



Australian Government

Department of Health, Disability and Ageing

Australian Industrial Chemicals Introduction Scheme

Lilial and Bourgeonal

Evaluation statement EVA00189

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Draft



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AICIS evaluation statement (EVA00189)

Subject of the evaluation

Lilial and Bourgeonal

Chemicals in this evaluation

CAS name	CAS number
Benzenepropanal, 4-(1,1-dimethylethyl)-.alpha.-methyl-	80-54-6
Benzenepropanal, 4-(1,1-dimethylethyl)-	18127-01-0

Reason for the evaluation

Evaluation Selection Analysis indicated a potential human health risk.

Parameters of evaluation

Benzenepropanal, 4-(1,1-dimethylethyl)-.alpha.-methyl- (CAS No. 80-54-6) and Benzenepropanal, 4-(1,1-dimethylethyl)- (CAS No. 18127-01-0), also known as Lilial and Bourgeonal respectively, are listed on the Australian Inventory of Industrial Chemicals (the Inventory). The chemicals are structurally related fragrance aldehydes that are being evaluated together due to their structural similarity, common industrial uses and common metabolic pathways.

This evaluation statement includes a human health risk assessment for all identified industrial uses of Lilial and Bourgeonal.

Lilial was previously assessed, including all endpoints, under the Inventory Multi-tiered Assessment and Prioritisation (IMAP) framework, under the former National Industrial Chemicals Introduction and Assessment Scheme (NICNAS). Bourgeonal has not been assessed previously. New information on Lilial and Bourgeonal has become available including reproductive and developmental toxicity data, exposure data and international activity.

This evaluation will:

- Review the weight of evidence for the hazards associated with these chemicals, including new toxicity information.
- Undertake a quantitative risk assessment to estimate potential public risks related to the chemicals used in personal care products and domestic products.
- Consider whether any means for managing risks are required based on the new information.

Summary of evaluation

Summary of introduction, use and end use

The chemicals are used in Australia as fragrance ingredients in domestic and personal care products (cosmetics).

Based on international information, these chemicals are used in a wide range of finished cosmetic products including skin-applied leave-on products such as body lotions, deodorants, fine fragrances, and rinse-off personal care products. The chemicals are also used in domestic products such as cleaning and furniture care products, laundry and dishwashing products and air care products including scented candles.

The chemicals are also used in non-industrial products such as insecticides.

The Australian reported use volumes of Lilial and Bourgeonal as fragrance ingredients in 2023 were estimated to be 125,000 kg/year and 3,750 kg/year, respectively, based on data collected in the Asia-Pacific region by the International Fragrance Association (IFRA).

Human health

Summary of health hazards

The identified health hazards are based on available data for the chemicals. Data from the common metabolite, 4-tert-butylbenzoic acid (TBBA) (CAS No. 98-73-7) has also been used to support systemic toxicity findings.

Based on the available information the chemicals are moderately absorbed through human skin, with dermal absorption estimates ranging from approximately 9–15% depending on the formulation. Both substances are rapidly metabolised, with conversion to TBBA demonstrated *in vitro* and *in vivo*. The presence of TBBA in human biomonitoring studies and controlled exposure studies confirms human relevance of this metabolic pathway.

These chemicals have low to moderate acute toxicity. Oral median lethal dose (LD50) values are approximately 1,400–3,700 mg/kg bw for Lilial and about 2,550 mg/kg bw for Bourgeonal. Dermal toxicity is low, with LD50 values greater than 2,000 mg/kg bw for Lilial and greater than 5,000 mg/kg bw for Bourgeonal. Acute inhalation toxicity data for Lilial indicate low toxicity, with no mortality observed at the highest concentration tested.

Similar to Lilial (NICNAS 2016), Bourgeonal is a skin irritant, producing severe erythema and oedema in rabbit studies, with supporting positive results in an *in vitro* assay. Both chemicals cause slight and reversible eye irritation.

The chemicals are moderate skin sensitisers. The chemicals are positive in local lymph node assays, with three-fold increase concentration in lymphocyte proliferation (EC3) values of >2%. Data for Lilial indicate the observed potency is impacted by the vehicle used. Human data for Lilial indicate that it is an established sensitiser, but not common. Bourgeonal may cause sensitisation at lower exposure levels compared to Lilial.

Only limited data are available for repeat-dose toxicity. Based on the available data, the main target for Lilial and Bourgeonal is the male reproductive system. The metabolite TBBA causes effects on other organs including the kidney and urinary tract at doses as low as

6 mg/kg bw/day. No significant effects were seen in available studies for Lilial and Bourgeonal; however, these studies were either short duration or conducted with doses up to 50 mg/kg bw/day (Lilial) and 5 mg/kg bw/day (Bourgeonal). Therefore, there is insufficient data to determine whether the chemicals can cause other systemic health effects at higher doses.

Available data indicate the chemicals are not likely to be genotoxic. The majority of the *in vitro* data were negative, and any positive results were not reproducible. These results are supported by negative *in silico* predictions. No reliable *in vivo* data are available. No carcinogenicity data are available for either chemical.

Both substances produce adverse effects on male reproductive organs and sperm quality, consistent with the known reproductive toxicity of the common metabolite TBBA, which is classified for Reproductive toxicity – Category 1B.

Animal studies in rats and dogs identified testicular toxicity and reduced fertility parameters associated with Lilial exposure, including testicular degeneration, impaired sperm quality and decreased fertility indices. Bourgeonal similarly produced testicular degeneration, Sertoli cell vacuolation, epididymal lesions and reduced sperm motility in rats, with effects observed at the lowest dose tested (5 mg/kg bw/day). Although a guideline reproductive screening study did not identify clear fertility effects, the highest dose tested was considered insufficient to adequately investigate the testicular findings observed in range-finding studies. Based on the current available data, the human relevance of these effects cannot be excluded. The metabolite TBBA is formed in humans, and no species-specific mechanism has been established.

For developmental toxicity, reduced pup body weights were observed in rat studies for both chemicals with evidence of post-implantation loss observed for Lilial. The developmental effects were not unequivocally attributable to the maternal toxicity seen in the studies.

Hazard classifications relevant for worker health and safety

The chemicals satisfy the criteria for classification according to the Globally Harmonized System of Classification and Labelling of Chemicals (GHS) for hazard classes relevant for work health and safety as follows. This does not consider classification of physical hazards and environmental hazards. This is the current classification listed in the Hazardous Chemical Information System (HCIS) (Safe Work Australia).

Lilial (CAS No. 80-54-6)

Health hazards	Hazard category	Hazard statement
Acute toxicity – oral	Acute Tox. 4	H302: Harmful if swallowed
Skin corrosion/irritation	Skin Irrit. 2	H315: Causes skin irritation
Skin sensitisation	Skin Sens. 1B	H317: May cause an allergic skin reaction
Reproductive toxicity	Repr. Tox 1B	H360Fd: May damage fertility; Suspected of damaging the unborn child

Bourgeonal (CAS No. 18127-01-0)

Health hazards	Hazard category	Hazard statement
Skin corrosion/irritation	Skin Irrit. 2	H315: Causes skin irritation
Skin sensitisation	Skin Sens. 1B	H317: May cause an allergic skin reaction
Reproductive toxicity	Repr. Tox 1B	H360Fd: May damage fertility; Suspected of damaging the unborn child

Summary of health risk

Public

Based on the available data there is widespread public exposure to the chemicals in personal care and domestic products.

Based on modelled exposure estimates, body lotion, fine fragrances and air care products contribute most to daily human exposure. This is supported by the available biomonitoring data. Therefore, these products have the highest potential to contribute to adverse risk outcomes.

The critical health effects for risk characterisation are skin sensitisation and reproductive and developmental toxicity. Developmental toxicity effects are often triggered by toxicant exposure during brief, highly sensitive developmental windows and, therefore, are relevant to acute exposures to the chemical.

Skin sensitisation

The chemicals are moderate sensitisers with the potency increasing in alcoholic solvents such as those used in fine fragrances. Lilial is an established skin sensitiser. Although it is a relatively uncommon contact allergen, risk estimates indicate there is a risk of induction of skin sensitisation to the public when using Lilial and Bourgeonal in fine fragrances at the reported levels. For both chemicals, the concentrations reported in fine fragrances are higher than the calculated acceptable exposure concentrations. Based on the quantitative risk assessment for skin sensitisation (see **Human Health Risk Characterisation – Public risk**), acceptable exposure concentrations are 1.09 % and 0.09 % for Lilial and Bourgeonal, respectively. Regarding other categories of cosmetic products and domestic products, the risk of skin sensitisation is considered to be low for both chemicals. However, the risk of elicitation or cross sensitisation cannot be ruled out for sensitised individuals.

Reproductive and developmental toxicity

There is also a potential risk of systemic toxicity when using the chemicals in cosmetic and domestic products. The chemicals may cause adverse effects on fertility (toxicity to sperm) and development with a no observed adverse effect level (NOAEL) of 4.5 mg/kg bw/day for Lilial and 1 mg/kg bw/day for Bourgeonal.

A margin of exposure (MOE) methodology was used to characterise the risk to human health associated with systemic exposure to the chemical. For this risk characterisation, an MOE is considered protective when it is >100, to account for intra- and inter-species differences.

While exposure to most individual cosmetic products containing Lilial or Bourgeonal does not pose a significant risk, the MOE calculations show there is a risk to the public from exposure to continuous-action air care products. These include scented candles containing these chemicals, with MOEs being under or very close to the reference value of 100.

There is a potential risk to the public from combined exposure to cosmetic and domestic products (excluding air care products) containing Lilial at reported 95th percentile concentrations, with an MOE of 75 calculated. This assumes simultaneous use of all products containing the chemical at the 95th percentile concentrations and, therefore represents a worst-case scenario. Revised risk estimates using the IFRA maximum acceptable concentrations (MAC) for body lotion (0.06%) resulted in an MOE >100. Combined dermal exposure to Bourgeonal at reported levels in cosmetic and domestic products (excluding continuous-action air care products) does not pose a significant risk, with an MOE of 131. However, it is noted that the concentrations modelled for the high exposure scenarios of body lotion (0.005%) and fine fragrance (0.12 %) were significantly lower than those permitted under the IFRA Standards. Use of Bourgeonal at higher concentrations may result in an unacceptable risk.

Overall, there is a risk to the public that requires management. The risk could be managed by including the chemicals in The Poisons Standard (SUSMP) (see **Proposed means for managing risk**).

Workers

During product formulation and packaging, dermal, inhalation and ocular exposure might occur, particularly where manual or open processes are used. These could include transfer and blending activities, quality control analysis, and cleaning and maintaining equipment. Worker exposure to these chemicals at lower concentrations could also occur while using formulated products containing these chemicals. The level and route of exposure will vary depending on the method of application and work practices employed. Good hygiene practices to minimise incidental oral exposure are expected to be in place.

Given the critical local and systemic health effects, the chemicals could pose a risk to workers.

Control measures to minimise dermal and inhalation exposure are needed to manage the risk to workers (see **Proposed means for managing risk**).

Proposed means for managing risk

Public health

Recommendation to Department of Health and Aged Care

It is recommended that the delegate of the Secretary for Poisons Scheduling lists the chemicals in the Poisons Standard (the Standard for the Uniform Scheduling of Medicines and Poisons—SUSMP).

It is recommended that, to manage the potential risk associated with the use of these chemicals, the entry:

- Restricts the concentration of the chemicals in body lotions, fine fragrances and prohibit use in continuous-action air care products including scented candles.

Consideration should be given to the following:

- The chemicals have widespread use in cosmetic and domestic products available in Australia.
- Body lotion, fine fragrances and air care products likely contribute most to daily exposure and, therefore, have the highest potential to contribute to adverse risk outcomes.
- These chemicals are sensitising and may induce sensitisation when used in fine fragrances at current use levels. A reduction in concentration in these products would mitigate the risk.
- Calculated MOE values indicate that exposure to the chemicals in continuous-action air care products could present a risk of reproductive and developmental effects.
- A restriction of the concentration of the chemicals in body lotion would reduce exposure and potential risks of reproductive and developmental effects.
- The chemicals are metabolised to a common hazardous metabolite (TBBA) metabolite and could be present in the same products which may increase the overall risks. However, the conservative assumptions in the risk estimates are expected to account for this uncertainty.

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 **Summary of health hazards**).

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 (PCBU) at a workplace (such as an employer) to determine the appropriate controls under the relevant jurisdiction Work Health and Safety laws.

Recommended control measures that could be implemented to manage the risk arising from dermal and inhalation exposure to these chemicals include, but are not limited to:

- using closed systems or isolating operations
- minimising manual processes and work tasks through automating processes
- adopting work procedures that minimise splashes and spills
- cleaning equipment and work areas regularly
- using protective equipment that is designed, constructed, and operated to ensure that the worker does not come into contact with the chemicals.

