Australian Government
Department of Health and Aged Care
Australian Industrial Chemicals Introduction Scheme

Salicylic acid and its salts

Evaluation statement

15 April 2024

Draft

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AICIS evaluation statement

Subject of the evaluation

Salicylic acid and its salts

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Reason for the evaluation

Evaluation Selection Analysis indicated a potential human health and environmental risk.

Parameters of evaluation

This evaluation considers the human health and environmental risks associated with industrial uses of salicylic acid (SA) and its salts. These chemicals are listed on the Australian Inventory of Industrial Chemicals (the Inventory).

For human health, chemicals reported on in this evaluation were previously assessed under the Inventory Multi-tiered Assessment and Prioritisation (IMAP) Framework (NICNAS 2013). Since then, a number of regulatory bodies including the European Chemicals Agency (ECHA), Scientific Committee on Consumer Safety (SCCS) and the Government of Canada (ECHA 2016a; Government of Canada 2020; SCCS 2023c) have reconsidered the data for developmental toxicity. Furthermore, new information has become available regarding eye irritation of the salts of SA.

This evaluation will:

- evaluate the new information that has become available
- reconsider the developmental toxicity classification
- re-evaluate the risk to workers and the public
- propose means for managing any identified risks.

The risks posed to the environment associated with the industrial uses of these chemicals in this group have been assessed according to the following parameters:

- Imported and manufactured volume of 10,000–99,999 tonnes (t) per annum for SA.
- Default domestic introduction volumes of 100 tonnes per year for the salts.

- Industrial uses listed in the ‘Summary of introduction, use and end use’ section.
- Expected emission to sewage treatment plants (STPs) following consumer and commercial use.

These chemicals have been assessed as a group because they have similar use patterns, have similar chemical structure and will all form the same chemical species under normal environmental conditions or under physiological conditions in the human body. Environmental and health risks of the sodium, calcium, and potassium cations of the corresponding salts in this evaluation are not considered, as they are either ubiquitous in the environment and the human body or have previously been assessed.

Summary of evaluation

Summary of introduction, use and end use

The Australian introduction volume of SA is in the range of 10,000–99,999 tonnes per annum. No specific Australian uses were reported. Cosmetic products containing SA including in at home chemical peels have been identified in Australia. No specific Australian use, import or manufacturing information has been identified for the salts.

Based on international use information, these chemicals have a variety of functions and industrial applications in consumer products ranging from personal care products to household cleaning and washing products, as well as a variety of commercial and site limited uses.

The following end use categories were identified:

- adhesive and sealant products
- arts, crafts and hobby products
- personal care products
- paint and coating products
- plastic and polymer products
- construction products
- fabric, textile and leather products
- automotive care products
- cleaning and furniture care products
- laundry and dishwashing products
- water treatment products
- other (e.g. use as an intermediate in chemical manufacturing).

Chemicals in this group are used in a wide range of leave-on (up to 3%) and rinse-off cosmetic products (up to 5%, except peels which are up to 30%). SA is used in cosmetic products as a denaturant, a hair and skin conditioning agent, an exfoliant, and a preservative. Salts in this group have reported uses in cosmetics as preservatives and biocides (up to 2%).

Internationally SA is a high production volume chemical. Sodium salicylate (NaS) and potassium salicylate (KS) are introduced in smaller quantities. No current international use volume information was identified for calcium salicylate (CaS). It does not appear to have widespread industrial use.

Human health

Summary of health hazards

The identified health hazards are based on available data for these chemicals. The previous assessment of SA and its salts should be read in conjunction with this evaluation statement (NICNAS 2013). This evaluation statement reviews new evidence of eye irritation, toxicokinetics and developmental toxicity. Available data for methyl salicylate and acetyl SA (ASA), which metabolise to SA, are used to support conclusions for developmental toxicity. Available data for NaS is used to support conclusions for eye irritation of the salts of SA.

Based on the toxicokinetic studies the chemical is well absorbed orally and dermally and rapidly distributed, metabolised and excreted.

Based on the available data these chemicals (NICNAS 2013):

- have moderate acute oral toxicity and low acute dermal toxicity
- are not irritating to skin
- are not considered to be sensitisers
- are not expected to cause serious systemic health effects following repeated oral or dermal exposure
- are not considered to have genotoxic potential
- are not expected to be carcinogenic
- are not expected to cause specific adverse effects on fertility.

Based on the results from available in vivo and in vitro studies SA is considered to cause irreversible eye damage. At low concentrations (2%) the chemical was at most slightly irritating. Based on the available data for NaS, the salts are irritating to eye. Reversible eye irritation (mean conjunctival redness score of 2 in all 3 animals) was observed in an eye irritation study in rabbits (OECD TG 405). A range of severity of effects was observed in non-guideline in vivo studies and predicted by in vitro studies.

Based on the available data, these chemicals may cause adverse effects on development. This is based on adverse developmental effects in two animal species (rat and monkey). The main effects observed in rats were increased incidences of neural tube defects (craniorachischisis), increased incidences of skeletal variations, a lower pup body weight, foetal growth retardation and increased foetal mortality in pups born from rats who were exposed to SA, NaS, methyl salicylate or ASA during gestation. The lowest no observed adverse effect level (NOAEL) for developmental toxicity is considered to be 75 mg/kg bw/day based on a non-guideline pre-natal developmental toxicity study similar to OECD TG 414 in Wistar rats. In monkeys neural tube defects (craniorachischisis), and kidney cysts were observed at 150 mg/kg bw. There were no developmental effects observed in rabbits. Epidemiology studies from the extensive human use of ASA as aspirin do not indicate an increased risk of birth defects.

For further details of the health hazard information see **Supporting Information**.

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) for hazard classes relevant for work health and safety as follows. This does not consider classification of physical hazards and environmental hazards. The classification for serious eye damage only applies to SA

(CAS No. 69-72-7). The classification for eye irritation only applies to the salts of SA (CAS Nos. 54-21-7; 824-35-1 and 578-36-9).

Health hazards	Hazard category	Hazard statement
Acute toxicity	Acute Tox. 4	H302: Harmful if swallowed
Serious eye damage/eye irritation	Eye Irrit. 2	H319: Causes serious eye irritation
Serious eye damage/eye irritation	Eye Damage 1	H318: Causes serious eye damage
Reproductive toxicity	Repr. 2	H361d: Suspected of damaging the unborn child

Summary of health risk

Public

Based on the available use information, the public may be exposed to these chemicals in:

- cosmetic and personal care products at concentrations up to 3% in leave on products and up to 5% in rinse off products (which the exception of peels that are up to 30%)
- household products (no concentration information is available).

Exposure to these products may occur by:

- the dermal route, when using leave on and rinse off skin products or cleaning products
- incidental eye contact
- inhalation if used in spray or aerosol products.

The critical health effect for risk characterisation is systemic long term effects (developmental toxicity).

The European Commission's Scientific Committee on Consumer Safety (SCCS) recently reassessed the safety of SA in cosmetics and personal care products. A quantitative risk assessment based on EU concentration restrictions resulted in a calculated margin of safety (MoS) of 167. In general, an MoS value greater than or equal to 100 is considered acceptable to account for intra- and inter-species differences. Although some additional exposure scenarios were identified in this evaluation that were not considered in the SCCS calculations. These are unlikely to significantly change the MoS value to <100.

These chemicals are also acutely toxic by the oral route and can cause eye irritation. Under the typical conditions of use in most cosmetic and household products with low concentrations of use, the risk of these adverse effects in the public is low. However, SA is reported to be used in chemical peels up to concentrations of 30%. Accidental spillage of any chemical peel agents in the eyes can cause eye injuries in the form of corneal damage.

Overall for the majority of cosmetic and household uses these chemicals are unlikely to pose a risk. However, given that SA is a severe eye irritant and has potential use in cosmetic products that are applied to the face at high concentrations there is a potential risk which requires management (see **Proposed means for managing risk**). The risk could be

managed by amending the entry in the *Poison Standard – Standard for the Uniform Scheduling of Medicines and Poisons (SUSMP).*

Workers

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

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

Control measures to minimise dermal and ocular exposure are needed to manage the risk to workers (refer to **Proposed means of managing risk**).

Environment

Summary of environmental hazard characteristics

Based on the information presented in this evaluation statement and according to the environmental hazard thresholds stated in the Australian Environmental Criteria for Persistent, Bioaccumulative and/or Toxic Chemicals, these chemicals are:

- not persistent (Not P)
- not bioaccumulative (Not B)
- not toxic (Not T).

