Australian Government
Department of Health
Australian Industrial Chemicals Introduction Scheme

Alkyl pyridinium surfactants

Evaluation statement

14 September 2021

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AICIS evaluation statement

Subject of the evaluation

Alkyl pyridinium surfactants

Chemicals in this evaluation

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Pyridinium, 1-tetradecyl-, bromide	1155-74-4
Pyridinium, 1-hexadecyl-, chloride, monohydrate	6004-24-6
Pyridinium, 1-dodecyl-, sulfate (1:1)	17342-21-1

Reason for the evaluation

The Evaluation Selection Analysis indicated a potential risk to human health.

Parameters of evaluation

A human health risk assessment for all identified uses of the chemicals.

These chemicals have been assessed as a group as they are structurally very similar and share the same use patterns.

Summary of evaluation

Summary of introduction, use and end use

There is currently no information about the use and volume of use for this group of chemicals in Australia.

Based on international use information, some of the chemicals in this group are used in cosmetic products, such as mouthwashes (up to 0.1%) and other oral hygiene products (up to 0.5%), skin lotions and creams (up to 0.2%), antiperspirant deodorants (up to 2.0%), and wet wipes (up to 0.064%). While other uses may also be regulated as therapeutic goods in Australia. A number of these chemicals are used in domestic cleaning products. These

chemicals also have reported use in various site-limited applications, including in the manufacture of other chemicals and materials.

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 irritation and eye damage.

Based on limited data for this group apart from one member, cetylpyridinium chloride (CAS No. 123-03-5), alkyl pyridinium surfactants are expected to have moderate acute oral toxicity (median lethal dose (LD50) = 50–560.3 mg/kg bw), low acute dermal toxicity (LD50 >1000 mg/kg bw), and high acute inhalation toxicity (median lethal concentration (LC50) = 0.054–0.51 mg/L; 4 hours) in rats.

As cationic surfactants, chemicals in this group are expected to be skin and eye irritants. Skin irritation was observed in rabbits exposed to cetylpyridinium chloride, and positive results were seen in an in vitro study using reconstructed human epidermis with dodecylpyridinium chloride (CAS No. 104-74-5). Although cetylpyridinium chloride was reported to have corrosive effects in a non-guideline in vivo study on the skin of guinea pigs, the data are insufficient to warrant hazard classification as corrosive.

Based on available data, cetylpyridinium chloride is considered to be potentially irritating to the oral mucosa. In 26 studies, slight oral mucosal irritation was observed in beagle dogs exposed to cetylpyridinium chloride at concentrations up to 0.45%.

Based on the available data, alkyl pyridinium surfactants are expected to be damaging to the eyes. In two studies performed according to the Organisation for Economic Co-operation and Development (OECD) Test Guideline (TG) 405, treatment with cetylpyridinium chloride produced irreversible effects to the eyes of rabbits, including corneal opacity, iritis, conjunctival redness and chemosis.

Based on experimental animal data for cetylpyridinium chloride, chemicals in this group are considered to be non-sensitising to the skin. However, observations in human volunteers showed that in some individuals, allergic reactions may be observed following exposure to dodecylpyridinium chloride.

Based on available data, chemicals in this group are not expected to cause serious systemic health effects following repeated oral exposure. Cetylpyridinium chloride was reported to have a no observed adverse effect level (NOAEL) of 5 mg/kg bw/day in rats, but this is related to local effects in the gastrointestinal (GI) tract. The GI irritation is expected to limit the amount available for systemic circulation.

There is currently no evidence that alkyl pyridinium surfactants have genotoxic or teratogenic potential. Negative results were reported for cetylpyridinium chloride in 3 in vitro genotoxicity studies (bacterial reverse mutation test, mammalian chromosomal aberration test, mammalian cell gene mutation test). Negative results were also reported for cetylpyridinium chloride monohydrate (CAS No. 6004-24-6) in one in vivo erythrocyte micronucleus study in mice. No foetal effects were observed in two teratogenic studies in pregnant rabbits and rats exposed to cetylpyridinium chloride.

No data are available to assess respiratory irritation and sensitisation, carcinogenicity, neurotoxicity, neurodevelopmental toxicity, immunotoxicity and endocrine effects.

The majority of toxicity data for alkyl pyridinium surfactants comes from studies using cetylpyridinium chloride and dodecylpyridinium chloride. Minimal toxicity data are available for cetylpyridinium bromide and cetylpyridinium chloride monohydrate. No toxicity data are available for other chemicals in this group.

Health hazard classification

The 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.

The proposed hazard classification is based on read across principle (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.