These control measures may need to be supplemented with:

- conducting health monitoring for any worker who is at significant risk of exposure to the chemicals, if valid techniques are available to monitor the effect on the worker's health.

Measures required to eliminate, or manage risk arising from storing, handling and using hazardous chemicals depend on the physical form and the manner in which the chemicals are used.

Personal protective equipment should not solely be relied upon to control risk and should only be used when all other reasonably practicable control measures do not eliminate or sufficiently minimise risk.

Model codes of practice, available from the Safe Work Australia website, provide information on how to manage the risks of hazardous chemicals in the workplace, prepare an SDS and label containers of hazardous chemicals. Your Work Health and Safety regulator should be contacted for information on Work Health and Safety laws and relevant Codes of Practice in your jurisdiction.

Conclusions

The Executive Director proposes to be satisfied that the identified risks to human health from the introduction and use of these industrial chemicals can be managed.

Note:

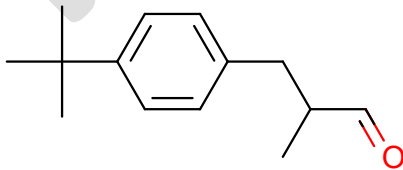
1. Obligations to report additional information about hazards under section 100 of the *Industrial Chemicals Act 2019* apply.
2. You should be aware of your obligations under environmental, workplace health and safety and poisons legislation as adopted by the relevant state or territory.

Supporting information

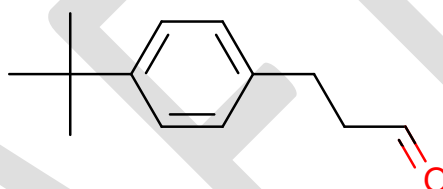
Grouping rationale

Lilial and Bourgeonal are grouped together based on structural similarity and common metabolite 4-tert-butylbenzoic acid (TBBA) (CAS No. 98-73-7). Lilial and Bourgeonal also share common use in cosmetic and domestic products, as fragrance ingredients.

Chemical identity

CAS number	80-54-6
CAS name	Benzenepropanal, 4-(1,1-dimethylethyl)-.alpha.-methyl-
Molecular formula	C ₁₄ H ₂₀ O
Associated names	Lilial Butylphenyl methylpropional α -Methyl- β -(p-tert-butylphenyl)propionaldehyde 2-Methyl-3-(p-isopropylphenyl)propionaldehyde Hydrocinnamaldehyde, p-tert-butyl- α -methyl p-tert-Butyl- α -methylhydrocinnamic aldehyde 2-(4-tert-butylbenzyl)propionaldehyde
Molecular weight (g/mol)	204.31
SMILES (canonical)	<chem>O=CC(C)CC1=CC=C(C=C1)C(C)(C)C</chem>
Structural formula	

CAS number	18127-01-0
CAS name	Benzenepropanal, 4-(1,1-dimethylethyl)-
Molecular formula	C ₁₃ H ₁₈ O
Associated names	Bourgeonal p-tert-Butylhydrocinnamic aldehyde 3-(4-tert-butylphenyl)propionaldehyde
Molecular weight (g/mol)	190.28
SMILES (canonical)	O=CCCC1=CC=C(C=C1)C(C)(C)C
Structural formula	



Relevant physical and chemical properties

Chemical	Lilial	Bourgeonal
Physical form	liquid	liquid
Melting point	-20°C at 1013 hPa	-10.7°C
Boiling point	280.03°C (calculated)	207°C
Vapour pressure	0.0025 hPa at 20°C	0.20 Pa at 20°C
Water solubility	33 mg/L at 20°C	132 mg/L at 20°C
Density	0.941 g/mL at 20°C	0.959 g/mL at 20°C
log K_{ow}	4.2	3.2

Introduction and use

Australia

Limited specific Australian import, or manufacturing information for the chemicals has been identified. The Australian reported use volumes of Lilial and Bourgeonal as fragrance ingredients in 2023 were estimated to be 125,000 kg/year and 3,750 kg/year, respectively,

based on data collected in the Asia-Pacific region by the International Fragrance Association (IFRA).

Information provided to AICIS indicated that:

- Lilial is introduced in concentrations ranging from <0.01% to 0.05% in personal care products (volume not provided), 0.25% in fabric softeners (for a total of 1.5 t/y) and from <0.01% to 0.15% in other domestic products (volume not provided).
- Bourgeonal is introduced in personal care products at <0.005%, and in domestic products from <0.005% to 0.24% (volume not provided).

International

The chemicals both have functional use as fragrance in a wide range of finished personal care products (cosmetics) and domestic products.

Based on information provided to AICIS regarding reported use levels of Lilial in Europe, 44% of the total reported products are for cosmetic use and 56% for domestic use (RIFM 2025). The major contributing categories of cosmetic products are (in percent of total reported cosmetic products):

- Category 9 – rinse-off products (45%)
- Category 4 – fine fragrance products (25%)
- Category 5A – body lotion (15%)
- Category 2 – deodorant products (7%).

Other use categories accounted for 2% or less percent of total reported cosmetic products. There is no reported use in oral hygiene products. For domestic products, the most frequently reported products were cleaning, laundry and dishwashing products (90% of domestic products reported) with 10% as air-care products. The mean and 95th percentile concentrations of Lilial in various products were reported (**Table 1**):

Table 1: Mean and 95th percentile concentrations of Lilial in personal care and domestic products based on European data

Category*	Representative Product type	Mean C (%)	95th percentile C (%)
2	Deodorant	0.04	0.120
4	Fine fragrances	0.46	1.300
5A	Body lotion	0.071	0.240
5B	Face cream	0.011	0.033
5C	Hand cream	0.016	0.050
7	Hair styling product	0.015	0.042
9	Hand wash soap	0.037	0.120
9	Shampoo	0.025	0.069
9	Conditioner	0.022	0.064
9	Shower gel	0.043	0.120
10A	Laundry liquid	0.02	0.062
10A	Dishwashing liquid	0.008	0.025
10A	All-purpose cleaner	0.009	0.029
10B	Air freshener aerosol	0.085	0.41
12	Air freshener plugin	2.5	8.9
12	Scented candle	0.31	1

*As defined in the Guidance for the use of IFRA Standards (IFRA 2023)

Limited concentration data are available for Bourgeonal in cosmetic products. A 95th percentile value in fine fragrances of 0.12% was calculated by RIFM (Api et al. 2024).

Bourgeonal was reported in the REACH dossier to be used at the following concentrations in domestic products (ECHA CHEM n.d.-b):

- laundry regular/compact/additives, dishwashing products (0.05%)
- laundry aids (0.025%)
- fabric conditioners (0.099%)
- cleaning products (surface cleaners (liquid/gel), toilet cleaners, automotive care, oven cleaners) (0.099%)
- polishes, wax/cream (floor, furniture, shoes) (0.099%)
- polishes, spray (furniture, shoes, floor) (0.002%)
- non-aerosol air fresheners (gel/diffuser) (0.99%)
- non-aerosol air fresheners (candles) (0.5%)
- aerosol air fresheners (0.055%).

The USA Consumer Product Information Database (CPID) identified uses of these chemicals in domestic products with Lilial having more widespread uses (DeLima n.d.). This included reported use in:

- air fresheners including scented candles (up to 1% for Bourgeonal)
- laundry products (up to 1% for Lilial)
- cleaning products (up to 5% for Lilial).

Lilial and Bourgeonal are also reported to be used in non-industrial products including insect repellents and insecticides at concentrations up to 0.9% (DeLima n.d.; ECHA CHEM n.d.-b).

The Asia-Pacific use volume of Lilial and Bourgeonal in 2023 was estimated to be 2,500 and 75 tonnes/year respectively, based on data collected by IFRA. Lilial is on the US EPA High

Production Volume Program Chemical List and OECD List of High Production Volume (HPV) Chemicals (US EPA; OECD). Global volumes of up to 100 tonnes per year for Bourgeonal and up to 10,000 tonnes/year for Lilial have been reported in the European Union (ECHA).

Existing Australian regulatory controls

Public

No specific controls are currently available for the industrial use of these chemicals.

Workers

Lilial is currently classified in the Hazardous Chemical Information System (HCIS) with the following hazard categories and statements (SWA n.d.):

Health hazards	Hazard category	Hazard statement
Acute toxicity – oral	Acute Tox. 4	H302: Harmful if swallowed
Skin corrosion/irritation	Skin Irrit. 2	H315: Causes skin irritation
Skin sensitisation	Skin Sens. 1	H317: May cause an allergic skin reaction
Reproductive toxicity	Repr. 2	H361f: Suspected of damaging fertility

Bourgeonal is not listed in the HCIS (SWA n.d.).

International regulatory status

Exposure standards

No specific exposure standards are available for these chemicals in Australia (SWA n.d.).

Canada

Lilial

Lilial was assessed by Health Canada in a draft report 'Phenylpropanoids and Aldehydes Group' (Health Canada 2024). The report concluded that Lilial met one or more of the criteria set out in section 64 of the Canadian Environmental Protection Act (CEPA) 1999 (defining a substance as toxic), as the chemical is *'entering or may enter the environment in a quantity or concentration or under conditions that constitute or may constitute a danger in Canada to human life or health'*.

European Union

Lilial

Lilial is prohibited for use in cosmetic products (Annex II of the EU Regulation (EC) No 1223/2009–List of Substances Prohibited in Cosmetic Products) (Chemwatch n.d.).

This ban followed the Risk Assessment Committee's (RAC) decision (ECHA 2019) to reclassify Lilial for reproductive toxicity, upgrading it from Reproductive toxicity – Category 2 (H361f) to Reproductive toxicity – Category 1B (H360Fd) under the EU Classification, Labelling and Packaging (CLP) Regulation.

The chemical has been identified as a Substance of Very High Concern (SVHC) under the REACH legislation, due to reproductive toxicity (ECHA 2021). It has been recommended for inclusion in Annex XIV (the authorisation list) (ECHA 2023).

Bourgeonal

Bourgeonal is allowed at a maximum concentration of 0.6% in cosmetic products (Annex III of the EU Regulation (EC) No 1223/2009 - List of Substances which cosmetic products must not contain except subject to the restrictions laid down) (Chemwatch n.d.)

New Zealand

Both chemicals are listed on the New Zealand Cosmetic Products Group Standard (Chemwatch n.d.):

- Lilial is prohibited for use in cosmetic products (Schedule 4 - Table 1: Components Cosmetic Products must not contain).
- Bourgeonal is allowed at a maximum concentration of 0.6% in cosmetic products (Schedule 5 - Table 1: Components Cosmetic Products Must Not Contain Except Subject to the Restrictions and Conditions Laid Down).

Asia

In ASEAN countries, Lilial is prohibited for use in cosmetic products (ASEAN Cosmetic Directive Annex II Part 1: List of substances which must not form part of the composition of cosmetic products). There is no restriction on Bourgeonal (Chemwatch n.d.).

Other

The chemicals are listed in the IFRA Standard (51st Amendment) restrictions of concentrations (see **Table 2**). Lilial is prohibited for use in any finished product application included under IFRA Categories 1 and 6 (lipsticks and oral care products).

Table 2. Maximum acceptable concentrations in finished products (IFRA 2024)

IFRA Product Categories	Lilial Concentration (%)	Bourgeonal Concentration (%)
Category 1 Products applied to the lips	0	0.0041
Category 2 Products applied to the axillae	0.09	0.025
Category 3 Products applied to the face/body using fingertips	0.04	0.025
Category 4 Products related to fine fragrance	1.4	0.47
Category 5A Body lotion products applied to the body using the hands (palms), primarily leave-on	0.06	0.12
Category 5B Face moisturiser products applied to the face using the hands (palms), primarily leave-on	0.05	0.029
Category 5C Hand cream products applied to the hands using the hands (palms), primarily leave-on	0.05	0.037
Category 5D Baby Creams, baby Oils and baby talc	0.017	0.0096
Category 6 Products with oral and lip exposure	0	0.087
Category 7A Rinse-off products applied to the hair with some hand contact	0.04	0.029
Category 7B Leave-on products applied to the hair with some hand contact	0.04	0.029
Category 8 Products with significant anogenital exposure	0.017	0.0096
Category 9 Products with body and hand exposure, primarily rinse off	0.1	0.099
Category 10A Household care products with mostly hand contact	0.1	0.099
Category 10B Household care products with mostly hand contact, including aerosol/spray products (with potential leave-on skin contact)	0.63	0.24
Category 11A Products with intended skin contact but minimal transfer of fragrance to skin from inert substrate without UV exposure	0.017	0.0096
Category 11B Products with intended skin contact but minimal transfer of fragrance to skin from inert substrate with potential UV exposure	0.017	0.0096
Category 12 Products not intended for direct skin contact, minimal or insignificant transfer to skin	16	6.9

Human exposure

Public

As Lilial and Bourgeonal are used in a wide range of cosmetic and domestic products (see **Introduction and use**), public exposure is expected to be significant. Dermal and inhalation routes of exposure are likely to occur predominantly, depending on the type of product. Dermal exposure may be limited to specific areas of the body or may be more extensive depending on the type of product. The duration of exposure for various products is expected to differ significantly as the chemical is used in both rinse-off and leave-on products. For rinse-off products such as soaps or shampoos, exposure might only be for a few minutes, although some residual product can remain. Whereas for leave-on products, the period of exposure could last for several hours. Australian use patterns for the various product categories are assumed to be similar to those internationally.

