0.0715
Shampoo	10,460	6.0	0.01	0.1046
Conditioner	3,920	6.0	0.01	0.0392
Shower gel	18,670	6.0	0.01	0.1867
Hair styling products	4,000	2.0	0.1	0.1333
Total				**1.6453**

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

Household products (Indirect dermal exposure – 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	7.00	0.95	10	0.2549
Fabric softener	90	7.00	0.95	10	0.0998
Total					**0.3547**

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

Household products (Direct dermal exposure)

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	7.00	1,980	0.01	0.01	0.007	0.0023
Dishwashing liquid	3	7.00	1,980	0.009	0.01	0.03	0.0187

All-purpose cleaner	1	7.00	1,980	1	0.01	0.007	0.1617
Total							**0.1827**

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

Hair spray (inhalation exposure)

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	**0.7986**	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) × body weight)] + Daily systemic exposure in zone 2 [(amount × C × inhalation rate × exposure duration (zone 2) × fraction inhaled) / (volume (zone 2) × body weight)]

The worst-case scenario estimation using these assumptions 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 2.9813 mg/kg bw/day for the assessed chemical. It is acknowledged that inhalation exposure to the assessed chemical from use of other cosmetic and household 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 applied products, which assumes a conservative 100% dermal absorption rate, is sufficiently protective to cover additional inhalation exposure to the assessed chemical from use of other spray cosmetic and household products with lower exposure factors (e.g. air fresheners).

All cosmetic use concentrations shown in the above tables were within the allowable exposure level (AEL) concluded by the quantitative risk assessment calculation using an EC3 of 9.3%.

Health hazard information

Toxicokinetics

Given the low water solubility (24.67 mg/L at 25°C) and the partition coefficient (log Kow = 3.53 - 3.67 at 30°C) of the assessed chemical, absorption across biological membranes is expected to be limited.

Acute toxicity

Oral

In an acute oral toxicity study (OECD TG 420), an analogue chemical was administered by oral gavage to 5 female Wistar rats at 2,000 mg/kg bw. There were no deaths and no signs of systemic toxicity. All animals showed expected gains in body weight. The acute oral LD50 value for the analogue 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 corrosive to the skin in an *in vitro* skin corrosivity test using the EpiDerm™ reconstructed human epidermis tissue model (EpiDerm™ tissue) (OECD TG 431). The relative mean viability of the test chemical-treated tissues was 97.9% after the 3 minutes exposure period and 102.8.% after 60 minutes exposure period. Under the conditions of this study and according to the test guideline, the assessed chemical was not considered to be corrosive to the skin.

The assessed chemical was irritating to the skin in an *in vitro* skin irritation test using reconstructed human epidermis tissue model (EPISKIN Small model) (OECD TG 439). The relative mean viability of the test item treated tissues, as compared to the negative control tissues, was 32.9% after the 15-Minute exposure period (followed by the 42-Hours post-exposure incubation period). Under the conditions of the study and according to the test guideline, as the relative mean tissue viability is ≤ 50%, the assessed chemical was considered to be irritating to the skin, warranting hazard classification.

Considering the above results, the assessed chemical is classified as a skin irritant Category 2 (H315: Causes skin irritation Category 2) according to the GHS criteria.

Eye irritation

The assessed chemical was tested using Reconstructed Human Cornea-like Epithelial (RhCE) Model (EpiOcular™ Eye Irritation Test) (OECD TG 492) to determine whether it is not an eye irritant or requires classification for serious eye damage. Duplicate tissues were treated with the test item for an exposure period of 30 minutes. At the end of the exposure period, each tissue was rinsed before incubating for 120 minutes. The relative mean tissue viability obtained after 30 minutes exposure period with the test item, compared to the negative control tissues, was 106.5%. Based on these results and as per the test guideline, the assessed chemical was determined not to be an eye irritant.

The eye irritation potential of the assessed chemical was further tested in an isolated chicken eye (ICE) test (OECD TG 438). The test item (30 µL) was applied onto the cornea of each of three enucleated chicken eyes for 10 seconds before being rinsed with 20 mL of saline solution. Damages by the test item were assessed by determination of corneal swelling, cornel opacity, and fluorescein retention (only determined at 30 minutes) at 30, 75, 120, 180 and 240 minutes after the post-treatment rinse with saline solution. The observed maximal mean score for corneal opacity was 0.8 (ICE Class II), maximal mean corneal swelling observed was 1.55% (ICE Class I), and the observed mean score for fluorescein retention was 0.5 (ICE Class I). The combination of the three endpoints (IIx I, Ix 2) fall under the 'No Category' in the TG. Under the conditions of this study and according to the test guideline, the assessed chemical does not require classification for eye irritation or serious eye damage.