Environmental hazard classification

These chemicals satisfy the criteria for classification according to the Globally Harmonized System of Classification and Labelling of Chemicals (GHS) for environmental hazards as follows. This evaluation does not consider classification of physical hazards:

Environmental Hazard	Hazard Category	Hazard Statement
Hazardous to the aquatic environment (acute / short-term)	Aquatic Acute 3	H402: Harmful to aquatic life

Summary of environmental risk

Salicylic acid and its salts have a variety of industrial uses, including in personal care, cleaning, and washing products, that will be released to the water compartment. According to Australian criteria, these chemicals are not persistent, not bioaccumulative, and not toxic. While there is some evidence that these chemicals interact with the thyroid and glucocorticoid endocrine systems at high doses, there is currently insufficient evidence to suggest harmful effects in the environment. Data from a monitoring study of Australian rivers has been used to give a predicted environmental concentration of 1.53 µg/L. Available ecotoxicity data and an assessment factor of 100 have been used to derive a predicted no effect concentration of 56 µg/L. As the Risk Quotient (RQ) obtained is < 1.0, the industrial

use of these chemicals in Australia is not expected to pose a significant risk to the environment.

Proposed means for managing risk

Public health

Recommendation to Department of Health and Aged Care

It is recommended that the delegate of the Secretary for Poisons Scheduling amends the entry for salicylic acid in the *Poisons Standard (the SUSMP).*

It is recommended that the management of the potential risk associated with the use of these chemicals:

- results in a labelling requirement that provides warning statements and safety directions relating to eye damage.

Consideration should be given to the following:

- The use of SA in at home chemical peels at concentrations up 30% has been identified in Australia.
- Another acid used in chemical peels (glycolic acid) which has similar local irritation effects as salicylic acid is listed in Schedule 6 when used in cosmetic products at a certain concentration and/or pH, based on it being also an irritant to the skin and eyes.
- Based on the results from available in vivo and in vitro studies SA is considered to cause irreversible eye damage. The available data indicates the salts are less irritating to eyes compared with SA.

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 inhalation exposure to these chemicals include, but are not limited to:

- using closed systems or isolating operations
- minimising manual processes and work tasks through automating processes
- adopting work procedures that minimise splashes and spills
- cleaning equipment and work areas regularly

- using protective equipment that is designed, constructed, and operated to ensure that the worker does not come into contact with these chemicals.

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

These control measures may need to be supplemented with:

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

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

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

Conclusions

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

Note:

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

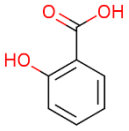
Supporting information

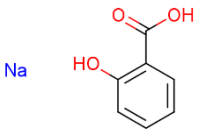
Rationale

This evaluation considers the environmental and human health risks associated with industrial uses of 2-hydroxybenzoic acid, hereinafter referred to as salicylic acid (SA), and its salts. Chemicals in this evaluation are used in high volumes and were selected for evaluation because the Evaluation Selection Analysis indicated a potential risk to the environment and human health. These chemicals have been assessed as a group because they have similar use patterns, chemical structure and will all form the same chemical species under normal environmental conditions and under physiological conditions in the human body. Salicylic acid also forms many esters that are industrial chemicals. This evaluation provides a reference for consideration of those esters, which will have SA as a potential environmental degradant or metabolite in humans.

Chemical identity

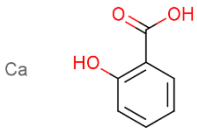
Salicylic acid is prepared on an industrial scale by the Kolbe-Schmitt synthesis from dry sodium phenoxide in a stream of carbon dioxide at elevated temperature and pressure. It is recovered from the resulting sodium salicylate (NaS) by adding sulfuric acid (Boullard et al. 2012). Following synthesis, reported purity of SA exceeds 99.5%, with phenol, p-hydroxybenzoic acid and 4-hydroxyisophthalic acid 0.05–0.1% (as impurities); ash <0.1%; water 0.2%. The sodium, calcium, and potassium salts of SA are formed by the action of the corresponding metal carbonate on the carboxyl group in SA (Boullard et al. 2012).

Chemical name	Benzoic acid, 2-hydroxy-
CAS RN	69-72-7
Synonyms	salicylic acid (SA) 2-hydroxybenzoic acid orthohydroxy benzoic acid 2-carboxyphenol phenol-2-carboxylic acid
Molecular formula	C7H6O3
Molecular weight (g/mol)	138.12
SMILES (canonical)	O=C(O)C=1C=CC=CC1O
Chemical description	-
Structural formula:	

Chemical name	Benzoic acid, 2-hydroxy-, sodium salt (1:1)
CAS RN	54-21-7
Synonyms	sodium salicylate (NaS)
	2-hydroxybenzoic acid, sodium salt
	o-hydroxybenzoic acid, sodium salt
	sodium 2-hydroxybenzoate
Molecular formula	C7H6O3.Na
Molecular weight (g/mol)	161.11
SMILES (canonical)	[Na].O=C(O)C=1C=CC=CC1O
Chemical description	-
Structural formula:	

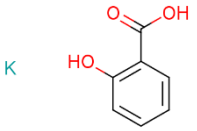
Chemical name	Benzoic acid, 2-hydroxy-, calcium salt (2:1)
CAS RN	824-35-1
Synonyms	calcium salicylate (CaS)
	calcium disalicylate
	calcium 2-hydroxybenzoate
Molecular formula	C7H6O3.1/2Ca
Molecular weight (g/mol)	316.32
SMILES (canonical)	[Ca].O=C(O)C=1C=CC=CC1O
Chemical description	-

Structural formula



Chemical name	Benzoic acid, 2-hydroxy-, monopotassium
CAS RN	578-36-9
Synonyms	potassium salicylate (KS) o-hydroxybenzoic acid potassium salt potassium 2-hydroxybenzoate
Molecular formula	C7H6O3.K
Molecular weight (g/mol)	177.22
SMILES (canonical)	[K].O=C(O)C=1C=CC=CC1O
Chemical description	-

Structural formula



Relevant physical and chemical properties

Measured physical and chemical property data for SA and NaS were retrieved from the registration dossiers under the Registration, Evaluation, Authorisation and Restriction of Chemicals (REACH) legislation in the European Union (REACH n.d.-a; n.d.-c). The Henry's Law constants were calculated from the reported values for water solubility and vapour pressure. Other calculated or experimental database values were obtained using EPI Suite (US EPA 2017).

Chemical	Salicylic acid	Sodium salicylate
Physical form	Solid	Solid
Melting point	157–160°C (exp.)	208.5–213.5°C (exp.)
Boiling point	256°C (exp.)	233.3°C (exp.)
Vapour pressure	0.0208 Pa at 25°C (exp.)	4.9×10^{-9} Pa at 25°C (calc.)
Water solubility	2,240 mg/L at 25°C (exp.)	575,708 mg/L (exp.)
Henry's law constant	0.00128 Pa·m^3/mol	1.36×10^{-12} Pa·m^3/mol
pKa	pKa_1 = 2.98 and pKa_2 = 13.4	same
Ionisable in the environment?	Yes, the pKa values indicate that the carboxylate anion (conjugate base) is the dominant species in the environmental pH range (4-9). The hydroxy group is not expected to ionise in the environment.	The sodium salt is expected to ionise into the carboxylate anion (conjugate base) and sodium cation in the environmental pH range.
log K_{ow}	2.26 (exp.)	-1.594 (exp.)

Physical and chemical properties of potassium salicylate (KS) are expected to be similar to the sodium salt. Calcium salicylate (CaS) is expected to be less soluble than the other salts based on solubility of the corresponding benzoate salts (LMC 2020). The HPLC method for the log K_{OW} of SA used trifluoroacetic acid in the mobile phase and has hence measured this value for the neutral form. The shake flask method used for NaS obtains the log K_{OW} of the carboxylate anion, which is the more environmentally relevant value (REACH n.d.-a; n.d.-c).

Introduction and use

Australia

Based on information reported to the former National Industrial Chemicals Notification and Assessment Scheme (NICNAS) under previous mandatory and/or voluntary calls for information, the annual introduction volume of SA was reported to be in the range of 10,000–99,999 tonnes (NICNAS 2006). Annual introduction volumes are expected to remain in this range. No specific Australian uses were reported. No specific Australian use, import or manufacturing information has been identified for the salts.

The use of SA in at home chemical peels at concentrations up 30% has been identified in Australia.

International

The following uses were identified from:

- the European Union Registration, Evaluation and Authorisation of Chemicals (REACH n.d.-a; n.d.-b; n.d.-c)
- United States Environmental Protection Agency Chemical Data Reporting (CDR) (US EPA 2012; 2016; 2020b)
- INCIpedia (Personal Care Products Council n.d.)
- CPID (DeLima Associates n.d.)
- IFRA transparency list (IFRA 2022)
- SCCS 2023 (SCCS 2023c)
- Government of Canada (Government of Canada 2020)
- CIR (CIR 2019).

