RISK PROFILE

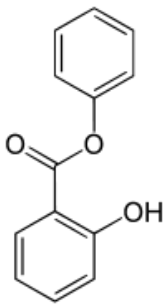
Phenyl salicylate

CAS No.118-55-8

Date of reporting 05.06.2012

Content of document

1. Identification of substance

Chemical name (IUPAC):	Phenyl -2-hydroxybenzoate
INCI	Phenyl salicylate
Other name	Salol
CAS No.	118-55-8
EINECS No.	204-259-2
Molecular formula	$C_{13}H_{10}O_3$
Chemical structure	
Molecular weight	214.22 g/mol
Contents (if relevant)	
Physiochemical properties	Appearance: solid, white crystalline substance Density: 1.25 g/cm^3

	Boiling point:	172-173 ^{o}C at 12 mm Hg
	Melting point:	44 ^{o}C
	Flash point:	160 °C
	log P_{ow} :	3.54
	Vapor pressure:	0.1 mm (i.e. 0.0000627) Hg at 25 ^{o}C
	Solubility (water):	<0.1% (25 °C:) (150 mg/L at 25 ^{o}C)
	pH:	5 - 7 (at 10 g/l, H_2O, 25 °C)
	References: ChemicalSpider [online]; Chemicalbook [online], Goodscentcompany [online].	

2. Uses and origin

Uses	➢ **Cosmetic products** *Functions according to* • CosIng database (CosIng [online]): - perfuming: used for perfume and aromatic raw materials. - antimicrobial: helps control the growth of micro-organisms on the skin. - denaturant: renders cosmetics unpalatable. Mostly added to cosmetics containing ethyl alcohol. • Other: - UV filtering without claiming protection against UV damage but instead, for example, protection against chapped lips. - Antibacterial additive in mouthwash for control of bacterial growth that may cause small bleeding in the gum (gingivitis). See also under “medicinal products” in the text below. - Softener – smooth dry skin; hands and face cream - Prophylatic usage – Usage as active ingredient in products resembling medicinal products, but not allowed used as a claim from the cosmetics industry because borderline to medicinal product. *Concentrations of PS being applied* • Perfuming 0.02 %, and is based on the assumption that the fragrance mixture is used at 20% in a consumer product (International Fragrance Association (IFRA) Survey; The RIFM Expert Panel, 2007). • Antibacterial 1.5 % salol, the amount was requested by a Norwegian industry company for use in an oral hygiene product. • UV filtering Use levels: 2 – 10 %; e.g. 10 % in a lip product (“salve” for chapped lip (Annex 1 and references therein). *Frequency of use*

	- Limited applications today, apart for perfuming purposes, but PS is still used in mouth wash, hair spray and softeners; e.g. moisturizers or semi-solid stick for dry skin, chapped hands and feet A search on the internet March 2011 showed at least 10 concrete products containing PS. Examples of cosmetic products containing PS are listed in Annex 2. EWG Skin Deep Cosmetic Database contained zero products with PS, and the German database (Codecheck.info) only one product with PS. ➢ **Food** PS is a flavoring substance [FL-no: 09.689]. EFSA had no safety concerns at an estimated "Maximised Survey-Derived Intake" (MSDI) of 7.3 µg /capita (EFSA, 2008). PS is not allowed in plastic products meant for food packaging (EU food packaging directive). ➢ **Medicinal products** - PS has antiseptic effects in tablet formulations ("coatings") for intestinal release. - PS is also a mild analgesic, antipyretic, anti-rheumatic agent (similar to other salicylates like aspirin). - PS is used against cheilitis (red, blistery, itchy rash cracked lips susceptible to Staphylococcus infections); products against sore throat; laryngitis. (Council of Europe, 2006; (Chemicalland [online]). ➢ **Other products** Once used in sunscreens, PS today is mostly used in the manufacture of some polymers, lacquers, adhesives, waxes and polishes (Wikipedia [online]). PS stabilizes plastic against degradation by blocking UV light from penetrating plastic and cosmetic packaging (Fimiani et al., 1990), and also has some plasticizing properties.
Origin (natural/synthesis)	PS is a synthetic compound and there is no evidence that PS is among the naturally occurring salicylates.

3. Regulations

Norway	The Norwegian cosmetics regulation (FOR 1995-10-26 nr 0871, Annex 3), which is in force until 11th June 2013, determines that *phenyl salicylate* is allowed in mouth hygiene products provided concentration do not exceed 1.5 % (Annex 5).
EU	No regulation[1]

[1] PS has not been taken up in the preservatives positive list of the EU cosmetics directive. Presumably because of dermatitis, some of allergic nature, PS was not taken up in the UV filter positive list of the EU Cosmetics

Rest of the world	Japanese regulation of PS with a **maximum limit of 1 % in any cosmetics** (Annex 4; Science links Japan [online])[2].

Directive when adopted in 1983 (amending directive 83/574/EEC). The Council of Europe expert committee on cosmetics in 2006 thought that perhaps PS is still used for UV protection purposes (Room Document: RD P-SP-CO-AI/RD2-4. April 2006).

[2] Part of the, Drugs, Cosmetics and Medical Instruments Act was revised 1 April 2001. Formerly, PS had been allowed at a maximum proportion of 1.0% in cleansing preparations, 0.2% for hair care, treatment and makeup preparations, and condemned for eye liner, lipstick, inner mouth preparations, and bathing preparations. Since revision of the law, however, PS can be used at a maximum proportion of 1.0% in any cosmetics.

