Australian Government
Department of Health
Australian Industrial Chemicals Introduction Scheme

Benzalkonium halides

Evaluation statement

30 June 2022

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AICIS evaluation statement

Subject of the evaluation

Benzalkonium halides

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Reason for the evaluation

An evaluation is required to provide information on the risks to human health.

Parameters of evaluation

These chemicals are benzalkonium halides listed on the Australian Inventory of Industrial Chemicals (the Inventory). This evaluation is a human health risk assessment for all identified industrial uses of these chemicals. This includes use as preservatives in cosmetic products.

It should be noted that benzalkonium chloride and stearalkonium chloride (C18 alkyldimethylbenzylammonium chloride) have reported non-industrial uses as excipients in pharmaceutical products (TGA 2022) and in hospital grade or household/commercial grade disinfectants. As these are excluded uses under the *Industrial Chemicals Act 2019*, they have not been considered in this evaluation.

Summary of evaluation

Summary of introduction, use and end use

Australian uses were reported under previous mandatory and/or voluntary calls for information for C12-18 (CAS No. 68391-01-5), C12-16 (CAS No. 68424-85-1) and C12-14 (CAS No. 85409-22-9) alkyldimethylbenzylammonium chlorides. These chemicals have reported domestic use including in cleaning and washing agents, and additives.

Based on international use information, chemicals in this group are used in personal care products, such as hair care products (1–7%), makeup and nail care products (0.01–0.1%), hand soap (0.1–1%) and hand sanitiser. Some of these chemicals are used in domestic and commercial liquid, spray, and powder cleaning products at concentrations up to 20%. These chemicals are also used in various site limited applications including in the manufacture of building materials, paper products and textiles.

Human health

Summary of health hazards

The critical health effects for risk categorisation include:

- systemic acute effects from oral, dermal and inhalation exposure
- local effects including skin corrosion and eye damage.

Chemicals in this group are expected to be poorly absorbed (<10%) following oral and dermal exposure. Although skin absorption is expected to be low, absorption may occur through damaged skin.

Although data are limited for some of chemicals in this group, benzalkonium halides are expected to have moderate acute oral toxicity (median lethal dose (LD50) = 240–795 mg/kg bw in rats and 150–340 mg/kg bw in mice) and low to moderate acute dermal toxicity (LD50 930–2848 mg/kg bw in rats and 2730–3413 mg/kg bw in rabbits). The chemicals have high acute inhalation toxicity (median lethal concentration (LC50) = 0.053–0.25 mg/L in rats; 4

hours). However, as chemicals in this group are not expected to be volatile, inhalation exposure is expected to be limited to scenarios where aerosols may be formed.

Based on the available data, benzalkonium halides are expected to be corrosive to skin and cause serious eye damage.

Although data are limited, based on skin and eye irritation properties and effects seen in acute and repeat does inhalation toxicity studies, these chemicals are expected to cause irritation/corrosion of the mucous membranes of the respiratory tract. Inhalation exposure is expected to be limited to scenarios where aerosols may be formed.

Based on the weight of evidence, chemicals in this group are not considered to be skin sensitisers. Rare clinical reports of skin sensitisation appear more common in individuals with damaged skin barriers. In some instances, clinical reports of skin sensitisation may result from misinterpretation of skin irritation effects as skin sensitisation.

Benzalkonium halides are not expected to cause serious systemic health effects following repeated oral or dermal exposure. Effects including reduced food consumption and, consequently, body weight may be attributed to local gastrointestinal irritation rather than systemic effects.

Chemicals in this group are not considered to have genotoxic potential. Negative results were reported for various chemicals in this group in bacterial reverse mutation assays, in vitro mammalian chromosome aberration assays, an in vitro mammalian gene mutation assay and an in vivo micronucleus assay.

Based on results from three chronic toxicity/carcinogenicity studies and a lifetime dermal study, the chemicals in this group are not expected to be carcinogenic.

Chemicals in this group are not expected to cause specific adverse effects on fertility/sexual function and development following exposure.

The majority of toxicity data for benzalkonium halides comes from studies using benzalkonium chloride (CAS No. 8001-54-5) and C12-C16 benzalkonium chloride (CAS No. 68424-85-1). Some toxicity data are available for C8-C18 alkyldimethylbenzylammonium chloride (CAS 63449-41-2), coco alkyldimethylbenzylammonium chloride (CAS No. 61789-71-7), C12-C18 alkyldimethylbenzylammonium chloride (CAS No. 68391-01-5), C16 alkyldimethylbenzylammonium chloride (CAS No. 122-18-9) and C14 alkyldimethylbenzylammonium chloride (CAS No. 139-08-2). No toxicity data are available for the other chemicals in this group.

Hazard classifications relevant for worker health and safety

These chemicals satisfy the criteria for classification according to the Globally Harmonized System of Classification and Labelling of Chemicals (GHS) (UNECE 2017) for hazard classes relevant for work health and safety as follows. This does not consider classification of physical hazards and environmental hazards. In addition, the chemicals satisfy the criteria for the following non-GHS hazard statements (SWA 2012):

- AUH071 – Corrosive to the respiratory tract

The proposed hazard classification is based on read across principles (see **Grouping Rationale** section). It should be used as a default for all members of the group. If empirical

data become available for any member of the group indicating that a lower or higher classification is appropriate for the specific chemical, these may be used to amend the default classification for that chemical.

Classification for acute inhalation toxicity applies in situations where dusts and mists are formed. Dusts and mists generally have sizes ranging from less than 1 to 100 μm. Mixtures and products containing the chemicals at concentration of <1% would not need classification although this would be dependent on other ingredients in the formulation.

Health hazards	Hazard category	Hazard statement
Acute toxicity – oral	Acute Tox. 4	H302: Harmful if swallowed
Acute toxicity – dermal	Acute Tox. 4	H312: Harmful in contact with skin
Acute toxicity – inhalation	Acute Tox. 2	H330: Fatal if inhaled
Corrosion/Irritation	Skin Corr. 1B	H314: Causes severe skin burns and eye damage

Summary of health risk

Public

Australian and international data suggests widespread and repeated exposure of the public to these chemicals through the use of rinse-off (up to 7%) and leave-on (up to 1%) cosmetic products, as well as domestic cleaning products (up to 20%). However, based on international restrictions (see **International regulatory status** section), these chemicals are likely to be used at up to 3% in rinse-off hair products and at <0.1% as preservatives in cosmetic products.

The public is unlikely to regularly be exposed to high concentrations (>10%) of these chemicals in domestic cleaning products, but this may occur when diluting concentrated products prior to use. The main route of public exposure is expected to be through the skin. Inhalation exposure may occur in scenarios where aerosols are formed. Incidental ingestion and contact with the eyes may also occur.

Several risk assessments have been conducted for use of benzalkonium chloride in consumer products. Acceptable margins of exposures were calculated based on concentrations up to 3% in rinse off products and 0.1% in leave on products. Calculations do not take into consideration aggregated exposure resulting from simultaneous use of all products (e.g., domestic cleaning products) containing the chemical. Where domestic cleaning products are used as directed, exposure is not expected to be significant.

Indirect dermal exposure, for example from wearing clothes treated with laundry detergents and/or fabric softener, is not expected to be significant, although overuse of products may result in disrupted skin microbiome and/or skin irritation.

Chemicals in this group are currently covered by the generic entries for quaternary ammonium compounds in Schedules 5 and 6 of the Poisons Standard, except when at concentrations of 5% or less (SUSMP 2021). Internationally benzalkonium chloride is restricted in cosmetic products at lower concentrations. These restrictions more closely align with the irritation potential of the chemicals.

The observation of irritation effects at low concentrations are consistent with other quaternary ammonium compounds used in cosmetics such as alkyl pyridiniums. A revised entry for quaternary ammonium compounds in the Poison Standard that provides controls specific to cosmetic chemicals would be more appropriate to manage the risks to the public.

Workers

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

Given the critical systemic acute and local health effects, these chemicals could pose a risk to workers. Control measures to minimise dermal and inhalation exposure are needed to manage the risk to workers (see **Proposed means for managing any risks** section).

Proposed means for managing risk

Public health

Recommendation to Department of Health

It is recommended that the delegate of the Secretary for Poisons Scheduling revise the schedule entries for quaternary ammonium compounds in the Poisons Standard. This report should be considered together with previous reports addressing other cationic surfactants with cosmetic use.

In order to manage the potential risk associated with the use of these chemicals, the new entry should restrict the concentration of the chemicals (singly or cumulatively) in cosmetic/domestic products.

Consideration should be given to the following:

- the likely use of the chemicals in multiple products available in Australia
- the current entry for quaternary ammonium compounds does not take into account the potential risk arising from using these chemicals in cosmetic applications at concentrations lower than 5%
- international restrictions regarding the use of benzalkonium halides in cosmetic products.

Workers

Recommendation to Safe Work Australia

It is recommended that Safe Work Australia (SWA) update the Hazardous Chemical Information System (HCIS) to include classifications relevant to work health and safety.

Information relating to safe introduction and use

The information in this statement including recommended hazard classifications, should be used by a person conducting a business or undertaking at a workplace (such as an

employer) to determine the appropriate controls under the relevant jurisdiction Work Health and Safety laws.