SA has reported cosmetic uses:

- as a preservative
- as a denaturant
- in exfoliants/peels
- as a fragrance ingredient
- as a hair conditioning agent
- as a skin conditioning agent
- in tanning products
- in massage oils
- in shaving products
- in deodorants.

CaS is used as a preservative. KS is used as a cosmetic biocide and preservative. NaS is used as a denaturant and preservative in personal care products.

Concentrations in personal care products have restrictions in some countries (see international regulatory status). Reported concentrations of SA include 0.5–3% in leave on products, 1–5% in rinse off products except for peels which are up to 30% (CIR 2019; DeLima Associates n.d.). Use data submitted by industry stated that NaS was used at concentrations of ≤2% (CIR 2019).

SA is used in a wide range of cosmetic products including as a denaturant, a hair and skin conditioning agent, an exfoliant, and a product preservative (Table 1). According to a consumer exposure survey in Europe in 2017 (presenting use data from 2016), the salts of SA were reported to be used as preservatives in all cosmetic products except toothpaste or mouthwash products (SCCS 2023c).

Table 1 Percent of total product category (% by tonnage) salicylic acid

Category	Total Formulations	Formulations with SA	Occurrence %
Body Lotion	3200	61	1.9
Deodorant Roll On	1374	16	1.2
Eye makeup	6140	4	0.1
Eyeliner	1599	0	0
Face Moisturiser	5218	432	8.3
Hair styling	2311	20	0.9
Hand Cream	641	8	1.2
Lipstick	9751	4	0.0
Liquid hand soap	409	33	8.1
Liquid make up foundation	8336	194	2.3
Make up remover	1454	163	11.2
Mascara	906	0	0.0
Mouthwash	68	0	0.0
Rinse off conditioner	2071	39	1.9
Shampoo	2692	575	21.4
Shower gel	2985	386	12.9
Toothpaste	517	0	0

According to 2019 voluntary reporting data in the United States of America (USA) SA was used in 1429 products, NaS was used in 186 products and KS and CaS were not reported to be in use (CIR 2019).

In Canada, SA is found in approximately 2000 cosmetic products. The concentration of SA in these products ranges from less than 0.1% to its maximum permissible concentration of 2% (Government of Canada 2020).

Use in spray or aerosol products was not reported in Europe (SCCS 2023c); however, use in hairspray was identified in Canada (Government of Canada 2020).

SA appears on the International Fragrance Association Transparency List (IFRA 2022).

SA has reported potential domestic use as a biocide and preservative in washing and cleaning products such as dishwashing liquid.

SA has reported commercial uses in:

- polishes and waxes
- hydraulic fluids
- heat transfer fluids
- lubricants
- metal surface treatment products.

SA has reported site limited uses in:

- pH regulators and water treatment products

- the manufacture of chemicals
- the manufacture of rubber products.

SA is a high production volume (HPV) chemical (OECD n.d.). The total registered volumes for SA, NaS and KS in the European Economic Area are 10,000–100,000, 100–1,000 and 1–10 tonnes/year, respectively (REACH n.d.-a; n.d.-b; n.d.-c). In the USA, SA is on the US EPA HPV list (US EPA 2020a), with reported annual use volume of about 454–4,540 tonnes/year (US EPA 2020b). In Japan from 2012–2022, SA was manufactured and/or imported in quantities of 10,000–30,000 tonnes/year (NITE n.d.). Average use of SA and NaS in the Nordic countries over the five years from 2015–2019 was 1448.6 and 1.3 tonnes/year, respectively (Nordic Council of Ministers n.d.).

Site limited uses are reported to account for a large proportion of application volumes (Boullard et al. 2012; NCBI n.d.).

SA has reported non-industrial uses in pharmaceutical, veterinary products, and agricultural chemicals. SA is used to synthesise acetyl salicylic acid (ASA, aspirin). Aspirin is a widely used as an analgesic drug. Aspirin metabolises to SA in the human body.

Existing Australian regulatory controls

Environment

The reported industrial use of these chemicals in this evaluation is not subject to any specific national environmental regulations.

Public

Salicylic acid and sodium salicylate are listed in the *Poisons Standard* (*SUSMP)* as follows (TGA 2024):

Schedule 3:

SALICYLIC ACID in preparations for dermal use **except** in preparations containing 40% or less of salicylic acid.

Schedule 4:

SODIUM SALICYLATE in preparations for internal use for the treatment of animals.

SA has restrictions for its non-industrial use in listed medicines (TGA 2023). Only for use in topical medicines for dermal application. The concentration in the medicine must be no more than 40%.

Schedule 3 chemicals are labelled with ‘Pharmacist Only Medicine’ and are described as “Substances, the safe use of which requires professional advice but which should be available to the public from a pharmacist without a prescription.”

Schedule 4 chemicals are labelled with ‘Prescription Only Medicine or Prescription Animal Remedy and are described as: “Substances, the use or supply of which should be by or on the order of persons permitted by State or Territory legislation to prescribe and should be available from a pharmacist on prescription.”

Workers

These chemicals are listed on the Hazardous Chemical Information (HCIS) with the following hazard categories and statements for human health (SWA) (the listing for serious eye damage only applies to SA (CAS No. 69-72-7).

Health hazards	Hazard category	Hazard statement
Acute toxicity	Acute Tox. 4	H302: Harmful if swallowed
Serious eye damage/eye irritation	Eye Damage 1	H318: Causes serious eye damage

International regulatory status

United Nations

Chemicals in this evaluation are not currently identified as persistent organic pollutants (UNEP 2001), ozone depleting substances (UNEP 1987), or hazardous substances for the purpose of international trade (UNEP & FAO 1998).

Canada

Prohibited and Restricted Cosmetic Ingredients Hotlist (Health Canada 2022):

- SA is 'permitted at concentrations equal to or less than 2%'.

European Union

Cosmetics Directive Annex III List of Restricted Substances (EC) restricts SA to:

- 3.0% for rinse off hair products
- 2.0% for cosmetic products other than rinse off hair products, except body lotion, eye shadow, mascara, eyeliner, lipstick and roll on deodorant
- 0.5% for body lotion, eye shadow, mascara, eyeliner, lipstick and roll on deodorant.

SA is not to be used in preparations for children under three years of age. Not to be used in applications that may lead to exposure of the end-user's lungs by inhalation. Not to be used in oral products. For purposes other than inhibiting the development of micro-organisms in the product. This purpose has to be apparent from the presentation of the product. These levels are inclusive of any use of SA.

Cosmetics Directive Annex VI List of Preservatives Allowed (EC) restricts SA and its salts to:

- 0.5% maximum (as acid) for use as preservatives in cosmetic products other than products for children under 3 years of age.

SA is subject to an ongoing Biocidal Product Regulation assessment which is considering whether SA has endocrine modulating properties for humans and non-target organisms (ANSES 2021). Depending on the outcome of this assessment, the SCCS has noted that the potential endocrine modulating properties of SA in cosmetic products may need to be

reconsidered (SCCS 2019). Further to this, the substance evaluation conclusion under REACH for methyl salicylate indicates that the evaluating member state for SA has to revise its assessment of the endocrine modulating properties of SA in light of the 2018 guidance document setting scientific criteria to identify endocrine disruptors in biocides (ANSES 2021). The outcome of that assessment may impact regulation of SA in the European Union.

New Zealand

The chemical is listed 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. The maximum authorised concentrations in finished cosmetic products are the same as that in the EU Cosmetic Regulation' (see **European Union**) (NZ EPA 2020).

Asia

SA is listed in the ASEAN Cosmetic Directive Annex VI Part A - List of preservatives allowed for use in cosmetic products at a maximum authorised concentration of 0.5%.

SA and its salts are restricted under a group entry in the Japan Ministry of Health and Welfare's Standards for Cosmetics (Ministry of Health and Welfare Notification No.331 of 2000). The entry in "Appendix 3: The ingredients restricted in all types of cosmetics" states that total concentration of all salicylates in cosmetics has a concentration limit of 1.0% and SA has a concentration limit of 0.2% (Japan 2000; Ministry of Health and Welfare Japan 2000).

Human exposure

Public

As these chemicals are used in cosmetic and household products (see **Introduction and use**), there is expected to be significant public exposure to these chemicals. Australian use patterns for the various product categories are assumed to be similar to those in Europe and the United States. Therefore, existing international exposure estimates are suitable for estimating Australian public exposure to these chemicals.

Depending on the type of product, dermal contact with cosmetics products can be limited to specific areas on the body such as the eye region, face, hands, nails, or feet, or it can be more extensive, covering large areas of the trunk as well as the face. The duration of exposure for various products may differ substantially; for rinse off products such as soaps or shampoos, exposure might only be for a few minutes, although some residual products can remain. Whereas for leave on products, the period of exposure could last for several hours.

