HEALTH RISK ASSESSMENT:

BUTYLPHENYL METHYLPROPIONAL IN COSMETIC PRODUCTS

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Prepared by: Abhishek Gautam

PREPARED FOR: Health New Zealand, National Public Health Service

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REVIEWED BY: Peter Cressey, Risk Assessment, Food and Social Systems Group

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Manager	Peer reviewer	Author
		
Daniel Bohnen	Peter Cressey	Abhishek Gautam
Service Lead and Manager, Risk Assessment, Food and Social Systems Group	Science Leader, Risk Assessment, Food and Social Systems Group	Senior Scientist, Risk Assessment, Food and Social Systems Group

DISCLAIMER

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ABBREVIATIONS

AICIS	Australian Industrial Chemicals Introduction Scheme
BMD	Benchmark dose
bw	Body weight
CAS RN	Chemical Abstract Service Registry Number
CLP	Classification, Labelling and Packaging
CMR	Carcinogenic, mutagenic or toxic to reproduction
DAp	Dermal absorption
EC	European Commission
ECHA	European Chemicals Agency
ESR	Institute of Environmental Science and Research Limited
EU	European Union
GLP	Good Laboratory Practice
IMAP	Inventory Multi-tiered Assessment and Prioritisation
INCI	International Nomenclature of Cosmetic Ingredients
i.p.	Intraperitoneal
IUPAC	International Union of Pure and Applied Chemistry
LD_{50}	Median lethal dose (causes death in 50% animals)
LOAEL	Lowest observed adverse effect level
MoE	Margin of exposure
MoS	Margin of safety
NICNAS	National Industrial Chemicals Notification and Assessment Scheme
NOAEL	No observed adverse effect level

NZ EPA	New Zealand Environmental Protection Authority
p.c.	Post-coitum
POD	Point of departure
Pow	Octanol-water partition coefficient
RAC	Risk Assessment Committee
RIFM	Research Institute for Fragrance Materials
SCCS	Scientific Committee on Consumer Safety
SED	Systemic exposure dose
UF	Uncertainty factor
US FDA	United States Food and Drug Administration

EXECUTIVE SUMMARY

The purpose of this report is to summarise generic health risk assessment data for exposure to butylphenyl methylpropional from the use of cosmetic products. This report will only consider domestic, non-occupational, incidental exposure to butylphenyl methylpropional.

Butylphenyl methylpropional (commonly known as lilial) is an aromatic aldehyde that is widely used as a fragrance ingredient in many cosmetic products, including perfumes, deodorants and antiperspirants, as a masking agent to reduce and/or inhibit the base product odour while giving a floral scent with a lily-of-the-valley note.

Exposure to butylphenyl methylpropional is considered incidental while using cosmetic products and will depend on the intended uses of the product. However, in general, dermal exposure is the most important exposure route for cosmetic products.

Fragrance use in cosmetic products is regulated in some jurisdictions. In the European Union, butylphenyl methylpropional was recently banned for use in cosmetic products due to its classification as Repr. 1B (may damage fertility and is suspected of damaging the unborn child). Consequently, there have been increased recalls of cosmetic products in the EU due to the presence of butylphenyl methylpropional. By contrast, the use of butylphenyl methylpropional in cosmetic products is not banned in the USA or Australia.

In New Zealand, cosmetic products are regulated by the New Zealand Environmental Protection Authority. Butylphenyl methylpropional is now listed as a component that cosmetic products must not contain except subject to the restrictions and conditions laid down under Schedule 4 of the updated Cosmetic Products Group Standard.

To assess the risk posed by exposure to butylphenyl methylpropional in cosmetic products, risk assessments by the European Scientific Committee on Consumer Safety and the Research Institute for Fragrance Materials were reviewed, summarised and critiqued. The Scientific Committee on Consumer Safety concluded that butylphenyl methylpropional at the maximum proposed concentrations in cosmetic products could not be considered safe as the aggregate margin of safety was less than 100. However, the individual margin of safety for respective products were in the range of 300-22,022. The Scientific Committee on Consumer Safety also pointed out that the actual aggregate exposure would be higher than estimated, as exposure from non-cosmetic products had not been considered. By contrast, the risk assessment by Research Institute for Fragrance Materials indicated an acceptable health risk (margin of safety>100) for the use of butylphenyl methylpropional in hydroalcoholics (e.g. eau de toilette, perfume, aftershave, cologne) following dermal, inhalation or oral exposure.

These risk assessments were made using different estimation methods. The Scientific Committee on Consumer Safety performed a Tier I deterministic exposure estimation based on conservative or worst-case assumptions (point estimates). Exposures from different cosmetic products were considered by the Scientific Committee on Consumer Safety which is standard practice when performing a risk assessment. By contrast, the Research Institute for Fragrance Materials performed a Tier II deterministic exposure estimation using the Crème Research Institute for Fragrance Materials Aggregate Exposure Model and only considered hydroalcoholics in the assessment, excluding products such as hand creams, face creams, lotions, hair cosmetics, cleansing products and makeup products.

The Scientific Committee on Consumer Safety found that hydroalcoholics were the biggest contributor to the overall aggregate exposure to butylphenyl methylpropional across all cosmetic products. Both Research Institute for Fragrance Materials and Scientific Committee on Consumer Safety used a concentration of 1.42% for estimating consumer exposure to butylphenyl methylpropional in hydroalcoholics, but Research Institute for Fragrance Materials

also assumed 100% absorption after inhalation and oral exposure. Consequently, it was expected that the estimated exposure would be higher following Research Institute for Fragrance Materials approach. However, the exposure dose determined by the Scientific Committee on Consumer Safety was twice that estimated by the Research Institute for Fragrance Materials. It is not possible to ascertain the reasons for this difference in the estimated exposure as no information is available on the amount or frequency of product disclosed in the Research Institute for Fragrance Materials assessment.

There have been arguments that the findings of the Scientific Committee on Consumer Safety may have led to the ban on the use of butylphenyl methylpropional in cosmetic products in the EU. However, it should be emphasised that the classification of butylphenyl methylpropional as Repr. 1B would have seen it banned from use in cosmetic products in the EU regardless of the outcome the risk assessment. In contrast, the recent ban on butylphenyl methylpropional in New Zealand was based in the findings of the Scientific Committee on Consumer Safety risk assessment.

