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HEALTH RISK ASSESSMENT: BENZENE IN COSMETICS

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ACRONYMS AND ABBREVIATIONS

ADI	Acceptable daily intake
ATSDR	Agency for Toxic Substances and Disease Registry
BMD	Benchmark dose
bw	Body weight
CIR	Cosmetic Ingredient Review
CSF	Cancer slope factor
ECHA	European Chemicals Agency
ESR	Institute of Environmental Science and Research Limited
EU	European Union
FDA	Food and Drug Administration
IARC	International Agency for Research on Cancer
JECFA	Joint FAO/WHO Expert Committee on Food Additives
LCR	Lifetime cancer risk
LD_{50}	Lethal dose (which causes death in 50% animals)
LCR	Lifetime cancer risk
LOAEL	Lowest observed adverse effect level
MoS	Margin of safety
NIFDC	China National Institutes for Food and Drug Control
NOAEL	No observed adverse effect level
NZ EPA	New Zealand's Environmental Protection Authority
POD	Point of departure
RfD	Reference dose
SED	Systemic Exposure Dose

SCCP	Scientific Committee on Consumer Products (European)
TGA	Therapeutic Goods Administration
TWA	Time weighted average
USEPA	United States Environmental Protection Agency
WHO	World Health Organization

EXECUTIVE SUMMARY

The purpose of this report is to develop a generic health risk assessment for incidental exposure to benzene in cosmetics. This report will only consider domestic, non-occupational, routine and incidental exposure to benzene in cosmetics.

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

Benzene is an industrial solvent which is found naturally in crude oils and as a by-product of oil-refining processes. It is colorless and has a sweet, aromatic, gasoline-like odor. Benzene is classified as carcinogenic to humans by the International Agency for Research on Cancer (IARC). Therefore, it is not intentionally added to cosmetic formulations/products. However, sometimes its presence can be technically unavoidable in final products as a residual solvent or impurity (in organic propellants) or as a contaminant.

There are restrictions for the use of benzene in cosmetics overseas and in New Zealand. In the European Union (EU), United States (US), Australia and China, regulatory agencies have defined concentration limits for benzene (residual solvent or impurity) in final products or ingredients. In New Zealand, under the cosmetic group standard, cosmetics must not contain benzene, other than at a trace level, provided that such presence is technically unavoidable in good manufacturing practice. It should be noted that there are no concentration limits defined for this trace level.

In 2021, several types of cosmetic products (deodorants, antiperspirants, sunscreens) in the US and Australia were tested and found to contain benzene. The products were voluntarily recalled from the market by the respective companies. Benzene was detected in deodorants at concentrations up to 17.7 ppm. Similarly, benzene was detected in sunscreen products at concentrations up to 5.2 ppm and 2.4 ppm for products intended for use by adults and children, respectively. No information was found on benzene in products other than deodorants/antiperspirants and sunscreen and hence, the current risk assessment was confined to these products.

Exposure to benzene while using deodorants/antiperspirants and sunscreen is considered incidental. For both the product categories, the dermal route of exposure is considered relevant, while for deodorants/antiperspirants the inhalation route of exposure was also considered relevant. Exposure via the oral route is likely to be negligible.

In this assessment, both non-cancer and cancer human health risks of benzene in cosmetic products (deodorants and sunscreen) through dermal and inhalation pathways were evaluated. Non-carcinogenic human health risk from exposure to benzene in the cosmetic products was evaluated by applying a margin of safety (MoS) approach. The MoS was greater than 100 for children and adults (aggregated risk), which indicates that deodorants (in adults) and sunscreen (in adults and children) are not of toxicological concern for non-cancer risks due to benzene.

Lifetime cancer risk was estimated for adults (sunscreen and deodorant use) and children (sunscreen use only). Risks were estimated based on the dermal and inhalation pathways of exposure. The result indicates that lifetime exposure to benzene from cosmetic use will equate

to an excess cancer risk of $<10^{-5}$, or 1 excess cancer in 100,000 individuals, which has been used in New Zealand for standard setting.

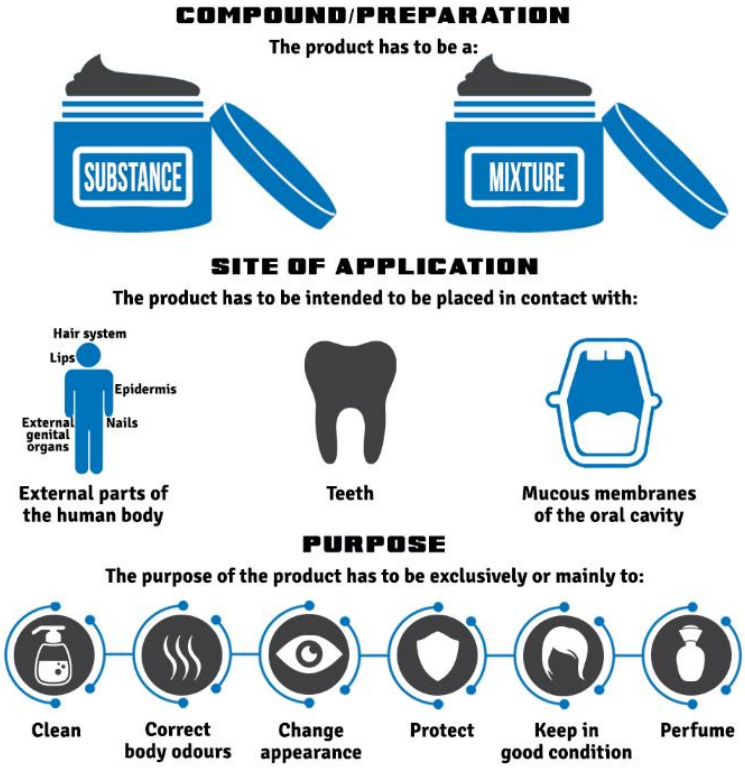
1 INTRODUCTION

The purpose of this report is to develop a generic health risk assessment for benzene (impurity) in cosmetic products. This report will only consider domestic, non-occupational, incidental exposure to benzene in different cosmetic products. Exposure scenarios will be developed for the most common or likely exposure events.

1.1 CONSUMER PRODUCTS DESCRIPTION – COSMETICS

The definitions for cosmetic products differ slightly around the world. However, similar definitions are used in the 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).

