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

Santalum austrocaledonicum, ext.

Assessment statement (OA214)

13 December 2023

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AICIS assessment statement (OA214)

Chemical in this assessment

Name	CAS registry number
Santalum austrocaledonicum, ext.	91845-48-6

Reason for the assessment

An application to vary the terms of an Inventory listing under section 88 of the *Industrial Chemicals Act 2019* (the Act).

The chemical has been previously assessed (LTD/2142) and is listed on the *Australian Inventory of Industrial Chemicals* (the Inventory). An introducer applied to vary the specific requirements to provide information (see **Supporting information**) to increase the end use concentrations in cosmetic and household products that exceed the current limit of 0.1%.

This assessment statement should be read in conjunction with the assessment report for LTD/2142 (AICIS 2020).

Defined scope of assessment

The chemical has been assessed in relation to the proposed variation to the terms of the Inventory listing.

Summary of assessment

Summary of introduction, use and end use

The introduction, use and end use details of the chemical are described in the assessment report of LTD/2142 and have not changed in this assessment apart from the increase of import concentration (from up to 1% to up to 100%) and end use concentration (from up to 0.1% to up to 5%).

The proposed maximum use concentrations of the assessed chemical in end use products are at up to 0.23% concentration in leave-on cosmetic products, at up to 1.5% concentration in rinse-off cosmetic products, at up to 0.41% concentration in fine fragrances, at up to 5% concentration in household products and at up to 0.1% concentration in hairspray.

The cosmetic and household end use products containing the chemical are proposed to be used by professional workers under industrial or non-industrial settings and by members of the general public.

Human health

Summary of health hazards

The toxicological data submitted for LTD/2142 (see **Supporting information**) indicate that the assessed chemical is:

- of low acute oral toxicity
- irritating to skin
- not irritating to eyes
- a weak skin sensitiser
- not expected to be genotoxic

Repeated dose toxicity information was not submitted for the assessed chemical. However, the applicant of the variation submitted studies on an analogue chemical for repeated dose toxicity, and reproductive and developmental toxicity screening, which were appropriate for read across to the assessed chemical. The studies indicate that the assessed chemical is:

- not expected to cause adverse systemic health effects following repeated oral exposure

The submitted data (see **Supporting information**) were used to estimate the health risk of repeated exposure to the assessed chemical in end use products at the proposed concentrations (see **Public** subsection of **Summary of health risk**).

No inhalation toxicity data were provided for the variation application for LTD/2142.

Hazard classifications relevant for worker health and safety

Based on the data submitted for this variation application and LTD/2142, 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 as follows:

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

Summary of health risk

Public

There will be widespread and repeated exposure of the public to the assessed chemical at up to 5% concentration through the use of a wide range of cosmetic and household 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.

The assessed chemical in neat form is expected to be irritating to the skin. However, irritation effects at the proposed end use concentrations (that are below the GHS cut-off concentration for classification of chemicals as irritants) in cosmetic and household products are not expected.

As described in the assessment report of LTD/2142, a risk associated with use of the assessed chemical is its potential to cause sensitisation by skin contact. When tested in an LLNA study in mice, the assessed chemical was determined to be a skin sensitiser with an EC3 value of 18.9%. A quantitative risk assessment (QRA) was carried out to assess the possibility of skin sensitisation from the use of the assessed chemical in various cosmetic and household products at the proposed new maximum end use concentrations (see **Summary of introduction, use and end use**). The calculated acceptable exposure level (AEL) of 15.38 µg/cm^2/day was equal to or greater than the derived consumer exposure levels (CELs) for all typical consumer products, indicating the induction of skin sensitisation risk to consumers using various products containing the assessed chemical is not expected. It is acknowledged that consumers may be exposed to multiple products containing the chemical, and a quantitative assessment based on aggregate exposure has not been conducted.

The assessed chemical is not persistent in the air and therefore, not expected to cause inhalation risk when used at up to 0.1% in hairspray, up to 0.41% in fine fragrances, or up to 5% concentration from spray products for short durations.

The health risk of repeated exposure to 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 consumer. The total daily systemic exposure was estimated as 0.97 mg/kg bw/day (see **Supporting information**). Using a No Observed Adverse Effect Level (NOAEL) of 144 mg/kg bw/day for the assessed chemical (derived from a dietary reproductive/developmental screening study in rats on an analogue chemical), the MoE was calculated to be 148. A MoE value greater than or equal to 100 is considered acceptable to account for intra- and inter-species differences. Therefore, the risk of adverse effects following repeated dermal exposure from the use of various cosmetic and household products is not expected.