Exposure estimates for the chemicals are provided below.

Daily systemic exposure – Lilial

The daily Systemic Exposure Dose (SED) to Lilial from cosmetic and domestic products (excluding household air care products) was determined based on the following information:

- 95th percentile concentrations of Lilial used in various consumer products based on the Research Institute for Fragrance Materials (RIFM) report (RIFM 2025); where a product category was reported multiple times, duplicate products were removed from calculation and those with the highest reported concentration were used. The exception to this was cleaning, laundry and dishwashing products where the reported concentrations in Australia were used.
- Typical use patterns of cosmetic and domestic cleaning product categories (SCCS, 2012; Cadby et al., 2002; ACI, 2010; Loretz et al., 2006), assumed to be similar to those in Europe.
- Dermal absorption (DA) rates of 13.5% for hydroalcoholic-based fragrances and deodorant/antiperspirant products; 8.9% for oil-in-water-based products like make-up products, body lotions, hair styling, and bath cleansing products; 10.5% for water in oil based products like face and hand cream products; and a default 100% for all other products (see **Toxicokinetics**).
- 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 m³/day (enHealth, 2012) was used. It was conservatively assumed that the fraction of the notified chemical inhaled is 50%, which accounts for a number of other exposure considerations (e.g., the amount ending up on the hair, as intended)
- A standard adult body weight (BW) value of 60 kg was applied.

Personal care products (cosmetics)

The worst-case daily systemic exposure to Lilial from personal care products if present at the 95th percentile was estimated to be 0.0587 mg/kg bw/day. The highest exposures related to use in body lotion and fine fragrances (see **Table 3** and **4**).

Table 3. Daily systemic exposure to Lilial from personal care products (dermal exposure) based on the 95th percentile concentration data

Product type	Amount (mg/day)	C (%)	Retention Factor (RF)	Dermal Absorption (DA) (%)	Daily systemic exposure (mg/kg bw/day)
Body lotion	7820	0.240	1.000	8.9	0.0278
Face cream	1540	0.033	1.000	10.5	0.0009
Hand cream	2160	0.050	1.000	10.5	0.0019
Fine fragrances	750	1.300	1.000	13.5	0.0219
Deodorant (non-spray)	1500	0.120	1.000	13.5	0.0041
Shampoo	10460	0.069	0.010	8.9	0.0001
Conditioner	3920	0.064	0.010	8.9	0.0000
Shower gel	18670	0.120	0.010	8.9	0.0003
Hand wash soap	20000	0.120	0.010	8.9	0.0004
Hair styling products	4000	0.042	0.100	8.9	0.0002
Total	-	-	-	-	0.0577

Daily systemic exposure = (Amount × Chemical concentration × RF × DA)/BW
(C = chemical concentration; RF = retention factor; DA = dermal absorption; BW = body weight)

Table 4. Daily systemic exposure to Lilial from aerosol cosmetic products (inhalation exposure) based on the 95th percentile concentration data

Product type	(g/day)	C (%)	Exposure Duration (Zone 1) (min)	Exposure Duration (Zone 2) (min)	Volume (Zone 1) (m3)	Volume (Zone 2) (m3)	Daily systemic exposure (mg/kg bw/day)
Hairspray	9.89	0.028	1	20	1	10	0.0010

Daily systemic exposure = [(Amount × C × 20 m3/day Inhalation Rate × 50% Fraction Inhaled × 0.1) / BW × 1440] × (Exposure Duration Zone 1/Volume Zone 1 + Exposure Duration Zone 2/Volume Zone 2)(C = chemical concentration; BW = body weight)

Domestic products

The worst-case daily systemic exposure to Lilial from domestic products if present at the 95th percentile concentration reported overseas (air care products) and maximum concentration reported in Australia (all other products) was estimated to be 0.1711 mg/kg bw/day and 0.0011 mg/kg bw/day (excluding air care products) (see **Tables 5 and 6**).

Table 5 Daily indirect systemic exposure to Lilial from household products (from wearing clothes) based on Australian concentration data

Product type	Amount (g/use)	C (%)	PR (%)	PT (%)	DA (%)	Daily systemic exposure (mg/kg bw/day)
Laundry liquid	230	0.15	0.95	10	8.9	0.0005
Fabric softener	90	0.25	0.95	10	8.9	0.0003
Total	-	-	-	-	-	0.0008

Daily systemic exposure = (amount x C x PR x PT x DA)/body weight
(C = chemical concentration; PR = product retained; PT = product transferred; DA = dermal absorption; BW = body weight)

Table. 6 Daily systemic exposure to Lilial from household products (Direct dermal exposure) based on Australian concentration data

Product type	Freq. (use/day)	C (%)	Contact Area (cm ²)	Product Use C (g/cm ³)	Film Thickness (cm)	Time Scale Factor (unitless)	Daily systemic exposure (mg/kg bw/day)
Laundry liquid	1.43	0.15	1980	0.01	0.01	0.007	Negligible
Dishwashing liquid	3	0.15	1980	0.009	0.01	0.03	Negligible
All-purpose cleaner	1	0.15	1980	1	0.01	0.007	0.0003
Total	-	-	-	-	-	-	0.0003

Daily systemic exposure = Frequency × C × Contact Area × Product Usage × Film Thickness × Time Scale Factor × DA 8.9% / BW
(C = chemical concentration)

Inhalation exposure from the use of domestic air care products was estimated using the ConsExpo web tool v1.2.1 (RIVM n.d.). The assessment applied standard assumptions and exposure parameters as outlined in the Dutch National Institute for Public Health and the Environment (RIVM) Air Fresheners Fact Sheet (RIVM 2021), with the exception of adult body weight, which was set at 60 kg. A default inhalation absorption rate of 100% was applied.

The following product scenarios and associated inhalation exposure models were selected within the relevant product categories:

- a. Instant-action air fresheners – volatile substances
Scenario: Spraying volatile substances by adult users
Product: Instant air refreshment sprays (aerosol can)
Category: Home air fresheners
- b. Continuous-action air fresheners
Scenario 1: Electric Evaporation - adult users
Product: Electric plug-in evaporation
Product category: Home air fresheners
Scenario 2: Burning scented candles by adult users
Product: Scented candles
Category: Home air fresheners.

These scenarios were selected to represent typical consumer use patterns and product types within the air care category. In addition, air freshener plugin was modelled due to the high concentrations used.

The estimated daily systemic exposure based on these assumptions are presented in **Table 7:**

Table 7. Daily systemic exposure to Lilial from air care products (inhalation exposure)

Product type	C (%)	Internal year average dose (mg/kg bw/day)
Air Freshener Aerosol	0.41	0.0228
Air Freshener Plugin	8.9	0.0436
Scented Candles	1	0.104
Total	-	0.17

(C = chemical concentration)

The combined daily inhalation exposure to Lilial air care products is estimated to be 0.17 mg/kg bw/day.

Aggregate exposure

A combined internal dose of 0.0598 mg/kg bw/day for cosmetic and domestic products was determined for Lilial based on these parameters (excluding air care products) with body lotion and fine fragrance products contributing to 83% of the total exposure. The remaining daily exposure amount comes from other leave-on products (hand cream, deodorant non spray), while the contribution from other cosmetic or domestic products is negligible. When considering air care products, the combined internal dose is 0.2298 mg/kg bw/day. The worst-case exposure estimate assumes simultaneous use of all products containing the chemical at the highest reported concentration.

Based on modelled exposure estimates body lotion, fine fragrances and air care products contribute most to daily exposure. This is supported by the available biomonitoring data (see **Toxicokinetics**). Therefore, changes in exposure assumptions for these products would have the greatest impact on estimated exposure. A comparison of 95th percentile concentrations with Australian use information and concentrations proposed in the IFRA Standard indicate that lower concentrations may be typically present in body lotions compared to the 95th percentile value (0.06% v 0.24%). If this concentration is applied, the combined internal dose is 0.0389 mg/kg bw/day (excluding air care products). A range of scenarios is presented in **Table 8**.

Table 8. Combined exposure to Lilial based on different exposure assumptions for body lotion, fine fragrance, and air care products

Exposure scenario	Body lotion concentration (%)	Fine fragrance concentration (%)	Air care products	Daily systemic exposure (mg/kg bw/day)
Use in all products (95 th percentile conc)	0.24	1.3	All included	0.2298
Use in all products (95 th percentile conc) excluding all air care	0.24	1.3	All excluded	0.0598
Use in all products (95 th percentile conc) excluding all continuous-action air care	0.24	1.3	Instant action only	0.0826
Use in all products (95 th percentile conc) excluding all air care but with body lotion at 0.06%	0.06	1.3	All excluded	0.0389
Use in all products (95 th percentile conc) excluding all continuous-action air care but with body lotion at 0.06%	0.06	1.3	Instant action only	0.0617

By comparison, the Research Institute for Fragrance Materials (RIFM) calculated a total systemic exposure of 0.0065 mg/kg bw/day (95th percentile; dermal, oral and inhalation), and a chronic inhalation exposure of 0.0033 mg/kg bw/day using probabilistic modelling (Api et al., 2020). These exposure estimates assume same absorption values above and consider 25 product categories, including personal care products and air care products.

Daily systemic exposure – Bourgeonal

The combined daily systemic exposure to Bourgeonal from cosmetic and domestic products (excluding household air care products) was determined based on the following information:

- reported levels of up to 0.005% in cosmetic products, 0.12% in fine fragrances, and up to 0.24% in household products
- reported levels in air care products of 1%
- typical use patterns of cosmetic and domestic cleaning product categories (SCCS, 2012; Cadby et al., 2002; ACI, 2010; Loretz et al., 2006), assumed to be similar to those in Europe
- dermal absorption (DA) rates of 13.5% for hydroalcoholic-based fragrances and deodorant/antiperspirant products; 8.9% for oil-in-water-based products like make-up products, body lotions, hair styling, and bath cleansing products; 10.5% for water-in-oil-based products like face and hand cream products; and a default 100% for all other products (see **Toxicokinetics**)
- 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 m³/day (enHealth, 2012) was used, and it was conservatively assumed that the fraction of the notified chemical inhaled is 50%, which accounts for a number of other exposure considerations (e.g., the amount ending up on the hair, as intended)
- a standard adult body weight (BW) value of 60 kg was applied.

Personal care products (cosmetics)

The worst-case daily systemic exposure to Bourgeonal from personal care products if present at the reported concentrations was estimated to be 0.0034 mg/kg bw/day (see **Table 9** and **10**).

Table 9. Daily systemic exposure to Bourgeonal from Personal care products (dermal exposure) based on reported concentration data

Product type	Amount (mg/day)	C (%)	RF (unitless)	Dermal Absorption (DA) (%)	Daily systemic exposure
Body lotion	7820	0.005	1.000	8.9	0.000580
Face cream	1540	0.005	1.000	10.5	0.000135
Hand cream	2160	0.005	1.000	10.5	0.000189
Fine fragrances	750	0.120	1.000	13.5	0.002025
Deodorant (non-spray)	1500	0.005	1.000	13.5	0.000169
Shampoo	10460	0.005	0.010	8.9	0.000008
Conditioner	3920	0.005	0.010	8.9	0.000003
Shower gel	18670	0.005	0.010	8.9	0.000014
Hand wash soap	20000	0.005	0.010	8.9	0.000015
Hair styling products	4000	0.005	0.100	8.9	0.000030
Total	-	-	-	-	0.0032

Daily systemic exposure = (Amount × Chemical concentration × RF × DA)/BW
(C = chemical concentration; RF = retention factor; DA = dermal absorption; BW = body weight)

Table 10. Daily systemic exposure to Bourgeonal from aerosol personal care products (inhalation exposure) based on reported concentration data

Product type	Amount (g/day)	C (%)	Exposure Duration (Zone 1) (min)	Exposure Duration (Zone 2) (min)	Volume (Zone 1) (m³)	Volume (Zone 2) (m³)	Daily systemic exposure (mg/kg bw/day)
Hairspray	9.89	0.005	1	20	1	10	0.0002

Daily systemic exposure = [(Amount × C × 20 m³/day Inhalation Rate × 50% Fraction Inhaled × 0.1) / BW × 1440] × (Exposure Duration Zone 1/Volume Zone 1 + Exposure Duration Zone 2/Volume Zone 2)
(C = chemical concentration; BW = body weight)

Domestic products

The worst-case daily systemic exposure to Bourgeonal from domestic products if present at maximum concentration reported in Australia and overseas was estimated to be 0.0947 mg/kg bw/day and 0.0017 mg/kg bw/day (excluding air care products) (see **Tables 11** and **12**).