In the United States, the Food and Drug Administration (FDA) defines cosmetic products 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 scope of cosmetic products is shown graphically in Figure 1.



Source: https://ceway.eu/

Figure 1. Graphical representation of the range of products considered to be cosmetic

Cosmetics range from everyday hygiene products such as soap, shampoo, deodorant, and toothpaste to luxury beauty items including perfumes and makeup. They can also be categorised as:

Rinse-off: cosmetic product intended to be removed after application on the skin, the hair or the mucous membranes e.g. soap, shampoo etc. (EC, 2009; NZEPA, 2020).

Leave-on: cosmetic product which is intended to stay in prolonged contact with the skin, the hair or the mucous membranes e.g. perfumes, deodorants, lotions, creams etc. (EC, 2009; NZEPA, 2020).

1.2 PHYSICO-CHEMICAL PROPERTIES OF BENZENE

Benzene, also known as benzol, is a colorless compound and has a sweet, aromatic, gasoline-like odor. Benzene is found in crude oils and as a by-product of oil-refining processes. In industry, benzene is used as a solvent, as a chemical intermediate, and is used in the synthesis of numerous chemicals. Benzene is found in high concentrations in cigarette smoke along with other incomplete combustion products (RIVM 2018). Benzene is found to exhibit a unique set of physical and chemical properties (Table 1) (Bayliss *et al.*, 2002).

Table 1. Chemical identification and physico-chemical properties of benzene

Property	**Value**
IUPAC Name	Benzene
Synonyms	Annulene, benzeen (Dutch), benzen (Polish), benzol, benzole; benzolo (Italian), coal naphtha, cyclohexatriene, fenzen (Czech), phene, phenyl hydride, pyrobenzol, pyrobenzole
CAS No	71-43-2
Chemical formula	C_6H_6
Molecular weight	78.11
Boiling point	80.1°C at 760 mm Hg
Density	0.88 g/cm^3
Vapour pressure	75 mm Hg at 20°C
Partition coefficient (log Pow)	2.13 at 25 °C
Solubility	In water: 1750 mg/L at 25°C Miscible with ethanol, ethyl ether, acetone, and chloroform.

1.3 BENZENE IN COSMETICS

Benzene has been classified as carcinogenic to humans (IARC group 1), which may cause potential hazards to human health. Hence, it is not used as an active ingredient or is intentionally added in cosmetic formulations. However, recently its presence in small amounts has been detected in various cosmetics. The presence of benzene in finished products can result from its introduction at one or more stages of a product's lifecycle and may be due to the following reasons:

1) Benzene may be used as a solvent in the production of raw materials such as carbomer (polyacrylic acid) or butylated hydroxyanisole (BHA, an antioxidant). It is possible that there may be some residual benzene remaining in such products (Fiume *et al.*, 2017).

2) Organic propellants (such as propane, butane, etc.) are added to aerosol products. These organic propellants may contain residues of benzene (P&G, 2021).

3) Some cosmetic ingredients can degrade during shipping, storage, or as a result of unusual or unexpected exposure to environmental conditions, which may produce traces of benzene.

4) Cosmetic ingredients may come into contact with benzene during storage and transportation.

1.3.1 Recent surveys for benzene contamination in cosmetics

Valisure (an independent laboratory in the US) analysed 108 unique batches from 30 different brands of antiperspirant and deodorant body spray products for benzene. Significant variability from batch to batch was observed, even within a single brand. Twenty-four lots of body spray products from 8 different brands contained benzene at concentrations in the range 2.24 – 17.7 ppm of benzene; 14 lots from 8 brands contained detectable benzene between 0.20 – 1.89 ppm; and 21 lots from 8 brands contained detectable benzene at < 0.1 ppm. Benzene was not detected in an additional 49 lots of body sprays from 19 different brands through initial analysis of at least one sample. These products contain propellants such as butane, isobutane, propane, and alcohol which were also tested. There was benzene contamination in five major propellants (Valisure, 2021).

Propellant	No. of products	% Products with benzene
Hydrofluorocarbon 152a	95	54%
Butane	77	69%
Isobutane	74	58%
Propane	60	52%
Alcohol	47	36%

In Australia, cosmetic products that make therapeutic claims, including sunscreen, are regulated by the Therapeutic Goods Administration (TGA). The level of benzene must be below 2 ppm in sunscreen products that are regulated as listed medicines in Australia. TGA tested nine aerosol sunscreen products and found three of them to contain levels of benzene above the 2 ppm limit. Benzene was found in the range of 2.3 – 5.2 ppm and was suspected to be a contaminant from raw materials used in product manufacture (TGA, 2022).

1.3.2 Product recalls due to benzene in cosmetics

Recently, there have been product recall of various cosmetic products due to benzene contamination.

1) Aerosol spray products (dry conditioner and dry shampoo) from Pantene and Waterless produced in the United States were voluntarily recalled from New Zealand and Australian markets due to the presence of benzene in some products. Exposure modelling and a cancer risk assessment revealed that daily exposure to benzene in the recalled products at the levels detected would not be expected to cause adverse health consequences (P&G, 2021a).

2) Aerosol antiperspirants from the same company (Proctor and Gamble) sold in the United States were voluntarily recalled due to the presence of benzene detected.

Exposure modelling and the cancer risk assessment revealed that daily exposure to benzene in the recalled products at the levels detected would not be expected to cause adverse health consequences (USFDA, 2021a).

3) In Australia, cosmetic products that make therapeutic claim are regulated by Therapeutic Goods Administration (TGA). Sunscreen is one of the examples. In New Zealand, sunscreens are cosmetic products regulated by the NZEPA. The level of benzene must be below 2 ppm in sunscreen products that are regulated as listed medicines in Australia. The TGA tested nine aerosol sunscreen products and found three of them from the same manufacturer to contain levels of benzene above the 2 ppm limit. Benzene was found in the range of 2.3 – 5.2 ppm and was suspected to be a contaminant from raw materials used in product manufacture. In consultation with the TGA, the company took a precautionary approach and commenced a recall of all batches of these three products from the Australian market (TGA, 2022).

4) Benzene was also found by a manufacturer in sunscreen products specifically for babies, supplied in Australia and New Zealand. The concentration of benzene was around 2.4 ppm which was above the 2ppm limit that TGA had set. The health risk to consumers who may have used these products was considered extremely low. The company made the decision to recall the two lots of the affected product. Benzene may have been unintentionally introduced during the manufacturing process (SunBum, 2022).