1. INTRODUCTION

The purpose of this report is to summarise generic health risk assessment data for exposure to butylphenyl methylpropional through the use of cosmetic products. This report will only consider domestic, non-occupational, incidental exposure to butylphenyl methylpropional from the use of cosmetic products.

1.1 CONSUMER PRODUCT DESCRIPTION – COSMETIC PRODUCTS

The definition of cosmetic products differs slightly around the world.

The United States Food and Drug Administration (US FDA) defines a cosmetic product as:

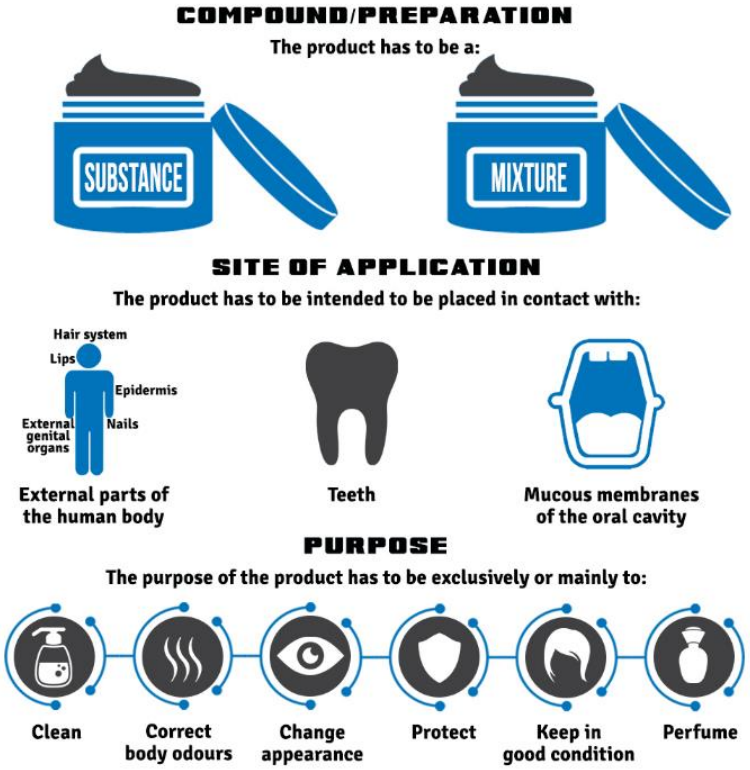
> *A product (excluding pure soap) intended to be applied to the human body for cleansing, beautifying, promoting attractiveness, or altering the appearance.*
> (USFDA, 2021)

The definition of a cosmetic product is same in the European Union (EU) and New Zealand:

> *A cosmetic product means any product or preparation intended to be placed in contact with the various external parts of the human body (epidermis, hair system, nails, lips and external genital organs) or with the teeth and the mucous membranes of the oral cavity with a view exclusively or mainly to cleaning them, perfuming them, changing their appearance and/or correcting body odours and/or protecting them or keeping them in good condition.*
> (EC, 2009; NZEPA, 2020)

The scope of cosmetic products in the EU and New Zealand is shown in Figure 1.

Figure 1. Scope of cosmetic products in the European Union and New Zealand (source: https://ceway.eu/)



Cosmetic products range from everyday hygiene products, such as soap, shampoo, deodorant and toothpaste, to luxury beauty items, including perfumes and makeup. In general, they are categorised as:

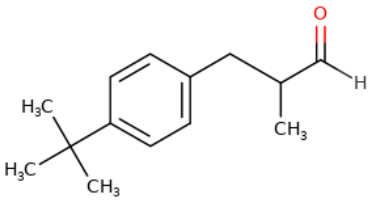
- **Rinse-off:** the cosmetic product is intended to be removed after application on the skin, hair or mucous membranes (e.g. soap, shampoo) (EC, 2009; NZEPA, 2020).
- **Leave-on:** the cosmetic product is intended to stay in prolonged contact with the skin, hair or mucous membranes (e.g. perfumes, deodorants, lotions, creams) (EC, 2009; NZEPA, 2020).

Cosmetic products often contain fragrances like butylphenyl methylpropional to mask unpleasant odours from other chemicals used in their preparation. Studies have suggested that fragrances are the most common allergens in these products, causing allergic contact dermatitis, irritant contact dermatitis, photosensitivity dermatitis, urticaria and asthma in sensitive users (USFDA, 2024a; Uter, 2017).

1.2 PHYSICO-CHEMICAL PROPERTIES OF BUTYLPHENYL METHYLPROPIONAL

Butylphenyl methylpropional is a colourless to pale yellow liquid with a unique odour (mildly floral, reminiscent of cyclamen and lily of the valley). Some of its physical and chemical properties are presented in Table 1.

Table 1. Chemical identification and physico-chemical properties of butylphenyl methylpropional (SCCS, 2019)

Property	**Value**
INCI name	Butylphenyl methylpropional
IUPAC name	3-(4-tert-Butylphenyl)-2-methylpropanal
Other names	Lilial, lysmeral
CAS RN	80-54-6
Chemical structure	
Chemical formula	$C_{14}H_{20}O$
Molecular weight	204.31 g/mol
Partition coefficient (log Pow)	4.2 at 24°C
Water solubility	33 mg/L at 20°C

INCI: International Nomenclature of Cosmetic Ingredients, IUPAC: International Union of Pure and Applied Chemistry, CAS RN: Chemical Abstract Service Registry Number, Pow: octanol-water partition coefficient

1.3 BUTYLPHENYL METHYLPROPIONAL IN COSMETIC PRODUCTS

Butylphenyl methylpropional (or lilial as it is commonly known) is an aromatic molecule that is widely used as a fragrance ingredient in many cosmetic products, including perfumes, deodorants, antiperspirants and hair products. Butylphenyl methylpropional is also used in many non-cosmetic products, such as household cleaners and detergents. It is added to cosmetic formulations and non-cosmetic products as a masking agent to reduce and/or inhibit the base product odour while giving a floral scent with a lily-of-the-valley note (SCCS, 2019). Since it is a fragrance ingredient, the concentrations of butylphenyl methylpropional in the final products are low and often restricted by regulatory authorities (Charles and Darbre, 2009), with typical values of 1.9% in perfumes, 0.6% in aftershave lotions and up to 0.12% in cosmetic products (SCCS, 2019).

