Amended Safety Assessment of Salicylic Acid and Salicylates as Used in Cosmetics

Status: Draft Final Amended Report for Panel Review
Release Date: March 15, 2019
Panel Date: April 8-9, 2019

The 2019 Cosmetic Ingredient Review Expert Panel members are: Chair, Wilma F. Bergfeld, M.D., F.A.C.P.; Donald V. Belsito, M.D.; Ronald A. Hill, Ph.D.; Curtis D. Klaassen, Ph.D.; Daniel C. Liebler, Ph.D.; James G. Marks, Jr., M.D.; Ronald C. Shank, Ph.D.; Thomas J. Slaga, Ph.D.; and Paul W. Snyder, D.V.M., Ph.D. The CIR Executive Director is Bart Heldreth, Ph.D. This report was prepared by Wilbur Johnson, Jr., M.S., Senior Scientific Analyst, and Jinqiu Zhu, Ph.D., Toxicologist.

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Memorandum

To: CIR Expert Panel Members and Liaisons
From: Wilbur Johnson, Jr.
Senior Scientific Analyst
Date: March 15, 2019
Subject: Draft Final Amended Report on Salicylic Acid and Salicylates

Enclosed is a draft final amended report on Salicylic Acid and Salicylates (*salicy042019FR*). At the December 2018 CIR Expert Panel (Panel) Meeting, the Panel issued a revised tentative amended report for public comment with the conclusion that Salicylic Acid and the 18 salicylate ingredients reviewed in the safety assessment are safe in cosmetics in the present practices of use and concentration described in the safety assessment, when formulated to be non-irritating and non-sensitizing, which may be based on a quantitative risk assessment (QRA). The Panel's actions prior to issuance of this revised tentative amended report are summarized below.

A CIR Final Report on Salicylic Acid and 16 salicylates was published in 2003. The conclusion in that safety assessment states that these ingredients are safe as used when formulated to avoid skin irritation and when formulated to avoid increasing the skin's sun sensitivity, or, when increased sun sensitivity would be expected, directions for use include the daily use of sun protection.

Based on discussions at the June 2018 Panel meeting, the qualification in the original conclusion relating to formulating products to avoid increasing the skin's sun sensitivity was removed, based on results from a National Toxicology Program photocarcinogenicity study indicating that Salicylic Acid had some protective effect at lower light intensities. A tentative amended report with a conclusion that these ingredients are safe when formulated to be non-irritating was issued at this meeting. However, at the December 2018 Panel meeting, in addition to concern for irritation potential, the Panel acknowledged positive sensitization data on salicylates. The Panel noted that the potential for induction of skin sensitization varies depending on a number of factors, including the area of product application; thus, formulators should assess the potential for final formulations to induce sensitization using a QRA or other accepted methodologies. Therefore, the Panel issued a revised tentative amended report with qualifications addressing sensitization as well as irritation at the December 2018 Panel meeting.

The safety assessment has been revised to include comments that were received from the Council (*salicy042019pcpc1* and *salicy042019pcpc2)* and 2019 FDA VCRP data (*salicy042019FDA)*, both of which are attached. Regarding the new FDA data, it should be noted that Hexyl Salicylate is now being used in perfumes, i.e., cosmetic products in which inhalation is a route of exposure. Comments that were received from the Council have been addressed.

Also included in this package for your review are the CIR report history (*salicy042019hist*), flow chart (*salicy042019flow*), literature search strategy (*salicy042019strat*), ingredient data profile (*salicy042019prof*), and minutes from the 1999, 2000, and 2018 CIR Expert Panel meetings (*salicy042019min*). The published CIR safety assessment on Salicylic Acid and 16 salicylates is available on the CIR website (https://www.cir-safety.org/ingredients).

However, it has come to our attention that Capryloyl Salicylic Acid appears to have been seriously mischaracterized. This ingredient has thus been removed from this report and is proposed for a separate and individual safety assessment. Accordingly, the draft final amended report for Panel review is actually on Salicylic Acid and the ***17*** salicylate ingredients.

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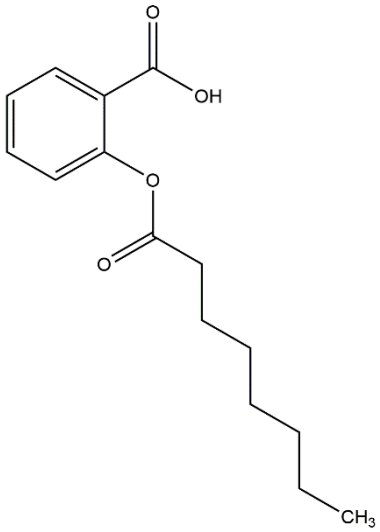
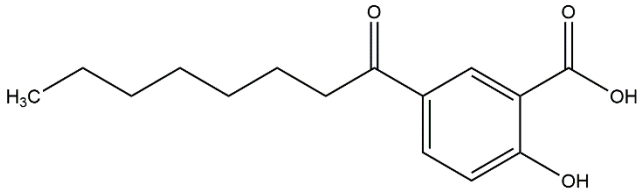
The definition of Capryloyl Salicylic Acid, according to the *Dictionary*, is the ester of Salicylic Acid and caprylic acid. Consequently, the only structure in line with this definition is the following ester:



This definition and associated structure, however, do not appear to accurately reflect the actual ingredient. Consulting data and information from the CAS file, NICNAS and ECHA dossiers, and publicly available literature (including at least one by a cosmetic manufacturer), the ingredient in use instead appears to be the following ketone (2-hydroxy-5-octanoyl benzoic acid):

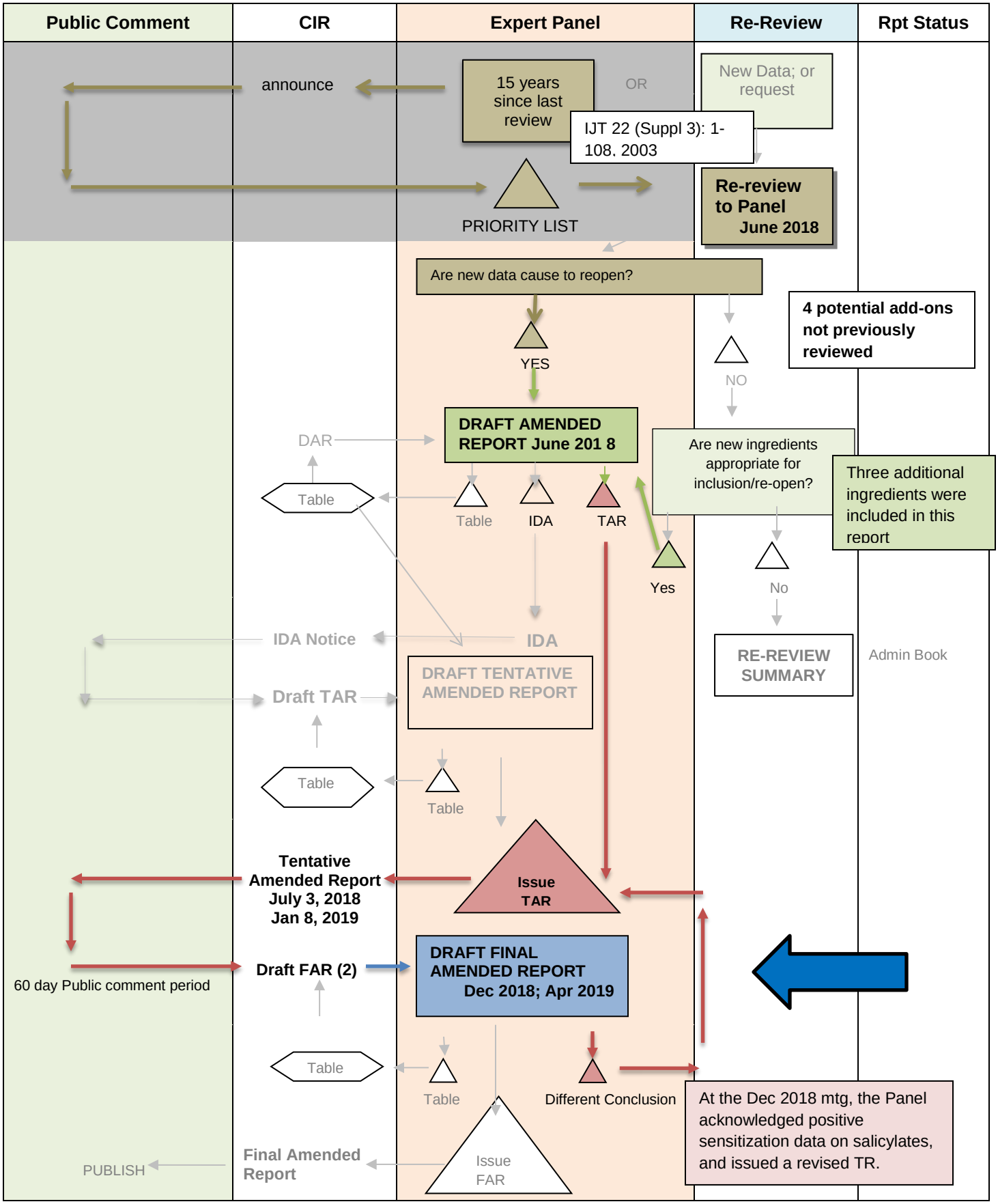


It is proposed that this ingredient be re-reviewed separately and independently, in a new safety assessment with the appropriate characterization, at a future meeting. Thus, at this current meeting, the Panel is being asked to carefully review the Abstract, Discussion, and Conclusion in this safety assessment of Salicylic Acid and the ***17*** salicylate ingredients (18 minus Capryloyl Salicylic Acid). If these are satisfactory, the Panel should issue a final amended report.

RE-REVIEW FLOW CHART

INGREDIENT/FAMILY Salicylic Acid and Salicylates

MEETING April 2019



CIR History of:

Salicylates

Salicylic Acid, Calcium Salicylate, Magnesium Salicylate, MEA-Salicylate, Potassium Salicylate, Sodium Salicylate, TEA-Salicylate, Capryloyl Salicylic Acid, C12-15 Alkyl Salicylate, Isocetyl Salicylate, Isodecyl Salicylate, Methyl Salicylate, Myristyl Salicylate, Octyl Salicylate,Tridecyl Salicylate, Butyloctyl Salicylate, and Hexyldodecyl Salicylate

Draft Report, Teams/Panel: September 9-10, 1999

The combined list of data requests (both Teams) is as follows:
(1) A risk assessment for developmental/reproductive toxicity of concentrations delivered by cosmetic products alone and in combination with salicylic acid from other common sources (e.g., acne medications, aspirin, etc.)
(2) Additional uses intended by industry, i.e., exfoliant use
(3) Dermal irritation data using pH vs. concentration (like in the AHA report)
(4) Studies similar to those requested for the AHA report examining the effect of use and sun exposure, i.e., sunburn cell or pyrimidine dimer studies

Draft Report, Teams/Panel: February 14-15, 2000

The Panel voted unanimously in favor of issuing a Tentative Report with the conclusion that Salicylic Acid and its salts and esters are safe as used when formulated to avoid irritation, and when formulated to avoid increased sun sensitivity. It was also concluded that if enhanced sun sensitivity is expected, then directions for use including the daily use of sun protection should be provided.

Draft Final Report, Teams/Panel: September 11-12, 2000

The Panel voted unanimously in favor of issuing a Final Report on this group of ingredients with the following conclusion: Based on the available information, the CIR Expert Panel concluded that Salicylic Acid, the salts Calcium Salicylate, Magnesium Salicylate, MEA-Salicylate, Potassium Salicylate, Sodium Salicylate, and TEA-Salicylate, the esters Capryloyl Salicylic Acid, C12-15 Alkyl Salicylate, Isocetyl Salicylate, Isodecyl Salicylate, Methyl Salicylate, Myristyl Salicylate, Myristyl Salicylate, Ethylhexyl Salicylate, and Tridecyl Salicylate, and the compounds Butyloctyl Salicylate and Hexyldodecyl Salicylate are safe as used when formulated to avoid irritation and when formulated to avoid increasing sun sensitivity, or, when increased sun sensitivity would be expected, directions for use include the daily use of sun protection.

Rereview, Teams/Panel: June 4-5, 2018

The Panel issued a tentative amended report for public comment with the conclusion that Salicylic Acid and the 18 salicylate ingredients listed below are safe in cosmetics in the present practices of use and concentration described in the safety assessment, when formulated to be non-irritating.

Butyloctyl Salicylate
Calcium Salicylate*
C12-15 Alkyl Salicylate*
Capryloyl Salicylic Acid
Ethylhexyl Salicylate
Hexyldodecyl Salicylate*
Isocetyl Salicylate*
Isodecyl Salicylate
Magnesium Salicylate
Methyl Salicylate
Myristyl Salicylate*
Potassium Salicylate*
Salicylic Acid
Sodium Salicylate
TEA-Salicylate
Tridecyl Salicylate
Amyl Salicylate
Hexyl Salicylate
Isotridecyl Salicylate*

*Not reported to be in current use. Were ingredients in this group not in current use to be used in the future, the expectation is that they would be used in product categories and at concentrations comparable to others in this group.

The original conclusion (stated above) has been revised to omit the qualification relating to formulating products to avoid increasing the skin's sun sensitivity. The reason for omitting the qualification relating to the skin's sun sensitivity is based on results from an NTP photocarcinogenicity study indicating that Salicylic Acid had some protective effect against photocarcinogenicity, at lower light intensities. In the NTP study, the effects of synthetic solar light on the skin of hairless mice that had been treated with creams containing 2% or 4% Salicylic Acid were evaluated. Creams containing Salicylic Acid decreased the incidence of skin tumors in mice receiving the lower of the two light intensities.

The Panel also expressed concern over the reproductive toxicity of Salicylic Acid, after learning that, in the third trimester, the use of Salicylic Acid can potentially cause early closure of the ductus arteriosus and oligohydramnios. Thus, the Panel requested that CIR calculate a margin of safety for Salicylic Acid exposure, taking into consideration the extent of dermal absorption during cosmetic product use (at highest maximum use concentration of 30% in leave-on products), for inclusion in a future iteration of the report.

Draft Amended Final Report, Teams/Panel: December 3-4, 2018

This safety assessment has been updated to include data from the following sources: Chemical registration dossiers submitted to the European Chemicals Agency, in comformity with the European Union's Registration, Evaluation, Authorization and Restriction of Chemicals (REACH) regulation; a 2002 Scientific Committee on Cosmetic Products and Non-Food Products Intended for Consumers (SCCNFP; SCCS formerly known as SCCNFP) opinion document on Salicylic Acid; and a 2018 Scientific Committee on Consumer Safety (SCCS) preliminary opinion document on Salicylic Acid. The Draft Amended Final Report also references the various restrictions relating to the use of Salicylic Acid and salicylates in cosmetics that have been established by the European Union (EU). Additionally, it should be noted that the updated 2018 use concentration data on Salicylic Acid and salicylates that were received from the Council have been added, and that comments on the Tentative Amended Final Report that were received from the Council have been addressed.

The Panel issued a revised tentative amended report for public comment with the conclusion that Salicylic Acid and the 18 salicylate ingredients listed below are safe in cosmetics in the present practices of use and concentration described in the safety assessment, when formulated to be non-irritating and non-sensitizing, which may be based on a quantitative risk assessment (QRA).

Butyloctyl Salicylate
Calcium Salicylate*
C12-15 Alkyl Salicylate*
Capryloyl Salicylic Acid
Ethylhexyl Salicylate
Hexyldodecyl Salicylate*
Isocetyl Salicylate*
Isodecyl Salicylate
Magnesium Salicylate
Methyl Salicylate
Myristyl Salicylate*
Potassium Salicylate*
Salicylic Acid
Sodium Salicylate
TEA-Salicylate
Tridecyl Salicylate
Amyl Salicylate
Hexyl Salicylate
Isotridecyl Salicylate*

*Not reported to be in current use. Were ingredients in this group not in current use to be used in the future, the expectation is that they would be used in product categories and at concentrations comparable to others in this group. Ingredients identified by blue text were not included in the original safety assessment.

The Panel originally published a Safety Assessment of Salicylic Acid and 16 salicylates in 2003 with the conclusion that Salicylic Acid; the salts, Calcium Salicylate, Magnesium Salicylate, MEA-Salicylate, Potassium Salicylate, Sodium Salicylate, and TEA-Salicylate; the esters, Capryloyl Salicylic Acid, C12-15 Alkyl Salicylate, Isocetyl Salicylate, Isodecyl Salicylate, Methyl Salicylate, Myristyl Salicylate, Ethylhexyl Salicylate, and Tridecyl Salicylate; and the compounds, Butyloctyl Salicylate and Hexyldodecyl Salicylate, are safe as used when formulated to avoid skin irritation and when formulated to avoid increasing the skin's sun sensitivity, or, when increased sun sensitivity would be expected, directions for use include the daily use of sun protection.

The qualification relating to formulating products to avoid increasing the skin's sun sensitivity that was included in the original conclusion is now omitted, based on results from a National Toxicology Program (NTP) photocarcinogenicity study indicating that Salicylic Acid had some protective effect at lower light intensities. In the NTP study, the effects of synthetic solar light on the skin of hairless mice that had been treated with creams containing 2% or 4% Salicylic Acid were evaluated. Creams containing Salicylic Acid decreased the incidence of skin tumors in mice receiving the lower of the two light intensities.

At their June 2018 meeting, the Panel issued a tentative amended report with a conclusion that these ingredients are safe when formulated to be non-irritating. However, upon further review at this December 2018 Panel meeting, meeting, in addition to concern for irritation potential, the Panel acknowledged positive sensitization data on salicylates. The Panel noted that the potential for induction of skin sensitization varies depending on a number of factors, including the area of product application; thus, formulators should assess the potential for final formulations to induce sensitization using a QRA or other accepted methodologies. Therefore, the Panel issued a revised tentative amended report with qualifications addressing sensitization as well as irritation, as stated above.

Draft Amended Final Report, Teams/Panel: April 8-9, 2018

The safety assessment has been revised to include comments that were received from the Council and 2019 FDA VCRP data. Regarding the new FDA data, it should be noted that Hexyl Salicylate is now being used in perfumes, i.e., cosmetic products in which inhalation is a route of exposure. Comments that were received from the Council have been addressed. Because Capryloyl Salicylic Acid appears to have been mischaracterized, it should be noted that it is no longer included in this re-review.

Data Profile on Salicylates for April 8-9, 2019 Panel - Wilbur Johnson

	Dermal Penetration			Nail Penetration	Penetration Enhancement	ADME					Acute Toxicity			Short-Term Toxicity	Sub-Chronic Toxicity	Chronic Toxicity	DART		Genotoxicity	Carcinogenicity	Other Relevant Studies		Dermal Irritation*	Dermal Sensitization/Photosensitization		Ocular Irritation *		Clinical Studies	Case Reports/ Clinical Reports (other)		Epidemiology Studies
	In Vivo -Animal	In Vitro	In Vivo-Human	In Vitro-Human	In Vitro-Animal	In Vitro	Animal-Dermal	Animal-Oral	Animal-Inhalation	Human-Oral	Animal-Dermal	Animal-Oral	Animal-Inhalation	Animal	Animal	Animal	In Vitro	In Vivo	In Vitro/In Vivo	In Vivo	In Vitro	In Vivo-Animal/Human	Animal/Human/In vitro	Animal/In Vitro/In Silico	Human	In Vitro	Animal	Human-MulticenterStudy	Human-Dermal	Human-Inhalation	Human
Butyloctyl Salicylate								X			X	X		X					X		X		X	X	X		X				
Calcium Salicylate																															
C12-15 Alkyl Salicylate																															
Ethylhexyl Salicylate		X	X				X	X			X	X						X	X		X	X	X	X	X		X		X		
Hexyldodecyl Salicylate																															
Isocetyl Salicylate																															
Isodecyl Salicylate								X				X			X				X				X				X				
Magnesium Salicylate								X		X																					
Methyl Salicylate	X	X	X				X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X		X		X		
Myristyl Salicylate																															
Potassium Salicylate																															
Salicylic Acid	X	X	X		X	X		X		X	X	X	X	X	X		X	X	X	X		X	X	X	X		X	X	X		
Sodium Salicylate	X	X	X					X		X	X	X		X	X		X	X	X	X		X	X		X	X	X		X		
TEA-Salicylate	X		X																				X								
Tridecyl Salicylate								X			X	X							X				X	X	X		X				
Add - Ons																															
Amyl Salicylate														X	X								X	X				X	X		
Hexyl Salicylate			X					X			X	X											X	X	X			X			
Isotridecyl Salicylate																															
Silver Salicylate																															

X = data

[Salicylates–4/6/2018; 3/1/2019 update]

Ingredient	CAS #	InfoBase	SciFinder	PubMed	TOXNET	FDA	EU	ECHA	IUCLID	SIDS	HPVIS	NICNAS	NTIS	NTP	WHO	FAO	ECET-OC	Web
Butyloctyl Salicylate	190085-41-7	1	116/0	1/1	1/1		No	1996 data	No									
Calcium Salicylate	824-35-1	1	12/0	5/0	4/2		Yes	No	No									
C12-15 Alkyl Salicylate		1	1/1	1/1	1/1		No	No	No									
Ethylhexyl Salicylate	118-60-5	1	52/10	41/3	19/1		Yes	1990 data	No									
Hexyldodecyl Salicylate	220778-06-3	1	8/0	1/1	1/1		No	No	No									
Isocetyl Salicylate	138208-68-1	1	15/1	1/1	1/1		No	No	No									
Isodecyl Salicylate	85252-25-1	1	20/1	1/1	1/1		No	No	No									
Magnesium Salicylate	18917-89-0; 551-37-1	1	36/2	14/1	1/1		Yes	No	No									
Methyl Salicylate	119-36-8	1	427/34	19/3	60/1		No	60s and 70s data	No									
Myristyl Salicylate	19666-17-2	1	15/1	1/1	1/1		No	No	No									
Potassium Salicylate	578-36-9	1	205/0	3/1	1/1		Yes	No	No									
Salicylic Acid	69-72-2	1	331/21	105/3	176/7		Yes	70s and 90s data	No									
Sodium Salicylate	54-21-7	1	283/8	29/2	19/2		Yes	80s and 2000s data	No									
TEA-Salicylate	2174-16-5	1	310/4	1/1	2/1		Yes	No	No									
Tridecyl Salicylate	19666-16-1	1	30/0	2/1	1/1		No	No	No									
ADD ONS - Below																		
Amyl Salicylate	2050-08-0	1	487/13	4/1	4/1	Yes	No	Yes	No									
Hexyl Salicylate	6259-76-3	1	45/15	10/3	2/1	Yes	No	Yes	No									
Isotridecyl Salicylate	1863871-63-9	1	1/0	0/0	0/0	Yes	No	No	No									
Silver Salicylate	19025-97-9	1	149/5	3/0	1/1	Yes	No	No	No									

Search Strategy

[*document search strategy used for SciFinder, PubMed, and Toxnet*] years 1999-2018 for previously reviewed ingredients; all years for 4 new ingredients

LINKS

InfoBase (self-reminder that this info has been accessed; not a public website) - http://www.personalcarecouncil.org/science-safety/line-infobase
ScfFinder (usually a combined search for all ingredients in report; list # of this/# useful) - https://scifinder.cas.org/scifinder
PubMed (usually a combined search for all ingredients in report; list # of this/# useful) - http://www.ncbi.nlm.nih.gov/pubmed
Toxnet databases (usually a combined search for all ingredients in report; list # of this/# useful) – https://toxnet.nlm.nih.gov/
(includes Toxline; HSDB; ChemIDPlus; DAR; IRIS; CCRIS; CPDB; GENE-TOX)

FDA databases – http://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfcfr/cfrsearch.cfm (CFR); then,
list of all databases: http://www.fda.gov/ForIndustry/FDABasicsforIndustry/ucm234631.htm; then,
http://www.accessdata.fda.gov/scripts/fcn/fcnnavigation.cfm?rpt=eafuslisting&displayall=true (EAFUS);
http://www.fda.gov/food/ingredientspackaginglabeling/gras/default.htm (GRAS);
http://www.fda.gov/food/ingredientspackaginglabeling/gras/scogs/ucm2006852.htm (SCOGS database);
http://www.accessdata.fda.gov/scripts/fdcc/?set=IndirectAdditives (indirect food additives list);
http://www.fda.gov/Drugs/InformationOnDrugs/default.htm (drug approvals and database);
http://www.fda.gov/downloads/AboutFDA/CentersOffices/CDER/UCM135688.pdf (OTC ingredient list);
http://www.accessdata.fda.gov/scripts/cder/iig/ (inactive ingredients approved for drugs)

EU (European Union); check CosIng (cosmetic ingredient database) for restrictions and SCCS (Scientific Committee for Consumer Safety) opinions - http://ec.europa.eu/growth/tools-databases/cosing/
ECHA (European Chemicals Agency – REACH dossiers) – http://echa.europa.eu/information-on-chemicals;jsessionid=A978100B4E4CC39C78C93A851EB3E3C7.live1
IUCLID (International Uniform Chemical Information Database) - https://iuclid6.echa.europa.eu/search
OECD SIDS documents (Organisation for Economic Co-operation and Development Screening Info Data Sets)- http://webnet.oecd.org/hpv/ui/Search.aspx
HPVIS (EPA High-Production Volume Info Systems) - https://ofmext.epa.gov/hpvis/HPVISlogon
NICNAS (Australian National Industrial Chemical Notification and Assessment Scheme)- https://www.nicnas.gov.au/
NTIS (National Technical Information Service) - http://www.ntis.gov/
NTP (National Toxicology Program) - https://ntp.niehs.nih.gov/
WHO (World Health Organization) technical reports - http://www.who.int/biologicals/technical_report_series/en/
FAO (Food and Agriculture Organization of the United Nations) - http://www.fao.org/food/food-safety-quality/scientific-advice/jecfa/jecfa-additives/en/ (FAO);
FEMA (Flavor & Extract Manufacturers Association) - http://www.femaflavor.org/search/apachesolr_search/
Web – perform general search; may find technical data sheets, published reports, etc
ECETOC (European Center for Ecotoxicology and Toxicology Database) - http://www.ecetoc.org/

Fragrance Websites, if applicable
IFRA (International Fragrance Association) – http://www.ifraorg.org/
RIFM (the Research Institute for Fragrance Materials) should be contacted

Qualifiers

Absorption
Acute
Allergy
Allergic
Allergenic
Cancer
Carcinogen
Chronic
Development
Developmental
Excretion
Genotoxic
Irritation
Metabolism
Mutagen
Mutagenic
Penetration
Percutaneous
Pharmacokinetic
Repeated dose
Reproduction
Reproductive
Sensitization
Skin
Subchronic
Teratogen
Teratogenic
Toxic
Toxicity
Toxicokinetic
Toxicology
Tumor

September 9-10, 1999 (72nd) Meeting of the CIR Expert Panel

Salicylic Acid, Calcium Salicylate, Magnesium Salicylate,
MEA-Salicylate, Potassium Salicylate, Sodium Salicylate,
TEA-Salicylate, Capryloyl Salicylic Acid, C12-15 Alkyl Salicylate,
Isocetyl Salicylate, Isodecyl Salicylate, Methyl Salicylate,
Myristyl Salicylate, Octyl Salicylate,Tridecyl Salicylate, Butyloctyl Salicylate,
and Hexyldodecyl Salicylate

Dr. Schroeter said that his Team determined that additional data are needed to complete the safety assessment on this group of ingredients. He noted that the data requests on this group of ingredients, also known as beta hydroxy acids, would be similar to those that were issued on the alpha hydroxy acids. Dr. Schroeter's Team issued the following informal data request:

(1) Data to determine dermal irritation that is pH-dependent, as well as concentration-dependent
(2) Data that determines the possibility of promotion of carcinogenicity, such as a dermal sunburn cell study of pyrimidine dimers and/or MEDs to determine the photosensitivity that may occur
(3) Request that industry submit information on any additional uses or expected uses of these ingredients

Dr. Schroeter indicated that a discussion of his Team's concern regarding the use of these ingredients on children and any toxicity needs to be developed, but this can be done at a later date, after data requested informally have been reviewed.

Dr. Belsito said that no additional studies on irritancy are needed because of data indicating that these ingredients can be used at a level that is nonirritating. He also said that the Panel could take the same approach that was used during its review of alpha hydroxy acids, to indicate that products containing these ingredients should be formulated so as to be nonirritating. Dr. Belsito indicated that the following data are needed:

(1) Risk assessment for teratogenicity
(2) Some type of study (similar to alpha hydroxy acid sunburn cell study or thymidine dimers study)
(3) Update on the ways in which these ingredients are being used in cosmetics

The combined list of data requests (both Teams) is as follows:
(1) A risk assessment for developmental/reproductive toxicity of concentrations delivered by cosmetic products alone and in combination with salicylic acid from other common sources (e.g., acne medications, aspirin, etc.)
(2) Additional uses intended by industry, i.e., exfoliant use
(3) Dermal irritation data using pH vs. concentration (like in the AHA report)
(4) Studies similar to those requested for the AHA report examining the effect of use and sun exposure, i.e., sunburn cell or pyrimidine dimer studies

Dr. Andersen said that the list of data requests will be provided to Dr. McEwen as an informal request for industry data.

Dr. Belsito noted that his Team had also discussed the possible exclusion of MEA and TEA Salicylate from the present report, given the ongoing research activities on the ethanolamines.

The Panel agreed that MEA and TEA Salicylate should remain in the present report.

February 14-15, 2000 (74th) Meeting of the CIR Expert Panel

Salicylic Acid, Calcium Salicylate, Magnesium Salicylate,
MEA-Salicylate, Potassium Salicylate, Sodium Salicylate,
TEA-Salicylate, Capryloyl Salicylic Acid, C12-15 Alkyl Salicylate,
Isocetyl Salicylate, Isodecyl Salicylate, Methyl Salicylate,
Myristyl Salicylate, Octyl Salicylate, Tridecyl Salicylate, Butyloctyl Salicylate,
and Hexyldodecyl Salicylate

Dr. Belsito noted that the following data on these ingredients were requested (informal data request) at the September 9-10, 1999 Panel meeting:

(1) A risk assessment for developmental/reproductive toxicity of concentrations delivered by cosmetic products alone and in combination with salicylic acid from other common sources (e.g., acne medications, aspirin, etc.)
(2) Additional uses intended by industry, i.e., exfoliant use
(3) Dermal irritation data using pH vs. concentration (like in the AHA report)
(4) Studies similar to those requested for the AHA report examining the effect of use and sun exposure, i.e., sunburn cell or pyrimidine dimer studies

Dr. Belsito also recalled that data on mutagenicity, phototoxicity, and skin irritation potential were received since the September Panel meeting. After considering these data along with the ingredient use concentration data, Dr. Belsito's Team concluded that Salicylic Acid and the other ingredients in this group are safe as used when formulated to avoid irritation and when formulated to avoid increased sun sensitivity. Furthermore, it was concluded that if these ingredients have an effect on sun sensitivity, it is expected that directions for use would include the daily use of sun protection.

Dr. Shank noted that the new data indicate that exposure to low ingredient concentrations in cosmetics leads to blood levels that would be considered insignificant.

Concerning the issue of exfoliant use, Dr. Bailey recalled that data on sunburn cell formation and MED's were included in the Panel's original request for data. He wanted to know whether the Panel plans to issue a safe as used conclusion in the absence of these data.

Dr. Belsito noted that Salicylic Acid and its salts are sunscreens to some extent. He also speculated that if the sunburn cell study were done, the results would indicate either no increase in sun sensitivity or protection against sun exposure; however, concern about the need for photoprotection would remain. Dr. Belsito also considered that the study results may be similar to those reported for AHA's, which would serve as the basis for restrictions/qualifications (proposed by Belsito Team) relating to the safe use of Salicylic Acid and its salts and esters.

Dr. Bailey expressed the view that the expectation is that industry will test products to determine whether or not there is any increase in sun sensitivity. This would entail the performance of both MED and sunburn cell studies.

The Panel voted unanimously in favor of issuing a Tentative Report with the conclusion that Salicylic Acid and its salts and esters are safe as used when formulated to avoid irritation, and when formulated to avoid increased sun sensitivity. It was also concluded that if enhanced sun sensitivity is expected, then directions for use including the daily use of sun protection should be provided.

September 11-12, 2000 (76th) Meeting of the CIR Expert Panel

Salicylic Acid, Calcium Salicylate, Magnesium Salicylate,
MEA-Salicylate, Potassium Salicylate, Sodium Salicylate,
TEA-Salicylate, Capryloyl Salicylic Acid, C12-15 Alkyl Salicylate,
Isocetyl Salicylate, Isodecyl Salicylate, Methyl Salicylate,
Myristyl Salicylate, Octyl Salicylate, Tridecyl Salicylate, Butyloctyl Salicylate,
and Hexyldodecyl Salicylate

Dr. Belsito stated that a tentative conclusion on the safety of these ingredients was issued at the February 14-15, 2000 Panel meeting. He then indicated that it has been requested that the Panel consider adding the ingredient, Amyl Salicylate to this review, with the understanding that this is the only salicylate listed in the International Cosmetic Ingredient Dictionary and Handbook that is not included. However, Dr. Belsito's Team noted that Amyl Salicylate is listed only as being used as a fragrance ingredient in cosmetics, and that assessing the safety of ingredients that function only as fragrance materials is not within the Panel's purview. Dr. Belsito recalled that Benzyl Salicylate (used as fragrance ingredient and UV light absorber) also is not included in the present review.

Dr. Schroeter asked for Dr. McEwen's opinion on the proposed addition of other salicylates to the present review.

Dr. McEwen said that one might expect that Amyl Salicylate might be used in a fashion that is similar to that of the other salicylates in the group. He added that because Benzyl Salicylate is an aromatic compound, it probably is not in the same family of use.

Dr. McEwen stated that his reason for requesting the addition of Amyl Salicylate to the present review is based on the observation that the data already in the report are applicable to this ingredient. He added that if an additional function(other than that of a fragrance material) is assigned to this ingredient in the future, it would then be a candidate for the CIR review process. Thus, issuing a conclusion on Amyl Salicylate now would be more feasible.

Dr. Andersen said that the CIR Procedures are very specific in terms of exempting fragrance ingredients from the review process, and that this is the reason why Amyl Salicylate is not included in the report that is being reviewed.

Dr. Bergfeld asked if it would be appropriate to include information on the chemistry of Amyl Salicylate in the current report even though its safety in cosmetics is not being evaluated, and to also indicate why this decision was made in the report discussion.

Dr. Andersen said that the rationale for excluding Amyl Salicylate from this review could be stated in the introduction and report discussion, and that the chemical structure could also be included in the report.

The Panel agreed that the current report should be revised to reflect the preceding comments on Amyl Salicylate by Drs. Bergfeld and Andersen.

The Panel voted unanimously in favor of issuing a Final Report on this group of ingredients with the following conclusion: Based on the available information, the CIR Expert Panel concluded that Salicylic Acid, the salts Calcium Salicylate, Magnesium Salicylate, MEA-Salicylate, Potassium Salicylate, Sodium Salicylate, and TEA-Salicylate, the esters Capryloyl Salicylic Acid, C12-15 Alkyl Salicylate, Isocetyl Salicylate, Isodecyl Salicylate, Methyl Salicylate, Myristyl Salicylate, Myristyl Salicylate, Ethylhexyl Salicylate, and Tridecyl Salicylate, and the compounds Butyloctyl Salicylate and Hexyldodecyl Salicylate are safe as used when formulated to avoid irritation and when formulated to avoid increasing sun sensitivity, or, when increased sun sensitivity would be expected, directions for use include the daily use of sun protection.

June 4-5, 2018 CIR Expert Panel Meeting – Dr. Belsito's Team

Salicylic Acid and Salicylates

DR. BELSITO: Okay. You're ready, Wilbur. Thank you. This was a re-review that was given to us in Wave 2, and there was a final report on salicylic acid and 16 salicylates in 2003, so we need to re-review it. And if we need to open it, we need to open it, or we can open it to add on these four new salicylate groups; amyl salicylate, hexyl salicylate, isotridecyl, and silver salicylate. I just had a question for Dan. I was okay with all of them, but what about the silver?

DR. LIEBLER: I didn't throw it out right now, but, with an inorganic, it could be more about the silver than the salicylates. So, I would say actually, we could delete it as an add-on; it's not a no-brainer.

DR. BELSITO: Okay.

DR. LIEBLER: The others are fine.

DR. BELSITO: And then, having said that, in the original report we actually reviewed something, called capryloyl salicylic acid, that structurally looks very different from all the other salicylates. Should that be thrown out?

DR. LIEBLER: No, I thought that was okay. I mean, it's just esterifying the hydroxyl group next to the carboxylic acid on the salicylic. But it's similar enough to a salicylate that I think it belongs in the report.

DR. BELSITO: Okay.

DR. EISENMANN: My question is MEA salicylate, because it's in the MEA report and it has a more conservative conclusion in the MEA report. I don't know if you want to just leave it in the MEA report. In the MEA report it says, "safe in the present practice of use and concentration describe in the safety assessment, when formulated to be non-irritating, rinse-off products only. The Panel cautions the ingredients should not be used in product in which N-nitroso compounds may be formed." In that report, it's limited to rinse-off products only.

MR. JOHNSON: It also said when formulated to be non-irritating.

DR. EISENMANN: Right, when formulated to be non-irritating, right.

DR. BELSITO: Well, would that apply to TEA salicylate as well?

DR. EISENMANN: That was just in the Monoethanolamine report. No, I think TEA is salicylates; it's not involved.

DR. BELSITO: But weren't we told, somewhere in this document -- it's been awhile since I reviewed -- that these aren't metabolically broken down very easily on the skin? Because we're dealing with salicylic acid absorption? Wasn't there someplace in the report where it states that? Is it in the metabolism section?

DR. LIEBLER: Somewhere in the metabolism section, I think it referred to only a small percentage of the applied material was hydrolyze.

DR. BELSITO: Yeah, I seem to recall that.

DR. LIEBLER: Like 5 or 10 percent, maybe less than that even. And I don't think that's particularly noteworthy.

You know what? On second thought, I think we can get rid of the capryloyl salicylic acid. The more I think about that, the more I think that just doesn't go with the rest.

MS. KOWCZ: It's also used more as emollient.

DR. LIEBLER: It's a different use, okay.

MS. KOWCZ: Yes, it's a different use.

DR. BELSITO: So, we're removing it?

DR. LIEBLER: Yes.

MS. FIUME: So, procedurally, this is a re-review because it's been 15 years. And it was part of the original group.

DR. LIEBLER: It was part of the original group?

DR. BELSITO: So, we're including ingredients and we're --

MS. KOWCZ: Are we excluding any?

DR. LIEBLER: I don't remember ever taking one out of a re-review. All right. I won't fight the battle.

MS. FIUME: You can change is conclusion, or you can ask for information, if you don't think it's covered; but procedurally, I don't remember us removing one either.

DR. LIEBLER: We have enough new turf with polyaminopropyl biguanide, let's just leave it in.

DR. BELSITO: How do we review it? Do we have any data on it?

DR. BERGFELD: Do you have to review it now? You're just considering opening and adding four.

DR. BELSITO: I'm just pointing out that I don't know that there is data in the document to support it. Is there another group where it would more logically belong?

MS. FIUME: Salicylic acid is in this group, I guess that would be a question for Dr. Liebler. I mean, as I said, you can reopen if you don't think that the conclusion is still supported, or if the conclusion should have been different the first time around; and ask for information if you can't support the conclusion.

DR. BELSITO: Okay.

MS. FIUME: I just don't know if you can delete it, from the original group, because of re-review.

DR. LIEBLER: Yeah, I don't want to go there. We don't need to go there. Like I said, obviously the fact that at first I wanted it, and then I didn't want it, it's a close call. If it's already in there that's fine. Where I am on this, is reopen it and add the new ingredients, safe as used. But try and simplify the conclusion a little bit. See if we can take a run at that issue.

DR. BELSITO: I'm just curious, under cosmetic use; so, we see this huge increase in the amount of ethylhexyl salicylate and salicylic acid. Is that a huge increase because of cosmetic use, or is it a huge increase because of OTC use?

Because ethylhexyl salicylate is a sunscreen; and salicylic acid is an acne medication and a wart remover, that are both OTC. When you go out and do surveys, are you asking for cosmetic use?

DR. EISENMANN: Yes.

DR. BELSITO: Or are you asking for total sales?

DR. EISENMANN: No, I've been asking for cosmetic use.

DR. BELSITO: So, there's just a lot more cosmetic exfoliators and anti-aging creams putting salicylic acid and TEA salicylate into their formulas, is that it?

DR. EISENMANN: Don't know.

DR. BELSITO: Don't know. Okay. It's just, it's striking, the huge increase. It doesn't bother me in terms of safety.

MR. JOHNSON: Dr. Belsito, back to Carol's concern, should the MEA salicylate be deleted, you know, in that a published report on this ingredient occurred in 2015?

DR. BELSITO: Well the published report was on MEA, not MEA salicylates. The question was the MEA report was more restrictive.

DR. EISENMANN: But it included MEA salicylates in the report.

DR. BELSITO: It did?

DR. EISENMANN: Yes.

DR. BELSITO: Oh, I didn't realize that.

DR. EISENMANN: So, it's more restrictive based on the MEA, than on the salicylate.

MS. FIUME: And for that one I wouldn't necessarily have the same objection, because it has been looked at again; it's not that it's in 15 years it hasn't been reviewed.

DR. BELSITO: I don't know, Dan, what do you want to do?

DR. LIEBLER: If you won't get struck dead by lighting for deleting an ingredient from a re-review, then if we ended up reopening this, I think we could delete that because it's already been reviewed. Because it might have a different conclusion.

DR. BERGFELD: If you do that, then you can put that deletion to a discussion, and the reason why, and refer them to the other manuscript.

DR. LIEBLER: Yeah. Right.

DR. BELSITO: Okay. So, we're deleting MEA salicylate.

DR. BERGFELD: As you're thinking, I think we have to take another look at the conclusion.

DR. BELSITO: Well, before we get that.

DR. BERGFELD: When you get there.

DR. BELSITO: Yeah. I had a problem with a statement on Page 43 of the PDF. Under discussion, from published CIR Final Reports on Salicylates, it said, "The Panel did not consider it likely that consumers would simultaneously use multiple cosmetic products containing salicylic acid; thus, the serum levels of salicylic acid that will result for dermal application will likely be less than the serum levels from ingestion."

And now we have a huge number of uses for salicylic acid. We have a huge number of uses for ethylhexyl salicylate. I'll turn this over to my tox colleagues, but do you think that statement is still relevant? Or do we need a margin of exposure calculation, based off of absorption and aggregated exposure of multiple cosmetic products that might contain salicylates?

DR. SNYDER: What's the concentration in the sunscreen?

DR. BELSITO: Usually around five-ish percent.

DR. LIEBLER: There's a 5 percent max.

DR. BELSITO: But then you have salicylic acid in body washes for exfoliation. You have salicylates in other products.

DR. SNYDER: I was just thinking about 24-hour exposure in a sunscreen mode of application.

DR. LIEBLER: Yeah, but it's that low.

DR. BELSITO: But then it's not just sunscreen. So, you go out and you have a little dry skin, and you use a bath wash with salicylic acid to exfoliate a little bit, and then you put another chemical on that has --

MS. FIUME: That's a rinse-off.

DR. BELSITO: -- TEA salicylate. I'm just saying. You know, what we have here are -- you know, we've gone from two orders of magnitude, to three orders of magnitude, and cosmetics containing TEA -- or ethylhexyl salicylate. Presumably, we're told they're not sunscreen use, they're cosmetic use.

DR. BERGFELD: Lower percentage of concentration.

DR. BELSITO: What?

DR. BERGFELD: The concentration levels are reasonably low.

DR. BELSITO: But there are multiple products out there. I'm just pointing it out.

DR. LIEBLER: Yeah, the sentence actually compares the exposure to multiple products, from that which might be encountered by using a baby aspirin; which is, I believe, half of a 325mg dose.

DR. BELSITO: 81mg.

DR. LIEBLER: 81, okay. So, it's even less. Okay. For those that take aspirin, I don't know how many people -- maybe older people still take aspirin, but older people --

DR. KLAASSEN: Older than what?

DR. LIEBLER: You know.

DR. BELSITO: Yeah. Watch what you say, Dan.

DR. LIEBLER: Everybody in Kansas. I don't know, but it just seems to me like -- I don't know for sure, but I think the aspirin is kind of like the dial phone. Are people taking aspirin anymore, except for people are taking single tablet prescriptions for anti-platelet?

DR. BERGFELD: Pretty common.

DR. LIEBLER: Really?

DR. KLAASSEN: I think so.

DR. LIEBLER: Analgesic dosage?

DR. BERGFELD: Well they relate to baby aspirin, mainly.

DR. LIEBLER: Yeah, okay.

DR. BELSITO: No, but Dan's talking about using aspirin for analgesic.

DR. BERGFELD: I know.

DR. BELSITO: Like 325mg tablets, one or two.

DR. LIEBLER: As opposed to Ibuprofen and naproxen and so forth.

DR. BERGFELD: And NSAIDs.

DR. LIEBLER: Okay, maybe that's not the right issue to bring up then. So, I honestly don't know if that's true. I mean, I think you've got a good point, Don. If you were using more than one skincare product that contained a salicylate -- I mean these can be absorbed for sure. And if you do absorb them, what's the aggregate dosage from that versus your 81mg a day?

And that would require some consumer use data and -- that would require some data to do the calculation. I don't think we can just say that now and get away with it in a report.

DR. BELSITO: This also has to do with lack of reproductive and developmental toxicity seen. And quite honestly, most women of childbearing age are not taking 81mg of aspirin daily; it's being taken by people like Curt and I, who are not female and are well over 50. I mean, I just couldn't believe this language. This is a leap of faith to say that.

You know, we have data showing that there's reproductive toxicity, in terms of failing to close the ductus arteriosus as a result of aspirin; and then we're just saying, oh, well, there are no reports that 81mg causes a problem. And most pregnant women don't take aspirin, they take pre-natal vitamins and that's it.

DR. LIEBLER: So, you were on the panel that agreed to this language.

DR. BELSITO: I must had been sleeping.

DR. LIEBLER: Okay. But it might've been arguably true then; and it might arguably be not true now. Is what you're saying, basically.

DR. BELSITO: The levels of concern now are quite different from what they were 15 years ago; and the way we approach things are quite clearly different. So, I just don't agree with that statement.

