Salicylic acid and its salts: Human health tier II assessment

28 June 2013

Chemicals in this assessment

Chemical Name in the Inventory	CAS Number
Benzoic acid, 2-hydroxy-, monosodium salt	54-21-7
Benzoic acid, 2-hydroxy-	69-72-7
Benzoic acid, 2-hydroxy-, calcium salt (2:1)	824-35-1
Benzoic acid, 2-hydroxy-, monopotassium salt	578-36-9

Preface

This assessment was carried out by staff of the National Industrial Chemicals Notification and Assessment Scheme (NICNAS) using the Inventory Multi-tiered Assessment and Prioritisation (IMAP) framework.

The IMAP framework addresses the human health and environmental impacts of previously unassessed industrial chemicals listed on the Australian Inventory of Chemical Substances (the Inventory).

The framework was developed with significant input from stakeholders and provides a more rapid, flexible and transparent approach for the assessment of chemicals listed on the Inventory.

Stage One of the implementation of this framework, which lasted four years from 1 July 2012, examined 3000 chemicals meeting characteristics identified by stakeholders as needing priority assessment. This included chemicals for which NICNAS already held exposure information, chemicals identified as a concern or for which regulatory action had been taken overseas, and chemicals detected in international studies analysing chemicals present in babies' umbilical cord blood.

Stage Two of IMAP began in July 2016. We are continuing to assess chemicals on the Inventory, including chemicals identified as a concern for which action has been taken overseas and chemicals that can be rapidly identified and assessed by using Stage One information. We are also continuing to publish information for chemicals on the Inventory that pose a low risk to human health or the environment or both. This work provides efficiencies and enables us to identify higher risk chemicals requiring assessment.

The IMAP framework is a science and risk-based model designed to align the assessment effort with the human health and environmental impacts of chemicals. It has three tiers of assessment, with the assessment effort increasing with each tier. The Tier I assessment is a high throughput approach using tabulated electronic data. The Tier II assessment is an evaluation of risk on a substance-by-substance or chemical category-by-category basis. Tier III assessments are conducted to address specific concerns that could not be resolved during the Tier II assessment.

These assessments are carried out by staff employed by the Australian Government Department of Health and the Australian Government Department of the Environment and Energy. The human health and environment risk assessments are conducted and published separately, using information available at the time, and may be undertaken at different tiers.

This chemical or group of chemicals are being assessed at Tier II because the Tier I assessment indicated that it needed further investigation.

For more detail on this program please visit:**www.nicnas.gov.au**

Disclaimer

ACRONYMS & ABBREVIATIONS

Grouping Rationale

The four chemicals assessed in this report belong to the group of salicylic acid (SA) and its salts which share the same regulatory restrictions under EC Cosmetics Directive (see Regulatory section for details). They were also reviewed by the Cosmetic Ingredient Review Panel based on their structure similarities and/or their functions in cosmetic products (CIR, 2003). The cations in each case are of low systemic toxicity (see IMAP Tranche One—Identification of chemicals of low concern to human health, NICNAS, 2012). In addition, the salts are expected to protonate to SA after oral ingestion.

Import, Manufacture and Use

Australian

SA is the only chemical within the group that is listed on the 2006 High Volume Industrial Chemicals List (HVICL) with a total reported volume between 10000 and 99999 tonnes, although specific functions were not reported (NICNAS, 2006).

International

Annual production and/or import volumes of SA and sodium salicylate (NaS) were reported between 10000−100000 and 1−10 tonnes respectively in the REACH dossiers. Calcium salicylate (CaS) and potassium salicylate (KS) have not yet been registered under REACH.

The following international uses have been identified through the European Union Registration, Evaluation and Authorisation of Chemicals (EU REACH) dossiers, Galleria Chemica, Substances in Preparations in Nordic Countries (SPIN) database, the European Commission Cosmetic Substances and Ingredients (CosIng) database, United States (US) Personal Care Products Council International Nomenclature Cosmetic Ingredients (INCI) directory, US Household Products database, and Cosmetic Ingredient Review (CIR, 2003).

Members of this group have reported cosmetic use including:

- SA: preservative, denaturant, exfoliant, fragrance ingredient, antidandruff, keratolytic, hair conditioning, skin conditioning agent (in a range of rinse-off and leave-on products including make-up products).
- NaS: preservative, denaturant.
- CaS: preservative.
- KS: cosmetic biocide, preservative.