1.4 BUTYLPHENYL METHYLPROPIONAL IN COSMETIC PRODUCTS

1.4.1 New Zealand

In New Zealand, cosmetic products are regulated by the NZ EPA through the Cosmetic Products Group Standard 2020 under the Hazardous Substances and New Organisms Act 1996 (NZEPA, 2020).

The updated Cosmetic Products Group Standard 2020 released in January 2024 listed 2-(4-tert-Butylbenzyl)propionaldehyde or butylphenyl methylpropional (entry 1666) as a component that cosmetic products must not contain under Schedule 4 (NZEPA, 2024) on the basis that aggregate exposure to it in multiple products could be above the safe threshold, which is in line with a precautionary approach for regulating the substance.

The Institute of Environmental Science and Research Limited (ESR) notes that there is no human health hazard classification proposed by the NZ EPA.

1.4.2 European Union

The European Chemicals Agency (ECHA) Risk Assessment Committee (RAC) evaluated a classification proposal on butylphenyl methylpropional for it to be considered as toxic to reproduction (Repr. 2 – Reproductive Toxicity class 2). The RAC concluded that this fragrance ingredient should instead be categorised as Repr. 1B (may damage fertility and is suspected of damaging the unborn child) (RAC, 2019).

Under the European Cosmetic Products Regulation (No. 1223/2009), the use of substances classified as carcinogenic, mutagenic or toxic to reproduction (CMR) under the Classification, Labelling and Packaging Regulation is banned in cosmetic products. According to the harmonised classification and labelling approved by the EU, butylphenyl methylpropional may damage fertility and is suspected of damaging the unborn child (Repr. 1B, H360FD) (ECHA, 2024a). Consequently, the European Commission included butylphenyl methylpropional in Annex II (prohibited substances) of the Cosmetic Products Regulation (EU, 2024), leading to a ban on its use in cosmetic products in the EU from March 2022.

1.4.3 USA

The cosmetic industry is largely unregulated in the USA. The US FDA has only banned or restricted nine cosmetic ingredients (USFDA, 2024b). Butylphenyl methylpropional has been identified as one of the most common fragrance allergens present in cosmetic products (EWG, 2022), but no restrictions or conditions for its use in cosmetic products were found.

1.4.4 Australia

In Australia, cosmetic ingredients are regulated as industrial chemicals under the Industrial Chemicals Act 2019, which is administered by the Australian Industrial Chemicals Introduction

Scheme (AICIS). The use of butylphenyl methylpropional in cosmetic products is not banned in Australia, and no restrictions or conditions for its use in cosmetic products were found.

The AICIS has a Rolling Action Plan for chemicals that they have 'just reviewed', 'are in the process of reviewing' or are 'about to review' (Body+Soul, 2022). Butylphenyl methylpropional was reviewed in 2022 for environmental risks under a group assessment for chemical category phenyl propionaldehydes. The health risks were evaluated in 2016 by National Industrial Chemicals Notification and Assessment Scheme (NICNAS) using the Inventory Multi-tiered Assessment and Prioritisation (IMAP) framework (NICNAS, 2016).

1.5 COSMETIC PRODUCT RECALLS DUE TO THE PRESENCE OF BUTYLPHENYL METHYLPROPIONAL

1.5.1 Number and types of products recalled

As discussed in section 1.4 above, the use of butylphenyl methylpropional in cosmetic products is banned in the EU due to its Repro. 1B classification. Hence, all the product recalls and alerts for products containing butylphenyl methylpropional are from the EU.

The European Commission Safety Gate is used by EU market surveillance authorities to notify Member States about unsafe and noncompliant products, including those that present a risk to the health and safety of consumers. The online system serves as a single rapid alert system for dangerous consumer products. All non-food products that are intended for consumers or likely to be used by consumers under reasonably foreseeable conditions are included within the scope of this online system, with the exception of pharmaceutical and medical products.

The Safety Gate alert system contained 377 alerts or recalls for various cosmetic products due to the presence of butylphenyl methylpropional between January 2020 and March 2024. A wide range of cosmetic products were recalled but, overall, perfumes and deodorants (≈ 52%) had the highest frequency of recalls, which would be expected as these products are mainly used for their fragrance properties. Examples of the types of products that have been recalled are shown in Figure 2.

Most of the recalls of cosmetic products due to the presence of butylphenyl methylpropional prior to 2020 were due to a failure to disclose this ingredient as an allergen on the label. However, an increase in recalls was observed from 2020, when butylphenyl methylpropional was banned for use in cosmetic products in the EU. This may have been due to manufacturers still having products containing butylphenyl methylpropional in the market and some small companies not being aware of the ban. It is expected that the number of recalls will decrease significantly in the future.

Figure 2. Examples of cosmetic product recalls in the EU due to the presence of butylphenyl methylpropional from the EU (January 2020 – March 2024)

Breeze deodorant 	Body Basics dead sea minerals shampoo 
Men Only shower gel 	Tesori d'Oriente shower cream – white musk 
Viva Luck perfume 	Amalfi hair styling foam 
Face Facts hand cream 	Neutro Roberts fresco zero sali deodorant spray 
Denim 1976 aftershave 	Proraso aftershave balm 

Olaz regenerist night cream 	L'Oréal Paris skin tonic 
Comin parfum Amore e Psiche perfume stick 	Venus tonic lotion 
Noxzema shaving foam 	Nivea eye makeup remover 
L'Oreal Paris Elvive hair conditioner 	Intesa aftershave cream 
L'Oreal Paris Elvive hair mask 	Protex liquid hand wash 

1.5.2 Concentrations of butylphenyl methylpropional in cosmetic products

Butylphenyl methylpropional was one of 24 fragrances that must be declared in the ingredient list on a cosmetic product's label if present at concentrations above 0.001% in leave-on products or 0.01% in rinse-off products. This was to ensure that sensitive, i.e. allergic, consumers are informed of the presence of allergens in a cosmetic product.