Health hazards	Hazard category	Hazard statement
Acute toxicity – oral	Category 3	H301: Toxic if swallowed
Acute toxicity – dermal	Category 4	H312: Harmful in contact with skin
Acute toxicity – inhalation	Category 2	H330: Fatal if inhaled
Skin irritation	Category 2	H315: Causes skin irritation
Eye damage	Category 1	H318: Causes serious eye damage

Summary of health risk

Public

Australian use data are not available for the chemicals in this group. International data suggests widespread and repeated exposure of the public to these chemicals through the use of rinse-off and leave-on cosmetic products. Therefore, widespread public exposure is also expected in Australia. The main route of public exposure is expected to be through the skin and oral mucosa. Incidental inhalation, ingestion and contact with the eyes may also occur.

The EU Scientific Committee on Consumer Safety (SCCS) determined that cetylpyridinium chloride and cetylpyridinium chloride monohydrate are safe for consumers when used in a single cosmetic product for oral or dermal use, at concentrations up to 0.1% in mouthwashes, 0.5% in other oral hygiene products, 0.2% in skin lotions and creams, and 2.0% in antiperspirant deodorants. The NOAEL values used in the calculation of the Margin of Safety (MoS) were 5 mg/kg bw/day for the oral application of the chemical, and 18 mg/kg bw/day for dermal application. This conclusion excluded the use of these chemicals in spray

cosmetics and the aggregated exposure resulting from the simultaneous use of products containing these chemicals (SCCS 2015).

The 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). Given the identified health hazards, the evidence indicates that there is still a risk to the public that requires management (see **Recommendations** section). The risk could be managed by including the chemicals in a revised entry in the Poisons Standard.

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, ocular and inhalation exposure are needed to manage the risk to workers (refer to **Recommendations** section).

Conclusions

The conclusions of this evaluation are based on the information described in the statement. Obligations to report additional information about hazards under Section 100 of the Industrial Chemicals Act 2019 apply.

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

Recommendations

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 forthcoming evaluation reports addressing other cationic surfactants reported to have 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 highly 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%
- the restrictions in place in other countries including Japan regarding the use of cetylpyridinium chloride in cosmetic products
- the SCCS conclusions and proposed restrictions for cetylpyridinium chloride in different types of 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.

Advice to Industry

The information in this report, including recommended hazard classifications, should be used by PCBU at workplace (such as an employer) to determine the appropriate controls.

Recommended control measures that could be implemented to manage the risk arising from occupational exposure to the chemical include, but are not limited to:

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

Measures required to eliminate, or manage risk arising from storing, handling and using a hazardous chemical depends on the physical form and the manner in which the chemical is 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. Guidance in selecting personal protective equipment can be obtained from Australian, Australian/New Zealand or other approved standards.

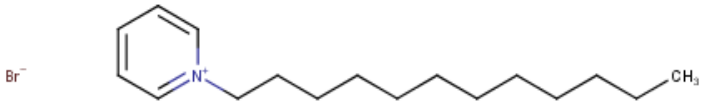
Model codes of practice, available from the SWA website, provide information on how to manage the risks of hazardous chemicals in the workplace, prepare an SDS and label containers of hazardous chemicals. Your Work Health and Safety regulator should be contacted for information on Work Health and Safety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

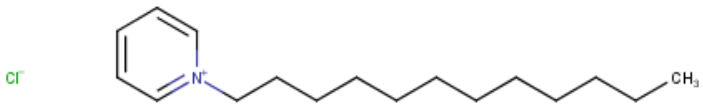
Supporting information

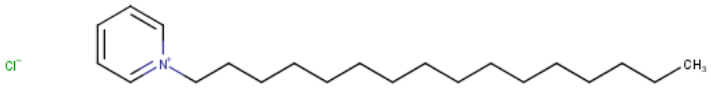
Rationale

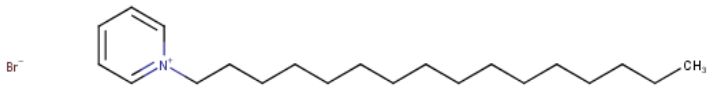
The 7 chemicals in this evaluation are salts of alkyl pyridinium cations. The most prominent one is cetylpyridinium chloride, for which its anhydrous form (CAS No. 123-03-5) and monohydrate form (CAS No. 6004-24-6) are also addressed in this evaluation. The other salts are dodecylpyridinium bromide (CAS No. 104-73-4) and chloride (CAS No. 104-74-5), cetylpyridinium bromide (CAS No. 140-72-7), tetradecylpyridinium bromide (CAS No. 1155-74-4) and laurylpyridinium sulfate (CAS No. 17342-21-1). Although there is limited data available for some of the chemicals, they are assumed to have similar uses and toxicological properties as cetylpyridinium chloride.