Members of this group have reported domestic use including:

- SA: adhesive, binding agent, cleaning/washing agent, corrosion inhibitors, paint, lacquer, varnish, and surface treatment agent.
- NaS: cleaning/washing agent, colouring agent, paint, lacquer, varnish, and surface treatment agent.

Members of this group have reported commecial use including:

- SA: antistatic agents, construction materials, fillers, process regulators, and viscosity adjustors.

Members of the group have reported site-limited use including:

- SA: electroplating agent, intermediate, laboratory agent.
- NaS: electroplating agent, laboratory agent.

Members of the group have reported non-industrial use including:

- SA: non-agricultural pesticides and preservatives, pharmaceuticals.
- NaS: pharmaceutical.

Restrictions

Australian

Two members of this group are listed in the Poison Standard (SUSMP−Standard for Uniform Scheduling of Medicines and Poisons) as follows:

- SA: Schedule 3 'Salicylic acid in preparations for dermal use **except** in preparations containing 40 per cent or less of salicylic acid.'
- NaS: Schedule 4 'Sodium salicylate in preparations for injection for the treatment of animals.'

These restrictions do not apply to industrial use of these chemicals.

International

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

- SA is restricted to '3 % maximum in rinse-off hair products and to 2 % maximum in other products. Not to be used in preparations for children under three years of age, except for shampoos. 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'.

EC Cosmetics Directive Annex VI (List of Preservatives Allowed):

- SA and its salts are restricted to '0.5 % maximum for use as preservatives. Not to be used in preparations for children under three years of age, except for shampoos'.

Health Canada List of Prohibited and Restricted Cosmetic Ingredients (Hotlist):

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

Existing Worker Health and Safety Controls

Hazard Classification

The chemicals are not listed on the Hazardous Substances Information System (HSIS) (Safe Work Australia).

Exposure Standards

Australian

No specific exposure standards are available.

International

STEL (short-term exposure limit) = 0.1 mg/m³, skin [Russia] (Galleria Chemica).

Health Hazard Information

Toxicokinetics

Orally administered SA is readily and extensively absorbed into the blood. The salts will be absorbed orally as SA. In vitro, dermal absorption of SA through rat skin was around 20 % over 24 hours and through human skin at a dermal penetration coefficient of 88 µg/cm²/h and a lag time of ~3 h to reach steady state (REACH). According to SCCNFP (2001), the human dermal absorption of SA is also in the range of 20 % of the topically applied dose and is strongly dependent on the vehicle composition, pH, skin structure and application conditions (single dose, repeated doses, occlusion). Dermal absorption of the salts will similarly depend on formulation.

After absorption, SA is distributed throughout the extracellular fluid and several organs of the body (including liver, kidney, lungs, bone marrow, stomach, intestine, spleen and the placenta). As for acetylsalicylic acid (aspirin), SA and its salts are expected to specifically accumulate in inflamed tissues.

SA is rapidly excreted, predominantly in the urine as oxidative metabolites such as 2,3- and 2,5-dihydroxybenzoic acids, after conjugation with glycine (salicyluric acid 75 %), with glucuronic acid (salicyl acyl and phenolic glucuronides 5 %) and/or after hydroxylation (gentisic acid < 1 %) in addition to free unchanged SA (10 %). There are reports of more salicylate glucuronides and less salicyluric acid and SA after dermal than oral absorption. NaS is excreted also as SA within 96 h (12.7 % of the oral dose). The rate of formation and excretion of the metabolites depends on various factors, in particular the urinary pH and increases in glucuronidation with age (REACH; SCCNFP, 2001). Human activities also affect both tissue levels and urinary excretion (Rabinowitz and Baker, 1984).

Acute Toxicity

Oral

SA and its salts are not currently classified in HSIS (Safe Work Australia). Human data are strongly supportive of the classification of SA and its salts as hazardous with the risk phrase 'Harmful if swallowed (Xn; R22) in HSIS.

Available animal data for SA and NaS indicate that the chemicals of this group are of moderate acute oral toxicity. Median lethal dose (LD50) of SA for the rat is 400−3700 mg/kg bw and of NaS is < 2000 mg/kg bw. Reported signs of toxicity include hypoactivity and muscle weakness or muscle spasticity. At necropsy, inflammation of the gastrointestinal tract was observed (REACH; RTECS; SCCNFP, 2001).

Dermal

Available animal data for SA and NaS indicate that the chemicals of this group exhibit low acute dermal toxicity. Median lethal dose (LD50) for the rat and rabbit is > 2000 mg/kg bw (REACH; SCCNFP, 2001).