5) Neutrogena aerosol sunscreen, manufactured by Johnson and Johnson, was found to have low levels of benzene in some samples. The sunscreen was recalled in the US and Australia as the levels of benzene were above the threshold of 2 ppm. In New Zealand, benzene is banned in cosmetics under the Cosmetic Products Group Standard, except at trace levels that are “technically unavoidable in good manufacturing practice”. While the company has withdrawn the sunscreen in New Zealand, it was not required to issue a public recall (ConsumerNZ, 2021; J&J, 2021).

1.4 REGULATION OF BENZENE IN COSMETICS IN NEW ZEALAND

In New Zealand, sunscreens are cosmetic products regulated by the New Zealand Environmental Protection Authority (NZEPA). Regulation of cosmetic products is covered by the Cosmetic Products Group Standard 2020 under the Hazardous Substances and New Organisms Act 1996. Under the group standard, cosmetics in New Zealand must not contain benzene. The group standard excludes any cosmetic product that contains a component listed in Schedule 4, including benzene, other than at a trace level of that component provided that such presence is technically unavoidable in good manufacturing practice (NZEPA, 2020).

According to the NZEPA, benzene is fatal in contact with skin, harmful if swallowed, causes serious eye irritation (Eye Irrit. 2), causes skin irritation (Skin Irrit. 2), causes damage to organs through prolonged or repeated exposure (STOT RE 1), may damage fertility or the unborn child (Repr. 1), may cause genetic defects (Muta. 1) and may cause cancer (Carc. 1) (CCID, 2022).

ESR notes that the NZEPA may not have updated the hazard classifications for benzene, and these may differ from other regulatory bodies such as the European Chemicals Agency (ECHA) and the US Environmental Protection Agency (USEPA).

1.5 OVERSEAS REGULATION OF BENZENE IN COSMETICS

European Union (EU): According to the European Commission Cosmetics Directive (76/768/EEC), benzene cannot be present as a constituent of other substances, or in mixtures, in concentrations equal to, or greater than 0.1% by weight (CosIng, 2022).

According to the harmonised classification and labelling (CLP00) approved by the EU, benzene may be fatal if swallowed and enters airways (Asp. Tox. 1), may cause genetic defects (Muta. 1B), may cause cancer (Carc. 1A), causes damage to organs through prolonged or repeated exposure (STOT RE 1), is a highly flammable liquid and vapour (Flam. Liq. 2), causes serious eye irritation (Eye Irrit. 2) and causes skin irritation (Skin Irrit. 2) (C&L_Inventory, 2022).

US: The US Food and Drug Administration (FDA) classifies benzene as a Class 1 solvent "that should not be employed in the manufacture of drug substance. However, if their use is unavoidable in order to produce a drug product with a significant therapeutic advance, then their levels should be restricted". For these particular situations, benzene is restricted to 2 ppm, unless otherwise justified (USFDA, 2022). The same regulations are applicable to cosmetic products.

USEPA has classified benzene as a known human carcinogen for all routes of exposure.

Canada: In order for a cosmetic product to be sold in Canada, it must meet the requirements of the Food and Drugs Act and the Cosmetic Regulations (CR). Section 16 of the Food and Drugs Act stipulates that cosmetics manufactured, imported or offered for sale in Canada must be safe for use. Benzene is one of the prohibited ingredients that should not be present in cosmetic products sold on Canada (HealthCanada, 2019).

China: Recently, China's National Institutes for Food and Drug Control (NIFDC) has proposed a limit value for benzene of 2 mg/kg in cosmetics, according to the results of relevant risk assessments (CIRS, 2022).

2 HAZARD IDENTIFICATION

2.1 PREVIOUS ASSESSMENTS

No previous health impact assessments for benzene in cosmetics were found for New Zealand.

The Cosmetic Ingredient Review (CIR) Expert Panel conducted a safety assessment on cross-linked alkyl acrylates used in cosmetics. These acrylates are used in cosmetics as absorbents, film formers, emulsion stabilisers, viscosity increasing agents, suspending agents, binders, and/or skin-conditioning agents. It was reported that some acrylates/C10-30 alkyl acrylate cross polymers are polymerised in benzene. These polymers can have residual benzene up to a maximum concentration of 0.5%. The Panel concluded that cross-linked alkyl acrylates are safe in the present practices of use and concentration, provided that they are not polymerised in benzene. For those ingredients polymerised in benzene, the data available were insufficient to make a determination of safety (Fiume *et al.*, 2017).

2.2 HEALTH EFFECTS – BENZENE IN COSMETICS

2.2.1 Incident surveillance and case reports

There are no cases of toxicity reported in humans because of cosmetics contaminated with benzene. This was expected, due to the chronic nature of health effects associated with benzene.

2.3 TOXICITY OF BENZENE

The toxicity of benzene is well established in humans and animals. The toxicity data has been reviewed and published by various authorities, including ECHA, USEPA, and the Agency for Toxic Substances and Disease Registry (ATSDR). Hence, the toxicity endpoints are only briefly summarised in this assessment.

2.3.1 Absorption, Distribution, Metabolism and Excretion of Benzene

Absorption: Benzene is readily and rapidly absorbed through oral and inhalation routes. However, dermal absorption is poor. Studies in mice and rats indicate that >97% of an oral dose (0.5 to 150 mg/kg bw) was absorbed. It is reasonable to assume that oral absorption from aqueous solutions would be nearly 100% (ATSDR, 2007). There are no definitive oral absorption studies in humans (WHO, 1994).