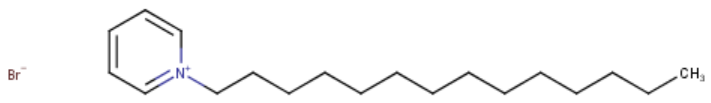
Chemical identity

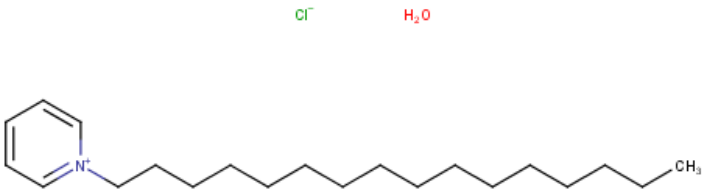
Chemical name	pyridinium, 1-dodecyl-, bromide
CAS	104-73-4
Synonyms	dodecylpyridinium bromide
Structural formula	
Molecular formula	C17H30BrN
Molecular weight (g/mol)	328.3
SMILES	[Br-].C=1C=C[N+](=CC1)CCCCCCCCCCCC
Chemical description	N/A

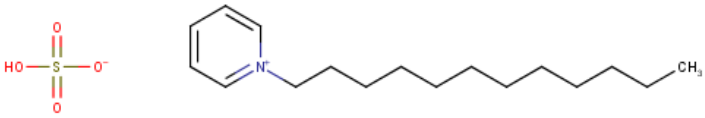
Chemical name	pyridinium, 1-dodecyl-, chloride
CAS	104-74-5
Synonyms	dodecylpyridinium chloride laurylpyridinium chloride
Structural formula	
Molecular formula	C17H30ClN
Molecular weight (g/mol)	283.9
SMILES	[Cl-].C=1C=C[N+](=CC1)CCCCCCCCCCCC
Chemical description	N/A

Chemical name	pyridinium, 1-hexadecyl-, chloride
CAS	123-03-5
Synonyms	cetylpyridinium chloride
Structural formula	
Molecular formula	C21H38ClN
Molecular weight (g/mol)	340
SMILES	[Cl-].C=1C=C[N+](=CC1)CCCCCCCCCCCCCCCC
Chemical description	N/A

Chemical name	pyridinium, 1-hexadecyl-, bromide
CAS	140-72-7
Synonyms	cetylpyridinium bromide
Structural formula	
Molecular formula	C21H38BrN
Molecular weight (g/mol)	384.4
SMILES	[Br-].C=1C=C[N+](=CC1)CCCCCCCCCCCCCCCC
Chemical description	N/A

Chemical name	pyridinium, 1-tetradecyl-, bromide
CAS	1155-74-4
Synonyms	tetradecylpyridinium bromide
Structural formula	
Molecular formula	C19H34BrN
Molecular weight (g/mol)	356.4
SMILES	[Br-].C=1C=C[N+](=CC1)CCCCCCCCCCCCCC
Chemical description	N/A

Chemical name	pyridinium, 1-hexadecyl-, chloride, monohydrate
CAS	6004-24-6
Synonyms	cetylpyridinium chloride monohydrate
Structural formula	
Molecular formula	C21H40ClNO
Molecular weight (g/mol)	358
SMILES	[Cl-].O.C=1C=C[N+](=CC1)CCCCCCCCCCCCCCCC
Chemical description	N/A

Chemical name	pyridinium, 1-dodecyl-, sulfate (1:1)
CAS	17342-21-1
Synonyms	laurylpyridinium sulfate
Structural formula	
Molecular formula	C17H31NO4S
Molecular weight (g/mol)	345.5
SMILES	O=S(=O)([O-])O.C=1C=C[N+](=CC1)CCCCCCCCCCCC
Chemical description	N/A

Introduction and use

Australia

No information is available on the introduction and use of this group of chemicals in Australia. Cetylpyridinium chloride has a reported non-industrial use as an excipient in topical therapeutic products (TGA 2007).

International

The following international uses have been identified through the Consumer Product Information Database (CPID); the European Chemicals Agency (ECHA); the Environmental Working Group (EWG) Skin Deep Cosmetics database; the European Commission Cosmetic Ingredients & Substances (CosIng) database; the Substances in Preparations in Nordic countries (SPIN) database; National Centre for Biotechnology Information (NCBI) PubChem; and the United States Personal Care Products Council International Nomenclature of Cosmetic Ingredients (INCI) Dictionary.