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

- using closed systems or isolating operations
- using local exhaust ventilation to prevent these chemicals from entering the breathing zone of any worker
- minimising manual processes and work tasks through automating processes
- adopting work procedures that minimise splashes and spills
- cleaning equipment and work areas regularly
- using protective equipment that is designed, constructed, and operated to ensure that the worker does not come into contact with these chemicals.

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

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

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

Conclusions

The conclusions of this evaluation are based on the information described in this statement.

Considering the proposed means of managing risks, the Executive Director is satisfied that the identified human health risks can be managed within existing risk management frameworks. This is provided that all requirements are met under environmental, workplace health and safety and poisons legislation as adopted by the relevant state or territory and the proposed means of managing the risks identified during this evaluation are implemented.

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

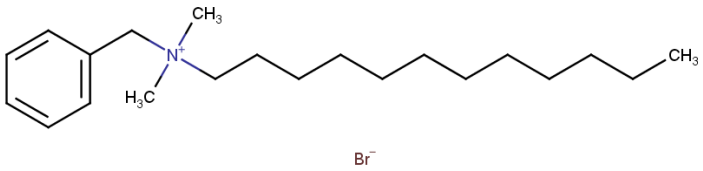
Supporting information

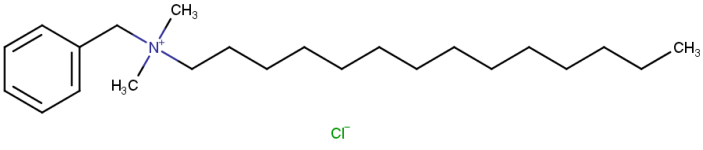
Grouping rationale

Chemicals in this evaluation are quaternary ammonium compounds, alkyldimethylbenzylammonium salts, with chloride or bromide counterions. These chemicals are cationic surfactants for which the carbon chain length of the hydrophobic alkyl moieties varies from 7-22 (C7-C22). Although there is limited data available for some of these chemicals in this group, they are expected to have similar uses and toxicological properties.

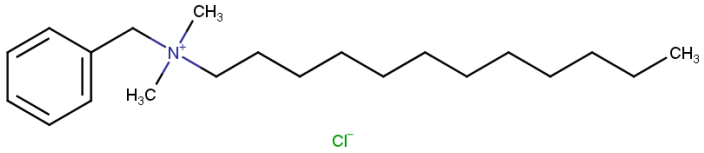
A number of chemicals (CAS Nos. 8001-54-5, 63449-41-2, 61789-71-7, 68391-01-5, 68424-85-1, 85409-22-9) in this group were previously assessed under the former National Industrial Chemicals Notification and Assessment Scheme (NICNAS) IMAP framework (NICNAS 2015). Additional hazard information particularly relating to sensitisation, irritation and respiratory effects is available since this IMAP assessment was completed.

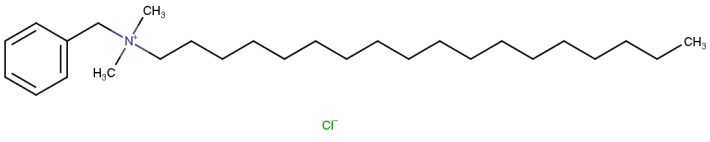
Chemical identity

Chemical name	Benzenemethanaminium, N-dodecyl-N,N-dimethyl-, bromide
CAS No.	7281-04-1
Synonyms	lauryldimethylbenzylammonium bromide lauralkonium bromide (INCI) C12 alkyldimethylbenzylammonium bromide
Structural formula	
Molecular formula	C21H38N.Br
Molecular weight (g/mol)	384.44
SMILES	[Br-].C=1C=CC(=CC1)C[N+](C)(C)CCCCCCCCCCCC
Chemical description	-

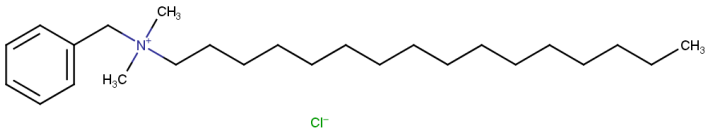
Chemical name	Benzenemethanaminium, N,N-dimethyl-N-tetradecyl-, chloride
CAS No.	139-08-2
Synonyms	myristyldimethylbenzylammonium chloride myristalkonium chloride (INCI) C14 alkyldimethylbenzylammonium chloride
Structural formula	

Molecular formula	C23H42N.Cl
Molecular weight (g/mol)	368.08
SMILES	[Cl-].C=1C=CC(=CC1)C[N+](C)(C)CCCCCCCCCCCCCC
Chemical description	-

Chemical name	Benzenemethanaminium, N-dodecyl-N,N-dimethyl-, chloride
CAS No.	139-07-1
Synonyms	dodecyldimethylbenzylammonium chloride lauralkonium chloride (INCI) C12 alkyldimethylbenzylammonium chloride
Structural formula	
Molecular formula	C21H38N.Cl
Molecular weight (g/mol)	339.99
SMILES	[Cl-].C=1C=CC(=CC1)C[N+](C)(C)CCCCCCCCCCCCC
Chemical description	-

Chemical name	Benzenemethanaminium, N,N-dimethyl-N-octadecyl-, chloride
CAS No.	122-19-0
Synonyms	stearyl dimethylbenzylammonium chloride stearalkonium chloride (INCI) C18 alkyldimethylbenzylammonium chloride
Structural formula	
Molecular formula	C27H50N.Cl
Molecular weight (g/mol)	424.15
SMILES	[Cl-].C=1C=CC(=CC1)C[N+](C)(C)CCCCCCCCCCCCCCCCCC
Chemical description	-

Chemical name	Benzenemethanaminium, N-hexadecyl-N,N-dimethyl-, chloride

CAS No.	122-18-9
Synonyms	hexadecyldimethylbenzylammonium chloride cetalkonium chloride (INCI) C16 alkyldimethylbenzylammonium chloride
Structural formula	
Molecular formula	C25H46N.Cl
Molecular weight (g/mol)	396.09
SMILES	[Cl-].C=1C=CC(=CC1)C[N+](C)(C)CCCCCCCCCCCCCCCC
Chemical description	-

Chemical name	Quaternary ammonium compounds, alkylbenzyldimethyl, chlorides
CAS No.	8001-54-5
Synonyms	benzalkonium chloride (INCI) ammonium, alkyldimethylbenzyl-, chloride
Structural formula	unspecified
Molecular formula	unspecified
Molecular weight (g/mol)	unspecified
SMILES	-
Chemical description	UVCB predominant alkyl chain lengths reported to be C12, C14 and C16

Chemical name	Quaternary ammonium compounds, benzyl-C8-18-alkyldimethyl, chlorides
CAS No.	63449-41-2
Synonyms	alkyl dimethyl benzyl ammonium chloride benzyl-C8-18-alkyldimethylammonium chloride C8-18-alkydimethylbenzyl ammonium chlorides
Structural formula	unspecified
Molecular formula	unspecified
Molecular weight (g/mol)	unspecified
SMILES	-
Chemical description	UVCB

Chemical name	Quaternary ammonium compounds, benzylcoco alkyldimethyl, chlorides
CAS No.	61789-71-7
Synonyms	benzyl (coconut oil alkyl)dimethyl ammonium chloride benzyl chloride quaternary salt of N,N'-dimethylcocoamine dimethyl cocobenzyl ammonium chloride coco alkyldimethylbenzylammonium chloride
Structural formula	unspecified
Molecular formula	unspecified
Molecular weight (g/mol)	unspecified
SMILES	-
Chemical description	UVCB The CAS number is listed under INCI entry for benzalkonium chloride

Chemical name	Quaternary ammonium compounds, benzyl-C12-18-alkyldimethyl,chlorides
CAS No.	68391-01-5
Synonyms	(C12-18) alkyldimethylbenzyl ammonium chloride
Structural formula	unspecified
Molecular formula	unspecified
Molecular weight (g/mol)	unspecified
SMILES	-
Chemical description	UVCB The CAS number is listed under INCI entry for benzalkonium chloride

Chemical name	Quaternary ammonium compounds, benzyl-C12-16-alkyldimethyl, chlorides
CAS No.	68424-85-1
Synonyms	(C12-16) alkyldimethylbenzylammonium chloride
Structural formula	unspecified
Molecular formula	unspecified
Molecular weight (g/mol)	unspecified
SMILES	-

Chemical description	UVCB The CAS number is listed under INCI entry for benzalkonium chloride

Chemical name	Quaternary ammonium compounds, benzyl-C12-14-alkyldimethyl,chlorides
CAS No.	85409-22-9
Synonyms	benzyl-C12-14-alkyldimethylammonium chlorides C12-14 alkyldimethylbenzylammonium chloride
Structural formula	unspecified
Molecular formula	unspecified
Molecular weight (g/mol)	unspecified
SMILES	-
Chemical description	UVCB The CAS number is listed under INCI entry for benzalkonium chloride