You can make it. But then you better come up with some margins of safety or some data to compare what your tox endpoints are; which I presume with the DART effects, what the levels we're seeing in the DART effects, and what you would assume to be absorption of salicylates as in aggregate exposure in cosmetic products.

And I point that out, particularly, because of the huge increase in salicylic acid and ethylhexyl salicylate, which I hope you were going to tell me was all sunscreen in OTC, but it's not.

DR. LIEBLER: But if there's a lot of sunscreen in OTC and it's part of the body burden --

DR. BELSITO: Right. I mean, it's part of the --

DR. LIEBLER: -- then they added the amount from cosmetics, it's still worth considering.

DR. BELSITO: Exactly.

DR. LIEBLER: So, it's something we need to consider, whether or not it's true cosmetic uses. I don't think it's an issue we need to solve right now if we're going to -- we're basically talking about reopening the report, adding new ingredients, and then we'll deal with this later.

DR. BELSITO: Well, what I'm saying, is that when we reopen the report we cannot simply argue that we're blowing off the potential systemic toxicity of salicylic acid, based upon the fact that 81mg doesn't cause any issue. I mean that whole last sentence should go away.

DR. LIEBLER: Oh, I agree.

DR. BELSITO: And there should be a little bit better justification as to why we're not concerned about the DART effects from cosmetic exposure.

DR. LIEBLER: Right, I complete agree with that.

DR. BELSITO: David?

MR. STEINBERG: I think your comment on the use of ethylhexyl salicylate increase in cosmetics can be explained that OTC drugs, it's called octisalate.

MS. KOWCZ: Octyl silicide.

MR. STEINBERG: Octisalate.

MS. KOWCZ: Yeah.

MR. STEINBERG: Okay. And what happens is that, if you make cosmetic claims, your labeling for drug facts are totally different.

DR. BELSITO: Right.

MR. STEINBERG: So, a company who's making a sunscreen, using octisalate, might register as a cosmetic to show that they're actually making cosmetic claims, and they've registered it with the FDA. But instead of using the drug names they're using the INCI names.

So, it's possible that the surge has been the companies who want to cover themselves both ways. They're not selling it as a cosmetic, but they're registering it as a cosmetic. And now they might be selling it as a cosmetic for Europe or places where sunscreens are cosmetics.

And then again, they can't use our drug names, they have to use the INCI names. The surge could be explained that way.

DR. SNYDER: So, in those products, is it used as an active ingredient, or is it used as an inactive ingredient?

DR. BELSITO: Well except that the point that Wilma made, is when you do look at levels of use for ethylhexyl, they're not at levels that typically would be used in sunscreens.

MR. STEINBERG: What levels are they using?

DR. BELSITO: They're reporting use up to 5.1 percent in leave-ons. So, yeah, they are reporting them as sunscreen uses.

MR. STEINBERG: That's what I think it is. Now your question?

DR. SNYDER: In those products, is it used as an active ingredient, or is it used as some inactive component?

MR. STEINBERG: In the United States, it's an active ingredient. But you have to remember, that if you get outside of the United States, Australia, and Canada, sunscreens are all cosmetics. Okay, so you have totally different labeling issues.

DR. BELSITO: But the other thing, Paul, is when they might not market it as a sunscreen. If they market it as an anti-aging, then it will contain a sunscreen. So, it's just like there're a whole number of fragrance-free products out there that contain fragrances, because they're not added as fragrances supposedly.

DR. SNYDER: They're essential oils.

DR. BELSITO: Right, or biocides; some of the fragrances are biocides. I mean Cetaphil has farnesol in it. Farnesol is a fragrance, yet it's labeled fragrance-free.

DR. SNYDER: We have data under absorption. It says that a sunscreen was tested and only 1 to 2 percent is dermally absorbed. We're only talking 1 to 2 percent of maximum 5 percent. So again, I think we're --

DR. BELSITO: But that's one product.

DR. SNYDER: Right.

DR. BELSITO: So, we need to look at aggregate exposure; because these are used in a huge number of different products. We cannot simply say that the absorption -- we're looking at safety as used in cosmetics. And this is used in a huge number of cosmetic products. I don't understand the magnitude of increases that have occurred with the ethylhexyl salicylate and salicylic acid.

Are these being used in one product type, where it would be unlikely that I would use more than one body scrub or more than one anti-aging product? Or are they being used in a multitude of other products that I, as a consumer, might be using, like a shampoo, a conditioner, a hair gel, a body moisturizer, a facial sunscreen, yada, yada, yada.

I don't know. You know, it's just usage has increased dramatically. And I think that we need to know what kind of products these increases have occurred in, so we get some sense of what the aggregate exposure of the consumer is.

Because right now we have no good data. We have absorption of a sunscreen, we had some data, again, I believe, that says that on the skin these esters don't metabolize to much sal acid. Is that correct? It's just doing this off of memory. Where's the ADME here?

So, methyl salicylate. If you look at methyl salicylate it says, "The presence of unhydrolyzed methyl salicylate was only observed at the 30-minute timepoint. The fraction of methyl salicylate observed in tissues as a proportion of total salicylate varied from 0 to .26." Then it says, "The tissue and plasma concentrations after application of methyl salicylate increased rapidly within the first hour of application." It was rats. But it doesn't tell you the total absorption, it just says the concentrations increased rapidly in the first hour.

And then they looked at site-specific absorption. And they found the usual variation of behind the ear 11 micrograms/cm2 per minute, initial flux, the abdomen, 3. And 1 to 2 percent of the sunscreen in the applied product was absorbed. But it doesn't tell you which sunscreen, because it was an aggregate of sunscreens. Hexyl salicylate, micrograms/m2, it's pretty low, 4.1 micrograms/1.4m2. What's the average body surface area, two point something m2?

DR. KLAASSEN: I don't know off the top of my head.

MS. FIUME: Don, as you're looking at that, as far as usage for ethylhexyl salicylate, on PDF Page 166, there are probably over 2,000 uses that are used in fragrances. 1,200 are cologne and toilet waters, almost 650 of perfumes, and 422 are other fragrance preparations.

So, for the ethylhexyl salicylate, that's probably where a large number of those come in. As far as looking to see how these are being used, a salicylic acid, it is used probably in almost every category; half are rinse-off, half are leave-on. But it's used in probably almost every category reported to FDA.

DR. BELSITO: So, the mean male body surface area peaks at about 2 m2. And the mean female peaks at about 1.8 m2.

DR. SNYDER: So, your only concern is that the difference between the 2003 report, and this report, is that we have this markedly increase number of uses?

DR. BELSITO: Well, my concern, too, is that our argument for why we weren't concern about DART effects in the prior report is bogus.

DR. SNYDER: Well, maybe not. I mean we had -- there's five pages of dermal absorption studies in that old report. Table 8 --

DR. BELSITO: I understand. But we were basically saying, you know, in the discussion, that we weren't worried because people take baby aspirin and we're not seeing that. That's not the way we should approach it, that's all I'm saying.

DR. SNYDER: Okay. So, our current conclusion discussion could talk about an accumulative effect with multiple product use. And to make that scientifically sound, we need some kind of a number to do some kind of an aggregate max worst case scenario exposure is what you need.

DR. BELSITO: Right.

DR. SNYDER: Okay. But I don't know that we can get that.

DR. BELSITO: You can get it. The fragrance industry gets it all the time. You should be able to get it. There are habits and practices that tell you what -- I mean, right, Dan? Creme Global has that.

DR. LIEBLER: Right.

DR. BELSITO: And you can look at the product types and you can look at the ranges of the various salicylates. You could assume a worst-case scenario of absorption from the salicylates, and you can come up with a number.

DR. SNYDER: Did we have a NOAEL for the reported effects.

DR. BELSITO: DART effects?

DR. SNYDER: I'm looking back at the old report and I'm having a hard time finding it.

DR. BELSITO: No, I don't think we do. There are just clinical reports of patent ductus arteriosus, with -- you know, salicylism and the effects of salicylism.

I don't think there are dose responses; which is why I think we came up with this bogus claim that saying, well 81mg is not likely cosmetic exposure; it's going to result in the same exposure as low-dose aspirin and we don't see problems with that. I just think that argument is -- I mean, it just doesn't cut science in 2018.

DR. BERGFELD: It sounds, to me, like we're taking on a new tact, and that tact is to get the aggregate information, because we've mentioned it now in two or three documents. And so maybe it should be, when Carol makes the call, that we ask for that immediately up front.

DR. SNYDER: This is a re-review, so we can say, during this meeting, we agreed to reopen and here are now the issues that we are concerned about.

DR. BELSITO: Right. That's what I'm saying. Yeah, I'm not making a big deal of it. I'm just saying that we can't use the argument, we used before, to dismiss the DART effects.

DR. SNYDER: So, like we would come up with a --

DR. BELSITO: So, as you're looking at trying to accumulate data, please try and find us any information you can get on dose response relationships for the DART effects of salicylic acid and salicylism, in terms of, you know, hearing and all the other side effects of excess salicylic acid. All we have are really just more case reports, someone consumed a whole jar of aspirin and presented to an emergency room, and here were the symptoms.

Okay, so we're going to reopen the report. We're going to add everything but silver. We're going to delete MEA. And we're going to leave capryloyl salicylic in there for now; but caution we may not be able to rule on its safety.

MS. FIUME: Well, it sounds like you're going to be issuing an IDA, based on what the conversation has just demonstrated.

DR. BELSITO: Yes.

MS. FIUME: If there are data that can help you rule on the safety of that ingredient, that can be part of your IDA; if there's specific information, that you're missing, that you feel you need to rule on the safety of that ingredient, since you're reopening anyway.

DR. BELSITO: Well, Dan, what I'm hearing from you is that the rest of these salicylates are not really good read-acrosses, would that be fair?

DR. LIEBLER: For?

DR. BELSITO: Capryloyl salicylic acid.

DR. LIEBLER: They're all going to differ substantially in dermal penetrations, just based on the size of the molecules. The methyl salicylate, being the smallest, might be best penetrator. And it said esterifies would probably penetrate better than the salicylic acid. And the others will probably decline with the size of the substituents.

DR. BELSITO: Basically, I'm just searching the document for what we have on capryloyl salicylic acid. We have a case report of an allergy, and a woman with dermatitis of the face. And they thought it was not due to the capryloyl salicylic acid, but a structural isomer, the 3-capryloyl salicylic acid -- whatever that means -- that was a contaminant. And basically, that is it.

And then we have a split clinical report, split-face, 44 female volunteers. No significant changes in erythema, so I guess not irritating. And then case reports of that positive patch test; and that's it. So, we have very little data on it.

If you think the toxicity is going to be different, we don't have method of manufacture. We don't have impurities. We have no tox data. We have no data, essentially, except for case reports. So, are we going to needs -- based upon your looking at this molecule, are we going to need data for it?

DR. LIEBLER: For the?

DR. BELSITO: Capryloyl.

DR. LIEBLER: Capryloyl, no. I mean as far as its absorption, distribution, and its pharmacology toxicology, I think it's going to be pretty similar. So, you know, I don't think this stuff is going to get absorbed very much.

DR. BELSITO: Okay. So, you think that we can use the rest of the materials here as read-across to go with the safety of this, even though, structurally, it's a different molecule.

DR. LIEBLER: Yeah, it's not dramatically different. And so, I think it's reasonable to read across from any several of the others here of what we've got.

DR. BELSITO: Okay. So, we're not asking for any additional data on this, because we have none.

DR. LIEBLER: I don't think we need it.

DR. BELSITO: Okay.

MS. FIUME: Don? PDF Page 131, does --

DR. SNYDER: It's a risk assessment.

MS. FIUME: Does that help you? Does that help inform any of the decisions for salicylic acid; and how much is actually absorbed, based on the new data that you have, now, with increase use?

DR. BELSITO: Actually, there's a lot of dermal data on methyl salicylate. There's oral exposure data on salicylic.

DR. SNYDER: And that section that Monice is talking about, they actually tested a facial product containing 2 percent. And they referenced that to 20 percent of that following the ingestion of a single baby aspirin.

DR. BELSITO: Yeah, I think this data is great. So, I guess I didn't go and look at it because I didn't think we had the data given the way we put it in the discussion. But we clearly have the data to -- I mean, this just needs a lot more summarization, under the DART, than what's currently done in the document.

MS. FIUME: We'll take care of that.

DR. BELSITO: Yeah, I think we'll be fine. And then we just need to change the way we discuss it. We need to summarize this huge amount of data, and whatever we can, so we're not accused of double dipping our data in the publication.

DR. SNYDER: To your point, this is actually referenced in the other document as a risk assessment support, so we could add that.

DR. BELSITO: Yes.

DR. SNYDER: That based upon a previous risk assessment, we still don't need --

DR. BELSITO: Yeah. And then bring into the document. Yeah. I mean, we need to, in the summary, instead of just saying associated with developmental toxicity, give the NOECs, more than just saying associated. So, a little bit more information when we're summarizing what we previously saw.

MS. FIUME: We'll go ahead and expand that.

DR. BELSITO: And then I think develop in the discussion, a little bit better point that given the levels of use in cosmetics, the absorptions that we've seen, the relative lack of metabolism of the esters to salicylic acid in the skin, that these levels would not likely be achieved with cosmetic use.

DR. BERGFELD: In summary, you're going to reorganize this material, and you're going to go with it?

DR. BELSITO: Yeah, we're going to drop silver. We're going to keep capryloyl salicylate. We're just going to beef of the summary of the DART sections from the prior reports. We're going to drop that silly comment that taking 81mg of aspirin isn't a problem, so we're not worried about reproductive toxicity; and we're going to strengthen that argument with a little science. And add in the other salicylate other than silver.

DR. BERGFELD: There's no insufficient data announcement or request?

DR. BELSITO: Not at this point. Dan, are you comfortable going with safe as used?

DR. BERGFELD: Are you retracting the need for aggregate information regarding --

DR. BELSITO: Yeah. I think that when you look at the dose levels that were used in the DART studies, you know, again, if you start summarizing them rather than simply saying there were teratogenic effects; yeah, we have NOAELs. We have huge NOAELs that we can go by; and we can incorporate them into our discussion to show the margin of safety in cosmetics is sufficient.

MR. JOHNSON: Dr. Belsito, are there any concerns about estrogenic activity, comedogenicity or skin sensitization potential?

DR. BELSITO: Well, the comedogenicity really surprise me because we use those for acne treatment. So, I didn't understand that at all. But in terms of sensitization, I think that --

DR. SNYDER: Sun sensitivity is addressed in the old report.

DR. BELSITO: Oh, you mean in terms of sun protection? Yeah. I think that that type of language probably should be maintained. The conclusion, in terms of with use of sunscreen -- how was it worded? It was somewhere between the alpha hydroxy acid report and this. We weren't as harsh with the restriction. But yeah, that restriction should remain, just because of stripping of the stratum corneum.

DR. BERGFELD: Is that in the discussion or the conclusion?

DR. BELSITO: No, it was actually in the conclusion of the old one. Like the alpha-hydroxy.

DR. SNYDER: Page 42, second and third paragraph.

DR. BELSITO: Our conclusion was, based on the available data, expert panel conclude, yada, yada, yada, yada, are safe as used when formulated to avoid skin irritation and when formulated to avoid increasing the skin's sun sensitivity, or when increased sun sensitivity would be expected, directions for use include the daily use of sun protection.

DR. BERGFELD: You want to keep all that?

DR. BELSITO: Yep. Do you?

DR. BERGFELD: Well, how did we handle the alpha-hydroxy as this is a beta-hydroxyl.

DR. BELSITO: That was even stronger in the conclusion. That was not if, that was needs to be labeled.

DR. BERGFELD: I think it was a SPF of 2 had to cover that.

DR. BELSITO: No, we didn't put an SPF.

DR. BERGFELD: No, but I think that was, you had to have a SPF 2 to protect with the alpha-hydroxy.

DR. SNYDER: Dialkyl Dimer.

DR. BELSITO: What?

DR. SNYDER: Dialkyl Dimers?

DR. BELSITO: You trying to move on?

DR. KLAASSEN: How'd you get that idea?

MS. FIUME: It actually refer to MED.

DR. BERGFELD: Are you looking at the outside document?

MS. FIUME: SPF 4.

DR. BERGFELD: A 4. It was high as 4? Was it in the discussion, or was it in the conclusion?

MS. FIUME: It was added as a note, added and approved to the conclusion.

DR. BERGFELD: Okay.

DR. BELSITO: Okay.

MS. FIUME: I didn't look at the re-review.

DR. BELSITO: So again, we need to summarize the DART data a little bit better in this re-review. And the conclusion will be pretty much what we had before, with a sun sensitivity.

MR. JOHNSON: Are there any concerns about the sensitization potential --

DR. BELSITO: No.

MR. JOHNSON: -- for hexyl salicylate?

DR. BELSITO: What?

MR. JOHNSON: Hexyl salicylate. Because like we have positive guinea pig sensitization data on Page 30. And also human sensitization data on Page 34.

DR. BELSITO: So, we have a LLNA of .18 percent. And it was noted that this was very low, maybe due to its irritating properties, or sensitizing impurities. And then DRAS (phonetic) testing showed some alert sensitization reactions.

And then in a photo allergy test in guinea pigs, it was negative. And they were topically challenged with 50 percent. I did not make much of those other tests, so I'm not concern. And then they did a Magnusson Kligman guinea pig maximization test; and a challenge at 10 percent hexyl salicylate, no sensitization reactions were observed. So, no I'm not concerned. Okay? No, I'm not concerned.

MR. JOHNSON: Okay. What about the human data on Page 34?

DR. BELSITO: I'm not concerned. I'm not concerned. I'm concerned about irritation, not sensitization. Okay? Done? Paul, you're happy?

DR. SNYDER: Yeah.

DR. BELSITO: Okay.

June 4-5, 2018 CIR Expert Panel Meeting – Dr. Marks'Team

Salicylic acid and Salicylates

DR. MARKS: Yes. The salicylates. This is a re-review document on the salicylates. In 2003, a final report was published on salicylic acid and 16 salicylates. The conclusion of these ingredients are safe as used when formulated to avoid skin irritation, and when formulated avoid increasing the sun sensitivity. Or when increased sun sensitivity would be expected. Directions for use include the daily use of sun protection.

You didn't like that previous conclusion, this one is really -- and then let me see here.

DR. SLAGA: Sound like Trump put that together.

DR. MARKS: What else do I have here. Exfoliate -- reopen question mark. Then there was a question of adding four new ingredients. Were they okay. And actually, I had to dig for those, Wilbur. Did you put those four ingredients on this memo right at the beginning? If you look at page 4. Let's see, where are they? Nope, that's not the right one. Let me see, what was the other page I had.

MR. JOHNSON: They're in the Introduction.

DR. MARKS: Yeah, 13. Is that right, page 13?

MR. JOHNSON: Page 12.

DR. MARKS: Twelve, okay. Actually 13. Yeah and the four ingredients that would be added are the ones -- so I'm on page 13. Those four at the end of the list with the asterisk. The amyl, hexyl, isotridecyl and the silver -- oh, here's silver again, Ron Hill. Silver salicylate. So, they would be the four add-ons.

I guess the first question is, do we want to reopen this and massage the conclusion; or do we want to just leave it the way it is? And then the second question is, do we want to reopen it to add these ingredients and is that a no-brainer? And once we open it, are we going to have a no-brainer or are we going to spend a lot of time on a conclusion?

DR. SHANK: I have a question. The new data came in, it's on page 26. Two references on salicylic acid, dermal application to pregnant women; it suggests that it could cause ductus arteriosus and oligohydramnios. I think we should read -- at least I should read -- I couldn't get them.

DR. MARKS: And this is new.

DR. SHANK: Yes, it's new. Because that could potentially change the conclusion. But I haven't read the paper, so I don't know.

DR. MARKS: So, page 26, under relevant studies, the estrogenic activity?

DR. SHANK: Let me look.

DR. HILL: No, it's above that. Right at the top of the page.

DR. MARKS: Oh, okay. Under salicylic acid. It's that first paragraph?

DR. HILL: Um hmm.

DR. MARKS: The NTP?

DR. HILL: Um hmm. Is that not the one?

DR. MARKS: Creams containing salicylic were applied to skin groups of 18 and 18 -- that's mice.

DR. HILL: That's not the ductus -- no, that's not the one.

DR. MARKS: You mentioned this is other relevant -- this is to pregnant females this was applied, and there was question. Were they pregnant female animals or humans?

DR. SHANK: Women. Humans.

DR. MARKS: Yeah.

MR. JOHNSON: That's on page 24.

DR. SHANK: Twenty-four?

DR. MARKS: Twenty-four.

DR. SHANK: Thank you.

MR. JOHNSON: You're welcome. Under dermal and salicylic acid -- human dermal salicylic acid.

DR. MARKS: There's dermal, oral.

DR. HELDRETH: That's 25. Page 25.

DR. MARKS: Human dermal -- yeah, we're on 25. Oh, can potentially cause early closure of the ductus arteriosus and oligohydramnios. Therefore, it should not be applied over large surface areas for prolonged time periods or under occlusive dressing. That may enhance systemic absorption.

I like this, the primary reference upon which these statements are based has been ordered for

further details. Okay. So, with that alone, new data, we have to reopen it.

DR. SHANK: Yeah, it caught my eye.

DR. MARKS: I would agree.

MR. JOHNSON: Now, I note that reproductive and development toxicity are addressed in the discussion section of the final report on salicylic acid.

DR. SHANK: The old report?

MR. JOHNSON: Yes. That discussion is in this report.

DR. SHANK: Okay.

DR. MARKS: What page were you on?

DR. SHANK: Where can I find it?

DR. MARKS: So premature closure, the ductus arteriosus probably -- maybe that's not a bad thing. But you wonder if there's so much absorption, and this is occurring prematurely --

DR. SHANK: If it happens in utero, the baby dies.

DR. MARKS: Yes.

MR. JOHNSON: It's on page -- I think, for some reason, I'm one page off. It begins on page 43, I think, because mine says 42.

DR. SHANK: Forty-three?

MR. JOHNSON: Yes.

DR. HELDRETH: It's actually 42.

MR. JOHNSON: It is 42? So that's right this time. Page 42.

DR. SHANK: Forty-two?

MR. JOHNSON: Right.

DR. HELDRETH: You'll see some italicized text there.

DR. SHANK: I'm going there.

DR. MARKS: You're going there. Page 24.

MR. JOHNSON: Yeah. It's the last paragraph.

DR. MARKS: So that's reproductive tox --

DR. SHANK: Was it a positive patch test on 42?

DR. HELDRETH: So, at the bottom of 42 bleeding onto to 43, the paragraph that starts with reproductive and developmental tox associated with.

DR. SHANK: Okay. Thank you. Well, I think we need to read the new papers.

DR. SLAGA: Yeah. I sent them to several people.

MR. JOHNSON: And also, in the other team, it was mentioned that the reproductive and developmental toxicity data in the published file report should be included, you know, in summary form and this safety attachment. Because the summary, as written, contains very few or no details regarding dosage and no effect levels.

DR. SHANK: Okay.

DR. MARKS: So, we handle this by reopening with an insufficient data notice -- or announcement? Because we can move on to a tentative.

DR. SHANK: Well, I'd like to read the papers.

DR. MARKS: Oh. Well, then would you table it?

DR. SLAGA: Until we get those papers?

DR. SHANK: Can you get those papers?

DR. HELDRETH: We're going to get the papers and we can incorporate them in the draft iteration.

MR. JOHNSON: You mean the two that relate to ductus arteriosus?

DR. SHANK: Yes.

MR. JOHNSON: Just those publications?

DR. SHANK: Those two.

MR. JOHNSON: Just those. Okay. Yeah, we'll probably have those.

DR. SHANK: For some reason I couldn't get them.

MR. JOHNSON: Okay.

DR. SHANK: Just an abstract, but I couldn't read the paper.

MR. JOHNSON: I might add the MEA-salicylate safety assessment on that ingredient was published in 2015. So, this is an ingredient that really should be considered for re-review. So, should that MEA-salicylate be removed from this document?

MS. LORETZ: It has a different conclusion; so that, I think, would be reason to perhaps remove it. It has some complexity there.

DR. HILL: Say what you said again.

MS. LORETZ: It has a different conclusion.

DR. HILL: What Wilbur said.

MS. LORETZ: Oh, I'm sorry.

DR. HILL: No, that's all right. I heard you.

MR. JOHNSON: Yeah, I was saying that a final report was published in 2015, in which a MEA-salicylate was one of the ingredients in that review. So that means, given the 15 year, you know, timetable for re-review, that would not fit into that scheme.

So, with that in mind, should MEA-salicylate be removed from this document?

DR. HILL: What do we have in the way of hard data? I mean, it still fits -- so that must have been the MEA group, right? Yeah. But from a salicylate standpoint, it definitely fits here too.

DR. MARKS: So, does that get two asterisks, previously reviewed? Because that's important particularly if the conclusion of the MEA-salicylates don't have all these restrictive language in it. Sun sensitivity, direction for use of sun protection.

MS. LORETZ: Except that it's restricted to rinse off products. So, it goes both ways.

MR. JOHNSON: And there's also, you know, when formulated to nonirritating as a qualification as well.

DR. MARKS: Well, that's in the present -- the rest of these ingredients that were reviewed all have the irritation -- to avoid irritation. But if rinsed off -- that's interesting.

DR. ANSELL: Is the argument that the MEA-salicylate data would help inform the discussion of this salicylate group? I mean, we could bring the data in without --

DR. HELDRETH: It's in the original, so --

DR. ANSELL: -- could then draw a conclusion about --

DR. HELDRETH: It was in the original so it's a matter of kind of taking it out.

MR. JOHNSON: And there would be a brief summary in the safety assessment, you know, regarding any data that were in the original published file report on salicylates and salicylic acid.

DR. MARKS: If there's a previous report, it's just a couple years old and it was limited to rinse offs and avoid irritation. Why would it be included in this one, other than it has salicylate in the title?

DR. SHANK: Depends on if you want to keep them in the family.

DR. MARKS: Well, you could start doing that with a lot of things. I assume that the MEA-salicylate, there was a whole different family with that. Was that based on the MEA?

DR. HELDRETH: Yeah, called MEA --

DR. MARKS: Not the salicylates, yeah. So now we could be double dipping in a lot of things if we do that. I don't see, as you said I think, Jay, unless it adds something to the toxicologic data in this report, why add as an ingredient? The other, if it does, we've done this before. Just mention it in the report, the pertinent toxicologic --

DR. SHANK: Developmental tox was not a problem for the MEA salicylate was it?

DR. MARKS: I can't imagine it was.

DR. HILL: It not listed in the VCRP as being in use or in the concentration survey.

DR. MARKS: Okay.

DR. HILL: In the data table that we got with this report.

DR. MARKS: Okay. So that means that it probably was just included as part of the group. And the group as a whole we said rinse off.

DR. HILL: And there was actually discussion as to whether to keep it in with Dr. Anderson, Belsito and -- yeah, so this was in 1999. Way before my -- Dr. Schroder was still on the panel then.

DR. MARKS: So, team, what do we want to do? Now another thing has come up with the MEA salicylates. Let's kind of dispense with that. Do we want to keep it in this report or not? Remove it and it's already been reviewed. You said that was just 2015, Wilbur, right?

MR. JOHNSON: That's right. Published in 2015.

DR. HELDRETH: Right. So it came out in IJT in 2015. That means that we likely looked at it in 2012.

DR. HILL: Was it in use then or did we just read across without really further consideration of the salicylate aspect, which I hate to think might have happened, but.

DR. MARKS: My feeling is remove it.

DR. SHANK: So, I'm confused.
DR. HELDRETH: No. It wasn't reported to be in use at the time.
DR. HILL: There's nothing else popping up here at all.
DR. HELDRETH: So, likely it would not be informative.
DR. SLAGA: You know what year the two papers related to --
MR. JOHNSON: Ductus arteriosus?
DR. SLAGA: -- the pregnant women --
MR. JOHNSON: Ductus arteriosus?
DR. SLAGA: Yeah.
MR. JOHNSON: Let me check.
DR. SLAGA: It's been very, very recent?
DR. SHANK: So, what is the question on MEA salicylate? It's not in the old report and not a suggested add-on.
DR. HILL: I thought it was a suggested add-on.
DR. SHANK: It is?
DR. MARKS: It's a suggested add-on.
DR. HILL: Yes.
DR. MARKS: Yes.
DR. HELDRETH: MEA?
DR. MARKS: It's right here. It's in the first column there. See it?
DR. ANSELL: Even though it has its own -- it's already been reviewed within the last --
DR. HILL: And that was his question.
DR. SHANK: Okay. It's just not in the table. All right.
DR. HILL: No. It's not in the read across table.
DR. MARKS: Oh, it isn't?
MR. JOHNSON: Dr. Slaga, those were published in 2008 and 2016.
DR. SLAGA: If that amyl was -- let's say it was possibly, you know, that was reviewed in between so to speak.
MR. JOHNSON: Oh. Yeah.
DR. HILL: It's not a proposed add-on. It was already there in the original report, in the salicylate report.
DR. ANSELL: It was?
DR. HILL: That's what it says here in the original salicylates report. And somehow it ended up in the MEA report.
MR. JOHNSON: Right.
DR. MARKS: Okay. So, it's not an add-on.
DR. SHANK: It's not in the data profile.
DR. HILL: It's not an add-on.
DR. HELDRETH: Let's not forget the other add-ons, though, that this team suggested, the titanium.
DR. HILL: I did.
DR. MARKS: No, it isn't. I was going to bring that up, but thank you, Bart. So actually, I mean, we have to include the MEA salicylate in this, if it's in the original report.
DR. HELDRETH: You don't have to. It's up to you. It already has a new conclusion. But if you feel, for some reason, it would be helpful to this report, you can choose to include it.
DR. MARKS: That comes down to, obviously, if we don't reopen it, it stays there. We made a decision to reopen?
DR. SLAGA: No. Well other than --
DR. SHANK: Well, I guess table because --
DR. MARKS: We have the pregnancy issue.
DR. HELDRETH: It's either reopen or table it.
DR. SHANK: That's the issue. And if those paper shows there's a real problem --
DR. SLAGA: They may not.
DR. SHANK: In the original review, they were worried about reproductive developmental toxicity. And said the concentrations in cosmetics are so low, it's not going to be a problem. But now with the new data, I think we should read that.

DR. HELDRETH: So, at his point we can reopen it to look at the new data. And in the next iteration of the report that data will be put in there. If you look at that data and decide you know what, this was no big deal, nothing's changed, then you can close it out and put out a re-review summary.

DR. SHANK: Okay.

DR. HELDRETH: Like we would if we never opened in the first place. But if you decide to open it for add-ons, you can still continue it. But, it's the panel's prerogative.

DR. ANSELL: Yeah, I guess this is exactly what the reopens intended. There's new data that people want, but not prejudge what it'll do to the conclusion.

DR. SLAGA: Very good.

DR. HILL: I have a question for Wilbur. In your read across table on page 5 -- because I didn't go back and look at everything in the old reporting detail yet. If there's an X in the box, is that old data plus new data?

MR. JOHNSON: Yes.

DR. HILL: Okay. Because there's no data, whatsoever, on capryloyl salicylic acid, which is an interesting compound. It's disparate from the others. And it looks like lipophilic aspirin.

MR. JOHNSON: Yes.

DR. HILL: And aspirin is a unique compound, because irreversibly acetylate serine and cyclooxygenase is one in two. So, it's an irreversible cyclooxygenase inhibitor.

And I don't know if this one does or not, but it appears that that was handled strictly by read across in the original report. Because the only thing we shown here is case report.

But there is reported use now for up to 62 percent, if it's accurate, in a leave-on formulation; which got my attention because most of these salicylates are reporting use below 1 percent. And then there are a small number that are at 5 percent, 3 percent. Most of them are below 1 percent. And so, I wondered how we managed to read across to that in the absence of data.

DR. HELDRETH: Just to be clear, it wasn't my fault.

DR. HILL: No, I didn't say it was. I wasn't here either.

DR. HELDRETH: I didn't include that search outlier. I wasn't here.

DR. HILL: But I'm just saying it seem like -- and there's quite a few uses if I'm not mistaken. Most of them, I think, the concentration might be low. But that 62 percent certainly got my attention, if that's accurate.

DR. MARKS: Well, that actually feeds into my question. No sensitization data, however. on page 50 that capryloyl salicylic acid leave-on is 63 percent.

DR. HILL: Right.

DR. MARKS: Rounding off, it's 62.9. And salicylic acid is 30 percent. And that 30 percent for salicylic acid, if these concentrations are correct, then we need the irritation sensitization. Particularly if you look at the look at the local lymph node assay, that was positive with salicylic acid at 20 percent. I'd want to see HRIPT at 30 percent.

So, that would be when we reopen; and I'd like to see irritation and sensitization data on the capryloyl salicylate acid, and the salicylic acid at their highest use concentration.

DR. ANSELL: They're probably neutralized. They're not going to be --

DR. SHANK: We can do that in formulation, right?

DR. MARKS: Yes.

DR. SHANK: Not pure salicylic, yeah.

DR. ANSELL: It would be pH adjusted, so you'd really be testing the salt.

DR. MARKS: So, you're saying because it's a salt, we don't have to worry about it?

DR. ANSELL: No. But I don't want -- you know, you won't get a HRIPT on salicylic acid.

DR. MARKS: Right.

DR. ANSELL: You're going to get a HRIPT on --

DR. MARKS: Some ingredient.

DR. HILL: Salicylate solution.

DR. ANSELL: A salicylate solution, which has been pH adjusted or probably a formulation which contains it at some level. But even there -- I mean some of them are going to be --

DR. MARKS: I guess I'd want to make sure it's both neither -- at that concentration, it's neither an irritant or sensitization. If it's being used at that concentration, it should be.

DR. ANSELL: Some of the products are intended to be irritating, right? Aren't they face scrubs and --

DR. STEINBERG: Twenty percent is a wart remover.

DR. ANSELL: Yeah. So, we'd have titrate, exactly, where in between cosmetic and wart remover, we wanted to test them. Because we're pretty sure the wart remover is going to be irritating.

DR. MARKS: No question of that.

DR. SLAGA: They're going to be something.

DR. MARKS: It's actually interesting now you bring that up; because they're 40 percent salicylic acid plasters which clearly cause irritation. This is of course OTC drug. And that data could be brought into this just to support it.

And I'm not aware -- I can't remember seeing sensitization to a 40 percent salicylic acid plaster. It would be nice to just have that in there. Either that or we can say the expert opinion at 30 percent -- it's clearly irritating; I agree with you, Jay, no question about that. But sensitization, I don't think is an issue either.

DR. SLAGA: It shouldn't be.

DR. MARKS: So, do we want to request that or just say the expert opinion in the discussion, we know that OTC drug at 40 -- not just 20. But MediPlast is the brand name. That's at 40 percent. And it's used for both calluses and warts. Mainly for calluses. And as I said, I've never seen allergic contact dermatitis to that.

DR. STEINBERG: I think it's an NDA drug, not a monograph drug. There's a monograph for wart removers and it's 20 percent. I think it's 19 or 20 percent.

DR. MARKS: It's 17 percent in a liquid and actually to get the increased efficacy. I suggest to my patients use the plaster. And then now you're going up to 40 percent.

DR. ANSELL: Yeah. The ones you --

DR. MARKS: So, I guess the question is, can we get any data on that? Or just say the expert opinion is we know it causes irritation. And we have in there these products should be formulated so they're nonirritating. So that covers that. Even at 30 percent it covers it.

DR. ANSELL: The question would be what data would you want? Because we know it's going to be irritating so that's not -- we've answered that question.

DR. MARKS: Yeah. Now how about the capryloyl salicylic acid at 63 percent? I'm not aware of a medical use of that. Do we know that that's -- I would assume that's very irritating. But again, when you put formulate to be nonirritating, you've covered that issue. And I assume it's a non-sensitizer.

DR. ANSELL: I guess it depends where you tie it.

DR. STEINBERG: You're tying up the hydroxy group and leaving it free.

DR. ANSELL: I mean, if it's an ester then --

DR. HILL: No. But the carboxylic acid part of salicylic acid is free in that compound.

DR. ANSELL: Yeah. Then it would be --

DR. STEINBERG: Yeah. But the phenolic group is not.

DR. HILL: But the phenolic group is esterified uniquely in that one, compared to all the rest.

DR. MARKS: Interesting. As I mentioned, there was a local lymph node assay; that's page 119. Which suggests that 20 percent salicylic acid is a sensitizer. But in point of fact, and clinical experience, I haven't seen it with 40 percent. Did I interpret that right, Jay? Page 119.

DR. ANSELL: Yeah. Sensitization --

DR. MARKS: And those concentrations are correct, right, Wilbur? Because they are, I think, higher than the original report.

MR. JOHNSON: What page are you on?

DR. MARKS: Page 50, I think, is where they had the concentrations.

MR. JOHNSON: Fifty, okay. On the capryloyl?

DR. MARKS: Yeah.

MR. JOHNSON: Yeah. That's correct value.

DR. MARKS: Yeah. That's 62.9 and --

DR. HILL: What's odd about that is that everything else reported for that particular compound is very low.

DR. MARKS: Yeah. That's why I wanted -- and if you look at salicylic acid the range is huge; .000001 to 30 percent. Did I read the local lymph node assay right, Jay? That 20 percent is a sensitizer?

DR. ANSELL: I'm not seeing it on 114.

DR. MARKS: No, 119.

DR. ANSELL: Oh, 119. Salicylic acid, yeah the LLNA was --

DR. MARKS: Yeah. If you look under the sensitization salicylic acid on the right-hand column. Toward the bottom of that second paragraph from the bottom, 20 percent salicylic acid produced a .9, 1.8 and 7.2-

fold increase, a positive response.

DR. ANSELL: So, they're saying the highest concentration, 20 percent in acetone --

DR. MARKS: Gave a 7.2-fold increase, which would be a sensitizer. But I think if we had from MediPlast that there's no incidence of sensitization with that, that's fine with me. And I would have thought I would have seen that multiple times over the years. Okay.

MR. JOHNSON: But Dr. Marks, that 62.9 percent of concentration relates to use in body and hand products, not spray products.

DR. MARKS: Right. Leave-on.

DR. HILL: Leave-on, that's the point.

DR. MARKS: Yeah.

DR. ANSELL: And then the next one is kind of an odd 20 percent acetone/olive oil, and those were sacked by IP injection?

DR. MARKS: Yeah. I didn't --

DR. ANSELL: And they didn't find any significant T-cell proliferation.

DR. SLAGA: Could it be something with the acetone working?

DR. ANSELL: Yeah. Well, or --

DR. SLAGA: Helps things penetrate a lot better.

DR. ANSELL: And the use of salicylic acid does -- just as an acid at 20 percent.

DR. MARKS: Okay. So maybe I'll forego those issues with irritation sensitization, because we have the irritation in the conclusion as it stands now. Right now, if we reopen, what we really want to see is what's the reproductive and developmental toxicity of salicylic acid and that's relevant to those papers which -- on page 24 that you highlighted, Ron Shank.

Do we have any other needs? And we still haven't voted or commented on the add-ons.

MR. JOHNSON: Dr. Marks, before I forget, you know, are there any concerns about estrogenic activity?

DR. HILL: Estrogenic?

MR. JOHNSON: Yes. On page 26.

DR. MARKS: You're in the endocrine -- 26.

MR. JOHNSON: The data indicate that butyloctyl salicylate binds to the estrogen receptor.

DR. HILL: Yeah, but not very strongly. I mean, it appears to be a very weak binder.

MR. JOHNSON: Okay.

DR. MARKS: Does that need to be put in the discussion or that's obvious when you look in here?

DR. SHANK: I don't think so.

DR. MARKS: Not in the discussion, Ron Shank?

DR. SHANK: I don't think so.

DR. MARKS: Yeah, okay. Okay so let's go to the add-ons because we didn't really settle on that. So, we have now five add-ons. It would be amyl, hexyl, isotridecyl, silver and titanium. You brought the titanium from the other report. Do you like those add-ons?

DR. SLAGA: Seems okay to me.

DR. MARKS: If we include the add-ons, then it's going to move forward. We will reopen and have a new report.

DR. SLAGA: Yeah.

DR. MARKS: And then in the interim we'll get that clarified as far as the reproductive and developmental.

DR. SHANK: Is the silver a no brainer?

DR. HILL: Probably not.

DR. ANSELL: So, if we choose to reopen for data purposes, then we would discuss the add-ons?

DR. SLAGA: Right.

DR. MARKS: Yes.

DR. ANSELL: Okay.

DR. HELDRETH: We can do it either way.

DR. ANSELL: Yes, but one way I argue. The other way I just nod my head.

DR. HELDRETH: We can choose to reopen and add or just reopen based on data.

DR. MARKS: Well, we're reopening at this point based on --

DR. SHANK: New data.

DR. MARKS: -- the new data for the reproductive and developmental toxicity. Clarify that.

DR. HELDRETH: So, the current salicylates in there that are salts are all just alkyl and earth metals, instead of being a transition metal like silver or titanium.

DR. HILL: Yeah. There is that although --

DR. HELDRETH: But is that significant?

DR. HILL: Titanium is actually not really a true transition element. It's a group for --

DR. HELDRETH: Right. But definitely different than the --

DR. HILL: I guess it might be regarded as such. Huh?

DR. HELDRETH: Definitely different than the alkaline earth metals.

DR. HILL: Oh yeah, it definitely is. I mean, we didn't have any data on it, as I recall, in the survey. And it would be nice to know more of the chemistry. So maybe I'm just -- doesn't need to be.

DR. MARKS: Do you want yes for those five?

MR. JOHNSON: What about the silver salicylate? Is that going to remain or be removed?

DR. MARKS: Well, that's why I said for those five. That includes silver and titanium.

MR. JOHNSON: Okay.

DR. MARKS: Sounds like not discussion in terms of amyl, hexyl or isotridecyl. Those are no-brainers it sounds like. Silver?

DR. ANSELL: I only see two asterisks.

DR. HILL: Page 14.

DR. MARKS: I'm on page 13. Is this not correct?

MR. JOHNSON: There are four.

DR. MARKS: Yeah. There are four. Right here. And there are the four.

DR. ANSELL: Okay.

DR. MARKS: And then what we decided to do was add the titanium also from the salicylate report which we -- I mean, from the titanium. The organo-titanium or however we're going to -- maybe we'll just call it titanium ingredients. Okay, team?

DR. SLAGA: Add them.

DR. MARKS: Add them. Ron Shank, add all five?

DR. SHANK: Okay.

DR. MARKS: Yup.

DR. HILL: Okay.

DR. MARKS: Okay. Good. So tomorrow I'll move we open the salicylate report from 2003, and what we want to clarify is the new data on reproductive and development toxicity of salicylic acid, which was on page 24. We want to review those original papers. And then we want to add on the amyl, hexyl, isotridecyl, sliver and titanium salicylates.

Now, I almost hate to bring this up, but we're going to have to cross this path anyway. Do we like the conclusion with all this sun business? It seems cumbersome to me, but I don't know which way to -- you know, now since we've reopened it, we're going to put add-ons, we have the opportunity to change the conclusion.

Safe for use when formulated to avoid skin -- and when formulated to avoid increasing the skin's sun sensitivity. And I'm sure that's because the exfoliant nature of salicylic acid. If it's formulated to be nonirritating, is it really exfoliant?

MS. LORETZ: Also, there's an NTP report that shows that it's protective against sun damage. And that was subsequent to the last report. So that could affect that recommendation.

DR. MARKS: Oh. Nonirritating, and NTP report that it was protective, you said, Linda?

MS. LORETZ: Yeah.

DR. SLAGA: It's protecting against the sun, yeah.

DR. MARKS: And what page is that on?

DR. HELDRETH: PDF page 26.

DR. ANSELL: It hasn't been added.

DR. MARKS: Oh, it hasn't been added yet.

DR. HELDRETH: No. It's in there. PDF page 26.

DR. MARKS: Okay.

DR. HELDRETH: Very top of the page.

DR. MARKS: That's what I want, page 26.

DR. HILL: Protection is tumor formation.

DR. MARKS: Sun -- it reduce tumor -- photo-tumor induction?

DR. HILL: Mm-hmm. Some protective affect against photo-carcinogenicity at lower intensities.

DR. MARKS: Okay. And obviously, that would be highlighted in the discussion because it's a significant change in the -- any other?

So, do you like that -- although we aren't to the conclusion, at this point, because we aren't going to suggest reopening a tentative report; but presumably we're going to move to a tentative report with formulated to be nonirritating, and get rid of all the sun business, at least at this point.

Does that sound reasonable, Tom? And we can obviously go back. But I kind of, as you know, like thinking ahead. And I like that we have -- it seems to me it's the irritating part, which would be really concerning with sun exposure. Because you would induce more potential for sunburn. And if the NTP report says it's sun protective --

DR. SLAGA: Well, that's probably the lower concentration protects against skin-induced tumors.

DR. ANSELL: Well, it seems to parallel the alpha hydroxy acid language.

DR. SLAGA: Yeah.

DR. ANSELL: I don't know whether that's relevant here or not.

DR. HILL: Yeah. They're talking about skin abrasion, or what's the word I'm looking for?

DR. MARKS: Yeah, exfoliant.

DR. HILL: Exfoliation. Yes.

DR. MARKS: Basically. removing the stratum corneum.

DR. HILL: So, increasing sun sensitivity.

DR. MARKS: Yes.

DR. HILL: But it has a sunscreen affect. Probably similar to PABA in terms of its sun screening.

DR. MARKS: It's not phototoxic. Okay. So, I'm going to move, tomorrow, we reopen it. And get more data from the original papers on the reproductive and development toxicity of salicylic acid. We add on the amyl, hexyl, isotridecyl, sliver, titanium salicylates. And we're going to suggest that a conclusion will be formulate when nonirritating down the line. But we're just reopening at this point.

DR. HILL: I would like to know more about the basis for the read across to the capryloyl compound, which is mostly used at low concentrations. But again, would seem to be a lipophilic aspirin.

Is there any biological data on that compound out there at all, at the moment? We seem to have this prohibition of looking at anything that resembles pharmacology, which I find very artificial.

DR. MARKS: Okay.

DR. HILL: And also, one more question was the butyloctyl salicylate is used at up to 35 percent in a lipstick. But I only found sensitization data to 5 percent in the old report.

DR. MARKS: That one I missed. The butyl --

DR. HILL: Butyloctyl. If you go to page 172, is it, somewhere near the end. I'm looking. Page 172, 35.9 percent. Also, 10 percent in a body and hand products, not spray. And 5 to 10 percent in other skin preparations. Suntan products, up to 10 percent, not spray.