Overall, based on the submitted information, the assessed chemical is not classified as an eye irritant.

Sensitisation

Skin sensitisation

One *in chemico* and one *in vitro* cell based assays were conducted to evaluate the skin sensitisation potential of the assessed chemical. The applicant also submitted One *in chemico* and one *in vitro* cell based assays on an analogue chemical to further evaluate the skin sensitisation potential of the assessed chemical. These tests are 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, 2016), and (DASS GD 497, June 2021).

The direct peptide reactivity assay (DPRA) is a *chemico* method and aims to address the first key event (KE) (molecular initiation) of the AOP by measuring the interaction of the assessed chemical with cysteine and lysine, small synthetic peptides representing the nucleophilic centres in skin proteins (OECD TG 442C). The ARE-Nrf2 luciferase assay aims to address the second key event (keratinocyte activation) of the AOP by measuring the expression of a reporter luciferase gene under the control of a promoter from the antioxidant response element (ARE), a responding gene known to be upregulated by contact sensitisers (OECD TG442D). The results of these assays are considered using the applicable Defined Approaches (DA) in the DASS Guideline for Classification and Labelling purposes.

The assessed chemical and the analogue chemical showed negative results in the first key event (molecular initiating) of the AOP for skin sensitisation (OECD TG 442C) and positive results in the second key event (keratinocytes response) of the AOP for skin sensitisation in the *in Vitro* Skin Sensitisation Assay (OECD TG 442d). The applicant did not provide results from the third key event assay of the AOP for skin sensitisation, the Human Cell Line Activation test (h-CLAT) assay (OECD TG 442E), as required for the '2 out of 3' DA in the DASS GL (OECD 497, June 2021) to determine the skin sensitisation conclusion for the assessed chemical.

To confirm the skin sensitisation potency of the assessed chemical, the applicant has provided data from an analogue chemical using a local lymph node assay (LLNA) (OECD TG 429). Groups of five mice were treated with the undiluted test item or the test item at concentrations of 25%, 50% or 100% v/v in acetone/olive oil 4:1. The mice were treated by daily application of 25 µl of the appropriate concentration of the test item to the dorsal surface of each ear for three consecutive days (Days 1, 2, 3). The preliminary screening test suggested that the test item would not produce systemic toxicity or excessive local irritation at the highest suitable concentration. On day 6, all mice were injected with 250 µL (20 µCi/mouse) of ^{3}HTdR (80

μCi/mL) solution via the tail vein and the animals were euthanised approximately 5 hours afterward for further processing.

There were no deaths or signs of systemic toxicity. The analogue chemical at 25%, 50% and 100% (v/v) concentrations in acetone/olive oil (4:1) (w/v) produced a Stimulation Index (SI) of 6.19, 13.93 and 15.06, respectively. The analogue chemical was characterised as a skin sensitiser and the concentration of the analogue chemical expected to cause a 3-fold increase in ^{3}HTdR incorporation (extrapolated EC3 value) was calculated to be 9.3%.

The positive results of the analogue chemical in the LLNA test confirmed that the assessed chemical is a skin sensitiser. Using the EC3 value of the analogue chemical (9.3%) with GHS criteria for classification, the assessed chemical is determined to be a Category 1B skin sensitiser (H317: May cause an allergic skin reaction).

The skin sensitising potential of an analogue chemical was further evaluated in a human repeat insult patch test (HRIPT) in 105 human subjects out of 120 subjects enrolled. The analogue chemical (0.3 mL) at 3% concentration was applied under occlusive patch to the left side of back of each subject and was allowed to remain in direct skin contact for a period of 24 hours. Patches were applied to the same site for a total of 9 applications during the induction period. After a 2-week rest period, the subjects were rechallenged at a virgin site for 24 hours and the reactions were scored over a period of 3 days. The human subjects exposed to the analogue at 3.0% concentration (0.3 mL) under occlusive patch area of (2.54 cm^{2}) did not induce dermal sensitisation in the human subjects.