Chemical name	Quaternary ammonium compounds, benzyl(hydrogenated tallow alkyl)dimethyl, chlorides
CAS No.	61789-72-8
Synonyms	hydrogenated tallow alkyldimethylbenzylammonium chloride
Structural formula	unspecified
Molecular formula	unspecified
Molecular weight (g/mol)	unspecified
SMILES	-
Chemical description	UVCB

Chemical name	Quaternary ammonium compounds, benzyl-C10-16-alkyldimethyl,chlorides
CAS No.	68989-00-4
Synonyms	C10-C16 alkyl benzyl dimethyl ammonium chloride C10-16 alkyldimethylbenzylammonium chloride
Structural formula	unspecified
Molecular formula	unspecified
Molecular weight (g/mol)	unspecified
SMILES	-

Chemical description	UVCB

Chemical name	Quaternary ammonium compounds, benzyl-C10-21-alkyldimethyl,chlorides
CAS No.	91080-30-7
Synonyms	C10-21 alkyldimethylbenzylammonium chloride
Structural formula	unspecified
Molecular formula	unspecified
Molecular weight (g/mol)	unspecified
SMILES	-
Chemical description	UVCB

Chemical name	Quaternary ammonium compounds, benzyl-C16-18-alkyldimethyl,chlorides
CAS No.	68607-20-5
Synonyms	(C16-18) alkylbenzyldimethylammonium chloride C16-18 alkyldimethylbenzylammonium chloride
Structural formula	unspecified
Molecular formula	unspecified
Molecular weight (g/mol)	unspecified
SMILES	-
Chemical description	UVCB

Chemical name	Quaternary ammonium compounds, benzyl-C16-22-alkyldimethyl,chlorides
CAS No.	91080-31-8
Synonyms	C16-22 alkyldimethylbenzylammonium chloride
Structural formula	unspecified
Molecular formula	unspecified
Molecular weight (g/mol)	unspecified
SMILES	-
Chemical description	UVCB

Chemical name	Quaternary ammonium compounds, benzyl-C7-17-alkyldimethyl, chlorides
CAS No.	85665-42-5
Synonyms	C7-17 alkyldimethylbenzylammonium chloride
Structural formula	unspecified
Molecular formula	unspecified
Molecular weight (g/mol)	unspecified
SMILES	-
Chemical description	UVCB

Chemical name	Quaternary ammonium compounds, benzyldimethylsoya alkyl, chlorides
CAS No.	61789-74-0
Synonyms	soya alkyldimethylbenzylammonium chloride
Structural formula	unspecified
Molecular formula	unspecified
Molecular weight (g/mol)	unspecified
SMILES	-
Chemical description	UVCB

Chemical name	Quaternary ammonium compounds, benzyldimethyltallow alkyl, chlorides
CAS No.	61789-75-1
Synonyms	benzyldimethyl tallow quaternary ammonium chloride tallowalkonium chloride tallow alkyldimethylbenzylammonium chloride
Structural formula	unspecified
Molecular formula	unspecified
Molecular weight (g/mol)	unspecified
SMILES	-
Chemical description	UVCB

Introduction and use

Australia

The following Australian industrial uses were reported under previous mandatory and/or voluntary calls for information for C12–18, C12–16 and C12-14 alkyldimethylbenzylammonium chlorides.

These chemicals have reported domestic use including in cleaning and washing agents, and additives.

The total volume introduced into Australia, reported under previous mandatory and/or voluntary calls for information, was between 100 and 1000 tonnes (NICNAS 2015).

Benzalkonium chloride and stearalkonium chloride (C18 alkyldimethylbenzylammonium chloride) have reported non-industrial use as excipients in pharmaceutical products.

No specific Australian use, import, or manufacturing information has been identified for the other chemicals in this group.

International

The following international uses have been identified through the:

- Consumer Product Information Database (DeLima Associates)
- European Union (EU) Registration, Evaluation and Authorisation of Chemicals (REACH)
- European Commission Cosmetic Ingredients & Substances (CosIng) database
- Substances in Preparations in Nordic countries (SPIN) database
- United States Environmental Protection Agency (US EPA)
- Chemical and Product Categories database (CPCat)
- Cosmetic ingredient reviews (CIR 1989; CIR, 2003; CIR 2008).

C12 alkyldimethylbenzylammonium bromide; benzalkonium chloride; and hydrogenated tallow, C12-C14, C12-C16, C12-C18, C14 and C18 alkyldimethylbenzylammonium chlorides are listed in the Compilation of Ingredients Used in Cosmetics in the United States (Personal Care Products Council 2011) indicating use in 1, 101, 101, 101, 101, 101, 7 and 279 cosmetics products, respectively.

C12 alkyldimethylbenzylammonium bromide; benzalkonium chloride; and coco, hydrogenated tallow, tallow, C8-C18, C12-C14, C16, C18, C12 and C14 alkyldimethylbenzylammonium chlorides have reported use as preservatives, antimicrobial agents, surfactants and antistatic agents in personal care products including:

- hair and skin care products such as hair conditioner (1–7%)
- baby products (0.03–0.1%)
- makeup (0.1%) and nail care products (0.01–0.1%)
- fragrance products (0.08–0.1%)
- oral hygiene products (0.03%)
- personal hygiene products e.g., deodorant (0.1%)
- liquid hand soap (0.1–1%) and hand sanitisers (wipes 0.01–1%).

Benzalkonium chloride, and coco, hydrogenated tallow, C8-C18, C12-C18, C14, C12-C14, C18 and C12 alkyldimethylbenzylammonium chlorides, have reported uses in domestic products including:

- domestic cleaning products such as, cleaning liquids (0.2–20%) sprays and powders (7.95%); multipurpose cleaners (<0.1– 0.62%), liquid detergents (6.25%) and fabric softener (1–5%)
- aerosol insect sprays (0.008%)
- pool care products (5–32%)
- pet care products (0.03%–1%)
- car care products
- paints, lacquers and varnishes
- adhesives, fillers and lubricants.

Benzalkonium chloride (CAS 8001-54-5), and hydrogenated tallow, C8-C18, C12-C18, C12-C16, C7-C17), C12-14, C16, C18, C12 and C14 alkyldimethylbenzylammonium chlorides have reported use in commercial cleaning products at concentrations of 0.1–10%, as process regulators and surface treatments.

Benzalkonium chloride, and coco, hydrogenated tallow, C8-C18, C12-C18, C16-C18, C12-C16, C10-C16, C12-C14, C16, C18, C12 and C14 alkyldimethylbenzylammonium chlorides have reported site limited use in the manufacture of building materials, paper products, textiles and chemical products.

Tallow, C10-C16, C12-C16, C16, C12 and C14 alkyldimethylbenzylammonium chlorides have a reported site limited use in oil and gas drilling including as components of hydraulic fracturing products.

Many of these chemicals in this group (CAS 7281-04-1, 139-08-2, 139-07-1, 122-18-9, 8001-54-5, 63449-41-2, 61789-71-7, 68391-01-5, 68424-85-1, 85409-22-9, 61789-72-8, 68989-00-4, 68607-20-5, 61789-75-1, 122-19-0) have non-industrial uses in pesticides and biocides.

Benzalkonium chloride, and coco, C8-C18, C12-C16, C10-C16, C12-C14, C18 and C12 alkyldimethylbenzylammonium chlorides have non-industrial uses in the manufacture of food, beverages and pharmaceutical products.

Existing Australian regulatory controls

AICIS

No specific controls are currently available for these chemicals in this group.

Public

Chemicals in this group are covered by the generic entries for quaternary ammonium compounds in Schedule 5 of the Poisons Standard as follows:

‘QUATERNARY AMMONIUM COMPOUNDS in preparations containing 20 per cent or less of quaternary ammonium compounds **except**:

a) when separately specified in these Schedules;
b) dialkyl or dialkoyl quaternary ammonium compounds where the alkyl or alkoyl groups are derived from tallow or hydrogenated tallow or similar chain length (C16/C18) sources; or

c) in preparations containing 5 per cent or less of such quaternary ammonium compounds.'

Chemicals in this group are covered by the generic entries for quaternary ammonium compounds in Schedule 6 of the Poisons Standard as follows:

'QUATERNARY AMMONIUM COMPOUNDS **except**:

a) when separately specified in these Schedules;
b) when included in Schedule 5;
c) dialkyl or dialkoyl quaternary ammonium compounds where the alkyl or alkoyl groups are derived from tallow or hydrogenated tallow or similar chain length (C16/C18) sources; or
d) in preparations containing 5 per cent or less of such quaternary ammonium compounds.'

Two chemicals in this group have identified therapeutic uses in Australia. Benzalkonium chloride is only for use in topical medicines for dermal application and nasal sprays at a maximum concentration of 5%. Stearalkonium chloride is only for use in topical medicines for dermal application (TGA 2022).

Workers

Several chemicals (CAS Nos. 8001-54-5, 63449-41-2, 61789-71-7, 68391-01-5, 68424-85-1, 85409-22-9) in this group are listed on the HCIS with the following classifications (SWA HCIS):

- Acute Toxicity – Category 4; H302 (Harmful if swallowed)
- Acute Toxicity – Category 4; H312 (Harmful in contact with skin)
- Skin Corrosion – Category 1B; H314 (Causes severe skin burns and eye damage)

No exposure standards are available for chemicals in this group in Australia.