4. Relevant toxicity studies

Absorption Skin GI tractus	An experimental absorption rate of 2.32 µg /mm^2 /hr (equals 0.232 mg /cm^2 /hr) was recorded in a rat tail assay (Siddiqi & Ritschel, 1972; cited in Lapczynski et al., 2007). Salicylates are absorbed to different extents by the skin. Bioavailability in the range of 12% – 30.7% (predominantly from experiments with Methyl salicylate) are reported in humans (The RIFM Expert Panel, 2007).
Distribution **Metabolism** **Excretion**	The metabolism and pharmacokinetics of various salicylates, including PS, has been reviewed by The RIFM Expert Panel (2007), Lapczynski et al. (2007) and others (Fishbeck et al,1975). PS, similarly to other salicylate esters, is hydrolyzed by carboxyl esterase. This takes place, not in the acidic environment in the stomach, but in the intestine (alkaline conditions), thereby releasing salicylic acid and phenol. Salicylic acid is further metabolized in the liver and conjugated compounds are excreted together with phenol in the urine.
Local toxic effects Irritation Sensitivity	**Skin irritation and allergies** Toxicologic data related to the effects of PS on skin irritation and dermal allergy in humans have been reviewed by The RIFM Expert Panel (2007) and Lapczynski et al. (2007). See also Annex 1. Human and animal studies have shown that PS has only a moderate potency regarding initiation of contact allergy. Although PS is not a hapten in itself, the phenol hydrolysis product can be further metabolized into hydroquinone (which is a potent hapten). PS also exhibits low potency as to irritation of the eyes or skin. Oral intake may cause irritation in the gastrointestinal tract accompanied by dizziness, nausea /vomiting and diarrhea. ***Acute* <u>local</u> toxic** effects of PS are summarized in ***Annex 1.***
Systemic toxic effects (Acute; see local toxic effects above) Repeated dose	Acute toxicity data indicate LD_{50} of 3.0 g/kg (oral, rat) and LD_{50} of > 5.0 g/kg (dermal, rabbit), see Annex 2. The toxicological and dermatological effects of salicylates, including PS, have been reviewed by The RIFM[3] Expert Panel (2007). For toxic effects, see also Toxnet [online]. Lapczynski et al. (2007) performed a complete literature search on PS, surveying on-line databases including Chemical Abstract Services and the National Library of Medicine. In addition, fragrance companies were asked to submit pertinent test data. No adverse effects of PS were reported *in vitro* (Lapczynski et al., 2007) or *in vivo* (in the latter case only ethyl hexyl salicylate was tested) (The RIFM Expert Panel, 2007).

[3] The Research Institute for Fragrance Materials (RIFM).

Mutagenicity / genotoxicity / carcinogenicity Reprotoxicity / teratogenicity	Not reported *Reprotoxic effects*: There are known reproduction toxic effects of salicylates (mainly *methyl salicylate* tested) and *salicylic acid* in animals, such as malformations of the neural tube, the skeleton and internal organs (The RIFM Expert Panel, 2007). Neural tube defects in hamster are associated with exposure of the skin to high doses (3500 mg/kg/day) of salicylate. *Methyl salicylate* in the diet (25-250 mg/kg body weight) resulted in reduced fertility of 2nd and 3rd generation rats, but no fetal abnormalities were detected. NOAEL (for methyl salicylate) was 75 mg/kg/day (Collins et al., 1971; cited in The RIFM Expert Panel, 2007). RTECS (Registry of Toxic Effects of Chemical Substances) Osaka City Medical Journal found that oral administration of PS (100, 200, 300 and 400 mg/kg/day) to pregnant rats caused embryonic malformations (Baba et al., 1996; EWG's Skin Deep [online]). While these data did not allow calculation of a NOAEL for PS (since there were no doses without effect), the lowest dose for adverse effect (LOAEL) was 100 mg/kg/day. CIR (Cosmetic Ingredient Review) Expert Panel did not find any evidence that cosmetic skin care products containing 2% salicylic acid - was associated with increased risk for reproduction- or developmental defects in humans. Serum levels - corresponding to approx. 20% of a children' dose with aspirin - are considered to be below the critical limit for serious adverse effects (CIR, 2003, cited in The RIFM Expert Panel, 2007). *Teratogenic effects* In contrast to humans and primates, who seem to be (rather) resistant to the teratogenic effects of salicylates, rats are considered to be (more) responsive (cited in ref. Greenaway, 1984; Inchem [online]. A *NOAEL of 75 mg/kg/day* was reported for salicylic acid based on teratogenic effects of salicylic acid (REF: SCCNFP opinion).