Cetylpyridinium chloride, cetylpyridinium chloride monohydrate and dodecylpyridinium chloride have reported cosmetic uses internationally, including:

- as antimicrobial preservatives
- as antistatic agents
- as deodorising agents (up to 2.0%)
- in hair care products (conditioning, permanent waves, shampoos, tonics, rinses, dressings)
- in mouthwashes (cetylpyridinium chloride and cetylpyridinium chloride monohydrate only) (up to 0.1%)
- in other oral hygiene products (cetylpyridinium chloride and cetylpyridinium chloride monohydrate only) (up to 0.5%)
- in skin lotions and creams (cetylpyridinium chloride and cetylpyridinium chloride monohydrate only) (up to 0.2%)
- as surfactant cleansers (cetylpyridinium chloride and cetylpyridinium chloride monohydrate only)
- as surfactant emulsifiers (cetylpyridinium chloride and cetylpyridinium chloride monohydrate only)
- in baby wipes (cetylpyridinium chloride only) (up to 0.064%).

Dodecylpyridinium chloride has reported domestic uses, including in washing and cleaning products.

Cetylpyridinium chloride, cetylpyridinium chloride monohydrate and dodecylpyridinium chloride have reported site-limited uses, including:

- as intermediates in the manufacture of other chemicals
- in the manufacture of other materials, including rubber articles (e.g. tyres, shoes, toys) (cetylpyridinium chloride and dodecylpyridinium chloride only)
- in industrial abrasion processing (textiles and metal) (dodecylpyridinium chloride only).

Cetylpyridinium chloride has reported non-industrial uses, including in:

- pesticides
- water treatment
- food additives
- pharmaceuticals.

No information is available for dodecylpyridinium bromide, cetylpyridinium bromide, tetradecylpyridinium bromide and laurylpyridinium sulfate.

Existing Australian regulatory controls

AICIS

No specific controls are currently available for this group of chemicals.

Public

The 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 (The Poisons Standard 2021).'

The 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 (The Poisons Standard 2021).'

Workers

The chemicals are not listed on the HCIS and no specific exposure standards are available (SWA).

International regulatory status

Exposure standards

Temporary emergency exposure limits (TEELs) of 0.06 mg/m^3 (TEEL-1), 0.66 mg/m^3 (TEEL-2) and 4 mg/m^3 (TEEL-3) have been recommended for cetylpyridinium chloride monohydrate (Galleria Chemica).

Asia

Cetylpyridinium chloride is listed in the Japan Cosmetics Standards Appendix 3 – Table 2 – The Ingredients Restricted According to Types of Cosmetics, with the following restrictions:

- 5% in rinse-off products
- 1% in leave-on products
- 0.01% in products that may come into contact with the mucosa (EWG, Galleria Chemica).

Health hazard information

Toxicokinetics

The absorption, distribution and excretion of cetylpyridinium chloride was investigated in a GLP compliant study similar to OECD 417. Sprague Dawley (SD) rats (5/sex/dose) were administered a single dose of the radiolabelled chemical, via oral gavage (25 mg/kg bw) or intravenously (2.5 mg/kg bw). Following oral dosing, moderate absorption occurred (13% in females and 14% in males). The majority of the chemical was excreted via the faeces (85% in females and 87% in males). Urinary excretion was low (3.3% in females and 4.6% in males) and respiratory elimination was negligible (<0.01%). The highest distribution of the chemical was to the heart, followed by the kidneys and pancreas. Following intravenous dosing, faecal excretion was 37%, indicating that the chemical and/or its metabolites are eliminated through the bile. Urinary excretion was 26% in females and 32% in males (REACHa).

In another GLP compliant study similar to OECD TG 417, beagle dogs (5 males) were administered a single dose of radiolabelled cetylpyridinium chloride by oral gavage (25 mg/kg bw). Maximum absorption was approximately 22%. Faecal excretion was 40%, and urinary excretion was 22% (REACHa).

The dermal absorption of cetylpyridinium chloride monohydrate was investigated in a GLP compliant study conducted in accordance with OECD TG 428. Frozen human epidermis specimens were exposed to the chemical at 4 µg/cm^2 for 24 hours. Washing at the end of the exposure period removed the majority of the chemical (93.7 ± 18.2%). The mean absorbed value was determined to be 1.3%. The chemical was considered to have very low systemic absorption in this study (SCCS 2015).