Table 11. Daily systemic exposure to Bourgeonal from household products (Indirect dermal exposure - from wearing clothes)

Product type	Amount (g/use)	C (%)	Product Retained (PR) (%)	Percent Transfer (PT) (%)	Dermal Absorption (DA) (%)	Daily systemic exposure (mg/kg bw/day)
Laundry liquid	230	0.24	0.95	10	8.9	0.0008
Fabric softener	90	0.24	0.95	10	8.9	0.0003
Total	-	-	-	-	-	0.0011

Daily systemic exposure = (amount x C x PR x PT x DA)/body weight

(C = chemical concentration; PR = product retained; PT = product transferred; DA = dermal absorption; BW = body weight)

Table 12. Daily systemic exposure to Bourgeonal from household products (Direct dermal exposure)

Product type	Freq. (use/day)	C (%)	Contact Area (cm ²)	Product Use C (g/cm ³)	Film Thickness (cm)	Time Scale Factor (unitless)	Daily systemic exposure (mg/kg bw/day)
Laundry liquid	1.43	0.24	1,980	0.01	0.01	0.007	Negligible
Dishwashing liquid	3	0.24	1,980	0.009	0.01	0.03	0.0001
All purpose cleaner	1	0.24	1,980	1	0.01	0.007	0.0005
Total	-	-	-	-	-	-	0.0006

Daily systemic exposure = Frequency x C x Contact Area x Product Usage x Film Thickness x Time Scale Factor x DA 8.9% / BW

(C = chemical concentration)

Inhalation exposure from the use of domestic air care products was estimated using the ConsExpo web tool v1.2.1 (RIVM n.d.). The assessment applied standard assumptions and exposure parameters as outlined in the Dutch National Institute for Public Health and the Environment (RIVM) Air Fresheners Fact Sheet (RIVM Report 2021), with the exception of adult body weight, which was set at 60 kg. A default inhalation absorption rate of 100% was applied.

The same product scenarios and associated inhalation exposure models used for estimates for Lilial were selected for Bourgeonal.

The estimated daily systemic exposure based on these assumptions are presented in **Table 13**.

Table 13. Daily systemic exposure to Bourgeonal from air care products (inhalation exposure)

Product type	C (%)	Internal year average dose (mg/kg bw/day)
Air Freshener Aerosol	0.055	0.00267
Air Freshener Plugin	1	0.00427
Scented Candles	1	0.0903
Total	-	0.097

(C = chemical concentration)

The combined daily exposure to air care products is estimated to be 0.097 mg/kg bw/day.

Aggregate exposure

A combined internal dose of 0.005 mg/kg bw/day was determined for Bourgeonal based on these parameters (excluding air care products), with fine fragrances contributing to 41% of the total exposure. The remaining daily exposure amount is mostly from cleaning products (34%) while the contribution from other cosmetic products is negligible. If air care products are included, the combined internal dose is 0.1022 mg/kg bw/day or 0.0077 mg/kg b/day if only instant-action air fresheners are included. The concentrations modelled for the high exposure scenarios of body lotion (0.005%) and fine fragrance (0.12%) were significantly lower than those permitted under the IFRA Standard. If higher concentrations were used in these products, this would increase exposure.

The worst-case exposure estimate assumes simultaneous use of all products containing the chemical at the 95th percentile identified. The Research Institute for Fragrance Materials (RIFM) calculated a total systemic exposure of 0.0026 mg/kg bw/day (95th percentile; dermal, oral and inhalation), and a chronic inhalation exposure of 0.00028 mg/kg bw/day using probabilistic modelling (Api et al., 2020). These exposure estimates assume same absorption values above and consider 25 product categories, including personal care products and air care products.

Health hazard information

These chemicals metabolise to 4-tert-butylbenzoic acid (TBBA; CAS No. 98-73-7). TBBA has been previously assessed under our former scheme, the National Industrial Chemicals Notification and Assessment Scheme (NICNAS 2016). Data for TBBA has also been used to support systemic toxicity findings.

Toxicokinetics

Absorption

Based on physicochemical properties and metabolism studies (see below) the chemicals are expected to be readily absorbed via the oral route. Systemic bioavailability of Lilial after oral and dermal exposure was demonstrated in both humans and experimental animals.

In a guideline study following OECD TG 428, human skin samples (200–400 µm) were used to test skin penetration of Lilial formulated in different preparations, representative of cosmetic formulations: 1.9% Lilial in 70% ethanol in water, 0.1% Lilial in a “silicone in water” formulation 0.1% Lilial in a “water in oil” and 0.1% Lilial in a “oil in water” formulation. After a single topical application of target doses of 95.0 µg/cm² and 5.0 µg/cm² of test substance,

absorption of Lilial was evaluated by collecting receptor fluid every hour from 0 to 8 hours post dose, then every 2 hours from 8 to 24 hours post dose (SCCS 2019).

In their latest Opinion on the safety of Lilial, Scientific Committee on Consumer Safety (SCCS) concluded that the following dermal absorption values derived from this study should apply for risk assessment (SCCS 2019). The same dermal absorption values were used in the RIFM fragrance ingredient safety assessments for Lilial and Bourgeonal (Api et al 2020; Api et al. 2024):

- “Ethanol in water” (24h) = 13.5%
- “Silicone in water” (24h) = 8.5%
- “Water in oil” (24h): = 10.5%
- “Oil in water” (24h): = 8.9%

These values were derived by including the fraction of the dose in the receptor fluid and the fraction found in the epidermis plus 1 standard deviation (SD) unit. An additional SD was added to the fractions from “ethanol in water” and “silicone in water” due to deviations from SCCS requirements related to recovery of test substance.

No experimental dermal absorption data are available for Bourgeonal. Bourgeonal and Lilial are structurally similar aldehydes with similar molecular weights (190.3 and 204.3 g/mol, respectively) and lipophilicity (log Kow 3.2 and 4.2, respectively). These properties are both relevant for estimating dermal absorption. The predicted skin permeability using the Potts and Guy model indicates dermal absorption potential for both substances. Although Lilial was predicted to have a higher permeability coefficient, Bourgeonal has greater water solubility (132 mg/L versus 33 mg/L), resulting in similar predicted maximum dermal fluxes. Therefore, based on the available physicochemical data the chemicals are expected to have similar dermal absorption (Potts RO & Guy RH 1992; SCCS 2012).

Metabolism

Although the majority of data are available for Lilial, both chemicals form the metabolite TBBA *in vivo*. In studies with Lilial, other detected metabolites include lysmerol (CAS No. 56107-04-1), lysmerylic acid (CAS No. 66735-04-4), hydroxylated lysmerylic acid (CAS No. 1897559-05-5) and tert-butyl-hippuric acid (TBHA) (CAS No. 87015-91-6) with lysmerylic acid the main metabolite in hepatocytes of all tested species. Metabolic pathways include oxidation to lysmerylic acid or reduction to lysmerol. These can be oxidised at the tert-butyl group to form hydroxy-metabolites. beta-Oxidation of the alpha-branched carboxylic acid leads to the identified metabolite TBBA. This metabolite conjugates with glycine to form TBHA. Limited metabolism data are available for Bourgeonal. However, due to the absence of the alpha-methyl group present in Lilial, there may be quantitative differences in the formation of TBBA with Bourgeonal potentially forming relatively higher amounts.

Despite some quantitative differences, TBBA was formed in all tested species including rats, rabbits, guinea pigs, dogs, rhesus monkeys and humans. *In vitro* studies indicated that formation of TBBA is lower in humans compared to rats but studies in monkeys gave mixed results (see below). TBBA was detected in human urine after exposure to Lilial (controlled human studies) and in biomonitoring studies (see below) (ECHA 2019; ECHA 2024; SCCS 2015).

Bourgeonal

In a non-GLP compliant 14 day dose range finding study, Sprague Dawley (SD) rats (n = 5/sex/dose) were administered Bourgeonal by gavage 3 times/day, at 0, 5, 25 or 50

mg/kg bw/day. A dose-dependent increase in plasma TBBA levels was reported in rats, which were almost twice as high in females than in males after 14 days of exposure; parent compound was also detected, but at much lower levels compared to TBBA (ECHA 2023).

In a GLP-compliant toxicity screening test, male Crl:CD (SD) IGS BR rats (n = 6 /dose) were administered Bourgeonal by gavage at doses of 0, 25, 100 or 250 mg/kg bw/day for 5 consecutive days. Urine was collected within 24 hrs after administration of the last dose and analysed to detect TBBA. Males treated with 100 or 25 mg/kg bw/day demonstrated presence of TBBA at concentrations of 275 and 35.8 µg/ml, respectively (ECHA 2023).

In an *in vitro* metabolism study, rat hepatocytes in suspension were incubated with Lilial or Bourgeonal at 100 µM for 4 hrs. Benzoic acid derivatives were determined by GC-MS at 0.5, 4 and 22 hrs. Formation of CoA conjugates following 0.5, 4 and 22 hrs of exposure to the chemicals at 5 and 50 µM was also assessed by LC-HRMS. The parent aldehydes tested were no longer detectable after 1h incubation. Results showed formation of p-alkyl-benzoic acids, including 4-tert-butylbenzoic acid (TBBA), in suspended rat hepatocytes. On average, higher amounts of TBBA were detected with Bourgeonal than with Lilial. High and stable TBBA-CoA conjugates were detected in plated hepatocytes incubated with both Bourgeonal and Lilial (ECHA 2024).

Studies investigating species differences

In an *in vivo* study in male mice (n=5), rats (n=8/dose), Guinea pigs(n=5), dogs (n=6) and monkeys (n=2) urinary metabolites (TBBA and TBHA) were analysed after oral application of Lilial via gavage for five consecutive days. The animals were dosed with 100 mg/kg bw/day except dogs that received 44.6 mg/kg bw/day and rats that received 50, 100, 200, 400 mg/kg bw/day. TBBA was the main metabolite in rats, dogs and monkeys. TBBA accounted for 7–15% of the applied dose in rats and 3–4% of the applied dose in dogs. In 2 monkeys, TBBA levels in one animal were as high as in rats (11%), while in the other animal these levels were comparable to the levels in dogs (3%) (ECHA 2019; ECHA 2023).

In an *in vitro* metabolism study plated rat, rabbit and human hepatocytes were exposed to 5 or 50 µM of Lilial for 0.5, 4, 8 (only rabbit hepatocytes) and 22 hrs in triplicate. Coenzyme A conjugates were analysed. Lower concentrations of TBBA were detected in human hepatocytes compared to rat hepatocytes. In rat hepatocytes, TBBA-CoA conjugate levels increased from about 1.4 µM at 0.5 h to about 2 µM (50 µM test dose). In human hepatocytes initial levels of TBBA- CoA were about 0.25 µM which decreased to levels close to the limit of detection at 22 hrs (ECHA 2019; ECHA 2023).

Controlled human studies and in biomonitoring studies

The chemical TBBA has been detected in the urine (ECHA 2019) in dermal and oral controlled studies involving exposure to Lilial. In a dermal pilot study with one volunteer, urine samples were collected including all fractions voided up to 48 hrs after using a sunscreen (5 g) containing 6.5 mg/g Lilial (total 32.5 mg). Peak levels of lysmerol and lysmerylic acid were excreted into the urine about 3–6 hrs after application, whereas TBBA and TBHA appeared about 12 hrs after application. Of the applied dermal dose, TBBA accounted for 0.67%. In the oral study, 5 people were orally dosed with 5.26 mg Lilial dissolved in ethanol. Urinary excretion was fast, with more than 90% of all measured metabolites excreted after 12 hrs, and the excretion was found to be complete by 48 hrs after intake. The sum of the four metabolites assessed in urine reflected about 16.5% of the administered dose with TBBA representing about 14.3% of the administered dose, followed by lysmerol (1.82% of the dose) (ECHA 2019).

Four Lilial metabolites (TBBA, lysmerol, lysmerylic acid, and hydroxy-lysmerylic acid) were measured in 329 urine samples from the Environmental Specimen Bank collected between 2000 and 2018. The two major metabolites TBBA and lysmerol were detected in almost all samples in the study. TBBA was identified at the highest concentrations (mean across all years 13.73 µg/L). The levels of TBBA and lysmerol generally correlated with each other indicating that they are a result of Lilial metabolism. There was a significant decline in levels of TBBA and lysmerol for the monitored years with the most pronounced decrease from 2012 to 2015 (Scherer 2020).