International regulatory status

Exposure standards

No international exposure standards are available for chemicals in this group.

Canada

Four chemicals in this group (CAS Nos. 8001-54-5, 61789-71-7, 68391-01-5, 68424-85-1), are listed on the Health Canada List of prohibited and restricted cosmetic ingredients (The Cosmetic Ingredient "Hotlist") with the following conditions of use:

- as a preservative (i.e. benzalkonium chloride with chain lengths ≤14 C) at a concentration of 'up to 0.1%', and
- as a conditioning agent in rinse-off hair care products, (i.e. benzalkonium chloride with chain lengths ≥16 C) at a concentration of 'up to 3%' (Canadian Cosmetic Ingredient Hotlist 2019).

European Union

Six chemicals in this group (CAS Nos. 8001-54-5, 63449-41-2, 68424-85-1, 68391-01-5, 61789-71-7, 85409-22-9) are listed on the EU Cosmetic Regulation 1223/2009 Annex V (list of preservatives allowed in cosmetic products) with the maximum concentration in ready-for-use preparations being '0.1% as benzalkonium chloride'.

Five chemicals in this group (CAS Nos. 63449-41-2, 68424-85-1, 68391-01-5, 61789-71-7, 85409-22-9) are listed under 'benzalkonium chloride, bromide and saccharinate' in EU Cosmetic Regulation 1223/2009 Annex III (list of substances which cosmetic products must not contain except subject to the restrictions laid down) with the maximum concentration allowed in rinse-off hair products being '3%' (as benzalkonium chloride). Furthermore, the concentration of benzalkonium chloride, bromide and saccharinate with an alkyl chain of C14, or less must not exceed 0.1% (as benzalkonium chloride) in the final product.

New Zealand

Chemicals in this group are covered by a group entry for 'Benzalkonium Chloride, bromide and saccharinate' in the New Zealand Cosmetic Products Group Standard—Schedule 7: Preservatives cosmetic products may contain with restrictions—with a maximum authorised concentration of 0.1% (calculated as benzalkonium chloride).

Chemicals in this group are covered by a group entry for 'Benzalkonium Chloride, bromide and saccharinate' in the New Zealand Cosmetic Products Group Standard—Schedule 5: Components cosmetic products must not contain except subject to the restrictions and conditions laid down with a maximum authorised concentration in the finished cosmetic product of 3% for 'Rinse-off (head) care' products and 0.1% for other products. The concentration of benzalkonium chloride and bromide with an alkyl chain of C14, or less must not exceed 0.1% (as benzalkonium chloride) in the final product.

Asia

Chemicals in this group are covered by a group entry for 'Benzalkonium Chloride, bromide and saccharinate' in the ASEAN Cosmetic Directive Annex VI Part 1 List of preservatives allowed for use in cosmetic products–with a maximum authorised concentration being 0.1%.

Five chemicals in this group (CAS Nos. 63449-41-2, 68424-85-1, 68391-01-5, 61789-71-7, 85409-22-9) in this group are listed under 'benzalkonium chloride, bromide and saccharinate' in the ASEAN Cosmetic Directive Annex III Part 1 List of substances which cosmetic products must not contain except subject to restrictions and conditions laid down with a maximum authorised concentration in the finished cosmetic product of 3% for 'Rinse-off (head) care' products and 0.1% for other products. The concentration of benzalkonium chloride and bromide with an alkyl chain of C14, or less must not exceed 0.1% (as benzalkonium chloride) in the final product.

United States of America

The CIR Expert Panel concluded that Benzalkonium Chloride, at concentrations up to 0.1% free, active ingredient, is safe as a cosmetic ingredient as presently used (CIR 1989; CIR 2008)

Human exposure

Public

Available use information indicates that benzalkonium halides are widely used in cosmetic and domestic products. The formulations of similar products on the market in Australia are unlikely to be significantly different to those found internationally. Therefore, benzalkonium halides are expected to be found in a range of personal care and domestic products for use in Australia. The principal route of exposure will be dermal.

Several exposure assessments have been conducted for use of benzalkonium chloride in consumer products.

Based on dermal absorption of 10%, systemic exposure dosage (SED) was calculated for a range of consumer products including shampoo/hair conditioner (SED 0.044–0.176 mg/kg bw/day), body lotion (SED 0.016–0.128 mg/kg/day) and face cream (SED 0.062 mg/kg/day). These were based on concentrations of up to 2% in rinse off hair products and 0.1% in other products. Assuming simultaneous and maximum use of all products the SED was calculated as 0.5 mg/kg/day. Assuming average use SED was reduced to 0.1 mg/kg/day (Choi et al. 2017).

An estimated daily exposure of 269 mg/kg bw/day was calculated for coco alkyldimethylbenzylammonium chloride using a 'worst-case scenario' in which consumers use a set of cosmetic products containing the same preservative at maximum concentration of 0.1% and dermal absorption rate of 100%. From this an SED of 0.269 mg/kg bw/day was derived (Canavez et al. 2020).

Dermal and inhalation exposure to quaternary ammonium compounds following use of a trigger spray product were recently assessed. Based on data generated by the Antimicrobial Exposure Assessment Task Force II (AEATG II) which included occupational trigger spray and wipe exposure scenarios (average of 124 minutes of cleaning; average surface area cleaned of 176 m^2 (1897 square feet)), resulted in a dermal exposure to didecyldimethylammonium chloride (DDAC) of 2 mg (95^{th} percentile 4.78 mg) and an average air concentration of 0.0098 mg/m^3 (95^{th} percentile 0.0199 mg/m^3) (Osimitz and Droege 2021).

Health hazard information

Toxicokinetics

Alkyldimethylbenzylammonium salts are expected to be poorly absorbed (<10%) following oral and dermal exposure. Although skin absorption is expected to be low, absorption may occur through damaged skin (e.g. at corrosive concentrations).

In a toxicokinetic study, Sprague Dawley (SD) rats (n=10/sex/group) received C12-C16 alkyldimethylbenzylammonium chloride as a single oral dose of 10 or 50 mg/kg (radiolabelled); a single intravenous (i.v.) dose of 10 mg/kg (radiolabelled); or in food at a concentration of 100 ppm (non-radiolabelled) for 14 day, followed by a single oral dose of 10 mg/kg (radiolabelled, ^{14}C) on day 15. Residual ^{14}C in tissues was negligible after oral administration of radiolabelled test substance following both single and repeated dosing. Approximately 5–8% and 87–99% of orally administered test substance was excreted in the urine and faeces, respectively. Based on data from oral and intravenous

experiments, gastro-intestinal tract absorption is predicted to be low (~10%). The chemical was not readily metabolised with over 50% of the faecal radioactivity attributed to the parent compound. Four metabolites including hydroxy and hydroxyketo derivatives on the alkyl side chains were reported. The authors concluded that the metabolites were likely to have been produced by intestinal flora (ECHA 2015; Luz et al. 2020; REACHa; REACHf; REACHg).

In a toxicokinetic study conducted according to OECD TG 417, SD rats (n=3/sex/time/group) received 50 or 200 mg/kg bw (orally) of radiolabelled C8-18 alkyldimethylbenzylammonium chloride. Approximately 3–4% of orally administered test substance was excreted in the urine and approximately 4% was recovered in bile indicating low oral bioavailability. After 24 hours, 70–80% of the test compound was excreted, primarily in faeces. Following a single oral dose of 50 mg/kg bw, radioactivity levels were below the limit of quantification at all timepoints and in all organs except for the liver and intestines. Following a single oral dose of 200 mg/kg bw radioactivity levels were highest in the intestines, and trace levels were reported in abdominal fat, heart, kidney, liver, lung, lymph nodes and pancreas (REACHa).

In a toxicokinetic study, SD rats (n=3/males/group) received 250 mg/kg benzalkonium chloride as a single oral dose. Four animal mortalities occurred prior to designated time of sacrifice (1, 2, 4, 8 or 24 hours) and were replaced with additional animals. Clinical signs of toxicity, including respiratory distress, shortly after treatment were considered indicative of the treatment being aspirated into the animal's lungs. These animals were shown to have higher blood, lung, liver and kidney concentrations of benzalkonium chloride (Xue et al. 2004).

In a dermal absorption study conducted according to OECD TG 428, human skin membranes, were treated with 0.030% or 0.300% benzalkonium chloride. The mean absorbed dose was 3.20% and 5.32% of the applied dose, respectively (REACHa; REACHf; REACHg).

Acute toxicity

Oral

Based on the available data and read across from group members, chemicals in this group have moderate acute oral toxicity, warranting hazard classification.

Several chemicals (CAS Nos. 8001-54-5, 63449-41-2, 61789-71-7, 68391-01-5, 68424-85-1, 85409-22-9) in this group are classified as hazardous with the hazard statement 'harmful if swallowed' in the HCIS (Safe Work Australia). The majority of reported LD50 values are consistent with this classification.