But I only saw sensitization -- well, what I saw when I just looked at the old report is that they did the initiating at 5 percent. But then they came back and patch tested at 50 and 100. So they did -- was it the induction phase, you call it, at 5 percent, initially. I found it in the report and I left it.

DR. MARKS: Well, let's see what falls out with the reopening. Any other comments?

DR. SHANK: Not from me.

DR. MARKS: Okay. Anything else? Did I skip any ingredients? Any other unfinished business? If not, I think we'll adjourn.

June 4-5, 2018 CIR Expert Panel Meeting – Full Panel

Salicylic Acid and Salicylates

DR. MARKS: Okay. The salicylates. This is a re-review document on the salicylates. A final report was issued by the expert panel on salicylic acid and 16 salicylates, which was published in 2003.

The conclusion was that the safety assessment, that these ingredients are safe as used when formulated to avoid skin irritation, and when formulated to avoid increasing sun sensitivity, or when increased sun sensitivity would be expected; directions for use include the daily use of sun protection. So, it's a pretty long conclusion.

And then there was a suggestion to add five new ingredients, amyl, hexyl, isotridecyl and silver salicylates.

Our team felt we should reopen this. So that's a motion, I guess?

DR. BERGFELD: Yes.

DR. MARKS: And including in that motion would be to issue a tentative amended report, with a conclusion safe when formulated to be nonirritating, with these ingredients.

DR. BERGFELD: You're changing the conclusion as well?

DR. MARKS: Exactly.

DR. BERGFELD: Okay.

DR. MARKS: We made it simpler. In the discussion concerning sun sensitivities, since that was prominently mentioned in the previous conclusion, we felt that because it would be formulated to be nonirritating, because there's an NTP report, which found sun protective effect on carcinogenicity by the salicylates, and then it was non-phototoxic, that we could change the conclusion. But we would handle that in the discussion.

DR. BERGFELD: And that's a motion?

DR. MARKS: Yes.

DR. BERGFELD: Motion to reopened with those comments.

DR. HILL: Did you talk about the add-ons in that motion?

DR. MARKS: Yes.

DR. HILL: Okay, I missed that.

DR. MARKS: Yeah, those five new ingredients would be included in the reopened report, with a tentative amended.

DR. HILL: So, five would include the titanium that we just talked about --

DR. MARKS: No. I'm sorry, four. Four new ingredients; yeah, I didn't eliminate that one. I had the ingredients right, the number wrong, it's four. As was proposed in this, we decided not to move the titanium salicylate over to this report.

DR. BERGFELD: Is there a second or comment?

DR. BELSITO: Yeah, we did not feel that silver salicylate belonged in this group; that the toxicity would be driven by the silver and not the salicylate. I'll let Dan comment.

DR. LIEBLER: That's exactly how I felt. It's not a no-brainer; add-ons are no-brainers, this one's not, in my opinion. So, otherwise, I'm fine with the add-ons.

DR. BERGFELD: Do you want to reconsider your motion then?

DR. MARKS: Yeah, that's fine. We actually had that discussion back and forth and decided to include it; but, Dan, well taken, and we'll eliminate silver.

DR. BERGFELD: So, motion is just for four ingredients.

DR. MARKS: It will be three add-ons.

DR. BERGFELD: Three add-ons. Okay. Goes from five to three.

DR. BELSITO: Second.

DR. BERGFELD: Any further discussion regarding this re-review?

DR. BELSITO: No, I think Jim pointed out, very correctly, about the issue of the sun sensitivity and why we're slightly changing our conclusion to be a little bit more simpler and when formulating to be nonirritating. But that should be part of the discussion why we've changed that.

DR. BERGFELD: Okay. Ron Hill?

DR. HILL: I don't know why we are sufficient where the capryloyl -- that's a mouthful. That molecule is quite disparate than the others. It's actually a lipophilic aspirin. Aspirin has the ability, uniquely, among all nonsteroidal and disparate from all other salicylates, to acetylate cyclooxygenase irreversibly.

We don't have information on this particular molecule, at least not available in the old report, and

I didn't see anything new yet to indicate whether that can or cannot happen. And we have no biological data on that molecule, at all, based on what Wilbur told us yesterday and what's in the read across table. And I don't know if that was an oversight in the original report. I looked to see what, if anything, in the original report addressed that and there really was nothing, because there isn't anything.

So, for me, I would like to have an insufficiency for essentially everything related to biology for that capryloyl. But I wasn't around for the previous review, so.

DR. BERGFELD: Dan, do you want to comment on that?

DR. LIEBLER: I noted the chemical difference -- this is a little bit of an oddball -- but it was in the previous report. And the fact is, is that although the esterification, the attachment of the lipophilic modifier, is on a different site, when metabolized, you get back salicylate and capryloyl acid.

So, I didn't really feel that this was enough of an unknown quantity to be of concern. And I think that even if the data were a little thin on this one, the other materials would allow us to read across satisfactorily.

DR. HILL: My point is, and I've looked at the mechanistic detail of nonsteroidal anti-inflammatories repeatedly, and over the years, and follow this story, and I teach in this area at multiple levels. Aspirin does something different than everything else. If we can be sure that this particular molecule does not enter the binding pocket of cyclooxygenases, all is well.

But we have a lipophilic aspirin that should be very dermally penetrable, based on its log P, despite the presence of the carboxylic acid and based on its physical chemical properties. And I can't read across to it. Based on the possibility that it could irreversibly acetylate comparably to aspirin, cyclooxygenases; and there's lots of skin biochemistry involving cyclooxygenases in the skin itself, even if it doesn't make the systemic circulation. I put that out there as a comment, for me, it's insufficient.

DR. BERGFELD: Curt, do you want to respond?

DR. KLAASSEN: But isn't the acetylation of the COX due to the acetyl part of the acetylsalicylic acid?

DR. HILL: Yes, which is exactly what you've got with the acetyl moiety of the capryloyl, and this is the only one that's like that versus all the rest. So, if you look at the exact molecular mechanism by which -- and a lot is known about this now -- by which that acetyl group gets transfer to the serine of cyclooxygenase, which is the business end of cyclooxygenase. This could do that provided it can get into the binding pocket very nicely and comparably. There would be nothing to shut down that mechanism, if it could get in there and bind.

And I would be stunned if there isn't some information somewhere about that molecule. So, if it's being used as a skin anti-inflammatory, that potentially makes it a drug and not a cosmetic.

DR. LIEBLER: So, one of my best friends is one of the world leading authorities on cyclooxygenase biochemistry, and I've endured hole after hole of cyclooxygenase trivia. I can't exactly answer Ron's question, but I know there's enough data out there to be able to say whether or not this molecule would be able to access the active site of cyclooxygenases. I'd say let's keep it in and we can deal with that later.

DR. HILL: I didn't suggest removing it. I just said for me it's insufficient.

DR. MARKS: Okay. And then the other discussant point I'd like to bring up -- I think, Dan, that's an excellent suggestion. And then we'll figure out whether we want to make it insufficient the next time around.

Ron Shank pointed out, on Page 25 of the document, under Human Dermal Salicylic Acid, the paragraph there, in the third trimester, the use of Salicylic Acid can potentially cause early closure of ductus arteriosus and oligohydramnios. Therefore, it should not be applied over large surface areas for prolonged time periods, or under occlusive dressings that may enhance systemic toxicity. And Ron wanted to see the primary references on that, but I wonder what your team felt about that statement. Because I think, obviously, that raises a red flag and either we have to deal with it in a discussion or -- I don't think we can leave it hanging without addressing that.

DR. BELSITO: This was part of the discussion that we had, that we really need to do a margin of safety calculation based off of the absorption; particularly, in light of the significant increase in number of cosmetic products. And, again, I specifically asked Carol whether the huge increase in salicylic acid and ethylhexyl salicylate were due to over-the-counter products, i.e., exfoliants for acne for salicylic acid, and sunscreens for ethylhexyl salicylate. And I was told no they are cosmetic uses that have increased.

Our explanation, quite honestly, in the original report was quite lame. It basically said the exposure assessment contends that the reproductive and developmental toxicity, from a daily use of baby aspirin, is not significant. I don't know that we know that, how many pregnant women take baby aspirin.

I think we do need to go back in the document and do some margin of exposure, to assure that the absorption from aggregate use of these products would be below levels that would cause any type of reproductive

toxicity. But it is clearly known that aspirin does do that.

DR. HILL: And this is again, in my mind, when I was concerned about the capryloyl, because the log P of capryloyl analog is 3.9; that's right in the spot for transdermal delivery. If you're going to transdermal deliver a drug, the molecular weight needs to be low like that, and log P of four to six is the sweet spot, and we're right at four.

So, again, we don't have concentrations of use, that's the other issue here; if we knew that it was low, fine. But that's a serious, serious, potential biological effect were it to turn out that this would have high cyclooxygenase-inhibiting activity, plus the possibility of systemic availability.

DR. BERGFELD: Well the motions been made and seconded to reopen. And so, all of these discussant points will be recorded in the minutes and hopefully those that we'll address later. Obviously, at that time when we're readdressing it, it's possible to relieve or move out some of these ingredients, and to also address some of these issues. So, if we can call for the vote now, all those in favor of reopening?

DR. HELDRETH: Excuse me, hold on. Coming out of our re-review here, we either need to put out an insufficient data announcement, or we put out a draft tentative report.

DR. MARKS: The motion was to reopen, issue a tentative amended report, safe when formulated to be nonirritating and address these issues the next time around.

DR. BERGFELD: And that was seconded, I believe.

DR. BELSITO: Right. But we also discussed deleting the MEA salicylate because of restrictions on MEA. And actually, that MEA salicylate was in the MEA report. Deleting that would just leave it with MEA and not in this report.

DR. BERGFELD: Can we do that automatically now?

DR. HELDRETH: Yes. That already has a new conclusion and that's the one that will stand for that one, and it'll just continue with that report.

DR. MARKS: Right. And we're just adding three new ingredients.

DR. BERGFELD: Okay. Wilbur?

MR. JOHNSON: Back to Dr. Hill's concern about the capryloyl salicylic acid, what is happening with that?

DR. BERGFELD: My understanding is it's being left in for now. Is that correct? Ron Hill? Capryloyl?

DR. HILL: Yes. But if we're not going out insufficient on that, then I'm going to vote against the tentative amended report.

DR. BERGFELD: Dr. Marks, you want to respond to that?

DR. MARKS: Let's take the vote.

DR. BERGFELD: Okay. All those in favor of reopening and a tentative amended report, please indicate by raising your hand. Against? One opposed. Okay. And that will be recorded in our minutes. So, we don't have to deal with the salicylates anymore, we have dealt with them.

December 3-4, 2018 CIR Expert Panel Meeting – Dr. Belsito's Team

DR. BELSITO: So, in 2003, we reviewed Salicylic Acid and 16 salicylates, so it was time for re-review. We decided to add on a few more salicylates and look at the whole package. That's what we have here. I said safe as used when formulated to be non-irritating and non-sensitizing. The question I had is Amyl Salicylate is listed only as a fragrance ingredient. Yet, it's in this report. Shouldn't it be dropped? Its function, if you look, it's just fragrance, as opposed to hexyl cinnamate, which has nonfragrance functions -- or Hexyl Salicylate rather.

DR. HELDRETH: According to our procedures, any specific ingredient to review, of which may otherwise be deferred, shall none the less be included at the discretion of the expert panel when other chemically related or otherwise conveniently grouped ingredients are considered. So, if the panel feels it helps to have that ingredient in there, whether it be for data or otherwise, it is their prerogative to use it.

DR. BELSITO: But should it be among the ingredients listed as we are reviewing? We can certainly rely on the data, but right now it's listed as one of the materials we're reviewing. No?

DR. HELDRETH: Yes. The way that the procedures are written, if it's incorporated in there, it's counted, if you're assessing the safety of it. Now, the panel has the prerogative to choose not to have it in the report at all, but that's your choice.

DR. BELSITO: I don't care one way or the other. I just was under the assumption that if it were fragrance only, we weren't reviewing it.

DR. HELDRETH: It's a reason that it may be excluded.

DR. BELSITO: Okay. Then, I guess, I had a question. If you look at the use limits for Salicylic Acid and TEA-Salicylate, we're exceeding the limits that the EU talks about. I didn't understand this on PDF 41, where it says that it was a maximum of 0.5 percent acid as preservatives. But not as preservatives, there's no restriction? I didn't understand that. "The European Union has established a maximum use concentration of 0.5 percent acid for the following ingredients as preservatives."

DR. EISENMANN: It's in the preservative, right?

DR. BELSITO: I understand. But is the limit only if they say they're using it as a preservative? And if they're not using it as a preservative, they can go above 0.5? Which is how I'd interpreted it. Then it begs the question, why they set that limit? Because we have Salicylic Acid being used at a much higher concentration than .5 percent. We're covering it by saying not sensitizing, right -- or irritating, rather? I just found it very curious that, in parenthesis, (as preservatives); it didn't make any sense to me. Because TEA-Salicylate and Salicylic Acid are both above those 0.5 percent levels.

DR. EISENMANN: It's also on Annex 3. I don't know the details of what it says on Annex 3. So it's in the preservative annex and it's on Annex 3. I don't know the details of the Annex. I'd have to find the report and look at it.

DR. BELSITO: It didn't bother me. I was just curious as to how and why they set that limit. And then I made a note to myself and failed to do it. They restricted baby products. Is it listed to be used in any baby products? No reported --

DR. BERGFELD: No, none reported, no.

DR. EISENMANN: One thing is, there's an opinion that's not finalized yet versus the regulation, so it has to be clarified a little bit. Remember the opinion that's not finalized has some of this additional warning. He's, like, intertwined what's the regulation and what's the opinion, and so that kind of has to be separated. Because the opinion has not been finalized, and has not been made into a regulation yet.

DR. BELSITO: Okay.

MR. JOHNSON: About the baby product, Sodium Salicylate is being used in baby shampoos at maximum use concentrations up to 0.31 percent. That's the only ingredient used in baby products.

DR. HELDRETH: For concentration of use. Salicylic Acid has two reported uses, according to VCRP, in baby products.

MR. JOHNSON: I'm just referring to the concentration data.

DR. BELSITO: I have a question, Wilbur, on page 59 where we're looking at LLNA was used to evaluate the effects of inhalation exposure. It says, "Methyl Salicylate (a respiratory and skin irritant) served as the negative control in both assays." Normally, you don't use skin irritants as a control for the LLNA.

MR. JOHNSON: That is as stated in the report, Dr. Belsito.

DR. BELSITO: Then another question on PDF page 61, the in vitro sensitization, you see, " The allergen–peptide/protein interaction in vitro assay." Is that the direct peptide reactivity assay?

MR. JOHNSON: That's one of the three assays that was used.

DR. BELSITO: But is it the DPRA, because I've never heard of that assay.

MR. JOHNSON: Actually, I mentioned three in vitro methods: One is the direct peptide reactivity assay. The other one is the SENS-IS assay. That assay measures the gene expression of irritation and the sensitization biomarkers. And the h-CLAT. I'm sorry the other one was --

DR. BELSITO: That was the old one? Right. So, you have the h-CLAT. So the allergen-peptide/protein interaction is the DPRA?

MR. JOHNSON: DPRA measures reactivity with mock peptides.

DR. BELSITO: I know what DPRA measures, Wilber. What I'm asking you is, in the first paragraph you say, "allergen peptide/protein interaction in vitro assay." Is that the DPRA? Because I'd never --

MR. JOHNSON: Yes.

DR. BELSITO: -- then it should just be DPRA.

MR. JOHNSON: Okay.

DR. LIEBLER: Wait a second. Are you talking about on Page 61, under sensitization in vitro, the first sentence?

DR. KLAASSEN: Third sentence.

DR. LIEBLER: Okay. Third sentence, "the allergen–peptide/protein interaction in vitro." Okay.

DR. BELSITO: Okay. Then in the discussion, PDF page 72, the first paragraph you say, "When formulated to avoid increasing the skin's sun sensitivity." I thought we were getting rid of that restriction based upon the data we have here. Because we actually saw that Salicylic Acid reduced the incidents of photo --

DR. EISENMANN: He's discussing what the conclusion was on the old report, I think.

DR. BELSITO: But this should not be in the discussion of the current report.

MR. JOHNSON: Okay. That will be deleted.

DR. LIEBLER: So, do you want to just delete that entire first paragraph, the discussion?

MR. JOHNSON: Yes.

DR. BELSITO: Yeah.

DR. LIEBLER: Okay.

DR. KLAASSEN: And I think this was also stated earlier in the report. You have the same sentence, and I think that needs to be clarified. Now it is true that in 2003, we thought this, but not anymore because we now have data. We'll have to make sure that it's clear.

MR. JOHNSON: Sure.

DR. BELSITO: So, say safe as used when formulated to be non-irritating and non-sensitizing. Are we all good with that?

DR. LIEBLER: I agree.

DR. SNYDER: Agree.

DR. BELSITO: Yes, Wilber.

MR. JOHNSON: A handout was distributed this morning. It contains IFRA's limits on Hexyl Salicylate. And one of the limitations relates to use in products that are applied to the lip. And Butyloctyl Salicylate is used in concentrations above 30 percent in lipstick. And this 1 percent limit is for products that are applied to the lip. So, are there any concerns about that high concentration in relation to IFRA's limit?

DR. BELSITO: Yeah, because we're now saying that you have to formulate it to -- IFRA's limit was based upon a QRA for Hexyl Salicylate. I don't know what the QRA would come out for this specific salicylate, but what we're saying is not, safe as currently used; we're saying safe as used when formulated to be non-irritating and non-sensitizing. They could apply a QRA for that product or whatever. That concentration reported here may be unsafe. We don't know.

This is not a blanket, okay, safe as reported in this, this is -- we're restricting it. I don't care what the concentrations are here. What I'm saying is some of them may be wrong. Companies need to do their homework.

DR. LIEBLER: Right. I think that's the only way we can deal with this, because we don't know, Butyloctyl Salicylate is a bigger molecule or hydrophobic, less likely penetration in the epidermis than Hexyl Salicylate. So, the numbers, if they did a QRA for Butyloctyl, would probably be substantially different. I think, we can't know that, so we just say, when formulated to be non-irritating, non-sensitizing.

MR. JOHNSON: Yeah, because the tentative conclusion that was issued stated, safe when formulated to be non-irritating.

DR. BELSITO: There's been no tentative. This is the first time we're looking at this whole group.

MR. JOHNSON: What, salicylates?

DR. BELSITO: The 2003 said non-irritating, but this is the first time -- I mean, we didn't come

out with a conclusion in 2018 or 17. We added four ingredients, and this is a complete, new relook. And we're changing -- we're saying non-irritating, non-sensitizing.

DR. LIEBLER: Wilber, the conclusion you have at the top of PDF page 74, says formulating to be non-irritating. Is that simply distilled down from the previous report, and you take out the sun UV exposure stuff?

DR. BELSITO: The previous report from 2003, correct.

DR. LIEBLER: Correct. Is that what you're referring to, Wilber?

MR. JOHNSON: No, the panel, at the June meeting, issued a tentative amended report with the safe when formulated to be non-irritating conclusion. So, that was the tentative amended conclusion.

DR. BELSITO: No, we determined to reopen the safety assessment to amend the conclusion. That MEA-Salicylate would not be included. Yeah, I guess.

DR. LIEBLER: Wilber's right.

DR. BELSITO: We're reassessing it, so we're changing the conclusion.

DR. LIEBLER: Right.

DR. HELDRETH: It's more restrictive. So, it likely should go out again.

DR. KLAASSEN: I have a question on page 67, right before the summary. We have a margin of safety, and I don't quite understand how that was calculated. It says, from 125 to 2.5 million, which is a pretty big range. But how did we -- I guess we calculated that or --

DR. SNYDER: Yeah. Mm-hmm.

DR. KLAASSEN: How?

DR. BELSITO: Eighty-seven.

DR. KLAASSEN: No, it's page 67.

DR. BELSITO: Sixty-seven.

DR. KLAASSEN: I mean, it says, with the assumption of 12 to 100 percent bioavailability, which is an 8-fold difference.

DR. BELSITO: That's RIFM's safety assessment.

MR. JOHNSON: No, the risk assessment is on PDF page 56, that we did, our calculations.

DR. HELDRETH: He's talking about what's on page 67, the RIFM safety assessment.

MR. JOHNSON: That's RIFMs, yeah, that's not ours.

DR. KLAASSEN: It says, "Depending upon the assumption of either 12-30 or 100 percent." But the difference between 12 and 100 is 8-fold. Then there's 125; if you multiply that by 8, it would be a thousand, but it's two and a half million. That's what I'm confused about.

MR. JOHNSON: Well, that is taken directly from the RIFM safety assessment on salicylates, Dr. Klaassen.

DR. LIEBLER: So, you can see how it seems inconsistent. It seems like it doesn't make sense. And I noticed the same thing with the numbers not scaling in parallel. If indeed that's taken correctly from the RIFM assessment, and there's not a number problem there, then there's something else about the calculation, having to do with more than probably the assumption of bioavailability.

DR. BELSITO: Well, it's product use. Remember RIFM has access to the Creme database.

DR. LIEBLER: Right.

DR. BELSITO: So, they know 95 percentile across all cosmetic products.

DR. LIEBLER: So, you need to change that sentence to bioavailability and product use.

MR. JOHNSON: Okay.

DR. LIEBLER: Kurt, the product use would definitely explain that.

DR. KLAASSEN: That's fine. That's fine.

DR. LIEBLER: So, Wilber, what we're referring to is on PDF 67, under the description of the RIFM safety assessment. The second short paragraph.

MR. JOHNSON: Yeah.

DR. LIEBLER: Maybe calculate the range from 125 to 2.5 million, depending on the assumptions of -- and I would take out the numbers, 12 to 30 percent, because it's needlessly confusing. Just say, "depending on assumptions of bioavailability and product use."

DR. BELSITO: "Following dermal application."

MR. JOHNSON: Okay.

DR. LIEBLER: Okay.

DR. BELSITO: Okay. Anything else on this?

MR. JOHNSON: One other thing. Given the use in baby products, as stated in the use

concentration data from the council as well as FDA, should there be any statement relating to any concerns about ingredient use in baby products?

DR. BELSITO: I understand why the Europeans limited it. I think when formulated to be non-irritating -- and there's really not good data that baby skin is necessarily more hyperirritable than adult skin.

DR. KLAASSEN: I think the reason for that is that the main toxicity of salicylates is --

DR. BELSITO: Phototoxic.

DR. KLAASSEN: No, it's actually, as far as death is concerned -- which used to be a major problem in this country. It's not so much anymore, because we have these safety caps. But if you're as old as I am, we used to have to teach this to medical students, because a lot of kids were getting killed every year from aspirin on the kitchen table.

The real problem, for children and adults, is metabolic acidosis and respiratory alkalosis. It is known that children, at that time, were more sensitive to lethality from aspirin. So, that's, I think, where this is kind of going back to; that children are more sensitive to the electrolyte imbalance and the death that can occur from acute exposure.

DR. BELSITO: Okay. So, is anyone concerned about the use in a baby shampoo?

DR. KLAASSEN: No.

DR. LIEBLER: Wilber, I want to call your attention one typo, I think, in the risk assessment on page 56. So the second -- about the seventh line or eighth line down where you have at the top, margin of safety rinse-off peel product equals NOAEL over SED peel product. The third line of that little calculation is 75 mg per kg per day divided by .19. That should be divided by .475. You got that already? You guys got that?

MR. JOHNSON: Yes.

DR. LIEBLER: Okay. Good.

DR. EISENMANN: My question, is that actually needed, that exposure assessment? You have a study where they actually measure -- people use the peel product containing 30 percent Sal. Acid and they measured blood levels. So, I'm not sure why you need to do this calculation, anyway, because you have the real data.

DR. LIEBLER: Did we have that study when we suggested we needed to do this calculation?

DR. EISENMANN: No, you did not.

DR. LIEBLER: Well, okay. Data talks.

DR. EISENMANN: I thought that you could also compare this concentration to -- there's levels of toxic blood levels of Salicylic Acid. So, you could also do -- not just compared to the blood levels when you take an aspirin, which is what they did in the paper, but also to the toxic levels which are later on in the report.

DR. LIEBLER: So the study you're referring to, is that in the document before us?

DR. EISENMANN: It follows right after. In the less conservative estimation -- so it's not an estimation, it's an actual study, where people used the peel formulation and they measured Salicylic Acid in the blood.

DR. BELSITO: Safety margin was 50 to 1.

DR. EISENMANN: And they compared it to -- so the same people, then, took an aspirin and they measured the blood level.

DR. BELSITO: Well, does it hurt to have it all in, since we already did it?

DR. EISENMANN: Well, personally, real data trumps -- especially, since you don't really know --

DR. BELSITO: I don't like that verb.

DR. EISENMANN: Sorry.

DR. LIEBLER: Yeah, we don't use that verb right now.

DR. BELSITO: Real data bests --

DR. EISENMANN: Okay. Real data bests -- if you had data on how much peel a person uses, but this isn't -- they're using how much shower gel you used in place of that.

DR. BELSITO: Right.

DR. EISENMANN: So, the actual study where you have people using the product, as they would use it, and you measure the levels of Salicylic Acid in -- what was it, plasma -- yes. To me is much more appropriate. To say it's a less conservative estimate, well, it's not a less conservative estimate, it's actual --

DR. BELSITO: It's a more realistic estimate.

DR. LIEBLER: It's data.

DR. EISENMANN: It's an actual measurement.

DR. LIEBLER: If we already have these data, we wouldn't have asked for the QRA calculation. I think given that, that's the way we normally operate, working from data. I agree that we probably should delete the

calculation.

DR. BELSITO: Okay.

DR. BERGFELD: And you're inferring, by doing this, you send a message that it was a little bit more concerning than you have stated. Is that why you want to remove it? I understand that you have data, but --

DR. LIEBLER: I didn't understand what you just said. Something about sedated?

DR. BERGFELD: I said, the fact that it would appear with the known data, why would you have to remove it? Does it have the appearance of your worry, without stating it or what?

DR. LIEBLER: Oh, stated. I thought you said sedated, and I was wondering what you were talking about.

DR. BERGFELD: Stated. Doesn't it somewhat support?

DR. LIEBLER: We normally don't have these in if we have data. The argument seems to be that, well, since we did it, it needs to stay in, even after we have data. I certainly wasn't suggesting that I didn't have any faith in the calculation, but it simply an --

DR. BERGFELD: Overkill.

DR. LIEBLER: -- an estimate. Why don't we do that more often when we have data? That's what that suggests to me. Why don't we have these calculations all over the place? We did this because we didn't have data. Now, we have data.

DR. BERGFELD: But you said RIFM does it all the time.

DR. BELSITO: When we don't have data.

DR. LIEBLER: Yeah, right.

DR. BELSITO: Yeah, I mean, I guess the question is, does it set a precedent that whenever there's a concern, even if we have data, we also need to calculate a risk assessment?

DR. SNYDER: I don't want to set that precedent.

DR. BELSITO: I mean, I'm comfortable dropping it.

DR. LIEBLER: I think dropping it when we have sufficient data is more consistent with our practice. RIFM certainly has its practice, but there are a lot of differences.

DR. HELDRETH: Do we want to add something to the discussion section? Saying something about, originally, we requested this when there was lack of data, now that we have the data it's -- so that way, if someone is looking at the record, "why did they not pay any attention to their old risk assessment?" It's explained there.

DR. BELSITO: Sure.

DR. LIEBLER: Yeah. Okay.

DR. BELSITO: I mean, oftentimes, we do add it in the discussion, that we had asked for a risk assessment, and in the interim we got this data.

DR. BERGFELD: Well, you will also say it supported the actual data. I would think it did.

MR. JOHNSON: Dr. Belsito, the only data from that publication by Funk (phonetic) is that statement here. Does any additional information from that publication need to be included? Or is this information as stated sufficient?

DR. BELSITO: I think we should ask that to the toxicologist, not the dermatologist. Dan, Curt, Paul?

DR. LIEBLER: What page, what paragraph were you --

MR. JOHNSON: This is PDF Page 56, and it's the paragraph just below the MOS of 157.

DR. KLAASSEN: In the less conservative estimation?

MR. JOHNSON: Yeah, that's the only information that we have that --

DR. KLAASSEN: That paragraph.

MR. JOHNSON: Yes. Well, just that sentence.

DR. BELSITO: Wilber's asking, I think, is that do more details from that paper need to be included? I think Carl was suggesting yes.

DR. EISENMANN: My suggestion is that you could also compare the results to -- in other places in the report, there's blood concentration of Salicylic Acid that's toxic. So, you'd have a comparison to the aspirin level, and you'd have a comparison to -- and I wrote it in my notes.

DR. SNYDER: Blood levels are down and toxic levels are down.

DR. EISENMANN: Toxic levels -- greater than 300 micrograms per mil is considered toxic; it says that later in the report. There was also a statement that salicylism occurs at greater than 35 milligrams per deciliter, so slightly different units. So you could compare it to that, too, just to show you where you are. So, you're lower on one aspirin, but you're much lower than what's considered toxic too.

MR. JOHNSON: Now, what section of the report should this be included in?

DR. EISENMANN: It can be right in that risk assessment section, where it's at.

DR. BELSITO: Risk assessment.

MR. JOHNSON: Okay. But you'll just only have information from this report in relation to the blood concentration of Salicylic Acid, that is toxic, and the toxic dose that's associated with salicylism?

DR. EISENMANN: Um hmm.

MR. JOHNSON: And that's the only information that should be in the risk assessment section?

DR. BELSITO: As a comparison.

DR. EISENMANN: Well, what you have already is in there --

MR. JOHNSON: So, delete everything else and just add that information, only, in the risk assessment section?

DR. BELSITO: No. I mean, you're going to use the study that was done on the individuals who used the 30 percent rinse-off product. You're going to show the margin of safety. You're going to show the levels that are -- and they're less than what we would get from taking one 325 milligram aspirin, and then you're going to say, and by the way, the level of toxicity for salicylates is this.

DR. BERGFELD: Right.

MR. JOHNSON: When you say show the margin of safety, you're talking about based upon our calculation?

DR. BELSITO: No. You're simply going to get rid of all our calculations. And you're going to get rid of, "In a less than conservative estimation." And you're going to start, "The relative bioavailability of Salicylic Acid following facial application of 30 percent" blah, blah, blah. Continue with all that.

Then second paragraph, in comparison, they looked at individuals who took an aspirin, and this was the level. And then you're going to say, and by the way, the toxic level for salicylate is this.

MR. JOHNSON: Okay.

DR. BELSITO: The question becomes, do we keep the estimates for leave-on? And we do. So, then the rest of it is fine, you're just changing the rinse-off. Okay?

DR. LIEBLER: So, you're going to delete the calculation at the top of PDF page 56, right?

DR. BELSITO: Yeah.

DR. LIEBLER: And then you're also going to delete the lead-in two paragraphs at the bottom of page 55? If you drop that calculation at the top of 56, is there lead-in material, right before it, that you can also delete? I think they can go, right? Did you get that, Wilber? Did you -- are you still thinking about it?

MR. JOHNSON: I have it.

DR. LIEBLER: Oh, you got it. Okay.

DR. BELSITO: Then in the discussion, I think the biggest thing we need to do, in addition to saying why we dropped the risk assessment for the rinse-off, is to explain why we've gotten rid of the photosensitizing sunscreen use. And just point out the new data we have on the actual protective effect of Salicylic Acid.

Okay. Anything else? Okay. Save this baby and move on. So, this has to go out for another review since we've restricted the conclusion. Okay.

December 3-4, 2018 CIR Expert Panel Meeting – Dr. Marks' Team

DR. MARKS: Team, are we ready?

DR. SLAGA: As ready as I'm going to be.

DR. MARKS: We'll start with the draft final amended report on salicylic acid and salicylates. As you recall, these ingredients, 16 of them, were published in 2003. In June of this year, we added additional ingredients. And the panel issued a tentative amended report, with a safe when formulated to be non-irritating conclusion, on salicylic acid and the 18 salicylate ingredients.

Wilbur has updated the report. A margin of safety exposure was accomplished. And, Ron, Ron and Tom, comments? There are lots of updates. Were those okay? Was the margin of safety okay? There was EU limits mentioned in the report. We also have a memo, from this morning, which we just saw. So, I'll let you read that, from Wilbur.

And Wilbur do you want to say anything about this that you supplied this morning, and then also, this accompanying page on categories?

MR. JOHNSON: Just like it says, the International Fragrance Association has established concentration limits for Hexyl Salicylate in different categories of cosmetic products. And you have a handout with those limitations. And also, a handout indicating the product categories -- definitions of the product categories.

DR. MARKS: This is this sheet that, at the top, has 1 percent, category one, 1.3 percent, category 2, et cetera?

MR. JOHNSON: Yes.

DR. MARKS: Yeah, okay. So how is that incorporated in the conclusion when this is so specific and extensive? Is this going to be in the discussion? How do we handle this?

MR. ANSELL: The inclusion of the IFRA?

DR. MARKS: Yes, in other words, our conclusion now is formulated to be non-irritating, a safe conclusion. Wave 2, there were no side effects of the 2 percent salicylic acid cream. And then Wave 3, we had Council comments. Were those Council comments -- that would be after this document. Did that change anything?

DR. SHANK: Well, our margin of safety was based on rinse-off peel products. And I don't see that on any of these categories. I thought the rinse-off peel was the worst case we could consider for margin of safety. I don't see how this changes the margin of safety. It's just more information. I did have a question on the margin of safety calculation on Page 56.

DR. HILL: That's Wave 3 -- or no that's in the --

DR. SHANK: PDF, Page 56.

DR. HILL: -- the main document.

DR. SHANK: And at the very top of the page is a calculation for the systemic exposure dose. And the figure derived was 0.475 mg/kg/day. But in the margin of safety calculation, the systemic exposure dose value is .19. And I don't know where the .19 comes from.

DR. HILL: Yeah. I think that might be a mistake but I'm not sure, because when I divide 75 by .19, I got 396, not 157. So, something is amiss.

DR. SHANK: I didn't do the higher math.

DR. HILL: Well, I just did a back of the envelope with the 75 divided by .2, and said it can't be 157; so then that prompted me to pull out the calculator. But 75 divided by .475 is probably in the neighborhood of 157. So, maybe that just didn't get -- but I don't know.

DR. SHANK: Yeah.

DR. HILL: I can do it --

MR. JOHNSON: I would have to check with Jinqiu, the toxicologist, who did the calculation. But specifically, which value is in question?

MR. SHANK: In the calculation for the MOS. The value inserted there for SED is 0.19, and I don't know where that comes from. And just above that, the SED was calculated to be 0.475.

DR. HELDRETH: Yeah. I think he accidentally transposed the number. You can see the first number in the systemic exposure dose calculation. It was the 0.19. He accidentally carried that down there. But Dr. Hill's right, if you do the math with 75 divided by the .475 it comes out to 157. So, I think it's just a misprint with 0.19 the second time.

DR. MARKS: Thank you.

DR. HILL: Yeah, because that .19 is grams per day if you look, leaving that off; so, that's what

happened.

DR. MARKS: That's Page 56, that would be editorial, the margin of -- pardon?

DR. SHANK: Well, the value of the margin of safety doesn't change.

DR. MARKS: Right, the 157.

DR. SHANK: So, it's okay. We just need to correct the number for the SED. It isn't 0.19, it's 0.475 mg/kg/day.

DR. HILL: Yes.

DR. SHANK: That's in the MOS calculation.

DR. HILL: But I also like the comment that came from the SSC that -- and actually, pretty much the data's in here, it's just a matter of exactly how it's addressed; in that you'd use the plasma concentrations and area end of the curves, and then you can do the direct calculation and compare. And I think the point was the plasma concentrations are available for that peel.

And so, while we the margin of safety calculation, calculating one that relies directly on the relative AUCs, or the CMAX, is actually two different numbers, also makes sense. But that's in here. Right?

DR. SHANK: Yes. And I would say that the conclusion remains safe as used when formulated to be non-irritating.

DR. SLAGA: I agree.

MR. JOHNSON: Just one concern regarding the IFRA limitations. One of the limitations relates to lip products, and there's a 1 percent concentration limit. And please note that Butyloctyl Salicylate is being used in cosmetic products at a much higher concentration, specifically, the 35.9 percent.

DR. SHANK: Quite different.

MR. JOHNSON: Quite different, yes. And it's my understanding that these limitations relate to concern about sensitization.

DR. SHANK: Okay. And they all pertain to Hexyl --

MR. JOHNSON: Hexyl Salicylate?

DR. SHANK: -- Salicylate?

MR. JOHNSON: Yes. I know those are different chemicals, but I was just, you know.

DR. HILL: No, that's very important. Because I'm not sure we fully have captured the absorbability information for the Butyloctyl, for that concentration of use, which I think I flagged the last time. And I thought that was one of the ones that was on my mind in calculating margin of safety.

MR. JOHNSON: We do have log P value for that chemical in Table, I think it's Table 2 --

DR. HILL: Table 2.

MR. JOHNSON: -- for the Butyloctyl Salicylate.

DR. HILL: But the complication there is the ionization, that physiological pH, because the acid is free. So, you really need log D to get a proper picture. Then again, put in a vehicle like a cream and it changes again. What is that leave-on use again? I looked at this, but it's been a while?

MR. JOHNSON: For Butyloctyl, it's 35.9 percent.

DR. HILL: But what's the use? It says mucous membrane, that sort of suggests lips.

DR. SHANK: Lipstick, isn't it? It's used in the lipstick?

MR. JOHNSON: Yeah, it is used in lipstick at 35.9 percent.

DR. HILL: Hence, the incidental ingestion, which, again, incidental, I'm not worried about that. Yeah, so the body area -- it's mucous -- but the body area in a lipstick would be very small. If you did a cumulative estimate for that, which due diligence suggests we really ought to do; and you could use -- is it IFRA that has -- well, the European Union, in general, they have surface areas that one can use.

But I don't guess we have any dermal penetration that would be relevant to lips in here. Yes, all we've got is Methyl Salicylate, and that bugged me the whole time I looked at this. And so, log P, that would be the free acid, and again sitting on lips. It's not really in aqueous solution, it's the free acid that's in there. Log P of 6 puts it in the sweet spot for transdermal delivery, so that's interesting.

DR. MARKS: Enough, Ron Hill, that you'd want to change the final amended conclusion, safe when formulated to be non-irritating?

DR. HILL: No, because I don't think you could get enough salicylate into the system fast enough by that route, from a lipstick, applied a few times a day maximally. But still, you'd think we should have a margin calculation, given that high percentage of use.

DR. MARKS: Ron Shank? I mean if we need another margin of safety calculation, obviously, we can't move forward. We would have to want to see that before we issue a final conclusion.

DR. HILL: Well, we could do it between now and tomorrow, and see what we come up with. I

don't think it's a hard calculation.

DR. SHANK: I thought we were using the 30 percent peel? It would be a lot greater impact on the skin, and 39 percent in a lipstick.

DR. HILL: But the substance in the peel is what?

DR. SLAGA: And then we have a limited area.

DR. HILL: What's the substance in the peel?

DR. SHANK: Salicylic acid.

DR. MARKS: Salicylic acid.

DR. HILL: Yeah. So, that's going to be a very different absorption profile than Butyloctyl Salicylate. Salicylic acid is not particularly lipophilic. Yeah, a smaller molecular weight, but I doubt very dermally absorbable. I mean, we've looked at that, so we know that answer. But by comparison, these lipophilic esters would get across skin barrier, or at least into the skin, where there might or might not be esterases in the lips that will take that out rapidly, or not, in humans.

DR. MARKS: Tom?

DR. SLAGA: I don't think we need another calculation. I think what Ron Shank is saying is correct, that we have it for the skin. And I think, we take into consideration that they are less on the lips, so even if it wasn't --

DR. MARKS: Well, why don't we -- and then, Ron Shank, I hear you feel comfortable with the margin of safety calculation we have and the conclusion. Ron Hill, we could see, Wilbur, see if you have a margin of safety, but you can certainly bring that up tomorrow, Ron Hill.

DR. HILL: I just feel like there have got to be available numbers for if we smear lipsticks on a fairly large person's lips, how many milligrams of lipstick, at 36 percent, and how much of that is Butyloctyl Salicylate? We've got the surface area, the lips, then make a conservative assumption; and I think you'll see it's not going to get into the system at a level of concern.

Even if you put the lipstick on ten times a day -- which people don't. It seems to like, again, a due diligence or credibility thing, I think would be the better way to put it, by having that in there. I'm not suggesting we should have to delay the process. I feel like that number could be produced by tomorrow, if somebody feels inclined to do it.

DR.MARKS: Well, that would be Jinqiu who did this. He's going to be correcting that. I'll mention that tomorrow. Our team will be seconding the Belsito's motion. Presumably, it would be safe when formulated to be non-irritating. I'll mention that we need to edit the margin of safety calculation, on Page 56, that the SED is 0.475 mg/kg/day, producing a margin of safety of 157 as shown. So, that change will be made.

And then, Ron Hill, I'll mention if you want to comment about another margin of safety for lip exposure to the Butyloctyl Salicylate at 35.9 percent use. And I think, was there anything from Wave 3 in the council's comments that we needed to react to?

DR. SHANK: Not for me.

DR. MARKS: Okay, okay.

DR. ANSELL: We do want to raise a concern that the Hexyl Salicylate, which is the subject of the IFRA conclusions, this is essentially, exclusively a fragrance ingredient, and we always run into a little problem with jurisdiction. But if we choose to continue to carry it forward, we think the IFRA conclusion should be included but in the cosmetic use section.

MR. JOHNSON: I might mention that, according to the dictionary, there is another function for the Hexyl Salicylate, other than just fragrance material.

DR. HELDRETH: Right, skin conditioning agent.

MR. JOHNSON: Yeah, it's a skin conditioning agent.

DR. ANSELL: The dictionary, itself, is not a normative reference for use.

DR. HILL: Well, it shows a maximum use in our table of .12 percent for leave-on, and .52 for rinse-off, for Hexyl Salicylate; not Ethylhexyl, but Hexyl. We don't really have a problem, from that point of view. And if it's used in cosmetic products -- no matter it's used in a fragrance ingredient or not. If the use in the cosmetic product is not fragrance, then I don't see any jurisdictional issue.

If we were exceeding the limits that IFRA was setting, then I could -- I mean, I think we may still need to incorporate that information, that they've set those limits, somehow in the report. Where, was I thought what we started this discussion with, and we never answered it. In the discussion section, or would it be up at the front in the non-cosmetic use? I think non-cosmetic use if it's a fragrance. I mean, I don't know.

DR. ANSELL: Yeah, our suggestion is to put it in the use section.

DR. MARKS: In the use section.

DR. HILL: And you could put those limits in there, just in the text, I think.

DR. ANSELL: Yeah.

MR. JOHNSON: Dr. Marks.

DR. MARKS: Yes.

MR. JOHNSON: Just one thing. We talked about the concern about percutaneous absorption, you know, through the lip. Are there any concerns about incidental ingestion?

DR. HILL: I don't. Because under those circumstances we would know intact Butyloctyl would reach any place where it would be absorbed in any other way than salicylate, and the levels would be far lower. That wouldn't be worth doing the calculation.

I had a couple of other things, but I wanted to make sure -- just a general comment from me is, again, the Capryloyl is structurally different; and there's information I asked about, in the last go-round, that I don't think I need to repeat again here, that I still think due diligence suggests one ought to have. So, I have a problem with that particular compound, myself.

I wondered what we're doing, with not just this ingredient but all of them with things about inhalation, given our state of evolution on our aerosols work? I don't think we were suggesting we should table all of these ingredients so we can get the new aerosol language in there. But yet, I wondered how we planned -- because you know how I feel about this stuff about the -- I could go to Page 41 and find it. But I wrote a note here, "Please consider moving that to the discussion." Some of the language related to that to discussion, related to particle size, whatever, and then whatever we end up landing on.

MR. JOHNSON: Well, Dr. Hill, the last paragraph of the discussion does address inhalation exposure.

DR. HILL: Right, it does. But then the question is why do we need -- here's the language, let me go to Page 41 of the PDF. The language says, "in practice, 95 to 99 percent of the droplets/particles released from cosmetics sprays going down in lungs to any appreciable amount." And then again, "conservative estimates of inhalation exposures." All of that.

I mean, that's discussion, and it's been discussion since I've started reading these. And I wonder why this goes right up front here? You just say, they're used in these sprays. Then down further, we may or may not have aerosol inhalation toxicology. When you get to the discussion section you either say, here's what we have on inhalation toxicology, or we don't have it, and we think we don't need because here's why.

But it always bugs me, it always is glaring, when you have it right up here in the use section; and we get into the practice 95 to 99 percent, blah, blah. And then conservative estimates. Those are not introductory or use comments, those are discussion of why the inhalation toxicology is or isn't important, and to what extent, to me.

And then there was always the concern, well, we don't put references in the discussion section. And I say every journal I've ever published in, you put references in the discussion section, so what's the problem here?

DR. MARKS: Tom, Ron, any comments?

DR. SHANK: No.

DR. MARKS: It's okay the way it is.

MR. SLAGA: Right.

DR. SHANK: For me, yes.

DR. MARKS: Okay. So, again, I'll reiterate we'll be seconding a motion. Presumably, it'll be a final amended report with a conclusion, safe when formulated in the non-irritating. We edit the margin of safety calculation on Page 56. I presume the Belsito team will catch this, but if not, I'll mention that the SED is really .475 mg/kg/day in the calculation.

I'll mention, Ron Hill, about another MOS for lip exposure. Is that necessary at the 35.9 percent concentration of Butyloctyl Salicylate? And the IFRA consolation limits in the memo, which Wilbur just gave us, will be in the cosmetic use section for Hexyl Salicylate.

DR. HILL: Two more things. One is just a general comment. On Page 43, there's dermal penetration study and it has three women skin samples in the formulation; and it gives an amount in microgram per cubic centimeters was applied to the skin, in so much time.

My question that I wrote in here, "But what was the concentration?" Because amount doesn't tell you anything about diffusion rate. Concentration drives diffusion rate. The higher the concentration, the higher the mass transfer rate, plain and simple. So, we always need to know, when we write up dermal penetration studies, and certain surface areas. Surface area is always important to know because the mass transfer rate is directly proportional to surface area. The other important factor is concentration. It didn't capture, and so that might be

available.

And then the last thing is, on the Capryloyl, which again is problematic for me because of the structural dissimilarity and the lack of information about is this really a souped-up aspirin? We put to bed the sensitization, in part, by saying the contamination with a 3-capryloyl isomer is the likely isomer. And I wanted to know is that conjecture added by us; or if it was conjecture in the reference report, and on what basis does anybody actually believe this?