Human biomonitoring data from 2,133 German children and adolescents were analysed for presence of four main metabolites of Lilial. TBBA was identified at the highest concentrations (geometric mean 10.21 µg/L) and was detected in all participants. The specific metabolite lysmerol was detected in 99% of samples. Exposure was strongly associated with frequency of use with some product types such as perfumes, body lotions, air fresheners and fabric softeners linked with higher exposures. Metabolite concentrations were generally higher in girls than in boys (Murawski 2020).

Acute toxicity

Oral

Based on the available data these chemicals have low to moderate acute toxicity via the oral route. Lilial is currently classified for acute oral toxicity in HCIS (Category 4). The available data support the current classification. Based on the available LD50 value (>2000 mg/kg bw/day) classification of Bourgeonal is not warranted.

Lilial

In a non-GLP compliant acute oral toxicity study conducted in accordance with OECD TG 401, Sprague Dawley rats (n = 6/sex/dose) were treated with a single dose of Lilial at doses of 681, 1000, 1470, 2150 or 3160 mg/kg bw. The median lethal dose was 1390 mg/kg bw. Reported sublethal signs of toxicity included dyspnoea, apathy, spastic gait, rough fur coat and poor general condition. Necropsy of the dead animals revealed acute dilation, acute hyperaemia in the heart and discoloured lobes of the liver (SCCS 2015; ECHA CHEM n.d.-a).

In a non-GLP, non-guideline study, Lilial was administered orally to rats (n = 10/dose) at doses of 1220, 2470, 5000 or 10140 mg/kg bw. Mortality rates were 0, 1/10, 7/10 and 10/10 for increasing doses, respectively. The median lethal dose (LD50) in this study was 3,700 mg/kg bw (SCCS 2019).

In another non-GLP, non-guideline screening study, rats (n = 1/sex/dose) were administered by gavage Lilial in vegetable oil at dose levels of 100, 500, 1000, 2000 or 5000 mg/kg bw. Mortality occurred in the 2 highest dose groups. The oral LD50 in this study ranged between 1,000–2,000 mg/kg bw (SCCS 2019).

Bourgeonal

In a non-GLP, non-guideline study, Bourgeonal was administered by gavage to Wistar rats (n = 5/sex/dose) at doses of 2.4, 2.9, 3.2 or 4.2 ml/kg bw. Mortality rates were 30%, 70%, 90% and 100% with increasing doses, respectively. The LD50 in this study was 2.66 mL/kg bw, equivalent to 2550 mg/kg bw (density = 0.959 g/ml) (ECHA CHEM n.d.-b).

Dermal

Based on the available data the chemicals have low toxicity via the dermal route.

In a non-GLP acute dermal toxicity study conducted in accordance with OECD TG 402, Sprague Dawley rats (n = 3/sex/dose) were treated with a single occlusive dose of 2,000 mg/kg bw of Lilial. No mortality was observed and the LD50 was > 2,000 mg/kg bw. Reported signs of toxicity included dyspnoea, agitation, apathy, staggering, rough fur coat, lacrimation, poor general condition and slight erythema/oedema followed by desquamation (ECHA CHEM n.d.-a; SCCS 2015).

In a non-GLP acute dermal toxicity study similar to OECD TG 402, female New Zealand White (NZW) rabbits (n = 6) were treated with a single occlusive dose of 5,000 mg/kg bw of Bourgeonal. One animal died on day 4 post-exposure, after showing signs of toxicity including diarrhoea, shallow breathing, prostration, flaccid muscle tone and spasm. The LD50 was > 5,000 mg/kg bw. Reported signs of toxicity in other rabbits included lethargy and diarrhoea (ECHA CHEM n.d.-b).

Inhalation

Based on the limited data the chemicals have low toxicity via the inhalation route.

In a non-GLP, non-guideline acute inhalation toxicity study, SD rats (n = 3/sex/dose) were exposed to Lilial (vapour, whole body) for 7 hrs at concentrations of 0.1 or 0.18 mg/L. No mortality was observed so the median lethal concentration (LC50) in this study was > 0.18 mg/L (ECHA CHEM n.d.-a; SCCS 2015).

Corrosion/Irritation

Skin irritation

Lilial is classified as hazardous in the HCIS (SWA n.d.) as 'Skin corrosion/irritation - Category 2'. Data are consistent with this classification (NICNAS 2016). Based on the available data for Bourgeonal and read across from Lilial, it is a skin irritant warranting hazard classification.

In a GLP-compliant *in vitro* skin irritation study conducted in accordance with OECD TG 439 (*in vitro* reconstructed human epidermis (RHE) test method for skin irritation), Bourgeonal was applied to RHE for an exposure period of 15 min, followed by an observation period of 42 hrs. A mean tissue viability value of 19.5% was reported for the chemical in this study, and it was determined to be irritating to the skin, supporting the *in vivo* findings (ECHA CHEM n.d.-b). Interpretation of results obtained from OECD TG 439 studies do not allow for distinction between irritation and corrosion.

In a non GLP-compliant skin irritation study conducted according to FDA guidelines, 6 N Z W rabbits were treated with undiluted Bourgeonal for 72 hrs. Observations were recorded at 24 and 72 hrs. The following mean scores were reported for observations at 24 and 72 hrs: 2, 3, 3 for erythema and 2, 3, 3 for oedema respectively (maximum score of 8). Signs of irritation included focal haemorrhages, slight to distinct ischemia and incrustation. In this study Bourgeonal was considered to be a severe skin irritant (ECHA CHEM n.d.-b).

Eye irritation

Lilial was considered to be slightly irritating to eyes based on 2 *in vivo* studies (NICNAS 2016). Based on the available data, Bourgeonal is slightly irritating to eyes. The effects were not severe enough to warrant hazard classification.

In a GLP-compliant *ex vivo* eye corrosivity/irritation study conducted according to OECD TG 437, Bourgeonal was applied to 3 bovine corneae per experiment. The mean *in vitro* irritancy score (IVIS) was 11.6 (IVIS >55 is regarded as serious eye damage and IVIS ≤3 is UN GHS No Category). Based on the prediction model criteria, no conclusion can be drawn regarding the eye irritation potential of chemicals with IVIS values of >3 and ≤55 (ECHA CHEM n.d.-b).

In a non GLP-compliant eye irritation study conducted according to FDA guidelines, Bourgeonal was instilled into 1 eye each of NZW rabbits (n = 6). The eyes were washed out after 24 hrs and observed at 24, 48 and 72 hrs. The following mean scores per rabbit were reported at 24, 48 and 72 hrs: corneal opacity (0 for all animals), iritis (0 for all animals), conjunctival redness (1 for all animals), chemosis (0.67 and 0 for animals 1 and 2, not reported for the others) (ECHA CHEM n.d.-b).

Sensitisation

Skin sensitisation

Based on the available data, both Lilial and Bourgeonal are likely to be moderate skin sensitisers warranting classification (see **Hazard classifications relevant for worker health and safety**). The observed potency is impacted by the vehicle used. Lilial is classified as Skin Sensitiser Cat. 1 in the HCIS (SWA n.d.). The available animal and human data (NICNAS 2016; SCCS 2017; SCCS 2019; ECHA CHEM n.d.-a) support classification. However, there is sufficient data to sub-categorise (Cat 1B). Bourgeonal produced positive results in a Local Lymph Node Assay (LLNA) study. Based on mechanistic considerations (Schiff base formation may be slower for the alpha-alkyl aldehydes Lilial), Bourgeonal may cause sensitisation at lower exposure levels compared to Lilial. This is supported by the comparative EC3 values from LLNA with similar vehicles (4.3% for Bourgeonal vs 13.91% Lilial).

Animal studies

Lilial

There are several LLNA studies for Lilial. The concentrations producing a three-fold increase in lymphocyte proliferation (EC3) ranged between 2.97% and 18.7% depending on vehicle (**Table 14**) (NICNAS 2016; SCCS 2015).

Table 14 Summary of Local Lymph Node Assay (LLNA) study results for Lilial.

Vehicle	EC3 (%)	NESIL (µg/cm ²)
EtOH	2.97	743
EtOH	9.6	2256
DEP	4.17	1043
EtOH:DEP 1:3	13.91	3478
EtOH:DEP 3:1	8.85	2213
acetone/olive oil 4:1	18.7	4394.5
acetone/olive oil 4:1	18.1	4253.5

Lilial tested negative in a Buehler test (OECD TG 406) (GLP not reported), where groups of 10 male Hartley albino guinea pigs were treated with 2% Lilial in ethanol (EtOH) under occlusion for 24 hrs for a total of 5 exposures. The animals were challenged with 2% Lilial in EtOH after 18 days. One treated animal showed skin reactions during induction phase. None of the challenged animals had a positive response to the chemical at 2% (SCCS 2015).

Lilial tested positive in a guinea pig maximisation test (GPMT) (OECD TG 406), using 1% for intradermal induction and 25% for topical induction. Challenge with 0.25 or 2.5 % in acetone/PEG 400 gave 1/10 and 9/10 positive animals, respectively (NICNAS 2016, SCCS 2015).

Lilial tested negative in a GPMT (OECD TG 406) using 5% for intradermal induction and 100% for topical induction. Challenge with 10%, 30% and 100% in EtOH gave no skin reactions (NICNAS 2016; SCCS 2015). Mixed results for skin sensitisation were also observed in non-guideline GPMTs.

Bourgeonal

In a GLP-compliant LLNA following OECD TG 429, groups of CBA mice (n = 4/dose) received topical applications of Bourgeonal at 1, 2.5, 5, 10 or 25% w/v in 1:3 ethanol/ diethyl phthalate for 3 days. The reported stimulation indices (SI) were 0.9, 1.4, 3.6, 4.2 and 9.8 for concentrations of 1, 2.5, 5, 10 and 25%, respectively. The reported EC3 was 4.3%, indicating moderate sensitisation potential for Bourgeonal (ECHA CHEM n.d.-b).

In silico

These chemicals have a structural alert for protein binding based on the mechanistic and endpoint-specific profiling functionality of the Organisation for Economic Co-operation and Development (OECD) QSAR Application Toolbox (OECD QSAR Toolbox v4.8). The alerts include protein binding via Michael additions and Schiff base formation.

The knowledge based expert system Deductive Estimation of Risk from Existing Knowledge (DEREK) Nexus version Derek Nexus v.6.6.0 was utilised to estimate the skin sensitisation potential of the chemical. The chemicals are predicted positive with an aldehyde alert for skin sensitisation. Aldehydes have skin sensitisation potential because of their ability to undergo Schiff base formation with nucleophilic groups present in skin proteins. Therefore, they are likely to interact with skin proteins by such a mechanism. The predicted effective concentrations for a 3-fold increase in lymphocyte proliferation in local lymph node assay (LLNA EC3) for the chemicals are 14% and 4.3% for Lilial and Bourgeonal, respectively, indicating moderate skin sensitisation potential (Lhasa Limited n.d.).

Lilial and Bourgeonal are part of the OASIS-TIMES 2.31.2.82 (Optimised Approach based on Structural Indices Set–Tissue Metabolism Simulator) training set and were assigned skin sensitisation Category 1B by the GHS skin sensitisation model. The chemicals were predicted to react with proteins via Schiff base formation (LMC n.d.).

Observations in humans

Lilial results were reported to be mostly negative in human repeat insult patch tests (HRIPTs) (see **Table 15**). There was 1 (n=119) positive reaction to Lilial at 25% in 75% EtOH/25% DEP (29528 mg/cm²). However, in a maximisation test when Lilial was formulated in petrolatum (pet.) and sodium lauryl sulfate (SDS) (skin barrier disruptor), there were 9/25 positive responses at 5%. No response was seen in a similar study (Api et al. 2020; SCCS 2015).

Table 15: Summary of human patch test data for Lilial

Test	Concentration (%)	Vehicle	Result	NESIL ($\mu\text{g}/\text{cm}^2$)
HRIPT (n=119)	25	75% EtOH/25% DEP	1/119	NA
HRIPT (n=106)	25	25% EtOH/75% DEP	negative	29535
HRIPT (n=64)	5.5	99% EtOH/1% DEP	negative	4125
HRIPT (n=43)	4	petrolatum	negative	2760
HRIPT (n=103)	5	DEP	negative	7500
Maximisation test (n= 25)	4 (+SDS pretreatment)	petrolatum	negative	2760
Maximisation test (n=25)	5 (+SDS pretreatment)	petrolatum	9/25	NA

Based on published data on positive patch-test reactions from clinical studies, Lilial was reported to be an established but relatively uncommon contact allergen. In various clinical studies the frequency was below 0.6% (SCCS 2012). This includes:

- 0.2% positive reactions (10% pet.) in 1855 patients
- 0.4% (95% CI: 0.2 – 0.8%) positive reactions in 2004 patients
- 0.62% (95% CI: 0.04 – 1.21%) positive reactions 1947 patients
- 0.6% (95% CI: 0.1 – 2.2%) positive reactions in 320 patients (1% pet.)
- 0.4% positive reactions in 1825 patients (5% pet.).