The reported oral lethal doses (LD50s) in rats were:

- 240–525 mg/kg bw for benzalkonium chloride (CIR 1989; Danish EPA 2001, NICNAS 2015; RTECS, Świercz et al. 2008)
- 525 mg/kg bw for C12-C18 alkyldimethylbenzylammonium chloride (CIR 1989)
- 358–795 mg/kg bw for coco alkyldimethylbenzylammonium chloride (ECHA 2015REACHa)
- 304–344 mg/kg bw for C12-C16 alkyldimethylbenzylammonium chloride. Reported sublethal signs of toxicity included lethargy and diarrhoea (ECHA 2015; Luz et al. 2020; REACHf; REACHg).

The reported oral median lethal doses (LD50s) in mice were:

- 150–340 mg/kg bw for C14-C18 alkyldimethylbenzylammonium chloride (Danish EPA 2001)
- 242 mg/kg for C8-C18 alkyldimethylbenzylammonium chloride (Lee and Park 2019).

Dermal

Based on the available data and read across from group members, chemicals in this group have low to moderate acute dermal toxicity. Although chemicals in this group are poorly absorbed through intact skin, application at corrosive concentrations (see **Corrosion/Irritation** section) resulting in absorption following local skin damage should be considered harmful, warranting hazard classification.

Several chemicals (CAS 8001-54-5, 63449-41-2, 61789-71-7, 68391-01-5, 68424-85-1, 85409-22-9) in this group are classified as hazardous with the hazard statement 'harmful in contact with skin' in the HCIS (Safe Work Australia).

The median lethal doses (LD50s) in rats were:

- 930 mg/kg bw for benzalkonium chloride when applied at a concentration of 82.26% (NICNAS 2015)
- 2848 mg/kg bw for C12-16 alkyldimethylbenzylammonium chloride when applied undiluted (ECHA 2015; NICNAS 2015)
- 2300 mg/kg bw, for C12-C18 alkyldimethylbenzylammonium chloride when applied undiluted (NICNAS 2015)
- 1420 mg/kg bw for C14-C18 alklydimethylbenzylammonium chloride (Danish EPA 2001).

The median lethal doses (LD50) in rabbits were:

- 2730–3413 mg/kg bw for C12-C16 alkyldimethylbenzylammonium chloride when applied undiluted (ECHA 2015; Luz et al. 2020; REACHf; REACHg).

Inhalation

Based on available data and read across from group members chemicals in this group have high acute inhalation toxicity. Chemicals in this group are not expected to be volatile and inhalation exposure is expected to be limited to scenarios where aerosols may be formed.

In an acute inhalation toxicity study, female Wistar rats (5/concentration) were exposed to a single dose (0.037 or 0.053 mg/L, head/nose inhalation, 4 hrs); or a single or repeated dose (3 days) at 0.028 mg/L (6 hours/day) of aerosol benzalkonium chloride. In the high dose group (52.84 mg/m^3) 40% of animals did not survive treatment and the median lethal concentration—LC50 was determined to be approximately 0.053 mg/L. After both single and repeated exposure, relative lung weight, total protein, lactate dehydrogenase (LDH) activity in bronchoalveolar lavage fluid (BALF) and BALF interleukin-6 (IL-6) and immunoglobin E (IgE) concentrations were increased indicating a strong inflammatory response (Świercz et al. 2008).

In an acute inhalation toxicity study, SD rats (5/sex/concentration) were exposed to a single dose (0, 0.17, 0.24 or 0.34 mg/L, aerosol, whole body, 4 hrs) of a mixture of C12-C16 alkyldimethylbenzylammonium chloride 40% w/v) and dicocodimethylammonium chloride (37.5% w/v). Mass median aerodynamic diameters (MMADs) and geometric standard deviation (GSD) of the particles were 0.8–1.9 µm and 0.8–3.5, respectively. The

LC50 was 0.25 mg/L air. Consistent with inhalation of an irritant aerosol, animals were reported to partially close eyes and exhibited exaggerated respiratory movements. The animals that died had increased relative lung weights, congestion in the lungs and gas filled stomach and intestines. A dose dependent increase in the severity of histopathological changes was observed with focal alveolar wall necrosis occurring at the highest dose. In animals that survived treatment histopathological lung changes included focal alveolitis and bronchiolitis (REACHa).

In an acute inhalation toxicity study in rats an LC50 of >0.054 to < 0.51 mg/L was reported for alklydimethylbenzylammonium chloride (unspecified). No further details were available (US EPA 2017; Luz et al. 2020)

Observation in humans

Following ingestion of higher concentrations of benzalkonium chloride, mild to severe caustic burns on the lips, tongue, mouth, throat, hypopharynx, oesophagus, and stomach can occur. Hypersalivation, vomiting, haematemesis (vomiting blood), diarrhoea and confusion can also occur. In severe cases, there could be hypotension, shock, respiratory paralysis, convulsions, coma, and cardiorespiratory arrest (IPCS 1999).

Benzalkonium chloride (11%) was mistakenly given orally to two and a half month old twins for candidiasis. Both children developed irritability, fever, anorexia, dehydration, cough, swelling around the mouth, drooling and numerous oral and pharyngeal lesions within 24 hours. One twin also developed chemical pneumonitis (IPCS 1999).

In separate incidences, one patient survived and one elderly patient died following accidental ingestion of 10% benzalkonium chloride (Choi et al. 2017).

Corrosion/Irritation

Skin irritation

Although limited information is available for some group members, based on the available data, chemicals in this group are considered to be corrosive to skin warranting hazard classification. Skin irritation has been reported at concentrations above 0.1% (CIR 1989; ECHA 2015).

Several chemicals (CAS 8001-54-5, 63449-41-2, 61789-71-7, 68391-01-5, 68424-85-1, 85409-22-9) in this group are classified as hazardous with the hazard statement ‘Causes severe skin burns and eye damage’ in the HCIS (Safe Work Australia).

Undiluted C12-C16 alkyldimethylbenzylammonium chloride was applied to both abraded and intact rabbit skin (n = 6) under occlusive conditions for 24 hours. Severe erythema and oedema were observed in all the test animals (REACHf).

An aqueous solution of coco alkyldimethylbenzylammonium chloride at a concentration of 50% was applied to rabbit skin under occlusive conditions. After 1 hour, evidence of skin necrosis was reported (REACHa).

An aqueous solution of benzalkonium chloride was applied at a concentration of 13 or 50% to the skin of mice (n=48/dose). Treatment resulted in death of 9/48 and 20/48 mice in the low and high dose treatment groups, respectively. Surviving mice developed skin necrosis and alopecia (REACHd).

An aqueous solution of benzalkonium chloride was applied at a concentration of 0.1, 1 and 5% to the skin of female albino guinea pigs (number and strain not available) under occlusive conditions for 24 hours. After 24 hours skin samples were excised and examined microscopically. Exposure to the 1% and 5% solution resulted in spotted areas of necrosis and total necrolysis of the epidermis, respectively (CIR 1989).

In a 3 month study, skin irritation potential of benzalkonium chloride (1% or 0.1%) was evaluated in rats (n=40). Hyperaemia and necrotic changes were reported following 1.5–2 months exposure at 1% (CIR 1989).

Eye irritation

Based on the available data, chemicals in this group are considered to cause serious eye damage. Eye irritation has been reported at various concentrations depending on the exposure period and method of detection.

Several chemicals (CAS 8001-54-5, 63449-41-2, 61789-71-7, 68391-01-5, 68424-85-1, 85409-22-9) in this group are classified as hazardous with the risk phrase ‘Causes severe skin burns and eye damage’ in the HCIS (Safe Work Australia).

In 3 Draize tests, C8-C18 alkyldimethylbenzylammonium chloride, C12-C16 alkyldimethylbenzylammonium chloride or coco alkyldimethylbenzylammonium chloride were applied to the eyes of rabbits (n=3) at a concentration of 10%, 50% and at an unspecified concentration, respectively. The severe irritation/corrosion was not reversible within the study periods (21 days, 72 hours and 72 hours, respectively) (REACHa; REACHd).

In a Draize test, C18 alkyldimethylbenzylammonium chloride was applied to the eyes of New Zealand White (NZW) rabbits (n = 7) at a concentration of 0.002%. Mild conjunctival hyperemia was reported 4 hours after treatment, effects were reversible within 24 hours (REACHd).

In an acute eye irritation/corrosion study, C8-C18 dimethylbenzylammonium chloride was applied to the eyes of rabbits (n=3) at a concentration of 0.1%. After 1 hour moderate effects on the conjunctivae were reported; however, these effects were reversible within 24 hours (REACHa).

In an acute corneal epithelial toxicity test, C16 dimethylbenzylammonium chloride (was applied to the eyes of anaesthetised Japanese White rabbits for 60 seconds. A significant reduction in corneal transepithelial electrical resistance (TER) was reported at 0.005 and 0.01% indicating that the chemical can be considered irritating to the eye at these concentrations (REACHd).

Several eye irritation studies were available for various concentrations of benzalkonium chloride in rabbits. The chemical was determined not to be an ocular irritant following single instillation of concentrations up to 0.1% in NZW rabbits. Results following repeated application were mixed. In some studies concentrations <0.5% did not cause damage, whereas in other studies concentrations as low as 0.01% caused damage. Notably, different methods for assessing ocular damage were utilised (Choi et al. 2017).