Australian use patterns for the various product categories are assumed to be similar to those in Europe and the USA. Therefore, existing international exposure estimates are suitable for estimating Australian public exposure to the chemical.

The SCCS conducted exposure assessments to determine the aggregate exposure to SA from a range of cosmetic and personal care products at the current EU concentration limits (see **International restrictions**). The SCCS based their aggregate exposure modelling on two different exposure scenarios. Scenario 1 was based on the SCCS Notes of Guidance recommendations. Scenario 2 was based on consumer aggregate exposure assessment

P95 use data from a Cosmetics Europe use survey data for 2016 (Cosmetics Europe 2017 report). The calculated daily systemic exposure doses were 1.67 mg/kg bw/day and 0.45 mg/kg bw/day for Scenario 1 and Scenario 2, respectively (SCCS 2023c).

The exposure assessments were considered conservative as they included all product types which contain the chemical and used maximum concentrations permitted in the EU. Dermal exposure to SA was calculated as an internal dose which is proportional to the use volumes, product retention factors (reflecting proportions of product remaining on the skin during normal use) and dermal bioavailability of SA. Dermal bioavailability was assessed based on dermal absorption of SA. SA has been reported to readily permeate the skin, although several factors may affect the dermal absorption such as the vehicle (matrix), occlusion, and the duration of contact. The absorption varied significantly under various exposure conditions both in vitro and in vivo from 8–71% (ECHA 2016a; SCCS 2023a). An in vivo study in monkeys demonstrated that dermal application of SA is followed by significant absorption (approximately 60% of a single dose and approximately 80% for 14 days of repeated doses). This value is supported by in vitro studies using human or porcine skin (see **Toxicokinetics**). Therefore, a worst case-scenario dermal absorption percentage of 60% was used for exposure calculations. (ECHA 2016a; SCCS 2023c). For lipstick and oral care products, a worst case value of 100% absorption is used for passage across the oral mucosa (SCCS 2023c).

The SCCS exposure estimates did not consider two potential exposure scenarios that have been identified.

The SCCS exposure estimates did not include inhalation exposure as spray or aerosol products as they were not identified in the use survey. The Government of Canada calculated exposure from the use of hairspray. Calculated exposure levels were up to 0.00077 mg/kg bw (Government of Canada 2020) indicating negligible contribution to overall exposures.

The SCCS exposure estimates also did not consider use in peels. In a 2 period crossover study investigating systemic exposure to salicylic acid (SA) in humans the plasma concentrations in the present study following facial application of a 30% SA cosmetic skin peel formulation applied for 5 min were similar to that of a low concentration (2%) applied in a leave on product to the same body surface area (Fung et al. 2008). The latter scenario was considered in the SCCS opinion.

Although there is some reported use at concentrations in rinse off and leave on products at concentrations slightly higher than current EU concentrations (see **Introduction and use)** this is not expected to significantly change exposure estimates. The SCCS reported exposure estimates are considered relevant for risk characterisation.

The SCCS opinion did not consider the risks of the salts of SA. Based on frequency of use and reported use concentrations (see **Introduction and use**), exposure to the salts would be significantly lower than exposure to SA.

Health hazard information

The previous assessment of these chemicals should be read in conjunction with this evaluation statement (NICNAS 2013). This evaluation reviews new data available for these chemicals relating to toxicokinetics, eye irritation and developmental toxicity.

Toxicokinetics

SA is rapidly absorbed via the oral route. It is also readily absorbed when applied to the skin. Dermal absorption is dependent on the vehicle composition, pH, application site and structure of the skin, as well as conditions of the application on the skin (number of applications and occlusive versus non-occlusive conditions). In in vitro studies using porcine skin, dermal absorption was between 40–58%. In an in vitro study using human skin, dermal absorption was 50% (SCCS 2019). In a study in rhesus monkeys, the percutaneous absorption of radiolabelled SA after a single topical application was 59%. In a multiple dose study in rhesus monkeys, the cumulative absorption was 67% and 78% after the 1st and the 8th dose, respectively (SCCS 2019). Human studies gave dermal absorption values ranging between 8–71% (ECHA 2016b; SCCS 2019). In vitro and animal studies suggest that NaS has a lower dermal absorption than SA (CIR 2019).

SA is found in blood both bound to plasma albumin and as the unbound (free) moiety. In a study investigating the distribution of ASA in rats and monkeys, serum concentration of SA (unbound salicylate) was lower in monkeys (17% to 30% of the total plasma concentration) compared to rats (30% to 50% of the total plasma concentration). Similar concentrations were observed in rat and monkey embryos. (ECHA 2016a). After oral administration of a single dose of SA on GD 14, the highest concentration of SA was obtained in serum. The concentration in the foetus and placenta was approximately 25% and 35% of the serum concentration, respectively (Tanaka et al. 1973). Animal studies with methyl salicylate (that hydrolyses to SA) have indicated that the free salicylate can reach the developing foetus within the first 2.5 hours after either oral or topical administration of methyl salicylate. The concentrations of free salicylates in the foetus were 50–90% of concentrations in the dam (Overman and White 1983). The potential for SA to cross the placenta was confirmed using 14C-SA in an in vitro model of placental absorption (SCCS 2019).

Metabolism of salicylic acid in rats and humans follows a similar route. It is metabolised mainly to salicyluric acid, and conjugated salicylic acid compounds, with a small proportion of oxidative metabolites. The majority of salicylic acid is excreted in the urine (SCCS 2023c).The elimination half-life increases with dose as elimination pathways switch from first order to zero order kinetics (IPCS 1996).

Corrosion/Irritation

Eye irritation

SA is classified as hazardous with hazard category ‘Eye damage – Category 1’ and hazard statement ‘H318 (Causes serious eye damage) (SWA).The available data support this classification. Based on the weight of evidence of the available data for NaS, the salts of SA are expected to be irritating to eyes, warranting hazard classification. In a guideline in vivo study in rabbits reversible irritation was observed. Given the range of results observed in in vivo and in vitro studies sub-categorisation is not proposed.

Salicylic acid

In a non-guideline non-GLP compliant eye irritation study, SA was instilled into 1 eye each of 3 female New Zealand white (NZW) rabbits. The eyes were examined, and the grade of ocular reaction was recorded at 1, 4, 24, 48, 72 96 hours and 7, 14 and 21 days after administration. The following scores were reported: corneal opacity 54.1/80 and conjunctival redness 10.3/20. The effects were not fully reversible within 21 days. The raw data for each

individual animal are not available. Iris score was not evaluated due to the corneal opacity. SA was considered to be a severe eye irritant on the basis of this study (REACH n.d.-a).

In a non-guideline non-GLP compliant ex vivo eye corrosivity/irritation study (bovine corneal opacity and permeability test), SA was applied to corneas at 0.1%, 1%, 5% or 10% (number of corneas not reported). Opacity measurements were classified into four groups: Opacity units 0–20: mild; 21–40: mild/moderate; 41–70: moderate; 70 + severe. The following opacity readings were reported: 7.2, 70.2, 88.2, and 98.7 for 0.1%, 1%, 5% or 10%, respectively. SA was considered to be a severe eye irritant on the basis of this study (REACH n.d.-a).

A number of product formulations or alcohol solutions containing up to 2% SA (low volume eye tests) with pH between 2.3–5.7 were not irritating to slightly irritating to the eye of the animals treated. The intensity of the eye irritation with SA containing formulations was strongly related to the composition and formulation of the matrix and the capacity to migrate into the eyes (SCCNFP 2001).

Sodium salicylate

In a GLP compliant eye irritation study conducted according to OECD TG 405, NaS was instilled into 1 eye each of 3 female NZW rabbits. The eyes were washed out after 24 hours and observed at 1, 24, 48, 72 hours, 7 days. Mean scores were as follows:

- Animal 1: corneal opacity 1/4, iritis 0/2, conjunctival redness 2/3 and chemosis 1/4.
- Animal 2: corneal opacity 0.67/4, iritis 0/2, conjunctival redness 2/3 and chemosis 1/4.
- Animal 3: corneal opacity 0.67/4, iritis 0/2, conjunctival redness 2/3 and chemosis 1/4.

The irritation was reversible in all animals within 7 days (REACH n.d.-c).

In a non-GLP compliant eye irritation study similar to OECD TG 405 (using an old scoring system), NaS was instilled into 1 eye each of 3 female NZW rabbits. The reported maximum average scores (MAS) at 24 hours and 7 days were 37.7/100 and 83.7/100, respectively. According to this old scoring system chemicals with scores of ≤25 – <50 at 24 hours are considered to be moderate eye irritants (REACH n.d.-c).