There is one reported case of confirmed allergic contact dermatitis associated with exposure to Lilial-containing fragrances (SCCS 2015).

There are no human data available for Bourgeonal.

Repeat dose toxicity

Oral

Based on the available data, the main target for Lilial and Bourgeonal is the male reproductive system (see **Reproductive and development toxicity**). In repeat-dose toxicity studies, Lilial is reported to have some effects on the liver. There is limited systemic toxicity data available for Bourgeonal. The metabolite TBBA is currently classified as STOT RE 1. Target organs include the central nervous system, liver, kidneys, urinary tract and male reproductive system with effects starting at doses as low as 6 mg/kg bw/day (ECHA 2011; NICNAS 2013). There is insufficient evidence to justify a similar classification for Lilial and Bourgeonal. No significant effects were seen in available studies; however, these are either short duration or conducted with doses up to 50 mg/kg bw/day for Lilial and 5 mg/kg bw/day for Bourgeonal. These chemicals may cause effects in other organs at higher doses.

Lilial

In a GLP-compliant 90 day oral study (OECD TG 408) with groups of SPF rats given doses of 2, 5, 25 or 50 mg/kg bw/day, the target organs were the liver and the adrenals from 25 mg/kg bw/day. Effects were mostly reversible (ECHA CHEM n.d.-a; ECHA 2017).

In a GLP-compliant 90 day oral study (OECD TG 409) in Beagle dogs, no adverse systemic effects were reported at doses up to 44.6 mg/kg bw/day (NICNAS 2016).

In the recent OECD TG 443 study (see **Reproductive and development toxicity**), reported general systemic effects included slight changes in haematological and liver parameters at 15.1 mg/kg bw/day (highest dose tested). Haematological effects included: prolonged prothrombin time, increases in red blood cell (RBC) counts, haematocrit and haemoglobin, and an increase in absolute monocyte counts at the highest dose. Liver effects included: increased weight (absolute and relative), slight centrilobular hypertrophy, presence of apoptosis/single cell necrosis, an increase in γ -glutamyl transferase (GGT) activity and slightly increased albumin levels. No other signs of general toxicity were reported (ECHA 2017; ECHA 2019).

Overall, the systemic effects of Lilial were not severe enough to warrant hazard classification.

Bourgeonal

In a GLP-compliant OECD TG 422 study (combined repeated dose toxicity study with the reproduction/developmental toxicity screening test), SD rats (n = 10/sex/dose) were administered Bourgeonal via gavage once daily at 0, 0.5, 1 or 5 mg/kg bw/day from 14 days before mating to day 43 to 46 post during mating. There were no effects on clinical signs, body weight, body weight gain, food consumption, functional observation battery, motor activity, organ weights, hematology, clinical chemistry, or coagulation. There were reductions in thyroid hormone (T4) (see **Developmental toxicity** section). No test substance-related organ weight changes were noted and there were no organ macroscopic findings (ECHA 2023; ECHA 2024; ECHA CHEM n.d.-b).

In a GLP-compliant toxicity screening test, male Crl:CD (SD) IGS BR rats (n = 6 /dose) were administered Bourgeonal by gavage at doses of 0, 25, 100 or 250 mg/kg bw/day for 5 consecutive days. Rats in the 250 mg/kg bw/day dose group were euthanised on day 2. Clinical signs of toxicity included underactivity, reduced body temperature, irregular breathing, piloerection, loose faeces and partially closed eyelids at 100 and 250 mg/kg bw/day after the first dose. Body weight loss was observed at 100 mg/kg bw/day (14 g following administration of the first dose) followed by mean body weight loss during days 3–5 of the study. At 25 mg/kg bw/day the mean body weight loss was 10 g following administration of the first dose. Thereafter, there was no clear effect on body weight. Generalised hepatocyte vacuolation and pale liver was observed at 25 mg/kg bw/day and cortical tubular vacuolation at 100 mg/kg bw/day. At 100 mg/kg bw/day there was also hyperplasia and hyperkeratosis of the forestomach. The metabolite TBBA was detected in the urine at 25 and 100 mg/kg bw/day. No other effects were reported (ECHA CHEM n.d.-b; ECHA 2023; ECHA 2024).

In a non-GLP-compliant 14 day dose range finding study, SD rats (n = 5/sex/dose) were administered Bourgeonal by gavage 3 times/day, at 0, 5, 25 or 50 mg/kg bw/day. In male rats, no clinical signs of toxicity were reported, apart from mortality at the highest dose (two rats). In male rats, there were changes in absolute and relative liver weight at all doses, correlated with hypertrophy or atrophy/degeneration (no details provided). In female rats, clinical signs of toxicity included suspected dehydration, hunched posture and thin appearance at 25 and 50 mg/kg bw/day, but no mortality was reported (ECHA CHEM n.d.-b; ECHA 2023; ECHA 2024).

Dermal

No data are available.

Inhalation

No data are available.

Genotoxicity

Based on the available *in vitro* data for Lilial (NICNAS 2016; SCCS 2015; SCCS 2019) and Bourgeonal (ECHA CHEM n.d.-b), the chemicals are unlikely to have genotoxic potential. The majority of the *in vitro* data were negative, and any positive results were not reproducible. These results are supported by negative *in silico* predictions. No reliable *in vivo* data are available.

Lilial

In vitro mutagenicity assays using Lilial (described in NICNAS 2016) were overall negative. New data (SCCS 2019) suggested that Lilial may be positive in bacterial strain TA 1535. However, 2 additional studies included in SCCS 2019 gave negative results in all bacterial strains (including TA 1535). Ambiguous results were reported from an OECD TG 476 mammalian cell gene mutation assays (NICNAS 2016, SCCS 2015); however, new data (SCCS 2019) showed that Lilial was negative in another *in vitro* mammalian cell gene mutation assay (OECD TG 476). An *in vitro* comet assay in mammalian cells was negative. The metabolite lysmerylic acid was negative in an Ames test in all strains including TA 1535. Overall, based on these *in vitro* data Lilial is unlikely to be mutagenic.

One *in vitro* chromosome aberration test (OECD TG 473) using Chinese hamster ovary (CHO) cells was reported as positive (NICNAS 2016); however, additional data published in SCCS 2019 including 2 negative micronucleus tests (OECD TG 487) using human peripheral blood lymphocytes produced negative results. The only available *in vivo* micronucleus study showed a statistically significant increase in micronucleated polychromatic erythrocytes (PCE) in the high-dose male group 48 hrs after exposure. However, these results were reported as not biologically significant as they were within the range of historical solvent controls. This study was reported to be inadequate to 'draw a firm conclusion' on genotoxicity *in vivo* (SCCS 2015). The metabolite Lysmerylic acid showed negative results in a micronucleus test (OECD TG 487) using human peripheral blood lymphocytes. Overall, based on the available *in vitro* data Lilial is unlikely to be clastogenic or to cause aneuploidic damage.

Additional data not included in the 2016 NICNAS report are listed below (SCCS 2019):

- Positive results in a bacterial reverse mutation assay (OECD TG 471) in *Salmonella typhimurium* strain TA 1535, at concentrations starting at 150 µg/plate with and without metabolic activation (Lilial with 200 ppm of alpha-tocopherol).
- Negative results in a bacterial reverse mutation assay (OECD TG 471) in *S. typhimurium* strains TA98, TA100, TA1535, TA1537, *Escherichia coli* strain WP2uvrA up to 2000 µg/plate with and without metabolic activation (Study limitations noted by SCCS).
- Negative results in a bacterial reverse mutation assay (OECD TG 471) in *S. typhimurium* strains TA98, TA100, TA1535, TA1537, *E. coli* strain WP2 uvrA up to 5000 µg/plate with and without metabolic activation (Lilial with 200 ppm of alpha-tocopherol).
- Negative results in an *in vitro* mammalian cell gene mutation assay (OECD TG 476) using L5178Y mouse lymphoma cell line (Tk+/-) at concentrations up to 72 µg/mL (Lilial with 200 ppm of alpha-tocopherol).

- Negative results in an alkaline Comet assay in Human colonic epithelial cells at concentrations up to 100 µM.
- Negative results in a micronucleus test comparable to OECD TG 487 using human peripheral blood lymphocytes at concentrations up to 500 µM (Study limitations noted by SCCS).
- Negative results, when tested with 200 ppm of alpha-tocopherol, in a micronucleus (OECD TG 487) using human peripheral blood lymphocytes at concentrations up to 2000 µg/mL (Lilial with 200 ppm of alpha-tocopherol).

Bourgeonal

The following *in vitro* data are available for Bourgeonal (ECHA CHEM n.d.-b):

- Negative results in a bacterial reverse mutation assay (OECD TG 471) in *Salmonella typhimurium* TA 1535, TA 1537, TA 98, TA 100 and *Escherichia coli* (E. coli) WP2 with and without metabolic activation at concentrations up to 5000 µg/plate.
- Negative results in a GLP compliant *in vitro* mammalian gene mutation assay (OECD TG 490) in mouse lymphoma L5178Y cells with and without metabolic activation at concentrations up to 65 µg/mL.
- Negative results were reported in an *in vitro* micronucleus test (OECD TG 487) in human lymphocytes with and without metabolic activation at concentrations up to 60 µg/mL.

In silico

Lilial and Bourgeonal have a structural alert for mutagenicity based on the mechanistic and endpoint-specific profiling functionality of the OECD QSAR Application Toolbox (OECD QSAR Toolbox 4.8). These alerts include DNA binding via Michael additions and Schiff base formation. There were no alerts found for DNA binding for Ames, CA and MNT by OASIS as well as for protein binding alerts for chromosomal aberrations by OASIS.

These chemicals are predicted to be negative in the Ames test (within the applicability domain) and negative for *in vitro* chromosome aberration (80% in domain for Lilial and 89% in domain for Bourgeonal) using OASIS–TIMES (Optimised Approach based on Structural Indices Set–Tissue Metabolism Simulator; version 2.34.1.123)

The chemicals were out of domain in the *in vitro* model for mouse lymphoma thymidine kinase locus assay and in all *in vivo* models in OASIS-TIMES.

The knowledge based expert system DEREK Nexus version v.6.6.0 was used to estimate the genotoxicity potential of the chemicals. The chemicals did not match any structural alerts or examples for bacterial *in vitro* mutagenicity or contain any unclassified (not found in the reference set) or misclassified features (found in non-alerting mutagens).

The chemicals are also predicted negative in the *in vivo* micronucleus test in mouse in 3 statistical QSAR models including CaseUltra, Leadscope and SciQSAR (Danish QSAR).

Carcinogenicity

No animal data are available for these chemicals. Based on Quantitative Structure Activity Relationship (QSAR) modelling, these chemicals are not expected to be carcinogenic.

As aldehydes, both chemicals have a structural alert for binding to DNA based on the mechanistic profilers of the OECD QSAR Toolbox v4.8. However, based on the Danish EPA QSAR models, the chemicals only have negative alerts inside applicability domain for carcinogenicity (Danish EPA 2026).

Reproductive and development toxicity

Based on the weight of evidence of the available data, these chemicals are expected to cause specific adverse effects on fertility and development, warranting hazard classification as Reproductive toxicity – Category 1B H360Fd. Although the available data for Bourgeonal is limited, the consistency of the observed effects support read across from Lilial and the metabolite TBBA. Both chemicals caused testicular toxicity and spermatotoxicity with effects for Lilial shown in two species (rats and dogs). Adverse fertility outcomes have been shown for Lilial and the observed metabolite TBBA (NICNAS 2013). Based on the current available data, human relevance of effects cannot be excluded. The metabolite TBBA is formed in humans, and no species-specific mechanism has been established. For development reduced pup body weights were observed in rat studies for both chemicals with evidence of post-implantation loss observed for Lilial. The developmental effects were not unequivocally attributable to the maternal toxicity seen in the studies.

Sexual function and fertility

Lilial

Lilial caused adverse effects on the male reproductive system in several studies including testicular toxicity in rats and dogs and reduced fertility parameters in a one-generation study in rats (ECHA 2019; NICNAS 2016). Since Lilial was assessed by NICNAS in 2016, new data include a range finding study and an OECD TG 443 study. In the 8 week range finding study, effects on sperm, testes and fertility index were reported from 27.5 mg/kg bw/day. Only minor effects on sperm were observed in the OECD TG 443 study at 15.1 mg/kg bw/day. However, this was the highest dose tested.

The following testicular adverse effects were observed from 50 mg/kg bw/day in diet studies in rats ranging from 6 to 13 weeks (NICNAS 2016):

- decreased relative testes and cauda epididymis weights
- testes degeneration and aspermia (absence of sperm) of the epididymis
- decrease of seminal vesicle and prostate weights and hyperplasia of Leydig cells.