In separate studies, corneal damage was observed at concentrations ranging from 0.0001 to 0.01%. Exposure periods ranged from 2 min (0.01%) to 110 min (0.0001%) (CIR 1989).

Respiratory Irritation

Given the skin/eye irritation properties and data from acute inhalation studies, chemicals in this group are expected to be respiratory irritants.

In an acute inhalation study, female BALB/cJ mice (7–8/dose) were exposed to saline aerosol for 15 minutes to establish a baseline, followed by benzalkonium chloride aerosol at 0.049, 0.19, 0.57, 1.8, 5.3 and 19 mg/m^3 (head only) for 30 minutes. Respiratory parameters including respiratory rate (breaths per min.), time from end of inspiration until the beginning of expiration (time of brake, msec), time from end of expiration until beginning of the next inspiration (time of pause, msec), tidal volume (mL) and mid-expiratory flow rate (mL/sec) were recorded. Following a 16-hour recovery period, bronchoalveolar lavage fluid (BALF) was collected to assess lung irritation. A concentration dependent reduction in tidal volume and increase in respiration rate, indicating pulmonary irritation, and an increase in the number of inflammatory cells (neutrophils and alveolar macrophages) in BALF was reported. At the highest concentration the increase in breathing frequency was counteracted by an increased ‘time of pause’. An increase in ‘time of break’, a marker of sensory irritation, was not reported. The authors reported the no observed effect level (NOEL) as less than 0.049 mg/m^3 (Larsen et al. 2012).

In other acute inhalation toxicity studies (see **Acute inhalation toxicity** section) inflammation of the lung was observed. An increase in the severity of histopathological changes in the lungs was observed in animals that died. Overall, there is evidence that the mechanism of toxicity was corrosivity warranting classification.

Observation in humans

Depending on concentration, chemicals in this group may cause mild to severe burns of the skin, conjunctivae and mucous membranes.

Benzalkonium chloride has been reported to be a severe human skin and eye irritant, and corrosivity has been reported with diluted solutions (1:2000, 1:5000, 1:20000). Accidental spillage of concentrated solution of benzalkonium chloride on the skin can produce corrosive skin lesions with deep necrosis and scarring (IPCS 1999).

Primary irritant dermatitis was reported in all patients (n = 13 and 12) tested with 10% benzalkonium chloride (CIR 1989).

In another study, 200 volunteers were treated with 0.5% benzalkonium chloride in a patch test for 48 hours. A mean irritation score of 3 (erythema, homogenous) was reported (CIR 1989).

Sensitisation

Skin sensitisation

Based on the weight of evidence, chemicals in this group are not considered to be skin sensitisers. Rare clinical reports of skin sensitisation appear more common in individuals with damaged skin barriers (see **Observation in humans** section).

In some instances, clinical reports of skin sensitisation may result from misinterpretation of skin irritation (see **Skin irritation** section) or the effects on skin biota as skin sensitisation.

The sensitisation potential of benzalkonium chloride (CAS No. 8001-54-5) was previously evaluated by NICNAS. Although positive reactions were reported in some animal, epidemiological and case studies, given the widespread exposure to the chemical, and evidence of sensitisation in relatively small proportions of individuals, benzalkonium chloride was not considered a skin sensitiser (NICNAS 2005).

In 2 guinea pig maximisation tests, alkyldimethylbenzylammonium chloride (unspecified) was reported as non-sensitising. Further details were not available (Luz et al. 2020).

In silico

Chemicals in this group have structural alerts (α activated benzyls) for protein binding based on the mechanistic profiling functionality of the Organisation for Economic Co-operation and Development (OECD) QSAR Application Toolbox (OECD QSAR Toolbox). The knowledge based expert system Deductive Estimation of Risk from Existing Knowledge (DEREK) Nexus version 6.0.1 was utilised to predict the skin sensitisation potential of representative chemicals in this group. Although alerts for skin sensitisation by quaternary ammonium cations (hapten acting through ion pair formation) were reported, insufficient data were available to make an EC3 prediction and the confidence level of the prediction was equivocal.

The molecular initiating event (MIE) leading to dermal sensitisation in the OECD AOP for dermal sensitisation is covalent binding of a relatively low molecular weight electrophilic chemical with key nucleophilic sites of skin proteins. Given their chemical structures (i.e. relatively large and sterically hindered), chemicals in this group are unlikely to bind with proteins in this manner (Osimitz and Droege, 2021).

Respiratory sensitisation

Limited data are available.

Benzalkonium chloride has been reported to cause bronchoconstriction in asthmatic patients (Beasley et al. 1987; Lee and Kim 2007; Miszkiel et al. 1988). The mechanisms leading to this response are not well elucidated but have been reported to be caused following a combination of mast cell activation and stimulation of peripheral and central neural pathways (Miszkiel et al. 1988).

Observation in humans

In a single centre retrospective review of patch test data collected for 7390 patients between 2003 and 2019, 1.5% were reported to have a positive reaction to 0.1% benzalkonium chloride, with 0.3% (n=21) considered clinically relevant. Common exposure sources included ophthalmic drops, topical antiseptic, cosmetics, disinfectant, hand sanitiser and hand washes. The authors noted a ‘dramatic increase’ in the number of positive reactions since 2017 (Dear et al. 2021).

In a retrospective review of patch test data collected for 615 patients between June 2015 and October 2016, 0.1% aqueous benzalkonium chloride, 32% were reported to have tested positive (10% with strong or extreme reactions) (Isaac and Scheinman 2017).

In a retrospective review of patch test data collected between 2000–2012, the sensitisation potential of aqueous 0.1% benzalkonium chloride was assessed in 8448 unique patients. Positive patch test and irritation results were reported as 8.8% and 1.3% of patients,

respectively. These values were comparable to those previously reported – 5.5% and 1.5% from 1998-2000 (1324 patients), 8.3% and 1.6% from 2001-2005 (3854 patients) and 8.8 and 0.7% from 2006-2010 and 3115 patients) (Wentworth et al. 2016).

The sensitisation potential of benzalkonium chloride was investigated in a human patch test in 2295 patients with suspected allergic contact dermatitis. Following exposure to 0.1% benzalkonium chloride 5.5% of patients were reported to have a positive reaction. The irritation potential even at low concentrations may have contributed to false positives (Danish EPA 2001; NICNAS 2005).

In a separate study, 2.1% of patients (n = 60 of 2806) with eczema were reported to have positive reactions following a patch test with 0.1% benzalkonium chloride in petrolatum (CIR 1989; NICNAS 2005).

In a sensitisation study, a moisturising cream containing 0.13% benzalkonium chloride was applied under occlusive conditions to the back of 150 volunteers. During weeks 1–3, patches were applied Monday, Wednesday and Friday and removed after 24 hours, for a total of 9 treatments. After a 2 week non-treatment period, two challenge patches were placed adjacent to the induction site for 48 hours. No positive reactions were reported. In a separate study conducted using the same protocol, it was reported that 0.13% benzalkonium chloride did not induce positive reactions in 155 volunteers (CIR 1989).

Occupational asthma has been reported after prolonged exposure to benzalkonium chloride (IPCS 1999).

Repeat dose toxicity

Oral

Although limited information is available for some group members, chemicals in this group are not considered to cause serious damage to health from repeated oral exposure at doses below acutely toxic doses. Effects including reduced food consumption and consequently, body weight may be attributed to local gastrointestinal irritation/corrosion rather than systemic effects.

In a combined chronic toxicity/carcinogenicity study, SD rats (n=50/sex/dose) received alkyldimethylbenzylammonium chloride (unspecified) in feed at 0, 300, 1000 or 2000 ppm (equivalent to 13, 44 or 88 mg/kg bw/day and 17, 57 or 116 mg/kg bw/day in male and female rats, respectively). A significant decrease in mean body weight was reported in high dose male rats between weeks 1–26 (and sporadically between week 27–104), and high dose female rats between weeks 1–60. No treatment related effects on clinical chemistry, haematology or urinalysis parameters were reported. Based on reduced body weight and weight gain NOAELs of 44 and 57 mg/kg bw/day was reported for females and males, respectively (Luz et al. 2020, US EPA 2017).

In a combined chronic toxicity/carcinogenicity study conducted according to OECD TG 453, SD rats (n=60-70/sex/dose) received alkyldimethylbenzylammonium chloride (unspecified) in feed at 0, 1000, 2000 or 4000 ppm (equivalent to 24, 48 97 mg/kg bw/day and 29, 58 or 119 mg/kg bw/day in male and female rats, respectively). No treatment related effects on clinical chemistry, haematology or urinalysis or organ weight parameters were reported.

As reported in similar studies, reductions in food consumption and mean body weight were reported in the high dose treatment groups. An NOAEL of 48 and 58 mg/kg bw/day was reported for female and male rats, respectively (Luz et al. 2020).