Overall, this assessment does not identify any risks to public health that require specific risk management measures if the assessed chemical is introduced and used in accordance with the terms of the Inventory listing.

Workers

Reformulation workers may be exposed to the assessed chemical at up to 100% concentration during reformulation processes mainly via the dermal route, while ocular and inhalation exposures are also possible. It is anticipated by the applicant that engineering controls such as enclosed, automated processes and local ventilation will be implemented where possible. The exposure of workers is further expected to be minimised through the use of PPE such as protective clothing, eye protection and suitable gloves.

Based on the information provided for risk assessment, the potential health effect of the assessed chemical to workers is skin sensitisation and skin irritation. Control measures are required (see **Means for managing risk**) to manage the risk to workers. Control measures to minimise inhalation exposure may also be needed if aerosols or mists are formed during the reformulation process.

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 5% concentration. Such professional workers 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 end use products containing the assessed chemical (see above **Public** subsection).

Environment

Environmental hazard classification

The data submitted for LTD/2142 assessment warrants environmental hazard classification of the chemical according to the GHS (UNECE 2017) as presented below.

Environmental Hazard	Hazard Category	Hazard Statement
Acute Aquatic	Category 1	H400: Very toxic to aquatic life

Summary of environmental risk

The increase in end use concentrations for the chemical requested under variation does not impact the original environment risk assessment. On the basis of the predicted environmental concentration (PEC)/predicted no-effect concentration (PNEC) ratio and assessed use pattern, the risk of the assessed chemical to the aquatic life can be managed with the recommended control measures described in the assessment report of LTD/2142.

Means for managing risk

Details on means for managing risks are described in the original assessment report of LTD/2142 (under **Recommendations** section).

Inventory listing

As a result of this assessment, the following specific requirement to provide information under the **Regulatory Obligations** section of the original assessment report (LTD/2142) is varied

from:

- The Executive Director of AICIS must be notified in writing within 20 working days by the applicant or other introducers if: the final use concentration of the assessed chemical exceeds 0.1% in cosmetic and household products;

to:

- The Executive Director of AICIS must be advised in writing within 20 working days by the applicant or other introducers if: the final use concentration of the assessed chemical exceeds 0.23% in leave-on cosmetic products, 1.5% in rinse-off cosmetic products, 0.41% in fine fragrances, 5% in household products and 0.1% in hairspray.

Other specific requirements to provide information under the **Regulatory Obligations** section of the original assessment report (LTD/2142), remain unchanged.

Conclusions

The conclusions of this assessment are based on the information described in this assessment statement and the assessment report of LTD/2142.

Considering the means of managing risks, the Executive Director is satisfied that when the assessed chemical is introduced and used in accordance with the varied terms of the Inventory listing the human health and environment risks can be managed within existing risk management frameworks. This is provided that all requirements are met under environmental, workplace health and safety, and poisons legislation as adopted by the relevant state or territory and the means for managing the risks identified during this assessment are implemented.

Note: Obligations to report additional information about hazards under section 100 of the *Industrial Chemicals Act 2019* apply.

Supporting information

Existing Australian regulatory controls

AICIS

The chemical is listed on the Inventory with specific requirements to provide information as a term of the inventory listing. This term is published as:

- Obligations to provide information apply. You must tell us within 28 days if the circumstances of your importation or manufacture (introduction) are different to those in our assessment.

The assessment report of the chemical (LTD/2142) states under the **Regulatory Obligations** section the following circumstances under which the Director must be notified, by an introducer in writing, within 20 working days:

- the importation volume exceeds one tonne per annum assessed chemical;
- the final use concentration of the assessed chemical exceeds 0.1% in cosmetic and household products;
- the function or use of the chemical has changed from a fragrance ingredient, or is likely to change significantly;
- the chemical has begun to be manufactured in Australia; and
- additional information has become available to the person as to an adverse effect of the chemical on human health, or the environment.

Human exposure

Public

There will be widespread and repeated exposure of the public to the assessed chemical at up to 5% concentration through the use of a range of cosmetic and household products. The principal routes of exposure will be dermal and inhalation, while incidental oral or ocular exposures are also possible, particularly if the products are applied by spray or when used in air care products.