None of the individual cosmetic product recalls (from year 2020) reported the concentration of butylphenyl methylpropional in the product. There are few studies which quantify different fragrances in cosmetic products, butylphenyl methylpropional being one of them. A summary of their findings is presented in Table 2.

The data from these limited studies suggest that butylphenyl methylpropional was found in higher concentrations in perfumes than other products. The highest mean concentration in perfume was up to 4026 mg/kg and the maximum concentration was 34,945 mg/kg. Therefore, the high concentrations could be the reason for perfume recalls in the EU before the ban to use butylphenyl methylpropional in the EU.

2. HAZARD IDENTIFICATION

2.1 PREVIOUS ASSESSMENTS

No previous health impact assessments for butylphenyl methylpropional in cosmetic products were found for New Zealand. However, two overseas risk assessments performed by the Research Institute for Fragrance Materials (RIFM) and the Scientific Committee on Consumer Safety (SCCS) are summarised in sections 4 and 5.

2.2 HEALTH EFFECTS – INCIDENT SURVEILLANCE AND CASE REPORTS

No incident surveillance or case reports on the health effects of butylphenyl methylpropional in cosmetic products were found via a literature search using various search engines such as Google, Google Scholar, Science Direct, PubMed and Web of Science.

TOXICITY

The toxicity of butylphenyl methylpropional is well established in animals. The toxicity data have been reviewed and summarised by various authorities, including ECHA, RIFM and SCCS. Hence, the toxicity endpoints are only briefly summarised below.

2.2.1 Absorption

There is clear evidence that butylphenyl methylpropional is systemically absorbed after acute and repeated oral and dermal administration. It is considered to have a high bioavailability via the oral route based on its physico-chemical properties (water solubility = 33 mg/L at 20°C, partition coefficient log Pow = 4.2 at 24°C; (RIFM, 2020). However, the dermal absorption is limited in humans compared with rats.

In a Good Laboratory Practice (GLP) compliant study in *in vitro* human skin, the dermal absorption of butylphenyl methylpropional in water-in-oil (0.1%) and oil-in-water (0.1%) formulations was calculated to be 10.5% and 8.9%, respectively. However, since recovery levels were not in the acceptable range (85–115%), these estimates also included the non-absorbable fraction of butylphenyl methylpropional, i.e. the amount remaining on living epidermis. Similarly, the dermal absorption levels of ethanol-in-water (1.9%) and silicone-in-water (0.1%) formulations were calculated to be 13.5% and 8.5%, respectively. These absorption values were used by the SCCS and RIFM in their exposure assessments of cosmetic products (RIFM, 2020; SCCS, 2019).

2.2.2 Metabolism

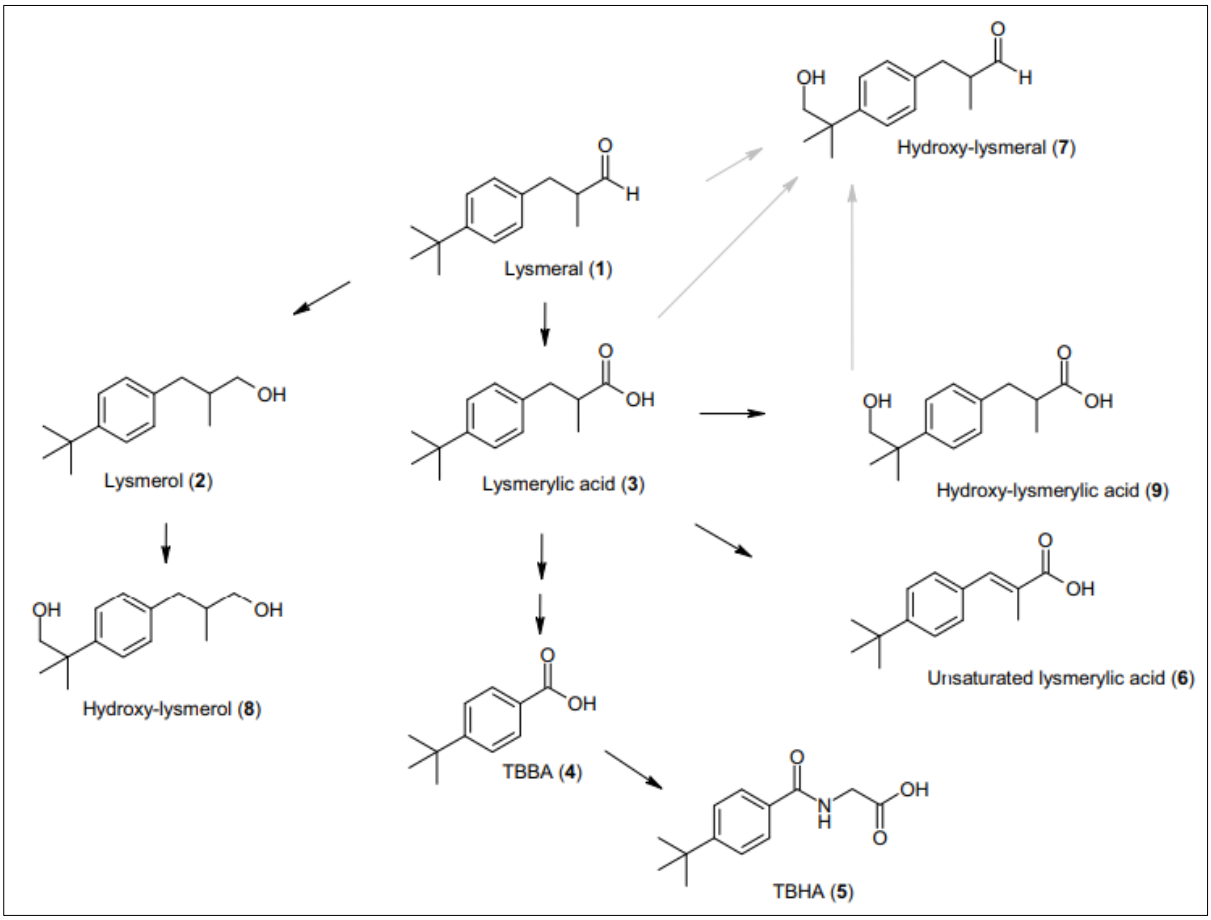
Metabolism: There were no *in-vivo* studies available that studied the metabolism of butylphenyl methylpropional. However, metabolism has been explored *in vitro* in liver microsomes and hepatocytes of rats, mice and humans (ECHA, 2024a; Scherer *et al.*, 2017).