In a non-GLP compliant eye irritation study NaS was instilled into 1 eye each of 3 female rabbits (strain not specified). No information regarding washing the eyes were provided. On day 14 after application corneal opacity was 4 in 2 rabbits. Iris and conjunctival chemosis, conjunctival redness scores on day 14 were 0, 2 and 2, respectively. No further details of the study were provided (REACH n.d.-c).

In a non-GLP compliant in vitro eye irritation/corrosion study similar to OECD TG 491 (but prior to adoption of test guideline), NaS was suspended in physiological saline and applied to a single layer of rabbit corneal cells at 0.05 % and 5%. After a 5 minute exposure, the percentage cell viability was reported to be 2.5 and 2.7% for 0.05 % and 5 %, respectively. Based on the decision criteria for this test (cell viability at 5 and 0.05 % <70%) predicts category 1) (REACH n.d.-c).

In 2 non-GLP compliant in vitro eye corrosion studies conducted according to OECD TG 492, NaS was topically applied to reconstructed human cornea like epithelium (RhCE) using the EpiOcularTMEIT protocol. Tissue viability was measured following exposure and a post treatment incubation period. The tissue viability was ≤60%. Therefore, based on the decision criteria for this test, no prediction can be made (REACH n.d.-c).

In a non-GLP compliant in vitro eye irritation study similar to OECD TG 494 (but prior to adoption of test guideline) with NaS, the reported time lag was 0 seconds, intensity was 1.01% and the plateau level was 60%. Based on the decision criteria for this test (time lag ≤ 180 second or intensity ≥0.05% or plateau level ael >5%) no stand-alone prediction can be made (REACH n.d.-c).

Reproductive and development toxicity

There are no data available for SA from standard two generation guideline studies. Based on studies with methyl salicylate and ASA, RAC and SCCS concluded that SA did not have adverse effects on sexual function and fertility. This decision was based on GLP compliant fertility studies conducted according to ICH guidelines and non-guideline studies (AICIS 2024; ECHA 2016a; SCCS 2023c). No statistically significant adverse effects were reported in 1, 2 and 3 generation studies at doses up to 648 mg/kg bw/day in rats and 450 mg/kg bw/day in mice (see AICIS 2024 for study descriptions).

Based on the weight of evidence of the available data, SA and its salts may cause specific adverse effects on development, warranting hazard classification. The classification is based on adverse developmental effects including neural tube defects (craniorachischisis), growth retardation and skeletal malformation in rats and neural tube defects (craniorachischisis), and growth retardation in rats and monkeys. The adverse effects on development caused by SA are supported by data for chemicals that metabolise to SA (methyl salicylate and ASA). There were no developmental effects in rabbits. There is extensive human use of ASA as aspirin (which metabolises to SA). There is a lack of evidence to support an increased risk of birth defects following exposure to aspirin. Several international organisations (ECHA 2016a; Government of Canada 2020; SCCS 2023c) have drawn similar conclusions regarding the potential SA to cause developmental toxicity.

In some studies, developmental effects occurred only at doses causing maternal toxicity; however, as the effects seen in these studies are similar to those seen in studies in the absence of maternal toxicity, these studies have been considered to be supportive of the hazard conclusions.

Key studies for hazard characterisation

Salicylic acid

In a non-guideline pre-natal developmental toxicity study similar to OECD TG 414 pregnant Wistar rats (20/dose) were administered SA by gavage at 75, 150 or 300 mg/kg bw/day on gestation day (GD) 8–14. Foetuses were examined on GD 20 and offspring examined on day 56 after birth. At 300 mg/kg bw/day body the dams did not gain weight. Clinical signs of toxicity included salivation and piloerection. There were no effects on dam body weight or clinical sings of toxicity at the two lower doses. Uterine weights were decreased in dams receiving 150 and 300 mg/kg bw/day. Foetal mortality was observed at 150 (25.7%) and 300 (100%) mg/kg bw/day. Litter size and neonatal body weight, body length, and tail length were significantly decreased in the 150 mg/kg bw dose group. The incidences of external, internal, and skeletal anomalies in foetuses (GD 20) were 1.8%, 0%, and 2.5%, respectively, for the 75 mg/kg bw group and 27.8%, 12.7%, and 65.7%, respectively for the 150 mg/kg bw group. Neural tube defects (craniorachischisis) were observed in 8% of the foetuses at 150 mg/kg bw. On day 56 after birth, the incidences of external organ, internal organ, and skeletal anomalies in offspring were 0%, 5.0%, and 0%, respectively, for the 75 mg/kg bw group and 13.7%, 17.2%, and 79.2%, respectively, for the 150 mg/kg bw group. The maternal no adverse effect level (NOAEL) was 150 mg/kg bw/day and the NOAEL for

developmental toxicity was 75 mg/kg bw/day (ECHA 2016a; SCCS 2023c; Tanaka et al. 1973).

In a non-guideline pre-natal developmental toxicity study similar to OECD TG 414 pregnant Wistar rats (20/dose) received SA in diet at 0.06, 0.1, 0.2 or 0.4% (equivalent to 50.7, 77.4, 165 and 205.9 mg/kg bw/day) on GD 8–14. Foetuses were examined on GD 20 and offspring examined on day 56 after birth. At the highest dose, the dams had a temporary bodyweight loss (GD 8–11). Clinical signs of toxicity included salivation and piloerection. No dam toxicity was observed at any of the other doses. At the highest dose there was high foetal mortality (no live foetuses in 9/15 dams examined), high frequency developmental defects (skull deformation, neural tube defects and limb deformities) and foetal growth retardation (very low uterine weights of foetuses). At this dose there was also a reduction in placental weights, litter size, body weight, body length and tail length. There were no differences in the number of corpora lutea or implantation rate in any of the groups. At 0.2% (165 mg/kg bw/day) there was a statistically significant reduction in foetal body weight, body length and the tail length. Effects observed in offspring on day 56 after birth included external anomalies (3.8%) and skeletal anomalies (14.6%). The two lowest doses (50.7 and 77.4 mg/kg bw/day) did not affect either dams or pups. The maternal NOAEL was 165 mg/kg bw/day based on bodyweight loss at the highest dose. The NOAEL for developmental toxicity was 77.4 mg/kg bw/day based on reductions in body weight body length and the tail length (ECHA 2016a).

Sodium salicylate

In a non-guideline pre-natal developmental toxicity study similar to OECD TG 414, pregnant albino rats (12–15/dose) received NaS in tap water at 25, 75, or 150 mg/kg bw/day on GD 15–20 or at 4.2, 12.5, or 25 mg/kg bw on GD 20–21. Maternal body weight gain was comparable for all groups. No clinical signs of toxicity were observed. Parturition was delayed in one female of the control and 25 mg/kg group and in 2 females of the 150 mg/kg bw group. Litter size and male to female ratios were similar for all groups. The neonatal mortality rate in the 150 mg/kg bw dose group dosed on GD 15–20 and in the 12 and 25 mg/kg bw dose groups dosed on GD 20–21 was increased. No developmental abnormalities were observed. The NOAEL for maternal toxicity was 150 mg/kg bw. The NOAEL for developmental toxicity was 90 mg/kg bw day (CIR 2019).

In a non-guideline pre-natal developmental toxicity study similar to OECD TG 414, pregnant Sprague Dawley rats (17–19/dose) received NaS in distilled water at 30, 90, or 180 mg/kg bw/day via oral gavage on GD 6–15. The dams were euthanised on GD21. Maternal toxicity was only observed at the highest dose and described as a slight reduction in food intake. Foetal body weight was decreased in the 90 and 180 mg/kg bw dose groups. At these doses skeletal maturation was also decreased. At the highest dose, malformations indicative of teratogenicity occurred in 30% of the foetuses. The most prominent malformation in the high-dose group was neural tube defects (craniorachischisis) (22.7%). No foetal toxicity was observed in the mid or low dose groups. The NOAEL maternal toxicity was 90 mg/kg bw/day and the NOAEL for developmental toxicity was 90 mg/kg bw/day (ECHA 2016a).

Supporting studies

Salicylic acid

In a non-guideline developmental toxicity study SA was dermally applied to the back of CD rats as a single dose at 0, 450, 670, 1000, 1500, and 2250 mg/kg bw (n=3) on GD 12. Treatment with SA resulted in reduced number of implantation sites, reduced number of live foetuses, and increased number of early resorptions. A dose level of 1500 mg/kg bw/day was

determined to be lethal to the pregnant animals. No details at which dose these effects occurred are available and no statistical analyses was performed (Government of Canada 2020).