In another GLP compliant study conducted in accordance with OECD TG 428, frozen human epidermis specimens were exposed to cetylpyridinium chloride monohydrate at 100 µg/cm^2 for 24 hours. Washing at the end of the exposure period removed majority of the chemical (87.2 ± 4.0%). The mean absorbed value was determined to be 0.597%. The chemical was considered to have very low systemic absorption in this study (SCCS 2015).

In the safety assessment of cetylpyridinium chloride by SCCS, a dermal absorption value of 10% was used in the MoS calculation, based on the two in vitro dermal absorption studies above (SCCS 2015).

Acute toxicity

Oral

In a GLP compliant study conducted in accordance with OECD TG 425, SD rats (3 female/dose) were administered a single dose of cetylpyridinium chloride at dose levels of 300 or 950 mg/kg bw. The LD50 was determined to be 560.3 mg/kg bw. Mortality rates during the 14-day observation period for the dose groups 300 mg/kg bw and 950 mg/kg bw were 0% and 100%, respectively. Reported sublethal signs of toxicity included diarrhoea,

ano-genital staining, piloerection, hypoactivity, hunched posture and reduced faecal volume. Observations at necropsy included discolouration of the intestines and/or lungs, and/or gaseous distension of the intestines (REACHa; SCCS 2015).

In a non-GLP compliant study conducted in accordance with OECD TG 420, Wistar rats (7 female/dose) were administered a single dose of cetylpyridinium chloride at dose levels of 50, 300 or 2000 mg/kg bw. The LD50 was determined to be between 50–300 mg/kg bw (REACHb).

In other acute oral toxicity studies, the LD50 for cetylpyridinium chloride was determined to be 108 mg/kg bw in mice, 200 mg/kg bw in rats and 400 mg/kg bw in rabbits. Sublethal signs of toxicity were not reported (Galleria Chemica; RTECSa).

In a GLP compliant study conducted in accordance with OECD TG 423, SD rats (9 female) were administered a single dose of dodecylpyridinium chloride at dose levels of 50 or 300 mg/kg bw. The LD50 was determined to be between 50 mg/kg bw and 300 mg/kg bw. Mortality rates during the 14-day observation period for the dose groups 50 mg/kg bw and 300 mg/kg bw were 0% and 100%, respectively. Reported sublethal signs of toxicity included diarrhoea and reduced locomotor activity. No abnormalities were observed at necropsy (REACHb).

In an acute oral toxicity study, the LD50 for cetylpyridinium chloride monohydrate was determined to be 400 mg/kg bw in rabbits. Sublethal signs of toxicity included GI hypermotility and diarrhoea (Galleria Chemica).

In an acute oral toxicity study, the LD50 for cetylpyridinium bromide was determined to be 475 mg/kg bw in rats. Sublethal signs of toxicity were not reported (Galleria Chemica; RTECSb).

No data are available for the other chemicals in this group.

Dermal

In a GLP compliant study conducted in accordance with OECD TG 402, SD rats (5/sex) were treated with a single dose of cetylpyridinium chloride at 5000 mg/kg bw. The LD50 was determined to be >5000 mg/kg bw. No mortalities occurred during the 14-day observation period. Reported sublethal signs of toxicity included erythema, oedema, hyperkeratosis and eschar (REACHa; SCCS 2015).

In a GLP compliant study conducted in accordance with OECD TG 402, SD rats (5 female) were treated with a single dose of dodecylpyridinium chloride at dose levels of 200, 1000 or 2000 mg/kg bw. The LD50 was determined to be >1000 mg/kg bw. Mortality rates during the 14-day observation period for the dose groups 200 mg/kg bw, 1000 mg/kg bw and 2000 mg/kg bw were 0%, 0% and 100%, respectively. Reported sublethal signs of toxicity included minimal to moderate erythema (REACHb).

No data are available for the other chemicals in this group.

Inhalation

In a GLP compliant study conducted in accordance with OECD TG 403, SD rats (5/sex/dose) were exposed to cetylpyridinium chloride as a dust through the nose for 4 hours at dose levels of 0.05 or 0.5 mg/L. The mass median aerodynamic diameter was estimated to be 2.8 and 2.9 µm, respectively. The LC50 was determined to be between 0.054 and 0.51 mg/L. Mortality rates during the 14-day observation period for the dose groups 0.05 mg/L and 0.5

mg/L were 0% and 90%, respectively. Reported sublethal signs of toxicity included hypoactivity and reduced faecal volume. Observations at necropsy included discolouration and oedema of the lungs and mucous-filled tracheas (REACHa; SCCS 2015).

In another acute inhalation toxicity study, the LC50 for cetylpyridinium chloride was determined to be 0.09 mg/L/4 hours in rats. Reported sublethal signs of toxicity included chromodacryorrhea (bloody tears), dyspnoea (laboured breathing) and weight loss (Galleria Chemica).