Inhalation

Available animal data are limited providing inadequte evidence concerning the acute inhalation toxicity of SA and its salts. Rats survived an exposure to 0.9 mg/L SA as a dust for one hour, although it was noted that both exposure duration and concentration were lower than the standard limit dose. Reported signs of toxicity include salivation, nasal discharge and lacrimation in 1/6 rats at 15−30 min post exposure (REACH). Median lethal concentration (LC50) was also reported at > 0.3 mg/L with no further information on species and exposure duration (RTECS).

Observation in humans

No data are available for SA. The oral lethal dose for NaS is estimated between 20000−30000 mg in human adults. Toxic effects were also reported after a single or divided oral doses of 10000 mg or more of salicylates within 12−24 hours. Children (particulaly under the age of 3 years) are more sensitive than adults to salicylates (SCCNFP, 2001).

Corrosion / Irritation

Skin Irritation

Available animal data for SA and NaS suggest that the chemicals of this group are not likely to be skin irritants.

In humans, SA is considered a mild transient irritant based on repeated aplication under occlusive or semi-occlusive patches of 3 % SA with a pH range 2.5−3.8 (SCCNFP, 2001).

Eye Irritation

Available animal data for SA suggest that this chemical causes severe and irreversible eye irritation effects. No concern is expected for use of the salts on the basis of NaS data.

SA induced severe irritation without recovery up to 3 and 21 days of observation (REACH) although product formulations or alcohol solutions containing up to 2 % SA (low volume eye tests) with pH between 2.3−5.7 were mildly to not irritating to the eye of the animals treated (SCCNFP, 2001). NaS was not irritating to the rabbit eyes when applied at the dose level of 0.1 g with 3-day observation (REACH).

Sensitisation

Skin Sensitisation

Available animal data for SA and NaS suggest that the chemicals of this group are not likely to be skin sensitisers.

SA was not considered a skin sensitiser according to the local lymph node assay (LLNA), QSAR prediction and modified Buehler test protocols. In addition, applications of SA at 20 % and 10 % respectively during the induction and challenge phase resulted in no evidence of sensitisation in 25 healthy adult subjects. NaS was also not sensitising in human tests (REACH). Information on the phototoxicity or photoallergenic potential of SA was not available (SCCNFP, 2001).

Observation in humans

Topical application of formulations containing up to 2 % SA have not been reported to cause skin sensitisation (SCCNFP, 2001).

Repeated Dose Toxicity

Oral

Available animal data for SA and NaS suggest that the chemicals of this group are not likely to cause serious damage to health via repeated oral exposure.

The only one 28-day rat dietary study available for SA reported a no observed effect level (NOEL) of 237 mg/kg bw/d, the highest dose tested (REACH). It is noted that acetylsalicylic acid (which rapidly hydrolyses to SA after oral absorption) also showed no significant toxic effects at 200 mg/kg bw/d following 200-day repeated oral gavage dosing in rats (SCCNFP, 2001). The lowest published toxic doses (TDLo) in rats for NaS were varied, ranging from 480 mg/kg bw/3 days (biochemical changes, effects on inflammation or mediation of inflammation) to 16350 mg/kg bw/15 weeks (muscle weakness and weight loss) (RTECS). The accuracy of the calculated upper dose of the range was questionable considering the moderate acute toxicity of this group.

Dermal

Available animal data for SA suggest that the chemicals of this group are not likely to cause serious damage to health via repeated dermal exposure.

One 14-day and several 91-day dermal toxicity studies conducted on the intact skin of the rabbit reported no systemic toxicity at doses up to 120 mg/kg bw/d. Local irritation was the main observation recorded (SCCNFP, 2001).

Observation in humans

SCCNFP (2001) indicates that oral doses of acetylsalicylic acid of 100 mg/kg bw or higher can induce salicylism or SA intoxication with symptoms occuring at plasma level of 35 mg/100 mL or higher.

Salicylism was also described after topical application and can be developed within a short period of treatment. Children are particularly susceptible due to their specific exposure surface/body weight ratio. Severe manifestations are linked with degenerative and/or diseased skin, multiple applications on large body areas of formulations containing high concentrations of SA. For example, two fatal cases of percutaneous salicylate poisoning were reported with an alcoholic solution containing 20 % SA used for treatment of a fungal infection (SCCNFP, 2001).