MR. JOHNSON: Where are you reading from?

DR. HILL: Page 65 is the contamination with the 3-capryloyl. And I'm not sure I know what that is, because 3 is kind of ambiguous in salicylic acid, but I think I know what it is. And that would be acylation on the aromatic ring if that's what they're asserting. I'm assuming that's not something we added, it was something drawn from the literature reference; but I wondered on what basis they made that conclusion.

MR. JOHNSON: Which ingredient and which paragraph?

DR. HILL: All right, let me get there. I'm sorry. It should be Page 65, I thought. Under sensitization, it would be -- yeah, okay, case reports. And I agree that it stated that Capryloyl --

DR. MARKS: Is it the Capryloyl Salicylic acid, the case reported of that female patient you're talking about?

DR. HILL: Yes, yes, sir.

DR. MARKS: To me, a case report is a case report, it's an alert. Unless I see multiple followed up, a mini-epidemic, I take it as is, it's sensitized in this case, and kind of leave it at that.

DR. HILL: I agree with you, but my question was, where did that statement about the 3-capryloyl come from? I want to make sure that it's taken from the reference and not our suggestion. Because if it's coming from us, there's a credibility issue.

DR. MARKS: Yeah. No, I'm sure it's from the reference.

DR. HILL: And if it is coming from Reference 92, which I didn't look to verify, I wondered where they got that? But it doesn't matter. I think it needs to be written to indicate this was the authors' of that articles' conjecture, and not ours.

MR. JOHNSON: Okay. So, I should revise it to indicate that's the authors' opinion?

DR. HILL: Just -- then that would be editorial.

MR. JOHNSON: Okay.

DR. MARKS: Any other comments? If not, we'll move on to Vinylpyrrolidone Polymers.

December 3-4, 2018 CIR Expert Panel Meeting – Full Panel

DR. BELSITO: So, this came up as a re-review at the September meeting, and we decided to reopen it to add three additional ingredients: Amyl Salicylate, Hexyl Salicylate, and Isotridecyl Salicylate. We looked at all the material. There are some points in the discussion that I'll get to later, but in general our conclusion was safe as used when formulated to be non-irritating and non-sensitizing; and non-sensitizing, you could use QRA or other methodologies.

DR. MARKS: Interesting, yeah. I'll second that. I'd be interested in the reasoning with the non-sensitizing, Don. We went just not irritating.

DR. BELSITO: Well, because IFRA has limits on hexyl cinnamate, and there's evidence of sensitization -- or Hexyl Salicylate. There's some evidence of sensitization there. So, we need to respect, I think, those limits and what IFRA has found.

DR. BERGFELD: And that is included as a reference here in the document?

DR. BELSITO: Yeah, the data for IFRA is in the document.

DR. BERGFELD: Thank you. Any other comments? Okay. Could we take the vote first and then go to the discussion?

DR. MARKS: Second.

DR. BERGFELD: All those in favor indicate by raising your hand. It's safe. Okay. It's unanimous? Are you voting yes or no right now?

DR. HILL: We aren't discuss -- you said go to the discussion.

DR. BERGFELD: We're going to go to the discussion afterwards, because there are discussant points too.

DR. HILL: Okay. All right.

DR. BERGFELD: All right.

DR. HILL: I thought we usually discuss before we vote.

DR. BERGFELD: Oh, no.

DR. HILL: Oh -- I'm sorry. I thought we usually discuss before we vote and then --

DR. BERGFELD: We're going to the discussion now. Thank you. The discussion?

DR. BELSITO: So, first we had originally asked for a risk assessment for both rinse-off and leave-on products. We actually got actual data on rinse-off products. And my panel felt that we could drop the risk assessment for the rinse-off since we have the actual data, and data bests, a risk assumption. We would keep the risk assumption for the leave-ons; and then, just to point out further in that risk assumption, there was the mention of what happens when you take one aspirin and a big concentration of salicylate. It was recommended that we also add in a short sentence as to what the actual toxic levels for salicylate would be, to point out exactly how good our margin of safety is. There was one comment.

DR. BERGFELD: Mark's team?

DR. MARKS: Our edits included, on page 56, the margin of safety calculations. I assume you wanted to keep that. The SED in that was really 0.475 milligrams per kilo per day, that produces a margin of safety of 157 as shown. So, there's a typo in that formula.

DR. BELSITO: Yeah, we picked that up, but we're dropping on that because that's for rinse-offs, and we actually have hard data for rinse-offs now. And we felt that the hard data is superior to a risk assessment.

DR. BERGFELD: Ron Shank, what do you think?

DR. SHANK: It's okay. It gives more confidence in the risk assessment. And now we have the hard data that support the risk assessment. But if you don't want, take it out, I don't object.

DR. BELSITO: Well, we were just concerned that it may set a precedent that we have hard data and then we also do a risk assessment on it. If we actually have the data, then there's no need to do the risk assessment.

DR. BERGFELD: Ron Hill?

DR. HILL: Just for clarification, that was the peel, correct?

DR. SHANK: Rinse-off peel.

DR. BELSITO: Rinse-off, yes.

DR. HILL: Rinse-off, peel? Yeah, okay. Because that's where we had serum levels and exposure estimates.

DR. BELSITO: Exactly.

DR. HILL: AUCs, all of that, yeah.

DR. BERGFELD: Paul? Dan? Curt?

DR. KLAASSEN: Fine.

DR. BELSITO: Okay. Another discussion point? Are we done with that?

DR. BERGFELD: Please.

DR. BELSITO: Previously, we had restricted this and asked that a warning be put on the label for sun protection. We now have data that that is not an issue. So, I think, in the discussion, we need to point out why we've dropped that restriction for Salicylic Acid.

MR. JOHNSON: That's already in the discussion, Dr. Belsito. It's there.

DR. BELSITO: Yeah.

DR. BERGFELD: Okay. Ron Hill?

DR. HILL: I expressed concern about the capryloyl ester last time, and I still have the concern. I am encouraged that there's only one percent maximum use in leave-ons, but I still think I would want to see whether it is, or is not, a direct cyclooxygenase inhibitor. I still feel uncomfortable with that particular one.

DR. BERGFELD: Okay. Dan.

DR. LIEBLER: So, I remember our discussion last time, Ron, about that. I talked my colleague Larry Marnett; he's kind of one of the foremost biochemistry experts on cyclooxygenase inhibition. He said that the longer chain acyl derivatives have increasingly lower activity as inhibitors, so acetyl was the most. And then a longer chain one may not even be able to access the active site very well. The other thing is, I actually found a reference we could add to the report that actually compared platelet aggregation efficacy up to, like, butyl. But it's consistent with what Larry mentioned to me. So, I think that the concern about the capryloyl is mitigated by that.

DR. HILL: Okay, I'm good, too, then. That was my suspicion, but I didn't have any hard documentation. That sounds right in terms of what's known about the SAR, so, I'm good.

DR. BERGFELD: So, have you added that to the --

DR. LIEBLER: So, Wilbur, I'll email you the reference.

MR. JOHNSON: Okay.

DR. BERGFELD: Okay. Thank you.

DR. HILL: Yeah, if we could add that, that would be great.

DR. BERGFELD: Any other discussion or comments or editorial comments? Wilber?

DR. MARKS: Well, I was going to ask, Ron Hill, yesterday you brought the question of whether another margin of safety should be calculated for the lip exposure of 35.9 percent of Butyloctyl Salicylate. Are you still concerned about that, Ron Hill? I'd be interested in what the Belsito team feels about it.

DR. HILL: I feel like it's going to show us that everything is fine. Just that it's a high concentration, 36 percent, if I'm not mistaken, almost in the leave-on in lip. But the surface area is small. It just feels like -- and so, total systemic exposure from that has got to be really small because the rate of access to the system should be low. I mean, I slept on this since then. I don't think it's crucial.

DR. HELDRETH: Overnight, though, Jinqiu actually did a MOS calculation for that and it was well over a hundred.

DR. HILL: Well over a hundred. That would have been my guess. That's great.

DR. BERGFELD: Can that be added?

DR. HELDRETH: Absolutely.

MR. JOHNSON: So does that need to be added to the safety assessment, that risk assessment?

DR. BELSITO: Yes.

MR. JOHNSON: One other concern. On PDF Page 60, we have irritation and sensitization data. The discussion doesn't contain any information relating to irritation or sensitization potential; so, what information should be included in the discussion to support the conclusion?

DR. BERGFELD: Don?

DR. BELSITO: I think just a summary of that irritation and sensitization data. And that we realize that irritation is a very variable phenomenon, depending upon product formulation; so that we really can't really give a percentage number. Sensitization is less variable; and that's why I said that it should be assessed by methodologies, such as QRA or other excepted methodologies, since I can't give a specific number for that.

DR. BERGFELD: Okay.

DR. MARKS: Don, you were going to include the IFRA concentration limits, cosmetic use for Hexyl Salicylate in the use section, or not? You had mentioned that was one of the tipping points for having the sensitization portion of the conclusion.

DR. BELSITO: I don't know where that appeared. But, yeah, I mean it could be put into the cosmetic use section that there's a limit that's been set.

DR. BERGFELD: Bart has whispered to me that this will have to go out again because of the

change in the conclusion; so it will go out for 60 days.

DR. BELSITO: Yes.

DR. BERGFELD: And we've already voted on this, so we can move forward then to the next group. The next group of reports advancing, these are at various levels. The first one is Dr. Marks and the lactate salts.

Amended Safety Assessment of Salicylic Acid and Salicylates as Used in Cosmetics

Status: Draft Final Amended Report for Panel Review
Release Date: March 15, 2019
Panel Date: April 8-9, 2019

The 2019 Cosmetic Ingredient Review Expert Panel members are: Chair, Wilma F. Bergfeld, M.D., F.A.C.P.; Donald V. Belsito, M.D.; Ronald A. Hill, Ph.D.; Curtis D. Klaassen, Ph.D.; Daniel C. Liebler, Ph.D.; James G. Marks, Jr., M.D.; Ronald C. Shank, Ph.D.; Thomas J. Slaga, Ph.D.; and Paul W. Snyder, D.V.M., Ph.D. The CIR Executive Director is Bart Heldreth, Ph.D. This report was prepared by Wilbur Johnson, Jr., M.S., Senior Scientific Analyst, and Jinqiu Zhu, Ph.D., Toxicologist.

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ABSTRACT: The Cosmetic Ingredient Review (CIR) Expert Panel (Panel) reviewed the safety of Salicylic Acid and 17 salicylates; 15 of these ingredients were previously reviewed by the Panel, and 3 are reviewed herein for the first time. Some of the reported functions in cosmetics for ingredients in this group are hair and skin conditioning agents, and, less frequently, preservatives and fragrance ingredients. Upon review of relevant new data, including frequency and concentration of use, and consideration of data from the previous CIR report, the Panel concluded that Salicylic Acid and 17 salicylate ingredients are safe in cosmetics in the present practices of use and concentration described in the safety assessment when formulated to be non-irritating and non-sensitizing, which may be based on a quantitative risk assessment (QRA). One ingredient previously reviewed, Capryloyl Salicylic Acid, appears to have been mischaracterized and is thus not rereviewed herein.

INTRODUCTION

The Cosmetic Ingredient Review (CIR) Expert Panel (Panel) published a safety assessment of Salicylic Acid and 16 salicylates in 2003.[1] Based on the available data, the Panel issued the following conclusion: Salicylic Acid, the salts Calcium Salicylate, Magnesium Salicylate, MEA-Salicylate, Potassium Salicylate, Sodium Salicylate, and TEA-Salicylate; Capryloyl Salicylic Acid, C12-15 Alkyl Salicylate, Isocetyl Salicylate, Isodecyl Salicylate, Methyl Salicylate, Myristyl Salicylate, Ethylhexyl Salicylate; and Tridecyl Salicylate, and the compounds Butyloctyl Salicylate and Hexyldodecyl Salicylate are safe as used when formulated to avoid skin irritation and when formulated to avoid increasing the skin's sun sensitivity, or, when increased sun sensitivity would be expected, directions for use include the daily use of sun protection. Additionally, in 2015, the Panel published a safety assessment of MEA-Salicylate with the following conclusion: MEA-Salicylate is safe in the present practices of use and concentration described in this safety assessment (rinse-off products only) when formulated to be nonirritating.[2] The Panel cautioned that this ingredient should not be used in cosmetic products in which *N*-nitroso compounds may be formed. Though only MEA-Salicylate is mentioned in this conclusion here, it should be noted that the conclusion also relates to ethanolamine and other ethanolamine salts that were reviewed in that safety assessment. The complete reports are available on the CIR website (https://www.cir-safety.org/ingredients). In accordance with its Procedures, the CIR evaluates the conclusions of previously-issued reports every 15 years; therefore, this re-review document has been prepared. Because MEA-Salicylate was recently re-reviewed via incorporation in the CIR safety assessment of Ethanolamine and Ethanolamine Salts, it is not included in this re-review. Because Capryloyl Salicylic Acid appears to have been mischaracterized, it is also not included in this re-review.

The following ingredients, in addition to those included in the original report, are included in this safety assessment: Amyl Salicylate, Hexyl Salicylate, and Isotridecyl Salicylate. These 3 ingredients are esters of Salicylic Acid, and are structurally similar to the ingredients that were reviewed in the original report. The expanded list of 18 ingredients (15 of 17 from the original Final Report + 3 additions) appears below:

Butyloctyl Salicylate
Calcium Salicylate
C12-15 Alkyl Salicylate
Ethylhexyl Salicylate
Hexyldodecyl Salicylate
Isocetyl Salicylate
Isodecyl Salicylate
Magnesium Salicylate
Methyl Salicylate
Myristyl Salicylate
Potassium Salicylate
Salicylic Acid
Sodium Salicylate
TEA-Salicylate
Tridecyl Salicylate

Amyl Salicylate
Hexyl Salicylate
Isotridecyl Salicylate

According to the web-based *International Cosmetic Ingredient Dictionary and Handbook* (wINCI; *Dictionary*), some of the functions in cosmetics that are reported for this group of salicylates include hair and skin conditioning agents, and, less frequently, preservatives and fragrance ingredients.[3] The complete list of functions is presented in Table 1.

The published data in this re-review document were identified by conducting an exhaustive search of the world's literature. A list of the typical search engines and websites used, sources explored, and endpoints that CIR evaluates, is available on the CIR website (https://www.cir-safety.org/supplementaldoc/preliminary-search-engines-and-websites; https://www.cir-safety.org/supplementaldoc/cir-report-format-outline). Unpublished data may be provided by the cosmetics industry, as well as by other interested parties.

Excerpts from the summaries of the 2003 report are disseminated throughout the text of this re-review document, as appropriate, and are identified by *italicized text*. (This information, except for chemical and physical properties, is not included in the tables or the Summary section.)

Chemical registration dossiers submitted to the European Chemicals Agency, in conformity with the European Union's (EU) Registration, Evaluation, Authorization and Restriction of Chemicals (REACH) regulation, are available on the following ingredients: Butyloctyl Salicylate, Ethylhexyl Salicylate, Methyl Salicylate, Salicylic Acid, and Sodium Salicylate. Some of the safety test data identified in REACH dossiers are included in the CIR final report on Salicylic Acid and 16 salicylates that was published in 2003. However, it should be noted that data from Salicylic Acid and salicylate REACH dossiers that became available subsequent to this final report publication are included in this report. The report also contains data that are summarized in the 2018 Scientific Committee on Consumer Safety (SCCS) preliminary opinion on Salicylic Acid,[4] and in a 2002 opinion by the Scientific Committee on Cosmetic Products and Non-Food Products Intended for Consumers (SCCNFP).[5]

CHEMISTRY

Definition and General Characterization

Salicylic Acid (Figure 1), an aromatic monohydroxybenzoic acid (specifically, 2-hydroxybenzoic acid) is a colorless, crystalline organic acid that can be derived from salicin (a β-glucoside in willow bark).[6] The rest of the ingredients in this report (salicylates) are esters or salts of Salicylic Acid (Figure 2). The definitions of the salicylates reviewed in this safety assessment are included in Table 1.

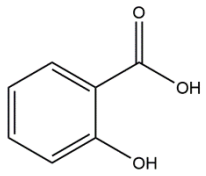


Figure 1. Salicylic Acid

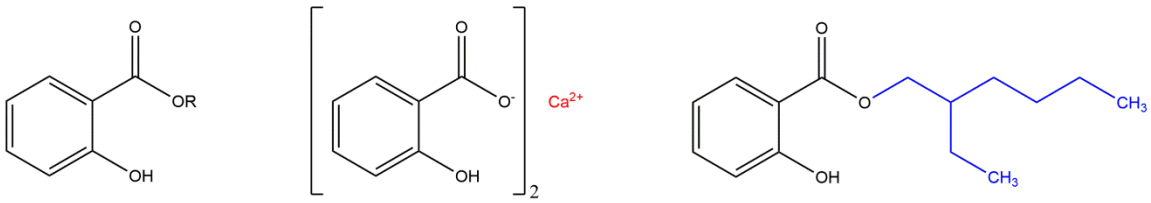


Figure 2. Salicylates generic structure (wherein R is a salt cation or an alcohol residue), and examples: Calcium Salicylate and Ethylhexyl Salicylate

Chemical and Physical Properties

The molecular weight of Salicylic Acid is 138 Da; its corresponding salts have formula weights from 160 to 298 Da. The acid and salts are solids at standard temperature and pressure (STP). The molecular weights are as small as 152 Da, and go up to 390 Da. These esters are liquids at STP and are acidic due to the phenolic hydroxyl group. The chemical and physical properties of Salicylic Acid and salicylates (salts and esters) are presented in Table 2.[7,8,9,10,11,12]

Method of Manufacture

Amyl Salicylate

Amyl Salicylate can be synthesized by heating a mixture of Salicylic Acid, *n*-amyl alcohol, and concentrated sulfuric acid under a reflux condenser for approximately 4 h.[13] After the unreacted alcohol has been removed by distillation at atmospheric pressure, the residue is washed with 10% aqueous potassium carbonate and dissolved in ether, and the ether solution is dried over anhydrous sodium sulfate. The high-boiling material that remains after removal of the ether is fractionated under reduced pressure. The Amyl Salicylate fraction boils at 116 to 121ºC and 1.4 mm Hg. According to another source, Amyl Salicylate can be synthesized from Salicylic Acid and *n*-amyl alcohol, using sodium hydrogen sulfate as a catalyst.[14]

Impurities

Magnesium Salicylate

According to the *United States Pharmacopoeia* (*USP*), Magnesium Salicylate contains not less than 98% and not more than 103% of this ingredient, and 0.004% heavy metals.[15]

Methyl Salicylate

According to the *National Formulary* (*NF*), Methyl Salicylate contains not less than 98% and not more than 100.5% of this ingredient, and contains heavy metals at 20 μg/g.[16]

Salicylic Acid

The *USP* specifies that Salicylic Acid contains not less than 99.5% and not more than 101% of this ingredient, calculated on the dried basis.[15] The limit on phenol content is not more than 0.02%, and the limit on total impurities is not more than 0.2%.

Sodium Salicylate

According to the *USP*, Sodium Salicylate contains not less than 99.5% and not more than 100.5% of this ingredient, calculated on the anhydrous basis, and not more than 0.0002% heavy metals.[15]

USE

Cosmetic

The safety of the cosmetic ingredients included in this safety assessment is evaluated based on data received from the United States (US) Food and Drug Administration (FDA) and the cosmetics industry on the expected use of these ingredients in cosmetics.[17] Use frequencies of individual ingredients in cosmetics are collected from manufacturers and reported by cosmetic product category in FDA's Voluntary Cosmetic Registration Program (VCRP) database. Use concentration data are submitted by the cosmetics industry in response to surveys, conducted by the Personal Care Products Council (Council), of maximum reported use concentrations by product category.

The greatest use frequency of 3974 uses is reported for Ethylhexyl Salicylate, followed by 1429 reported uses for Salicylic Acid.[17] (Reported use frequencies for the remaining ingredients are ≤ 186.) The frequency of use for both of these ingredients increased greatly when 2019 VCRP data are compared to the VCRP data from the original report; in 1998, Ethylhexyl Salicylate was reported to have 83 uses and Salicylic Acid was reported to have 107 uses. Furthermore, in 1998, there were no reported uses of Magnesium Salicylate, but 11 uses are being reported in 2019.

The results of a concentration of use survey conducted in 2018 indicate that Butyloctyl Salicylate is being used at concentrations up to 35.9% in leave-on products (lipstick), which is the highest maximum use concentration for leave-on formulations that is being reported for the salicylates that are reviewed in this safety assessment.[18] Salicylic Acid is being used at concentrations up to 30% in rinse-off products (peels); this is the highest maximum ingredient use concentration that is being reported for rinse-off products. In the published CIR final report on salicylates, the highest ingredient use concentrations in rinse-off and leave-on products were 3% (Salicylic Acid) and 8% (Ethylhexyl Salicylate), respectively.[1] Further use frequency and concentration of use data are presented in Table 3.

Collectively, according to 2019 VCRP data and the results from a 2018 Council use concentration survey, the following salicylates are not reported to be in use in cosmetic products in the US:

Calcium Salicylate
C12-15 Alkyl Salicylate
Hexyldodecyl Salicylate
Isocetyl Salicylate (was used at 3-5% in 2000; VCRP data were not reported at that time)
Isotridecyl Salicylate
Myristyl Salicylate
Potassium Salicylate

Cosmetic products containing salicylates may be applied to the skin (e.g., Salicylic Acid, up to 30% in peels) or, incidentally, may come in contact with the eyes (e.g., Ethylhexyl Salicylate, up to 0.1% in eye lotions). These ingredients are also applied to mucous membranes and could be incidentally ingested (e.g., Butyloctyl Salicylate, up to 35.9% in

lipsticks). Products containing salicylates may be applied as frequently as several times per day and may come in contact with the skin for variable periods following application. Daily or occasional use may extend over many years.

The highest maximum ingredient use concentration in a spray product is being reported for Ethylhexyl Salicylate, which is used in suntan aerosol and pump sprays at concentrations up to 5%. The use concentration data on Ethylhexyl Salicylate in spray products relate to cosmetic ingredient functions other than that of a sunscreen; sunscreens are considered over-the-counter (OTC) drugs in the United States (21 CFR 352.10). Salicylic Acid is being used in suntan product pump sprays at concentrations up to 0.5%. In practice, 95% to 99% of the droplets/particles released from cosmetic sprays have aerodynamic equivalent diameters > 10 µm, with propellant sprays yielding a greater fraction of droplets/particles below 10 µm, compared with pump sprays.[19,20,21,22] Therefore, most droplets/particles incidentally inhaled from cosmetic sprays would be deposited in the nasopharyngeal and bronchial regions and would not be respirable (i.e., they would not enter the lungs) to any appreciable amount.[19,20] The highest maximum ingredient use concentration in a powder is being reported for Butyloctyl Salicylate, which is being used at concentrations up to 3.6% in face powders. Conservative estimates of inhalation exposures to respirable particles during the use of loose powder cosmetic products are 400-fold to 1000-fold less than protective regulatory and guidance limits for inert airborne respirable particles in the workplace.[23,24,25]

According to the EU's list of preservatives allowed in cosmetic products, a maximum use concentration of 0.5% (acid) was established for the following ingredients for use as preservatives in ready-for-use cosmetic preparations: Salicylic Acid, Calcium Salicylate, Magnesium Salicylate, Sodium Salicylate, Potassium Salicylate, and TEA-Salicylate.[26] The following qualification relating to their use in cosmetics accompanies this concentration limit: Not to be used in products for children under 3 years of age, except for shampoos; this warning is associated with the use of these ingredients as preservatives, and applies to products which might be used for children under 3 years of age and which remain in prolonged contact with the skin. [For use other than as a preservative, See Annex III, No. 98].

Salicylic Acid is also included on the EU's list of substances which cosmetic products must not contain, except with the following restrictions: Maximum use concentrations in ready-for-use cosmetic preparations of 3% in rinse-off hair products and 2% in other products.[26] This restriction applies to the use of Salicylic Acid for purposes other than inhibiting the development of microorganisms in the product; this purpose has to be apparent from the presentation of the product. Additionally, wording of conditions of use and warnings state not to be used in products for children under 3 years of age; this is solely for products which might be used for children under 3 years of age and which remain in prolonged contact with the skin.

An SCCS 2018 Final Opinion on Salicylic Acid supports the EU's concentration limits that are stated above.[4] It found that Salicylic Acid is safe when used as preservative at a concentration of 0.5 % in cosmetic products, with the current restrictions as described. For uses other than a preservative, the Opinion supported concentrations up to 3.0 % for cosmetic rinse-off hair products and up to 2.0 % for other products, taking into considering the restrictions given. However, in body lotion, eye shadow, mascara, eyeliner, lipstick and roll on deodorant applications, Salicylic Acid is considered safe up to 0.5% only as preservative. Also, for both preservative and non-preservative use, the Opinion is not applicable to any oral products (such as toothpaste and mouthwash), with the exception of lipstick. Additionally, sprayable products that could lead to exposure of the consumer's lung by inhalation are also excluded.

The EU has also established a maximum use concentration of 5% for Ethylhexyl Salicylate (as a UV filter allowed in cosmetic products) in ready for use cosmetic preparations.[26]

The International Fragrance Association has established the following concentration limits (relative to sensitization potential) for Hexyl Salicylate in different categories of cosmetic products when utilized as a fragrance ingredient:[27]

1% (**Category 1**: lip products of all types [solid and liquid lipsticks, balms, clear, etc.]),

1.3% (**Category 2**: deodorants and antiperspirant products of all types, including any product with intended or reasonably forseeable use on the axillae or labeled as such [spray, stick, roll-on, underarm, deo-cologne, and body spray, etc.]),

5.3% (**Category 3**: hydroalcoholic products applied to recently shaved skin (includes after shave); eye products of all types [eye shadow, mascara, eyeliner, eye make-up, eye masks, eye pillows, etc.], including eye care; men's facial creams and balms; tampons; body creams, lotions, and oils; and body paint for children),

16% (**Category 4**: hydroalcoholic products applied to unshaved skin [includes aqueous based, alcoholic based, and hydroalcoholic), like cologne, eau de cologne, eau de parfum, or parfum; body sprays [including body mist] with no intended or reasonably foreseeable use on the axillae; hair styling aids and hair sprays of all types [pumps, aerosol sprays, etc.]; body creams, oils, and lotions; solid perfumes; fragrancing creams of all types [except baby creams and lotions]; ingredients of

perfume kits; fragrance compounds for cosmetic kits; scent pads; foil packs; scent strips for hydroalcoholic products; foot care products; hair deodorant; and body paint [except those for children],

8.4% (**Category 5**: women's facial creams/facial make-up; hand cream; facial masks; baby powder and talc; hair permanent and other hair chemical treatments [e.g. relaxers], but not hair dyes; wipes or refreshing tissues for face, neck, hands, and body; hand sanitizers; and dry shampoo or waterless shampoo),

25.7% (**Category 6**: mouthwash, including breath sprays, and toothpaste),

2.7% (**Category 7**: intimate wipes and baby wipes),

2% (**Category 8**: make-up removers of all types [not including face cleansers]; hair styling aids (non-spray) of all types [mousse, gels, leave-in conditioners, etc.]; nail care; powders and talcs of all types [except baby powders and talcs]; and hair dyes),

and **5%** (**Category 9**: bar soap [toilet soap]; bath gels, foams, mousses, salts, oils and other products added to bathwater; body washes of all types [including baby washes) and shower gels of all types; conditioner [rinse-of]; all depilatories [including waxes for mechanical hair removal]; face cleansers of all types [washes, gels, scrubs, etc.]; facial tissues; feminine hygiene – pads; feminine hygiene – liners; fragranced face masks [not intended to be used as medical device]; liquid soap; shampoos of all types [including baby shampoos]; and shaving creams of all types [stick, gels, foams, etc.])

Non-Cosmetic

Ethylhexyl Salicylate

Ethylhexyl Salicylate is an active ingredient, at the specified concentration of up to 5%, in OTC sunscreen drug products, whereby the finished product provides a minimum SPF value of not less than 2 [21 CFR 352.50]. When used as a sunscreen, this ingredient must be listed on the label as octisalate (which is the International Nonproprietary Name).

Methyl Salicylate

Non-aspirin salicylates (i.e., not acetylsalicylic acid), such as Methyl Salicylate, are found in many OTC brands of creams, ointments, lotions, liniments and medicated oils intended for topical application to relieve musculoskeletal aches and pains.[28]

Salicylic Acid

Salicylic Acid is a non-steroidal anti-inflammatory drug (NSAID), of which aspirin is a simple phenolic acetate derivative.[29] The FDA has issued a final rule for OTC drug products that permits the use of Salicylic Acid, at concentrations of 0.5 to 2%, as an active ingredient in topical acne drug products. [21 CFR 333.310]

TOXICOKINETIC STUDIES

Dermal Penetration

In Vitro

Salicylic Acid and Methyl Salicylate

In vitro skin penetration data indicate that Salicylic Acid was percutaneously absorbed through pig, mouse, and rat skin and that Methyl Salicylate was percutaneously absorbed through pig and guinea pig skin.[1]

Ethylhexyl Salicylate and Salicylic Acid

A skin penetration study on Ethylhexyl Salicylate was carried out using human female abdominal skin (full-thickness skin obtained at autopsy) in Franz diffusion cells.[30] The receptor fluid was phosphate buffered saline containing 6% (w/v) oleth-20. When [^{14}C]-Ethylhexyl Salicylate (labeled on salicylate portion; 5% in oil-in-water; target dose = 5 mg/cm^2) was applied as a finite dose, the average total absorption of radioisotope over 48 h was 0.65 ± 0.16% of the applied dose. This value represented a total flux of 1.58 ± 0.36 µg/cm^2. When applied as a finite dose in a representative hydroalcoholic formulation containing 5% Ethylhexyl Salicylate, the average total absorption of radioisotope over 48 h was

0.59 ± 0.09% of the applied dose. This value represented a total flux of 1.58 ± 0.25 µg/cm^2. The penetration of Salicylic Acid was also determined in this study. When [^{14}C]-Salicylic Acid (in oil-in-water emulsion) was applied as a finite dose, the average total absorption of radioisotope over 48 h was 1.14 ± 0.23% of the applied dose. This represented a total flux of 1.65 ± 0.39 µg/cm^2. The authors noted that the data obtained in this study suggest that the in vitro human skin permeation of Ethylhexyl Salicylate is relatively low. They also noted that, using similar vehicles, the flux of Salicylic Acid was similar to that of Ethylhexyl Salicylate over a 48-h period. The authors also offered the supposition that the [^{14}C]-label appearing in the receptor fluid may, in both cases, represent salicylic acid, giving rise to the possibility that the amount of Ethylhexyl Salicylate permeating through the skin is much less than suggested by the data.

Ethylhexyl Salicylate

The skin penetration of a sunscreen formulation containing 5% Ethylhexyl Salicylate was evaluated using human full-thickness skin (from 3 women) that was mounted in a Franz diffusion cell with a receptor volume of 12.4 ml.[31] The sunscreen formulation tested was either in an oil-in-water emulsion gel or in petrolatum. The receptor compartment was filled with an aqueous solution containing sodium chloride (0.9%) and bovine serum albumin (1.5%). The cell allowed skin (1.76 cm^2) to be exposed to the sunscreen formulation, and the formulation (3.0 ± 0.4 µg/cm^2) was applied to the skin for either 30 min or 6 h. Each value for skin penetration is reported as the mean value (n = 4). After either duration, Ethylhexyl Salicylate was not detected in the dermis. Skin penetration and the amount of Ethylhexyl Salicylate found in the epidermis were the same following the 30-min application using both vehicles and the 6-h application using the oil-in-water emulsion gel; skin penetration was 0.4 µg/cm^2, and 0.2% of the applied dose was detected in the epidermis. The 6-h value for skin penetration of Ethylhexyl Salicylate (in petrolatum) into the epidermis was 0.6 µg/cm^2, and 0.3% of the applied dose was detected in the epidermis.

Methyl Salicylate

The skin penetration of Methyl Salicylate was evaluated using rat full-thickness skin (cleared of excess subcutaneous tissue) from male Wistar rats.[32] The skin was cut into 15 x 15 mm pieces and mounted in Franz-type glass diffusion cells (surface area = 1.3 cm^2). The receptor fluid consisted of degassed, 20% ethanol:80% distilled water. A formulation containing 20% Methyl Salicylate (1 g) was placed on the skin and receptor fluid was removed and replaced during the experiment. Approximately 25% of the Methyl Salicylate that was absorbed through the skin was hydrolyzed to salicylate. At 24 h, the total amount of salicylate that penetrated through the skin was < 20%.

In vitro skin penetration tests on Methyl Salicylate were performed using fresh dermatomed (0.3 to 0.4 mm thick) female breast skin and leg skin in Bronaugh flow-through polytetrafluoroethylene diffusion cells.[33] Each dose of the test substance was applied to a 0.38-cm^2 skin area in each cell. The receptor fluid was Hank's HEPES buffered saline with 4% bovine serum albumin (pH of 7.4). Skin samples were exposed to Methyl Salicylate for 30 min, and there was a 6.5 h reservoir collection period. The skin penetration of Methyl Salicylate was described as rapid. There was 32% absorption at the low dose (2 mM Methyl Salicylate), 17% absorption at the medium dose (20 mM Methyl Salicylate), and 11% absorption at the high dose (200 mM Methyl Salicylate). Regarding these results, the authors noted that the percent absorption from a high concentration of test chemical may be lower than that observed from a lower dose level, but may still give rise to higher calculated µg/cm^2/h amounts absorbed.

Percutaneous absorption of Methyl Salicylate was evaluated in the isolated perfused porcine skin flap (IPPSF).[34,35] A dose of 400 µg/cm^2 of radiolabeled [^{14}C]-Methyl Salicylate was applied non-occluded to a 7.5 cm^2 Stomadhesive® dosing template on the IPPSF. Skin flaps were allowed to equilibrate for 1 h prior to chemical application. A total of 16 flaps were dosed and terminated at 2, 4, or 8 h. Percutaneous absorption into IPPSF was 2.39% of the applied dose at 8 h. With the amount in skin and fat added, the penetration was 3.04% of the applied dose. The rate of absorption was also evaluated. Radiolabeled Methyl Salicylate showed a rapid absorptive flux profile that peaked at approximately 30 min at 0.016% dose/min.

The ester cleavage of Methyl Salicylate to Salicylic Acid in hairless mouse skin, in vitro, following topical application of 1% Methyl Salicylate in acetate buffer to the skin was evaluated.[36] Less than 5% of the applied dose was metabolized to Salicylic Acid.

Salicylic Acid

The in vitro percutaneous absorption of Salicylic Acid was evaluated using Franz diffusion cells and porcine skin dermatomed to a thickness of 500 ± 50 µm.[4] The receptor fluid consisted of phosphate-buffered saline, distilled water, bovine serum albumin, and gentamicin sulfate. An ethanol-water (1:1) solution containing Salicylic Acid (~ 3% w/v) was applied for 24 h to the entire skin surface. Treated stratum corneum was removed by 8 successive tape strippings, after

which the dermis was separated from the epidermis. The different compartments for each active principle were analyzed using high-performance liquid chromatography. Dermal absorption of Salicylic Acid (epidermis, dermis, and receptor fluid) on intact skin was found to be 34.48% ± 2.56 (n = 6). Total recovery was 99.28% ± 4.31.

In another in vitro study, [^{14}C]-Salicylic Acid (in ethanol) was applied to porcine skin (dermatomed to a thickness of 500 µm) using a flow-through porcine skin diffusion system.[4] Each square section (1 cm^2) of skin was placed in a two-compartment flow-through diffusion cell, to which [^{14}C]-Salicylic Acid (in ethanol) was applied for 24 h. The dermal side of the skin sections was perfused using receptor fluid consisting of a Krebs-Ringer bicarbonate buffer spiked with dextrose and bovine serum albumin. The flow rate of the receptor solution was 4 ml/h. The treated area of skin was removed by 6 successive tape strippings, and samples were analyzed using a liquid scintillation counter. The dermal absorption of [^{14}C]-Salicylic Acid in ethanol was 40.05% (± 7.63%; n = 3).

The in vitro percutaneous absorption of [^{14}C]-Salicylic Acid (2% in ethanol:water vehicle; dose = 40 µg/cm^2) was evaluated using human abdominal skin samples (split-thickness).[4] There were 12 skin samples from 4 different donors. The skin was dermatomed to a thickness of 200 to 400 µm, and the surface area of exposed skin within the diffusion cells was 3.14 cm^2. The receptor fluid consisted of phosphate-buffered saline, newborn calf serum, amphotericin B, penicillin, and streptomycin. Topical application involved an exposure period of 24 h. The results of this study provided a high-end estimate of skin absorption (worst case) of 50.09% (± 5.26).

A single dose of [^{14}C]-Salicylic Acid was applied to dermatomed human skin (from cadaver) in vitro using Franz diffusion cell. The test substance (dose = 5 µl) was applied to skin under non-occlusion as well as various occlusive time periods (1 h, 4 h, and 8 h).[4] The receptor fluid consisted of phosphate-buffered saline. After 24 h, skin samples were removed and skin surface sites were tape-striped 10 times. Radioactivity in the epidermis and dermis represented the dose absorbed in the skin. The total amount of [^{14}C]-Salicylic Acid absorbed in the skin (epidermis + dermis + receptor fluid) as a percent of the applied dose increased from 4.5% under non-occlusion to 50.5% when under 8 h of occlusion.

Animal

Salicylic Acid, Methyl Salicylate,
Sodium Salicylate, TEA Salicylate

In vivo percutaneous absorption data on rabbits (Salicylic Acid, Sodium Salicylate, and TEA Salicylate), guinea pigs (Salicylic Acid), rats (Methyl Salicylate, Salicylic Acid, and TEA Salicylate), dogs (TEA Salicylate), pigs (TEA Salicylate), and monkeys (Salicylic Acid), are available.[1] These data describe the following percutaneous absorption patterns: rate of penetration is proportional to concentration applied; absorption is dependent on the vehicle (e.g., ethanol > water); absorption varies as a function of pH; and absorption is greater through damaged skin when compared to normal skin. Approximately 10% of applied salicylates can remain in the skin.

Methyl Salicylate

Twenty-seven 10-week-old Yorkshire-Landrace cross barrow pigs were used in a skin absorption study.[37] A circular plastic cup with two holes pierced through it to accept an 18-gauge needle was positioned over a piece of gauze cloth that was cut to a diameter slightly smaller than the cup, and that was placed over the skin. Four sites were challenged including ear, epigastrium, perineum, and inguinal crease with total area of exposure of 49.3, 132.4, 49.3 and 88.2 cm^2, respectively. Neat Methyl Salicylate was introduced into the cup through one of the holes at volumes of 848 µL for the ear, 2544 µl for the epigastrium, 848 µl for the perineum and 1696 µl for the inguinal crease. Arterial blood samples were taken every 10 min for the first 60 min and then every 15 min up to 360 min. The average dose absorbed through the skin at the ear region after 6 h was 11 µg/cm^2; at the perineum regions, the average dose absorbed was 8 µg/cm^2, and, through the epigastrium and inguinal crease regions, the average dose absorbed was 3 µg/cm^2. The initial flux (permeation rate) of Salicylic Acid through the skin after application of neat Methyl Salicylate was 0.063 µg/cm^2/min at the ear region, 0.025 µg/cm^2/min at the epigastrium region, 0.044µg/cm^2/min at the perineum region and 0.012 µg/cm^2/min at the inguinal crease region.

Human

Salicylic Acid, Ethylhexyl Salicylate,
and Sodium Salicylate

Data describing the penetration of salicylates through human skin are available.[1] These data describe the following percutaneous absorption patterns: rate of penetration is proportional to concentration applied; absorption is dependent on the vehicle (e.g., ethanol > water); absorption varies as a function of pH; and absorption is greater through damaged skin when compared to normal skin. Approximately 10% of applied salicylates can remain in the skin.

Ethylhexyl Salicylate

The skin penetration of two Ethylhexyl Salicylate sunscreen formulations was evaluated in a study involving 6 subjects.[31] Penetration was determined by tape-stripping. Each sunscreen formulation was applied to 2 cm x 2 cm areas on the volar side of the forearm. At 30 minutes post-application, the remaining product formulation was removed from the skin using cotton swabs, and the skin was tape-stripped 16 times. The mean value (6 subjects) for penetration of Ethylhexyl Salicylate in oil-in-water emulsion gel into the stratum corneum was 28.4 ± 6.6 μg/cm^2, which corresponds to penetration of 25.6% of the applied dose into the stratum corneum. The mean value for penetration of Ethylhexyl Salicylate in petrolatum was 10.1 ± 3.5 μg/cm^2, indicating that 11% of the applied dose penetrated into the stratum corneum. The authors noted that the concentration of Ethylhexyl Salicylate in the upper part of the stratum corneum was significantly higher (p-value not stated) after application of the emulsion gel formulation than after application of the petrolatum formulation. In the deeper parts of the stratum corneum, the concentration of Ethylhexyl Salicylate delivered form the emulsion gel formulation was significantly lower (p value not stated) than that achieved with the petrolatum formulation.

The systemic absorption of a sunscreen lotion, with the following composition, after dermal application was evaluated using 9 healthy volunteers: Ethylhexyl Salicylate (5% w/v), oxybenzone (6% w/v), octocrylene (7% w/v), and octyl methoxycinnamate (7.5% w/v).[38] All of these chemicals were identified as sun screening agents. The subjects were instructed to apply the product to the entire surface of their forearms generously in accordance with their normal sun protection behavior. In practice, 13.0 (± 1.0) g [mean and standard error of the mean values, respectively] of sunscreen product was applied to a surface area of 1051 (± 60.8) cm^2. The application density of the product was 12.4 mg/cm^2. The formulation remained unoccluded for 12 h prior to removal with soap and water. Urine samples were collected before product application and at 48 h post-application. Over the period of application, only 1 to 2% of the sunscreen in the applied product was absorbed and subsequently excreted in the urine. Urine samples were analyzed using high performance liquid chromatography. Data comparing the absorption of each ingredient were not provided.

Methyl Salicylate

The systemic exposure to Methyl Salicylate following the application of a number of adhesive patches (each containing 74.88 mg Methyl Salicylate) to the skin of 8 human subjects was evaluated.[39] The patches remained in place for 8 h. Blood samples were obtained for up to 12 h after placement of the patches. Exposure was quantified by determining the plasma concentration time profiles of the substance as a function of exposure to 2 patches (normal doses), 4 patches, or 8 patches (very high doses). Data were presented as a plot of the average plasma concentration-time data as a function of dose. For the 2-patch application, the average maximum plasma concentration (C_{max}) value for Methyl Salicylate was 8.6 ± 3.8 ng/mL (range: 4.0 - 12.7 ng/mL). For the 4-patch application, the average C_{max} for Methyl Salicylate was 16.8 ± 6.8 ng/mL (range: 8.9 - 25.7 ng/mL). For the 8-patch application, the average C_{max} was 29.5 ± 10.5 ng/mL (range: 15.8 - 45.9 ng/mL). The authors noted that although it was not possible to determine the absolute dermal bioavailability of Methyl Salicylate, there appeared to be relatively low systemic exposure, even when an unrealistically large number of patches were applied for an unusually long time.

Computational

Ethylhexyl Salicylate, Hexyl Salicylate, and Methyl Salicylate

A mathematical method was used to estimate total body absorption of Ethylhexyl Salicylate, Hexyl Salicylate, and Methyl Salicylate. Rate constants were calculated from the relevant physicochemical properties.[40] The applied dose of each ingredient used in the simulation was 40 μg/cm^2 based on the FDA recommendation (200 mg of product per 100 cm^2 of skin) and a value of 2% active ingredient in the formulation. The release rate from the formulation was fixed at 1 μm/cm^2/h. The simulations were conducted on a 12-h time scale. The estimated total body absorption values (skin area) for each ingredient were: 0.022 μg/1.4 m^2 at 2 h, 0.50 μg/1.4 m^2 at 6 h, and 3.3 μg/1.4 m^2 at 12 h (Ethylhexyl Salicylate); 0.18 μg/1.4 m^2 at 2 h, 4.1 μg/1.4 m^2 at 6 h, and 27 μg/1.4 m^2 at 12 h (Hexyl Salicylate); and 91 μg/1.4 m^2 at 2 h, 2000 μg/1.4 m^2 at 6 h, and 13,000 μg/1.4 m^2 at 12 h (Methyl Salicylate). It should be noted that 1.4 m^2 ≈ 75% of the total average area of human skin.

Penetration Enhancement

Salicylic Acid

Salicylic Acid is reported to enhance percutaneous penetration of vitamin A, ammoniated mercury, and triamcinolone acetonide, but not methyl nicotinate, (which itself rapidly penetrates the skin), hydrocortisone, diflucortolone-21-valerate, or cyclosporine.[1]

Absorption, Distribution, Metabolism, and Excretion

In Vitro

Placental

The placental absorption of Salicylic Acid was studied in vitro in an effort to devise a pharmacokinetic model of human placental absorption.[41] Salicylic Acid (8 µg/ml) was dissolved into the maternal perfusate on the maternal side of the placenta. Maternal- and fetal-side effluents were sampled for 60 min. Study results indicated the potential for Salicylic Acid to cross the placenta.

Animal

Dermal

Methyl Salicylate

The in vivo absorption of a formulation containing 20% Methyl Salicylate was studied using groups of 3 male Wistar rats.[32] The formulation (1 g) was applied to a 9.6 cm^2 area of abdominal skin, and a blood sample was removed from the tail vein at 0.5, 1, 2, 4, and 6 h thereafter. After blood removal at each time point, the animals (3 per time point) were killed, the formulation was removed from the skin, and tissue samples (skin, subcutaneous tissue, superficial muscle, deep muscle, and fat) were excised. The levels of unhydrolyzed Methyl Salicylate in tissues below the treated site were low, i.e., only 2 to 3 µg/ml throughout the study period. The highest concentrations were observed in the dermal and subcutaneous sites in the first hour of application. At 0.5 to 1 h after application of the formulation, there was a significant increase in the concentration of total salicylate in contralateral dermal tissue, corresponding to 4 to 5 times above the circulating systemic plasma levels. At 2 h, the dermal levels were below the observed plasma salicylate concentration. The presence of unhydrolyzed Methyl Salicylate was only observed at the 0.5 h time point. The fraction of Methyl Salicylate observed in the tissues as a proportion of total salicylate varied from 0 to 0.26. The results of this study indicate that tissue and plasma concentrations of salicylate after the application of Methyl Salicylate increased rapidly within the first hour of application.