No data are available for the other chemicals in this group.

Corrosion/Irritation

Skin irritation

In a GLP compliant study conducted in accordance with OECD TG 404, New Zealand White (NZW) rabbits (1 male, 2 female) were treated with 0.5 g cetylpyridinium chloride for 4 hours under semi-occlusive conditions. Observations were recorded at 1, 24, 48 and 72 hours, and at 7, 10 and 14 days after patch removal. Within 24 hours of patch removal, treated sites exhibited moderate to severe erythema and slight oedema. The following mean scores were reported at 24, 48 and 72 hours: 3 for erythema and 2 for oedema (maximum score of 4). Dermal irritation (erythema, oedema, desquamation and/or superficial eschar) was not reversible in all animals within the 14 day observation period; however, the severity of irritation gradually decreased. The determined primary dermal irritation index (PDII) was 4.9. The chemical was considered to be moderately irritating to the skin in this study (REACHa; SCCS 2015).

In a non-GLP compliant study similar to OECD TG 404, Hartley albino guinea pigs (6 female) were treated with cetylpyridinium chloride (concentration unspecified) for 24 hours under semi-occlusive conditions. Observations were recorded at 3, 24 and 48 hours after patch removal. The determined PDII was 8. The chemical was considered to have corrosive effects on the skin in this study (REACHb).

In a GLP compliant study conducted in accordance with OECD TG 439, 25 g dodecylpyridinium chloride was applied to reconstructed human epidermis (3) for an exposure period of 1 hour, followed by an observation period of 42 hours. The mean tissue viability value was determined to be 3.2%. The chemical was considered to be irritating to the skin in this study (REACHb). Interpretation of results obtained from OECD TG 439 studies do not allow for distinction between irritation and corrosion.

No data are available for the other chemicals in this group.

Eye irritation

In a GLP compliant study conducted in accordance with OECD TG 405, 0.04 g cetylpyridinium chloride was instilled into one eye each of NZW rabbits (3 male). Observations were recorded at 1, 24, 48 and 72 hours, and 4 days after application. All 3 animals exhibited corneal opacity, iritis and conjunctivitis. The following mean scores were reported at 24 hours: corneal opacity 1/4, iritis 2/2, conjunctival redness 2/3 and chemosis 4/4. The following mean scores were reported at 48 and 72 hours, and 4 days: corneal opacity 3/4, iritis 2/2, conjunctival redness 2/3 and chemosis 4/4. Eye irritation was not reversible in all animals within the 4-day observation period. The chemical was considered to be damaging to the eyes in this study (REACHa; SCCS 2015).

In a non-GLP compliant in vivo study similar to OECD TG 405, cetylpyridinium chloride was applied as a dry powder into one eye each of albino rabbits (6/dose) at dose levels of 100, 200, 500 or 1000 µg. Observations were recorded from 30 min up to 28 days after application. The following mean scores were reported at 24, 48 and 72 hours: conjunctival redness 2/4 and chemosis >2/4. Conjunctival redness and chemosis were fully reversible within 14 days. Corneal opacity and iritis were not fully reversible within 28 days. The chemical was considered to be damaging to the eyes in this study (REACHb).

In a non-GLP compliant study conducted in accordance with OECD TG 492, 50 mg dodecylpyridinium chloride was applied to reconstructed human cornea-like epithelium (2) using the EpiOcularTM test method for solids' protocol, for an exposure period of 6 hours and a post-exposure incubation period of 18 hours. The tissue viability was determined to be 1.3%. The chemical was considered to be irritating to the eyes in this study (REACHb).

In an eye irritation study (Draize test), dodecylpyridinium chloride (5% w/v solution) was instilled into the eyes of guinea pigs. The chemical was considered to be irritating to the eyes in this study. No further information is available for this study (REACHb).

No data are available for the other chemicals in this group.

Mucosal irritation

In 26 oral mucosal irritation studies conducted from 1969–1990, cetylpyridinium chloride (0.01–0.45%) was applied to the oral mucosa of beagle dogs using saturated dental plugs for 15 seconds, 3 or 5 times a day for 4 days, with and without rinsing. A fluorescein rinse was used to detect very minor changes on the oral mucosa of the animals. Based on these studies, the chemical was considered to have the potential to be slightly irritating to the oral mucosa when used in mouthwashes and cosmetic products up to 0.1%, and in other oral hygiene products up to 0.5% (SCCS 2015).