The reported NOAEL values were 25 mg/kg bw/day and 29 mg/kg bw/day for the 6 and 13 week studies, respectively.

Sperm or testicular effects were also observed in Beagle dogs treated with Lilial at 200 mg/kg bw/day for 2 weeks.

No testicular toxicity was observed in mice, rabbits, guinea pigs or Rhesus monkeys receiving 100 mg/kg bw/day for 5 days.

Additional studies, not available at the time of NICNAS 2016 assessment are described below.

In a range-finding study (ECHA 2019; ECHA 2024; ECHA CHEM n.d.-a), Wistar rats (n = 10/sex/dose) were fed Lilial in diet at 0, 230, 750 or 2300 ppm for 2 weeks before mating, until postnatal day (PND) 21 (~30 days). Actual dose intakes were estimated to 0, 2.3–2.8, 7.4–9.1 and 25.1–27.5 mg/kg bw/d in males and 0, 3.3–3.7, 10.6–11.9 and 21–34.7 mg/kg bw/d in females. No mortality was reported for parent animals. General signs of toxicity included decreased body weight and food consumption during premating phase, gestation and lactation. Changes in clinical chemistry and haematological parameters were observed in mid- and high- dose female rats and in high-dose male rats. There was no change in mating indices.

Statistically significant effects related to fertility at the highest dose included:

- a decrease of motile sperm
- an increase of abnormal sperm
- reduced sperm head count in the epididymis (no effect on testicular sperm head count)
- reduced fertility index (approx. 40%)
- a decrease in mean implantation sites.

A NOAEL of 750 ppm for fertility (7.4–9.1 mg/kg bw/day for males) was determined based on effects on sperm and fertility effects at the highest dose.

In a modified extended one-generation reproduction toxicity study conducted in accordance with OECD TG 443, Wistar rats (n = 35/sex/dose) were fed encapsulated Lilial in the diet at 75, 230 and 750 ppm (n = 40/sex/750 ppm group) (equivalent to 1.4, 4.5 and 15.1 mg/kg bw/day) (ECHA 2017; ECHA 2019). The study included an additional cohort and minor protocol deviations. Exposure started 13 days prior to mating for F0 male and female rats. Pups of the F1 litter were selected and assigned to 7 different cohorts which were subjected to specific post-weaning examinations. F1 Cohort 1B animals selected for breeding were maintained under the same dosing regimen as their parents to produce a F2 litter.

The following exposure periods applied:

- P0 males and females: at least 13 days before mating through breeding and for a maximum of 6 post- mating weeks (males) or gestation (3 weeks) and lactation (3 weeks) for females.
- F1 males and females:
 - 1A: euthanised on PND 90 (13 weeks)
 - 1B: same dose group as parents until 19-25 weeks
 - 2A: until PND 75-90 (11-13 weeks)
 - 2B: euthanised on PND 22 (3 weeks)
 - 3: euthanised at 8-9 weeks
 - 4A: euthanised on PND 22 (3 weeks)
 - 4B: euthanised at 10-12 weeks.

Histopathological examination occurred for the F1 Cohorts as follows:

- cohorts 1A and 1B: general organ and reproductive pathology
- cohorts 2A and 2B: nervous system pathology (central and peripheral)
- cohort 3: immune response investigations
- Cohort 4A and 4B: acetylcholinesterase activities in blood, erythrocytes, brain and muscle.

There were no test substance-related mortality or adverse clinical effects observed in any of the groups.

At the highest dose, F0 males had a slightly higher mean percentage of abnormal sperm (9.8%) above the control percentage (6.3%) and the historical control range (6.0-6.6 %). These effects were not observed in F1 males. No other effects related to male fertility (sperm head count and motility) were reported in F0 or F1 male rats. This included no findings in sperm motility or sperm head counts in testes and epididymides of these animals. The fertility index was not affected in any of the cohorts. Note that the exposure time for F0 males was only about 13 days prior to mating and therefore they had not gone through a full spermatogenic cycle. High-dose F1 females had a statistically significant decrease in the mean number of implantation sites (10.5 implants/dam); however, these were within historical control range (9.4-13.9 implants/dam)

No treatment-related effects were reported on oestrous cycle data, mating behaviour, conception, gestation, parturition, lactation and weaning as well as sexual organ weights and gross and histopathological findings of these organs in F0 and F1 female rats up to the highest dose. The NOAEL for fertility and reproductive performance in the F0 and F1 parental rats was 15.1 mg/kg bw/day in this study, although effects in the sperm were observed at this dose (F0 males only). Due to the low doses studied this study does not negate fertility effects observed in other studies.

At the highest dose, reduced food intake, reduced body weight during gestation and lactation were reported in F0 and F1 female rats. Significant absolute and relative liver weight increase were associated with minimal to slight centrilobular hypertrophy accompanied by minimal to slight apoptosis/single cell necrosis of hepatocytes in high-dose F0 and F1 females. Therefore, the NOAEL for general systemic toxicity was set at 4.5 mg/kg bw/day.

Bourgeonal

The available data for Bourgeonal indicate similar testicular effects at 5 mg/kg bw/day (lowest dose tested) in a 14 day range finding gavage study.

The observation of effects at lower doses for Bourgeonal compared to Lilial may be due to potential quantitative differences in metabolism (see **Toxicokinetics**) or differences in study design.

In a non GLP-compliant 14 day dose range finding study, SD rats (n = 5/sex/dose) were administered Bourgeonal by gavage 3 times/day, at 0, 5, 25 or 50 mg/kg bw/day (ECHA 2023; ECHA 2024).

In male rats, no clinical signs of toxicity were reported, apart from mortality at the highest dose (2 males). In female rats, clinical signs of toxicity included suspected dehydration, hunched posture and thin appearance at 25 and 50 mg/kg bw/day, but no mortality was reported. Effects related to fertility included:

- changes in absolute and relative weight of the testes (at 50 mg/kg bw/day) and liver (at all doses) in male rats and of the ovaries (at 25 and 50 mg/kg bw/day) and uterus (at 50 mg/kg bw/day) in female rats; these changes were correlated to histologic observations of hypertrophy or atrophy/degeneration
- microscopic findings in the testes of male rats at all doses, including vacuolation and degeneration of seminiferous tubular epithelium and Sertoli cell vacuolation
- cribriform change, cellular debris and hypospermia in the epididymides of male rats at 25 and 50 mg/kg bw/day

- reduced sperm motility at 5 mg/kg bw/day (77% vs 84% in controls) and little to no sperm at 25 and 50 mg/kg bw/day; all sperm samples at 25 and 50 mg/kg bw/day contained headless and detached sperm
- reduced sperm motility was linked to the infrequent increased spermatid head retention by the Sertoli cells, degeneration of maturing spermatids, round spermatids, and/or elongating spermatids, degeneration of germ cells, increased cellular debris, and moderate to marked hypospermia observed microscopically in the seminiferous tubules or epididymides
- uterine atrophy in female rats at 50 mg/kg bw/day.

Based on the microscopic findings in testes/seminiferous tubule and effects on sperm motility at all doses, a lowest observed adverse effect level (LOAEL) of 5 mg/kg bw/day was determined (ECHA 2023). In female rats, absolute and relative weights of ovaries and uterus were changed in the top dose and mid- and top dose groups, respectively. In uterus, the weight change was accompanied by uterine atrophy in top dosed females (ECHA 2023; ECHA 2024).

In a GLP-compliant OECD TG 422 study (combined repeated dose toxicity study with the reproduction/developmental toxicity screening test), Sprague-Dawley (SD) rats (n = 10/sex/dose) were administered Bourgeonal via gavage once daily at 0, 0.5, 1 or 5 mg/kg bw/day from 14 days before mating to day 43 to 46 post mating. No clinical signs of toxicity and mortality were reported in the treated groups. No effects were reported on reproductive function or performance and on oestrous cycle. Sperm was not examined. There were no effects on mating and fertility. In the F1 generation, a statistically significantly reduced mean pup body weight was reported at 5 mg/kg bw/day on days 9 and 12 postpartum (-11 and -12%, respectively). The NOAEL for fertility was 5 mg/kg bw/day in adult rats (ECHA 2023).

Both the CLH report and RAC Opinion stated that the doses used in the guideline study were rather low, with 5 mg/kg bw/day as the highest dose. In the dose range finding study, this dose elicited changes in the testes of male rats but no changes in female rats. The microscopic findings in the testes and changes in sperm motility seen in the range finding study that could have been investigated further in the main study were not addressed as sperm parameters were not examined. It is therefore not possible to draw a conclusion based on the lack of effects reported in the guideline study.

In a GLP-compliant toxicity screening test, male Crl:CD (SD) IGS BR rats (n = 6 /dose) were administered Bourgeonal by gavage at doses of 0, 25, 100 or 250 mg/kg bw/day for 5 consecutive days. Males treated at 250 mg/kg bw/day were all sacrificed on day 2 of the study due to welfare reasons. Clinical signs of toxicity included underactivity, reduced body temperature, irregular breathing, piloerection, loose faeces and partially closed eyelids at 100 and 250 mg/kg bw/day after the first dose.

Five of 6 animals treated with 100 mg/kg bw/day showed treatment-related effects on the testes and epididymides, and 3/6 animals had enlarged epididymides. Observations reported at 100 mg/kg bw/day were:

- Seminiferous tubular degeneration/atrophy
- Sertoli cell vacuolation
- multinucleate giant cell
- luminal sloughing of spermatogenic cells in the testes
- reduced numbers of spermatozoa
- sloughed germ cells in lumen
- inflammation in the epididymides.

Analysis of urine from males treated with 100 or 25 mg/kg bw/day demonstrated presence of the metabolite, TBBA, mean concentrations were 275 and 35.8 µg/ml, respectively.

Developmental toxicity

Reduced pup body weights were observed in rat studies for both chemicals, at doses of 15 mg/kg bw/day for Lilial and 5 mg/kg bw/day for Bourgeonal. Post-implantation loss was observed for Lilial at 45 mg/kg bw. The developmental effects were not unequivocally attributable to the maternal toxicity seen in the studies.

Lilial

In a developmental toxicity gavage study (following OECD TG 414), developmental effects included an increase in post-implantation loss at 45 mg/kg bw/day and reduced foetal body weights at 15 mg/kg bw/day (NICNAS 2016, ECHA 2017; ECHA 2019). At 15 and 45 mg/kg bw signs of maternal toxicity included liver effects (increased weight and liver enzymes) at the mid and top dose, and reduced body weight gain (GD13–20) resulting in a 32% lower mean body weight gain compared to controls. The NOAEL for maternal and pre-natal developmental toxicity was 4.1 mg/kg bw/day.

In a non-GLP compliant range finding study (see **Sexual function and fertility**) there was an increase in mean post implantation loss, decreased pup survival (PND 0–4) postnatal and decrease in pup birth weight at 21–34.7 mg/kg bw/day. The NOAEL for developmental toxicity was 10.6–11.9 mg/kg bw/day. At this dose level, maternal toxicity included decreased body weight gain and a decreased food consumption (ECHA 2017; ECHA 2019).

In another one generation range finding study, post-implantation loss was increased and reduced birth weights were observed starting from the dose of 10–15 mg/kg bw/day. At this dose level, maternal toxicity included decreased body weight gain and a decreased food consumption (ECHA 2017; ECHA 2019).

The NOAEL for developmental toxicity was 4.5 mg/kg bw/day in a GLP-compliant OECD TG 443 diet study (see **Sexual function and fertility**). This was based on persistent reductions in F1 and F2 pup body weights at 15.1 mg/kg bw/day. Pup body weight (F1 and F2) at the high dose weighed about 14–15% less than control after birth and did not recover until weaning. Mean post-implantation loss was slightly, but not statistically significantly, increased in F0 and F1 dams starting from the lowest dose. However, these changes were not dose-dependent and showed high variations. There were no effects on viability index (PND 0–4). Mean anogenital distance was decreased in male and female F2 pups but not in any other pup cohorts. This single result could have been a consequence of lower body weight rather than a treatment specific effect. There were no effects on postnatal survival, pup body weight gain or post-weaning development (F1 and F2 pups). There were no effects on the presence of nipples/areolas, vaginal opening, preputial separation. The observed 1-day delay in preputial separation in one male F1 offspring (10 mg/kg bw/day) was within the historical control range of the facility. There was no effect on the timing of male puberty in any other groups (ECHA 2019; SCCS 2019)

Bourgeonal

In the OECD 422 gavage study (see **Sexual function and fertility**) (ECHA 2023) a statistically significantly reduced mean pup body weight was reported at 5 mg/kg bw/day on days 9 and 12 postpartum (-11 and -12%, respectively). No clinical signs or effects on body

weights were reported in parental animals. The NOAEL for developmental toxicity was **1 mg/kg bw/day**.