5. Exposure estimate and critical NOAEL / NOEL

NOAEL/NOEL critical	The RIFM Expert Panel estimated (on the basis of animal experiments) that an oral **NOAEL-value of 50 mg/kg/day** can (in general) be used for risk assessments of salicylates as ingredients in cosmetic products (The RIFM Expert Panel, 2007).
Exposure cosmetic products	• **Fragrance** The systemic exposure dose (SED)[4] of PS in cosmetic products is estimated to be 0.0005 mg/kg on the basis of a default-value 0.02% representing the maximum skin levels for fine fragrances, assuming

[4] Systemic exposure dose is the concentration of the cosmetic ingredient absorbed through the skin and available in the circulation (default value 100% if the experimental number is unknown).

	that the fragrance mixture is used at 20% in a consumer product (The RIFM Expert Panel, 2007; Lapczynski et al., 2007). (IFRA Use Level Survey). See also Annex 2, Table 1. • **Total body (UV screen)** It has been reported that PS (up to 10%) also is utilized as a UV screen, without marketers claiming that it functions as a UV filter but as something else (e.g. softener), in which case it is allowed (Council of Europe, 2006). 10% PS (cream, body lotion) as illustrative example A: calculated relative daily exposure of product[5]: 123.20 mg/kg bw/day Concentration of ingredient in product: 10% = 0.1 Dermal absorption (SCCS default value): 100% = 1 SED = A (mg/kg bw/day) x C(%)/100 x Dap (%)/100 = 123.20 mg/kg bw/day x 0.1 x 1 = **12.32 mg/kg bw/day** SED (alt2)[6] = 30 mg/kg bw/day • **Lip balm** 10% PS (lip balm) as illustrative example A: calculated relative daily exposure of product: 0.90 mg/kg bw/day Concentration of ingredient in product: 10% = 0.1 Dermal absorption (SCCS default value): 100% = 1 SED = A (mg/kg bw/day) x C(%)/100 x Dap (%)/100 = 0.90 mg/kg bw/day x 0.1 x 1 = **0.090 mg/kg bw/day** SED (alt 2)[7] = 0.095 mg/kg bw /day. • **Mouthwash** 1.5% PS (mouth wash) as illustrative example A: calculated relative daily exposure of product: 32.54 mg/kg bw/day Concentration of ingredient in product: 1.5% = 0.015 Dermal absorption (SCCS default value): 100% = 1 SED = A (mg/kg bw/day) x C(%)/100 x Dap (%)/100 = 32.54 mg/kg bw/day x 0.015 x 1 = **0.49 mg/kg bw/day** SED (alt 2)[8] = 0.75 mg/kg bw /day. • **Face cream** 1.0% PS (face cream) as illustrative example A: calculated relative daily exposure of product: 24.14 mg/kg bw/day Concentration of ingredient in product: 1.0% = 0.01 Dermal absorption (SCCS default value): 100%% = 1

[5] Estimated daily exposure levels for different cosmetic product types according to Colipa data (SCCS, 2011).
[6] SED: (17900 x 0.1 x 1 /60) = 30 mg /kg bw /day.
[7] Use levels:10 % corresponds to 0.057 g/day according to SCCP guidelines.
SED (alt 2) = 57 x 0,1 / 60 = 0.095 mg/kg bw /day.
[8] Use levels: below 1.5 %; cf. SCCP guideline as to usage of products for this purpose is 3.0 g/day.
SED = 3000 x 0.015 /60 = 0.75 mg/kg bw /day.

	SED = A (mg/kg bw/day) x C(%)/100 x Dap (%)/100 = 24.14 mg/kg bw/day x 0.01 x 1 = **0.24 mg/kg bw/day** SED (alt2)[9] = 0.256 mg/ kg b.w. /day • **Hand cream** 1.0% PS (hand cream) as illustrative example A: calculated relative daily exposure of product: 32.70 mg/kg bw/day Concentration of ingredient in product: 1.0% = 0.01 Dermal absorption (SCCS default value): 100%% = 1 SED = A (mg/kg bw/day) x C(%)/100 x Dap (%)/100 = 32.70 mg/kg bw/day x 0.01 x 1 = **0.33 mg/kg bw/day** SED (alt 2)[10] = 0.39 mg/kg b.w./day
Margin of Safety (MoS)	MoS for fragrance use: 125-2500000, depending on bioavailability and the number of daily applications of the cosmetic product (The RIFM Expert Panel, 2007). MoS (NOAEL / SED): **MoS for total body:** SED = 12.32 mg/kg bw/day MoS = 50 / 12. 32 = **4.1** (alt.2: 50 / 30 = 1.67) **MoS for lip balm**: SED = 0.090 mg/kg bw/day MoS = 50 / 0.090 = **555.6** (alt 2: 526) **MoS for mouthwash:** SED = 0.49 mg/kg bw/day MoS = 50 / 0.49 = **102.0** (alt. 2 = 50 /0,75 =67) **MoS for face cream:** SED = 0.24 mg/kg bw/day MoS = 50 / 0.24 = **208.3** (alt. 2 = 50 /0.256 = 195) **MoS for hand cream:** SED = 0.33 mg/kg bw/day MoS = 50 / 0.33 = **152.0** (alt. 2 = 50 /0.390 = 128)

[9] Use levels: 1 % (illustrative purposes) :
SED (face) : (103 mg/grams * 1.54 grams/day * 0.01) /60 = 0.256 mg/ kg b.w. /day
[10] Systemic exposure dosage for hands (ratio default surfaces hands/face = 860 cm2 /565 cm2 = 1.522) with cosmetic product usage level at 1 % (illustrative purposes) :
SED (hands) : (103 mg/grams * 1.54 grams/day * 0.01) * 1.522 /60 = 0.390 mg/kg b.w./day.