Oral

Salicylates

Extensive data from oral delivery studies in animals are available.[1] Metabolism by hepatic microsomal enzyme systems conjugates salicylates to glycine, forms glucuronides, or oxidizes them to hydroxybenzoic acids.

Human

Oral

Salicylates

Extensive data from oral delivery human studies are available.[1] Metabolism by hepatic microsomal enzyme systems conjugates salicylates to glycine, forms glucuronides, or oxidizes them to hydroxybenzoic acids.

Methyl Salicylate

Reportedly, after oral ingestion, Methyl Salicylate is readily metabolized to Salicylic Acid.[28] No further details were provided.

Four (1 male/3 female) adult human volunteers participated in a study that was conducted as an open label, 4-way crossover design with randomized treatment order.[42] The subjects ingested 6.7 and 20 g of a Methyl Salicylate-containing cream (commercial 15% cream containing 900 or 2700 mg salicylate). Plasma was collected at 0, 20, 40, 60, 120, 240, 480,

720, and 1440 min for the determination of salicylate concentrations using the Abbott TDx® fluorescence polarization immunoassay. The times to reach maximum salicylate concentration (T_{max}) and the peak plasma salicylate concentration (Cp_{max}) were determined. The T_{max} for the low-dose cream (900 mg salicylate) was 2.4 h (1.5 - 4 h), and the Cp_{max} was 42 mg/l (36–51 mg/l). The T_{max} for the high-dose cream was 7 h (4 - 12 h), and the Cp_{max} was 145 mg/l (120 - 201 mg/l). As a part of the same experiment, four fasting adults ingested 1 ml of wintergreen oil (which is primarily Methyl Salicylate; 14.2 mg/kg mean). Plasma was collected for salicylate determination at 0, 20, 40, 60, 120, 240, 480, 720, and 1440 min. Time to reach maximum concentration was 2.4 h with the maximum concentration of 70 mg/l. The 4 subjects were also instructed to hold 5 g of the cream in the buccal cavity for 1 minute and then expectorate. No plasma salicylate was detected after the buccal treatment phase.

Salicylic Acid

After oral administration to humans, Salicylic Acid is found in unionized form in the stomach.[4] It is well absorbed from the gastrointestinal tract and is rapidly distributed throughout the extracellular fluid and most tissues. High concentrations (not specified) are found in the liver and kidneys and 50% to 80% of Salicylic Acid in the plasma is bound to albumin and other proteins.

TOXICOLOGICAL STUDIES

Acute Toxicity Studies

Dermal

Butyloctyl Salicylate, Methyl Salicylate, Salicylic Acid, and Tridecyl Salicylate

Acute dermal LD_{50}s of > 2 g/kg were reported when rats were exposed dermally to Butyloctyl Salicylate, Methyl Salicylate, Salicylic Acid, and Tridecyl Salicylate.[1]

Ethylhexyl Salicylate

Undiluted Ethylhexyl Salicylate was applied (under occlusion) to intact or abraded skin of 4 rabbits for 24 h.[7] The animals were observed for mortality and/or clinical signs for a 14-day period. No clinical signs were observed. The dermal LD_{50} in rabbits exceeded 5.0 g/kg.

Hexyl Salicylate

Ten rabbits received a single dermal application of neat Hexyl Salicylate at 5.0 g/kg.[8] The rabbits were observed for mortality and clinical symptoms. No clinical signs were observed. The acute dermal LD_{50} in rabbits exceeded 5.0 g/kg based on 0/10 deaths at that dose.

Methyl Salicylate

A single dermal application of neat Methyl Salicylate at 5 g/kg was applied to 4 rabbits (strain not stated) for 24 h under occlusion.[7] Animals were observed for a 14-day period. None of the animals died, and no clinical signs were observed. The dermal LD_{50} in rabbits exceeded 5 g/kg.

Salicylic Acid

In a study involving 3 New Zealand White rabbits, Salicylic Acid (0.5 g, moistened with 0.5 ml water) was applied, under a semi-occlusive patch, for 4 h to a 6.25 cm^2 area of skin. [4] The animals were observed for up to 14 days after application. None of the animals died, and there were no clinical signs of systemic toxicity during the study.

Sodium Salicylate

The acute dermal toxicity of Sodium Salicylate was evaluated using Wistar rats (5 males, 5 females).[43] The test substance (in 0.2 ml distilled water; dose = 2 g/kg) was applied to a dorsal area (~ 10% of body surface area) on the trunk, and the site was covered with an occlusive patch for 24 h. Dosing was followed by a 14-day observation period, after which the animals were killed. None of the animals died during the observation period. Clinical signs were described as normal

throughout the study, and the results of both external and internal gross pathological examinations were not indicative of any pathological abnormality. The acute dermal LD_{50} was considered to be > 2 g/kg.

Oral

Butyloctyl Salicylate, Ethylhexyl Salicylate, Isodecyl Salicylate, Methyl Salicylate, Salicylic Acid, Sodium Salicylate, and Tridecyl Salicylate

The following acute oral toxicity data for Salicylic Acid and salicylates have been reported in studies involving rats: Butyloctyl Salicylate (LD_{50} > 5 g/kg), Ethylhexyl Salicylate (LD_{50} > 2 g/kg), Isodecyl Salicylate (no toxicity at levels as high as 4.83 g/kg), Methyl Salicylate (LD_{50} between 0.887 g/kg and 1.25 g/kg), Salicylic Acid (LD_{50} ranging from 0.891 g/kg to 1.58 g/kg), Sodium Salicylate (LD_{50} between 0.9 g/kg and 1.7 g/kg); and Tridecyl Salicylate (LD_{50} > 1.98 g/kg).[1] *Values for acute oral toxicity in other species are consistent with these values.*

Ethylhexyl Salicylate

In an acute oral toxicity study involving 10 rats (strain not stated) dosed with Ethylhexyl Salicylate, the animals were observed for mortalities and/or clinical signs for 14 days post-dosing.[7] It was concluded that the acute oral LD_{50} exceeded 5.0 g/kg, based on one animal death at that dose on day 6 of the study. No clinical reactions were observed.

Hexyl Salicylate

The acute oral toxicity of Hexyl Salicylate was evaluated in a study involving 10 rats.[8] The rats were observed for mortalities and/or systemic effects for 14 day after dosing. Urinary incontinence was observed at 24 h. It was concluded that the LD_{50} exceeded 5.0 g/kg, based on one animal death at that dose on day 4 of the study.

Methyl Salicylate

The acute oral toxicity of Methyl Salicylate was determined in ddY male mice (10/dose).[44,9] Methyl Salicylate was administered at dose levels of 1.0, 1.2, 1.3, 1.5, or 1.7 g/kg. Mice were observed for a 7-day period. One animal died at 1.0 g/kg; 2/10 died at 1.2 g/kg; 4/10 died at 1.3 and 1.5 g/kg; and 9/10 died at 1.7 g/kg. Most animal deaths occurred on day 1. The LD_{50} was calculated to be 1.39 g/kg (95% CI 1.25 - 1.54 g/kg).

Methyl Salicylate was evaluated as a part of a study investigating the development of acute myocardiopathy in dogs.[45] Healthy mongrel dogs were lightly anesthetized with pentobarbital sodium. Methyl Salicylate was intragastrically administered at a dose of 0.7 g/kg. After 4 - 5 h, animals either died or were sacrificed. Increases in arterial concentrations of plasma salicylate, potassium and lactate were seen and a period of respiratory alkalosis was initially observed followed by metabolic acidosis after three hours. Microscopy studies revealed abnormalities in the mitochondria, swelling of cardiac muscles with separation of myofibrils and bulging of sarcolemma.

Salicylic Acid

A single dose of an aqueous solution of Salicylic Acid (in gum Arabic) was administered to 10 Wistar rats.[4] LD_{50} values in the range of 0.5 to 2 g/kg were reported.

Sodium Salicylate

The acute oral toxicity of Sodium Salicylate, in the diet, was evaluated using 6 Wistar rats.[43] Three animals (male/female) received a dose of 0.2 g/kg and another 3 animals (males) received a dose of 2 g/kg. All of the male rats dosed with 2 g/kg died, but there were no deaths at the lower dose. The mean lethal dose of Sodium Salicylate in male and female Wistar rats was considered to be > 0.2 g/kg to ≤ 2 g/kg.

Inhalation

Methyl Salicylate

The inhalation exposure of mice and rats to Methyl Salicylate (heated to 80°C) for an unknown duration did not cause death (LC_{50} > 400 mg/m^3).[1]

Salicylic Acid

The acute inhalation toxicity of Salicylic Acid was evaluated using 6 male rats (strain not stated).[46] The animals were exposed for 1 h to Salicylic Acid as a dust (0.9 mg/l, in inhalation chamber). Data on particle size distribution were not reported. However, the authors noted that data from typical production batches indicate that less than 5% of particles are in the respirable range (mass mean aerodynamic diameter [MMAD] = < 4 µm). Median MMAD is in the range of 35 to 50 µm, with up to 20% non-inhalable particles of > 100 µm. Exposure was followed by a 14-day observation period and necropsy. The only signs observed were: salivation, nasal discharge, and lacrimation. No significant gross pathological changes were reported. The 1 h LC_{50} was > 0.9 mg/l.

Short-Term Toxicity Studies

Dermal

Salicylic Acid

A 14-day dermal toxicity study was performed using groups of 6 (3 males, 3 females) New Zealand White rabbits.[5] The concentrations of Salicylic Acid (in 8% propylene glycol butyl ether in ethanol) tested were 2%, 10%, and 25% (corresponding to 40, 200, and 500 mg/kg/day, respectively). These concentrations were administered topically at a dose of 2 g/kg/day. The control group received topical applications of vehicle only. None of the animals died. Atonia was predominantly observed in the 10% and 25% Salicylic Acid groups. No remarkable changes in body weight were observed during the study. Results relating to visible changes in the skin are included in the section on Skin Irritation. Other than the observations relating to the skin, there were no visible abnormalities at necropsy.

Oral

Butyloctyl Salicylate

The short-term oral toxicity of a Butyloctyl Salicylate trade name material was evaluated according to the Organization for Economic Cooperation and Development (OECD) Test Guideline (TG) 407 using 3 groups of 5 albino Sprague-Dawley derived [Crl: CD BR] rats.[47] The 3 groups received the test substance (in corn oil, by gavage) at doses of 15, 150, and 1000 mg/kg/day, respectively, for 28 days. The animals were killed during week 4 (day 29). Mean prothrombin and activated partial thromboplastin times were increased in the 1000 mg/kg/day group. There were no test substance-related changes in the following in any dose group: body weights, food consumption, motor activity levels, functional observation batteries, organ weights, or macroscopic and microscopic pathology evaluations. The no-observed-effect level (NOEL) was considered to be 150 mg/kg/day dose.

Methyl Salicylate

Groups of 2 dogs (breed not stated) were dosed orally with Methyl Salicylate (in capsule form) at doses up to 1200 mg/kg daily (6 days per week) for up to 59 days.[1] Marked fatty changes in the liver were observed in both animals at the highest dose. No adverse effects were observed at doses of 50 to 250 mg/kg. Groups of 12 male and female rats (strain not stated) were fed diets containing methyl Salicylate at concentrations up to 12,000 ppm (i.e., 12,000 mg/kg) for 7 weeks. Bone lesions were observed at the highest dietary concentration only. In a shorter-duration study, that involved the feeding of 10 male rats with 12,000 ppm Methyl Salicylate in the diet for up to 5 days, bone lesions were not observed. However, when groups of 10 male and 10 female rats (strain not stated) were fed 12,000 ppm or 20,000 ppm Methyl Salicylate for 8 weeks, bone lesions were observed in all animals of both groups. Also, when groups of 5 male rats were fed 20,000 ppm Methyl Salicylate and a protein diet (75% basic feed and 25% casein) with water for 7 weeks, an increase in cancellous bone was reported. This finding was not reported in the group that was fed the same concentration of Methyl Salicylate plus the protein diet and 40% dextrose (dextrose, but no water). In a study that was longer in duration than the preceding 4 studies, groups of 10 male and 10 female Sprague-Dawley rats were fed a fat-enriched diet containing up to 2% Methyl Salicylate for 11 weeks. At the highest dietary concentration and the 1.2% concentration, but not at lower concentrations, bone lesions were observed at week 2; microscopic changes were observed at weeks 2 and 8 in these 2 groups, respectively. In another 11-week study, 5 male and 5 female rats were fed 12,000 ppm Methyl Salicylate and bone lesions were observed at 4 weeks (earliest time at which x-rays were taken). Decreased body weight was also observed in these studies.

The oral toxicity of Methyl Salicylate was determined in male and female CD-1 mice (8/sex/dose).[48] Methyl Salicylate was administered in corn oil by gavage once daily for 14 days at dose levels of 0.05, 0.1, 0.25, 0.50, and 1 g/kg. Two females died at 0.05 g/kg; 1female and 1 male died at 0.10 g/kg; and 2 females and 3 males died at 1 g/kg. Clinical signs observed prior to death were piloerection and dehydration. A probit analysis of the lethality data for the sexes combined projected an acute LD_{50} of 1.44 g/kg/day.

Salicylic Acid

In groups of rats dosed orally with Salicylic Acid (in distilled water, 500 mg/kg/day) for 3 days, hepatic and plasma parameters were determined 18 h after the last dose.[1] *When compared to controls, a significant increase in each of the following was reported: aniline hydroxylase, glutathione, plasma aspartate aminotransferase (AST), and plasma alanine aminotransferase (ALT) activities, and a significant decrease in glucose-6-phosphatase activity.*

Sodium Salicylate

Sodium Salicylate short-term oral exposures are linked with reduced growth and feed consumption, clear kidney damage, and some liver damage.[1] *In these studies, rats received up to 21,020 ppm (i.e., 21,020 mg/kg) Sodium Salicylate in the diet for 11 weeks or up to 600 mg/kg of 10% aqueous Sodium Salicylate for 4 to 21 days. In the 21,020-ppm study, a positive increase in cancellous bone was observed. In one of the studies, in which groups of Fischer 344 rats were dosed orally with aqueous Sodium Salicylate for 4 weeks, the 28-day LD_{50} was 646.5 mg/kg. Liver and kidney necrosis was observed in dogs that received 300 mg/kg of 10% aqueous Sodium Salicylate for 2 weeks. A group of 6 male and 6 female Sprague-Dawley rats was fed a 5% hydrogenated fat-enriched diet containing 2.1% Sodium Salicylate for 12 weeks. Mortality was 100% at week 11, and bone lesions were observed. Groups of 5 male Sprague-Dawley rats were fed a 5% fat enriched diet containing 0.7% or 2.1% Sodium Salicylate for 12 weeks. Mortality was 100% in the low-dose group at week 7 and in the high-dose group at week 2. Bone lesions were observed with 2.1% Sodium Salicylate.*

Inhalation

Amyl Salicylate

The short-term inhalation toxicity of a fragrance mixture containing 5.8% Amyl Salicylate was evaluated using groups of female CD rats or female Syrian hamsters.[49] The animals were exposed (whole body inhalation, in chamber) to the mixtures at 5 mg/m^3 (20 rats) or 9 mg/m^3 (12 rats and 12 hamsters), 5 days per week (4 h per day) for 6 weeks (26 exposures total). The doses used generally represented a 10- to 100-fold exaggeration of levels expected to be achieved during typical use by consumers. Particle sizes ranged from 0.5 to 7.5 µm. There were no exposure-related, toxicologically significant effects on the following: animal survival, behavior, body weights or weight gains, organ weights, or in hematology, clinical chemistry, or urinalysis parameters. Additionally, no test substance-related gross pathological or histopathological findings were observed.

Methyl Salicylate

In a study involving 4 female Alderley Park rats, no toxicity was observed after inhalation of Methyl Salicylate in a series of 20 exposures of 7 h each at 0.7 g/m^3.[1] *The organs appeared normal at necropsy.*

Subchronic Toxicity Studies

Dermal

Methyl Salicylate

Subchronic dermal exposures to Methyl Salicylate were associated with kidney damage.[1] *Groups of 3 rabbits were dosed dermally with synthetic Methyl Salicylate (doses up to 4 ml/kg) five days per week for up to 96 days.*

Salicylic Acid

Two 91-day studies involving New Zealand White rabbits (number of animals used per study not stated) were performed to evaluate the cutaneous and systemic toxicity of 2 cleansing formulations containing 0.5% Salicylic Acid.[5] The undiluted product or the product diluted to a concentration of 50% w/v in distilled water (effective Salicylic Acid concentration = 0.25%) was applied. The test article (dose volume of 2 ml/kg; dose = 10 mg/kg) was applied (method not stated) to intact skin 5 times per week (7 h per day). Control rabbits were treated with distilled water. Both gross and histopathological examinations were performed. Results relating to skin reactions are included in the Skin Irritation section of this report. None of the animals died, and there were no statistically significant differences in mean body weight or organ weights during the study. Clinical evaluations as well as clinical chemistry, hematology, and histopathological examinations provided no evidence of systemic toxicity.

Another 91-day study involving New Zealand White rabbits (number not stated) was performed to evaluate the systemic and cutaneous toxicity of cleansing formulations containing 0.5% to 6% Salicylic Acid in propylene glycol butyl ether/ethanol (vehicle).[5] This concentration range corresponded to topical doses of 10, 20, 40, or 120 mg/kg Salicylic Acid. Untreated and vehicle control groups were included in the study. The products tested were applied (method not stated) for 7 h to intact skin (once daily; dose volume = 2 ml/kg) 5 days per week. Five animals were killed after 28 days, and the remaining rabbits were killed at day 91. Serum salicylate (concentration not stated) was observed in all groups at 1 h post-dosing. None of the animals died during the study, and there were no test substance-related changes in appearance, behavior, body weights, or ophthalmoscopic examinations. Slight to moderate atonia was also observed at the application site. There were no treatment-related effects on body weight gain or changes in body weight. Regarding hematological, biochemical, or urological parameters, there were no test substance-related toxicological findings. At histopathologic examination (day 91), a low incidence of trace to mild myocardial degeneration was observed in all dose groups and in the vehicle control group. However, there was no dose-response relationship for this finding. Results relating to skin irritation are included in the Skin Irritation section of this report.

Oral

Isodecyl Salicylate

No toxicity is seen with subchronic oral exposure to Isodecyl Salicylate.[1] *Ten male and 10 female Wistar albino rats were fed 0.5% (~ 500 mg/kg/day) Isodecyl Salicylate in a basal diet for 15 weeks.*

Methyl Salicylate

Subchronic oral exposure to Methyl Salicylate results in reduced weight gain and bone lesions, which disappear when Methyl Salicylate is co-administered with calcium carbonate.[1] *All of the feeding studies involved rats, and the longest duration study involved groups of 20 Osborne-Mendel rats fed up to 1% synthetic Methyl Salicylate in the diet for 17 weeks.*

Sodium Salicylate

The neurotoxic potential of 138 to 550 mg/kg Sodium Salicylate was determined using groups of 9 to 10 Fischer 344 rats dosed 5 days per week for 15 weeks.[1] *The LD_{50} during 15 weeks of dosing was estimated to be 366.5 mg/kg; a dose-related decrease in hindlimb grip strength was noted.*

Tridecyl Salicylate

Ten male and 10 female Wistar rats were fed ~500 mg/kg/day Tridecyl Salicylate in a basal diet for 15 weeks.[1] *A control group of 10 males and 10 females was given untreated feed. There was no evidence of treatment-related effects. Oral administration of ~ 500 mg/kg/day Tridecyl Salicylate did not produce a significant toxic effect.*

Inhalation

Amyl Salicylate

The subchronic inhalation toxicity of a fragrance mixture containing 4% Amyl Salicylate was evaluated using groups of female CD rats or female Syrian hamsters.[49] The animals were exposed (whole body inhalation, in chamber) to the mixtures at 5 mg/m^3 (20 rats) or 9 mg/m^3 (12 rats and 12 hamsters), 5 days per week (4 h per day) for 13 weeks (62 to 67 exposures total). The doses used generally represented a 10- to 100-fold exaggeration of levels expected to be achieved during typical use by consumers. Particle sizes ranged from 0.5 to 7.5 µm. There were no exposure-related, toxicologically significant effects on the following: animal survival, behavior, body weights or weight gains, organ weights, or in hematology, clinical chemistry, or urinalysis parameters. Additionally, no test substance-related gross pathological or histopathological findings were observed.

Methyl Salicylate

Male white rats (number per group not specified) were exposed to 1.2, 8, or 40 mg/m^3 Methyl Salicylate for 4 months (4 h/day).[1] *The highest concentration caused changes in nervous system function. Also, pulmonary focal hemorrhages and hyperplasia were observed in the peribronchial lymphoid tissue. Focal hemorrhages in the kidneys were observed.*

Chronic Toxicity Studies

Oral

Methyl Salicylate

In the study with the highest administered dose, groups of 5 male and 5 female rats were fed a diet containing 2000, 3550, 6300, 11,250, or 20,000 ppm Methyl Salicylate for 30 weeks.[1] During weeks 1 and 2, Methyl Salicylate was given at 50%, and, during weeks 3 and 4, it was given at 75% of the final dose. At week 10, animals of the 11,250 ppm and 20,000 ppm groups had positive increased bone density in the femur and tibia. The largest 2-year feeding studies, involved groups of 50 rats fed up to 2% Methyl Salicylate in the diet. One of the 2 studies had no gross or microscopic findings. In the other study, statistically significant growth inhibition was observed in animals of the 1% and 2% dietary groups. Also, in the 1% dietary group, relative organ-to-body weight ratios for the testes (males) and for the heart and kidneys (females) were significantly increased. Gross lesions of the pituitary gland were observed in 10 animals of the 0.5% dietary group, compared to 4 animals in the control group. In the 2% dietary group, pneumonia was observed in 29 of the 50 animals. When groups of Beagle dogs received oral doses of Methyl Salicylate up to 350 mg/kg for 2 years (6 days per week), animals of the 150 and 350 mg/kg groups had retarded growth and enlarged livers. When Beagle dogs received oral doses of Methyl Salicylate up to 800 mg/kg/day for 6.6 to 7.5 months, an increase in liver and kidney weight was observed in treated animals, but the 150 and 300 mg/kg doses did not induce lesions or other deleterious alterations.

DEVELOPMENTAL AND REPRODUCTIVE TOXICITY STUDIES

In Vitro

Salicylic Acid

The effect of Salicylic Acid on human spermatozoa was determined after incubation with 50, 100, or 200 mg/L salicylate for 2 to 48 h.[1] A dose response effect was observed, with significant inhibition of motility at all time points.

Post-implantation day 11 rat embryos were cultured for 24 h with 10, 100, or 1000 µg/ml Salicylic Acid.[50] The growth and development of each embryo was evaluated and compared with control embryos for the presence of any malformations. Salicylic Acid decreased all growth and developmental parameters in a concentration-dependent manner, when compared with controls. However, exposure to Salicylic Acid at 10 µg/ml culture did not show any significant effect on embryonic growth and development. Parallel to this, flow cytometric analysis (cell cycle and annexin V binding) and DNA fragmentation assay were carried out followed via quantitation by 3′-OH labeling of cultured rat embryos to evaluate the role of apoptosis in bringing about Salicylic Acid-induced teratogenesis. All results were found to be dose-dependent and an increase in apoptosis in embryonic tissues may be related to the increased risk of congenital malformations. The data suggested that apoptosis might be involved in mediating teratogenesis of Salicylic Acid in vitro.

Salicylic Acid and Sodium Salicylate

The effects of Salicylic Acid and Sodium Salicylate on early organogenesis and the interaction of these chemicals with free radicals was investigated.[51] Post-implantation Wistar rat embryos were cultured in vitro from day 9.5 of gestation for 48 h; each test substance was added to whole rat serum at concentrations between 0.1 and 0.6 mg/ml. Also, each test substance (0.3 mg/ml) was added to the culture media in the presence of superoxide dismutase (30 enzyme units (U)/ml) or glutathione (0.5 µmol/ml). The growth and development of embryos was compared, and each embryo was evaluated for the presence of malformations. When compared to the growth of control embryos, both chemicals decreased all growth and developmental parameters in a concentration-responsive manner. There was also a concentration-related increase in overall dysmorphology, including the following: hematoma in the yolk sac and neural system, open neural tube, abnormal tail torsion, and the absence of forelimb bud. When superoxide dismutase was added in the presence of Salicylic Acid, the incidence of malformations was decreased. However, the addition of superoxide dismutase did not affect the growth and developmental parameters of Salicylic Acid and Sodium Salicylate. The addition of glutathione significantly decreased the incidence of the malformations that were observed in the presence of Salicylic Acid. The authors noted that the effects of salicylates might involve free oxygen radicals by the non-enzymatic production of the highly teratogenic metabolites 2,3-dihydroxybenzoic acid and 2,5-dihydroxybenzoic acid. Furthermore, they noted that an enhanced production of these metabolites in embryonic tissues may be directly related to the increased risk of congenital malformations.

Animal

Dermal

Methyl Salicylate

Methyl Salicylate was applied (at 7 days 9 h of gestation) to dorsal skin of timed-pregnant LVG hamsters (number not stated), at doses of 350 and 525 mg/100 g.[1] *Few embryos from the high-dose group survived beyond 12 days of gestation, but, of the 19 litters produced in this group, there were 53% neural tube defects. Of the 6 litters produced in the lower dose group, 6% of the fetuses had neural tube defects. A peak salicylate level of 50 mg/100 ml was obtained 5 to 6 h after topical application of 350 mg/100 g and a peak of 120 mg/100 g with the 525 mg/100g topical treatment level. Thus, dermal exposure to Methyl Salicylate is associated with reproductive and developmental toxicity as a function of blood levels reached as a result of exposure.*

Oral

Ethylhexyl Salicylate

Because the following 2 study summaries (from different sources) involve the same strain of rats and doses, and 1 maternal death in the highest dose group is reported in both, it is possible that results from the same study are being reported. However, because a NOAEL is being reported in one study summary, and a NOEL in the other, and the dose corresponding to each is not the same, the results are being presented separately.

The developmental toxicity of an Ethylhexyl Salicylate trade name material was evaluated using groups of 11 RccHanTM: WIST(SPF) male and female rats.[47] The test substance (in corn oil) was administered by gavage to 3 groups at doses of 25, 80, and 250 mg/kg/day, respectively. The exposure (once daily exposure) periods for males and females were 28 days and ~ 7 weeks, respectively. Males were treated over a 14-day pre-pairing period and during the pairing period up to 1 day before necropsy. Females were treated throughout the pre-pairing, pairing, gestation and lactation periods up to day 3 post-partum. Maternal toxic effects were described as slight, but non-significant, changes in weight gain at a dose of 250 mg/kg/day. Because of the reduced absolute body weights of pups from the 250 mg/kg/day dose group, the NOEL for developmental toxicity was considered to be 80 mg/kg/day. No test substance-related microscopic findings were observed in pups from any of the dose groups.

In another developmental toxicity study that was performed according to the preceding test procedure (same doses, number of animals per group, and species), 1 maternal death (in highest dose group) that was unrelated to dosing with the same Ethylhexyl Salicylate trade name material was reported.[30] There were no further reports of adverse effects in males or females that were mated. In the 80 and 250 mg/kg/day dose groups, a reduction in the gestation index as well as an increased incidence of post-implantation loss (i.e., reduced litter sizes) were observed. These findings were dose-related as well as statistically significant, and were deemed test substance-related. No test substance-related effects were observed during the first litter check or during lactation in any of the dose groups. Dosing with the test substance also had no effect on pup sex ratio. A test substance-related effect on pup body weight (reduction in absolute body weight) was observed in the highest dose group. There were no test substance related effects (on body weight or body weight gain) in the 2 lower dose groups. Furthermore, no test substance-related macroscopic findings in pups were observed in any of the dose groups. Based on observations of increased post-implantation loss, reduction in the gestation index, and lower litter size, the no-observed-adverse-effect-level (NOAEL) for developmental toxicity was determined to be 25 mg/kg/day.

Methyl Salicylate

Methyl Salicylate was delivered by oral intubation (1.75 g/kg) to timed-pregnant LVG hamsters at 7 days 9 h of gestation.[1] *Blood levels reached a peak at of 125 mg/100 ml at approximately 2 h after oral dosing. Of 35 litters (number of fetuses per litter not given) in the treatment group, 72% of the fetuses had neural tube defects. Groups of 24 to 27 rats were fed 4000 ppm or 6000 ppm Methyl Salicylate in a test diet containing calcium carbonate for 60 days prior to mating and through weaning at day 20 or 21. This procedure was repeated. Abnormalities were not observed in offspring. Neonate survival at weaning was greater in the test group than in the control group. Groups of F_0 generation mice (25/sex/group) and F_{1b} generation mice (30 males and 30 females/group) received 0.25% or 0.5% Methyl Salicylate in feed for 30 days prior to mating. The results are only from females in each generation that mated twice. There was no evidence of gross abnormalities in in any litter. All surviving neonates appeared normal, and no reproductive abnormalities were observed. Another experiment in the same study involved the same numbers of F_0 and F_{1b} animals (in this experiment, Wistar rats used) and the same concentrations of Methyl Salicylate administered in feed. The protocol was the same, except for the 60-day feeding period prior to mating. Gross abnormalities were not observed in any litter and all surviving neonates appeared normal. Mating performance and reproduction and viability indices were decreased, and the number of deaths between birth and day 5 were increased in the 0.5% group. Litter size was decreased in both test groups. Groups of F_0 generation*

Osborne-Mendel rats (10/sex/group) received 500, 1500, 3000, or 5000 ppm Methyl Salicylate in feed for 100 days, after which the animals were mated. There was no evidence of gross abnormalities. Various reproductive effects were observed, especially in the 2nd generation. In a continuous breeding reproductive toxicity study, male and female CD-1 mice (number not stated) were dosed orally with 25, 50, or 100 mg/kg Methyl Salicylate. Reproductive and fertility parameters were generally not affected. There also was no significant effect on mating behavior, fertility rate, or reproductive performance. Groups of CD-1 mice (20/sex/group) were dosed orally with 100, 250, or 500 mg/kg Methyl Salicylate in another continuous breeding reproductive toxicity study. A significant decrease in the mean number of litters, average number of pups/litter, proportion of live pups, and mean live pup weights was observed in the high dose group. CD rats (number not stated) received an oral dose of Methyl Salicylate (0.05 ml or 0.1 ml) on gestation day 10. The 0.1 ml dose group had decreased body weight gain, fewer and smaller neonates, and more resorptions and malformed neonates. Fetal kidney weight was decreased on gestation day 21, but was not different from the control on postnatal day 6.

Salicylic Acid

Groups of 20 gravid Wistar rats were fed a diet containing 0.06%, 0.1%, 0.2%, or 0.4% Salicylic Acid on gestation days 8 to 14.[1] Significant reproductive effects were observed in the 0.4% dietary group, and skeletal anomalies were observed in the 0.2% group. Only one dam gave birth to live neonates in the 0.4% dietary group, and skeletal anomalies were observed in 0.2% neonates. Groups of Wistar rats were dosed orally with Salicylic Acid at a dose of 75, 150, or 300 mg/kg on gestation days 8-14. Fetal mortality was 26% and 100% in the 150- and 300-mg/kg groups. Significant reproductive effects were observed in fetuses and neonates of the 150 mg/kg group. Groups of 10 Sprague-Dawley rats were

Sodium Salicylate

New Zealand White rabbits (number not stated) were dosed orally with 100 mg/kg Sodium Salicylate on gestation days 4 to 7.[1] The preimplantation ratio and average litter size were not affected, and teratogenic effects were not induced.

Two groups of 21 albino rats each received 200 mg/kg Sodium Salicylate orally on gestation days 6 to 15. A significant increase in resorptions and decrease in viable fetuses was observed in one group. A significant increase in external and internal abnormalities was observed in the second group, and skeletal anomalies were observed in both groups. Groups of 17 to 19 Sprague-Dawley rats received an oral dose of 30, 90, or 180 mg/kg Sodium Salicylate on gestation days 6 to 15. The incidence of teratogenicity was 30% in the 180 mg/kg group; marked embryotoxicity was observed and maternal toxicity was low. Regarding the 90- and 180-mg/kg groups, a dose-dependent decrease in growth was reported. Sprague-Dawley rats (number not stated) received oral doses of 1500 mg/kg and 300 mg/kg Sodium Salicylate, respectively, on gestation days 7, 8, 9, 10, or 11. Skeletal anomalies increased with dosing on days 8 and 10. Two groups of 2 CFE rats were dosed orally with 500 mg/kg Sodium Salicylate (on gestation day 8) or 100 mg/kg Sodium Salicylate (on gestation days 7 to 11). Results for the higher dose group included 50% maternal toxicity, 53% resorptions and dead fetuses, and 13% malformations. In the 100 mg/kg group, there was a 15% incidence of resorptions and dead fetuses. Groups of 12 to 15 albino rats received an oral dose of 25, 75, or 150 mg/kg Sodium Salicylate on gestation days15 to 20. Parturition was delayed in one and two dams of the 25 and 150 mg/kg groups. In the 150 mg/kg group, neonatal mortality increased in a dose-dependent manner. In another experiment, in the same study, groups of 12 to 15 albino rats received an oral dose of 4.2, 12.5, or 25 mg/kg Sodium Salicylate on gestation days 20 to 21. In the 12.5 and 25 mg/kg groups, neonatal mortality increased in a dose-dependent manner. Groups of 10 Sprague-Dawley rats received an oral dose of 10 mg/kg Sodium Salicylate twice daily on gestation days 20 and 21. The duration of bleeding at parturition was increased. Thirteen of 121 neonates were born dead. Sprague-Dawley and Long-Evans rats (number not stated) received an oral dose of 125 or 175 mg/kg Sodium Salicylate on gestation days 8 to 10. No malformations were observed.

CD-1 mice (number not stated) received oral doses of 1500 mg/kg and 300 mg/kg Sodium Salicylate, respectively, on gestation days 7, 8, 9, 10, or 11. Fetal mortality increased with dosing on day 10. Skeletal anomalies increased with dosing on days 8 and 9. Groups of 19 or 37 CD-1 mice received doses of 2000 and 2600 mg/kg Sodium Salicylate on gestation day 8. Results for the 2000 mg/kg group were: 11% maternal mortality, 71% viable litters, 14% fetal mortality, and 7% of fetuses with malformations. Results for the 2600 mg/kg group were: 24% maternal mortality, 79% viable litters, 7% fetal mortality, and 3% of fetuses with malformations. Twenty-two CD-1 mice received an oral dose of 800 mg/kg Sodium Salicylate on gestation days 8 to12. The average neonatal weight was decreased on postnatal days 1 and 3. Thirty ICR/SIM mice received an oral dose of 1600 mg/kg on gestation days 8 to 12, and 7 dams died. Neonate survival and the average number of viable neonates per litter on days 1 and 3 were significantly decreased and the number of dead neonates per litter on day 1 was significantly increased. Twenty-five A/Jax mice received an oral dose of 66.6 mg/ml Sodium Salicylate on gestation day 17. One dam delivered between 5-24 h. Fetal mortality was 47%, and the incidence of superficial, hepatic, and gastric hemorrhage was 6%, 1%, and 2% in dams killed at 24 h.[1]

Groups of 15 mated Crl:CD (SD)BR rats were given a single dose of 0 or 300 mg/kg (dose volume = 10 ml/kg) Sodium Salicylate (99.5% pure, in distilled water) on gestation day (GD) 9.[52] All fetal data, including all supernumerary ribs

data, are presented as the percentage mean per litter. No statistical analysis was carried out on mean incidences of supernumerary ribs and the number of presacral vertebrae. In the treated group, adverse effects were noted on body weight changes and food consumption during the 2 days following dosing. At birth, a high majority of pups had extra ribs at the 300 mg/kg dose. Specifically, on postnatal day 1, 89% of pups from dams exposed to 300 mg/kg Sodium Salicylate had supernumerary ribs. For these pups, evidence of postnatal reversibility was observed in 10 out of 14 pups with rudimentary ribs and 26 presacral vertebrae. Radiographs done on postnatal days 1, 6, 14, 28 and 54 showed a reduction in the incidence of rudimentary ribs only, whereas extra ribs, often associated with 27 presacral vertebrae, had the same incidence from birth to adult stage. Furthermore, extra ribs seemed to exhibit similar growth evolution to the other thoracic ribs. The authors noted that dosing with Sodium Salicylate resulted in a significant increase in the incidence of supernumerary ribs. The length of gestation was not affected by treatment. At birth, the number of dead pups was slightly higher in the treated group (7 dead pups out of 15 litters) in comparison with the control group (3 out of 14 litters) but no external malformations were significantly increased in the treated group.

In a study involving mated female Sprague-Dawley rats, Sodium Salicylate was administered by gavage on GD 9 at a dose of 300 mg/kg (in distilled water).[53] Control animals received distilled water only. The females were killed on GD 13. The mean number of live embryos was slightly lower than the control group value (11.9 as compared to 14.7), mainly due to a slight, but non-significant, increased number of early resorptions in the treated group. Because Sodium Salicylate is known to cause an increased incidence of supernumerary ribs (see preceding study), the molecular basis of this defect was evaluated in this study by analyzing the possible involvement of *Hox* genes, known to specify vertebrae identity. On GD 13, the expression of several *Hox* genes, selected according to the position of their anterior limit of expression, namely upstream (*Hoxa9*), at the level (*Hoxa10*) and downstream (*Hoxd9*) to the morphological alteration, were analyzed. Posterior shifts in the anterior limit of expression of *Hoxa10* and *Hoxd9* were observed following exposure to Sodium Salicylate, which could explain an effect at the level of the axial skeleton. This finding suggests that the appearance of ectopic ribs can be attributed to an anterior transformation of lumbar vertebrae identity into thoracic vertebrae identity. The authors noted that whether this transformation occurs with all compounds inducing supernumerary ribs in rats remains to be determined.

Sodium Salicylate served as the positive control in an embryo-fetal developmental toxicity study.[54] The positive control (in distilled water) was administered intragastrically (dose = 250 mg/kg/day; once daily) to a group of 22 to 24 gravid female Sprague-Dawley rats on GDs 8 to 10. Sodium Salicylate was administered at a dose volume of 10 ml/kg/day. There were 4.8% malformations in fetuses from the positive control group, including exencephaly, cranial meningocele, spina bifida, gastroschisis, and subcutaneous ecchymosis. The rate of abnormality was significantly higher than that of the vehicle control group ($p < 0.01$). Additionally, there were significant decreases in the body and tail length, and mean body weight of fetuses in the positive control group when compared with the vehicle control group ($p < 0.01$).

Human

Dermal

Salicylic Acid

In the third trimester, the use of Salicylic Acid can potentially cause early closure of ductus arteriosus and oligohydramnios. Therefore, it should not be applied over large surface areas for prolonged time periods, or under occlusive dressings that may enhance systemic absorption.[55,56] Study details relating to dermal Salicylic Acid application and closure of the ductus arteriosus and oligohydramnios were not included.

Risk Assessment

Dermal

Salicylic Acid

The relative bioavailability of Salicylic Acid following facial application of a 30% Salicylic Acid peeling product (rinse-off product) was quantified by using plasma exposure parameters such as area under the plasma concentration-time curve (AUC) or C_{max} values.[57] The measured plasma Salicylic Acid levels were then compared to a single oral dose of 650 mg aspirin (acetylsalicylic acid). Upon absorption, aspirin is rapidly converted to Salicylic Acid, which circulates in the blood as salicylate.[58] Serum levels of salicylate typically reach a maximum 2 h after ingestion of aspirin. Blood concentrations of salicylate in excess of 300 µg/mL are considered toxic, while the effective concentration range for a therapeutic dose of aspirin is 150-300 µg/mL.[59]

The skin peel formulation containing 30% Salicylic Acid (equal to 7.7 mg/kg bw Salicylic Acid for a 60 kg person) was topically applied for 5 min in nine healthy male and female subjects. The mean (SD) Salicylic Acid C_{max} was 0.81 (0.32)

µg/mL at 1.4 - 3.5 h after topical skin peel application, and was 56.4 (14.2) µg/mL at 0.5 - 1.5 h after oral aspirin administration.[57] The total area under the Salicylic Acid concentration versus time curve ($AUC_{0-\infty}$) was 6.4 µg × h/mL after dermal exposure and 320 µg × h/mL after oral exposure. The resulting AUC-based safety margin ratio was 50:1.

In comparison, the estimated Salicylic Acid C_{max} and AUC values at the maximum recommended oral aspirin dose (4000 mg, equivalent to 51 mg/kg bw Salicylic Acid for a 60 kg person) are 183 µg/mL and 1008 µg × h/mL, respectively. When compared to the C_{max} and AUC values at 30% Salicylic Acid rinse-off dermal dose, safety margin ratios of 229:1 and 158:1 for C_{max} and AUC, respectively, have resulted.[60] These results suggest a wide margin of safety with 30% Salicylic Acid use in rinse-off peeling products; when using human plasma exposure data, a margin of safety (MOS) of 10 is considered sufficient to ensure the safety of human exposure.[60,61]

The mean Salicylic Acid C_{max} of 0.81 µg/mL at 1.4 - 3.5 h after topical application of the peel product was compared to the blood concentrations of salicylate that are considered toxic (> 300 µg/mL)[58] as well as the blood concentrations of Salicylic Acid that are associated with salicylism (> 35 mg/dL [= 350 µg/mL]).[62] The results of these comparisons indicate that the blood concentration of Salicylic Acid resulting from application of the peel product (0.81 µg/ml) is substantially lower when compared to an approximation of the lowest blood concentration that is considered toxic (MOS = 300 µg/mL ÷ 0.81 µg/mL = 370), or an approximation of the lowest blood concentration that is associated with salicylism (MOS = 350 µg/mL ÷ 0.81 µg/mL = 432).

In order to determine the systemic burden after topical use of a skin care leave-on formulation (face and general creams) containing Salicylic Acid, another risk assessment was performed, taking into consideration the accumulative dose exposure to three leave-on skin care product types: body lotion, face cream, and hand cream. According to the Council's survey, Salicylic Acid is currently used in face and neck leave-on products at concentrations up to 2%, and in body and hand leave-on products at concentrations up to 0.2%.[18] For the purpose of this risk assessment, the estimated daily human exposure level to body lotion, face cream, and hand cream are 7.82, 1.54, and 2.16 g/day, respectively.[63]

In a risk assessment conducted by SCCNFP, a NOAEL of 75 mg/kg/day, derived from several rat oral teratogenicity studies on Sodium Salicylate, Acetyl Salicylate, Methyl Salicylate or Salicylic Acid, was used in the MOS calculation.[5] According to the test procedures, acetylsalicylic acid or Salicylic Acid was administered orally at various times during pregnancy (e.g., days 8 to 14 of gestation, days 9 and 11 of gestation, or days 7 to 17 of gestation) at daily doses of 75 to 500 mg/kg in rats. The results indicated that Salicylic Acid was neither teratogenic nor embryotoxic up to 75 mg/kg/day, and this NOAEL was derived from a series of animal studies in which Sodium Salicylate, Acetyl Salicylate, Methyl Salicylate, or Salicylic Acid were orally administered in rats. Above such dose, fetal malformations (skeletal malformations, cleft lip), resorptions and perinatal death were observed. Furthermore, in consideration of all available in vitro and in vivo data regarding human percutaneous absorption from topically applied Salicylic Acid, a dermal absorption value of 50% is chosen,[60] which also corresponds to the default absorption value proposed by SCCS.[63]

For leave-on skin care products, the relevant calculations are:

Systemic exposure dose (SED) of body lotion =
7.82 g/day of product × 0.2 % maximum use concentration ÷ 60 kg person ×
50% skin absorption × 1000 mg/g conversion factor
= 0.130 mg/kg/day

SED of face cream =
1.54 g/day of product × 2 % maximum use concentration ÷ 60 kg person ×
50% skin absorption × 1000 mg/g conversion factor
= 0.257 mg/kg/day

SED of hand cream =
2.16 g/day of product × 0.2 % maximum use concentration ÷ 60 kg person ×
50% skin absorption × 1000 mg/g conversion factor
= 0.036 mg/kg/day

Overall SED (leave-on skin care products, body lotion + face cream + hand cream) =
0.130 + 0.257 + 0.036
= 0.423 mg/kg/day

MOS (leave-on skin care products) =
NOAEL (rat oral teratogenicity study) / Overall SED (sum of the three leave-on skin care products SEDs)
= 75 mg/kg/day / 0.423 mg/kg/day
= 177

Plasma C_{max} and AUC values are available from kinetic studies involving applications of 2% Salicylic Acid leave-on formulations (either in cream or hydroalcoholic liquid) for 14 days, which resulted in a topical daily exposure to 0.45 mg/kg bw Salicylic Acid.[64] The AUC values for the cream and hydro-alcoholic formulations were about 366- to 252-fold lower than the AUC value from daily recommended oral therapeutic dose of aspirin (4000 mg, equivalent to 51 mg/kg bw Salicylic Acid).[60,64] In a kinetic-based safety assessment, total aggregate systemic exposure to Salicylic Acid from cosmetic products was calculated as 1.25 mg/kg bw/day, which yielded the C_{max} and AUC values of Salicylic Acid in human plasma at 7.0 μg/mL and 22 μg × h/mL, respectively. When compared to the estimated Salicylic Acid C_{max} and AUC values at the maximum recommended oral aspirin dose (183 μg/mL and 1008 μg × h/mL, respectively), the safety margins of 25- and 44-fold have resulted.[60]

Butyloctyl Salicylate

The following risk assessment was performed, taking into consideration that the maximum use concentration of 35.9% Butyloctyl Salicylate in lipsticks exceeds IFRA's 1% concentration limit (relative to sensitization potential) for Butyloctyl Salicylate in lip products of all types, and because of systemic toxicity concerns due to the potential for metabolism to salicylic acid.[27]

The Council survey of maximum reported use concentrations conducted in 2018 indicates that Butyloctyl Salicylate is being used at concentrations up to 35.9% in leave-on products (lipstick), which is the highest maximum use concentration.[18] In accordance with the SCCS Notes of Guidance, the estimated daily exposure level for lipstick is 0.057g.[63] Thus, a total dose of Butyloctyl Salicylate exposure during the application of lipstick can be estimated:

SED of lipstick= 0.057 g/day of product × 35.9% maximum use concentration ÷ 60 kg person × 50% skin absorption × 1000 mg/g conversion factor = 0.1705 mg/kg /day

MOS (Butyloctyl Salicylate, lipstick) = NOAEL (from rat oral teratogenicity studies; see above) / SED
= 75 mg/kg/day /0.1705 mg/kg/day
= 440

A more conservative assumption that 100% of lipstick is incidentally ingested would result in a MOS of 220.