Repeat dose toxicity

Oral

In a repeated dose oral toxicity study (OECD TG 407), an analogue chemical was administered to Wistar rats (n = 5/sex/dose) by oral gavage for 28 days at dose levels of 0, 30, 300 and 750 mg/kg bw/day.

Clinical findings were only confined to transient episodes of increased salivation, which developed during the first week of treatment in animals treated at 300 and 750 mg/kg bw/day and persisted (sporadically) through to Day 28 (the final day of treatment). Such observations are commonly observed following gavage administration of an unpleasant tasting or slightly irritant formulation rather than as a systemic toxicity effect to the test substance.

There were no treatment-related changes in the behavioural parameters, functional performance parameters, sensory reactivity, body weight gain, food consumption, haematology, blood chemistry, and at necropsy on macroscopic changes.

With respect to organ weights, statistically significantly increased kidney and liver mean weights were noted only in males at 750 mg/kg bw/day (absolute and relative to terminal body weight) when compared to controls; an increase of 3.5% (11.2%) kidneys weights and 0.5% (16.5%) liver weights, absolute and relative, respectively. However, as there were no supporting microscopic findings detected to suggest treatment-related hepatic changes, these changes were noted as adaptative response to the treatment by the study author.

Treatment-related microscopic findings were observed in the kidneys of both sexes at 300 and 750 mg/kg bw/day. These findings were characterised by mild or minimal basophilic epithelium in the collecting tubules of four males and one female at 300 mg/kg bw/day and in all the males and four females at 750 mg/kg bw/day. In the more severely affected animals

(750 mg/kg bw/day), associated single cell necrosis and/or increased mitoses (4 animals) were also noted, as compared to one animal at 300 mg/kg bw/day.

As a number of animals showed mitotic changes, which are indicative of renewal and repair, the study author indicated that it is likely that the renal changes at 300 mg/kg bw/day may have been an adaptive response to a slightly irritant test item. It is also likely that the single cell necrosis identified in the collecting tubule in one high dose male may be a result of biological variability. However, as this is a degenerative tissue change, it cannot be wholly excluded from animals from this test group. Therefore, based on the above findings, the study author established a No Observed Adverse Effect Level (NOAEL) of 300 mg/kg bw/day in this study, based on microscopic renal changes in either sex of animals treated at 750 mg/kg bw/day.

Genotoxicity

The assessed chemical was not mutagenic in a bacterial reverse mutation assay using *Salmonella typhimurium* strains TA98, TA100, TA1535, TA1537 and *Escherichia coli* strain WP2uvrA, with or without metabolic activation (OECD TG 471). There were no significant increases in the frequency of revertant colonies were recorded for any of the bacterial strains at any tested dose (5 to 150 µg/plate), with or without metabolic activation (S9-mix).

The assessed chemical did not induce the formation of micronuclei in an *in vitro* micronucleus test in cultured human lymphocytes cells, either in the presence or absence of a metabolic activation system (OECD TG 487). Three exposure conditions were used for the study using a 4-hour exposure in the presence and absence of a metabolising system (S9) (Experiment 1) and a 24-hour exposure in the absence of metabolic activation (Experiment 2). The selection of the concentrations used in experiment 1 (up to 64 µg/mL) and Experiment 2 (up to 128 µg/mL) were based on data from the pre-experiments. The test item did not induce any statistically significant increases in the frequency of cells with micronuclei, indicating that the assessed chemical was neither clastogenic nor aneugenic.

Overall, the assessed chemical is not considered to be genotoxic.

Environmental exposure

The assessed chemical will be imported into Australia in its pure form and as a component in a fragrance formula for blending into a wide variety of end use products, or as a component of finished personal and household care products. Significant releases of the assessed chemical to the environment are not expected during transport or storage. Any accidental spills are to be immediately collected with an absorbent, non-combustible material, placed in a suitable container, and disposed of via incineration. Environmental releases of the assessed chemical during blending and reformulation are expected to be minimal as the processes are highly automated and enclosed.

The assessed chemical is a fragrance ingredient to be included in a range of products, resulting in a variety of potential exposure scenarios. As a fragrance ingredient, a proportion of the assessed chemical is anticipated to volatilise during use, but this proportion is not expected to be significant for every use.