6. **Other sources of exposure than cosmetic products**

Food stuffs	Many salicylates (e.g. methyl salicylate) are regarded as safe in cosmetics given specified restrictions (CIR, Cosmetic Ingredient Review, 2003). See also FEMA[11] and GRAS evaluations. In some foods, 'non-aspirin' salicylates are naturally present at relatively high abundance, e.g. blueberries, raspberries, curry, cherries, peppers, prunes, and pickled cucumber. JECFA: The Joint FAO/WHO Expert Committee on Food Additives concluded that PS does not present a safety concern at current levels of intake when used as a flavoring agent (736).
Pharmaceuticals	
Other sources	
Adverse side effects apart from cosmetics	**The French database biam2.org - on pharmaceutical products:** Fatty liver (some, very rare); hepatomegaly (some, very rare); cochleovestibular (ear) disorder (some, rare) -vestibulocochlear toxicity most often reversible; accidents observed when salicylate exceeds 300 mg/l. Vertigo (some, rare) – large doses; deafness (some, rare) –large doses; http://www.biam2.org/www/Sub2878.html **Martindale***: «it [PS] was formerly used as an intestinal antiseptic, but effective doses were toxic owing to the liberation of phenol» .....«..a great number of individuals has produced irritation».* Medicinal products: Commonly used pain killers such as acetyl salicylic acid (aspirin) have been associated with abnormal sexual organ development in baby boys during pregnancy, a risk factor for infertility and testicular cancer in later life (Kristensen et al., 2010; Forskning.no, nov 2010 [online]; Cordis [online]). Aspirin was without significant effect on cryptorchidism in another Danish study (Jensen et al., 2010). While consumption of pain relievers are generally on the rise in the western world (Forskning.no, des 2010 [online), aspirin as an analgesic drug shows an opposite trend - only a minority (7%) of pregnant women took aspirin (Jensen et al., 2010). It is presently unknown whether PS has similar potential effects as aspirin on sexual organ development. Endocrine disruptors (see Annex 6): Although PS is capable of modulating endocrine activities in vitro, *in vivo* data are so far missing. Thus, there is not sufficient data to determine whether PS has a role as an endocrine disruptor.

[11] FEMA: Flavor and Extract Manufacturers Association – Generally Recognized as Safe as an ingredient – GRAS 19 (3960)

7. Assessment

Once used in sunscreens, PS is still found in a limited number of cosmetic products (Annex 2, Annex 3).

General toxicity
We did not find any evidence that PS has mutagenic or carcinogenic properties. ++++

Regarding the safety of the related substance salicylic acid, SCCNFP concluded in a previous risk assessment of salicylic acid that:

"*The SCCNFP considers that salicylic acid is safe for "other uses" than as a preservative, at a concentration up to 2.0 % for the leave-on and rinse-off cosmetic products, and at a concentration up to 3.0 % for the cosmetic rinse-off hair products*".
(REF: SCCNFP opinion 4 June 2001)

Cosmetics

Fragrances (perfume):
MoS = 125 - 2500000, based on an oral NOAEL of 50 mg/kg/day (The RIFM Expert Panel, 2007).
Thus, all use of PS in fragrances is considered safe.

Adverse dermal effects:
Acute local effects of PS, such as irritation and sensibilization (e.g. cheilitis), are described in Annex 1. PS in lip salve is deemed unacceptable, in light of reported cases of lip dermatitis (Calnan et al., 1981, references Annex 1) and cheilitis caused by PS in a lip salve preparations (Hindson, 1980, Annex 1). This is also consistent with marketplace practice (cf. SNOWFIRE Stick Mains 40g, France).
http://pharmacienligne.weezbe.com/SNOWFIRE-Stick-Mains-40g-p-299-c-15_104_17.html

A NOAEL value of 50 mg /kg bw/day was used for risk assessment of PS, according to the RIFM expert panel 2007 (see section 5). Furthermore, the estimated MoS values take into account specific illustrative use levels for different cosmetic product types. Estimated daily exposure levels are based on Colipa data, and a default value of 100% is used for dermal absorption (SCCS, 2011).

Because the NOAEL is based on animal data, a MoS of 100 (or more) represents a sufficient safety margin.

MoS (cream, total body): 50 / 12. 32 = **4.1**	(alt. 2: 1.67)
MoS (lip balm): 50 / 0.090 = **555.6**	(alt. 2: 526)
MoS (mouthwash): 50 / 0.49 = **102.0**	(alt. 2: 67)
MoS (face cream): 50 / 0.24 = **208.3**	(alt. 2: 195)
MoS (hand cream): 50 / 0.33 = **152.0**	(alt. 2: 128)

Total exposure
The total systemic exposure of PS is the sum of contributions from cosmetic products and other sources (e.g. environmental pollution, foods and pharmaceutical drugs). However, the contribution of food, fragrances and environmental pollution to the systemic exposure dose of PS is small (negligible) compared to that of cosmetics.

8. Conclusion

We propose the following usage limits for PS in cosmetics:

Maximum use levels:

MoS lip balm:	**not allowed**	
MoS body lotion:	**0.4%**	(10 x 4.1 / 100)
MoS mouth wash:	**1.5%**	(1.5 x 102 / 100)
MoS face:	**2.1%**	(1 x 208.3 / 100)
MoS hands:	**1.5%**	(1 x 152 / 100)

Remarks:

Lip balm: Although MoS values are acceptable[12] (i.e. MoS = 555 >>100), in light of reported cases on lip dermatitis and *cheilitis caused by* PS in a lip salve preparation, the usage of PS in lip salve is found unacceptable.

Mouth wash: A concentration of PS in mouth water of 1.5 % is according to current practice, and within the limits of an acceptable MoS = 100.

[12] (10 x 555.6) / 100 = 55.6% (use in cosmetics deemed unacceptable?)