Genotoxicity

Available data do not support a mutagenic or genotoxic potential for SA and its salts (REACH; SCCNFP, 2001).

SA, NaS and methyl salicylic (another analogue to SA) showed negative results in vitro Ames tests and in vivo tests for gene mutation such as chromosome aberrations assay and sister chromatid exchange assay.

Carcinogenicity

Data for SA and its salts are limited. Given SA is the main metabolite of acetylsalicylic acid and acetylsalicylic acid is not carcinogenic, SA is not likely to have carcinogenic potential. In addition, epidemiological studies have shown that acetylsalicylic acid reduces the risk of bowel, colorectal or gastric cancer (REACH, SCCNFP, 2001).

Reproductive and Developmental Toxicity

Based on the collective study results and weight of evidence (on SA and its analogues such as acetylsalicylic acid, methyl salicylate, NaS and CaS) (DART; REACH; RTECS; SCCNFP, 2001), a reported NOAEL of

75 mg/kg bw/d from Tanaka et al. (1973) is considered appropriate for developmental toxicity of SA and its salts (at equivalent doses). Above this dose level, SA and its analogues have been shown to cause foetal malformations (skeletal malformations, cleft lip, growth retardation), resorptions and perinatal death at maternally toxic doses. On the same basis, SA and its salts are not considered to impair fertility at doses up to 100 mg/kg bw/d or equivalent.

Risk Characterisation

Critical Health Effects

The main critical effects to human health of this chemical group are acute oral toxicity and developmental toxicity (foetotoxicity). SA also possesses hazardous properties such as causing serious eye damage.

Public Risk Characterisation

Taking into account the dermal absorption of SA and its salts, which is about 20 %, the application of these chemicals to extensive areas may involve a risk of toxicity, particularly in children due to their high surface area/body weight ratio.

Occupational Risk Characterisation

Given the critical health effects the risk to workers from these chemicals is considered high if adequate control measures to minimise occupational exposure to the chemicals are not implemented. The chemicals should be appropriately classified and labelled to ensure that a person conducting a business or an employee at a workplace has adequate information to determine appropriate controls.

NICNAS Recommendation

Further risk management is required. Sufficient information is available to recommend the chemicals to be risk managed for public safety from the potential use in cosmetics products through scheduling, and occupational health and safety through classification and labelling.

The chemicals are sufficiently assessed subject to implementation of risk recommendations.

Regulatory Control

Public Health

The chemicals are recommended for scheduling to restrict their sale, supply and use in cosmetic products, using the restrictions in the EC Cosmetics Directive as a guide.

Work Health and Safety

The chemicals are recommended for classification and labelling under the current approved criteria and adopted Globally Harmonized System of Classification and Labelling of Chemicals (GHS) as below. This does not consider classification of physical hazards and environmental hazards.

While the acute toxicity classification is applied to all members of this group, the irritation/corrosivity classification is only applicable to SA.

Hazard	Approved Criteria (HSIS)[a]	GHS Classification (HCIS)[b]
Acute Toxicity	Harmful if swallowed (Xn; R22)	Harmful if swallowed - Cat. 4 (H302)
Irritation / Corrosivity	Risk of serious eye damage (Xi; R41)	Causes serious eye damage - Cat. 1 (H318)

[a] Approved Criteria for Classifying Hazardous Substances [NOHSC:1008(2004)].

[b] Globally Harmonized System of Classification and Labelling of Chemicals (GHS) United Nations, 2009. Third Edition.

[*] Existing Hazard Classification. No change recommended to this classification

Advice for consumers

Products containing the chemical should be used according to the instruction on the label.

Advice for industry

Control measures

Control measures to minimise the risk from oral/dermal/inhalation exposure to the chemicals should be implemented in accordance with the hierarchy of controls. Approaches to minimise risk include substitution, isolation and engineering controls. Measures required to eliminate or minimise risk arising from storing, handling and using a hazardous chemical depend on the physical form and the manner in which the chemical is used. Examples of control measures which may minimise the risk include, but are not limited to:

- using closed systems or isolating operations;
- minimising manual processes and work tasks through automating processes;
- work procedures that minimise splashes and spills;
- regularly cleaning equipment and work areas; and
- using protective equipment that is designed, constructed, and operated to ensure that the worker does not come into contact with the chemical.

Guidance on managing risks from hazardous chemicals are provided in the *Managing Risks of Hazardous Chemicals in the Workplace—Code of Practice* available on the Safe Work Australia website.