Other older studies discussed in ECHA, SCCS or Government of Canada (ECHA 2016a; Government of Canada 2020; SCCS 2023c) with significant deviations form OECD TG 414 include studies in:

- SD rats dosed twice daily with SA at 10 mg/kg bw on GD 20 and 21. Adverse effects included: an increase in parturition onset and duration and increased bleeding at parturition. All foetuses survived the study.
- SD rats administered 380 mg/kg bw SA subcutaneously on GD 9. There was marked maternal weight loss, decreased foetal an increase in resorptions and foetal malformation.

Methyl salicylate

Decreased pup survival and increased incidences of neural tube defects (craniorachischisis), and skeletal abnormalities were observed in developmental studies in rats (subcutaneous injection) and hamsters (oral and dermal). These effects were observed when methyl salicylate was administered orally. For full study details, see the related AICIS Evaluation Statement on methyl salicylate (AICIS 2024).

Acetylsalicylic acid

In a developmental toxicity study following International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH) guidelines, pregnant SD rats were administered ASA by gavage at 50, 125 and 250 mg/kg bw/day (equivalent to 38, 96 and 192 mg/kg bw SA) on GD 6–17 (Gupta 2003). There was a dose dependent decrease in maternal body weight that was statistically significant at the mid dose (85% of control) and high dose (52% of control). Food consumption was significantly reduced at the high dose (85% of control). Irregular respiration and sporadic salivation were observed in the dams at 250 mg/kg bw/day. At the highest dose (250 mg/kg bw) early resorptions, increased post implantation loss, increased variations and malformations were observed. The malformations included:

- absence of eye lids
- neural tube defects (craniorachischisis)
- bent forepaw
- kinked tail
- protruding tongue
- abdominal wall defects
- ectopic adrenal
- ventricular septal defect (VSD)
- diaphragmatic hernia
- hypoplastic kidney
- hypoplastic testes.

At 125 mg/kg bw, foetal viability was reduced. No malformations were reported at this dose The NOAEL for maternal and developmental toxicity was 50 mg/kg bw (ECHA 2018; SCCS 2023c).

In a non-guideline developmental toxicity study, SD rats were administered ASA by gavage at 50, 100, or 200 mg/kg bw/day on GD 7–17. At the highest dose, dams had a decreased body weight. At this dose there was an increased number of resorptions, malformations, and skeletal abnormalities. At the middle dose (100 mg/kg bw/day) decreased foetal bodyweight was reported. There was no effects on dams at this dose. The NOAEL for maternal toxicity was 100 mg/kg bw/day. The NOAEL for developmental toxicity was 50 mg/kg bw/day based on reduced foetal bodyweight at 100 mg/kg bw/day (ECHA 2018).

In a non-guideline developmental toxicity study, rats (strain not reported) were administered ASA in their diet at 0.2 or 0.4% in diet equivalent to (99 or 224 mg/kg bw) on GD 6–15. Another group of animals were administered ASA by gavage at 250 mg/kg bw on GD 6–15. Maternal toxicities were reported at 0.2 and 0.4% in diet (reduced food intake and weight gain). Foetal toxicity was reported at all doses; skeletal malformations at 0.2% (99 mg/kg bw) and 100% resorptions at the two highest doses (ECHA 2016a; SCCS 2023c).

In non-guideline developmental toxicity study conducted according to ICH guidelines, NZW rabbits were administered ASA via oral gavage at 125, 250 or 350 mg/kg bw/day on GD7–19. Maternal body weight gain was significantly reduced in the mid and high dose groups from GD7 to GD13. Food consumption was also reduced in these groups. There were no treatment related effects on corpora lutea, implantation sites, pre-implantation losses or embryofoetal mortality. There were no treatment related visceral or external anomalies. Reduction in mean foetal weight was reported at the highest dose. The NOAEL for maternal toxicity was 125 mg/kg bw. The NOAEL for developmental toxicity was 250 mg/kg bw based on reduced foetal weights at the highest dose (ECHA 2016a).

In another study with limited information available, rabbits received ASA at 200 or 250 mg/kg on GD 6–13 or GD 6–18. ASA induced maternal toxicity but no skeletal malformations or other effects on offspring (ECHA 2016a).

In a non-guideline study, pregnant rhesus monkeys (8/dose), were administered ASA at 150 or 200 mg/kg bw via gavage twice daily on GD 23–32 (no report of a control group). There was an increase in intrauterine death (3/dose) and transitory growth retardation at both doses. Malformations at 150 mg/kg bw included neural tube defects (craniorachischisis), and kidney cysts. Limited information on maternal toxicity is available but the authors stated that dose below 200 mg/kg bw/day were well tolerated (ECHA 2016a; SCCS 2023c).

Observation in humans

Despite its long term historical usage, data regarding human exposure to SA itself is lacking. Extensive data is available for ASA as aspirin, which metabolises to SA. Aspirin is a widely used medicine and has been used for a long time. Most data indicates that low doses of aspirin do not increase risk of adverse effects on pregnancy. Although some adverse effects at higher doses such as maternal bleeding and changes in pregnancy duration and labour have been reported, no malformations were identified at any dose. The difference in the dose range between the animal studies and the human epidemiology studies is very high (ECHA 2016a).

Endocrine effects

There are indications from the literature that SA may have endocrine modulating properties; however, there are no in vivo or in vitro studies available that have explicitly examined the potential endocrine mode of action of SA itself. The current available data does not provide

sufficient evidence of an adverse effect of SA from an endocrine mode of action (SCCS 2023c).

In 2018, the Danish Centre for Endocrine Disrupters evaluated SA as meeting the WHO definition of an endocrine disruptor (IPCS 2002), with evidence of thyroid disruption and an anti-androgenic mode of action leading to adverse effects (CeHoS 2018). This assessment was largely based on available literature on SA and analogue chemicals including acetylsalicylic acid and methyl salicylate in humans or animal models. However, the American Chemistry Council has reviewed the Danish list of endocrine disruptors and critiqued several limitations and weaknesses in the assessments (ACC 2018). In a reassessment, SCCS considered that the Danish Centre for Endocrine Disrupters evaluation which relied heavily on data for acetylsalicylic acid to infer the endocrine effects of SA, with few data on SA itself. They suggested that more specific studies using SA are needed to conclude on its endocrine disrupting properties (SCCS 2023c). Endocrine effects of SA are still being reviewed under Biocidal Products Regulation (BPR) (ANSES 2021).

SA appears to have negligible oestrogenic or androgenic activity. A study of the oestrogenic activity of phenolic additives determined by an in vitro yeast bioassay reported no detectable oestrogenic activity for SA and no or very low oestrogenic activity for tested salicylate esters. This study found that major criteria for oestrogenic activity is the presence of an unhindered phenolic OH group in a *para* position, whereas SA and its esters have a hindered OH group in the *ortho* position (Miller et al. 2001). Additional oestrogen activity modelling and screening studies gave similar results. Modelling performed under the US EPA's Endocrine Disruptor Screening Program found negligible potential for oestrogen receptor agonist, antagonist, and bioactivity for SA (US EPA n.d.-b). Testing of SA within the US EPA Tox21 program found no activity in 18 oestrogen receptor assays, no activity in 9 thyroid receptor assays, and it was not steroidogenic in 2 assays. Of the 15 androgen receptor assays, only one was registered as positive above a cut off value, but this was a marginal and inconclusive observation. There was no indication that SA was endocrine active in these systems (SCCS 2023c; US EPA n.d.-a).

Several studies using rats, rat serum, or human blood samples summarised in CeHoS (2018) indicate that salicylate can displace the thyroid hormones T3 and T4 from thyroxine-binding globulin, a blood serum transport protein. These studies generally involved very high direct doses of salicylate. No studies that investigated endpoints relevant for evaluation of adverse effects related to thyroid disruption have been identified.

Other

The SCCS concluded that based on the reviewed data on humans and mice, SA does not have photo-irritant, photosensitising, or photocarcinogenic properties (SCCS 2023c).

Human health risk characterisation

Critical health effects

The critical health effects for risk characterisation are local effects (eye irritation) and systemic effects (developmental toxicity). The NOAEL selected for risk characterisation was 75 mg/kg bw based on a development toxicity studies in rats. Developmental effects including neural tube defects (craniorachischisis), growth retardation and skeletal malformation in rats and neural tube defects and growth retardation in monkeys, were consistently seen at doses of ≥150 mg/kg bw.

Public risk

The MoS (also referred to as margin of exposure or MOE) methodology is commonly used to characterise risks to human health associated with exposure to chemicals (US EPA 2003).

The MoS risk estimate provides a measure of the likelihood that a particular adverse health effect will occur under the conditions of exposure. As the MoS increases, the risk of potential adverse effects decreases. To decide whether the MoS is of sufficient magnitude, expert judgment is required. Such judgments are usually made on a case by case basis and should consider uncertainties arising in the risk assessment process such as the completeness and quality of available data, the nature and severity of effect(s) and intra/inter species variability. In general, an MoS value greater than or equal to 100 is considered acceptable to account for intra- and inter-species differences.