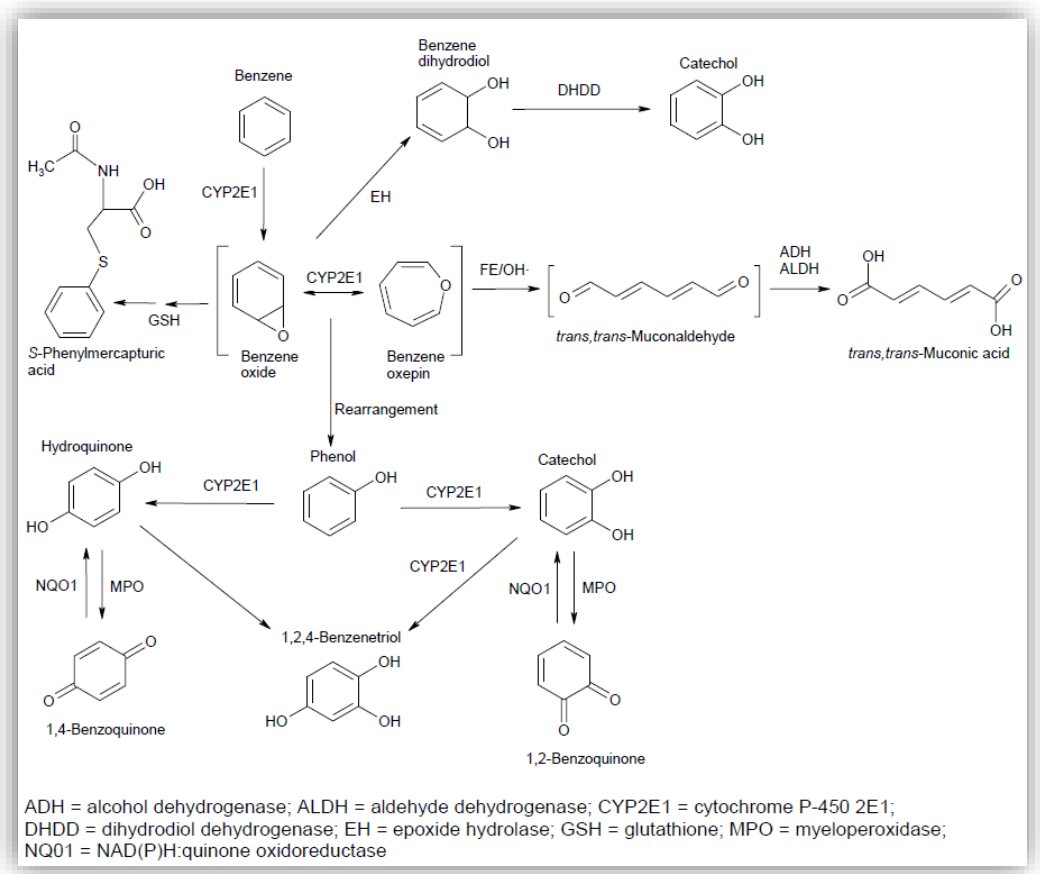
There are numerous inhalation studies conducted in humans. Inhalation studies at 160–320 mg/m^3 (50–100 ppm) suggest approximately 50% absorption and 30% retention of the inhaled dose, the rest being exhaled as unchanged benzene (ATSDR, 2007; WHO, 1994).

Dermal absorption of benzene vapour is possible; however, the uptake is low compared to the uptake via inhalation. Liquid benzene can be absorbed through human skin, although absorption is not as substantial as following inhalation or oral exposure. Evaporation of volatile benzene from the skin surface will decrease the dermally absorbed amount. In an *in vivo* experiment in humans, 0.0026 mg/cm^2 of carbon-14-labelled benzene was applied to forearm skin of four volunteers. The dermal absorption was 0.05% of the applied dose. Calculations were based on urinary excretion data and no correction was made for the amount of benzene that evaporated from the applied site before absorption occurred. In another study, the forearm was exposed to approximately 0.06 g/cm^2 of liquid benzene for

1.25–2 hours. The absorption was estimated from the amount of phenol eliminated in the urine. The absorption rate of liquid benzene by the skin (under the conditions of complete saturation) was calculated to be low, approximately 0.4 mg/cm^2/hour (<1% per hour). Benzene is also dermally absorbed by animals. In Rhesus monkeys, minipigs, and hairless mice, dermal absorption was <1% following a single direct (unoccluded) application of liquid benzene (ATSDR, 2007; Bayliss *et al.*, 2002).

Distribution: Benzene is distributed throughout the body with lipid-rich and well perfused tissues containing the highest levels (ATSDR, 2007; WHO, 1994). Benzene has also been shown to cross the human placenta and has been found in cord blood in amounts equal to or greater than those in maternal blood (ATSDR, 2007).

Metabolism: The metabolism of benzene is inherently complex and occurs principally in the liver and the lungs, with secondary metabolism occurring in the bone marrow (Figure 2) (ATSDR, 2007).



Source: (ATSDR, 2007)

Figure 2. Metabolic pathways for benzene

Benzene undergoes initial oxidation to benzene oxide by cytochrome P450 2E1 enzyme (CYP2E1). This enzyme is mainly expressed in the liver. Furthermore, since CYP2E1 is also expressed in the bone marrow of mice (Bernauer et al 1999) and in human bone marrow stem cells (Bernauer et al 2000) it can be assumed that benzene will also be metabolised directly in bone marrow stem cells.

Benzene oxide is then metabolised through several different pathways (ATSDR, 2007; Bayliss *et al.*, 2002; WHO, 1994):

- The predominant pathway involves nonenzymatic rearrangement to form phenol. Phenol is oxidised in the presence of CYP2E1 to catechol or hydroquinone, which are oxidised via myeloperoxidase to the reactive metabolites 1,2- and 1,4-benzoquinone, respectively. Both catechol and hydroquinone may be converted to the reactive metabolite 1,2,4-benzenetriol via CYP2E1 catalysis.
- Benzene oxide can undergo conjugation with glutathione (GSH), resulting in the eventual formation and urinary excretion of S-phenylmercapturic acid.
- Benzene may be further metabolised by epoxide hydrolase (EH) to benzene dihydrodiol and catechol.
- Benzene can undergo iron-catalysed ring-opening conversion to trans,trans-muconic acid, presumably via the reactive trans,transmuconaldehyde intermediate

Excretion: The main route for excretion of unmetabolised benzene is exhalation. Most of the absorbed benzene however, is metabolised and the metabolites are excreted after phase-II-conjugation predominantly in the urine (ATSDR, 2007).

2.3.2 Acute toxicity

Benzene is not generally regarded as acutely toxic and there are correspondingly few reports pertaining to the human health effects following a single exposure. Exposures in the general population that result in acute toxic effects are usually related to accidents and misuse or abuse of benzene.