In a 78 week chronic toxicity/carcinogenicity study, CD-1 mice (n=60/sex/dose) received alkyldimethylbenzylammonium chloride (unspecified) in feed at 100, 500 or 1500 ppm (equivalent to 14.9, 73.4 or 229.3 mg/kg bw/day and 17.8, 92.1 or 288.6 mg/kg bw/day in male and female mice, respectively). No treatment related effects on food consumption, organ weight, haematology parameters or histopathological findings were reported. Reductions in mean body weight and weight gain were reported in the high dose treatment groups. Based on reduced body weight and weight gain NOAELs of 73.4 and 92.1 mg/kg bw/day were reported for females and males, respectively (Luz et al. 2020; US EPA 2017).

In a 90 day oral toxicity study conducted according to OECD TG 408 SD rats (n = 15/sex/dose) received 0, 100, 500, 1000, 4000 or 8000 ppm C12-C16 alkyldimethybenzylammonium chloride in diet (equivalent to 0, 6, 31 and 62 mg/kg bw/day (males) and 0, 8, 38 and 77 mg/kg bw/day (females)). Corresponding daily intakes in the 4000 and 8000 ppm treatment groups were not calculated due to mortalities (80 and 100%, respectively). In the 4000 ppm group 12/15 males and 11/15 females died or were sacrificed in a moribund condition. Decreased body weight and food consumption were reported in animals in the 1000 (males only), 4000 and 8000 ppm treatment groups. Histopathological changes included mucosal cells degeneration of the villus tips of the small intestine and cecum, submucosal oedema of the stomach hepatocellular atrophy. NOAELs of 31 and 38 mg/kg bw/day were reported for male and female rats, respectively (REACHf).

In a 90 day oral toxicity study conducted according to OECD TG 408 SD rats (n = 10/sex/dose) received 0, 800, 2000 or 5000 ppm alkyldimethylbenzylammonium chloride (unspecified) in diet (equivalent to 0, 28, 68 or 166 mg/kg bw/day (males) and 0, 30, 74, 188 mg/kg bw/day (females)). Decreased body weight and food consumption were reported in the high dose treatment groups (5000 ppm). No stomach or gastrointestinal tract irritation was reported, and effects were attributed to the palatability of the test item. NOAELs of 166 and 188 mg/kg bw/day were reported for male and female rats, respectively (Luz et al. 2020).

In a 12 week oral toxicity study, male SD rats (n = 10/vehicle/dose) received 50 or 100 mg/kg bw/day benzalkonium chloride (1:20 or 1:10 dilutions of 10% benzalkonium chloride solution in water or milk). Two mortalities occurred in the high dose (vehicle unspecified) group on days 62 and 69. Body weights were significantly reduced in the high dose (water) treatment group. No haematological or histopathological changes were reported (CIR 1989).

In a 1 year oral toxicity study, beagle dogs (4/sex/dose) received 0, 120, 400 or 1200 ppm alkyldimethylbenzylammonium (unspecified) in diet (equivalent to 0, 3.79, 13.1 or 33.8 mg/kg bw/day (males) and 0, 3.67, 14.6 or 38.6 mg/kg bw/day (females). Reduced body weight gain was reported in the 400 and 1200 ppm female and 1200 ppm male treatment groups. Food consumption was reduced in high dose treatment groups for the entire study period. A NOAEL of 120 ppm and LOAEL of 400 ppm were reported based on reduced weight gain (US EPA 2017).

In a 52 week oral toxicity study, beagle dogs (3/vehicle/dose) received 12.5, 25 or 50 mg/kg bw/day benzalkonium chloride (10% solution in water or milk). One animal in the high dose (water) and 3 animals in the mid dose (water) did not survive the treatment period.

No significant changes in haematological or urine parameters were reported over the study period. Irritation of the small intestine and stomach was reported for animals receiving the treatment diluted in water (CIR 1989).

Dermal

Although limited information is available, as dermal absorption is low, systemic effects from percutaneous absorption through intact skin are not likely (see **Toxicokinetics** section). A range of dermal effects such as erythema and oedema have been noted at the treatment sites following repeated dermal application.

In a 90 day dermal toxicity study, alkyldimethylbenzylammonium chloride (unspecified) was applied to the skin of SD rats (n=15/sex/dose) at 0, 2, 6 or 20 mg/kg bw/day for 6–8 hours/day, 5 days/week for 13 weeks. Higher doses (60, 120 and 200 mg/kg bw/day) were tested in a preliminary study; however the 20 mg/kg bw/day dose was found to be the highest dose that did not produce excessive skin irritation. A significant dose dependent decrease in reticulocytes was reported in female rats, but was not considered to be treatment related based on similar decreases in control male rats and no evidence of anaemia. Hyperkeratosis was reported in the treated skin of high dose female rats, but similar lesions were reported in all male rats (including controls). A NOAEL of 20 mg/kg bw/day was reported for both male and female rats (Luz et al. 2020; US EPA 2017).

In a 20 day dermal toxicity study in rabbits, C14 alkyldimethylbenzylammonium chloride (1/sex/dose; 0.8 or 3.2 mg/kg bw/day) was diluted with water and applied to the skin under occlusive conditions. Mild erythema and oedema were reported at both test concentrations during the treatment period. The NOAEL for systemic effects and lowest observed adverse effect level (LOAEL) for dermal irritation was reported to be 3.2 and 0.8 mg/kg bw/day, respectively (REACHf).

Inhalation

In a 14 day inhalation toxicity study, Fischer 344 rats (5/sex/dose) were exposed to benzalkonium chloride aerosol at 0.8, 4 or 20 mg/m^3 for 6 hours/day for 14 days. Additional 2 and 4 week recovery groups were included at each dose. MMADs and GSD of the particles were 1.09-1.61 µm and 1.51-2.00, respectively. Nasal discharge was reported in all treatment groups. In the high dose group, deep breathing and rales were reported in 1 and 5 male rats, respectively. Body weight in the mid and high dose male and female groups were significantly reduced. Significant differences in haematology and blood biochemistry parameters, and changes in absolute and relative organ weights (including the lung, liver and spleen) were reported in mid and high dose treatment groups.

Degeneration and regeneration of terminal bronchiolar epithelium, smooth muscle hypertrophy of bronchioloalveolar junction, hypertrophy and hyperplasia of mucous cells in the bronchi or bronchiole and cell debris in the alveolar lumens were reported following histological examination in mid and high dose male and high dose female rats.

Consistent with nasal cavity irritation, ulceration with suppurative inflammation, squamous metaplasia and erosion with necrosis were observed in the respiratory and transitional epithelium across treatment groups. Atrophy of olfactory epithelium was seen in the high dose group only. Some of these changes, including hypertrophy and hyperplasia of mucous cells in respiratory epithelium, infiltration of submucosa, and squamous metaplasia in transitional epithelium, were also reported after a 4 week recovery period.

The authors considered the effects to be reversible responses to oxidative damage. Based on adverse effects at all doses, the authors considered the NOAEC to be less than 0.8 mg/m^3 (Choi et al. 2020).

An occupational exposure limit (OEL) was recently derived for total quaternary ammonium compounds including C12-C16 alkyldimethylbenzylammonium chloride, based on irritant toxicity, developmental and reproductive toxicity, and modified existing health based exposure limits (HBEL). A long term worker derived no effect level (DNEL) of 3.96 mg/m^3 was reported for C12-C16 alkyldimethylbenzylammonium chloride based on an NOAEL of 47.5 mg/kg bw/day, a point of departure (PoD) after route to route extrapolation of 23.75 mg/m^3 (NOAEC) and an uncertainty factor of 6× (intraspecies 3× and interspecies toxicokinetic 2×). While several OELs were calculated an OEL of 0.1 mg/m^3 (lowest DNEL/uncertainty factor) was selected and considered to be protective of all potential identified adverse health outcomes (Dotson et al. 2020).

Genotoxicity

Although data is limited for some chemicals in this group, chemicals in this group are not considered to have genotoxic potential.

Negative results were reported in the following in vitro genotoxicity studies:

- In a bacterial reverse mutation assay (OECD TG 471), *Salmonella typhimurium* TA 98, 100, 102, 1535 and 1537 were treated with C12-C16 alkyldimethylbenzylammonium chloride. Negative results were reported with and without metabolic activation at concentrations up to 50 µg/plate (REACHf).
- In a bacterial reverse mutation assay (OECD TG 471), *S. typhimurium* TA 98 and 100 were treated with C16 alkyldimethylbenzylammonium chloride. Negative results were reported with and without metabolic activation at concentrations up to 10 µg/plate (REACHd).
- In an in vitro mammalian chromosome aberration assay (OECD TG 473), human lymphocytes were treated with C12-C16 alkyldimethylbenzylammonium chloride. Negative results were reported with and without metabolic activation at concentrations up to 24 µg/mL (REACHf).
- Negative results were reported for C12-C16 alkyldimethylbenzylammonium chloride in a mammalian gene mutation assay in the hypoxanthine-guanine phosphoribosyl transferase (HGPRT) locus in Chinese hamster ovary (CHO) cells with and without metabolic activation at concentrations up to 100 and 65 µg/mL, respectively (REACHf).
- Negative results were reported benzalkonium chloride in an in vitro mammalian chromosome aberration assay in a pregnant Syrian golden hamster embryo cell line at concentrations up to 30 µM (Hikiba et al. 2005).
- Benzalkonium chloride was reported to induce repairable DNA damage in the *Escherichia coli* DNA polymerase A assay at concentrations of 0.1–1%. However, no mutagenic properties were reported (SCC 2000).