9. References

Baba T, Nagahama M, Akiyama N, Miki T (1966). Experimental production of malformations due to acetyl salicylate and phenyl salicylate in rats. Osaka City Med J.12:23-9. PubMed PMID: 5960839.

CIR (2003). Cosmetic Ingredient Review Expert Panel. 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. 2003;22 Suppl 3:1-108. Review. PubMed PMID: 14617432.

Council of Europe (2006). Room Document: RD P-SP-CO-AI/RD2-4. April 2006. Cf. Hans Jørgen Talberg, Norwegian Food Safety Authority.

EFSA. Scientific Opinion of the Panel on Food Additives, Flavourings, Processing Aids and Materials in Contact with Food on a request from Commission on Flavouring Group Evaluation 88, (FGE.88) Phenol and Phenol Derivatives. The EFSA Journal (2008) 857, 1-18.

Fimiani M, Casini L, Bocci S (1990) Contact dermatitis from phenyl salicylate in a galenic cream. Contact Dermatitis 22:239. PubMed PMID: 2347179.

Fishbeck W.A., Langer R.R. and Kociba R.J. (1975) Elevated urinary phenol levels not related to benzene exposure, American Industrial Hygiene Association Journal 36: pp. 820–824.

Greenaway JC, Bark DH & Juchau MR (1984) Embryotoxic effects of salicylates: Role of biotransformation. Toxicology and Applied Pharmacology 74:141-149.

Jensen MS, Rebordosa C, Thulstrup AM, Toft G, Sørensen HT, Bonde JP, Henriksen TB, Olsen J. (2010) Maternal use of acetaminophen, ibuprofen, and acetylsalicylic acid during pregnancy and risk of cryptorchidism. Epidemiology 21:779-85.

Kristensen DM, Hass U, Lesne L, Lottrup G et al. (2010) Intrauterine exposure to mild analgesics is a risk factor for development of male reproductive disorders in human and rat. Hum. Reprod. 2010 : deq323v1- deq323.

Lapczynski A, Jones L, McGinty D, Bhatia SP, Letizia CS, Api AM (2007) Fragrance material review on phenyl salicylate. Food Chem Toxicol. 45 (Suppl. 1): S472-6. Epub 2007 Sep 14. Review. PubMed PMID: 18031889.

The RIFM Expert Panel, D. Belsito, D. Bickers, M. Bruze, P. Calow, H. Greim, J.M. Hanifin, A.E. Rogers, J.H. Saurat, I.G. Sipes, H. Tagami (2007) A toxicologic and dermatologic assessment of salicylates when used as fragrance ingredients. Food and Chemical Toxicology 45 (suppl.1): S318–S361.

26. Kunz PY & Fent K (2006) Multiple hormonal activities of UV filters and comparison of in vivo and in vitro estrogenic activity of ethyl-4-aminobenzoate in fish. Aquatic Toxicology 79: 305-324.

27. Miller D, Wheals BB, Beresford N, and Sumpter JP (2001) Estrogenic Activity of Phenolic Additives Determined by an In Vitro Yeast Bioassay. Environmental Health Perspectives http://findarticles.com/p/articles/mi_m0CYP/is_2_109/ai_77276631/pg_2/

Online:

Chemicalbook. Available at: http://www.chemicalbook.com/CASEN_118-55-8.htm (accessed 26.04.2011).

Chemicalland. Available at: http://chemicalland21.com/lifescience/phar/phenyl%20salicylate.htm (accessed 26.04.2011).

Chemical spider. Available at: http://www.chemspider.com/Chemical-Structure.8058.html (accessed 25.05.2012).

Codecheck.info. Available at : http://www.codecheck.info/product.search?q=phenyl+salicylate&OK=Suchen (accessed 25.05.2012).

Cordis. Available at: http://cordis.europa.eu/fetch?CALLER=EN_NEWS_FP7&ACTION=D&DOC=2&CAT=NEWS&QUERY=012c39e73fea:6d92:4c017339&RCN=32749 (accessed 26.04.2011).

CosIng. Available at: http://ec.europa.eu/consumers/cosmetics/cosing/index.cfm?fuseaction=search.details&id=36532 (accessed 26.04.2011).

EWG's Skin Deep © Cosmetics database. Available at: http://www.ewg.org/skindeep/search.php?query=phenyl+salicylate (accessed May 24, 2012).

Fisher Scientific. Available at: http://fscimage.fishersci.com/msds/18607.htm; MSDS (Material Safety Data sheet). Fisher Scientific (accessed 26.04.2011).

Forskning.no, nov 2010. Available at: http://www.forskning.no/artikler/2010/november/270178 (accessed 26.04.2011).

Forskning.no, des 2010. Available at: http://www.forskning.no/artikler/2010/desember/274634/print (accessed 26.04.2011).

GoodscentCompany. Available at: http://www.thegoodscentscompany.com/data/rw1040381.html (accessed 26.05.2011).

IFRA. International Fragrance Association (IFRA), 2004. Volume of Use Survey.

Inchem. Available at: http://www.inchem.org/documents/pims/pharm/aspirin.htm (accessed 26.05.2012).

Science Links Japan. Determination of Phenyl Salicylate in Cosmetics. Available at: http://sciencelinks.jp/j-east/article/200313/000020031303A0255798.php (accessed 26.04.2011).

Store Norske Leksikon. Available at: http://www.snl.no/.sml_artikkel/salisylsyre (accessed 26.04.2011).