Acute inhalation and oral exposures of humans to high concentrations of benzene have resulted in central nervous system depression and death. The lethal oral dose for humans has been estimated to be 125 mg/kg (Bayliss *et al.*, 2002). Clinical signs of toxicity after acute oral exposure include staggering gait, vomiting, shallow and rapid pulse, somnolence, loss of consciousness, delirium, pneumonitis, profound CNS depression, and collapse. High, but sublethal, oral doses may produce one or more of the following symptoms: dizziness, visual disturbances, euphoria, excitation, pallor, flushing, breathlessness and constriction of the chest, headache, fatigue, sleepiness, and fear of impending death (WHO, 1994).

Benzene is a moderate eye irritant in animals. Two drops of benzene caused moderate conjunctival irritation and very slight, transient corneal injury in rabbits (WHO, 1994). Occupational exposures of >60 ppm for up to 3 weeks are known to cause skin irritation in humans. These effects are due to direct contact of the skin with the vapor, and other dermal effects resulting from direct contact with the skin (ATSDR, 2007).

Undiluted benzene was also a mild skin irritant in rabbits. Erythema, oedema, exfoliation, blistering and moderate necrosis were observed after 20 applications (WHO, 1994).

2.3.3 Subchronic/chronic toxicity

Chronic exposure to benzene primarily causes impairment of the haemopoietic system, with depression of bone marrow production leading to aplastic anaemia being the most common clinical manifestation. Other effects on the haemopoietic system include leukopenia, agranulocytosis, pancytopenia and myelodysplastic syndrome. Benzene is also leukaemogenic in humans. In addition to effects on the hematopoietic system, benzene

exposures have been implicated in neurological disorders, immune dysfunction and cancer. Detailed information on the general toxicity of benzene can be obtained from several comprehensive reviews (ATSDR, 2007; WHO, 1994). In animals, chronic inhalation and oral exposure to benzene produces the same effects as seen in humans.

2.3.4 Genotoxicity

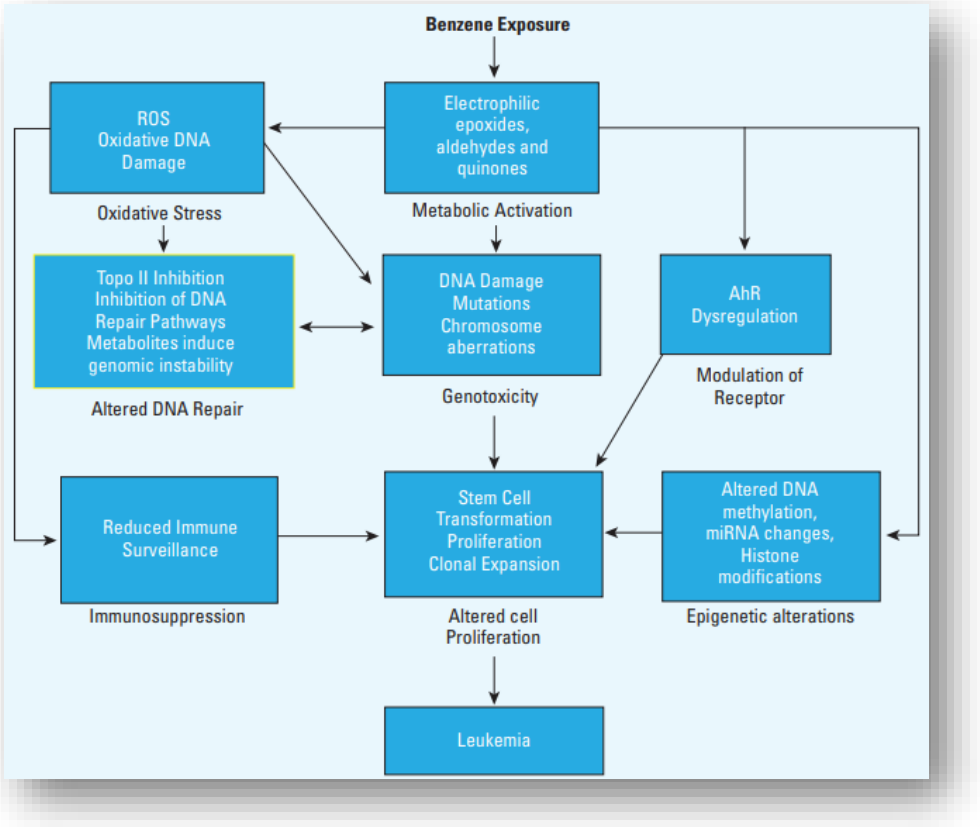
The genotoxic effects of benzene have been studied extensively *in vitro*, in animals and humans. Benzene causes both structural and numerical chromosomal aberrations in humans. Therefore, it is a clastogen. The same effects have been observed in animals. There were positive findings for chromosomal aberrations in bone marrow and lymphocytes in animals which support the human case reports and epidemiological studies in which chromosomal damage was linked to benzene exposure (ATSDR, 2007; IARC, 2018; WHO, 1994).

2.3.5 Carcinogenicity

The carcinogenicity of benzene has been established both in humans and in laboratory animals. Benzene is a human leukaemogen, which has been established by epidemiological and case studies. In humans, it causes acute myeloid leukaemia/acute non-lymphocytic leukemia. An increased mortality from leukaemia has been demonstrated in workers occupationally exposed to benzene. Several types of tumour, primarily of epithelial origin, have been induced in mice and rats after both oral and inhalation exposure. These include tumours in the Zymbal gland, liver, mammary gland and nasal cavity. Lymphomas/leukaemias have also been observed, but with lower frequency (IARC, 2018; WHO, 1994).

2.3.5.1 Mechanism of Carcinogenicity

Metabolism of benzene generates reactive electrophiles via multiple metabolic pathways in various tissues, including bone marrow. There is strong evidence, including in exposed humans, showing that benzene is metabolically activated, induces oxidative stress, is genotoxic, is immunosuppressive, and causes haematotoxicity. Experimental studies have also shown that benzene causes genomic instability, inhibiting topoisomerase II; modulates receptor-mediated effects relevant to aryl hydrocarbon receptor, and induces apoptosis (Smith *et al.*, 2016). The schematic representation in Figure 3 provides a brief overview of the probable mechanism of carcinogenicity.



Source: (Smith *et al.*, 2016)

Figure 3. Probable mechanism of carcinogenicity of benzene

2.3.6 Reproductive and developmental toxicity

A number of studies have investigated the effect of exposure to benzene during pregnancy. In humans, although benzene can cross the placenta, there is no evidence of teratogenic or other reproductive effects, although a few older studies report disturbed menstrual cycles in women with high exposures to benzene and other aromatic solvents (ATSDR, 2007).