Oral

Salicylic Acid

An exposure assessment of a representative cosmetic product (containing ≤ 2% Salicylic Acid) used on a daily basis estimated that the exposure from the cosmetic product would be only 20% of the level seen with ingestion of a "baby" aspirin (81 mg) on a daily basis. This exposure assessment further contends that the reproductive and developmental toxicity from the daily use of a baby aspirin is not significant.[1]

GENOTOXICITY STUDIES

Butyloctyl Salicylate, Ethylhexyl Salicylate, Isodecyl Salicylate, Methyl Salicylate, Salicylic Acid, Sodium Salicylate, and Tridecyl Salicylate

Studies on the genotoxic potential of Butyloctyl Salicylate, Ethylhexyl Salicylate, Isodecyl Salicylate, Methyl Salicylate, Salicylic Acid, Sodium Salicylate, and Tridecyl Salicylate are negative, except that Salicylic Acid is positive in a B. subtilis rec assay (negative in seven other bacterial tests and one mammalian test). Methyl Salicylate is positive in Salmonella typhimurium strains TA98, and TA100 with metabolic activation (negative in in 2 other Ames tests). Sodium Salicylate is positive in an in vivo chromosome aberration study in mice; it is negative for sister chromatid exchanges in vivo in mice, and in 4 in vitro test systems.[1]

Salicylic Acid

The mouse lymphoma assay (L5178Y mouse lymphoma cells) was used to evaluate the genotoxicity of Salicylic Acid (in deionized water) with and without metabolic activation.[46] Doses up to 1400 μg/ml were tested. Cyclophosphamide and methylmethanesulfonate served as positive controls. Salicylic acid was not genotoxic, with or without metabolic activation, at any of the doses tested.

Sodium Salicylate

The genotoxicity of Sodium Salicylate was evaluated in a mammalian cell genotoxicity test involving Chinese hamster ovary (CHO) cells.[43] The test substance was evaluated at concentrations up to 0.5 mM with and without metabolic

activation. Sodium Salicylate was not genotoxic over the range of concentrations tested (0.06 to 0.5 mM), both with and without metabolic activation. The positive control (*N*-ethyl-*N*-nitrosourea) was genotoxic.

CARCINOGENICITY STUDIES

Salicylic Acid has been classified as a non-carcinogen; however, relevant details that would have served as a basis for this classification were not provided .[1]

In Vitro

Salicylic Acid and Sodium Salicylate

Sodium Salicylate had dose-dependent inhibitory effects on adenoma, in vitro transformants of adenoma, and carcinoma cell lines. IC_{50} values of 1.65 to 7.28 mM were reported.

Animal

Dermal

Methyl Salicylate

A skin painting study was performed in which Methyl Salicylate was applied to the back of 39 mice, at biweekly intervals, for 400 days.[1] *Neoplasms were not induced.*

Parenteral

Groups of 15 male and 15 female A/He mice were dosed intraperitoneally with 100 or 500 mg/kg Methyl Salicylate in tricaprylin 3 times per week for 8 weeks (24 doses total).[1] *Two out of 13 males and 1 of 14 females of the low-dose group that survived until study termination had lung tumors. One out of 12 males and 5 of 13 females of the high-dose group that survived until study termination had pulmonary tumors. These compare with 10 of 46 males and 8 of 48 females with tumors in the untreated control group and 8 of 30 males and 10 of 28 females with tumors in the vehicle control group.*

Photocarcinogenicity

Salicylic Acid

In a National Toxicology Program (NTP) photocarcinogenicity study, the effects of synthetic solar light on the skin of hairless mice that had been treated with creams containing Salicylic Acid were evaluated.[65] Creams containing Salicylic Acid (0%, 2%, or 4%), were applied to the skin of groups of 18 male and 18 female hairless mice in the mornings. Additional groups of 36 male and 36 female mice were not exposed to the cream. In the afternoons, groups of animals were exposed to one of three strengths of synthetic solar light for 4 h. Other groups were not exposed to light and were control groups. The treatment and exposures were performed five days per week for 40 weeks, during which time the animals were monitored for the development of skin cancers. Greater strengths of light increased the incidences of skin cancers in mice not given a cream or given a cream with no acid included. Creams containing Salicylic Acid decreased the incidence of skin tumors in mice receiving the lower of the two light intensities. It was concluded that Salicylic Acid had some protective effect against photocarcinogenicity at lower intensities.

Tumor Promotion

Salicylic Acid inhibited tumor promoter 12-O-tetradecanoylphorbol-13-acetate-induced transformation in a concentration-dependent (concentrations not stated) manner, in a culture model (mouse epidermal JB6 cells)that was used to study tumor promotion and anti-tumor promotion.[1]

OTHER RELEVANT STUDIES

Estrogenic Activity

Butyloctyl Salicylate and Ethylhexyl Salicylate

The estrogenic activity of Butyloctyl Salicylate and Ethylhexyl Salicylate was studied.[66] A consensus modeling method to predict their qualitative and quantitative binding activity towards the estrogen receptor (ER) was used. The

consensus modeling comprised two Decision Forest (DF) models that were built using two different training data sets. The two DF models were validated using 5-fold cross validations and external chemicals. Similar predictions were made on unrelated compounds. Prediction confidence was defined as a number between 0 and 1, for indication of confidence for a prediction; the smaller the number, the less confident the binding affinity prediction. The experimental ER binding affinities were given as logarithmic relative binding affinity (log10RBA) values to the hormone estradiol. RBA is defined as the relative binding affinity to the natural estrogen, estradiol. The RBA of estradiol is set at 100; thus, its log10RBA = 2. Ethylhexyl Salicylate was classified as an estrogen receptor non-binder. Butyloctyl Salicylate was classified as having binding activity to the ER (prediction confidence value = 0.827; log10RBA = -0.853).

A recombinant yeast estrogen assay was used to assess the activity of Ethylhexyl Salicylate.[67] The ERα gene, together with expression plasmids (containing estrogen responsive elements and the lac-Z reporter gene encoding the enzyme β-galactosidase), were incubated in medium containing Ethylhexyl Salicylate (10 µl, serially diluted in ethanol) and the chromogenic substrate, chlorophenol red-β-D-galactopyranoside (CPRG). Active ligands (which bind to the receptor) induce β-galactosidase (β-gal). The relative potency of the test substance was determined only when the dose–response curve was parallel to that of 17-β-estradiol. To do so, the concentration of the test substance required to produce a half-maximal response (absorbance at 540 nm (A540) between 1.7 and 2.0) was divided by the concentration of 17-β-estradiol required to produce the same response. Compounds displaying a submaximal response were compared at the 10% response level. Ethylhexyl Salicylate generated a dose-response curve that was shallower than the one for 17-β-estradiol, and had a submaximal response for estrogenic activity (estrogenic potency relative to 17-β-estradiol = 1/2,000,000).

Effect on Cytokine Production

Methyl Salicylate

Respiratory and skin local lymph node assays (LLNAs) were used to evaluate the effects of inhalation exposure to respiratory and contact sensitizers on cytokine profiles. Methyl Salicylate (a respiratory and skin irritant) served as the negative control in both assays. Six male BALB/c mice were exposed (head/nose-only) to Methyl Salicylate (30 mg/m^3) in a short-term exposure respiratory LLNA.[68] The animals were exposed for 45, 90, 180, or 360 min/day on 3 consecutive days (days 0, 1, and 2). For inhalation exposure, the chemical was evaporated in air without solvent. A control group of 6 mice exposed to air only for 360 min/day. Three days after the last inhalation exposure, the draining lymph nodes were excised and cytokine production was measured after ex vivo stimulation with Concanavalin A. Cytokine profiles were assessed. Skin application was used as a positive control in this study. In the skin LLNA, the dermal route (single ear application; n = 3 male BALB/c mice) was used as a positive control. The negative control Methyl Salicylate (25%, 25 µl), dissolved in acetone:olive oil (4:1) solution (AOO), was applied on the dorsum of both ears (50 µl per animal) for 3 consecutive days (days 0, 1, and 2). A vehicle (AOO) control group of 6 mice was also included. On day 5, auricular lymph nodes were collected and used for ex vivo cell proliferation and cytokine measurements. After inhalation exposure and skin exposure, Methyl Salicylate did not induce a measurable interleukin-4 (IL-4) response (i.e., no significant cytokine production).

DERMAL IRRITATION AND SENSITIZATION STUDIES

The skin irritation and sensitization studies summarized below (except for italicized text) are presented in detail in Table 4. In addition to these studies, it should be noted that possible complications relating to the topical use of Salicylic Acid as a peeling agent include persistent erythema and pruritus (specific studies not included).[69]

Irritation

Animal

Dermal

The application of 500 mg (in 0.5 ml) of Isodecyl Salicylate (6 male New Zealand white rabbits) and Tridecyl Salicylate (6 female Dunkin-Hartley albino guinea pigs), and Butyloctyl Salicylate (rabbits, dose administered not stated) did not cause skin irritation.[1] Undiluted Ethylhexyl Salicylate produced mild skin irritation in rabbits (number not stated). Methyl Salicylate (concentration not stated) has been reported to cause severe skin irritation in guinea pigs (number not stated) and moderate skin irritation (abraded and intact skin) in rabbits (number not stated). Repeated applications of Methyl Salicylate (concentration not stated) to guinea pigs (number not stated) caused scaling, dryness, and isolated and multiple infiltrates by days 4 to 6. Threshold changes were noted with the application of a 50% oil solution. At concentrations of 1%, 3%, and 6% (in 70% ethanol), Methyl Salicylate was severely irritating to the skin of all 3 animals (species not stated) tested. However, this was not true for water suspensions of the 3 Methyl Salicylate concentrations.

The skin irritation potential of Amyl Salicylate (> 99.8%) was evaluated using 6 Albino angora rabbits and 6 male Hartley guinea pigs.[70] After 24 h, Amyl Salicylate was severely irritating to the skin of rabbits and mildly irritating to the skin of guinea pigs. The skin irritation potential of Amyl Salicylate (> 99.8%) was evaluated using 6 miniature swine of the Pitman-Moore Improved strain. Skin irritation was not observed following a 48-h application. When undiluted Ethylhexyl Salicylate was applied under occlusion to the skin of 4 rabbits for 24 h, mild erythema was observed.[7] These results are reported in the acute dermal toxicity study that is summarized earlier in this report. In another test, the application of undiluted Ethylhexyl Salicylate to the skin of 3 rabbits did not result in skin irritation.[30]

Groups of 5 male hrBR outbred hairless albino guinea pigs received a single ~ 2 h application of Hexyl Salicylate at a concentration of 1%, 5%, 10%, or 50% (in 3:1 diethyl phthalate:ethanol) or at 100%. Skin irritation was not observed. In a test involving 4 male albino Dunkin/Hartley strain guinea pigs, the animals were treated topically with patches saturated with 10%, 25%, or 50% Hexyl Salicylate in acetone.[8] After 24 h, no irritation was observed at the 10% concentration, and very slight erythema was observed in 3 animals at the 2 highest concentrations. In another test (same protocol), the skin irritation potential of Hexyl Salicylate (0.1 to 2% in 0.01% dodecylbenzenesulfonate/saline) was evaluated using 4 male albino Dunkin Hartley guinea pigs.[8] Very slight erythema was observed at a concentration of 0.1% and slight erythema and edema were observed at higher concentrations. The application of undiluted Hexyl Salicylate (20 µl/5 cm^2) to the skin of 2 miniature swine did not cause skin irritation.[8] In a study involving 3 or 4 female New Zealand white rabbits, Hexyl Salicylate was applied for 4 h to the skin at concentrations ranging from 10% to 100%. Skin irritation was not observed at concentrations of 10% and 25%, but irritation was observed at higher concentrations.[8] When undiluted Hexyl Salicylate was applied (5 g/kg) to the skin of 10 rabbits, skin irritation was observed in 8 animals.[8] Also, when undiluted Hexyl Salicylate (20 µl/5 cm^2) was applied to the skin of 6 hairless mice, skin irritation was not observed.[8]

In a study in which Methyl Salicylate was applied to the skin of 6 rabbits at concentrations up to 100%, skin irritation was observed only at concentrations of 25% and 100%.[46] The skin irritation potential of wintergreen oil (containing 80 – 99% Methyl Salicylate) was evaluated using 6 hairless mice and 2 miniature swine.[9] Flaking, hyperkeratosis and dry desquamation were observed. The application of Methyl Salicylate (3%) to the skin of 6 to 8 male and female outbred, Himalayan white-spotted guinea pigs for 21 days resulted in minimal skin irritation.[71] Also, when Methyl Salicylate (3%) was applied for 24 h to guinea pigs (6 to 8) of the same strain, mild erythema was observed in at least 25% of the animals.[71] A single dermal dose (5 g/kg) of undiluted Methyl Salicylate caused slight erythema and edema in 2 of 9 rabbits and moderate erythema and edema in 7 of 9 rabbits (skin irritation results from acute dermal toxicity study).[9] In a mouse ear swelling test, the minimal irritating concentration of Methyl Salicylate was determined to be 20%.[72] When Salicylic Acid (0.5 g in water) was applied to the skin of 3 rabbits, there was no evidence of skin irritation.[4,73] However, when alcoholic solutions containing 2% Salicylic Acid were applied to the skin of rabbits, mild to no skin irritation was reported.[4] Formulations containing 3.5%, 5.0%, and 7.5% Salicylic Acid caused significant macroscopic alterations (desquamation, inflammatory reaction and comedogenic effect), compared to the negative control, when applied daily to the ears of 6 male albino New Zealand rabbits.[74] Salicylic Acid concentrations of 10% and 25%, but not 2% (in propylene glycol ether in ethanol), applied repeatedly caused skin irritation in rabbits.[5] Cleansing formulations (containing 0.5% Salicylic Acid or diluted with water to contain 0.25% Salicylic Acid) caused transient irritation when applied repeatedly to the skin of rabbits.[5] Cleansing formulations containing 0.5% to 6% Salicylic Acid in propylene glycol butyl ether/ethanol (vehicle) caused slight to marked erythema when applied repeatedly to the skin of rabbits.[5] Repeated open applications of 2.5% and 5% hydroalcoholic solutions of Salicylic Acid to the skin of guinea pigs resulted in mild skin irritation.[4] Sodium Salicylate (0.5 g in water) was non-irritating to the skin of 3 rabbits.[43]

Intradermal Injection

After 0.1% Hexyl Salicylate (0.1 ml) was injected intradermally into the skin of 4 inbred Hartley strain albino guinea pigs, skin irritation was observed.[75] The intradermal injection of a higher concentration of Hexyl Salicylate (5%) into the skin of 4 guinea pigs (same strain) did not cause skin irritation. The vehicle was not reported in either experiment, and an explanation for the different results was not provided.

Human

Dermal

Clinical tests for cumulative irritation are available for the following ingredients at the specified concentrations: Salicylic Acid (27 subjects; 2% - minimal cumulative irritation; 1.5% - slight or no irritation); TEA-Salicylate (10% caused irritation in 1 of 12 subjects); Methyl Salicylate (12% to 50% - pain and erythema (5 subjects); 8% - no irritation (number of subjects not stated); 1% aerosol – erythema (4 subjects); Ethylhexyl Salicylate (4% - no irritation (number of subjects not stated)); and Tridecyl Salicylate (no irritation, 30 subjects).[1]

In a 48-h occlusive patch test, Amyl Salicylate (32% in acetone) was not irritating to the skin of 50 subjects.[70] In a 48-h closed patch test involving 23 male subjects, 4% Ethylhexyl Salicylate in petrolatum did not cause skin irritation.[7] Skin irritation was observed when undiluted Hexyl Salicylate was evaluated in a 4-h patch test using 30 volunteers.[76] In a 24-h patch test involving 56 subjects, Hexyl Salicylate was evaluated for skin irritation potential at concentrations of 0.3%, 3%, or 30% in 3:1diethyl phthalate:ethanol.[8] Results were negative. Skin irritation was not observed after 8% Methyl Salicylate (in petrolatum) was applied to the backs of 27 male subjects.[9] The same results were reported when or 12% wintergreen oil (containing 80 – 99% Methyl Salicylate) in petrolatum was applied to the backs of 25 subjects. Repeated applications of 30% and 60% Methyl Salicylate to the skin of 9 subjects resulted in skin irritation.[77] A cream containing 2% Salicylic Acid was classified as non-irritating after repeated patch applications to the skin of human subjects (number not stated).[5] Surfactant-based products containing 2% Salicylic Acid (pH 3.8; diluted test concentration not stated) were mildly irritating when applied repeatedly to the skin of human subjects (number not stated).[5] Repeated applications of a cream containing 1.5% Salicylic Acid to the skin of human subjects (number not stated) caused slight skin irritation.[5] A hydroalcoholic gel containing 2% Salicylic Acid was slightly irritating when applied repeatedly to the skin of human subjects (number not stated).[5] Different results were reported for two creams (1 non-irritating; the other moderately irritating) containing 2% Salicylic Acid that were applied repeatedly to the skin of human subjects (number not stated).[5] In a repeated open application test, a cream containing 2% Salicylic Acid that was applied to the backs of human subjects (number not stated) did not cause reactions that were different from those induced by the control.[5]

When a shampoo containing 3% Salicylic Acid was applied (as a 4% dilution) continuously under a patch to the skin of human subjects, a potential for skin irritation was demonstrated.[5] In exaggerated use repeated application tests in which results for shampoos containing Salicylic Acid at concentrations of 2% and 3% were compared with a placebo, there were no statistically significant differences in combined irritation or transepidermal water loss (TEWL).[5] It was noted that, at a concentration of 3% Salicylic Acid in rinse-off shampoo formulations, this concentration does not appear to be more irritating than other components of the formulations. Daily application (2 weeks) of a hydroalcoholic solution containing 0.5% Salicylic Acid (pH 2.82) to the skin of human subjects did not cause skin irritation.[5] In 2 home use tests (6 weeks) involving products containing 2% Salicylic Acid, mild skin irritation was observed.[5] In another home use test (14 weeks), involving products containing 2% Salicylic Acid, mild skin reactions were observed in 12 of 194 subjects.[5]

Sensitization

In Vitro/In Chemico

In a genomic allergen rapid detection assay utilizing an in vitro model of dendritic cells, Hexyl Salicylate was predicted to be a skin sensitizer.[78] An integrated testing strategy for skin sensitization that focuses on 3 methods (human cell line activation test (h-CLAT) [assesses surface markers on dendritic cell lines], direct peptide reactivity assay (DPRA) [measures reactivity with model proteins], and the Sens-IS assay [measures the gene expression of irritation and sensitization biomarkers]) covering the first three steps of the adverse outcome pathway was used to determine the skin sensitization potential of Salicylic Acid.[79] The results were equivocal, but, ultimately, were considered positive. The allergen–peptide/protein interaction assay was also used to predict the sensitization potential of Salicylic Acid.[80] Mass spectra of both target peptides revealed neither any modification of peptide-21 nor of peptide-20 by Salicylic Acid, under various pH conditions.

Animal

Maximization test data on Butyloctyl Salicylate indicate that none of the guinea pigs induced with 5% Butyloctyl Salicylate (intradermally) and 100% Butyloctyl Salicylate (topically) and challenged with 100% Butyloctyl Salicylate had a sensitization response.[1] However, one of the 10 guinea pigs challenged with 50% Butyloctyl Salicylate had a clear dermal response. Maximization test data on Ethylhexyl Salicylate indicate that skin sensitization was not observed in guinea pigs(number not stated) induced with 2.5% Ethylhexyl Salicylate (intradermally) and 50% Ethylhexyl Salicylate (topically) and challenged with a 25% solution of Ethylhexyl Salicylate in ethanol/diethyl phthalate (DEP) (1:1).[1] Results for Methyl Salicylate are negative at concentrations up to 25%, independent of vehicle, in the local lymph node assay.[1] A modified Magnusson-Kligman guinea pig maximization test on Methyl Salicylate was performed using 10 Dunkin-Hartley guinea pigs. The animals were induced with 2.5% Methyl Salicylate (intradermally) and 100% Methyl Salicylate (topically) and challenged with 10% Methyl Salicylate in acetone, and results were negative. In another maximization test, albino Dunkin-Hartley guinea pigs (number not stated) were induced with 2.5% Methyl Salicylate (intradermally) and 100% Methyl Salicylate (topically) and challenged with 10% Methyl Salicylate in acetone/PEG 400 (70:30). Test results were negative for skin sensitization. Although results for Salicylic Acid are positive in the LLNA at a concentration of 20% in acetone, this is not true for Salicylic Acid at a concentration of 20% in acetone/olive oil.[1]

In the murine LLNA, a very low EC3 (0.18%; EC3 = effective concentration that induces a 3-fold increase in local lymph node proliferative activity) was reported for Hexyl Salicylate.[79] The lower the EC3 value, the greater the sensitization

potency. It was noted that the low value reported may have been due to possibly sensitizing impurities. Hexyl Salicylate was tested in a sensitization study involving 10 inbred Hartley albino guinea pigs.[75] Sensitization was observed after the second challenge with 0.1% Hexyl Salicylate (intradermal injection) and 5% Hexyl Salicylate (topical application). In a sensitization test using groups of 5 Crl:IAF(HA)-hrBR outbred albino hairless guinea pigs, challenge with 50% Hexyl Salicylate in 3:1 diethyl phthalate (DEP):ethanol and 100% Hexyl Salicylate did not induce sensitization.[8] A maximization test was performed to evaluate the sensitization potential of Hexyl Salicylate in a group of 10 albino Dunkin Hartley guinea pigs.[8] Sensitization was not observed after challenge with 10% Hexyl Salicylate. The sensitization potential of Methyl Salicylate (0.7 µM) was evaluated using the LLNA.[81] Overall, the results were classified as negative. According to another source, 50% Methyl Salicylate was predicted to be a non-sensitizer using the LLNA.[82] Salicylic Acid has been tested and found to be a non-sensitizer in the LLNA.[83] In a modified Buehler test, Methyl Salicylate (25% w/v in hydro-alcoholic solution) did not cause skin sensitization in a group of 20 guinea pigs.[4] The same was true for Salicylic Acid (25% w/v in hydro-alcoholic solution) when tested according to the same procedure.[4]

Human

In a maximization test involving 25 subjects challenged with 10% Salicylic Acid, results were negative.[1] Results were also negative for skin sensitization in a human repeated insult patch test (HRIPT; 99 subjects) on a moisturizer cream containing 2% Salicylic Acid and in an HRIPT (101 subjects) on both a moisturizing cream and a moisturizing lotion containing 2% Salicylic Acid. Gels containing 2% Salicylic Acid were also non-sensitizers in HRIPTs involving 193 subjects and 198 subjects. In a maximization test involving 23 subjects, 4% Ethylhexyl Salicylate in petrolatum did not induce skin sensitization. Also, in a maximization test involving 27 subjects, 8% Methyl Salicylate in petrolatum did not induce skin sensitization.

Neither skin irritation nor sensitization was observed in a human repeated insult patch test (HRIPT) in which 52 subjects were patch tested with undiluted Butyloctyl Salicylate.[47] Hexyl Salicylate has been classified as a Category 4 substance (infrequent cause of contact allergy in relation to level of exposure) with regard to its human skin sensitization potential.[83] This classification by authors of the study is based on an analysis of human data adapted from a number of published references. Substances in Category 4 are rarely important clinical allergens, because they require considerable/prolonged exposure to higher dose levels to produce sensitization, which even then is unlikely to exceed 0.01% of those exposed. Furthermore, a human skin sensitization NOEL of 35,433 µg/cm^2 has been reported for Hexyl Salicylate. HRIPT results for 30% Hexyl Salicylate in 3:1DEP:ethanol were negative for skin irritation and sensitization.[8] In a human maximization test on Hexyl Salicylate, no induction was observed at a dose of 20,654 µg/cm^2.[79] In another maximization test involving 22 subjects patch tested with 3% Hexyl Salicylate, the results were negative for skin irritation and sensitization.[8]

Methyl Salicylate has been classified as a Category 5 substance (a rare cause of contact allergy except perhaps in special circumstances, e.g., use in topical medicaments) with regard to its human skin sensitization potential.[83] This classification by authors of the study is based on an analysis of human data adapted from a number of published references. It was also noted that there are insufficient data (availability of specific data not mentioned) to define a human skin sensitization NOEL. Category 5 consists of substances that have a very low intrinsic ability to cause skin sensitization. Here, typically only exceptionally prolonged exposure in combination with high use levels will lead to skin sensitization, for example, routine use in medicaments for treatment of chronic skin conditions. For these materials, sensitization in the general population is likely to be (extremely) rare. In a maximization test involving 25 subjects, 12% wintergreen oil (containing 80 – 99% Methyl Salicylate; at 12%, effective concentration range = 9.6% to 11.9%) in petrolatum did not induce skin sensitization.[9] In an HRIPT involving 39 subjects, 1.25% Methyl Salicylate was a non-sensitizer.[9] Product formulations containing 2% Salicylic Acid did not cause sensitization in HRIPTs (test populations: 84 to 198 subjects).[5] Salicylic Acid has been classified as a Category 6 substance with regard to its human skin sensitization potential.[83] This classification by authors of the study is based on an analysis of human data adapted from a number of published references. Substances in Category 6 are essentially free from skin sensitizing activity (i.e., non-sensitizers). Further details were not included.

Computational Analyses/Predictions

Amyl Salicylate, Hexyl Salicylate, and Methyl Salicylate

A database of 259 heterogeneous organic compounds (including Amyl Salicylate, Hexyl Salicylate, and Methyl Salicylate) evaluated in the guinea pig maximization test was subjected to multivariate quantitative structure-activity relationship (QSAR) analysis, utilizing principal component analysis and linear discriminant analysis.[84] Amyl Salicylate, Hexyl Salicylate, and Methyl Salicylate were classified as non-sensitizers. A QSAR system for estimating skin sensitization potency that incorporates skin metabolism and considers the potential of parent chemicals and/or their activated metabolites to react with skin proteins has also been developed.[85] Amyl Salicylate was one of the chemicals that was identified to fall within the model domain accounting for the first neighbors of centered atoms, and was predicted to be a non-sensitizer.

A study was performed to validate a QSAR rank model for grading allergenic potency using a database of 74 known allergens and non-allergens that were chosen among fragrance chemicals in common use.[86] The model's scoring system for class levels was: Class 1 (non-allergic; scores = 0.63 to 1.97), Class 2 (weak to mild; scores = 1.24 to 3.10), Class 3 (moderate; scores = 1.81 to 4.14), and Class 4 (strong to extreme; scores = 2.66 to 4.88). Hexyl Salicylate and Methyl Salicylate were classified as non-allergic.

Hexyl Salicylate

An exposure-based quantitative risk assessment (QRA) methodology was used to determine acceptable exposure limits (in finished product) for Hexyl Salicylate and a new International Fragrance Association (IFRA) standard was issued.[87] The following relevant sensitization data were used for implementation of the QRA: LLNA weighted mean EC3 value (45 µg/cm^2), human data: NOEL – HRIPT (induction) (35,433 µg/cm^2), experimental NOEL – MAX (induction) (2069 µg/cm^2), and weight of evidence (WoE) no expected sensitization induction level (NESIL) (35,400 µg/cm^2).[8]

Photosensitization/Phototoxicity

The photosensitization/phototoxicity studies summarized below are presented in detail in Table 5.

In Vitro

Ethylhexyl Salicylate

The phototoxicity of Ethylhexyl Salicylate (0.1 to 316 µg/mL) was evaluated in the 3T3 neutral red uptake phototoxicity test, using a cell suspension of 3T3 fibroblasts.[88] Phototoxicity test results were classified as negative.

Animal

Hexyl Salicylate

Undiluted Hexyl Salicylate (20 µl) was not phototoxic in 6 Skh:hairless-1 mutant mice exposed to light from a long arc xenon lamp and fluorescent blacklight lamps .[8,89] Phototoxicity also was not observed in 2 miniature swine tested with undiluted Hexyl Salicylate (20 µl) according to the same procedure.[8,89] In a phototoxicity study in which two groups of 5 Crl:IAF(HA)-hrBR outbred, albino hairless guinea pigs were exposed to Hexyl Salicylate (concentrations up to 100%) and then ultraviolet radiation (UV) from a long-arc xenon water-cooled lamp, results were also negative.[8] Photoallergy was not observed in 2 groups of 5 Crl:IAF (HA)-hrBR outbred albino hairless guinea pigs exposed to Hexyl Salicylate (50% and 100%) plus UV.[8]

Methyl Salicylate

Methyl Salicylate (50% in DEP) was evaluated for phototoxicity and photoallergenicity potential using 25 guinea pigs. Both evaluations involved exposure to long-wavelength ultraviolet radiation (UVA) and mid-wavelength ultraviolet radiation (UVB), and the test substance was classified as non-phototoxic and non-photoallergenic.[46] The phototoxicity of wintergreen oil (containing 80 – 99% Methyl Salicylate) in the presence of UVA was evaluated using 2 miniature swine. Results were negative.[9]

Salicylic Acid

The contact photosensitization potential of Salicylic Acid was determined using groups of 5 female albino outbred ICR mice.[1] The animals were challenged with 25% Salicylic Acid in alcohol (20 µl), followed by irradiation for 2.5 h, and results were negative.

Tridecyl Salicylate

Ten male Hartley albino guinea pigs were used to determine the phototoxicity potential of Tridecyl Salicylate.[1] During induction 2% Tridecyl Salicylate (0.5 ml) was applied to the back daily for 3 weeks, and the test site was irradiated with UVA + UVB. At challenge with 0.1% Tridecyl Salicylate in dehydrated alcohol, results were negative.

Human

Hexyl Salicylate

In a study involving 56 subjects patch tested with Hexyl Salicylate (0.3%, 3%, and 30% in 3:1 DEP:ethanol), followed by irradiation of sites with UVA and UVB, no reactions were observed.[8]

Ethylhexyl Salicylate and Salicylic Acid

Products containing 2% Salicylic Acid did not induce phototoxicity in studies involving groups of 10 human subjects. The same was true for these products in photoallergenicity studies involving groups of 25 to 28 humans subjects.[1] *A cream containing 2% Salicylic Acid had a photoprotective effect in a study involving 5 subjects. The same was true for a formulation containing Ethylhexyl Salicylate (concentration not stated) in groups of ≤ 38 subjects*.

OCULAR IRRITATION STUDIES

In Vitro

Sodium Salicylate

Sodium Salicylate was evaluated using the EpiOcular™ reconstructed human cornea-like tissue model.[90] The tissues are cultured from primary non-transformed human epidermal keratinocytes (NHEK) obtained from individual donors. The tissues were incubated with Sodium Salicylate (50 µl) for 30 minutes, and tissue viability was assessed using the MTT assay. If the treated tissue viability was ≤ 60% relative to negative control tissue viability, the test chemical was predicted as "in vitro irritant." Values for percent viability were 5% (run #1) and 5.1% (run #2) for Sodium Salicylate, classifying the chemical as an ocular irritant.

Animal

**Butyloctyl Salicylate, Ethylhexyl Salicylate,
Isodecyl Salicylate, Methyl Salicylate, and Tridecyl Salicylate**

The ocular irritation potential was negative for the following ingredients: Butyloctyl Salicylate (concentration not stated; 6 rabbits tested) Ethylhexyl Salicylate (50% solution; number of rabbits not stated), Isodecyl Salicylate (10% in liquid paraffin; 6 New Zealand albino rabbits tested), and Tridecyl Salicylate (0.1 ml dose; 3 male New Zealand white rabbits).[1] *Methyl Salicylate was not irritating in one study using rabbits, but was severely irritating in another study to the eyes of guinea pigs (test concentrations and number of animals not stated in either study).*

Ethylhexyl Salicylate

The ocular irritation potential of undiluted Ethylhexyl Salicylate was evaluated using 3 New Zealand White rabbits.[30] The test substance (0.1 ml) was instilled into 1 eye of each animal, and the eyes were not rinsed. Reactions were scored at ~1 h, 24 h, 48 h, and 72 h post-instillation. On day 1, a slight or moderate chemosis and a slight or moderate conjunctival redness were observed in all 3 animals. In 1 rabbit, slight chemosis remained on day 2. In 2 rabbits, slight redness was observed until day 3. Ocular reactions were not observed on day 4. The test substance was classified as non-irritating.

Methyl Salicylate

A rabbit eye irritation test was conducted in 5 healthy albino rabbits. A 0.005 ml aliquot of neat Methyl Salicylate was applied to the center of the cornea while the lids were retracted.[91] One minute later the lids were released. The eyes were examined 18 - 24 h later in strong diffuse daylight and then stained with fluorescein. Methyl Salicylate caused necrosis on 13 to 37% of the cornea (visible after staining).

A rabbit eye test was conducted in 3 healthy albino rabbits.[9] One-tenth ml of 1.25% Methyl Salicylate in specially denatured alcohol (SDA) 39C was instilled into the right eye of each rabbit with no further treatment. The untreated left eye served as control. Observations were made every 24 h for 4 days and then again on day 7 according to the Draize method. Intense conjunctival irritation accompanied by chemosis and considerable discharge was observed in all 3 rabbits. The treated eyes were normal on day 7 of observation.

Salicylic Acid

The Draize test was used to evaluate the ocular irritation potential of Salicylic Acid (purity not stated) in 3 rabbits (strain unknown).[73] The test substance (100 g) was instilled into the right eye of each animal, and the eyes were not rinsed. Instillation of the test substance was followed by a 21-day observation period. Salicylic Acid caused severe ocular irritation, and reactions did not clear during the 21-day observation period. Numerous formulations (non-alcoholic and hydroalcoholic) that contained Salicylic Acid at concentrations ranging from 0.05% to 2% have been evaluated in the Draize test (rabbits).[5] The study authors considered these formulations to be mild irritants when instilled into the eyes of rabbits.

Sodium Salicylate

The ocular irritation potential of Sodium Salicylate was evaluated using 3 female New Zealand White rabbits.[43] The test substance (0.1 g) was instilled into the left eye (followed by rising with saline), and reactions were scored at 1 h, 24 h, 48 h, 72 h, and day 7 post-instillation. None of the animals died, and there was no evidence of systemic toxicity. Ocular irritation was observed in all animals and reactions cleared within day 7. Sodium Salicylate was classified as mildly irritating to the eyes of rabbits.

CLINICAL STUDIES

Retrospective and Multicenter Studies

Amyl Salicylate

A total of 1323 patients (from 11 centers combined) were patch tested with fragrances.[92] Patch testing was performed with Finn chambers on Scanpor tape; patches were applied to the back for 2 days. Readings were made according to International Contact Dermatitis Research Group (ICDRG) guidelines on days 2 and 3, or on days 2 and 4. Twenty-eight irritant or doubtful reactions (on day 3 or 4) to a total of 19 fragrance materials were reported. Two reactions (irritant or doubtful) were reported for 1% Amyl Salicylate.

A population of 1855 patients (6 European dermatology departments combined), was patch tested with fragrances. [93] Finn Chambers on Scanpor tape were used in all centers except 1(at which van der Bend chambers were used). Readings were taken at most centers on days 2 and 4. The reading at day 3 or day 4 was used for overall evaluation of positive test results. Three patients had a positive reaction (+) to 5% Amyl Salicylate, and 5 had doubtful reactions.

Hexyl Salicylate

In a multicenter study, 218 fragrance sensitive patients with proven contact dermatitis were patch tested with various fragrance materials according to internationally accepted criteria.[94] No reactions were observed with 5% Hexyl Salicylate in petrolatum.

Case Reports

Methyl Salicylate

A man became acutely ill (within less than an hour) after using an herbal skin cream containing Methyl Salicylate (high concentration, value not stated) for the treatment of psoriasis.[95] The area of application was covered with an occlusive wrap. Signs of metabolic acidosis superimposed on respiratory alkalosis and a serum salicylate level of 48.5 mg/dL were reported. These signs declined after the patient received treatment for the metabolic acidosis and respiratory alkalosis. The author noted that the transcutaneous absorption (described as rapid) of Methyl Salicylate was enhanced due to the abnormal areas of skin and use of an occlusive dressing. It was concluded that acute salicylate toxicity may result from the topical administration of Methyl Salicylate.

Salicylic Acid

Although rare, toxicity can occur from topical application of Salicylic Acid (i.e., salicylism).[62] Salicylism can be acute or chronic and develops when blood concentrations of salicylate are greater than 35 mg/dL. Symptoms of salicylism include nausea, confusion, dizziness, delirium, psychosis, stupor, and coma.

Dermal Salicylic Acid hypersensitivity was observed in a case report on a woman with no medical history and no known allergies.[96] The patient had applied an OTC topical Salicylic Acid for the treatment of warts on both hands. The first

application was without incident, but a second application the next day caused finger swelling within minutes and then pain and loss of finger mobility. The authors noted that this hypersensitivity reaction to topical Salicylic Acid application is rarely seen.

Amyl Salicylate, Ethylhexyl Salicylate, Methyl Salicylate, Salicylic Acid, and Sodium Salicylate

A woman with a 12-year history of rosacea was advised to use a sunscreen that contained Ethylhexyl Salicylate during several months prior to intense pulsed-light treatment for facial telangiectasia.[97] One-half year later, the patient developed facial dermatitis. She had a positive (++) patch test reaction to 2% Ethylhexyl Salicylate in petrolatum, a positive (+) patch test reaction to 5% Ethylhexyl Salicylate in petrolatum, and a positive (++) patch reaction to the sunscreen product. Results of repeated open application tests (ROATs) with Ethylhexyl Salicylate, 2% and 5%, were positive from day 4 on. A total of 29 consecutive eczema patients acting as controls were negative to Ethylhexyl Salicylate (at 5% and 2% in petrolatum). The patient was retested after 1 year, and the (+) reaction to Ethylhexyl Salicylate was reproduced. Patch test results for the following other salicylates were negative: Amyl Salicylate (5% in petrolatum), Methyl Salicylate (2% in petrolatum), Salicylic Acid (2% in petrolatum), and Sodium Salicylate (2% in petrolatum).

A woman who used a sunscreen containing Ethylhexyl Salicylate and had a history of rhinitis and intrinsic bronchial asthma developed erythematous micropapules (that progressed to microvesicles and vesicles) on the back, chest, and abdomen.[98] A skin biopsy of the lesions revealed a dermal hypersensitivity reaction that was consistent with contact dermatitis. Epicutaneous tests of the components of the sunscreen spray product were performed. Results were positive for Ethylhexyl Salicylate (test concentration not stated), but not for any of the other ingredients tested. Patch test results for the following other salicylates were negative: Methyl Salicylate, Sodium Salicylate, and Salicylic Acid. Photopatch test results were positive for Ethylhexyl Salicylate (test concentration not stated), but not for Methyl Salicylate, Sodium Salicylate, or Salicylic Acid.

Methyl Salicylate, Salicylic Acid, and Salicylates

Numerous case studies report toxic reactions to oral ingestion of salicylates.[1] *Dermal toxicity is described in the case literature as follows: dermal application of Salicylic Acid with concomitant oral administration of a nonsteroidal anti-inflammatory drug; following dermal application of a Salicylic Acid ointment in an elderly subject recovering from acute renal failure; topical application of Methyl Salicylate (and methanol) followed by the application of heat (skin and muscle necrosis and interstitial nephritis); and severe urticarial and angioedema with Methyl Salicylate exposure. In 20 patients with eczema or contact dermatitis, Methyl Salicylate at 67% is reported to cause irritation in 8 subjects; at 40%, 2 subjects; and at 38%, 15%, and 3.75% - no irritation in any subject. In 2 case studies of reactions to a wart paint containing Salicylic Acid, Salicylic Acid (tested at 3% in petrolatum) was not the causative agent. Methyl Salicylate (2%) in arachis oil and 2% aqueous Sodium Salicylate produced positive patch results in a patient with acute dermatitis who had been using an ointment containing menthol and camphor. Methyl Salicylate (12%) and Salicylic Acid (5%) in yellow soft paraffin produced positive patch tests in 4 patients with dermatitis and one with psoriasis, all with some history of exposure to salicylates.*

Other Clinical Reports

Dermal

Salicylic Acid

In patients with venous leg eczema, Salicylic Acid augmented histidine release in 3/320 challenged with ragweed pollen.[1] *Salicylic Acid exacerbated urticarial reactions to aspirin; 13 of 18 patients in one study and 6 of 20 in another. At 5% in petrolatum, however, Salicylic Acid did not cause any urticarial reactions in atopic, urticarial, non-atopic, and non-allergic patients. Salicylic Acid is well-documented to have keratolytic action on normal human skin. It had a small therapeutic effect in patients with various forms of ichthyosiform dermatoses, but decreased clearing in 8 of 11 psoriasis patients when compared to UV therapy alone. Therapeutic toxicities include nausea, vomiting, tinnitus, dizziness, headache, dullness, confusion, sweating, rapid pulse and breathing, skin eruptions, and fever. One estimate is that a blood concentration > 300 µg/ml of a salicylate should be considered toxic. Toxic reactions occur more frequently in children. Care must be taken in prescribing salicylate-containing medications because systemic clearance of salicylates may be reduced with age. Severe poisoning can result in delirium, hallucinations, convulsions, coma, and respiratory or cardiovascular collapse. Reversible hearing loss and tinnitus are reported side effects of salicylates at therapeutic levels.*

A clinical trial was conducted using 34 patients with mild to moderate acne who were selected for treatment with supramolecular Salicylic Acid and benzoyl peroxide + adapalene gel.[99] The authors noted that the following factors greatly limit the application of Salicylic Acid as an anti-acne agent: (1) Salicylic Acid is poorly soluble in water and tends to

precipitate out in a low-pH alcoholic solution. (2) The re-crystallization of Salicylic Acid in the formulation not only decreases the bioavailability of the active ingredient, but also leads to skin irritation. (3) Salicylic Acid (2%; pH range: 2.5-2.8) tends to cause skin irritation upon application to the skin. Thus, in order to overcome technical difficulties, the authors noted that a supramolecular approach was developed to selectively self-assemble the poorly water-soluble Salicylic Acid into water-soluble, organized entities in the form of intermolecular complexes. This technology uses reversible and non-covalent bonding to form a water-soluble supramolecular Salicylic Acid complex, which results in a slow release upon application, achieves maximum efficacy in low pH, and reduces skin irritation. In this clinical trial, a 2% supramolecular Salicylic Acid cream (hydrogel) was applied randomly to one side of the face for 28 days. Benzoyl peroxide (5%) + 0.1% adapalene gel was applied to the other side of the face according to the same procedure. Common side effects, such as desquamation, dryness, burning, erythema, and pruritus were recorded and classified into mild, moderate, and severe grades. Three patients withdrew from the study due to the irritant contact dermatitis that was induced by benzoyl peroxide. There was no evidence of side effects to the 2% supramolecular Salicylic Acid cream.

Oral

Methyl Salicylate

Methyl Salicylate taken in quantities greater than or equal to 1 teaspoon are reported to be quite toxic (equivalent of the salicylate that could be derived from 20+ adult aspirin tablets.[1] *Accidental poisoning is not uncommon, especially in children; symptoms of poisoning include kidney irritation, vomiting, and convulsions. The average lethal dose of Methyl Salicylate is 10 ml for children and 30 ml for adults.*

Other

Sodium Salicylate

Sodium Salicylate injected in the skin of aspirin intolerant individuals affected several parameters as follows: 1/23 had a positive skin test to Sodium Salicylate; 2/31 were positive in the passive cutaneous anaphylaxis test; and 2/26 were positive in the lymphocyte transformation test.[1]

Salicylates

A review of radiographs taken in 155 cases of juvenile arthritis in which various forms of salicylates had been administered (method not stated) at concentrations ranging from 0.1 to 3.24 g for several months did not find any evidence of bone lesions.[1]

RIFM SAFETY ASSESSMENT CONCLUSION ON SALICYLATES

A published toxicologic and dermatologic assessment of salicylates used as fragrance ingredients is available from the Research Institute for Fragrance Materials (RIFM).[100] The RIFM Expert Panel concluded that, "based on the available data, and using the NOAEL values of 50 mg/kg body weight/day identified in subchronic and chronic toxicity studies, a MOS for systemic exposure of humans to the individual salicylates in cosmetic products may be calculated to range from 125 to 2,500,000 (depending upon the assumption of product use and bioavailability following dermal application) times the maximum daily exposure." This conclusion is based on a review of safety test data on salicylates that were available before and after publication of the initial CIR published final report on salicylates. Many of the studies are found in the original CIR Final Report on salicylates and in this report. Studies on salicylates with aromatic sidechains (i.e., Benzyl Salicylate) are also mentioned in the RIFM safety assessment conclusion. CIR is conducting a separate safety assessment of Benzyl Salicylate; therefore, such studies (on salicylates with aromatic sidechains) are not included in this re-review document or the original CIR Final Report, and are not relevant to this safety assessment. It should be noted that RIFM's conclusion should not be considered alone, but along with the more recent data summaries that are included in this report.

SUMMARY

The Panel published a Final Report on the Safety Assessment of Salicylic Acid and 16 salicylates in 2003. In accordance with its Procedures, the CIR evaluates the conclusions of previously-issued reports every 15 years; therefore, this re-review document has been prepared. MEA-Salicylate was recently re-reviewed via incorporation in the CIR safety assessment of Ethanolamine and Ethanolamine Salts; thus, it is not included in this re-review. Because Capryloyl Salicylic Acid appears to have been mischaracterized, it is also not included in this re-review and will be reassessed elsewhere.

The Final Report was reopened to revise the Panel's original conclusion and to add 3 structurally similar ingredients (Amyl Salicylate, Hexyl Salicylate, and Isotridecyl Salicylate). Thus, this re-review document relates to the ingredients in that original report (except MEA-Salicylate), as well as 3 additional salicylates that have been added to the safety assessment.

Of the 18 ingredients that are included herein, the greatest reported use frequency of 3974 uses is for Ethylhexyl Salicylate. The results of a concentration of use survey conducted in 2018 indicate that Butyloctyl Salicylate is being used at concentrations up to 35.9% in leave-on products (lipstick), which is the highest reported maximum use concentration for the salicylates that are being in this safety assessment. Salicylic Acid is used at concentrations up to 30% in rinse-off products (peels).