Uses of the assessed chemical in washing and cleaning and in cosmetic 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 moderately water soluble (water solubility = 24.67 mg/L at 25°C). If the assessed chemical is released to surface water, a proportion of the assessed chemical is expected to remain in water compartment and a proportion of the chemical is expected to partition to sediments based on its moderate water solubility.

The assessed chemical is moderately volatile (vapour pressure = 0.149 Pa at 25°C). However, the assessed chemical is not expected to partition to air during STP treatment, based on SimpleTreat 3.0 model outputs (Struijs, 1996). Additionally, when the assessed chemical is directly released to air it is not expected to partition to other compartments.

Degradation

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

Degradation studies in water indicate that the assessed chemical is readily biodegradable. The result of a biodegradation study for the assessed chemical was 83% degradation (OECD 301D) over 28 days and satisfied the 14-day-window criterion.

The half-life of the assessed chemical in air is calculated to be 1.08 hours, based on reactions with hydroxyl radicals (US EPA, 2012; calculated using AOPWIN v1.92). As the 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.

Bioaccumulation

Based on its log K_{OW} value, the assessed chemical is not considered to be bioaccumulative.

No bioaccumulation information was provided for the assessed chemical. The experimental partition coefficients of the assessed chemical (containing two main constituents represented by peak 1 and peak 2) are log K_{OW} = 3.53 and 3.67, which are 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 100% of the introduction volume is released into sewage treatment plants (STP). This calculated value is conservative as not all uses of the assessed chemical are expected to result in release to STP. Based on its moderate water solubility, log K_{ow} and ready biodegradability, a large proportion of the assessed chemical is expected to be removed by biodegradation and adsorption to biosolids during STP treatment. 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) and is estimated to be 89%. Therefore 11% of the

total introduction volume is estimated to be released to the aquatic environment. 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	200.0	L/person/day
Population of Australia	24.386	Million
Removal within STP	89%	Mitigation
Daily effluent production	4,877	ML/day
Dilution Factor - River	1.0	
Dilution Factor - Ocean	10.0	
PEC - River	0.06	µg/L
PEC - Ocean	0.01	µg/L

Environmental effects

Effects on Aquatic Life

Acute toxicity

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

Taxon	Endpoint	Method
Fish	96 h LC50 = 4.2 mg/L	*Danio rerio* (Zebra fish) Mortality OECD TG 203 Semi-static conditions Geometric mean of measured concentration
Invertebrate	48 h EC50 = 1.028 mg/L	*Daphnia magna* (water flea) Immobility OECD TG 202 Semi-static conditions Geometric mean of measured concentration
Algae	72 h ErC50 = 1.929 mg/L	*Pseudokirchneriella subcapitata* (green algae) Growth rate OECD TG 201 Static conditions Geometric mean of measured concentration

Chronic toxicity

The following measured 10th-percentile effective concentration (EC10) values for model organisms were supplied by the applicant:

Taxon	Endpoint	Method
Algae	72 h EC10 = 0.895 mg/L	*Pseudokirchneriella subcapitata* (green algae) Growth rate OECD TG 201 Static conditions Geometric mean of measured concentration

Predicted no-effect concentration (PNEC)

A predicted no-effect concentration (PNEC) of 10.28 µg/L was calculated for the assessed chemical in the aquatic environment. This value was derived using the most conservative endpoint value for aquatic invertebrate (1.028 mg/L). An assessment factor of 100 was applied to this endpoint as acute toxicity data were provided for all three trophic levels and chronic toxicity data were provided for one tropic level (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 EC10 value (ECHA 2008).

Categorisation of environmental hazard

The categorisation of the environmental hazards of the assessed chemical according to domestic environmental hazard thresholds is presented below:

Persistence

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

Bioaccumulation

Not Bioaccumulative (Not B). Based on the measured log K_{OW} value indicating a low potential to bioaccumulate, the assessed chemical is categorised as Not Bioaccumulative.

Toxicity

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

Environmental risk characterisation

The assessed chemical does not meet any of the PBT criteria and 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	PNEC	RQ
River	0.06 µg/L	10.28 µg/L	0.006
Ocean	0.01 µg/L	10.28 µg/L	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 likely be managed, based on consideration of the environmental hazard characteristics and estimated releases.

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