The metabolism of butylphenyl methylpropional involves formation of lysmerylic acid through oxidation or reduction forms its corresponding alcohol lysmerol which further oxidises at the tert-butyl group to form a hydroxy-metabolite (see Figure 3). Decarboxylation of lysmerylic acid, followed by oxidation to the propanoic acid derivative and beta oxidation leads to the formation of the identified metabolite p-tert-butyl benzoic acid (TBBA). The metabolites then form conjugates with glycine and glucuronic acid and are excreted from the body.

The metabolite TBBA have shown "clear evidence of adverse testicular and spermatotoxic effects, which are 'identical in quality' to the effects induced by butylphenyl methylpropional. Consequently, TBBA is classified as Repr. Cat. 1B (may damage fertility) under the CLP Regulation in the EU.

The formation of TBBA *in vitro* in human hepatocytes has been reported to be low compared with rat hepatocytes and similar to the levels found in rabbit hepatocytes – a species that is considered less sensitive in terms of testicular toxicity (NICNAS, 2016). Therefore, the conversion of butylphenyl methylpropional into TBBA may give rise to the species specificity of this effect.

Figure 3. Metabolism of butylphenyl methylpropional (lysmeral) (source: Scherer *et al.*, 2017)



2.2.3 Acute toxicity

Butylphenyl methylpropional is of low acute toxicity by oral and dermal routes of exposure. The acute oral median lethal dose (LD_{50}) value in rats is 1390 mg/kg body weight (bw) and the acute dermal LD_{50} value in rabbits is >2000 mg/kg bw (SCCS, 2019).

2.2.4 Skin sensitisation

Butylphenyl methylpropional is a moderate skin sensitiser based on positive results in several local lymph node assays (SCCS, 2019). The effective concentration values ranged from 2.97% (in ethanol) to 13.90% (in 25% ethanol/ 70% diethyl phthalate) and up to 18.7% in acetone/olive oil (4:1). However, no dermal reactions were observed in a number of guinea pig maximisation tests performed according to OECD test guidelines (ECHA, 2024b).

There is some clinical evidence that butylphenyl methylpropional induces sensitisation in humans. However, the results of human patch tests were ambiguous, with a very low frequency of positive findings (ECHA, 2024b).

2.2.5 Subchronic toxicity

The toxicity of butylphenyl methylpropional after repeated-dose exposure has been investigated in several species (RAC, 2019; SCCS, 2019). Rats appear to be more sensitive species to this chemical than mice and dogs, with both the liver and the male reproductive system being identified as the target organs. In rats, testicular toxicity and spermatotoxic effects were observed at the highest dose (50 mg/kg bw/day). The no observed adverse effect level (NOAEL) for fertility effects was 25 mg/kg bw/day. General toxicity effects like decreased plasma cholinesterase activity levels, effects on the adrenal glands in females and decreased cholesterol levels were observed at 25 mg/kg bw/day. The NOAEL for general toxicity in the rats was 5 mg/kg bw/day.

2.2.6 Genotoxicity

The genotoxic effects of butylphenyl methylpropional have been studied extensively in a wide range of validated and scientifically robust *in vitro* and *in vivo* studies (ECHA, 2024b; SCCS, 2019). Overall, butylphenyl methylpropional is unlikely to be genotoxic. There were some isolated equivocal findings in *in vitro* assays which were not considered relevant due to the lack of reproducibility and insufficiencies in terms of procedure and reporting. There was also no evidence of genotoxic potential of butylphenyl methylpropional in a micronucleus assay following intraperitoneal (i.p.) application in mice.

2.2.7 Carcinogenicity

No studies were available to assess the carcinogenicity of butylphenyl methylpropional (ECHA, 2024b). However, it is unlikely that butylphenyl methylpropional has carcinogenic potential as no pre-neoplastic lesions were reported in short-term toxicity studies and the compound was found to be non-genotoxic in an *in vivo* micronucleus assay.

2.2.8 Reproductive and developmental toxicity

A number of repeat-dose toxicity studies (5 days, 90 days) and reproductive toxicity studies have consistently observed adverse effects of butylphenyl methylpropional on the male reproductive system. In all studies available, testicular toxicity in rats was accompanied by signs of systemic toxicity. Testicular toxicity was also observed in dogs after treatment periods of 2 weeks and 3 months. However, no effects on fertility were seen up to oral doses of 100 mg/kg bw/d in rhesus monkeys, mice and guinea pigs, and 300 mg/kg bw/d in rabbits (RAC, 2019).

In the two one-generation range-finding studies, male fertility was markedly affected in rats at doses starting from 25 mg/kg bw/day (RAC, 2019). Effects on testes included reduced organ weights and degeneration. Spermatotoxic effects included reduced sperm counts and increased numbers of abnormal sperms resulting in markedly reduced fertility indices. At this dose, hepatotoxicity represented by increased organ weights and changes in clinical chemistry was also reported. The lowest NOAEL reported for male fertility was 9.1 (pre-mating) and 7.4 (post-mating) mg/kg bw/day.

In a pre-developmental toxicity study (following OECD Test Guideline 414), Wistar rats were orally administered butylphenyl methylpropional at nominal doses of 0, 5, 15 or 45 mg/kg bw/day (equivalent to measured dose levels of 0, 4.1, 12.7 and 40.7 mg/kg bw/day, respectively), from day 6 to 20 post-coitum (p.c.) (RIFM, 2020; SCCS, 2019). Mean post-implantation losses (early resorptions) were significantly higher in the 45 mg/kg bw/day group (15.1% compared with 4.4% in the control group). At this dose, there was a decrease in the mean number of foetuses and live foetuses per dam (7.4 compared with 8.1 in the control group. This was slightly below the historical controls for mean number of foetuses per dam.

Skeletal variations (delayed ossification and supernumerary ribs), post-implantation loss and decreased foetal weights were also observed in the mid- and high-dose groups. Mean foetal weights were statistically significantly reduced in the mid and high dose groups, but at the mid dose the reduction was only slight (8% below controls).