The critical health effect for these chemicals is developmental toxicity. The SCCS recently reassessed the safety of SA in cosmetic products. The SCCS concluded that the probabilistic assessments using 100% occurrence and maximum use levels of a substance (see **Human exposure - Public**) in each product category as adequately conservative for risk assessment. Therefore, the SCCS used the aggregate exposure of 0.45 mg/kg bw/day in margin of safety calculations. The calculated MoS was 167. Although some additional exposure scenarios were identified that were not considered in the SCCS calculations (see **Human exposure - Public**) these are unlikely to significantly change the MoS value to <100.

The SCCS concluded that based on their safety assessment of all available information, including potential endocrine effects, the use of SA is safe under the existing European restrictions on concentrations (SCCS 2023b). A similar conclusion was reached in an industry initiated review of SA in cosmetic products. They concluded that the use of SA as cosmetic ingredient at levels currently authorised by the EU cosmetic regulation is safe based on the calculated MoS values and clinical evidence with ASA (Labib et al. 2018).

Australian use patterns for the various product categories are assumed to be similar to those in Europe. Therefore, the calculated MoS indicating that SA is safe for use at international exposure levels indicates that current use levels in Australia are unlikely to pose a risk to the public.

Although the SCCS did not consider the risks of salts of SA, based on frequency of use and reported use concentrations (see **Introduction and use**), exposure to the salts would be significantly lower than exposure to SA. Therefore risks would also be lower.

Environmental exposure

Salicylic acid and its salts are used internationally in high volumes in a variety of industrial and other uses. These chemicals have a variety of functions and industrial applications in consumer products ranging from personal care products to household cleaning and washing products, as well as a variety of commercial and site limited uses with limited environmental release. They also have non-industrial uses in certain types of biocidal products, agricultural and veterinary products, and therapeutic goods, but those uses are outside the scope of this evaluation. These chemicals are expected to be found in products available for use in Australia that are formulated similarly to those available internationally.

Chemicals used in personal care, cleaning, and washing products are typically released to wastewater as a normal part of their use in consumer and commercial applications. Some

fraction of the quantity of chemicals in wastewater entering sewage treatment plants (STPs) can be emitted to:

- the air compartment
- rivers or oceans in treated effluent
- soil by application of biosolids to agricultural land (Struijs 1996).

Such uses of these chemicals are expected to be the main environmental exposure pathway.

Environmental fate

Dissolution, speciation and partitioning

Chemicals reported in this evaluation are expected to remain in or partition to water when released into the environment.

Salicylic acid and its salts are readily soluble and expected to dissociate into the carboxylate (salicylate) anion and the respective counter cations in the environment. The Henry's law constant indicates very slight volatility from water and moist soil. Salicylate anions have low lipophilicity, which will limit partitioning from water to organic matter.

Degradation

Salicylic acid and its salts are readily biodegradable in water.

The REACH dossier for NaS reports a key study performed according to OECD TG 301 D. After 28 days the degradation, estimated by the Biological Oxygen Demand (BOD), was 88.19%. Based on the results of this test, NaS is readily biodegradable (REACH n.d.-c).

The REACH dossier for SA reports a key study performed according to OECD TG 301 C and generated by the Japanese Competent Authorities (NITE n.d.). The percentage of biodegradation was estimated by the BOD, the Total Organic Carbon (TOC) and the test substance analysis (estimated by HPLC). The corresponding percentages of biodegradation obtained after 14 days were 88.1%, 97.6% and 100% respectively. Based on these results, SA is readily biodegradable (REACH n.d.-a).

The REACH dossier for SA reports another key study that was performed according to an inherent biodegradability method which has later been adopted as OECD TG 302 B. After 4 days, the biodegradation of SA, based on Dissolved Organic Carbon (DOC) removal, was higher than 90%. This result is consistent with the ready biodegradability of SA (REACH n.d.-a).

In another study according to OECD TG 301 F, SA showed a biodegradation of 94% (O_2 consumption) within 28 days, but no information was reported on the 10-day window criteria (REACH n.d.-a). This study is consistent with the ready biodegradability of SA.

Hydrolysis is not expected to be an important environmental fate process for SA due to the lack of hydrolysable functional groups (REACH n.d.-a).

Phototransformation in water is also not expected to be an important environmental fate process for SA. Calculated half-lives for the photochemical reaction of SA and the salicylate ion with hydroxyl radicals in water under conditions of continuous full intensity sunlight range from approximately 30–47 and 40–142 days, respectively (REACH n.d.-a).

Bioaccumulation

Salicylic acid and its salts have low potential to bioaccumulate in aquatic life. The measured log K_{OW} values for these chemicals and calculated bioconcentration factors of approximately 3 L/kg are lower than the Australian thresholds for bioaccumulation (log Kow ≥ 4.2 and BCF ≥ 2,000 L/kg) (DCCEEW n.d.).

Environmental transport

Chemicals in this evaluation are not expected to undergo long range transport based on their short half-lives in the environment.

In one monitoring study, SA was detected in the range from 1–11 µg/L in 17 out of 20 samples of the ocean waters around King George Island, Antarctica (Marcotti-Murua et al. 2020). However, the authors proposed that the distribution pattern and non-detects of this substance at some sample points with limited human activity suggests an anthropic origin.

Predicted environmental concentration (PEC)

The PEC of salicylate ions is 1.53 µg/L based on Australian river monitoring data.

While a salicylate concentration in STP effluent can be estimated using the Australian use volume of 10,000–99,999 tonnes per annum and STP modelling (Struijs 1996), this is likely to result in overestimated values. The total Australian use volume is expected to include substantial volumes associated with industrial uses of these chemicals with low release to the environment (e.g., as an intermediate) and potentially non-industrial uses of these chemicals as well. Modelling will also underestimate removal of this anionic chemical at Australian STPs that are consistently treating influent containing SA.

Australian and international studies indicate that salicylate is effectively removed from wastewater streams during sewage treatment. A recent study of 31 STPs in Victoria detected SA in 70% of influent samples (limit of reporting 20 µg/L), while it was not detected in any effluent samples (limit of reporting 2 µg/L) (Saaristo et al. 2023). At an STP in Sydney, salicylate concentrations in raw influent samples averaged 13 µg/L, primary effluent averaged 6.1 µg/L and secondary effluent averaged 0.38 µg/L indicating average removal of about 97% after secondary treatment (Khan and Ongerth 2005). At three German STPs in Berlin, high influent concentrations of 87, 109 and 184 µg/L were reduced by more than 99% to 0.21, 0.33 and 0.15 µg/L in effluent (Khan 2002). In a study of Canadian STPs, median influent concentrations were 330 µg/L and median effluent concentrations were 3.6 µg/L, suggesting removal rates of about 99% (Metcalfe et al. 2003). SA was found at a median concentration of 2.4 µg/L in the influent of STPs in Spain, where removal exceeded 90%, and, when detected, the concentrations found in surface water were typically lower than 0.01 µg/L (Rodil et al. 2012). In a separate study in Spain, average concentrations for influent, effluent, river water and river sediment were 0.295 µg/L, 0.03 µg/L, 0.07 µg/L and 0.318 µg/g, respectively (Carmona et al. 2014). SA was detected in German STP influent samples at concentrations up to 54 µg/L, however it was efficiently removed and only detected in very low concentrations in STP effluents (<0.05–0.14 µg/L) and river waters (<0.01–4.1 µg/L) (Heberer 2002; Ternes 1998).

For the purposes of risk characterisation, a PEC of 1.53 µg/L was selected. This is the highest concentration observed in a monitoring study of 73 Australian river sites. The study notes SA as the most frequently detected compound (82% of sites), as it is also an important metabolite of acetylsalicylic acid (aspirin) and a plant hormone found in many plant species,

most notably in willow trees. Willows are a pest species around many Australian waterways and this may partly explain the broad presence of SA in the study (Scott et al. 2014). As such, this may be an overestimate of the concentration of SA in Australian rivers due to industrial uses of these chemicals reported in this evaluation. It will; however, be used as a conservative PEC for the risk assessment.