Negative results were reported for C12-C16 alkyldimethylbenzylammonium chloride in an in vivo micronucleus assay in rat bone marrow following a single oral dose of 400 mg/kg. Further details were not available (ECHA 2015; Luz et al. 2020).

Carcinogenicity

Although limited information is available for some group members, based on available data and negative genotoxicity data chemicals in this group are not expected to be carcinogenic.

In a combined chronic toxicity/carcinogenicity study (see **Repeat dose toxicity** section), SD rats (n=50/sex/dose) received alkyldimethylbenzylammonium chloride (unspecified) in feed at

0, 300, 1000 or 2000 ppm (equivalent to 13, 44 or 88 mg/kg bw/day and 17, 57 or 116 mg/kg bw/day in male and female rats, respectively) for 104 weeks. The incidence of non-neoplastic and neoplastic lesions was not increased in any tissue (Luz et al. 2020, US EPA 2017).

In a combined chronic toxicity/carcinogenicity study (see **Repeat dose toxicity** section) conducted according to OECD TG 453, SD rats (n=60–70/sex/dose) received C12-C16 alkyldimethylbenzylammonium chloride (unspecified) in feed at 0, 1000, 2000 or 4000 ppm (equivalent to 24, 48 97 mg/kg bw/day and 29, 58 or 119 mg/kg bw/day in male and female rats, respectively). No increase in the incidence of non-neoplastic and neoplastic lesions was reported (Luz et al. 2020).

In a 78 week chronic toxicity/carcinogenicity study (see **Repeat dose toxicity** section) CD-1 mice (n=60/sex/dose) received alkyldimethylbenzylammonium chloride (unspecified) in feed at 100, 500 or 1500 ppm (equivalent to 14.9, 73.4 or 229.3 mg/kg bw/day and 17.8, 92.1 or 288.6 mg/kg bw/day in male and female mice, respectively). Evidence of carcinogenicity was not reported (Luz et al. 2020, US EPA 2017).

In a lifetime dermal study, female Swiss mice (n=50/dose) and NZW rabbits (n=5/dose) were treated with benzalkonium chloride (8.5% or 17%, 2 applications/week). A significant decrease in survival rate was not reported in either species. Tumours and lesions were recorded weekly. While the treatment induced fibrosis, ulceration and inflammation, treatment did not result in tumour formation or systemic toxicity (Stenbäck 1977).

Reproductive and development toxicity

Although limited information is available for some group members, chemicals in this group are not expected to cause specific adverse effects on fertility or sexual function and development following exposure.

In a two generation reproduction toxicity study, SD rats (28/sex/dose) were administered C12-C16 alkyldimethylbenzylammonium chloride in feed at 300, 1000 or 2000 ppm (equivalent to 16–31, 51–102 and 100–188 mg/kg bw/day in male rats and 21–32, 67–106 and 139–198 mg/kg bw/day in female rats). Treatment/exposure duration was 19 weeks (from first pre-breed dose to F0 sacrifice), 25 weeks (from weaning to F1 sacrifice) and until weaning for the F0, F1 and F2 generations, respectively. In the F0 generation, exposure started 10 weeks prior to mating. The day of observed presence of sperm or a vaginal plug was recorded as day 0 of pregnancy. Selection of parents from the F1 generation occurred when pups were 28 days old; mating occurred 17–18 weeks after selection. Reduced body weights and food consumption were reported in some of the high dose (2000 ppm) treatment groups. Exposure did not affect any reproductive parameters. The NOAELs (systemic toxicity) for both the parental (F0 and F1) and offspring (F1 and F2) was reported as 51–102 and 67–106 mg/kg bw/day in male and female rats, respectively. The NOELs for reproductive toxicity were reported as 100–188 and 139–198 in male and female rats, respectively (Hostetler et al. 2021)

In a teratogenicity study, aqueous benzalkonium chloride (0, 25, 50, 100 or 200 mg/L) was instilled (1 mL/kg bw) in the vagina of female Wistar rats (n=6–8/dose) on day 1 of gestation. Animals were sacrificed on day 21 of gestation and foetuses were examined for viability and external malformations. Dose dependent reduction in the number of live foetuses and litter weights were reported in the 50, 100 and 200 mg/L treatment groups. While no visceral anomalies were reported, the incidence of minor sternal defects including absent or non-aligned sternebrae or decreased ossification were increased in the 100 and 200 mg/L treatment groups (Buttar 1985; CIR 1989; Danish EPA 2001).

In a developmental toxicity study, female SD rats (n=25/dose) received 0, 10, 30 or 100 mg/kg bw/day alkyldimethylbenzylammonium chloride (unspecified) by oral gavage on gestational days 6−15 (period of major organogenesis). Animals were sacrificed on gestational day 21. A decrease in body weight gain was reported in the mid dose treatment group. Food consumption was not consistently reduced. No treatment related effects on any litter parameters, foetal development or foetal malformations were reported. Study authors identified maternal and developmental NOAELs of 10 mg/kg bw/day and 100 mg/kg bw/day, respectively (Luz et al. 2020; US EPA 2017).

In a prenatal developmental toxicity study conducted according to OECD TG 414, female NZW rabbits (n=22/dose) received 0, 3, 10 or 30 mg/kg bw/day C12-C16 alkyldimethylbenzylammonium chloride (unspecified) by oral gavage on gestational days 6–28. Three animals in the high dose treatment group did not survive treatment. A transient decrease in body weight gain was reported in the high dose treatment group on treatment day 9–12. Gross pathological findings including oedema in the stomach mucosa and dilated intestines and gall bladder in some mid and high dose treated animals were reported. No treatment related effects on any litter parameters, foetal development or foetal malformations were reported. Study authors identified maternal and developmental NOAELs of 3 mg/kg bw/day and 30 mg/kg bw/day, respectively (Luz et al. 2020)

C18 alkyldimethylbenzylammonium chloride was applied topically at a concentration of 6.6% to pregnant rats on day 6–15 of gestation. Although adverse maternal reactions were reported, no embryotoxicity was detected (Danish EPA 2001).

Human health risk characterisation

Public

Several risk assessments have been conducted for use of benzalkonium chloride in consumer products.

The EU Scientific Committee on Cosmetology (SCC) determined that benzalkonium chloride, bromide and sacchrinate are safe for consumers when used at a maximum concentration of 3% in rinse off hair care products and 0.1% for all other uses. The NOAEL value used in the calculation of the Margin of Safety (MoS) was 30 mg/kg bw/day. An acceptable aggregate MoS of 372 was calculated based on daily bioavailability when used as preservatives and in intimate hygiene, non-rinse off hair and skin products, and rinse off hair products at these levels (daily product exposure and daily bioavailability of 27.6 g/kg bw/day and 0.141 mg/kg bw/day, respectively; SCC 2000). This value does not take into consideration aggregated exposure resulting from simultaneous use of all products (e.g. domestic cleaning products) containing the chemical.

Based on a systemic and dermal NOAEL of 20 mg/kg bw/day and SED for a range of consumer products including shampoo/hair conditioner (at 2%), body lotion and face cream (at 0.1%) (see **Human exposure – public** section), MoS values of 39 and >200 were calculated for maximum and average use respectively (Choi et al. 2017).

Using a NOAEL of 70 mg/kg/day, an SED of 0.269 mg/kg bw/day (see **Human exposure – public** section) an acceptable MoS of 260 was derived for use of coco alkyldimethylbenzylammonium chloride in cosmetic products (Canavez et al. 2020).

Using an NOAEL of 20 mg/kg bw/day, the estimated dermal human exposure to didecyl dimethyl ammonium chloride (DDAC) following use of a trigger spray cleaning product and a

level of concern (LOC) for dermal exposure of 10 (calculated using an interspecies uncertainty factor of 3× and an intraspecies uncertainty factor of 3×) an acceptable margin of exposure (MOE) of 364–800 was calculated for alkyldimethylbenzylammonium chloride at concentration of 0.04% in trigger spray cleaning product. Based on the OEL of 0.1 mg/m^3 (see **Repeat dose toxicity** section) and a LOC of <1 (calculated noting the OEL incorporates uncertainty factors) an acceptable MOE of 10 was reported for inhalation exposure to alkyldimethylbenzylammonium chloride in the trigger spray cleaning product (Osimitz and Droege 2021).

Indirect dermal exposure, for example from wearing clothes treated with laundry detergents and/or fabric softener, is not expected to be significant. Chemicals in this group are expected to bind to fabric and not be available to for local irritation effects when used as directed. Overuse of products (e.g. as a result of increased germaphobia) or use of multiple products (e.g. laundry liquid, fabric softener and disinfectant) resulting in increased concentrations of free benzalkonium halides may result in disrupted skin microbiome and/or skin irritation (Kumarasinghe et al. 2019; Robinson et al. 2017; Tian et al. 2021).

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