In vitro skin penetration data (human or rat skin) indicated that Ethylhexyl Salicylate and Methyl Salicylate were percutaneously absorbed. The results from another in vitro skin penetration study on Ethylhexyl Salicylate and Salicylic Acid involving human skin indicated that the skin permeability of both ingredients was relatively low. Additionally, the conversion of Methyl Salicylate to Salicylic Acid in hairless mouse skin in vitro following topical application of 1% Methyl to the skin was evaluated. Less than 5% of applied dose was metabolized to Salicylic Acid. In an in vitro percutaneous absorption study (porcine skin) on Salicylic Acid, 34.48% dermal absorption was reported. A dermal absorption value of 40.05% for Salicylic Acid was reported in another in vitro study in which [^{14}C]-Salicylic Acid was applied to porcine skin. The in vitro percutaneous absorption of [^{14}C]-Salicylic Acid was also evaluated using human abdominal skin samples (split-thickness). Study results provided a high-end estimate of skin absorption (worst case) of 50.09 ± 5.12%. When [^{14}C]-Salicylic Acid was applied to cadaverous skin in vitro, the total amount of [^{14}C]-Salicylic Acid absorbed in the skin (epidermis + dermis + receptor fluid) as a percent of the applied dose increased from 4.5% without occlusion, to 50.5% under 8 h of occlusion.

In an in vitro study on human placental absorption, Salicylic Acid (8 µg/ml) was dissolved into the maternal perfusate on the maternal side of the placenta. Results indicated the potential for Salicylic Acid to cross the placenta.

In in vivo studies, the percutaneous absorption of Methyl Salicylate has been demonstrated in pigs and humans, and the percutaneous absorption of Ethylhexyl Salicylate has been demonstrated in humans. The in vivo absorption of a formulation containing 20% Methyl Salicylate was studied using male Wistar rats. The levels of unhydrolyzed Methyl Salicylate in tissues below the treated site were low, i.e., only 2 to 3 µg/ml throughout the study period. A mathematical method was used to estimate total body absorption of Ethylhexyl Salicylate, Hexyl Salicylate, and Methyl Salicylate. The estimated total body absorption (skin area) values at 12 h were: 3.3 µg/1.4 m^2 (Ethylhexyl Salicylate), 27 µg/1.4 m^2 (Hexyl Salicylate), and 13,000 µg/1.4 m^2 (Methyl Salicylate). Reportedly, after oral ingestion, Methyl Salicylate is readily metabolized to Salicylic Acid. After oral administration, Salicylic Acid is well absorbed from the gastrointestinal tract and is rapidly distributed throughout the extracellular fluid and most tissues. High concentrations (not specified) are found in the liver and kidneys; and, 50% to 80% of Salicylic Acid in the plasma is bound to albumin and other proteins.

In acute dermal toxicity studies of Ethylhexyl Salicylate, Hexyl Salicylate, and Methyl Salicylate involving rabbits, the LD_{50} was > 5 g/kg for each salicylate. No signs of systemic toxicity were observed in rabbits after application of Salicylic Acid (0.5 g, moistened with 0.5 ml water) to the skin. An acute dermal LD_{50} of > 2 g/kg was reported for Sodium Salicylate in a study involving rats. An acute oral LD_{50} of > 5 g/kg for Ethylhexyl Salicylate and Hexyl Salicylate in studies involving rats has also been reported. In acute oral toxicity studies on Methyl Salicylate involving mice, the LD_{50} was calculated to be 1.39 g/kg (95% CI of 1.25 to 1.54 g/kg) and a dose of 0.5 g/kg was selected as the maximum tolerated dose. LD_{50} values in the range of 0.5 to 2 g/kg were reported following administration of a single oral dose of Salicylic Acid (in gum Arabic) to rats. The mean oral lethal dose of Sodium Salicylate in male and female Wistar rats was considered to be > 0.2 g/kg to ≤ 2 g/kg. In an acute inhalation toxicity study on Salicylic Acid involving rats, no significant gross pathological changes were observed and the 1-h LC_{50} was > 0.9 mg/l.

None of the rabbits died and there were no visible abnormalities at necropsy in a short-term dermal toxicity study on Salicylic Acid (in 8% propylene glycol butyl ether in ethanol). A 150 mg/kg/day dose of a Butyloctyl Salicylate trade name material was considered the NOEL in a short-tern oral toxicity study involving rats. The highest dose (1000 mg/kg/day) caused an increase in in mean prothrombin and activated partial thromboplastin times, but no macroscopic or microscopic pathological changes. In a short-term inhalation toxicity study involving mice, there were no test substance-related gross pathological or histopathological findings after inhalation of a fragrance mixture containing 5.8% Amyl Salicylate. Also, in a short-term inhalation toxicity study evaluating respiratory sensitization potential, Methyl Salicylate did not induce a measurable IL-4 response. There were no test substance-related gross pathological or histopathological findings in rats in a subchronic inhalation toxicity study of a fragrance mixture containing 4% Amyl Salicylate.

Two subchronic dermal studies involving rabbits were performed to evaluate the cutaneous and systemic toxicity of 2 cleansing formulations diluted to 0.25 % Salicylic Acid (dose volume of 2 ml/kg; dose = 10 mg/kg). Repeated applications

were made. None of the animals died, and histopathological examinations provided no evidence of systemic toxicity. Another subchronic study using rabbits involved topical doses up to 120 mg/kg Salicylic Acid. None of the animals died, but a low incidence of trace to mild myocardial degeneration was observed in all dose groups and in the vehicle control group at histopathological examination; there was no dose-response relationship for this finding.

In an in vitro developmental toxicity study involving Salicylic Acid, post-implantation rat embryos were cultured with Salicylic Acid concentrations of 10 to 1000 µg/ml. Salicylic Acid decreased all growth and developmental parameters in a concentration-dependent manner. The same results were reported for rat embryos cultured with Salicylic Acid or Sodium Salicylate at concentrations in the 0.1 to 0.6 mg/ml range. Because of the reduced absolute body weights of pups from the 250 mg/kg/day dose group in an oral developmental toxicity study involving rats, the NOEL for developmental toxicity of Ethylhexyl Salicylate was considered to be the lower dose of 80 mg/kg/day. Another developmental toxicity study on Ethylhexyl Salicylate was performed according to the same test procedure. Based on observations of increased post-implantation loss, reduction in the gestation index, and lower litter size, the NOAEL for developmental toxicity was determined to be 25 mg/kg/day. On postnatal day 1, 89% of the pups from dams (rats) that had received a single oral dose of 300 mg/kg Sodium Salicylate had supernumerary ribs. No external malformations of pups were observed. In another study, a 4.8% incidence of malformations (including exencephaly and spina bifida) was reported for fetuses from rats dosed with Sodium Salicylate (250 mg/kg/day) on gestation days 8 to 10. It has been reported that the use of Salicylic Acid in the third trimester can potentially cause closure of the ductus arteriosus and oligohydramnios.

Salicylic Acid was not genotoxic in the in vitro mouse lymphoma assay at doses up to 1400 µg/ml, with or without metabolic activation. In a mammalian cell genotoxicity test involving CHO cells, Sodium Salicylate was not genotoxic over the range of concentrations tested (0.06 to 0.5 mM), with or without metabolic activation.

Hairless mice were evaluated for skin cancer in a study in which the effects of synthetic solar light on the skin after application of a cream containing 2% or 4% Salicylic Acid were evaluated. It was concluded that Salicylic Acid had a protective effect against the photocarcinogenicity of light at lower intensities.

In an estrogen receptor binding study using a consensus modeling method, Ethylhexyl Salicylate was classified as an estrogen receptor non-binder, whereas Butyloctyl Salicylate was classified as having binding activity to the estrogen receptor. When the estrogenic activity of Ethylhexyl Salicylate was compared to 17-ß-estradiol in a recombinant yeast estrogen assay, the dose response curve for Ethylhexyl Salicylate was shallower than the one for 17-ß-estradiol and Ethylhexyl Salicylate had a submaximal response for estrogenic activity.

Undiluted Amyl Salicylate (0.1 g) was severely irritating to the skin of rabbits, but mildly irritating to the skin of guinea pigs. Undiluted Amyl Salicylate (0.05 g) did not cause skin irritation in miniature swine. Mild erythema was observed in the acute dermal toxicity study on Ethylhexyl Salicylate that is summarized in this safety assessment. In another test, the application of undiluted Ethylhexyl Salicylate to the skin of rabbits did not result in skin irritation.

Following intradermal injection, 0.1% Hexyl Salicylate (vehicle not reported) produced an irritation reaction in guinea pigs, but 5% Hexyl Salicylate (vehicle not reported) did not. An explanation for these results was not provided. In an irritation test in which patches containing up to 2% Hexyl Salicylate (0.1 ml) were applied to Dunkin/Hartley albino guinea pigs, slight erythema and edema were observed at concentrations of 0.25%, 0.5%, 1%, and 2%; very slight erythema was observed at a concentration of 0.1%. Patches saturated with concentrations up to 50% Hexyl Salicylate were applied to Dunkin/Hartley albino guinea pigs in another test, and slight skin irritation was observed at concentrations of 25% and 50%, but not 10%. The patch testing of hairless guinea pigs with Hexyl Salicylate (0.3 ml per patch) at concentrations up to 100% yielded negative results. Skin irritation also was not observed in miniature swine tested with undiluted Hexyl Salicylate (20 µl/5 cm^2). When the irritation potential of Hexyl Salicylate at concentrations up to 100% was evaluated using rabbits, patch test (0.5 ml per patch) results for 10%, 25%, 50%, and 100% Hexyl Salicylate were negative. Slight to moderate edema and erythema was observed rabbits in an acute dermal toxicity study on Hexyl Salicylate that is summarized in this safety assessment. Skin irritation was not observed in hairless mice tested with Hexyl Salicylate (20 µl/5 cm^2).

In a study in which Methyl Salicylate was applied to the skin of rabbits at concentrations up to 100%, skin irritation was observed only at concentrations of 25% and 100%. Flaking, hyperkeratosis, and dry desquamation were observed after an aliquot of 20 µl of undiluted wintergreen oil (contained 80 to 99% Methyl Salicylate) was applied to miniature swine. When Methyl Salicylate was applied repeatedly (twenty-one 0.1 ml applications) to guinea pigs in an open epicutaneous test, the minimal irritating concentration was determined to be 3% Methyl Salicylate. A minimally irritating concentration of 20% was determined in a skin irritation test on Methyl Salicylate. Slight to moderate edema and erythema was observed rabbits in an acute dermal toxicity study on 5 g/kg Methyl Salicylate that is summarized in this safety assessment. Mixed results were observed in irritation studies of Salicylic Acid. When Salicylic Acid (0.5 g in water) was applied to the skin of rabbits, there was no evidence of skin irritation. Salicylic Acid was irritating to the skin of rabbits at concentrations of 10% and 25%. The

single application of alcoholic solutions containing 2% Salicylic Acid to the skin of rabbits resulted in mild to no skin irritation. Repeated open applications of 2.5% and 5% hydroalcoholic solutions of Salicylic Acid to the skin of guinea pigs caused mild skin irritation. In skin irritation tests on 2 cleansing formulations containing 0.5% Salicylic Acid, the undiluted product or the product diluted to a concentration of 50% w/v in distilled water (effective Salicylic Acid concentration = 0.25%) was applied repeatedly to the skin of rabbits. The products tested were considered slightly and transiently irritating to the skin when applied undiluted or diluted to a concentration of 50%. Cleansing formulations containing 0.5% to 6% Salicylic Acid in propylene glycol butyl ether/ethanol were applied repeatedly to the skin of rabbits. The formulations were classified as skin irritants. Sodium Salicylate (0.5 g in water) was non-irritating to the skin of rabbits.

Skin irritation was not observed in a 48-h occlusive patch test on 32% Amyl Salicylate (in acetone) involving 50 subjects. Skin irritation also was not observed in a 48-h closed patch test on 4% Ethylhexyl Salicylate (in petrolatum) involving 23 subjects. Using Hilltop® chambers on 30% Hexyl Salicylate involving 103 subjects, skin irritation was not observed. Skin irritation also was not observed in a 48-h patch test on 3% Hexyl Salicylate involving 22 subjects, in a 4-h patch (Hilltop® chamber) test on undiluted Hexyl Salicylate involving 30 subjects, or in a 24-h patch (Hilltop® chamber) test on Hexyl Salicylate at concentrations up to 30% in a study involving 56 subjects.

Skin irritation was not observed in a 48-h occlusive patch test involving 27 subjects or in a 48-h occlusive patch test on 12% wintergreen oil (containing 80 to 99% Methyl Salicylate) involving 25 subjects. In a study evaluating the skin irritation potential of Methyl Salicylate (in 80% ethanol and 20% deionized water) pipetted (25 ml) onto the skin of 9 subjects, 30% and 60% Methyl Salicylate caused skin irritation. It has been noted that possible complications relating to the topical use of Salicylic Acid as a peeling agent include persistent erythema and pruritus. A potential for skin irritation was demonstrated in a cumulative irritation study in which a shampoo containing 3% Salicylic Acid was applied (as a 4% dilution) continuously, under a patch, to human subjects (number not stated). Exaggerated use repeated application tests (4 studies; number of subjects not stated) were performed to compare shampoos (prototype or commercial formulations) containing 3% Salicylic Acid and shampoo formulations containing up to 2% Salicylic Acid with a placebo). Results indicated no statistically significant differences in combined irritation or TEWL. A cream containing 2% Salicylic Acid was classified as non-irritating when applied repeatedly to the skin of human subjects.

A surfactant-based product containing 2% Salicylic Acid (pH of 3.8; diluted concentration not stated) was mildly irritating when applied repeatedly to the skin of human subjects (number not stated). In another test, the same product was classified as probably mildly irritating under normal use conditions. Daily applications of a hydroalcoholic solution containing 0.5% Salicylic Acid (pH 2.82) to the skin of human subjects (number not stated) did not result in skin irritation. When a hydroalcoholic gel containing 2% Salicylic Acid was applied repeatedly to the skin of human subjects (number not stated), slight skin irritation was observed. Two creams containing 2% Salicylic Acid (each in a separate test) were applied repeatedly to the skin of human subjects (number not stated). One cream was classified as non-irritating, and the other was classified as moderately irritating. In a repeated open application test, a cream containing 2% Salicylic Acid was applied to the backs of human subjects (number not stated). The cream did not cause reactions that were different from those induced by the control. In a home use test, a non-alcoholic lotion containing 2% Salicylic Acid caused mild, transient reactions when applied repeatedly to the skin of human subjects (number not stated). In second home use test involving human subjects (number not stated; 50% had sensitive skin), repeated applications of a non-alcoholic cream containing 2% Salicylic Acid caused little or no skin irritation. In a third home use test involving 194 human subjects, non-alcoholic lotions and moisturizers containing 2% Salicylic Acid (pH 2.28) caused itching, stinging, mild erythema, and burning. Repeated applications of a cream containing 1.5 % Salicylic to the skin of human subjects (number not stated) for 21 days caused slight skin irritation.

Formulations containing up to 7.5% Salicylic Acid were applied to groups of 6 rabbits. The 3.5%, 5%, and 7.5% formulations caused desquamation, an inflammatory reaction, and a comedogenic effect.

Hexyl Salicylate was predicted to be a skin sensitizer in the Genomic Allergen Rapid Detection assay. Using an integrated testing strategy for skin sensitization that focuses on 3 in vitro methods that cover the first 3 steps of the adverse outcome pathway, results for the sensitization potential of Salicylic Acid were considered equivocal, but ultimately were considered positive results.

In the LLNA, a very low EC3 value (0.18%) was reported for Hexyl Salicylate, which may have been due to possibly sensitizing impurities. When Hexyl Salicylate was tested for sensitization potential in guinea pigs using a modified Draize procedure, sensitization was observed after intradermal challenge with 0.1% Hexyl Salicylate and topical challenge with 5% Hexyl Salicylate. In a photoallergy test involving hairless albino guinea pigs, sensitization reactions were not observed after challenge with 50% and 100% Hexyl Salicylate. In a Magnusson-Kligman guinea pig maximization test, skin sensitization was not observed in guinea pigs challenged with 10% Hexyl Salicylate in acetone.

Methyl Salicylate (50%) was predicted to be a non-sensitizer in the LLNA. The same was true for Salicylic Acid (concentration not stated) and 0.7 µM Methyl Salicylate. In a modified Buehler test, Methyl Salicylate (25% w/v in hydro-alcoholic solution) did not cause skin sensitization in a group of 20 guinea pigs. The same was true for Salicylic Acid (25% w/v in hydro-alcoholic solution) when tested according to the same procedure.

Neither skin irritation nor sensitization was observed in an HRIPT in which 52 subjects were patch tested with undiluted Butyloctyl Salicylate. A human skin sensitization NOEL of 35,433 µg/cm^2 (study details not provided) has been reported for Hexyl Salicylate. Also, in a human maximization test on Hexyl Salicylate, no induction was observed at a dose of 20,654 µg/cm^2 (study details not included). In an HRIPT (Hilltop® chamber system) involving 103 subjects, sensitization reactions to 30% Hexyl Salicylate were not observed. Maximization test results for 3% Hexyl Salicylate in petrolatum were negative in 22 subjects.

In a human maximization test on wintergreen oil (contains 80 to 99% Methyl Salicylate) involving 25 volunteers, sensitization was not observed at a concentration of 12%. Maximization test results for 8% Methyl Salicylate were also negative in 27 subjects. In an HRIPT involving 39 subjects, 1.25% Methyl Salicylate did not induce skin sensitization. Product formulations containing 2% Salicylic Acid did not cause sensitization in HRIPTs (test populations: 84 to 198 subjects).

Amyl Salicylate was classified as a non-sensitizer in a QSAR system for estimating sensitization potency that incorporates skin metabolism and considers the potential of parent chemicals and their activated metabolites to react with skin proteins. Hexyl Salicylate and Methyl Salicylate were classified as non-allergenic in a study that was performed to validate a QSAR rank model for grading allergenic potency. An exposure-based QRA methodology has been used to determine acceptable exposure limits (in finished product) for Hexyl Salicylate. Limitations for various finished product categories have been established, ranging from 1.3% to 25.7%.

Results for Ethylhexyl Salicylate were classified as negative in the 3T3 neutral red uptake phototoxicity test at concentrations ranging from 0.1 to 316 µg/ml. Undiluted Hexyl Salicylate was not phototoxic in studies involving mice or miniature swine. At concentrations ranging from 5% to 100%, Hexyl Salicylate was not phototoxic to albino hairless guinea pigs. Hexyl Salicylate did not induce photoallergenicity in groups of albino hairless guinea pigs tested with concentrations of 50% and 100%.

The phototoxicity of undiluted wintergreen oil (contained 80% to 99% Methyl Salicylate) was evaluated using miniature swine, and results were negative. Methyl Salicylate (50% in diethyl phthalate) was evaluated for phototoxicity and photoallergenicity potential using 25 guinea pigs. Both evaluations involved exposure to UVA and UVB light, and the test substance was classified as non-phototoxic and non-photoallergenic. There also was no evidence of phototoxicity in 56 subjects tested with Hexyl Salicylate at concentrations of 0.3%, 3%, and 30%.

Sodium Salicylate was classified as an ocular irritant using the EpiOcular™ reconstructed human cornea-like tissue model, whereby the tissues were incubated with 50 µl of Sodium Salicylate. Undiluted Ethylhexyl Salicylate was classified as a non-irritant in an ocular irritation study involving rabbits. In an ocular irritation test involving rabbits, the instillation of Methyl Salicylate (0.0005 ml) caused a grade 3 reaction (necrosis on 13 to 37% of the cornea). Intense conjunctival irritation, accompanied by chemosis and considerable discharge, was observed in rabbits in which 1.25% Methyl Salicylate (0.1 ml) was instilled into the eyes. Salicylic Acid (purity not stated) caused severe ocular irritation in rabbits. Numerous formulations (non-alcoholic and hydroalcoholic) that contained Salicylic Acid at concentrations ranging from 0.05% to 2% have been evaluated in the Draize test (rabbits). The investigators considered these formulations to be mild irritants when instilled into the eyes of rabbits. Sodium Salicylate was classified as mildly irritating to the eyes of rabbits.

In multicenter studies, an irritant or doubtful reaction was observed in 2 of 1323 patients patch (Finn chamber) tested with 1% Amyl Salicylate and 3 positive reactions and 5 doubtful reactions were observed in a population of 1855 patients patch tested with 5% Amyl Salicylate. No reactions were observed in a multicenter study in which 218 fragrance-sensitive patients with contact dermatitis were patch tested with 5% Hexyl Salicylate.

Positive patch test reactions to 2% and 5% Ethylhexyl Salicylate were reported in another case report (patient with facial telangiectasia and history of rosacea), but reactions to these test concentrations were negative in the 29 consecutive eczema patients that served as controls. Also, patch test reactions to the following salicylates were negative in this case report: 5% Amyl Salicylate, 2% Methyl Salicylate, 2% Salicylic Acid, and 2% Sodium Salicylate. A contact dermatitis patient had a positive patch test reaction to Ethylhexyl Salicylate (concentration not stated), but not to Salicylic Acid, Methyl Salicylate, or Sodium Salicylate. Topical Salicylic Acid hypersensitivity (pain and swelling of digits) was observed in a woman with no known allergies after use of OTC topical Salicylic Acid for the treatment of warts. In a clinical trial

involving 34 patients with mild to moderate acne, repeated applications of a 2% supramolecular Salicylic Acid cream (hydrogel) did not result in any adverse effects on the skin.

Due to concern over the potential reproductive toxicity of Salicylic Acid in humans, MOS calculations taking into consideration maximum use concentrations of this ingredient in rinse-off and leave-on cosmetic products were performed. The calculations yielded MOS values of 370 and 432 for rinse-off products containing 30% Salicylic Acid (actual exposure measurements were used for the 30% Salicylic Acid peel product) and a MOS of 177 for leave-on products (body lotion + face cream + hand cream) containing up to 2% Salicylic Acid. An additional risk assessment was performed because the maximum use concentration of 35.9% Butyloctyl Salicylate in lipsticks exceeds the IFRA's 1% concentration limit (relative to sensitization potential) for Butyloctyl Salicylate in lip products of all types. A MOS of 440 was calculated in this risk assessment.

In a toxicological and dermatological assessment of salicylates when used as fragrance ingredients, performed by RIFM, a MOS for systemic exposure is mentioned. Based on NOAEL values of 50 mg/kg body weight/day in subchronic and chronic toxicity studies, a MOS for systemic exposure of humans to the individual salicylates in cosmetic products may be calculated to range from 125 to 2,500,000 (depending upon the assumption of bioavailability and product use following dermal application) times the maximum daily exposure.

DISCUSSION

In accordance with its Procedures, the CIR evaluates the conclusions of previously-issued reports every 15 years. MEA-Salicylate was previously re-reviewed via incorporation in the CIR safety assessment of Ethanolamine and Ethanolamine Salts; thus, it is not included in this re-review. Because Capryloyl Salicylic Acid appears to have been mischaracterized, it is also not included in this re-review and will be reassessed elsewhere. After reviewing the available new data on the original group of ingredients and the available data on 3 additional, structurally similar salicylates (Amyl Salicylate, Hexyl Salicylate, and Isotridecyl Salicylate), the Panel re-opened the report to revise the original conclusion, add the 3 additional salicylates, and remove the qualification relating to formulating products to avoid increasing the skin's sun sensitivity. The reason for omitting this qualification is based on results from an NTP photocarcinogenicity study indicating that Salicylic Acid has some protective effect against photocarcinogenicity, at lower light intensities. In the NTP study, the effects of synthetic solar light on the skin of hairless mice that had been treated with creams containing 2% or 4% Salicylic Acid were evaluated. Creams containing Salicylic Acid decreased the incidence of skin tumors in mice receiving the lower of the two light intensities.

The Panel expressed concern over the reproductive toxicity of Salicylic Acid, having considered that, in the third trimester, the use of Salicylic Acid can potentially cause early closure of ductus arteriosus and oligohydramnios. Thus, the Panel requested that CIR calculate an MOS for Salicylic Acid exposure, taking into consideration the extent of dermal absorption during cosmetic product use (at the highest maximum use concentration in leave-on products). However, because the highest reported maximum use concentration of Salicylic Acid in cosmetic products is 30% in a rinse-off product (peel) and the highest reported maximum use concentration of Salicylic Acid in leave-on products is 2% (face and neck products), it was determined that the MOS calculations should involve these two concentrations. Furthermore, given the potential for whole-body exposure during the application of body and hand products (leave-on products) containing a highest maximum use concentration of 0.2% Salicylic Acid, it was determined that this concentration should also be included.

For the 30% peel product, two MOS were calculated. One compared the mean plasma Salicylic Acid concentration following application of the product to blood concentrations of salicylate that are considered toxic, and the other was a comparison to blood concentrations associated with salicylism. The calculations yielded MOS values of 370 and 432, respectively. An MOS of 177 was calculated for the combination of leave-on products containing 0.2% or 2% Salicylic Acid (body lotion (0.2%) + face cream (2%) + hand cream (0.2%)). It is very likely that these wide margins of safety ensure that exposure to Salicylic Acid at use concentrations in rinse-off or leave-on cosmetic products would not result in reproductive or developmental toxicity.

An additional risk assessment was performed because the maximum use concentration of 35.9% Butyloctyl Salicylate in lipsticks exceeds IFRA's 1% concentration limit (relative to sensitization potential) for Butyloctyl Salicylate in lip products of all types. In this risk assessment (assuming 50% skin absorption), a total dose of Butyloctyl Salicylate exposure during the application of lipstick was estimated and a MOS of 440 was calculated. It was also noted that a more conservative assumption that 100% of lipstick is incidentally ingested would result in a MOS of 220. It is very likely that these wide margins of safety ensure that exposure to Salicylic Acid at use concentrations in lipsticks would not induce toxicity.

The Panel acknowledged positive sensitization data on the salicylates and noted that the potential for induction of skin sensitization varies depending on a number of factors, including the area of product application. Thus, formulators should assess the potential for final formulations to induce sensitization using a QRA or other accepted methodologies. The Panel was also concerned that the potential exists for dermal irritation with the use of products formulated using salicylates. The Panel also specified that products containing salicylates must be formulated to be non-irritating.

The Panel discussed the issue of incidental inhalation exposure from powders and hair sprays. The Council's survey results indicate that the highest maximum ingredient use concentration in a spray product is being reported for Ethylhexyl Salicylate, which is used in suntan aerosol and pump sprays at concentrations up to 5%. Also, Salicylic Acid is being used in suntan product pump sprays at concentrations up to 0.5%. The highest maximum ingredient use concentration in a powder is being reported for Butyloctyl Salicylate, which is being used at concentrations up to 3.6% in face powders. The Panel noted that in aerosol products, 95% – 99% of droplets/particles would not be respirable to any appreciable amount. Furthermore, droplets/particles deposited in the nasopharyngeal or bronchial regions of the respiratory tract present no toxicological concerns based on the chemical and biological properties of these ingredients. Coupled with the small actual exposure in the breathing zone and the concentrations at which the ingredients are used, the available information indicates that incidental inhalation would not be a significant route of exposure that might lead to local respiratory or systemic effects. A detailed discussion and summary of the Panel's approach to evaluating incidental inhalation exposures to ingredients in cosmetic products is available at https://www.cir-safety.org/cir-findings.

CONCLUSION

The Panel concluded that the following ingredients are safe in cosmetics in the present practices of use and concentration described in the safety assessment, when formulated to be non-irritating and non-sensitizing, which may be based on a quantitative risk assessment (QRA):

Salicylic Acid
Amyl Salicylate
Butyloctyl Salicylate
Calcium Salicylate*
C12-15 Alkyl Salicylate*
Ethylhexyl Salicylate
Hexyl Salicylate
Hexyldodecyl Salicylate*
Isocetyl Salicylate*
Isodecyl Salicylate
Isotridecyl Salicylate*
Magnesium Salicylate
Methyl Salicylate
Myristyl Salicylate*
Potassium Salicylate*
Sodium Salicylate
TEA-Salicylate
Tridecyl Salicylate

**Not reported to be in current use. Were the ingredient in this group not in current use to be used in the future, the expectation is that it would be used in product categories and at concentrations comparable to others in this group.*

TABLES

Table 1. Definitions, idealized structures, and functions of the ingredients in this safety assessment.[3; *CIR Staff*]

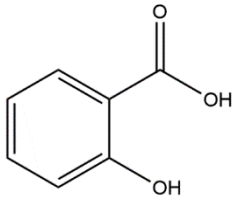
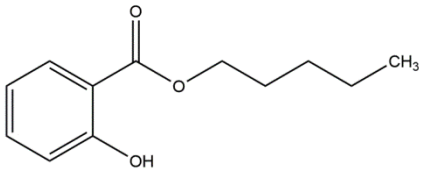
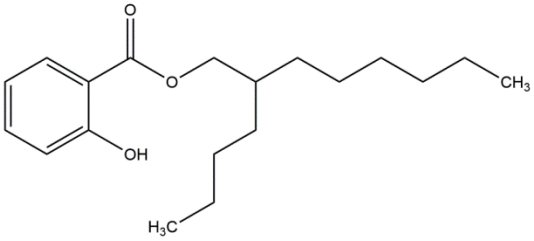
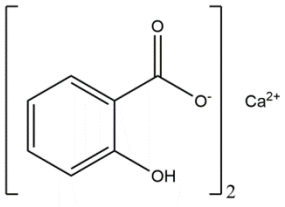
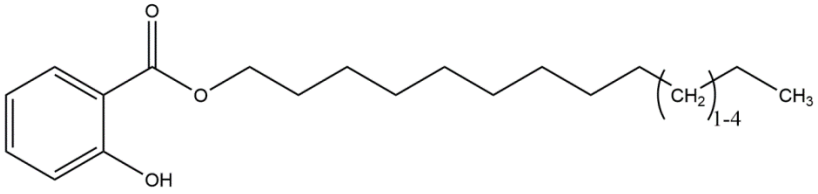
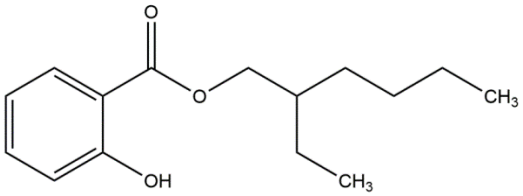
Ingredient CAS No.	Definition & Structures	Function(s)
Salicylic Acid 69-72-7	Salicylic Acid is the aromatic acid that conforms to the formula: 	Antiacne Agents; Antidandruff Agents; Corn/Callus/Wart Removers; Denaturants; Exfoliants; Fragrance Ingredients; Hair Conditioning Agents; Hair-Waving/Straightening Agents; Skin-Conditioning Agents - Miscellaneous
Amyl Salicylate 2050-08-0	Amyl Salicylate is the ester of amyl alcohol and Salicylic Acid that conforms to the formula: 	Fragrance Ingredients
Butyloctyl Salicylate 190085-41-7	Butyloctyl Salicylate is the organic compound that conforms to the formula: 	Hair Conditioning Agents; Skin-Conditioning Agents - Miscellaneous; Solvents
Calcium Salicylate 824-35-1	Calcium Salicylate is the calcium salt of Salicylic Acid that conforms to the formula: 	Preservatives
C12-15 Alkyl Salicylate	C12-15 Alkyl Salicylate is the ester of C12-15 alcohols and salicylic acid. It conforms generally to the formula: where R represents the C12-15 alkyl group. 	Skin-Conditioning Agents - Miscellaneous
Ethylhexyl Salicylate 118-60-5	Ethylhexyl Salicylate is the ester of 2-ethylhexyl alcohol and Salicylic Acid. It conforms to the formula: 	Fragrance Ingredients; Light Stabilizers; Sunscreen Agents

Table 1. Definitions, idealized structures, and functions of the ingredients in this safety assessment.[3; *CIR Staff*]

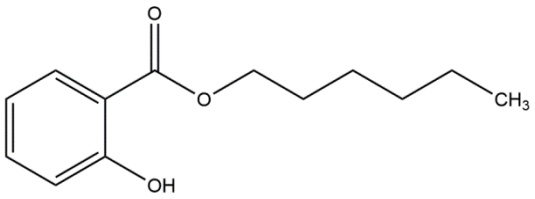
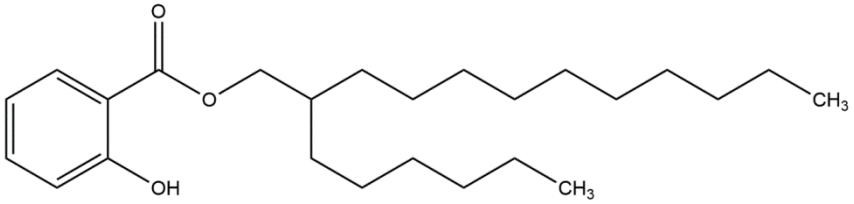
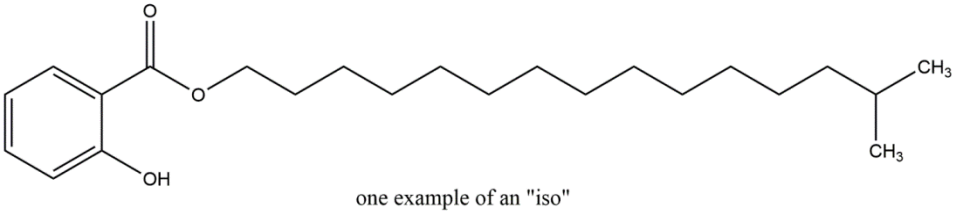
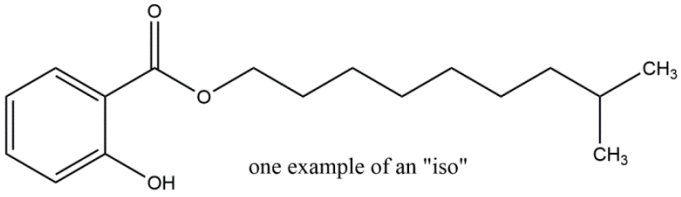
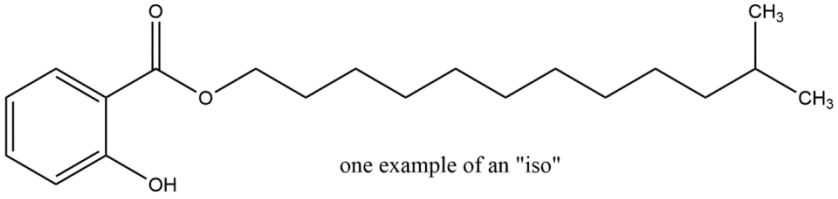
Ingredient CAS No.	Definition & Structures	Function(s)
Hexyl Salicylate 6259-76-3	Hexyl Salicylate is the organic compound that conforms to the formula: 	Fragrance Ingredients; Skin-Conditioning Agents - Occlusive
Hexyldodecyl Salicylate 220778-06-3	Hexyldodecyl Salicylate is the organic compound that conforms to the formula: 	Hair Conditioning Agents; Skin-Conditioning Agents - Miscellaneous; Solvents
Isocetyl Salicylate 138208-68-1	Isocetyl Salicylate is the ester of Isocetyl Alcohol and Salicylic Acid. It conforms to the formula:  one example of an "iso"	Skin-Conditioning Agents - Miscellaneous
Isodecyl Salicylate 85252-25-1	Isodecyl Salicylate is the ester of branched chain decyl alcohols and Salicylic Acid that conforms to the formula:  one example of an "iso"	Skin-Conditioning Agents - Miscellaneous
Isotridecyl Salicylate 1863871-63-9	Isotridecyl Salicylate is the organic compound that conforms to the formula:  one example of an "iso"	Antistatic Agents; Skin-Conditioning Agents - Miscellaneous

Table 1. Definitions, idealized structures, and functions of the ingredients in this safety assessment.[3; *CIR Staff*]

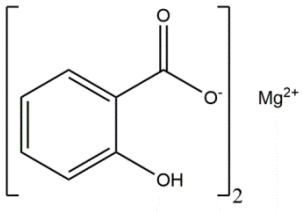
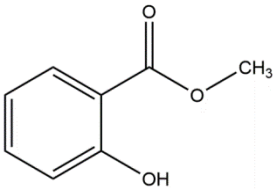
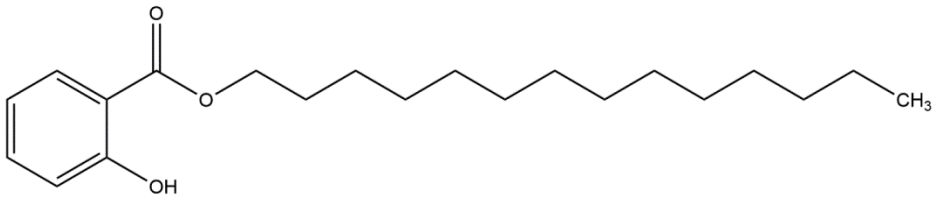
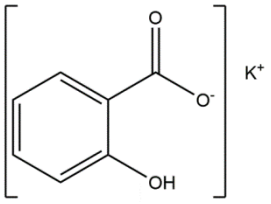
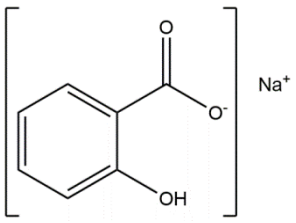
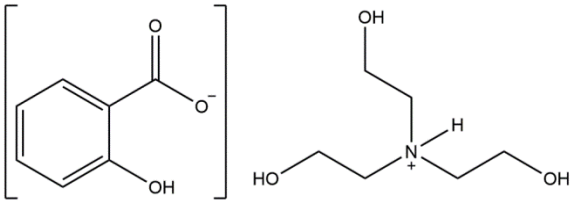
Ingredient CAS No.	Definition & Structures	Function(s)
Magnesium Salicylate 18917-89-0 551-37-1	Magnesium Salicylate is the magnesium salt of Salicylic Acid that conforms to the formula: 	Preservatives
Methyl Salicylate 119-36-8	Methyl Salicylate is the ester of methyl alcohol and Salicylic Acid. It conforms to the formula: 	Denaturants; External Analgesics; Flavoring Agents; Fragrance Ingredients; Oral Health Care Drugs
Myristyl Salicylate 19666-17-2	Myristyl Salicylate is the ester of myristyl alcohol and Salicylic Acid. It conforms to the formula: 	Not Reported
Potassium Salicylate 578-36-9	Potassium Salicylate is the potassium salt of Salicylic Acid that conforms to the formula: 	Cosmetic Biocides; Preservatives
Sodium Salicylate 54-21-7	Sodium Salicylate is the sodium salt of Salicylic Acid that conforms to the formula: 	Denaturants; Preservatives
TEA-Salicylate 2174-16-5	TEA-Salicylate is the triethanolamine salt of Salicylic Acid that conforms generally to the formula: 	Light Stabilizers; Sunscreen Agents

Table 1. Definitions, idealized structures, and functions of the ingredients in this safety assessment.[3; *CIR Staff*]

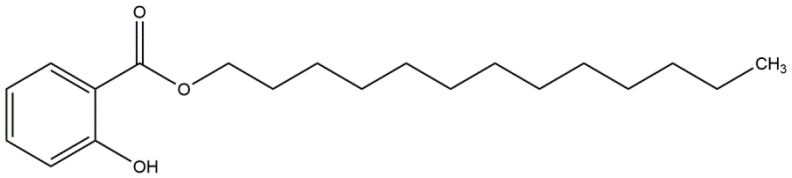
Ingredient CAS No.	Definition & Structures	Function(s)
Tridecyl Salicylate 19666-16-1	Tridecyl Salicylate is the ester of tridecyl alcohol and Salicylic Acid. It conforms to the formula: 	Skin-Conditioning Agents - Miscellaneous

Table 2. Chemical and Physical Properties of Salicylic Acid and Salicylates

Property	Value/Results	Reference
Amyl Salicylate		
Molecular weight (Da)	208.26	10
Density (g/cm^3)	1.0552 (experimental)	12
Boiling point (ºC)	270 (experimental)	12
log P	3.12 (estimated)	10
pK_a	10.4 (estimated)	10
Butyloctyl Salicylate		
Molecular weight (Da)	306.45	10
log P	6.03 (estimated)	10
pK_a	10.3 (estimated)	10
Calcium Salicylate		
Formula weight (Da)	314.31	10
C12-15 Alkyl Salicylate		
Molecular weight (Da)	306.45 – 348.53	10
Ethylhexyl Salicylate		
Form	Colorless liquid	7
Molecular weight (Da)	250.34	10
Water solubility (mg/l at 25ºC)	0.7171 (estimated)	7
Vapor pressure (mm Hg at 25ºC)	0.00000436	7
Flash point (ºC)	> 200	7
log K_{ow}	6.02 (estimated)	7
Hexyl Salicylate		
Form	Colorless, oily liquid	8
Molecular weight (Da)	222.28	10
Water solubility (mg/l at 25ºC)	6.084 (estimated)	8
Vapor pressure (mm Hg at 20ºC)	< 0.001	8
Boiling Point (ºC)	> 200	8
Log K_{ow}	5.06 (estimated)	8
Hexyldodecyl Salicylate		
Molecular weight (Da)	390.61	10
Density (g/cm^3)	0.960 ± 0.06 (predicted)	12
Boiling point (ºC)	474.3 ± 18.0 (predicted)	12
log P	8.53 (estimated)	10
pK_a	10.3 (estimated)	10
Isocetyl Salicylate		
Molecular weight (Da)	326.55	10
log P	7.63 (estimated)	10
pK_a	10.4 (estimated)	10
Isodecyl Salicylate		
Molecular weight (Da)	278.39	10
log P	5.12 (estimated)	10
pK_a	10.4 (estimated)	10
Isotridecyl Salicylate		
Molecular weight (Da)	320.47	10
log P	6.37 (estimated)	10

Table 2. Chemical and Physical Properties of Salicylic Acid and Salicylates

Property	Value/Results	Reference
pK_a	10.4 (estimated)	10
Magnesium Salicylate		
Formula weight (Da)	298.53	10
Methyl Salicylate		
Form	Clear, colorless liquid	9
Molecular weight (Da)	152.15	10
Specific gravity	1.18	9
Water solubility (mg/l at 25ºC)	1875 (estimated)	9
Vapor pressure (mm Hg at 25ºC)	0.09 (estimated)	9
Boiling point (ºC)	222	9
Flash point (ºF)	> 212	9
log K_{ow}	2.6 (estimated)	9
Myristyl Salicylate		
Molecular weight (Da)	334.50	10
log P	6.88 (estimated)	10
pK_a	10.4 (estimated)	10
Potassium Salicylate		
Formula weight (Da)	176.21	10
Salicylic Acid		
Molecular weight (Da)	138.12	10
Density (g/cm^3)	1.443 (experimental)	12
Melting point (ºC)	157-159 (experimental)	12
Boiling point (ºC)	211 (experimental)	12
log P	1.2 (estimated)	10
pK_a	3.01 (1^{st} - carboxylic; estimated)	10
Sodium Salicylate		
Formula weight (Da)	160.10	10
Melting point (ºC)	213 (decomposes, experimental)	12
TEA Salicylate		
Formula weight (Da)	287.31	10
Tridecyl Salicylate		
Molecular weight (Da)	320.47	10
Density (g/cm^3)	0.989 ± 0.06 (predicted)	12
Boiling point (ºC)	4.11 ± 18.0 (predicted)	12
log P	6.46 (estimated)	10
pK_a	10.4 (estimated)	10

Table 3. Frequency and Concentration of Use of Salicylates According to Duration and Exposure

	# of Uses		*Max Conc of Use (%)*		*# of Uses*		*Max Conc of Use (%)*	
	Amyl Salicylate				**Butyloctyl Salicylate**			
	2019[17]	**---**	**2018[18]**	**---**	**2019[17]**	**1998[1]**	**2018[18]**	**2000[1]**
Totals*	**10**		***0.0023-0.26***		**28**	NR	***1-35.9***	**0.5-5**
Duration of Use								
Leave-On	*1*		*0.0023-0.23*		*27*	*NR*	*1-35.9*	*0.5-5*
Rinse-Off	*9*		*0.02-0.26*		*1*	*NR*	*NR*	*NR*
Diluted for (Bath) Use	NR		*NR*		NR	*NR*	*NR*	*NR*
Eye Area	NR		NR		1	NR	3.6	NR
Incidental Ingestion	NR		NR		12	NR	35.9	NR
Incidental Inhalation-Spray	NR		0.0023-0.0058; 0.12[a]		6[a]; 3[b]	NR	1-3	4-5[a]
Incidental Inhalation-Powder	NR		NR		3[b]	NR	3.6	0.5
Dermal Contact	1		0.02-0.26		16	NR	1-10	0.5-5 NR
Deodorant (underarm)	NR		0.23		NR	NR	NR	NR
Hair - Non-Coloring	9		0.0023-0.12		NR	NR	NR	NR
Hair-Coloring	NR		NR		NR	NR	NR	NR
Nail	NR		NR		NR	NR	NR	NR
Mucous Membrane	NR		0.26		12	NR	35.9	NR
Baby Products	NR		NR		NR	NR	NR	NR
	Ethylhexyl Salicylate				**Hexyl Salicylate**			
	2019[17]	**1998[1]**	**2018[18]**	**2000[1]**	**2019[17]**	**---**	**2018[18]**	**---**
Totals*	**3974**	**83**	**0.0003-5.1**	**0.001-8**	**8**		**0.013-0.52**	
Leave-On	*3164*	*80*	*0.0003-5.1*	*0.001-8*	*5*		*0.013-0.12*	
Rinse-Off	*795*	*3*	*0.001-0.21*	*0.001-0.005*	*3*		*0.032-0.52*	
Diluted for (Bath) Use	*15*	*NR*	*0.2*	*NR*	*NR*		NR	
Eye Area	3	NR	0.1	NR	NR		0.00074	
Incidental Ingestion	54	2	4-4.5	8	NR		NR	
Incidental Inhalation-Spray	2660; 182[a]; 90[b]	18;2[b]	0.00099-5; 0.012-0.05[a]	0.001-0.01; 0.001-5[b]	2;1[a]; 1[b]		0.013-0.023; 0.11[a]	
Incidental Inhalation-Powder	5; 90[b]	2[b]	NR	5; 0.001-5[b]	1[b]		NR	
Dermal Contact	3777	45	0.0003-5.1	0.5-5	5		0.02-0.52	
Deodorant (underarm)	6	NR	0.0016	NR	NR		0.097	
Hair - Non-Coloring	132	35	0.00099-0.2	0.001-0.01	NR		0.013-0.21	
Hair-Coloring	5	NR	0.012	NR	3		0.5	
Nail	6	1	0.15	0.1	NR		NR	
Mucous Membrane	774	2	0.0012-4.5	8	NR		0.52	
Baby Products	NR	NR	NR	NR	NR		NR	
	Isodecyl Salicylate				**Magnesium Salicylate**			
	2019[17]	**1998[1]**	**2018[18]**	**2000[1]**	**2019[17]**	**1998[1]**	**2018[18]**	**2000[1]**
Totals*	**20**	**3**	**2.5**	NR	**11**	NR	**0.2**	NR
Leave-On	*19*	*2*	*2.5*	*NR*	*11*	*NR*	*0.2*	*NR*
Rinse-Off	*1*	*1*	*NR*	*NR*	*NR*	*NR*	*NR*	*NR*
Diluted for (Bath) Use	*NR*	*NR*	*NR*	*NR*	*NR*	*NR*	*NR*	*NR*
Eye Area	1	NR	NR	NR	11	NR	0.2	NR
Incidental Ingestion	NR	NR	NR	NR	NR	NR	NR	NR
Incidental Inhalation-Spray	11[a]; 7[b]	2[a]	NR	NR	NR	NR	NR	NR
Incidental Inhalation-Powder	7[b]	NR	NR	NR	NR	NR	NR	NR
Dermal Contact	20	3	2.5	NR	2	NR	0.2	NR
Deodorant (underarm)	NR	NR	NR	NR	NR	NR	NR	NR
Hair - Non-Coloring	NR	NR	NR	NR	NR	NR	NR	NR
Hair-Coloring	NR	NR	NR	NR	NR	NR	NR	NR
Nail	NR	NR	NR	NR	NR	NR	NR	NR
Mucous Membrane	NR	NR	NR	NR	NR	NR	NR	NR
Baby Products	NR	NR	NR	NR	NR	NR	NR	NR

Table 3. Frequency and Concentration of Use of Salicylates According to Duration and Exposure.