Sensitisation

Skin sensitisation

In a GLP compliant study conducted in accordance with OECD TG 406, Hartley albino guinea pigs (20, both sexes) were treated with cetylpyridinium chloride (0.4 mL of a 5% w/w mixture in distilled water) under occlusive conditions for 6 hours, once a week for three weeks. After 27 days, the animals were challenged with the chemical (0.4 mL of a 0.1% w/w mixture in distilled water). In addition, 10 guinea pigs were treated with the chemical at challenge only (control group). Observations were recorded 24 and 48 hours after each treatment. Very faint erythema was noted for 7/20 treated animals and 2/10 control animals. The chemical was considered to be non-sensitising in this study (REACHa; SCCS 2015).

In a non-GLP compliant study conducted in accordance with OECD TG 406, Hartley Albino guinea pigs (6, female) were treated with cetylpyridinium chloride. The chemical was considered to be slightly sensitising in this study. No further information is available for this study (REACHb).

In a skin sensitisation study, Hartley albino guinea pigs (20, both sexes) were treated with cetylpyridinium chloride (0.5 mL of a 5% solution in water) for 6 hours, once a week for three weeks. After 14 days, the animals were challenged with the chemical (0.5% solution in water). In addition, 10 guinea pigs were treated with the chemical at challenge only. Observations were recorded 24 and 48 hours after challenge. Slight patchy erythema was

noted for 1/10 control animals. None of the treated animals showed skin reactions. The chemical was considered to be non-sensitising in this study (SCCS 2015).

No data are available for the other chemicals in this group.

Observation in humans

In a patch test, dodecylpyridinium chloride was applied at 0.1% to the skin of a 28-year-old male for 72 hours. The chemical was considered to be irritating and sensitising to the skin in this study (REACHb).

In a patch test, dodecylpyridinium chloride was applied at 0.1% to the skin of 147 volunteers. Readings were made 20 minutes and 48 hours following application. After the first reading, positive reactions were recorded in 1% of the volunteers. No further information is available for this study. The chemical was considered sensitising in this study (REACHb).

No data are available for the other chemicals in this group.

Repeat dose toxicity

Oral

In a GLP compliant 26-week study conducted in accordance with OECD TG 452, SD rats (20/sex/dose) were administered cetylpyridinium chloride at dose levels of 0, 5, 15, 40 or 75 mg/kg bw/day for 6 months by gavage. Mortality rates in males for the dose groups at 5 mg/kg bw/day, 15 mg/kg bw/day, 40 mg/kg bw/day and 75 mg/kg bw/day were 5%, 0%, 6% and 5%, respectively. No mortalities occurred in females. Localised GI irritation was observed at dose levels >15 mg/kg bw/day. Reported effects included salivation, soft faeces, decreased food consumption, decreased body weight, thickened appearance of the non-glandular region of the stomach, increased stomach weights, and hyperplasia/necrosis/erosion/ oedema of the non-glandular stomach. Body weight was significantly lower at 75 and 40 mg/kg bw/day for both sexes, and at 15 mg/kg bw/day in females. Statistically significant haematological changes were reported at 40 and 75 mg/kg bw/day, including increased erythrocyte and haematocrit count, haemoglobin concentration, platelet count. There were significant changes in clinical chemistry parameters, including significantly lower glucose levels at 40 and 75 mg/kg bw/day. The NOAEL for local effects was determined to be 5 mg/kg bw/day. The NOAEL for systemic toxicity was considered to be 5 mg/kg bw/day, based on decreased body weight gain, although this may be secondary to the local effects in the stomach (REACHa; SCCS 2015).

In a GLP compliant 28-day toxicity study, SD rats (8/sex/dose) were administered cetylpyridinium chloride at dose levels of 0, 25, 50, 100, 200 or 400 mg/kg bw/day by gavage. Mortality rates for the dose groups 25 mg/kg bw/day, 50 mg/kg bw/day, 100 mg/kg bw/day, 200 mg/kg bw/day and 400 mg/kg bw/day were 0%, 0%, 62.5%, 100% and 100%, respectively. Localised GI irritation was observed at dose levels from 50 mg/kg bw/day. Reported effects included acanthosis and necrosis/erosion in the non-glandular stomach. The NOAEL for local effects was determined to be 25 mg/kg bw/day. The NOAEL for systemic toxicity was considered to be 25 mg/kg bw/day, based on decreased body weight gain, although this may be secondary to the local effects in the stomach (SCCS 2015).