Toxnet. Available at: http://toxnet.nlm.nih.gov/cgi-bin/sis/search/r?dbs+ccris:@term+@rn+118-55-8 (accessed 26.04.2011).

Wikipedia. Available at: http://en.wikipedia.org/wiki/Phenyl_salicylate#cite_note-Merck-0#cite_note-Merck-0 (accessed 24.05.2012).

10. Annexes

Annex 1: Acute toxic data –skin irritation and allergy

Sensitization in response to PS has been reported in only a few instances (Fimiani et al., 1990). Sensitization is the process by which an immunological reaction is increasing for each time the stimulus is presented; i.e.similar to an allergic reaction.
http://www.canis.se/canisleksikon/lexdef.php?lexid=1123&ukat=1

Skin sensitization is a critical and necessary event in the etiology of allergic contact dermatitis (VKM, 2009). It represents an acquired and irreversible immunological change, which makes the body more susceptible to the skin sensitizer and increases the risk of developing allergic contact dermatitis.

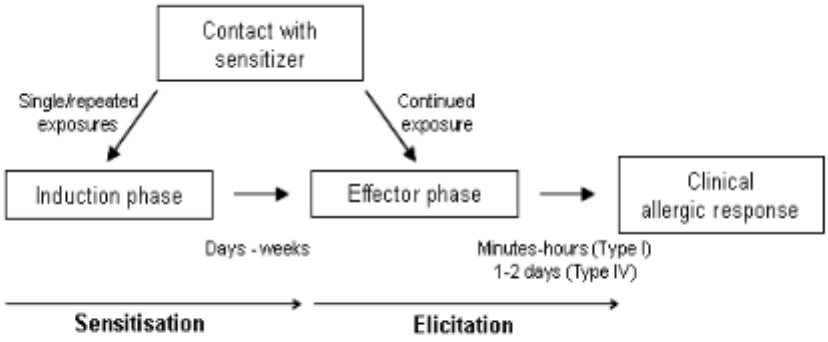


Figure 3. Flow chart showing the causal relationship between sensitisation and clinical allergic contact dermatitis.

The VKM report (2009) concludes as follows:
• Allergic responses are considered adverse health effects. Sensitization is a prerequisite for allergic responses and strongly increases the risk of an allergic response.
• Sensitization caused by exposure to cosmetic products must therefore be considered as an adverse health effect.
http://www.fhi.no/artikler?id=74383

Two cases of skin allergy related to PS in cosmetic products are found in the NIOSHTIC (National Institute for Occupational Safety and Health Technical Information Center) data base:

1. The first case describes a hair dresser who developed strong dermal allergy after application of skin lotion containing high amounts of PS (10%). Patch tests indicated that the allergic reaction was caused by salol (i.e. PS) (Fimiani et al., 1990).

2. PS as an ingredient in a certain brand of protective spectacles also has been shown to cause contact dermatitis (Sonnex *et a*l, 1986).
Excerpt from the abstract:
"We report 3 cases of allergic contact dermatitis behind the ears from wearing the same brand of industrial safely spectacles. In each case, a positive patch test was obtained with scrapings of the plastic frame. In 2 cases further patch tests with constituents of the plastic were carried out; positive patch tests were obtained with phenyl salicylate".

3. Additional presence of skin allergy has been related to PS as a sunscreen in lip salve (Calnan et al. 1981; Hindson, 1980). The product was subsequently removed by the manufacturer.
In Denmark, PS in sunscreen lotion/cream is not allowed
http://www.denstoredanske.dk/It,_teknik_og_naturvidenskab/Kemi/Cykliske_forbindelser/salol?highlight=salol

Lapczynski et al. (2007) have reviewed toxicologic data related to the effects of PS on skin irritation and dermal allergy in humans.

Skin irritation:
-"pretest for maximation-test"; patch-test did not show signs of skin irritation in 5 healthy volunteers exposed to 6% PS (in vaseline) on their back.
Skin allergy:
- "maximation-test" with 6% PS (in vaseline) in 25 healthy volunteers gave negative result; i.e. no allergic reactions.
- 150 women with dermal allergy tested negative in response to salve with 1% PS (patch-test; European standard series and cosmetics -series).
- 173 volunteers whom had developed dermal allergy at their working place were subjected to a patch-test (1% PS) and tested negative.

Consistent with these findings, Opdyke (1975) did not observe any allergic reactions in "maximation tests" in humans exposed to 6% PS.

Skin allergy associated with sunscreen lotion:
Increases in skin allergies or oversensitivity related to substances in UV protecting sunscreen lotions have been reported; e.g. salicylates, with octyl salicylate as the predominant form http://www.allergyclinic.co.nz/guides/66.html.

However, reported cases of dermal allergies caused by salicylates are rare (Dromgoole et al., 1990).

Excerpt abstract:
"Reports in the literature of sensitization associated with many commonly used sunscreening agents including p-aminobenzoic acid (PABA), PABA derivatives, anthranilates, salicylates, cinnamates, benzophenones, and dibenzoylmethane derivatives are reviewed. Several of these case reports involved subjects with various photodermatoses, implicating enhanced sensitivity of the patient's skin to both light and chemicals. Despite the widespread use of sunscreens, the small number of published reports of contact and photocontact sensitization to these agents suggests that either such sensitization is less than commonly perceived or is underreported. Establishment of a registry for reporting adverse effects associated with sunscreening agents would help to characterize the incidence of sensitization".