Signs of maternal toxicity signs were clearly observed in the mid and high dose group, including significant decreases in maternal weight gain (56 % below controls), and increased levels of alanine aminotransferase (20–30% above the control group), decreased levels of serum cholinesterase (20–45% below the control group) and increased absolute and relative liver weight (10% and 10–20% above controls, respectively). At the highest dose, transient salivation, a slight but significant reduction in food consumption, a significant decrease in mean body weight gain (32% below the control group), an increased level of glutamate dehydrogenase (79% above the control group) and a reduced mean uterus weight (20% below the control group) were also observed. A correlation was established between the observed skeletal variations, the significantly decreased foetal body weights and the maternal adverse effects.

A NOAEL of 4.1 mg/kg bw/day was established for maternal toxicity (increased relative liver weights and increased levels of alanine aminotransferase) and prenatal developmental toxicity (decreased foetal weights).

In an extended one-generation reproduction toxicity study, butylphenyl methylpropional was administered to young Wistar rats in encapsulated form at 1, 3 or 10 mg/kg bw/day (SCCS, 2019). The NOAEL for general systemic toxicity was established to be 3 mg/kg bw/day for the F0 and F1 parental rats as well as adolescent animals, based on evidence of distinct liver toxicity. This value was further supported by corresponding effects on food consumption, body weights and clinical pathological parameters, which were observed at 10 mg/kg bw/day predominantly in females. The NOAEL for fertility and reproductive toxicity was 10 mg/kg bw/day, while the NOAEL for developmental toxicity in the F1 and F2 progeny was 3 mg/kg bw/day (which was equivalent to a mean overall oral dose of 4.5 mg/kg bw/day) based on the observation of reduced pup body weights in the F1 and F2 offspring, observed at 10 mg/kg bw/day.

Hence, based on the testicular toxicity observed in male rats and its effects on post-implantation loss and pup body weights, butylphenyl methylpropional is classified as Repr. 1B, H360Fd (may damage fertility and is suspected of damaging the unborn child) by the ECHA (RAC, 2019).

3. DOSE-RESPONSE RELATIONSHIP

In this section, concerns associated with exposure to butylphenyl methylpropional in cosmetic products are considered in relation to chronic exposure.

The SCCS identified the most conservative NAOEL for the general toxicity of butylphenyl methylpropional and applied this for risk characterisation. RIFM derived three reference doses based on toxicological endpoints (developmental toxicity, testicular and sperm toxicity, and general reproductive toxicity), but used the same NAOEL identified by the SCCS for risk characterisation. The reference doses arising from these assessments are presented in Table 3.

Table 3. Reference doses for butylphenyl methylpropional

Study	**Key effects**	**POD (mg/kg bw/day)**	**UF**	**Reference dose* (mg/kg bw/day)**	**References**
Prenatal developmental toxicity study – rats	Reduced foetal body weight and increased incidences of skeletal variation of the foetuses	NOAEL: 4.1	100	0.041	(RIFM, 2020)
Extended one-generation reproduction toxicity study – rats	Testicular and sperm toxicity	NOAEL: 15.1** (highest dose tested)	100	0.15	(RIFM, 2020)
Extended one-generation reproduction toxicity study – rats	General toxicity in F0 and F1 parental rats as well as adolescent animals: liver toxicity and corresponding effects on food consumption, body weights, and clinical-pathological parameters (predominantly in females)	NOAEL: 4.5	100	0.045	(RIFM, 2020; SCCS, 2019)

POD: point of departure, UF: uncertainty factor, NOAEL: no observed adverse effect level, bw: body weight

* Reference doses were reported by RIFM only.

** Reproductive toxicity effects of butylphenyl methylpropional were observed at doses above 25 mg/kg bw/day in a 90-day study.

4. EXPOSURE ASSESSMENT

As previously discussed, butylphenyl methylpropional is intentionally added to cosmetic products as a fragrance component. The risk assessments carried out by the SCCS and RIFM were reviewed, summarised and critiqued. These assessments used the maximum allowed concentrations of butylphenyl methylpropional when estimating exposure to this chemical, meaning that a quantitative risk assessment was not required. However, it should be noted that some studies have detected maximum concentrations of up to 3.5% butylphenyl methylpropional, especially in perfumes (Soo Lim *et al.*, 2018).

4.1 SCIENTIFIC COMMITTEE ON CONSUMER SAFETY (SCCS)

The SCCS performed a risk assessment based on dermal exposure to butylphenyl methylpropional for different cosmetic product categories (hydroalcoholics, deodorants, makeup products, face creams, hand creams, lotions, etc.) and estimated an aggregate exposure dose (SCCS, 2019). The assessment was done following the SCCS notes of guidance for the testing of cosmetic ingredients and their safety evaluation (SCCS, 2021). The proposed maximum concentrations were selected from the dossier submitted by BASF/IFRA (see Table 4.).

Risk assessments of cosmetic products usually follow a tiered approach, whereby the initial (Tier I) exposure estimates are derived using highly conservative assumptions. If such estimates indicate no cause for concern, then more refined approaches (Tier II) are unnecessary (SCCS, 2021).

The Tier I assessment is generally used to screen consumer exposure based on the summation of high percentile product use levels and maximum concentrations of the substance of interest in the products, to give a worst-case exposure scenario. Therefore, the SCCS considered the first-tier deterministic aggregate exposure arising from the combined use of different product types.

The systemic dose due to dermal absorption was calculated using the following equation (SCCS, 2021):

$$\mathrm{SED} = E\mathrm{product} \times \frac{C}{100} \times \frac{\mathrm{DAp}}{100}$$

where SED (mg/kg bw/day) is the systemic exposure dose, $E_{product}$ (mg/kg bw/day) is the relative daily use amount of a cosmetic product per kg body weight based on the amount applied and the frequency of application, C (%) is the concentration of the substance under study in the finished cosmetic product at the application site, and DAp (%) is the dermal absorption expressed as a percentage of the test dose assumed to be applied in real-life conditions.