In a GLP compliant 28-day toxicity study, beagle dogs (3/sex/dose) were administered the cetylpyridinium chloride at dose levels of 0, 5, 25, 125, 250 or 500 mg/kg bw/day in a gelatin capsule. Localised GI irritation was observed at all dose levels. Reported effects included red discolouration/foci and necrosis/erosion/ulcers/inflammation of the GI organs. The NOAEL

for local effects was determined to be <5 mg/kg bw/day. The NOAEL for systemic toxicity was considered to be 25 mg/kg bw/day, based on mortality and thymus atrophy (SCCS 2015).

In a GLP compliant 13-week toxicity study, SD albino rats (10/sex/dose) were administered cetylpyridinium chloride at dose levels of 0, 125, 250, 500 or 1000 ppm in feed. The NOAEL was determined to be 250 ppm (18 mg/kg bw/day), based on increased caecum weights in males in the 500 ppm group (SCCS 2015).

In a 90 day toxicity study, rats (6/sex/dose) were administered cetylpyridinium chloride at dose levels of 0, 125, 300, 800, 2000, 5000, 10 000 ppm in feed. Mortality rates for the dose groups 5000 ppm and 10 000 ppm were 100%. The NOAEL was determined to be 18 mg/kg bw/day, based on increased caecum weights in males (SCCS 2015).

In the safety assessment of cetylpyridinium chloride by SCCS, the NOAEL value of 5 mg/kg bw/day from the 26-week rat study described above was used in the MoS calculation for the oral application of the chemical. The NOAEL value of 18 mg/kg bw/day from the dietary studies described above was used in the MoS calculation for dermal application, as dietary administration is less associated with local GI effects (SCCS 2015).

No data are available for the other chemicals in this group.

Dermal

No data are available for this group of chemicals.

Inhalation

No data are available for this group of chemicals.

Genotoxicity

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

- In a GLP compliant study conducted in accordance with OECD TG 471, *Salmonella typhimurium* strains TA98, TA100, TA1535, TA1537 and *Escherichia coli* WP2 were treated with cetylpyridinium chloride. Negative results were reported with metabolic activation at concentrations up to 100.0 µg/plate, and without metabolic activation at concentrations up to 33.0 µg/plate (REACHa).
- In a GLP compliant study conducted in accordance with OECD TG 473, Chinese hamster ovary (CHO) cells were treated with cetylpyridinium chloride. Negative results were reported with metabolic activation at concentrations up to 6.0 µg/mL, and without metabolic activation at concentrations up to 3.3 µg/mL (REACHa; SCCS 2015).
- In a GLP compliant study conducted in accordance with OECD TG 476, cetylpyridinium chloride was tested at the thymidine kinase (TK) locus of mouse lymphoma L5178Y cells. Negative results were reported with metabolic activation at concentrations up to 7.5 µg/mL, and without metabolic activation at concentrations up to 2 µg/mL (REACHa; SCCS 2015).

Negative results were reported in the following in vivo genotoxicity study:

- In a GLP compliant study conducted in accordance with OECD TG 474, CD-1 mice (5 –10 mice/sex/dose) were treated with cetylpyridinium chloride monohydrate at dose

levels of 0, 25, 50 or 100 mg/kg bw/day. The incidence of micronuclei in bone marrow polychromatic erythrocytes did not increase in any of the treated groups, indicating a lack of clastogenicity (SCCS 2015).

No data are available for the other chemicals in this group.

Reproductive and development toxicity

In a GLP compliant study similar to OECD TG 414, pregnant NZW rabbits (15/dose) were administered cetylpyridinium chloride at dose levels of 0, 2.5, 12 or 100 mg/kg bw, by gavage, once daily on gestational days (GD) 7–18. Due to lethality at the 100 mg/kg dose level, the remaining untreated animals of this group (6/15) received 25 mg/kg instead. The animals were sacrificed on GD 29. Reported maternal signs of toxicity included anorexia, weight loss and reduced food consumption. No teratogenic effects were reported. The maternal NOAEL was determined to be 12 mg/kg bw/day, and the foetal NOAEL was determined to be >25 mg/kg bw/day (REACHa; SCCS 2015).

In a GLP compliant teratogenicity study, pregnant SD rats (30/dose) were administered cetylpyridinium chloride at dose levels of 0, 5, 15 or 60 mg/kg bw, by gavage, once daily on GD 6–16. No mortalities occurred. The animals were sacrificed on GD 20. Reported maternal signs of toxicity included decreased defecation, hair loss, scabbed area, laboured breathing, weight loss, reduced weight gain and reduced food consumption. No teratogenic effects were reported. The maternal NOAEL was determined to be 15 mg/kg bw/day, and the foetal NOAEL was determined to be 60 mg/kg bw/day (SCCS 2015).

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