Reference list for Annex 1:

Protection spectacles:
- Sonnex TS, Rycroft RJ. Dermatitis from phenyl salicylate in safety spectacle frames. Contact Dermatitis. 1986 May;14(5):268-70. PubMed PMID: 2943554.
- Jordan WP Jr, Dahl MV. Contact dermatitis to a plastic solvent in eyeglasses. Cross-sensitivity to ethyl acetate. Arch Dermatol. 1971 Nov;104(5):524-8. PubMed PMID: 5120179.

"Hairdresser case"
Fimiani M, Casini L, Bocci S. Contact dermatitis from phenyl salicylate in a galenic cream. Contact Dermatitis. 1990 Apr;22(4):239. PubMed PMID: 2347179.

Lip salve:
- Hindson C. Phenyl salicylate (Salol) in a lip salve. Contact Dermatitis. 1980 Apr;6(3):216. PubMed PMID: 7389333.
- Calnan CD, Cronin E, Rycroft RJ. Allergy to phenyl salicylate. Contact Dermatitis. 1981 Jul;7(4):208-11. PubMed PMID: 7326927.

Other toxicological studies:
- Lapczynski A, Jones L, McGinty D, Bhatia SP, Letizia CS, Api AM. Fragrance material review on phenyl salicylate. Food Chem Toxicol. 2007;45 Suppl 1:S472-6. Epub 2007 Sep 14. Review. PubMed PMID: 18031889.
- Opdyke D.L.J (1975) Monographs on fragrance raw materials. Food and Cosmetic Toxicology, Suppl. 14, 837.
www.chemotechnique.pl/zamow/kat2008.pdf

Sunscreen lotion:
- Dromgoole SH, et al. Sunscreening agent intolerance: contact and photocontact sensitization and contact urticaria. J Am Acad Dermatol 1990; 22:1068-78
- VKM (2009). Sensitization caused by cosmetic products_2009. Opinion of the Panel on Food Additives, Flavourings, Processing Aids, Materials in Contact with Food and Cosmetics. The Norwegian Scientific Committee for Food Safety. ISBN 978-82-8082-298-7.

History:
The first documented use of sunscreen occurred in 1928 with the introduction of an emulsion composed of benzyl salicylate and benzyl cinnamate in the United States. In the 1930's, a south Australian chemist by the name of H.A. Milton Blake formulated a protective agent containing 10% salol (phenyl salicylate) (Groves G. The sunscreen industry in Australia; Past, present, and future, Sunscreen (N.J. Lowe and N.A. Shaath, eds.), Marcel Dekker, New York, 1997, Chap. 13.3).

PS absorbs UV light in the range 290-330 nm and was earlier because of that property employed to some degree in sun protection products and lip balm for chapped lips. Usage declined for these purposes in the early 80s when it turned out that phenol is released at workable concentrations (2- 10 %). Phenol has corrosive effect on the skin – and is banned in cosmetic products since 2005 (amending directive 2005/80/EF) due to classification as a CMR substance. Presumably because of dermatitis, some of allergic nature, PS was not taken up in the UV filter positive list of the EU Cosmetics Directive when adopted in 1983 (amending directive 83/574/EEC). The Council of Europe expert committee on cosmetics in 2006 thought that perhaps PS is still used for UV protection purposes (Room Document: RD P-SP-CO-AI/RD2-4. April 2006).

Annex 2. Cosmetic products containing phenyl salicylate

Table 1
Calculation of the total human skin exposure from the use of multiple cosmetic products containing phenyl salicylate

Type of cosmetic product	Grams applied	Applications per day	Retention factor	Mixture/product	Ingredient/mixture[a]	Ingredient (mg/kg/day)[b]
Body lotion	8.00	0.71	1.000	0.004	0.02	0.0001
Face cream	0.80	2.00	1.000	0.003	0.02	0.0000
Eau de toilette	0.75	1.00	1.000	0.080	0.02	0.0002
Fragrance cream	5.00	0.29	1.000	0.040	0.02	0.0002
Antiperspirant	0.50	1.00	1.000	0.010	0.02	0.0000
Shampoo	8.00	1.00	0.010	0.005	0.02	0.0000
Bath products	17.00	0.29	0.001	0.020	0.02	0.0000
Shower gel	5.00	1.07	0.010	0.012	0.02	0.0000
Toilet soap	0.80	6.00	0.010	0.015	0.02	0.0000
Hair spray	5.00	2.00	0.010	0.005	0.02	0.0000
Total						0.0005

[a] Upper 97.5‰ levels of the fragrance ingredient in the fragrance mixture used in these products.
[b] Based on a 60 kg adult.

Table 2
Summary of acute toxicity data

Route	Species	No. animals/dose group	LD_{50}	References
Oral	Rat	10	3.0 g/kg	RIFM (1975b)
Dermal	Rabbit	4	>5.0 g/kg	RIFM (1975b)

Table 3
Summary of animal sensitization studies

Test method	Concentration	Results	References
Buehler test	25%	No sensitization	Basketter and Gerberick (1996)
FCAT	5% (induction) 0.3% and 1.0% (challenge)	8/9 reactions at 0.3% 9/9 reactions at 1.0%	Marchand et al. (1982)
CET	30% (induction)1% (challenge)	No sensitization	Ishihara et al. (1986)

Annex 3

Identification of 10 products on the European market (per March 2011) containing Phenyl Salicylate, including 1 Norwegian product, i.e. SIKOTOL. Many more products are likely to exist.