The following parameters were used to calculate the SED for deodorants:

$E_{product}$ = 22.08 mg/kg bw/day (SCCS, 2021)

C = 0.09% (SCCS, 2019)

DAp = 13.5% for hydroalcoholics (SCCS, 2019)

This gave:

SED = 22.08 x 0.09% x 13.5% = 0.0027 mg/kg bw/day or **2.7 µg/kg bw/day**

The SED was also calculated for other cosmetic product types, as shown in Table 4.. Since this was a Tier I assessment, an aggregate exposure was then calculated by adding the individual SED values across all products.

Table 4. Concentration of butylphenyl methylpropional in different cosmetic products and the estimated systemic exposure doses

Product type	Finished product concentration (%)	Relative daily exposure (µg/kg bw/day)	Fraction absorbed	SED (µg/kg bw/day)
Hydroalcoholic-based fragrances (e.g. eau de toilette, perfume, aftershave, cologne)	1.42	7170	0.135	13.745
Deodorants	0.09	22,080	0.135	2.700
Makeup products	0.04			
eye make-up		330	0.089	0.012
make-up remover		8330	0.089	0.297
liquid foundation		7900	0.089	0.281
mascara		420	0.089	0.015
eyeliner		80	0.089	0.003
Face creams	0.05	24,140	0.105	1.267
Hand creams	0.05	32,700	0.105	1.717
Body lotions	0.06	123,200	0.089	6.579
Hair styling products	0.04	5740	0.089	0.204
Bath products	0.1			
soap		3330	0.089	0.296
shower gel		2790	0.089	0.248
rinse-off conditioner		670	0.089	0.060
shampoo		1510	0.089	0.134
			Aggregate SED	**27.558**

SED: systemic exposure dose

4.2 RESEARCH INSTITUTE FOR FRAGRANCE MATERIALS (RIFM)

RIFM performed a risk assessment on butylphenyl methylpropional used in hydroalcoholics (eau de toilette, perfume, aftershave, cologne) at a maximum concentration of 1.4% (RIFM, 2020). This concentration was selected from the data submitted to RIFM by fragrance houses and manufacturers of cosmetic and personal care products (Safford *et al.*, 2017). The aggregate exposure from dermal, inhalation and oral routes was estimated using the Creme RIFM Aggregate Exposure Model, which uses probabilistic (Monte Carlo; Tier II) simulations to allow the full distributions of datasets to be considered, providing a more realistic estimate of aggregate exposure to individuals across a population.

The findings of this risk assessment are provided in Table 5.

Table 5. Concentration of butylphenyl methylpropional in hydroalcoholics and the systemic exposure dose

Product type	P95 concentration (%)	Fraction absorbed	P95 SED (µg/kg bw/day)
Hydroalcoholic-based fragrances	1.42	Dermal: 0.135 Oral: 1 Inhalation: 1	6.5

P95: 95th percentile, SED: systemic exposure dose

4.3 EXPOSURE SUMMARY

The SCCS performed Tier I deterministic exposure estimation based on conservative or worst-case assumptions (point estimates) (SCCS, 2019) and considered dermal exposure to butylphenyl methylpropional in different cosmetic products, which is the usual practice for performing a risk assessment.

By contrast, RIFM used Tier II deterministic exposure estimation for hydroalcoholics only using the Creme RIFM Aggregate Exposure Model (RIFM, 2020; Safford *et al.*, 2017). RIFM also considered 100% oral and inhalation absorption for estimating the exposure to butylphenyl methylpropional. Whereas the SCCS did not considered oral and inhalation exposure in their assessment. It should be noted that products such as hand creams, face creams, lotions, hair cosmetics, cleansing products and makeup products were excluded from the RIFM assessment.

Both the SCCS and RIFM used a concentration of 1.42% to estimate consumer exposure to butylphenyl methylpropional in hydroalcoholics, The SCCS found that hydroalcoholics were the biggest contributor to the overall aggregate exposure to butylphenyl methylpropional across all cosmetic products.

Since, RIFM considered dermal, oral and inhalation exposures to butylphenyl methylpropional, it was expected that the estimated exposure would be higher with the RIFM approach. However, the exposure dose determined by the SCCS was twice that estimated by RIFM. The reason for this large difference in the estimated exposure is unclear as no information is available on the amount or frequency of product used in the RIFM assessment.

It should also be noted that non-cosmetic products such as washing/cleaning products were not included in either of the risk assessments due to a lack of availability of specific exposure data, so the actual total exposure of the consumer to butylphenyl methylpropional will be higher than indicated by these studies.

5. RISK CHARACTERISATION

Use rates for cosmetic products are not available for the New Zealand population, so it is not possible to undertake a New Zealand-specific risk assessment for butylphenyl methylpropional in cosmetic products. However, the risk assessments undertaken by the SCCS and RIFM are considered relevant to New Zealand, as cosmetic products imported here are expected to contain similar concentrations of butylphenyl methylpropional to those that were assessed. Therefore, risk characterisations from these assessments are summarised below.

5.1 SCIENTIFIC COMMITTEE ON CONSUMER SAFETY (SCCS)

A margin of safety (MoS) approach was used by SCCS to assess the expected level of risk associated with butylphenyl methylpropional in cosmetic products (Table 6). MoS is the ratio between a systemic POD (POD_{sys}; usually the NOAEL or benchmark dose [BMD] values from oral studies) and an estimate of the exposure (SCCS, 2021). A NOAEL value of 4.5 mg/kg bw/day, which is equivalent to 4500 µg/kg bw/day, was used for the POD_{sys}. This was then converted from an oral dose to a systemic dose by assuming 50% gastrointestinal absorption to calculate the MoS using the following equation:

$$\mathrm{MoS} = \frac{\mathrm{POD_{sys}}}{\mathrm{SED}}$$

For a chemical substance with health thresholds (i.e. not genotoxic and not carcinogenic), an MoS ≥ 100 is generally considered to be protective.