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.

Obligations under workplace health and safety legislation

Information in this report should be taken into account to assist with meeting obligations under workplace health and safety legislation as adopted by the relevant state or territory. This includes, but is not limited to:

- ensuring that hazardous chemicals are correctly classified and labelled;
- ensuring that (material) safety data sheets ((m)SDS) containing accurate information about the hazards (relating to both health hazards and physicochemical (physical) hazards) of the chemical are prepared; and

- managing risks arising from storing, handling and using a hazardous chemical.

Your work health and safety regulator should be contacted for information on the work health and safety laws in your jurisdiction.

Information on how to prepare an (m)SDS and how to label containers of hazardous chemicals are provided in relevant codes of practice such as the *Preparation of Safety Data Sheets for Hazardous Chemicals— Code of Practice* and *Labelling of Workplace Hazardous Chemicals—Code of Practice*, respectively. These codes of practice are available from the Safe Work Australia website.

A review of the physical hazards of the chemical has not been undertaken as part of this assessment.

References

Cosmetic Ingredient Review (CIR). 2003. Safety assessment of Salicylic Acid, Butyloctyl Salicylate, Calcium Salicylate, C12-15 Alkyl Salicylate, Capryloyl Salicylic Acid, Hexyldodecyl Salicylate, Isocetyl Salicylate, Isodecyl Salicylate, Magnesium Salicylate, MEA-Salicylate, Ethylhexyl Salicylate, Potassium Salicylate, Methyl Salicylate, Myristyl Salicylate, Sodium Salicylate, TEA-Salicylate, and Tridecyl Salicylate. Int J Toxicol 22 Suppl 3:1-108.

Developmental and Reproductive Toxicology Database (DART). Calcium salicylate (824-35-1). Accessed May 2013 at **http://toxnet.nlm.nih.gov/cgi-bin/sis/htmlgen?DARTETIC**

Developmental and Reproductive Toxicology Database (DART). Salicylic acid (69-72-7). Accessed May 2013 at **http://toxnet.nlm.nih.gov/cgi-bin/sis/htmlgen?DARTETIC**

Developmental and Reproductive Toxicology Database (DART). Sodium salicylate (54-21-7). Accessed May 2013 at **http://toxnet.nlm.nih.gov/cgi-bin/sis/htmlgen?DARTETIC**

European Commission Cosmetic Substances and Ingredients database (CosIng). Accessed May 2013 at **http://ec.europa.eu/consumers/cosmetics/cosing/**

Galleria Chemica. Accessed May 2013 at **http://jr.chemwatch.net/galleria/**

Health Canada List of Prohibited and Restricted Cosmetic Ingredients (Hotlist). Accessed May 2013 at **http://www.hc-sc.gc.ca/cps-spc/cosmet-person/indust/hot-list-critique/index-eng.php**

NICNAS 2006. Australian High Volume Industrial Chemicals List (AHVICL). Accessed May 2013 at **http://www.nicnas.gov.au/Industry/Australian_High_Volume_Industrial_Chemicals/NICNAS_AHVICL_2006_PDF.pdf**

NICNAS 2012. IMAP Assessments - Identification of chemicals of low concern to human health. Accessed June 2013 at **http://nicnas.gov.au/Industry/Existing_Chemicals/Chemicals_On_AICS/IMAP_Framework/Identification%20of%20Chemicals%20of%20Low%20Concern%20to%20human%20health.**

Personal Care Products Council International Nomenclature Cosmetic Ingredient (INCI). Accessed May 2013 at **http://www.ctfa-gov.org/jsp/gov/GovHomePage.jsp**

Rabinowitz JL, Baker D. 1984. Absorption of labeled triethanolamine salicylate in human and canine knee joints. II. J Clin Pharmacol 24:532-9.

REACH Dossiers. Salicylic acid (69-72-7). Accessed May 2013 at **http://echa.europa.eu/information-on-chemicals/registered-substances**

REACH Dossiers. Sodium salicylate (54-21-7). Accessed May 2013 at **http://echa.europa.eu/information-on-chemicals/registered-substances**

Registry of toxic effects of chemical substances (RTECS). Salicylic acid (69-72-7). Accessed May 2013 at **http://ccinfoweb.ccohs.ca/rtecs/search.html**

Registry of toxic effects of chemical substances (RTECS). Sodium salicylate (54-21-7). Accessed May 2013 at **http://ccinfoweb.ccohs.ca/rtecs/search.html**

Safe Work Australia Hazardous Substances Information System (HSIS). Accessed May 2013 at **http://hsis.safeworkaustralia.gov.au/HazardousSubstance**

Substances in Preparations in Nordic Countries (SPIN). Accessed May 2013 at **http://90.184.2.100/DotNetNuke/default.aspx**

Tanaka S, Kawashima K, Nakaura S, Nagao S, Kuwamura T, Takanaka A, Omori Y. 1973. Studies on teratogenic effects of salicylic acid and aspirin in rats as related to fetal distribution. Congen Anom (senten ijo) 13:73-84.