Annex 4:

Japanese regulation of Phenyl Salicylate

MORI KEN'ICHIRO, TERAJIMA KIYOSHI, NAKAMURA YOSHIAKI, ONUKI NAHOMI, YOKOYAMA TOSHIRO, ITO KOICHI (2002) Determination of Phenyl Salicylate in Cosmetics. Annual Report of Tokyo Metropolitan Research Laboratory of Public Health 53:65-67 (**ISSN:**0082-4771)

Abstract: Part of the, Drugs, Cosmetics and Medical Instruments Act was revised on April 1st. 2001. Formerly, phenyl salicylate(PS) had been allowed at a maximum proportion of 1.0% in cleansing preparations, 0.2% for hair care, treatment and makeup preparations, and condemned for eye liner, lipstick, inner mouth preparations, and bathing preparations. Since revision of the law, however, PS can be used at a maximum proportion of 1.0% in any cosmetics. We have not found PS in all cosmetics, but the amount of PS in cosmetics will likely increase hereafter. The method for determination of PS in cosmetics has not been reported.

Comment:

Salol has apparently been observed as an ingredient in various products in Japan. Presumably, the limit of 1 % is based on safety assessment.

Annex 5: Salol in mouth wash (Norway)

Annex 6: Endocrine disruptors

Table 2. Phenolic additives used as preservatives.

Compound	activity	MW
Benzophenone-1	1/3,000	214.2
Benzophenone-2	1/7,000	246.2
Benzophenone-3	Submax	228.3
Benzophenone-4	ND	308.3
Benzophenone-6	Submax	274.3
Benzophenone-7	Submax	232.7
Benzophenone-8	ND	244.2
Benzophenone-12	ND	326.5
4,4'-Dihydroxybenzophenone	1/40,000	214.2
Phenyl salicylate	1/300,000	214.2
Benzyl salicylate	Submax	228.3
Menthyl salicylate	Submax	276.4
Ethylhexyl salicylate	Submax	250.9
Triethanolamine salicylate	ND	287.3
Resorcinol monobenzoate	1/80,000	214.2
Octrizole	ND	323.4
2,4-Di-t-butyl-6(5-chloro-2H-benzotriazol-2-yl)phenol	ND	357.9
7-Hydroxycoumarin	ND	162.1

Abbreviations: CAS, Chemical Abstracts Service; MW, molecular weight; ND, not detected; Submax, submaximal response curve; usage group 1, cosmetic sunscreen; usage group 2, light stabilizer for polymers. Estrogenic activity shows the potency relative to 17[Beta]-estradiol.

Comment:
While Salol demonstrate both anti-androgenic and anti-estrogenic effects in vitro, the substance only displays very weak estrogen effects in this assay.

Reference:
Danielle Miller, Brian B. Wheals, Nicola Beresford, John P. Sumpter (2001) Estrogenic Activity of Phenolic Additives Determined by an In Vitro Yeast Bioassay Environmental Health Perspectives. http://findarticles.com/p/articles/mi_m0CYP/is_2_109/ai_77276631/pg_2/

Endocrine disruptors:
It has been suggested that the mechanism underlying the effect of mild painkillers on *cryptorchidism* may involve an endocrine disruptive effect, e.g. by inhibiting the formation of testosterone (Kristensen et al., 2010).

Precautionary principles to tackle adverse health effects in humans due to chemical pollutants are described at:

Endocrine disrupters website:
http://ec.europa.eu/environment/endocrine/strategy/substances_en.htm

List of 146 substances with endocrine disruption categorizations prepared in the Expert meeting:
http://ec.europa.eu/environment/docum/pdf/bkh_annex_13.pdf

Salicylates not listed.

PS has been shown to possess modest estrogenic activity, not detectable androgenic activity, strong anti-estrogenic as well as potent anti-androgenic activities in semi-quantitative *in vitro* assays (hERα og hAR) (Kunz & Fent, 2006, ref. 26).

Estrogenic activity of phenolic additives determined by an *in vitro* yeast bioassay showed that the potency of PS was only 1/300,000 relative to 17[Beta]-estradiol (Miller et al., 2001, ref 27).

Although PS is capable of modulating endocrine activities in vitro, *in vivo* data are so far missing. Thus, there is not sufficient data to determine whether PS has a role as an endocrine disruptor.

Annex 7: Calculations of concentration limits of PS in cosmetics

Hands and face cream :
A. Face : 565 cm^2 (default)
B. Hands : 860 cm^2 (default)

A. Systemic exposure dosage for face with cosmetic product usage level at 1 % (illustrative purposes) :

SED (face) : (10^3 mg/grams * 1.54 grams/day * 0.01) /60 = 0.256 ;

MoS : 50 /0.256 = 195

The maximum allowed levels of PS as an ingredient corresponding to MoS =100 : 1.9 %

(60 * 50 /1540) * X =100 -> X = (60 * 50) /(1540 * 100) ->X= 1.9 %

B. Systemic exposure dosage for hands (ratio hands/face = 860 cm^2 /565 cm^2 = 1.522) with cosmetic product usage level at 1 % (illustrative purposes) :

SED (hands) : (10^3 mg/grams * 1.54 grams/day * 0.01) * 1.522 /60 = 0.390;

MoS : 50 /0.390 = 128

The maximum allowed levels of PS as an ingredient corresponding to MoS =100 : 1.3 %

(60 * 50 /1540 * 1.522) * X =100 -> X = (60 * 50) /(1540 * 1.522 *100) -> X= 1.3 %