There was a dose-dependent reduction in T4 levels in males; however, it was not statistically significant. Similar T4 changes were observed in females. These changes were statistically significant at 1 and 5 mg/kg bw day. However, there were no microscopic changes in thyroid or parathyroid glands of the investigated pups (one male and one female pup per litter were investigated in the top dose). No differences in anogenital distance or nipple retention were observed.

Mode of action (MOA)

The common metabolite TBBA has been shown to cause adverse effects on male reproductive organs and spermatotoxicity, leading to adverse effects on male fertility. It is classified as Repro 1B. The formation of TBBA following exposure to Lilial and Bourgeonal is considered to be one of the potential underlying mechanisms of reproductive toxicity. The relevance of this mode of action to humans has been discussed in the RAC Opinion for Bourgeonal group (ECHA 2024). RAC's overall conclusion was that human relevance cannot be excluded and rejected the argument that the toxicity was specific to rats. The reasons are summarised below:

- The available data do not allow to clearly identify the underlying MoA of the observed toxicity.
- The proposed CoA-accumulation MoA is not consistently demonstrated even in rat cells.
- The causal link between CoA accumulation and testicular toxicity *in vivo* has not been established.
- There is no explanation for why CoA accumulation would occur in rats but not humans. Potential species differences in CoA-transferases have not been investigated, and polymorphisms in the human population cannot be ruled out.
- Similar toxic effects were seen in multiple species beyond the rat, indicating the responsible MoA(s) are active across species. No mechanistic data is available for dogs.
- Alternative MoAs have not been ruled out and are active in human cells as well.

The RAC Opinion on Lilial (ECHA 2019) considered *'the testicular toxicity and spermatotoxicity shown in two species (rats and dogs) relevant for humans despite a quantitatively different metabolism of the compound in different species'*.

No information is available on mode of action for observed developmental effects. No developmental toxicity data are available for the metabolite TBBA (NICNAS 2013).

Human Health Risk Characterisation

Critical health effects

The critical health effects for risk characterisation are skin sensitisation and adverse effects on fertility and developmental toxicity.

Public risk

There is potentially widespread public exposure to Lilial and Bourgeonal in various types of cosmetic and domestic products at low concentrations.

Quantitative risk assessment for skin sensitisation

The risk of induction of skin sensitisation was estimated by comparing a Consumer Exposure Level (CEL) with an Acceptable Exposure Level (AEL) for each personal care product type. Where $AEL < CEL$, this indicates a risk of induction of sensitisation. The CEL, defined as the total amount of chemical that may reach the skin, was calculated using information on product types and concentrations of the chemicals in different cosmetic categories (SCCS, 2012 Cadby et al., 2002). The AEL is estimated based on a No Expected Sensitisation Induction Level (NESIL) with safety factors applied. For product types where $AEL < CEL$, this indicates a potential risk and an acceptable exposure concentration (AEC) was calculated.

Based on the results of animal studies and human evidence, Lilial is a weak to moderate skin sensitiser depending on vehicle with the lowest EC3 in LLNA studies observed when ethanol was used as a vehicle. The chemical is mostly negative in HRIPT studies. The negative HRIPT using 5.5% Lilial dissolved in 99% EtOH/1% DEP is considered appropriate for determining sensitisation risk as it used the highest ethanol concentration present out of all HRIPT studies. Although study application details are not available, RIFM reports a value of $4125 \mu\text{g}/\text{cm}^2$ as the NESIL for this study (Api et al. 2020) which is similar to the $4200 \mu\text{g}/\text{cm}^2$ reported by SCCS (SCCS 2016). RIFM used a rounded value $4100 \mu\text{g}/\text{cm}^2$ as the weight of evidence NESIL. Based on this value, an AEL of $41 \mu\text{g}/\text{cm}^2$ /day is estimated for Lilial. In this instance, the factors employed included an interspecies factor (1), intraspecies factor (10), a matrix factor (3.16), use/time factor (3.16) and database factor (1), giving an overall safety factor of 100.

There is only one sensitisation study available for Bourgeonal and no human data. Based on the EC3 value of 4.3% from an LLNA, a NESIL of $1031 \mu\text{g}/\text{cm}^2$ was calculated. Based on the NESIL value and application of appropriate safety factors an AEL of $3.44 \mu\text{g}/\text{cm}^2$ /day is estimated for Bourgeonal. In this instance, the factors employed included an interspecies factor (3), intraspecies factor (10), a matrix factor (3.16), use/time factor (3.16) and database factor (1), giving an overall safety factor of 300.

For both Lilial and Bourgeonal, the $AEL < CEL$ when used in fine fragrances (see **Table 16**).

Table 16: Quantitative risk assessment for use of Lilial and Bourgeonal in fine fragrances

Chemical	C (%)	CEL (chemical) (ug/cm ² /day)	AEL (ug/cm ² /day)	Acceptable exposure concentration (%)
Lilial	1.3	48.75	41	1.09
Bourgeonal	0.12	4.50	3.44	0.09

(C = chemical concentration)

Based on these calculations, there is a risk of skin sensitisation induction to the public when using Lilial and Bourgeonal in fine fragrances at the reported levels. For both chemicals, the concentrations reported in fine fragrances are higher than the acceptable exposure concentrations.

Regarding other categories of cosmetic products and domestic products, the risk of induction skin sensitisation is considered to be low for both chemicals. However, it is acknowledged that consumers may be exposed to multiple cosmetic or domestic products containing Lilial and/or Bourgeonal. Cross-sensitisation between structurally related fragrance aldehydes cannot be ruled out; however, evidence demonstrating clinically significant cross reactivity among the Lily of the Valley fragrance aldehydes is limited.

Skin sensitisation includes two phases. The induction phase is the initial contact with a chemical that primes the immune system. The elicitation phase takes place after re-exposure to the same chemical that triggers the allergic reaction. A lower level of exposure is generally considered to be required for elicitation than for induction to occur (Palmer et al 2025). Therefore, the risk of elicitation at lower concentrations for sensitised individuals cannot be ruled out.

Quantitative risk assessment for systemic toxicity

The products with the highest systemic exposure dose levels (SEDs) are air care products, body lotion and fine fragrances for Lilial, and air care products and fine fragrances for Bourgeonal, based on the reported and/or maximum allowed concentrations in these products (see calculation of SED in **Human Exposure**).

An MOE methodology was used to characterise the risk to human health associated with systemic exposure to the chemicals. The MOE methodology is commonly used to characterise risks to human health associated with exposure to chemicals.

The MOE approach compares estimated human exposure with a toxicological point of departure (POD), to determine whether a sufficient margin exists to protect against a particular adverse health effect. As the MOE increases, the risk of potential of adverse effects decreases. To decide whether the MOE is of sufficient magnitude, expert judgment is required. Such judgments are usually made on a case-by-case basis and should consider uncertainties arising in the risk assessment process such as the completeness and quality of available data, the nature and severity of effect(s) and intra/inter species variability. In general, an MOE value greater than or equal to 100 is considered acceptable to account for intra- and inter-species differences.

The following values were chosen as (POD) for risk characterisation for chronic exposure:

- NOAEL = 4.5 mg/kg bw/day for Lilial based on the developmental effects reported in the OECD TG 443 study (see **Reproductive and developmental toxicity**); and
- NOAEL = 1 mg/kg bw/day for Bourgeonal based on developmental effects (see **Reproductive and developmental toxicity**)

For this risk characterisation, an MOE value greater than or equal to 100 is considered acceptable to account for uncertainty factors (UF) for intra- ($\times 10$) and inter-species ($\times 10$) differences.

Developmental toxicity effects are often triggered by toxicant exposure during brief, highly sensitive developmental windows and, therefore are relevant to acute exposures to the chemical. Therefore, the use of risk estimates for maximum/95th percentile concentrations is appropriate.

MOE were calculated for exposure from individual products (see **Tables 17 and 18**) and a range of exposure scenarios covering combined exposures (see **Table 19 and 20**). The combined exposure scenarios modelled were based on potential changes to product types that contribute most to exposure (body lotion, fine fragrance and air care products).

Table 17. MOE values for Lilial in cosmetic and domestic products based on 95th percentile concentrations overseas and reported Australian data

Product type	C(%)	Daily systemic exposure (mg/kg bw/day)	MOE
Body lotion	0.24	0.0278	162
Face cream	0.033	0.0009	5060
Hand cream	0.05	0.0019	2381
Fine fragrances	1.3	0.0219	205
Deodorant (non-spray)	0.12	0.0041	1111
Shampoo	0.069	0.0001	42033
Conditioner	0.064	0.0000	120923
Shower gel	0.12	0.0003	13541
Hand wash soap	0.12	0.0004	12640
Hair styling products	0.042	0.0002	18058
Laundry liquid	0.15	0.0005	9256
Fabric softener	0.25	0.0003	14193
Dishwashing liquid	0.15	0.0000	126105
All-purpose cleaner	0.15	0.0003	14592
Hairspray	0.028	0.0010	4500
Air fresheners plug in	8.9	0.0436	103
Scented candles	1	0.1040	43*
Aerosol air fresheners (instant-action)	0.41	0.0228	197

(C = chemical concentration)

*MOE < Total UF

Table 18. MOE values for Bourgeonal in cosmetic and domestic products based on reported overseas and Australian concentration data

Product type	C (%)	Daily systemic exposure (mg/kg bw/day)	MOE
Body lotion	0.005	0.0006	1724
Face cream	0.005	0.0001	7421
Hand cream	0.005	0.0002	5291
Fine fragrances	0.12	0.0020	494
Deodorant (non-spray)	0.005	0.0002	5926
Shampoo	0.005	0.0000	128902
Conditioner	0.005	0.0000	343958
Shower gel	0.005	0.0000	72218
Hand wash soap	0.005	0.0000	67416
Hair styling products	0.005	0.0000	33708
Laundry liquid	0.24	0.0008	1274
Fabric softener	0.24	0.0003	3285
Dishwashing liquid	0.24	0.0001	17514
All-purpose cleaner	0.24	0.0005	2027
Hairspray	0.005	0.0002	5824
Air freshener plug in	1	0.00427	234
Scented candles	1	0.0903	11
Aerosol air fresheners (instant-action)	0.055	0.0027	375

(C = chemical concentration)

*MOE<Total UF

Table 19. MOE values for Lilial for combined exposure to all cosmetic/domestic based on 95th percentile concentrations

Exposure scenario	Daily systemic exposure (mg/kg bw/day)	MOE (POD/SED)
Use in all products (95 th percentile conc)	0.2298	20*
Use in all products (95 th percentile conc) excluding all air care	0.0598	75*
Use in all products (95 th percentile conc) excluding all continuous-action air care	0.0826	54*
Use in all products (95 th percentile conc) excluding all air care but with body lotion at 0.06%	0.0389	116
Use in all products (95 th percentile conc) excluding all continuous-action air care but with body lotion at 0.06%	0.0617	73*

*MOE<Total UF

Table 20. MOE values for Bourgeonal for combined exposure to all cosmetic/domestic products

Exposure scenario	Daily systemic exposure (mg/kg bw/day)	MOE (POD/SED)
Use in all products (max reported conc)	0.1022	10*
Use in all products (max reported conc) excluding all air care	0.005	201
Use in all products (max reported conc) excluding all continuous-action air care	0.0077	130

*MOE<Total UF

While exposure to most individual cosmetic products containing Lilial or Bourgeonal does not pose a significant risk, the MOE calculations show there is a risk to the public from the exposure to continuous-action air care products including scented candles containing these chemicals at reported concentrations, with MOEs below or very close to the reference value of 100.

There is a potential risk to the public from combined exposure to cosmetic and domestic products (excluding air care products) containing Lilial at reported concentrations with an MOE of 75. Revised estimates using the IFRA maximum acceptable concentrations (MAC) for body lotion resulted in MOE >100. Combined dermal exposure to Bourgeonal in cosmetic and domestic products (excluding continuous-action air care products) at reported levels does not pose a significant risk, with an MOE of 131. However, it is noted that the concentrations modelled for the high exposure scenarios of body lotion (0.005%) and fine fragrance (0.12 %) were significantly lower than those permitted under the IFRA Standard (see **Table 2**). Use of Bourgeonal at higher concentrations may result in an unacceptable risk, for example, use of the chemical in body lotion at 0.12% results in an MOE < 100 whereas decreasing this concentration to 0.06% (maximum concentration for Lilial) provides an acceptable margin of safety.

Bourgeonal and Lilial have the same common hazardous metabolite and could be present in the same products which may increase the overall risks. However, the worst-case exposure estimate assumes simultaneous use of all products containing the chemical at the highest concentrations identified. International estimates of exposure based on probabilistic modelling (Api et al. 2020, Api et al. 2024) indicate that the MOE would likely be significantly higher. In addition, available toxicokinetic data indicates that rats may be more sensitive to effects compared to humans. Therefore, the conservative estimates are expected to account for this uncertainty.

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