Benzene can cross the placenta of experimental animals, and haematopoietic changes have been observed in the foetuses and offspring of mice exposed through inhalation to concentrations of 16–65 mg/m^3 during days 6–15 of gestation. Following inhalation exposure to high doses (400–1600 mg/m^3), decreased foetal weight, an increase in foetal resorptions and skeletal variants have been found in the offspring of mice, rats and rabbits. However, no clear teratogenic effects have been demonstrated (ATSDR, 2007; WHO, 1994).

3 DOSE-RESPONSE INFORMATION

In the current context, concerns associated with exposure to benzene in cosmetics will be related to chronic exposure events.

3.1 BENZENE

3.1.1 Non cancer effects

USEPA has derived oral and inhalation reference doses based on haematological effects in humans (Table 2).

Table 2. Reference dose for benzene

Study / key effect	POD	UF	Reference dose	Reference
Human occupational inhalation study / Decreased lymphocyte count	BMDL $_{(oral)}$: 1.2 mg/kg bw/day	300	0.004 mg/kg bw/day	(USEPA, 2002)
	BMDL $_{(inhalation)}$: 1.2 mg/m^3	300	0.03 mg/m^3	

POD: point of departure, UF: uncertainty factor, BMDL: Lower 95th percentile confidence limit of the benchmark dose, bw: body weight

3.1.2 Cancer effects

The US EPA has estimated an oral cancer slope factor for benzene published in the EPA's Integrated Risk Information System (USEPA, 2002). The cancer slope factor (CSF) is a parameter derived from the low-dose region of the dose-response relationship of chemicals or agents being evaluated as carcinogens. It represents a measure of cancer risk from a lifetime exposure to an agent and is typically expressed in units of proportion of a population affected per milligram of substance per kilogram of body weight per day (USEPA, 2002).

Human epidemiological data from occupational inhalation exposure studies were used for evaluation of the risk of cancer from exposure to benzene. There were similar toxic effects in animals through the oral or inhalation route of exposure. Hence, route-to-route extrapolation is justified. Experimental animal data also demonstrate that benzene is metabolised to the same products whether it is inhaled or ingested. Therefore, it is reasonable to extrapolate from inhalation dose-response to estimate an equivalent oral dose-response (USEPA, 2002). First-pass metabolism of ingested benzene may have significant effects on the dose of benzene metabolites that reaches the target bone marrow cells. Leukaemogenic metabolites may be produced more efficiently after ingestion, but on the other hand, rapid clearance of benzene and metabolites after ingestion may be a mitigating factor. The data are inadequate to address these questions for humans at this time, but a variety of biomarkers of benzene exposure can help to address questions of internal dose of benzene metabolites (USEPA, 2002).

USEPA derived CSF of 1.5 x 10^{-2} to 5.5 x 10^{-2} per (mg/kg)/day (0.015 to 0.055).

4 EXPOSURE ASSESSMENT

As previously discussed, benzene is not intentionally added to cosmetic products. However, it may be present as a byproduct, residual impurity or as a contaminant. Cosmetic products include many formulation types (shampoos, gels, creams, aerosols, etc.) with different uses such as on hair or skin, etc. They may be rinse-off or leave on products. The current exposure assessment was restricted to cosmetics where there is evidence for the presence of benzene in the particular cosmetic type. This included:

- Deodorants, anti-perspirants with benzene concentrations between 2.24 – 17.7 ppm (Valisure, 2021).
- Sunscreens with benzene detected in the range of 2.3 – 5.2 ppm (TGA, 2022). Benzene was also found in a sunscreen product specifically for babies at a concentration of 2.4 ppm (SunBum, 2022).

For the current exposure assessment, the maximum concentrations detected in the published surveys (18 and 5.2 ppm, for deodorants and sunscreens, respectively) were used. While it is possible that benzene residues may be present in other types of cosmetic products, the 'leave on' nature of deodorants and sunscreens means that these products will represent a worst-case scenario for exposure.

4.1 EXPOSURE ASSESSMENT APPROACH

4.1.1 Relevant exposure scenarios

The consumer exposure to deodorants/anti-perspirants and sunscreen containing benzene is considered incidental. The scenarios considered in the exposure assessment depend on the intended uses of the selected cosmetics. For deodorants/anti-perspirants, dermal exposure and inhalation exposure during application of aerosol products were considered relevant. For sunscreen, only the dermal route of exposure was considered relevant. While some aerosol sunscreen products exist, they will often be applied outdoors and inhalation exposure to benzene from use of such products is likely to be negligible. Oral exposure to benzene from use of cosmetic products was considered to be negligible (Table 3).

Table 3. Exposure routes considered for benzene in cosmetic products

Population	Product type	Exposure Pathway		
		Inhalation	Dermal	Oral
Adults	Deodorants, anti-perspirants	X	X	
Adults	Sunscreen		X	
Children	Sunscreen		X	

4.1.2 Exposure models and tiered approach

Risk assessment may follow a tiered approach. Under a tiered approach, initial exposure estimates are derived using highly conservative assumptions. If such estimates indicate no cause for concern, then more refined approaches are unnecessary.

Tier 1 assessment is usually used to screen consumer exposure based on the summation of high percentile product use levels and maximum concentrations of the substance of interest in products, to give a worst-case exposure scenario.

As the current study considered exposure by both inhalation and dermal exposure routes, combination of these exposures requires conversion of external exposure doses to internal (systemic) doses, through application of an absorbed proportion (SCCS, 2021).

4.1.2.1 Dermal exposure

The systemic dose due to dermal absorption is calculated from:

$$SED = Eproduct\ x \frac{C}{100} x\ \frac{DAp}{100}$$

Where:

SED (mg/kg bw/day): Systemic Exposure Dose

$E_{product}$ (mg/kg bw/day): Estimated daily use amount of a cosmetic product per kg body weight, based upon the amount applied and the frequency of application

C (%): Concentration of the substance under study in the finished cosmetic product at the application site

DAp (%): Dermal Absorption expressed as a percentage of the test dose assumed to be applied in real-life conditions

4.1.2.2 Inhalation exposure

For inhalation exposure, the potential concentration of the substance in the room air during application is estimated. For a Tier 1 evaluation, it is assumed that 100% of the substance in the consumer product will be released at once into the room and there is no ventilation:

$$Concentration\ (exposure) = \frac{Weight\ of\ ingredient\ in\ the\ released\ spray\ (mg)}{Volume\ of\ room\ (m3)}$$

To calculate the weight of ingredient in the released spray information is required on (FEA, 2013):

- Amount of product used
- Fraction of substance in the product (concentration)

$$Exposure = \frac{C\ x\ IR\ x\ ED}{BW}\ x\ IAp$$

Where, C= concentration of benzene (mg/m^3)
IR= inhalation rate (m^3/hr)
ED = exposure duration (min)
BW= body weight of adult (kg)
IAp = inhalation absorption (%)

4.2 EXPOSURE PARAMETERS

For exposure assessment, the amount of product/chemical sprayed or applied in a given time and realistic conditions should be taken into account. The exposure parameters used in the current assessment for deodorant and sunscreen are given in Table 4.