Environmental effects

Effects on Aquatic Life

Acute toxicity

The following measured median effective concentration (EC50) and median lethal concentration (LC50) values for freshwater fish and invertebrates were retrieved from the REACH dossiers for NaS and SA (REACH n.d.-a; n.d.-c). The algae data were obtained from the Japan Chemicals Collaborative Knowledge (J-CHECK) database (NITE n.d.). Several of the identified ecotoxicity tests had insufficient pH control, resulting in endpoints impacted by lowered pH in the test medium when SA was used as the test substance. Preference has been given to data from studies using NaS or where the test solutions were neutralised:

Taxon	Endpoint	Method
Fish	NaS: 96h LC50 = 1370 mg/L	*Pimephales promelas* (fathead minnow) Flow-through Measured concentrations Equivalent to OECD TG 203
Invertebrates	SA: 48h EC50 = 870 mg/L	*Daphnia magna* (water flea) Immobilisation Static conditions, pH neutralised Nominal concentrations Equivalent to OECD TG 202
Algae	SA: 72h EC50 = 65 mg/L	*Unreported species* (green algae) Growth rate Static conditions Nominal concentrations Unreported test guideline of NITE

A study on algae (Chlorella vulgaris) investigating NaS toxicity according to OECD TG 201 is presented in the REACH dossiers for NaS and as read across for KS (REACH n.d.-b; n.d.-c). That study reports a lower acute endpoint of 48.29 mg/L and the data presented leads to a low chronic EC10 of about 1.5 mg/L by logarithmic regression. However, there are doubts about the validity of this data as the mean coefficient of variation of the control (160%) exceeded the validity criteria of < 35% and the algae did not demonstrate exponential growth during the 72h test. The results of this study will not be used for the purposes of the risk characterisation.

A recent study reported sub-lethal effects of SA on *Daphnia magna* at low exposure concentrations (Szabelak and Bownik 2021). Behavioural effects on swimming speed, swimming height, distance travelled, and mandible movement were observed after 72 hours exposure at concentrations in the range of 2.8–370 µg/L. Physiological effects on heart rate were found at higher concentrations of approximately 2 mg/L. A 72-hour LC50 of 6.16 mg/L was also calculated. However, as test media were apparently not neutralised before the exposure period began, effects observed at higher concentrations were likely due to lowered

pH rather than substance toxicity. While the pH may not have been strongly affected at low test concentrations, the pH effects would disrupt any observed dose-response relationship and make endpoint derivation difficult.

Chronic toxicity

The following measured no observed effect concentration (NOEC) values were retrieved from a journal paper for fish (Zivna et al. 2016), the paper cited in the REACH dossier for SA for invertebrates (Marques et al. 2004; REACH n.d.-a), and the J-CHECK database for algae (NITE n.d.):

Taxon	Endpoint	Method
Fish	SA: 28d NOEC > 40 mg/L	*Danio rerio* (zebra fish) Growth Flow through Nominal concentrations OECD TG 215
Invertebrates	SA: 21d NOEC = 5.6 mg/L	*Daphnia longispina* (water flea) Mortality pH neutralised Nominal concentrations OECD TG 211
Algae	SA: 72h NOEC = 31 mg/L	*Unreported species* (green algae) Growth rate Static conditions Nominal concentrations Unreported test guideline of NITE

Endocrine effects

There is evidence that salicylate interacts with endocrine systems but limited evidence of adverse effects, even at high doses. Most of the current evidence is based on human or animal model studies, often with analogue chemicals such as acetylsalicylic acid and methyl salicylate (see **Health hazard information – Endocrine effects**). There are relatively few studies available on endocrine effects in more environmentally relevant organisms. There is currently insufficient evidence to suggest harmful effects in the environment. While some studies indicate that high concentrations of salicylate may interact with the thyroid hormone system, this is considered to have low environmental relevance.

In a study investigating the effects of acetylsalicylic acid in tilapia, van Anholt et al. (2003) observed that plasma cortisol concentrations varied in an inversely proportional manner to plasma salicylate concentrations after dosing with acetyl salicylic acid. A follow up study dosing rainbow trout with SA observed no variation of plasma cortisol levels compared to the control (Gravel and Vijayan 2006), suggesting that the effect observed in van Anholt et al. (2003) was likely due to acetylsalicylic acid rather than salicylate itself.

There is evidence to suggest that high doses of salicylate may affect steroidogenesis and stress-induced hormone release in fish. Gravel and Vijayan (2006) conducted both in vitro and in vivo tests on rainbow trout. They reported that SA disrupts interrenal steroidogenesis and brain glucocorticoid receptor expression in rainbow trout. However, the in vivo findings were observed following feeding for 3 days at relatively high doses of 100 mg/kg bodyweight, which substantially exceeds expected environmental intake levels.

An in vitro test using rainbow trout interrenal cells found that the presence of salicylate could depress cortisol production. Liquid cell cultures of trout interrenal cells with a series of salicylate test concentrations were incubated for 22 hours before cortisol production was induced by addition of acute adrenocorticotrophic hormone. Cortisol production was depressed compared to the control at salicylate concentrations from 1.38 mg/L to the highest test concentration of 137 mg/L. The maximum suppression observed was up to approximately 60% of the control.

In a separate in vivo test, the authors fed rainbow trout a diet laced with 100 mg/kg salicylate for 3 days before tissue samples were taken for tests. No effect on cortisol or glucose levels in sample blood plasma was found compared to control fish. Brain tissue was found to have significantly reduced glucocorticoid receptor content in the treated group compared to control. In interrenal tissue samples, transcription of some genes related to steroidogenesis and cortisol production were affected. Of the enzymes investigated, steroidogenic acute regulatory protein and peripheral-type benzodiazepine receptor mRNA transcript levels were depressed compared to control fish. The others, cytochrome P450 side chain cleavage enzyme and 11β-hydroxylase, were unaffected.

The interrenal tissue samples were used in a further cortisol induction test, where salicylate fed fish tissue produced significantly less cortisol (50%) compared to the control tissue.

The study authors conclude that salicylate exposure may disrupt cortisol production capacity in rainbow trout. While typical circulating cortisol levels are unaffected, cortisol production in response to acute external stressors may be depressed due to reduced expression of key steroidogenic enzymes.

Predicted environmental concentration (PEC)

A freshwater PNEC of 56 µg/L was derived for chemicals in this group from the measured invertebrates chronic ecotoxicity endpoint (21d NOEC = 5.6 mg/L), using an assessment factor of 100. This assessment factor was selected conservatively, as although chronic ecotoxicity data are available for three trophic levels, including the most acutely sensitive species, there may be non-standard sub-lethal effects at low concentrations (EPHC 2009).

Categorisation of environmental hazard

The categorisation of the environmental hazards of the assessed chemicals according to Australian Environmental Criteria for Persistent, Bioaccumulative and/or Toxic Chemicals is presented below:

Persistence

Not persistent (Not P). Based on being readily biodegradable in measured studies, chemicals in this group are categorised as not persistent.

Bioaccumulation

Not bioaccumulative (Not B). Based on low calculated bioconcentration factors (BCF) in fish and a low log K_{OW} value, chemicals in this group are categorised as not bioaccumulative.

Toxicity

Not toxic (Not T). Based on acute ecotoxicity values above 1 mg/L and chronic ecotoxicity values above 0.1 mg/L, chemicals in this group are categorised as not toxic.

Environmental risk characterisation

Based on the PEC and PNEC values determined above, the following Risk Quotient (RQ = PEC ÷ PNEC) has been calculated for release of chemicals in this group into water:

Compartment	PEC	PNEC	RQ
Water	1.53 µg/L	56 µg/L	0.0273

For water, an RQ less than 1 indicates that these chemicals are not expected to pose a significant risk to the environment based on estimated emissions, as environmental concentrations are below levels likely to cause harmful effects.

While there is some evidence that these chemicals interact with the thyroid and glucocorticoid endocrine systems at high doses, there is currently insufficient evidence to suggest harmful effects in the environment.

Uncertainty

This evaluation was conducted based on a set of information that may be incomplete or limited in scope. Some relatively common data limitations can be addressed through use of conservative assumptions (OECD 2019) or quantitative adjustments such as assessment factors (OECD 1995). Others must be addressed qualitatively, or on a case-by-case basis (OECD 2019).

The most consequential areas of uncertainty for this evaluation are:

- The importance of the reported sub-lethal acute effects in the environment. The PNEC is about the same order of magnitude as the 72h EC50s for sub-lethal effects noted above for invertebrate behaviour, where it is unclear how much impact pH may have had on the study results. However, the conservative PEC is lower than those non-standard endpoints and their importance to the environmental risk of these chemicals is not well established.
    - Further evaluation may be required if non-standard effects are found at low concentrations in a reliable study.
- The uncertainty around the endocrine activity of these chemicals, particularly pending the outcomes of any further testing on their endocrine effects.
    - Further evaluation may be required if data becomes available indicating environmentally relevant endocrine activity of these chemicals.
- The identity and environmental effects of the degradation products of these chemicals in this evaluation are limited.
    - Further evaluation may be required if more information becomes available in the future to indicate the potential for any environmental metabolites or degradants to cause harm in the environment (Scott et al. 2014).

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