The Poisons Standard (the Standard for the Uniform Scheduling of Medicines and Poisons (SUSMP)) 2012. Accessed May 2013 at **http://www.comlaw.gov.au/Details/F2012L01200**

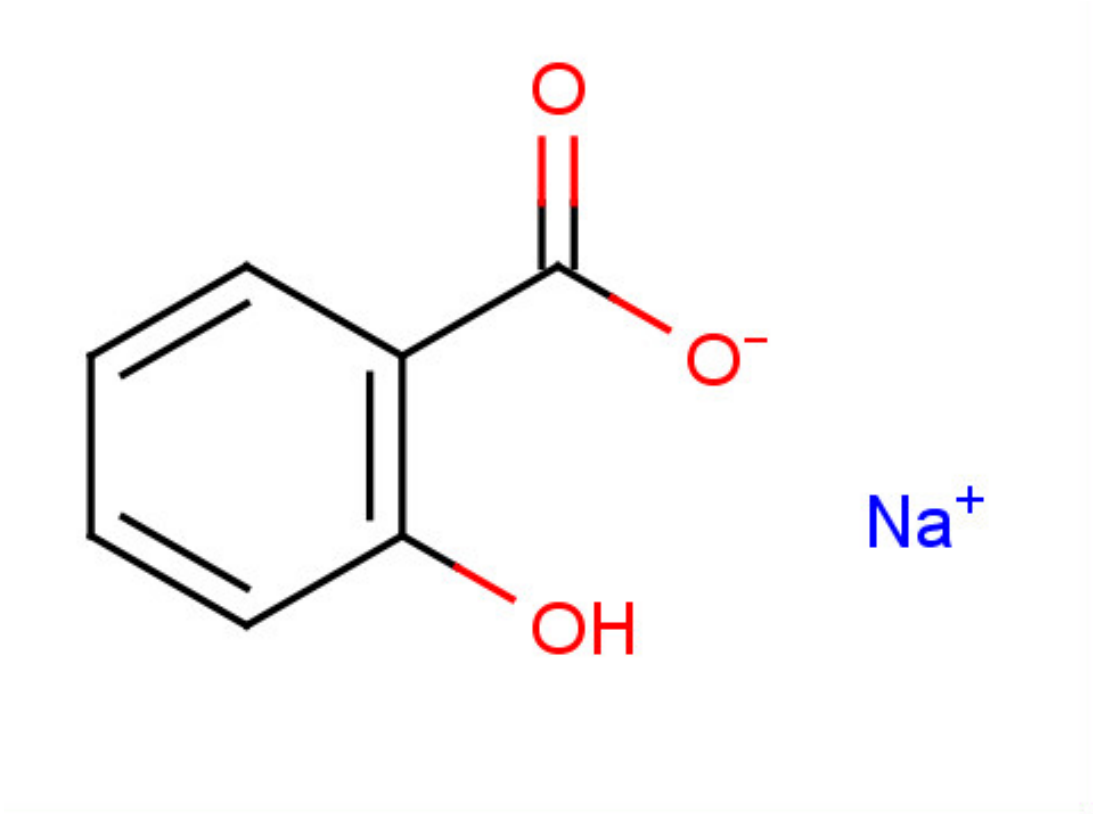
The Scientific Committee on Cosmetic Products and Non-Food Products intended for Consumers (SCCNFP). 2001. Opinion on salicylic acid. SCCNFP/0522/01, final. Assesssed May 2013 at **http://ec.europa.eu/health/archive/ph_risk/committees/sccp/documents/out170_en.pdf**

US Household Products Database. Accessed May 2013 at **http://householdproducts.nlm.nih.gov/advancedsearch.htm**