Table 6. Individual and aggregate margins of safety for exposure to butylphenyl methylpropional in cosmetic products

Product type	SED (µg/kg bw/day)	NOAEL (µg/kg bw/day)	Individual MoS
Hydroalcoholic-based fragrances (e.g. eau de toilette, perfume, aftershave, cologne)	13.745	4500 × 50%* = 2250	328
Deodorants	2.700		1677
Makeup products			7409
eye make-up	0.012		
make-up remover	0.297		
liquid foundation	0.281		
mascara	0.015		
eyeliner	0.003		
Face creams	1.267		3551
Hand creams	1.717		2621
Body lotions	6.579		684
Hair styling products	0.204		22,022

Bath products soap shower gel rinse-off conditioner shampoo	 0.296 0.248 0.060 0.134		6092
Aggregate SED & MoS	**27.558**		**80**

SED: systemic exposure dose, bw: body weight, NOAEL: no observed adverse effect level, MoS: margin of safety

* Correction for 50% oral bioavailability.

Based on these findings, the SCCS concluded that butylphenyl methylpropional at the proposed concentrations cannot be considered safe as the aggregate MoS was less than 100. However, the individual MoS values for respective products were in the range of 300–22,022. The SCCS also pointed out that the actual aggregate exposure would be higher as exposure from non-cosmetic products was not considered.

5.2 RESEARCH INSTITUTE FOR FRAGRANCE MATERIALS (RIFM)

RIFM undertook endpoint-specific risk characterisations for repeated dose toxicity, developmental and reproductive toxicity and calculated margin of exposure (MoE) (RIFM, 2020). The MoEs for these endpoints are provided in Table 7.. The MoE is essentially same as the MoS approach used by the SCCS.

Table 7. Margin of exposure for butylphenyl methylpropional in hydroalcoholics

Product type	P95 SED (µg/kg bw/day)	NOAEL (µg/kg bw/day)	MoE
Hydroalcoholic-based fragrances	6.5	Repeated dose toxicity: 4500 Developmental toxicity: 4100 Reproductive toxicity: 15,100	Repeated dose toxicity: 692 Developmental toxicity: 631 Reproductive toxicity: 2323

P95: 95th percentile, SED: systemic exposure dose, NOAEL: no observed adverse effect level, bw: body weight, MoE: margin of exposure

For all three risk characterisations, the MoE was greater than 100 for hydroalcoholics, indicating acceptable health risks to consumers. It should also be noted that the calculated MoE value was twice that of the SCCS assessment because RIFM did not refine the NOAEL for oral absorption (50%).

5.3 RISK CHARACTERISATION SUMMARY

The risk assessments by The European SCCS and the RIFM were reviewed, summarised and critiqued. The SCCS concluded that butylphenyl methylpropional at the proposed concentrations in different cosmetic products cannot be considered safe as the aggregate MoS was less than 100. However, the individual MoS for respective products were in the range of 300-22,022. The SCCS also pointed out that the actual aggregated exposure would be higher as they have not considered exposure from non-cosmetic products. On the other hand, the risk assessment by RIFM indicated an acceptable health risk (MoE>100) for hydroalcoholics (e.g. Eau de Toilette, perfume, aftershave, cologne) following dermal, inhalation and oral exposure.

6. CONCLUSIONS

Cosmetic products range from everyday hygiene products, such as soap, shampoo, deodorant and toothpaste, to luxury beauty items, including perfumes and makeup. Most cosmetic products are used by adults, but some products such as sunscreen and shampoo are also used by children.

Butylphenyl methylpropional (commonly known as lilial) is an aromatic aldehyde that is widely used as a fragrance ingredient in many cosmetic products to mask or reduce and/or inhibit the base product odour while giving a floral scent with a lily-of-the-valley note.

Butylphenyl methylpropional was recently banned for use in cosmetic products in the EU due to its classification as Repr. 1B (may damage fertility and is suspected of damaging the unborn child). Similarly, in New Zealand, where cosmetic products are regulated by the NZ EPA, butylphenyl methylpropional is now listed in Schedule 4 of the updated Cosmetic Products Group Standard, meaning that cosmetic products must not contain it except subject to the restrictions and conditions laid down. However, the use of butylphenyl methylpropional in cosmetic products is not banned in the USA or Australia.

The risk assessments undertaken by the SCCS and RIFM were reviewed, summarised and critiqued. The SCCS concluded that butylphenyl methylpropional at the proposed concentrations in cosmetic products could not be considered safe, as the aggregate MoS was less than 100. However, the individual MoS for respective products were in the range of 300-22,022. The SCCS also pointed out that the actual aggregate exposure would be higher than estimated because exposure from non-cosmetic products had not been considered. By contrast, the risk assessment carried out by RIFM indicated that butylphenyl methylpropional in hydroalcoholics (e.g. eau de toilette, perfume, aftershave, cologne) had an acceptable health risk (MoS > 100) following dermal, inhalation and oral exposure.

The SCCS performed Tier I deterministic exposure estimation based on conservative or worst-case assumptions (point estimates) and considered dermal exposure from different cosmetic products, which is a usual practice to perform a risk assessment. By contrast, RIFM used Tier II deterministic exposure estimation of hydroalcoholics only using the Creme RIFM Aggregate Exposure Model. RIFM also considered 100% oral and inhalation absorption for estimating the exposure to butylphenyl methylpropional. Whereas the SCCS did not considered oral and inhalation exposure in their assessment. It should be noted that products such as hand creams, face creams, lotions, hair cosmetics, cleansing products and makeup products were excluded from the RIFM assessment.

Both the SCCS and RIFM used a concentration of 1.42% to estimate consumer exposure to butylphenyl methylpropional in hydroalcoholics, The SCCS found that hydroalcoholics were the biggest contributor to the overall aggregate exposure to butylphenyl methylpropional across all cosmetic products.

Since, RIFM considered dermal, oral and inhalation exposures to butylphenyl methylpropional, it was expected that the estimated exposure would be higher with the RIFM approach. However, the exposure dose determined by the SCCS was twice that estimated by RIFM. The reason for this large difference in the estimated exposure is unclear as no information is available on the amount or frequency of product used in the RIFM assessment.

There have been arguments that the findings of the Scientific Committee on Consumer Safety may have led to the ban on the use of butylphenyl methylpropional in cosmetic products in the EU. However, it should be emphasised that the classification of butylphenyl methylpropional as Repr. 1B would have seen it banned from use in cosmetic products in the EU regardless of the outcome the risk assessment. In contrast, the recent ban on butylphenyl

methylpropional in New Zealand was based in the findings of the Scientific Committee on Consumer Safety risk assessment.

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