Table 4. Exposure parameters for exposure assessment

Parameter	Value	Comment	Reference
$E_{product}$ (adults)	Deodorants: 10 mg/kg bw/day	Default	(SCCS, 2021)
	Sunscreen: 257 mg/kg bw/day	Calculated in the next section	
Concentration of benzene	Deodorants: 18 ppm (0.0018%)	Maximum concentration	(Valisure, 2021)
	Sunscreen: 5 ppm (0.0005%)		(TGA, 2022)
Retention factor	1	Default for leave-on products	(SCCS, 2021)
Dap*	10%	Conservative value	(Fiume *et al.*, 2017)
Oral absorption*	100%	-	(USEPA, 2002)
Body weight (adult)	70 Kg	New Zealand adult weight	
$E_{product}$ (children)	Sunscreen Mean: 136 mg/kg bw/day P95: 368 mg/kg bw/ day	P95 is 95th percentile	(Gomez-Berrada *et al.*, 2018)
Room volume	10 m^3	Volume of bathroom	(Bremmer *et al.*, 2006)
Inhalation absorption	50%	Value from human studies	(ATSDR, 2007)
Inhalation rate (adult)	1.08 m^3/hr	Light exercise	(Bremmer *et al.*, 2006)
Spray time	1.4 sec	-	(Steiling *et al.*, 2014)
Discharge rate	0.8 g/s		(Bremmer *et al.*, 2006)
Time in bathroom	5 minutes		(Bremmer *et al.*, 2006)

*Dermal absorption for benzene is <1%. We have followed SCCS risk assessment of benzene and used a conservative value of 10%.
** Since oral absorption is 100%, external dose is equivalent to internal dose.

4.3 EXPOSURE ESTIMATES

4.3.1 Dermal exposure

For deodorants:

Based on the exposure parameters in Table 4, internal (systemic) exposure to benzene from dermal absorption from deodorant use can be estimated by:

$$SED = 10\ x \frac{0.0018}{100} x\ \frac{10}{100} = 1.77E-05\ mg/kg\ bw/day$$

For sunscreen:

For adult sunscreen use, SCCS (2021) recommends a standard use value of 18.0 g/day for the safety evaluation of sunscreen lotion. Sunscreen is considered as a leave-on product (retention factor = 1). This value was converted to a body weight basis by dividing by a standard adult body weight of 70 kg to give a use rate of 257 mg/kg bw/day.

Based on the exposure parameters in Table 4, internal (systemic) exposure to benzene from dermal absorption from sunscreen use can be estimated by:

$$SED = 257\ x \frac{0.00052}{100} x\ \frac{10}{100} = 1.34E-04\ mg/kg\ bw/day$$

Sunscreen is generally only used during the summer months. For the current assessment, it was assumed that sunscreen would be used daily for three months of the year. The resultant weighted lifetime daily exposure is 3.3 E-05 mg/kg bw/day.

For child sunscreen use, there is no standard use value in the SCCS guidance. Gomez-Berrada *et al.* (2018) assessed the use level of sunscreen products for adults and children. The amount of sunscreen spray applied per use was in the same order or magnitude between children and adults. As parents usually apply sun care products on their children, they probably apply the same amount of product to themselves as for their children.

Children had higher use levels of sunscreen spray on a body weight basis, with children aged 3-13 having mean and P95 (95th percentile) use rates of 136.3 mg/kg bw/day and 368.2 mg/kg bw/day respectively. Hence,

Based on the exposure parameters in Table 4, internal (systemic) exposure to benzene from dermal absorption from sunscreen use by children (mean and P95) can be estimated by:

$$SED = 368.2\ x \frac{0.00052}{100} x\ \frac{10}{100} = 1.91E-04\ mg/kg\ bw/day$$

$$SED = 136.3\ x \frac{0.00052}{100} x\ \frac{10}{100} = 7.09E-05\ mg/kg\ bw/day$$

As for adults, it is assumed that sunscreen use will only occur in the summer months and the corresponding adjusted exposure estimates are 1.91E-04 and 7.09E-05 mg/kg bw/day for the P95 and mean, respectively.

4.3.2 Inhalation exposure

Adults applying spray deodorants will be exposed to any vapour not adhering to the skin. For the tier 1 assessment, it is assumed that the sprayed vapour will be uniformly distributed within a small room, such as a bathroom.

Based on the exposure parameters in Table 4, 1.12 g of product containing 0.0018% benzene would be released into a 10m^3 room, this gives an initial benzene concentration of 0.002 mg/m^3

A European consumer exposure model (ConsExpo) factsheet reports that an adult spends 5 minutes in the bathroom after spraying and will have an inhalation rate (light exercise) of 1.08 m^3/hr (Bremmer *et al.*, 2006). Daily internal exposure to benzene from inhalation of aerosol applied deodorant can be estimated from:

$$Exposure = \frac{0.002\ x\ 1.08\ x\ 0.083\ X\ 0.5}{70} = 1.3E-06\ mg/kg\ bw/day$$

5 RISK CHARACTERISATION

5.1 NON-CANCER RISK

A margin of safety (MoS) approach was used to assess the expected level of safety in relation to non-cancer effects associated with benzene in cosmetic products. MoS (equation 1) is the ratio between a PoDsys (systemic POD, usually the NOAEL or BMD values from oral studies) and an estimate of the exposure (SCCS, 2021). It should be noted that, as oral absorption is effectively 100%, the oral external dose is equivalent to the oral systemic dose.