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. 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 70 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	0.23	1	0.26
Face cream	1,540	0.23	1	0.05
Hand cream	2,160	0.23	1	0.07
Fine fragrances	750	0.41	1	0.04
Deodorant (non-spray)	1,500	0.10	1	0.02
Shampoo	10,460	1.50	0.01	0.02
Conditioner	3,920	1.50	0.01	0.01
Shower gel	18,670	1.50	0.01	0.04
Hand wash soap	20,000	1.50	0.01	0.04
Hair styling products	4,000	1.50	0.1	0.09
Total				**0.64**

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 329 µg/kg bw/day systemic exposure, considering low concentrations and retention factors of these products.

Household products (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	5	0.95	10	0.16
Fabric softener	90	5	0.95	10	0.06
Total					**0.22**

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

Household products (dermal exposure from using products)

Product type	Frequency (use/day)	C (%)	Product use C (g/cm^3)	Time scale factor	Daily systemic exposure (mg/kg bw/day)
Laundry liquid	1.43	5	0.01	0.007	0.001
Dishwashing liquid	3	5	0.009	0.03	0.01

All-purpose cleaner	1	5	1	0.007	0.10
Total					**0.11**

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
Where the contact area value is 1980 cm^2 and film thickness on skin values is 0.01

Hair spray (inhalation exposure)

Amount of hairspray applied	9.89	g/day
Maximum intended concentration of the chemical	0.1	%
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	**3**	**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)]

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 0.97 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.

Health hazard information

Additional toxicological tests conducted on an analogue chemical were provided for this variation application and is summarised below.

Repeat dose toxicity

In a repeated dose oral toxicity study (OECD TG 407), an analogue chemical (1-propanol, 2-methyl-3-[(1,7,7-trimethylbicyclo[2.2.1]hept-2-yl)oxy]-, CAS No. 128119-70-0) was administered daily to Sprague Dawley (SD) rats (n = 5/sex/dose) in corn oil via oral gavage for 28 days at dose levels of 15, 150 and 1,000 mg/kg bw/day.

There were no test substance-related mortalities or effects on body weight, food consumption, behavioural parameters, functional performance, and sensory reactivity throughout the treatment period. Water consumption was markedly higher than control for high dose females and higher than control for high dose males and mid dose females. This finding was considered by the study authors to be related to the unpalatability of the test substance.

Clinical observations included increased salivation after dosing, wet fur, alopecia and red/brown perioral staining in high dose animals. Transient lethargy was observed in high dose males on Day 10. Thin appearance was noted in high dose females from Day 22 to termination; however, this observation was considered by the study authors to be due to starvation. Red/brown staining in the urogenital region on Day 21, 23 or 24 was noted in 2 females, but this was not considered by the study authors to be toxicologically relevant as there were no clear dose-related responses. Greasy fur was observed in all treatment groups; however, this was attributed by the study authors to the vehicle used.

In the high dose group, a statistically significant decrease in glucose levels (-39%), lymphocyte count (-31%) and total white blood cells (-30%) as well as increases in total protein (13%), albumin (7%) and globulin (15%) were noted in males but was not considered by the study authors to be toxicologically relevant as there were no clear dose-related responses. As the study didn't include a recovery period, reversibility of these changes could not be confirmed. There were also some haematology and clinical chemistry parameters with statistically significant differences but were within the historical control data for this strain of rats.

Increases in absolute liver weight were observed in high dose males (+33%) and females (+66%) when compared to control. Macroscopic examinations revealed an enlargement of the liver in both males (3/5) and females (5/5) of the high dose group. Microscopic analysis revealed minimal to moderate centrilobular and midzonal hepatocyte enlargement in the liver of all high dose male and female rats. The study author suggested that these effects are an adaptive response and related to the metabolism for the test substance. However, no recovery period was included in this study.

In the kidneys, eosinophilic inclusions in proximal tubular epithelium were observed in males at all doses. This effect is specific to male rats and not relevant to humans.

Based on these findings, the NOAEL for systemic toxicity was reported by the study authors as 1,000 mg/kg bw/day.