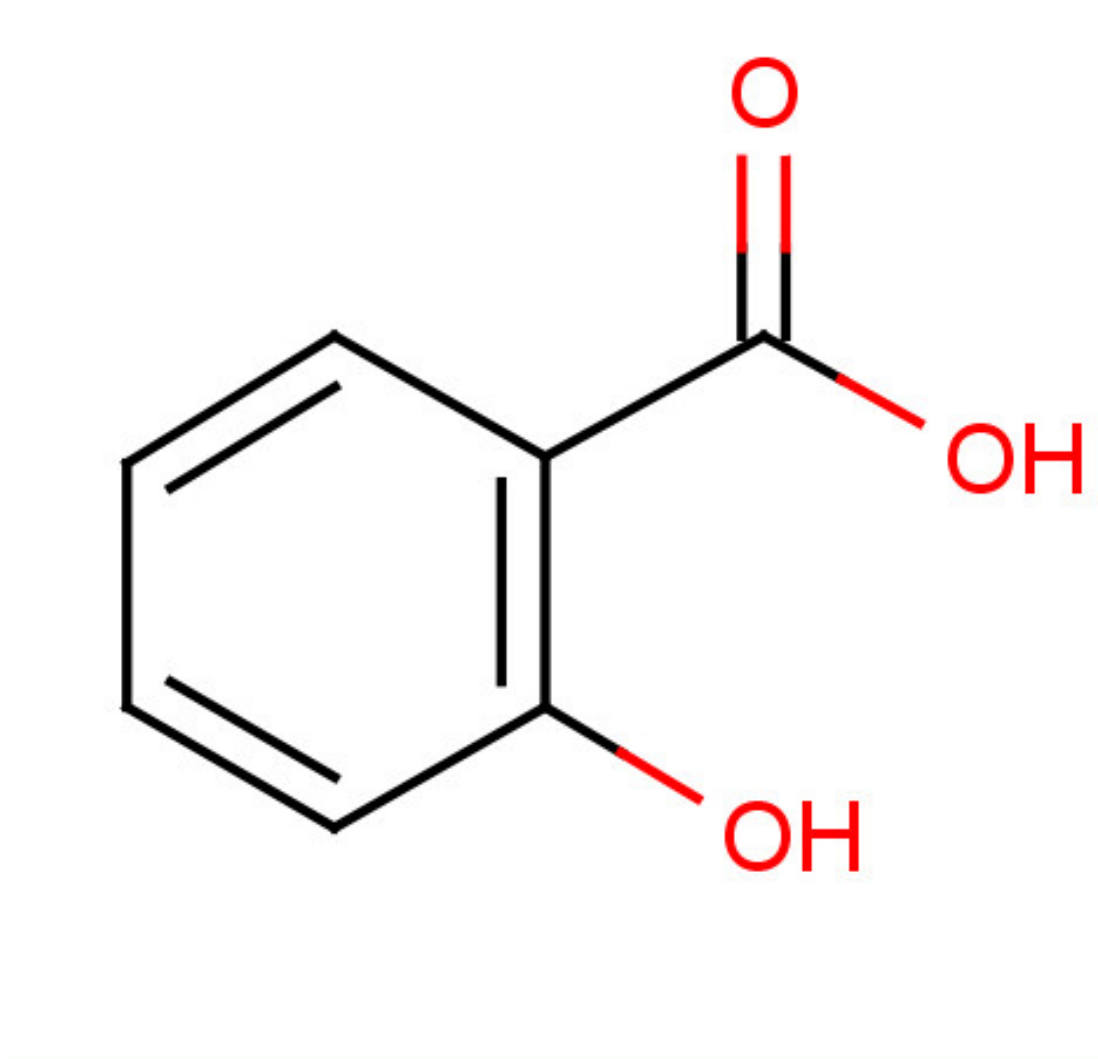
Last Update 28 June 2013

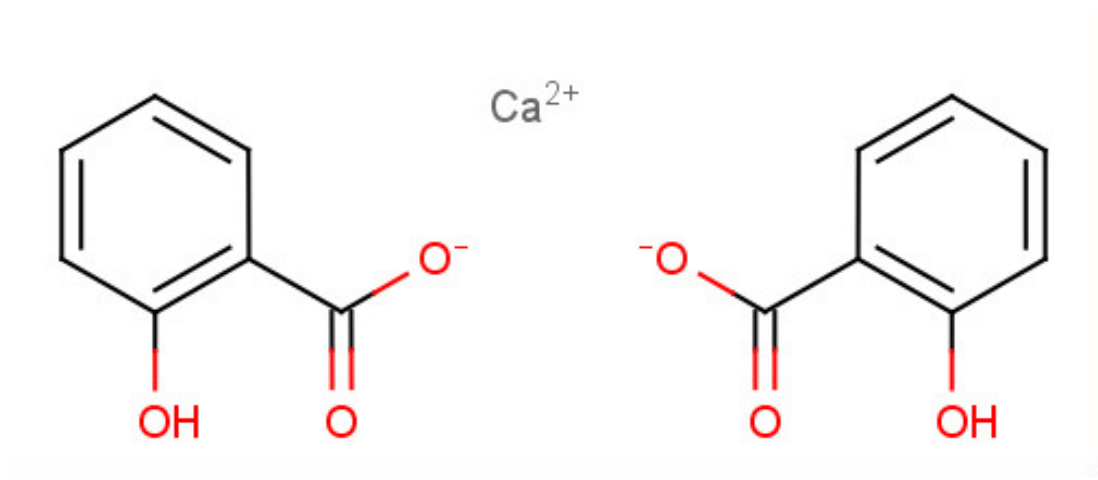
Chemical Identities

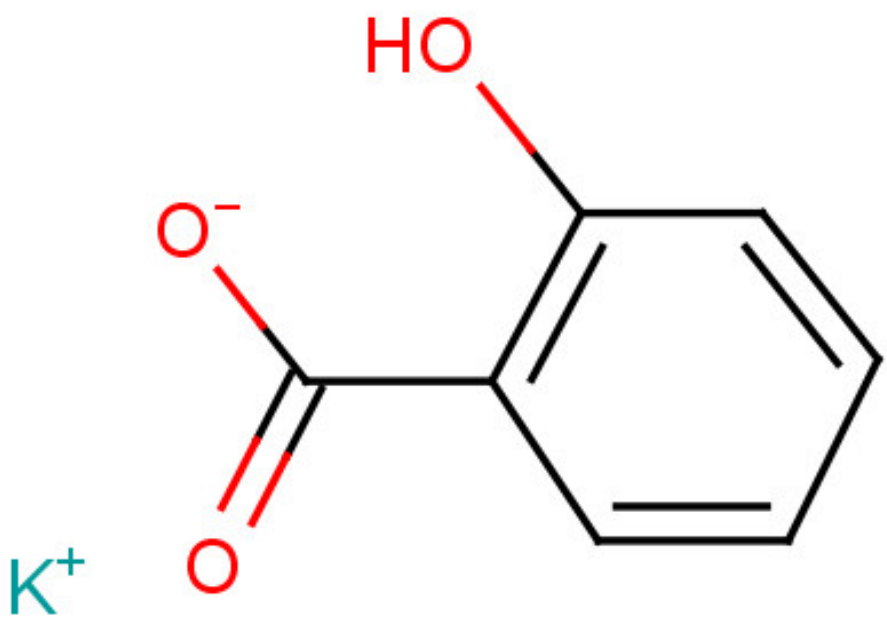
Chemical Name in the Inventory and Synonyms	**Benzoic acid, 2-hydroxy-, monosodium salt** Sodium salicylate (NaS) o-Hydroxybenzoic acid, sodium salt Sodium 2-hydroxybenzoate
CAS Number	54-21-7
Structural Formula	

	
Molecular Formula	C7H6O3.Na
Molecular Weight	160.10

Chemical Name in the Inventory and Synonyms	**Benzoic acid, 2-hydroxy-** Salicylic acid (SA) Orthohydroxy benzoic acid 2-Carboxyphenol Phenol-2-carboxylic acid
CAS Number	69-72-7
Structural Formula	

	
Molecular Formula	C7H6O3
Molecular Weight	138.12

Chemical Name in the Inventory and Synonyms	**Benzoic acid, 2-hydroxy-, calcium salt (2:1)** Calcium salicylate (CaS) Calcium disalicylate Calcium 2-hydroxybenzoate
CAS Number	824-35-1
Structural Formula	
Molecular Formula	C7H6O3.1/2Ca
Molecular Weight	314.31

Chemical Name in the Inventory and Synonyms	**Benzoic acid, 2-hydroxy-, monopotassium salt** Potassium salicylate (KS) o-Hydroxybenzoic acid potassium salt Potassium 2-hydroxybenzoate
CAS Number	578-36-9
Structural Formula	
Molecular Formula	C7H6O3.K
Molecular Weight	176.21

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