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

The BMD approach is preferred as the dose descriptor for the PoD and the MoS calculations. When no BMD can be calculated or is available, usually NOAEL values are applied. If a BMD or a NOAEL cannot be identified from the available data, other dose descriptors such as the Lowest Observed (Adverse) Effect Level (LOAEL) may be used in the MoS calculation.
For a chemical substance with health thresholds (i.e, not genotoxic and not carcinogenic), a MOS >= 100 is generally considered to be protective.

Table 5. Margin of safety (MoS) for non-carcinogenic risk

Product	Population	Exposure (mg/kg bw/day)		POD (mg/kg bw/day)#	MoS
		Daily	Time weighted		
Dermal					
Deodorants	Adult	1.80E-05	1.80E-05	1.2	-
Sunscreen	Adult	1.34E-05	3.35E-06*		-
	Child (P95)	1.91E-04 (P95)	7.78E-05*		>10000
	Child (Mean)	7.07E-05 (mean)	1.77E-05*		>10000
Inhalation					
Deodorant	Adult	1.3E-06	1.3E-06	1.2	-
Aggregated exposure (adults)			2.3E-05		>10000

The POD is for oral exposure. Due to the effectively complete oral absorption of benzene the oral value is equivalent to the POD_{sys}
* Assumption that sunscreen is applied daily for 3 months = exposure x 3/12

Non-carcinogenic human health risk on exposure to benzene in the cosmetic products was evaluated by a MoS approach. The MoS was much greater than 100 for children and adults (aggregated risk), which indicates that the presence of benzene in deodorants (in adults) and sunscreen (in adults and children) at the maximum concentrations determined is not a cause for concern with respect to non-cancer effects.

5.2 CARCINOGENIC RISK

Lifetime cancer risk (LCR) is usually investigated for carcinogenic chemicals. In this assessment, LCR was determined by using the following relationship:

LCR = ED X CSF

Where CSF represents the carcinogenicity slope factor (mg/kg/d) and it approximates the cancer risk per unit intake dose of an agent to cause cancer over an average lifetime. ED is the estimated daily exposure. As the CSF related to oral exposure, the ED should also be expressed in terms of oral exposure. However, for benzene oral absorption is effectively 100% and ED will be equal to SED determined above.

A lifestage weighted average was calculated for sunscreen exposure to child and adult to estimate the overall lifetime exposure. It was assumed that childhood refers to the first 15 years of life and adulthood is the balance (55 years) of a 70-year lifetime. Hence, the lifestage weighted average for adult and child sunscreen use is calculated as below:

Daily exposure (Adult) + Daily exposure (child) = (3.35E-05 x 55/70) + (1.80E-05 x 15/70)

= 2.6E-05 mg/kg bw/day

The WHO (2017) recommends that the lifetime cancer risk (LCR) for exposure to a carcinogenic contaminant in drinking water and air should be 10^{-5} or less. This value has been used in New Zealand for standard setting, notable for drinking-water. Table 6 summarises estimates of LCR due to benzene in cosmetic products.

Table 6. Lifestage weighted average exposure and lifetime cancer risk (LCR) for benzene in cosmetic products

Product	Population	Exposure (mg/kg bw/day)	SF (mg/kg/day)	LCR
Dermal				
Deodorants	Adult	1.8E-05	0.015 to 0.055	-
Sunscreen	Adult + child	2.6E-05		-
Inhalation				
Deodorants	Adult	1.0E-06	0.015 to 0.055	-
Aggregated exposure (lifetime)		4.50E-05		6.7×10^{-7} to 2.4×10^{-6}

The LCR for benzene in deodorants and sunscreen was 2.4×10^{-6} i.e. lower than an excess cancer risk of 10^{-5}.

6 CONCLUSIONS

Cosmetics range from everyday hygiene products such as soap, shampoo, deodorant, and toothpaste to luxury beauty items including perfumes and makeup. Most cosmetics are generally used by adults. There are some products like sunscreen, shampoo etc which are also used by children.

Benzene is an industrial solvent which is found in crude oils and as a by-product of oil-refining processes. It is colorless and has a sweet, aromatic, gasoline-like odor. Benzene is classified as carcinogenic to humans by IARC and regulatory authorities like ECHA, NZEPA and USEPA. Therefore, it is not intentionally used or added in cosmetic formulations/products. However, sometimes its presence can be technically unavoidable in final product. The presence of benzene in finished products can be at one or more stages of a product's lifecycle. It can be a residual solvent or impurity (in organic propellants) or a contaminant.

There are restrictions for the use of benzene in cosmetics overseas and in New Zealand. In the EU, US, Australia and China, regulatory agencies have defined concentration limits for benzene (residual solvent or impurity) in the final product or mixture. In New Zealand, under the cosmetic group standard, cosmetics in New Zealand must not contain benzene, other than at a trace level of that component provided that such presence is technically unavoidable in good manufacturing practice. It should be noted that there are no concentration limits defined for this trace level.

In 2021, several cosmetic products (deodorants, antiperspirants, sunscreens) in the US and Australia were found to contain benzene. The products were voluntarily recalled from the market by the respective companies. Benzene was detected in body spray products up to the concentration of 17.7 ppm. Similarly, benzene was also detected in sunscreen products at concentrations up to 5.2 ppm and 2.4 ppm used by adults and children, respectively. Since our literature search found the presence of benzene in deodorants/antiperspirants and sunscreen and hence, the risk assessment is performed for these products.

Exposure to benzene while using deodorants/antiperspirants and sunscreen is considered incidental. For both the product categories, inhalation and dermal routes are considered relevant for adults. Dermal exposure is also considered for children using sunscreen.

In this assessment, both non-cancer and cancer human health risk of benzene in cosmetics (deodorants and sunscreen) through dermal and inhalation pathways were evaluated. Non-carcinogenic human health risk on exposure to benzene in the cosmetic products was evaluated by applying Margin of Safety (MoS) methodology. The MoS was greater than 100 for children and adults (aggregated risk), which indicates that benzene in deodorants (in adults) and sunscreen (in adults and children) is of low concern for public health.

Lifetime cancer risk was estimated for adults (sunscreen and deodorant use) and children (sunscreen use only). Risks were estimated based on the dermal and inhalation pathways of exposure. The result indicates that lifetime exposure to benzene from cosmetic use will equate to an excess cancer risk of $<10^{-5}$, or 1 excess cancer in 100,000 individuals, which has been used in New Zealand for standard setting.

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