Reproductive and developmental toxicity

In a reproduction/developmental toxicity screening test (OECD TG 421), an analogue chemical (1-Propanol, 2-methyl-3-[(1,7,7-trimethylbicyclo[2.2.1]hept-2-yl)oxy]-, CAS No. 128119-70-0) was administered through diet to Wistar rats (n = 10/sex/group) at dose levels of 0, 1,000, 2,000 and 4,000 ppm (equivalent to 0, 64-70, 124-139 and 252-283 mg/kg bw, respectively for males and 0, 73-106, 144-238 and 264-395 mg/kg bw, respectively for females) for 32 days for males and 42-54 days for females.

There were no deaths of animals during the course of the study. There were no test substance-related effects on behavioural parameters, functional performance, sensory reactivity, haematology or blood chemistry.

Clinical observations included piloerection in females of the low dose (1/10), mid dose (1/10) and high dose groups (9/10). There were also statistically significant reductions in the mean body weight and body weight gain for high dose females due to a statistically significant reduction in food intake in the beginning of the study. By the end of the study, only a slight reduction in body weight was seen in the mid dose (-9%) and high dose (-12%) females in comparison to controls. The study authors stated the effects were due to palatability of the test substance.

At the end of the treatment period, absolute and relative mean liver weights increased in the mid dose (5% and 9%, respectively) and high dose (15% and 16%, respectively) males in comparison to controls. A decrease in absolute kidney weight (-13%) was observed in high dose females but was considered by the study authors as a secondary effect of the decrease in terminal body weight and not toxicologically relevant.

Macroscopic examinations of the kidneys revealed a yellowish, watery clear cyst in the left kidney of one low dose female and multiple cysts in the left kidney of one mid dose male. Microscopic analysis of these animals revealed a unilateral tubular renal carcinoma (malignant neoplasm), moderate unilateral tubular basophilia in the tubules compressed by the tumour and minimal focal atypical tubular hyperplasia in the contralateral kidney in the low dose female. In the mid dose male, a unilateral tubular adenoma (benign neoplasm), moderate focal atypical tubular hyperplasia in the contralateral kidney and a minimal amount of hyaline droplets in both kidneys were observed. Although these effects were considered atypical for the strain and age of rats used in the study, they were not considered test substance-related due to a lack of dose-response.

Microscopic analysis of the remaining high dose males revealed hepatocellular hypertrophy of the liver (3/10), tubular basophilia in the kidneys (9/10) and tubular necrosis and/or granular casts in the kidneys (4/10). Slight to moderate accumulation of hyaline droplets was also observed in the males of all dose groups. It is known that hyaline droplet accumulation in the kidneys of male rats is caused by certain chemicals binding onto α2μ-globulin, a protein is unique to rats. As the effects in the kidneys were only observed in male rats, it is likely that tubular basophilia, tubular necrosis and/or granular casts is caused by hyaline droplet accumulation, an effect that is not considered relevant for humans.

Additional microscopic findings in treated animals included cysts at the ovaries in a high dose female, foci at the clitoral glands in a low dose female and enlarged clitoral glands in a low dose female. As these effects were considered incidental, these effects were not considered test substance-related by the study authors.

Based on a test substance-related reduction in body weight gain during post-coitum which was statistically significant on Days 11-20 post-coitum, the NOAEL for systemic toxicity was reported by the study authors as 2,000 ppm for females (equivalent to 144-238 mg/kg bw/day).

The study authors considered tubular basophilia, tubular necrosis and/or granular casts found in the kidneys of high dose males to be irrelevant in human safety assessment and reported 4,000 ppm (equivalent to 252-283 mg/kg bw/day) as the NOAEL for males.

No toxicologically significant changes were observed in any of the reproductive parameters investigated in this study such as mating, conception and fertility indices, precoital time, number of corpora lutea and implantation sites.

The NOAEL for reproductive toxicity was reported by the study authors to be 4,000 ppm (equivalent to 264-395 mg/kg bw/day) based on no adverse effects noted at the highest tested dose.

Reduced body weight (-13%) in comparison to control were reported for the offspring of the high dose females. The study authors considered the findings to be a secondary effect caused by the reduced maternal body weights.

There were no test substance-related effects on gestation index and duration, parturition, maternal care and early postnatal pup development (i.e. mortality, clinical signs and macroscopy) in treated animals.

Based on the reduction of body weight in the offspring of high dose females, the NOAEL for developmental toxicity was reported by the study authors as 2,000 ppm (equivalent to 144-238 mg/kg bw/day during lactation).

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