	# of Uses		*Max Conc of Use (%)*		*# of Uses*		*Max Conc of Use (%)*	
	Methyl Salicylate				**Salicylic Acid**			
	2019[17]	**1998[1]**	**2018[18]**	**2000[1]**	**2019[17]**	**1998[1]**	**2018[18]**	**2000[1]**
Totals*	**34**	**25**	**0.00000006-1**	**0.0001-0.6**	**1429**	**107**	**0.00001-30**	**0.0008-3**
Leave-On	*18*	*4*	*0.0000013-1*	*0.02*	*665*	*62*	*0.00001-2*	*0.02-3*
Rinse-Off	*15*	*20*	*0.00000006-0.23*	*0.0001-0.6*	*760*	*45*	*0.01-30*	*0.0008-3*
Diluted for (Bath) Use	*1*	*1*	*0.0016*	*NR*	*4*	*NR*	*NR*	*NR*
Eye Area	NR	NR	0.0000013-0.000026	NR	26	2	0.00001-0.2	0.2-2
Incidental Ingestion	11	14	0.038-0.23	0.03-0.2	1	NR	NR	1
Incidental Inhalation-Spray	16[a]; 8[b]	1[b]	0.0000051-0.5; 0.000065-0.23[b]	0.1; 0.02-0.2[b]	5; 190[a]; 272[b]	3; 10[b]	0.1-0.5; 0.004-0.5[a]	0.02-3[b]
Incidental Inhalation-Powder	8[b]	1[b]	0.000065-0.23[b]	0.02-0.2[b]	7; 272[b]	1; 10[b]	NR	0.2-0.6; 0.02-3[b]
Dermal Contact	22	6	0.00000006-1	0.0001-0.6	1081	77	0.00001-30	0.0008-3
Deodorant (underarm)	NR	NR	NR	NR	6	1	NR	NR
Hair - Non-Coloring	1	3	0.0000051-0.0011	NR	297	28	0.004-4	0.002-0.2
Hair-Coloring	NR	NR	0.00000002	NR	40	2	0.015-0.1	0.1
Nail	NR	NR	NR	NR	3	NR	NR	0.2
Mucous Membrane	15	17	0.000018-0.23	0.0001-0.2	217	2	0.064-0.2	0.0008-2
Baby Products	1	NR	NR	NR	2	NR	NR	NR
	Sodium Salicylate				**TEA-Salicylate**			
	2019[17]	**1998[1]**	**2018[18]**	**2000[1]**	**2019[17]**	**1998[1]**	**2018[18]**	**2000[1]**
Totals*	**186**	**7**	**0.0008-0.5**	**0.09-2**	**5**	**5**	**NR**	**0.0001-0.75**
Leave-On	*76*	*5*	*0.0015-0.1*	*2*	*4*	*5*	*NR*	*0.0001-0.75*
Rinse-Off	*108*	*2*	*0.0008-0.5*	*0.09-0.3*	*1*	*NR*	*NR*	*0.0002*
Diluted for (Bath) Use	*2*	*NR*	*NR*	*NR*	*NR*	*NR*	*NR*	*NR*
Eye Area	6	NR	NR	NR	NR	NR	NR	NR
Incidental Ingestion	NR	2	NR	0.09-0.2	NR	NR	NR	NR
Incidental Inhalation-Spray	13[a]; 41[b]	1[b]	NR	0.09-2[b]	NR	1[b]	NR	0.001[b]
Incidental Inhalation-Powder	41[b]	1[b]	NR	0.09-2[b]	NR	1[b]	NR	0.001[b]
Dermal Contact	175	3	0.0015-0.5	2	NR	5	NR	0.0001-0.75
Deodorant (underarm)	NR	NR	NR	NR	NR	NR	NR	NR
Hair - Non-Coloring	9	2	0.0008-0.5	0.2	5	NR	NR	NR
Hair-Coloring	2	NR	NR	NR	NR	NR	NR	NR
Nail	NR	NR	NR	NR	NR	NR	NR	NR
Mucous Membrane	94	2	0.25-0.37	0.09-0.2	NR	NR	NR	0.0002
Baby Products	NR	NR	0.31	NR	NR	NR	NR	NR
	Tridecyl Salicylate							
	2019[17]	**1998[1]**	**2018[18]**	**2000[1]**				
Totals*	**13**	**2**	**NR**	**0.01**				
Leave-On	*10*	*2*	*NR*	*0.01*				
Rinse-Off	*3*	*NR*	*NR*	*NR*				
Diluted for (Bath) Use	*NR*	*NR*	*NR*	*NR*				
Eye Area	1	NR	NR	NR				
Incidental Ingestion	NR	NR	NR	NR				
Incidental Inhalation-Spray	3[a]; 4[b]	2[b]	NR	0.01[b]				
Incidental Inhalation-Powder	4[b]	2[b]	NR	0.01[b]				
Dermal Contact	13	2	NR	0.01				
Deodorant (underarm)	NR	NR	NR	NR				
Hair - Non-Coloring	NR	NR	NR	NR				
Hair-Coloring	NR	NR	NR	NR				
Nail	NR	NR	NR	NR				
Mucous Membrane	1	NR	NR	NR				
Baby Products	NR	NR	NR	NR				

*Because each ingredient may be used in cosmetics with multiple exposure types, the sum of all exposure types may not equal the sum of total uses.

[a] It is possible that these products may be sprays, but it is not specified whether the reported uses are sprays.

[b] Not specified whether a powder or a spray, so this information is captured for both categories of incidental inhalation.

NR - no reported use

Table 4. Skin Irritation and Sensitization Studies on Salicylic Acid and Salicylates

Test Substance	Animals/Subjects/Cells/ Peptides	Test Protocol	Results
Irritation (Animal)			
Amyl Salicylate (undiluted)	6 Albino angora rabbits	Test substance (0.1 g) applied (using glass syringe) for 24 h to 3 x 3 cm area on dorsal surface. Plastic collar (25-cm diameter) wrapped around the neck. Application repeated 30 min after end of 24-h contact period. Reactions scored 24 h after first application and 48 h and 72 h after 2nd patch application	Amyl Salicylate was severely irritating.[70]
Amyl Salicylate (undiluted)	6 male Hartley guinea pigs	Same protocol, but application to dorsal, mid-lumbar region	Amyl Salicylate was mildly irritating.[70]
Amyl Salicylate (undiluted)	6 miniature swine of the Pitman-Moore Improved strain	Test substance (0.05 g) applied, under 15 mm diameter patch, to dorsal skin for 48 h.	Amyl Salicylate was a non-irritant.[70]
Ethylhexyl Salicylate (undiluted)	4 rabbits (strain not stated)	Test substance applied (under occlusion) to intact or abraded skin for 24 h.	Mild erythema, lasting 24 h, was observed.[7]
Ethylhexyl Salicylate (undiluted)	3 male New Zealand White rabbits.	A semiocclusive patch containing the test substance (0.5 ml) was applied for 3 min to an ~ 6 cm^2 area on the anterior left flank of each animal. Similarly, a semiocclusive patch containing the test substance was applied for 1 h to the anterior right flank and for 4 h to the posterior right flank. Untreated skin served as the control. Reactions scored at ~1 h, 24 h, 48 h, and 72 h after patch removal.	Slight erythema observed at sites exposed for 3 minutes and 1 h, and well-defined erythema observed at sites exposed for 4 h. The erythema observed in 2 rabbits had resolved within 24 h, and the erythema observed in the third rabbit had resolved by 48 h. No evidence of edema at application sites of any animals. The test substance was considered a non-irritant.[30]
Hexyl Salicylate (1 to 100%)	Groups of 5 male hrBR outbred hairless albino guinea pigs	Single 0.1 ml application at a concentration of 1%, 5%, 10%, or 50% (in 3:1 diethyl phthalate:ethanol) or undiluted. Applied to dorsal skin using 25 mm Hilltop® chambers. Chambers removed after 2 h (± 15 min). Reactions scored at 1h and 4 h after removal and at 1, 2, and 3 days post-administration.	Skin irritation was not observed at any of the concentrations tested.[8]
Hexyl Salicylate (10 to 50%)	4 male albino Dunkin/Hartley guinea pigs	Topical treatment with 8 mm diameter filter paper patches saturated with 10%, 25%, or 50% Hexyl Salicylate (in acetone), using 1 mm aluminum patch test cups. Patch removal after 24 h, and reactions scored at 24 h and 48 h post-removal.	No evidence of skin irritation (at 10% concentration). Very slight erythema (at 25% and 50%, 3 animals).[8]
Hexyl Salicylate (5%)	4 inbred Hartley albino guinea pigs	Test substance (0.1 ml) injected intradermally into the shaved flank. Reactions read 24 h after injection.	Skin irritation was not observed.[75]
Hexyl Salicylate (0.1 to 2%, in 0.01% dodecylbenzenesulfonate /saline)	4 male albino Dunkin/Hartley guinea pigs	Same protocol	Very slight erythema (at 0.1%) and slight erythema and edema (at 0.25%, 0.5%, 1%, and 2%).[8]
Hexyl Salicylate (0.1%)	4 inbred Hartley albino guinea pigs	Same protocol.	Skin irritation was observed.[75]
Hexyl Salicylate (undiluted)	2 miniature swine	Test substance (20 µl/5 cm^2) applied to back	Skin irritation was not observed.[8]
Hexyl Salicylate (10 to 100%)	3 or 4 female New Zealand white rabbits	Surgical lint square (2.5 cm^2) containing 0.5 ml of 10%, 25%, or 50% Hexyl Salicylate in diethyl phthalate, or undiluted ingredient. Lint square (semi-occlusive patch) placed on 6 cm^2 area of clipped, intact dorsal skin for 4h. Reactions assessed at 1 h, 24 h, 48 h, 72 h, and 168 h after patch removal.	Skin irritation was not observed at concentrations of 10% and 25%, but was observed at higher concentrations.[8]

Table 4. Skin Irritation and Sensitization Studies on Salicylic Acid and Salicylates

Test Substance	Animals/Subjects/Cells/ Peptides	Test Protocol	Results
Hexyl Salicylate (undiluted)	10 rabbits (strain not stated)	Single dermal dose of 5 g/kg [skin irritation data from acute dermal toxicity study]	Skin irritation was observed: moderate edema (7 animals), slight edema (3 animals), moderate erythema (8 animals), and slight erythema (2 animals).[8]
Hexyl Salicylate (undiluted)	6 hairless mice	Test substance (20 µl/5 cm^2) applied to back	Skin irritation was not observed.[8]
Methyl Salicylate (undiluted)	9 rabbits (strain not stated)	Single dermal dose of 5 g/kg	Slight erythema and edema (2 animals) and moderate erythema and edema (7 animals).[9]
Methyl Salicylate (1%, 5%, 10%, 25%, and 100%; for 4 lower concentrations, the vehicle was ethanol/diethyl phthalate 1:1)	6 Albino Mol:Russian rabbits	Semiocclusive patch containing the test substance (0.5 ml) applied for 4 h to the back (2 sites, 2.5 x 2.5 cm area). Patch removal was followed by a 7-day observation period. Reactions scored for up to 14 days after end of exposure.	Undiluted test substance caused slight to well-defined erythema and/or edema in all 6 animals from the 1-h to 72-h grading periods. Reactions had cleared by day 14. The 25% concentration caused very slight erythema in 1 rabbit at the 24-h and 48-h grading periods. Reactions to lower test concentrations were not observed. The test substance was classified as slightly irritating.[46]
Wintergreen oil (contains 80 to 99% Methyl Salicylate)	6 hairless mice and 2 miniature swine	Test substance (20 µl) applied to 5 cm^2 area on back	Flaking, hyperkeratosis, and dry desquamation observed.[9]
Methyl Salicylate	Mice (strain not stated)	Mouse ear swelling test. Test substance (in 4:1 acetone to olive oil) applied in 4-day dosing protocol. The minimal irritating concentration (lowest concentration to produce a % ear swelling significantly greater than the vehicle) was determined.	Minimal irritating concentration was 20%.[72]
Methyl Salicylate (3%)	6 to 8 outbred Himalayan, white-spotted male and female guinea pigs	Test substance (0.1 ml) applied to 8 cm^2 area on clipped flank (uncovered) daily for 21 days	Minimal skin irritation.[71]
Methyl Salicylate (3%)	6 to 8 outbred Himalayan, white-spotted male and female guinea pigs	Test substance (0.025 ml) applied for 24 h to 2 cm^2 area on clipped flank (uncovered)	Mild erythema in at least 25% of animals.[71]
Salicylic Acid	3 New Zealand White rabbits (1 male, 2 females).	Test substance (0.5 g in 0.5 ml water) applied for 4 h, under semiocclusive patch, to 2.5 cm x 2.5 cm area of t left flank. Reactions scored at the following intervals after patch removal: 1 h, 24 h, 48 h, 72 h, 7 days, 10 days, and 14 days.	No evidence of skin irritation.[73]
Salicylic Acid	3 New Zealand White rabbits	Test substance (0.5 g, moistened with 0.5 ml water) applied, under semiocclusive patch, for 4 h to 6.25 cm^2 area of skin. Reactions scored for up to 14 days after application.	Non-irritating to the skin of rabbits.[4]
Salicylic Acid (in 8% propylene glycol butyl ether in ethanol). Test concentrations of 2%, 10%, and 25% (corresponding to 40, 200, and 500 mg/kg/day, respectively).	Groups of 6 (3 males, 3 females) New Zealand White rabbits.	14-day dermal toxicity study. Test concentrations were administered topically at a dose of 2 g/kg/day. The control group received topical applications of vehicle only.	Dose-related slight to marked erythema and edema was observed in all dose groups. Desquamation most often observed in the 25% Salicylic Acid group; fissuring (varying degrees) observed in all dose groups. Eschar observed in the 10% and 25% Salicylic Acid groups, and exfoliation also observed in the 25% Salicylic Acid group. Salicylic Acid was irritating to the skin of rabbits.[5]
Salicylic Acid (formulations containing 3.5%, 5%, and 7.5%)	Groups of 6 adult male albino New Zealand rabbits	Formulations applied to concave side of left ears. Distilled water (control) applied to right ears. Macroscopic evaluations performed daily	All 3 formulations caused significant macroscopic alterations (desquamation, inflammatory reaction, and comedogenic effect) when compared to the control.[74]

Table 4. Skin Irritation and Sensitization Studies on Salicylic Acid and Salicylates

Test Substance	Animals/Subjects/Cells/ Peptides	Test Protocol	Results
Cleansing formulations containing 0.5% to 6% Salicylic Acid in propylene glycol butyl ether/ethanol (vehicle)	New Zealand White rabbits (number not stated)	91-day study to evaluate systemic and cutaneous toxicity. Concentration range corresponded to topical doses of 10, 20, 40, or 120 mg/kg Salicylic Acid. Products tested applied for 7 h to intact skin (once daily; dose volume = 2 ml/kg) 5 days per week	Reactions observed at application site included slight to marked erythema, desquamation, fissuring, and edema. The most severe findings, particularly scab formation and desquamation, observed mostly in the highest dose group and during the first 28 days of the study. After 91 days, the severity and frequency of hyperkeratosis, acanthosis, and dermal inflammation were greatest in the high-dose group. Cleansing formulations tested classified as skin irritants.[5]
Alcoholic solutions containing 2%, 2.5%, and 5% Salicylic Acid	Rabbits and guinea pigs (numbers and strains not stated)	Single application of alcoholic solutions containing 2% Salicylic Acid to the skin of rabbits (protocol details not stated). Repeated open applications of 2.5% and 5% hydroalcoholic solutions of Salicylic Acid to the skin of guinea pigs. Each solution applied for 3 h to the skin of guinea pigs twice daily for 4 consecutive days.	Mild to no skin irritation in rabbits. Mild skin irritation in guinea pigs.[4]
2 cleansing formulations containing 0.5% Salicylic Acid	Rabbits (number per study not stated)	Two 91-day studies involving rabbits performed to evaluate cutaneous and systemic toxicity. Undiluted product or product diluted to 50% w/v in distilled water (effective Salicylic Acid concentration = 0.25%) applied to intact skin. Test article (dose volume of 2 ml/kg; dose = 10 mg/kg) applied to skin 5 times per week (7 h per day). Control rabbits treated with distilled water.	Treatment-related skin changes (varying up to moderate) included transient erythema, edema, atonia, desquamation, and fissuring. Products tested were considered slightly and transiently irritating to the skin when applied undiluted or diluted to a concentration of 50%.[5]
Sodium Salicylate	3 male New Zealand White rabbits	Test substance (0.5 g moistened with 0.5 ml distilled water) applied for 4 h to 6 x 6 cm area in dorsal lumbar region. Site was covered with an occlusive patch during application period. Reactions scored according to method of Draize.	In all 3 rabbits, very slight erythema (barely perceptible) was observed at 1 h, but not at 24 h, 48 h, or 72 h after patch removal; edema was not observed. It was concluded that Sodium Salicylate was non-irritating to the skin of male New Zealand White rabbits. The authors also noted that none of the animals died, and that there was no evidence of systemic toxicity.[43]
Irritation (Human)			
Amyl Salicylate (32% in acetone)	50 adult male subjects	A 15 mm diameter occlusive patch containing 0.05 ml of test substance applied for 48 h. Reactions scored 30 min after patch removal	Skin irritation was not observed.[70]
Ethylhexyl Salicylate (4% in petrolatum)	23 male subjects	48-h closed patch test	Skin irritation was not observed.[7]
Hexyl Salicylate (undiluted)	30 subjects	4-h patch (25 mm Hilltop® chamber) test. Patch contained 0.2 ml of test substance. Reactions read at 24 h, 48 h, and 72 h after patch removal	Skin irritation was not observed.[76]
Hexyl Salicylate (0.3%, 3%, or 30%, in 3:1 diethyl phthalate:ethanol)	56 subjects (15 males, 41 females)	24-h patch test. Test substance (0.3 ml) applied to back using 25 mm Hilltop® chambers. Duplicate patches placed on both sides of spine. Sites evaluated at ~1 h, 24 h, 48 h, and 72 h after patch removal	Skin irritation was not observed.[8]
Methyl Salicylate (30% and 60%)	9 subjects (3 males, 6 females)	25 ml of test substance (in 80% ethanol and 20% deionized water vehicle) pipetted onto the skin (forearm). A PTFE cap was placed over the application site to prevent evaporation. Test substance was applied every 48 h for a total of 6 applications.	Skin irritation was observed at both concentrations.[77]

Table 4. Skin Irritation and Sensitization Studies on Salicylic Acid and Salicylates

Test Substance	Animals/Subjects/Cells/ Peptides	Test Protocol	Results
12% wintergreen oil (contains 80 to 99% Methyl Salicylate; at 12%, effective concentration range = 9.6% to 11.9%)	25 male subjects	48-h patch test (occlusive patches)	Skin irritation was not observed.[9]
Methyl Salicylate (8% in petrolatum)	27 male subjects	48-h patch test (occlusive patches)	Skin irritation was not observed.[9]
Shampoo containing 3% Salicylic Acid	Human subjects (number not stated)	Cumulative irritation study. Product applied (as a 4% dilution) continuously under a patch for 12 days.	Potential for skin irritation demonstrated.[5]
Shampoos (prototype or commercial formulations) containing 3% Salicylic Acid and shampoo formulations containing up to 2% Salicylic Acid	Human subjects (number not stated)	Exaggerated use repeated application tests (4 studies) to compare shampoos containing 2% or 3% Salicylic Acid (with a placebo (not defined).	Results indicated no statistically significant differences in combined irritation or transepidermal water loss. Therefore, it was determined that Salicylic Acid at a concentration of 3% in rinse-off shampoo formulations does not appear to be more irritating than the other components of the formulation.[5]
Cream containing 2% Salicylic Acid	Human subjects (number not stated)	Applied to the skin repeatedly for 5 days using occlusive and semi-occlusive patches	Skin irritation was not observed.[5]
Surfactant-based product containing 2% Salicylic Acid (pH of 3.8; diluted concentration not stated)	Human subjects (number not stated)	Applied for 24 h to the skin repeatedly for 12 days using occlusive patches	Mildly irritating.[5]
Surfactant-based product containing 2% Salicylic Acid (pH of 3.8)	Human subjects (number not stated)	Applied for 24 h to the skin repeatedly for 14 days using occlusive patches	Probably mildly irritating under normal use conditions.[5]
Hydroalcoholic gel containing 2% Salicylic Acid	Human subjects (number not stated)	Applied to the skin repeatedly for 21 days using semi-occlusive patches.	Slightly irritating.[5]
Two creams containing 2% Salicylic Acid	Human subjects (number not stated)	Two creams (each in a separate test) applied to the skin of human subjects (number not stated) repeatedly for 21 days using occlusive patches.	One cream classified as non-irritating, and the other classified as moderately irritating.[5]
Cream containing 2% Salicylic Acid	Human subjects (number not stated)	Applied to back in repeated (14 days) open application test.	Did not cause reactions that were different from those induced by the control.[5]
Non-alcoholic lotion containing 2% Salicylic Acid	Human subjects (number not stated)	Home use test. Application for 6 weeks	Mild, transient reactions.[5]
Non-alcoholic cream containing 2% Salicylic Acid	Human subjects (number not stated; 50% had sensitive skin)	Home use test. Application for 6 weeks	Little or no irritation potential.[5]
Non-alcoholic lotions and moisturizers containing 2% Salicylic Acid (pH 2.28)	194 human subjects	Home use test.	Itching, stinging, mild erythema, and burning were reported.[5]
Cream containing 1.5 % Salicylic Acid	Human subjects (number not stated)	Applied for 24 h repeatedly for 21 days using occlusive patches.	Slightly irritating.[5]
Hydroalcoholic solution containing 0.5% Salicylic Acid (pH 2.82)	Human subjects (number not stated)	Daily applications (2 weeks) to the skin	No skin irritation.[5]

Table 4. Skin Irritation and Sensitization Studies on Salicylic Acid and Salicylates

Test Substance	Animals/Subjects/Cells/ Peptides	Test Protocol	Results
Sensitization (In Vitro/In Chemico)			
Hexyl Salicylate	In vitro model of dendritic cells	Genomic allergen rapid detection (cell-based alternative to animal testing). Assay based on a biomarker signature comprising 200 genes measured in in vitro model. Assay consistently reports predictive performances of ~90% .	Hexyl Salicylate was predicted to be a skin sensitizer.[78]
Salicylic Acid	Keratinocytes, dendritic cells, and peptides	Integrated testing strategy focusing on the following 3 methods covering the first 3 steps of the adverse outcome pathway: direct peptide reactivity assay (DPRA), keratinocyte activation assay, and dendritic cell line activation assay. Results compared to in vivo data (especially human)	The results for Salicylic Acid were equivocal, but, ultimately, were considered positive results.[79]
Salicylic Acid	Peptides	Allergen-peptide/protein interaction assay, which permits the profiling of all amino acid specific allergen-peptide interactions. Mass spectrometry of target peptides performed	No modifications of peptide-21 or peptide-20 by Salicylic Acid. Non-allergenic Salicylic Acid did not interfere with Cys containing peptide-21 or Cys-free peptide-20.[80]
Sensitization (Animal)			
Hexyl Salicylate	Mice	LLNA. EC3 determined.	A very low EC3 (0.18%) was reported., and thought to have been due to possibly sensitizing impurities.[79]
Hexyl Salicylate	10 inbred Hartley albino guinea pigs	Modified Draize procedure: Induction injections at 0.25%; challenge at 0.1% (injection) and at 5% (topical application). Induction consisted of 4 intradermal injections into flank (0.1 ml each), and challenge (left and right flanks) occurred 14 days later. Second challenge performed 7 days after first	Sensitization was observed after the second challenge.[75]
Hexyl Salicylate	Groups of 5 Crl:IAF(HA)-hrBR outbred albino hairless guinea pigs	Induction phase involved intradermal injection of a sterile water and Freund's complete adjuvant mixture (0.1 ml) into 2.5 cm^2 nuchal area of skin, and 2-h topical application (0.3 ml) of 100% Hexyl Salicylate in 3:1 diethyl phthalate:ethanol using 25 mm Hilltop® chamber patches. Procedure repeated on days 3, 5, 7, 10, and 12. On day 22, topical challenge with 50% Hexyl Salicylate in vehicle and 100% Hexyl Salicylate. Sites observed for up to 3 days post-application	Sensitization was not observed.[8]
Hexyl Salicylate	10 albino Dunkin/Hartley guinea pigs	Magnusson-Kligman maximization test. Induction involved 6 intradermal injections of 1% Hexyl Salicylate to a 2 x 4 cm area in dorsal shoulder region. 7 days later, occlusive patch containing 40% Hexyl Salicylate applied to shoulder for 48 h. At 13 to 14 days post-application of occlusive patch, 24-h challenge (flank) with 8 mm diameter occlusive patch containing 10% Hexyl Salicylate. Three additional challenge applications (on contralateral flanks) at weekly intervals.	Sensitization was not observed.[8]
Methyl Salicylate (50%)	Mice	LLNA	Non-sensitizer.[82]
Methyl Salicylate (0.7 µM)	Mice	LLNA	Number of positive tests / number of total tests was 1 in 4 (25% positive response). Overall, results were classified as negative (non-sensitizer).[81]

Table 4. Skin Irritation and Sensitization Studies on Salicylic Acid and Salicylates

Test Substance	Animals/Subjects/Cells/ Peptides	Test Protocol	Results
Methyl Salicylate (25% w/v in hydro-alcoholic solution)	20 guinea pigs (strain not stated)	Modified Buehler test protocol. Test substance applied for 6 h once per week for 3 weeks. After a 2-week non-treatment period, animals challenged with same concentration of Salicylic Acid.	No signs of skin sensitization.[4]
Sensitization (Human)			
Butyloctyl Salicylate (undiluted)	Fifty-two male and female subjects	Protocol described as essentially the Draize procedure. A 1" x 1" semiocclusive patch containing the test substance (0.2 ml) applied to upper back (between scapulae) for 24 h, 3 times weekly for total of 9 induction applications. Challenge phase initiated after 2-week non-treatment period. Challenge patch applied for 24 h to a new site (adjacent to induction site). Reactions scored at 24 h and 72 h post-application.	No evidence of a positive skin irritation or sensitization reaction during the study. Test substance was classified as a non-sensitizer.[47]
Hexyl Salicylate (30% in 3:1 diethyl phthalate:ethanol)	103 subjects (29 males and 74 females)	HRIPT. Induction (3 weeks): Occlusive patches (25 mm Hilltop® chamber system) containing test substance (0.3 ml) applied for 24 h to left side of back for 9 applications. Challenge: After 2-week non-treatment period, occlusive challenge patch containing test substance applied for 24 h. Reactions scored at 48 h, 72 h, and 96 h after application.	Neither irritation nor sensitization was observed.[8]
Hexyl Salicylate	Human subjects (number not stated)	Protocol not stated	Human skin sensitization no-observed – effect –level of 35,433 µg/cm^2.[83]
Hexyl Salicylate	Human subjects (number not stated)	Maximization test	No induction was observed at a dose of 20,654 µg/cm^2.
Hexyl Salicylate (3% in petrolatum)	22 subjects	Maximization test. Pre-treatment of test site for 24 h with 5% aqueous sodium lauryl sulfate (SLS), under occlusion. Test substance application, under occlusion, to same site on volar forearm or back for 5 alternate-day-48-h periods. After 10-day non-treatment period, occlusive challenge patches applied for 48 h to 2 new sites (SLS pre-treat- ment and no pre-treatment). Reactions were scored at the time of patch removal and 24 h later.	Neither irritation nor sensitization was observed.[8]
12% Wintergreen oil (contains 80 to 99% Methyl Salicylate; at 12%, effective concentration range = 9.6% to 11.9%) in petrolatum	25 subjects	Maximization test. Induction: Test substance applied, under occlusion, to same site on volar forearm for 5 alternate-day 48-h periods. Prior to initial application only, site pre-treated with 5% aqueous SLS for 24 h. Challenge: After 10- to 14-day non-treatment period, 48-h occlusive challenge patch application (2 patches; pretreatment with 5% SLS for 30 min and no pre-treatment) to new sites. SLS-treated sites served as controls.	Sensitization was not observed.[9]
Methyl Salicylate (8% in petrolatum)	27 subjects	Maximization test. Same protocol, except SLS pre-treatment between patch applications during induction and pre-treatment of challenge site with 10% SLS 1 h before challenge. Reactions read when patches removed and 24 h later	Sensitization was not observed.[9]

Table 4. Skin Irritation and Sensitization Studies on Salicylic Acid and Salicylates

Test Substance	Animals/Subjects/Cells/ Peptides	Test Protocol	Results
Methyl Salicylate (1.25%)	39 subjects (13 males, 26 females)	HRIPT. Induction: 24-h occlusive patch (1-inch square, at center of 1 x 3 inch adhesive bandage) containing 0.5 ml of test substance). 9 applications to same site over 3-week period. Challenge: On Monday of week 6, 24-h challenge patch containing test substance applied to new site. Reactions scored at 24 h and 72 h after patch removal	Sensitization was not observed.[9]
Formulations containing up to 2% Salicylic Acid	Test populations ranging from 84 to 198 human subjects	Total of 23 human repeated insult patch tests (semi-occlusive or occlusive patches). Patch test protocols not included.	No skin sensitization.[5]

Table 5. Photosensitization/Phototoxicity Studies on Salicylates

Test Substance	Animals/Subjects/Cells Tested	Test Protocol	Results
Phototoxicity (In vitro)			
Ethylhexyl Salicylate (0.1 to 316 µg/ml)	Cell suspension of 3T3 fibroblasts (1 x 10^5 cells/ml, 1 x 10^4 cells/well)	3T3 neutral red uptake phototoxicity test. Concentrations applied (in sextuplicate) in 96-well plates. After 1 h of incubation, irradiation with UVA light. Neutral red medium added after second incubation. Photoirritation factor (PIF, ratio of toxicity with and without UV light) was calculated, and value for mean photoeffect (MPE, statistical comparison of dose response curves obtained with and without UV) was determined. PIF > 5 (potential phototoxic hazard). MPE > 0.1 (predicted to be phototoxic). Substance with PIF of > 2 and < 5 or an MPE of > 0.1 and < 0.15 predicted as possibly phototoxic.	PIF = 1.756 (1^{st} run) and 1.043 (2^{nd} run). MPE = 0.109 (1^{st} run) and 0.109 (2^{nd} run). Phototoxicity test results were classified as negative.[88]
Phototoxicity/Photosensitization (Animal)			
Methyl Salicylate (50% in diethyl phthalate)	25 male Dunkin-Hartley guinea pigs, distributed among the following 4 groups: 5 animals irradiated without Methyl Salicylate treatment (Group 1); 5 animals treated with Methyl Salicylate without irradiation (Group 2); 10 animals treated with Methyl Salicylate followed by irradiation (Group 3); and 5 animals treated with vehicle only (Group 4).	Phototoxicity was determined on days 1 and 2. On day 1, 0.1 ml of the test substance was applied for 24 h to the interscapular area (9 cm^2) in Groups 2 and 3. Group 4 animals were similarly treated with vehicle (0.1 ml). Group 1 animals were not treated. At 30 min post-treatment, Group 1, 3, and 4 animals were irradiated with an infra-erythematogenic dose (erythema score $\leq$ 0.5) of UVA (~ 9 J/cm^2) and UVB (~ 0.1 J/cm^2). The non-irradiated part of the back and flanks were protected from UV light exposure. Cutaneous reactions were scored before and 1, 4, and 24 h after the single application and/or irradiation.[46]	In Group 3 (test substance + irradiation), discrete erythema (grade 1) was observed in 3 of 10 animals at 1 h and 4 h. The erythema observed did not persist to day 2. Questionable erythema (grade 0.5) was observed in a few animals (number not stated), but the reaction was within the range of that reported for Group 4 (irradiated vehicle controls). Based on these results, Methyl Salicylate was not considered phototoxic.[46]

Table 5. Photosensitization/Phototoxicity Studies on Salicylates

Test Substance	Animals/Subjects/Cells Tested	Test Protocol	Results
Methyl Salicylate (50% in diethyl phthalate)	Groups of Dunkin-Hartley guinea pigs (same as in preceding photoxicity test)	Photoallergy test involved 6 applications over 8 days. Induction and challenge phases separated by 20-day non-treatment period. Day 1 in preceding phototoxicity test considered first induction application. Five additional applications (from day 2 to day 8) made according to procedure followed on day 1. Cutaneous reactions scored at ~ 24 h after each application and/or irradiation. After 6th application, animals remained free of treatment for 20 days. On day 29 (challenge), test substance (0.1 ml) applied to 2 areas (4 cm^2) on distal part of back that remained untreated during induction (involved Groups 2 and 3). Group 4 animals similarly treated with vehicle (0.1 ml), and Group 1 animals were not treated. At ~ 30 min after treatment, Groups 1, 3, and 4 irradiated on left flank (UVB only) and right flank (UVA only). Cutaneous reactions scored before and 1, 4, and 24 h after challenge application and/or irradiation.	After challenge on day 29, questionable or discrete erythema observed in practically all animals of Groups 1, 3, and 4 at the 1 h and 4 h readings. These reactions persisted in a few animals (number not stated) at the 24 h reading. The authors noted that these slight and transient reactions (similar in controls and treated animals) remained within the range of a local reaction at an infraerythematogenic irradiated dose, and were not attributed to a test substance-related photoallergenic response.[46]
Hexyl Salicylate (undiluted)	12 Skh:hairless-1 mutant mice)	Single application of test substance (20 µl/2 cm^2) on back (6 mice). Application followed by exposure to 6 kW long arc xenon lamp (distance = 1 m; intensity = 0.1667 W/m^2) for 40 min and 4 fluorescent blacklight lamps (intensity of 3 W/m^2) for 1 h. Six controls treated with test substance only. Positive control group was treated with 8-methoxy-psoralen in methanol (0.01% w/v). Sites evaluated at 4 h, 24 h, 48 h, 72 h, and 96 h.	No reactions to Hexyl Salicylate + light were observed. Results for 8-methoxypsoralen + light were positive.[8,89]
Hexyl Salicylate (undiluted)	2 miniature swine	Single application of test substance (20 µl/5 cm^2) on back. Irradiation performed for 40 min using same light source and procedure as above.	Phototoxicity was not observed.[8,89]
Hexyl Salicylate (5%, 10%, 50%, or 100%)	2 groups of 5 hairless albino guinea pigs of the Crl:IAF(HA)-hrBR outbred strain	Each concentration (volume = 0.3 ml) applied to dorsal skin along midline using 25 mm Hilltop® chamber. 2 h later, patches removed and sites irradiated for ~ 2.25 h with UVR (2.25 x minimal erythemal dose [MED]) using 6.5 kW long-arc xenon water-cooled lamp with filter used to attenuate mid-range UVB. Sites evaluated immediately and 1h and 2 h later, and at 1, 2, and 3 days after application.	Phototoxicity was not observed.[8]
Hexyl Salicylate (50% and 100%, in 3:1 diethyl phthalate:ethanol)	2 groups of 5 Crl:IAF (HA)-hBR outbred albino, hairless guinea pigs	Induction: test substance (0.3 ml, on 25 mm-diameter Hill Top® patch) applied for 2 h to nuchal area of skin (2.5 cm^2). After patch removal, application site exposed for 2.25 h to UVR (2.25 x MED) from 6.5 kW long-arc xenon water-cooled lamp with filter used to attenuate mid-range UVB. Procedure repeated (once daily) on days 3, 5, 8, 10, and 12. Challenge: On day 22, patch containing test substance applied for 2 h. Exposure of site to UVR for 2.25 after patch removal. Sites scored at 1 h and 4 h after patch application.	Photoallergy was not observed.[8]

Table 5. Photosensitization/Phototoxicity Studies on Salicylates

Test Substance	Animals/Subjects/Cells Tested	Test Protocol	Results
Undiluted wintergreen oil (contains 80 to 99% Methyl Salicylate)	2 miniature swine	Test substance (20 µl/5 cm^2) applied to back. Site exposed for 1 h to UVA light (10 watts/m^2) from fluorescent black light lamps, filtered to limit exposure to long wave UV light only. The negative and positive controls were methanol and 8-methoxy-psoralen (in methanol), respectively	Phototoxicity was not observed.[9]
Phototoxicity (Human)			
Hexyl Salicylate (0.3%, 3%, and 30% in 3:1 diethyl phthalate:ethanol)	56 subjects (41 females, 15 males)	Test substance applied to duplicate patches (25 mm Hilltop® chambers) that were placed on the back (both sides of the spine, 24-h contact period). Each subject had 3 patches containing Hexyl Salicylate (applied to left paraspinal region) and 3 control patches (vehicle and saline controls at non-irradiated sites in right paraspinal region) applied. After removal of patches from the left paraspinal region, the sites were irradiated with 16 J/cm^2 of UVA for 10 min, and, then, with UVB (0.75 MED). Sites evaluated at 1 h, 24 h, 48 h, and 72 h after irradiation	No reactions were observed.[8]

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2019 FDA VCRP Data

Butyloctyl Salicylate

03C - Eye Shadow	1
07C - Foundations	1
07E - Lipstick	12
07F - Makeup Bases	1
07I - Other Makeup Preparations	1
12A - Cleansing	1
12C - Face and Neck (exc shave)	3
12F - Moisturizing	3
12G - Night	1
12J - Other Skin Care Preps	2
13A - Suntan Gels, Creams, and Liquids	1
13C - Other Suntan Preparations	1
Total	**28**

Calcium Salicylate

No FDA VCRP Data

C12-15 Alkyl Salicylate

No FDA VCRP Data

Ethylhexyl Salicylate

02A - Bath Oils, Tablets, and Salts	2
02B - Bubble Baths	7
02C - Bath Capsules	1
02D - Other Bath Preparations	5
03D - Eye Lotion	2
03G - Other Eye Makeup Preparations	1
04A - Cologne and Toilet waters	1260
04B - Perfumes	692
04C - Powders (dusting and talcum, excluding aftershave talc)	2
04E - Other Fragrance Preparation	691
05A - Hair Conditioner	27
05B - Hair Spray (aerosol fixatives)	17
05F - Shampoos (non-coloring)	30
05G - Tonics, Dressings, and Other Hair Grooming Aids	43
05H - Wave Sets	2
05I - Other Hair Preparations	13
06D - Hair Shampoos (coloring)	1
06H - Other Hair Coloring Preparation	4
07B - Face Powders	3
07C - Foundations	11
07E - Lipstick	54
07F - Makeup Bases	9
07I - Other Makeup Preparations	11
08A - Basecoats and Undercoats	2
08B - Cuticle Softeners	2

08E - Nail Polish and Enamel	2
10A - Bath Soaps and Detergents	507
10B - Deodorants (underarm)	6
10E - Other Personal Cleanliness Products	198
11A - Aftershave Lotion	39
11E - Shaving Cream	1
11G - Other Shaving Preparation Products	3
12A - Cleansing	22
12C - Face and Neck (exc shave)	52
12D - Body and Hand (exc shave)	37
12E - Foot Powders and Sprays	1
12F - Moisturizing	96
12G - Night	10
12I - Skin Fresheners	1
12J - Other Skin Care Preps	75
13A - Suntan Gels, Creams, and Liquids	25
13B - Indoor Tanning Preparations	4
13C - Other Suntan Preparations	3
Total	**3974**

Hexyldodecyl Salicylate
No FDA VCRP Data

Isocetyl Salicylate
No FDA VCRP Data

Isodecyl Salicylate

03D - Eye Lotion	1
12C - Face and Neck (exc shave)	7
12F - Moisturizing	8
12G - Night	3
12H - Paste Masks (mud packs)	1
Total	**20**

Magnesium Salicylate

03A - Eyebrow Pencil	1
03F - Mascara	9
03G - Other Eye Makeup Preparations	1
Total	**11**

Methyl Salicylate

01A - Baby Shampoos	1
02A - Bath Oils, Tablets, and Salts	1
07I - Other Makeup Preparations	1
09A - Dentifrices	1
09B - Mouthwashes and Breath Fresheners	10
10A - Bath Soaps and Detergents	1
10E - Other Personal Cleanliness Products	2

12C - Face and Neck (exc shave)	2
12D - Body and Hand (exc shave)	5
12E - Foot Powders and Sprays	1
12F - Moisturizing	4
12G - Night	1
12I - Skin Fresheners	1
12J - Other Skin Care Preps	3
Total	**34**

Myristyl Salicylate
No FDA VCRP Data

Potassium Salicylate
No FDA VCRP Data

Salicylic Acid

01A - Baby Shampoos	1
01C - Other Baby Products	1
02D - Other Bath Preparations	4
03A - Eyebrow Pencil	2
03B - Eyeliner	3
03D - Eye Lotion	8
03E - Eye Makeup Remover	4
03F - Mascara	1
03G - Other Eye Makeup Preparations	8
04E - Other Fragrance Preparation	1
05A - Hair Conditioner	24
05B - Hair Spray (aerosol fixatives)	4
05E - Rinses (non-coloring)	5
05F - Shampoos (non-coloring)	224
05G - Tonics, Dressings, and Other Hair Grooming Aids	23
05I - Other Hair Preparations	16
06A - Hair Dyes and Colors (all types requiring caution statements and patch tests)	1
06D - Hair Shampoos (coloring)	3
06F - Hair Lighteners with Color	1
06G - Hair Bleaches	6
06H - Other Hair Coloring Preparation	29
07B - Face Powders	7
07C - Foundations	19
07E - Lipstick	1
07F - Makeup Bases	2
07I - Other Makeup Preparations	10
08B - Cuticle Softeners	1
08C - Nail Creams and Lotions	2
10A - Bath Soaps and Detergents	177
10B - Deodorants (underarm)	6
10C - Douches	6

10E - Other Personal Cleanliness Products	29
11A - Aftershave Lotion	2
11D - Preshave Lotions (all types)	1
11E - Shaving Cream	2
11F - Shaving Soap	1
11G - Other Shaving Preparation Products	3
12A - Cleansing	199
12B - Depilatories	11
12C - Face and Neck (exc shave)	202
12D - Body and Hand (exc shave)	66
12E - Foot Powders and Sprays	4
12F - Moisturizing	118
12G - Night	20
12H - Paste Masks (mud packs)	33
12I - Skin Fresheners	23
12J - Other Skin Care Preps	109
13A - Suntan Gels, Creams, and Liquids	2
13B - Indoor Tanning Preparations	1
13C - Other Suntan Preparations	3
Total	**1429**

Sodium Salicylate

02D - Other Bath Preparations	2
03B - Eyeliner	1
03D - Eye Lotion	2
03G - Other Eye Makeup Preparations	3
05A - Hair Conditioner	2
05F - Shampoos (non-coloring)	2
05I - Other Hair Preparations	5
06A - Hair Dyes and Colors (all types requiring caution statements and patch tests)	1
06H - Other Hair Coloring Preparation	1
07C - Foundations	1
07I - Other Makeup Preparations	1
10A - Bath Soaps and Detergents	75
10E - Other Personal Cleanliness Products	17
12A - Cleansing	8
12B - Depilatories	2
12C - Face and Neck (exc shave)	32
12D - Body and Hand (exc shave)	9
12F - Moisturizing	11
12G - Night	1
12I - Skin Fresheners	1
12J - Other Skin Care Preps	9
Total	**186**

TEA-Salicylate

05A - Hair Conditioner	1
05I - Other Hair Preparations	4

Total	**5**

Tridecyl Salicylate

03D - Eye Lotion	1
07I - Other Makeup Preparations	2
10E - Other Personal Cleanliness Products	1
12C - Face and Neck (exc shave)	3
12D - Body and Hand (exc shave)	1
12F - Moisturizing	2
12G - Night	1
12H - Paste Masks (mud packs)	2
Total	**13**

Amyl Salicylate

05A - Hair Conditioner	8
05F - Shampoos (non-coloring)	1
11B - Beard Softeners	1
Total	**10**

Hexyl Salicylate

04B - Perfumes	2
06A - Hair Dyes and Colors (all types requiring caution statements and patch tests)	3
07I - Other Makeup Preparations	1
12C - Face and Neck (exc shave)	1
13B - Indoor Tanning Preparations	1
Total	**8**

Isotridecyl Salicylate

No FDA VCRP Data

Personal Care Products Council
Committed to Safety, Quality & Innovation

Memorandum

TO: Bart Heldreth, Ph.D.
Executive Director - Cosmetic Ingredient Review (CIR)

FROM: Alexandra Kowcz, MS, MBA
Industry Liaison to the CIR Expert Panel

DATE: November 26, 2018

SUBJECT: Draft Final Report: Amended Safety Assessment of Salicylic Acid and Salicylates as Used in Cosmetics (draft prepared for the December 3-4, 2018 CIR Expert Panel Meeting)

The Council respectfully submits the following comments on the draft final report, Amended Safety Assessment of Salicylic Acid and Salicylates as Used in Cosmetics.

Key Issues

As Hexyl Salicylate is a fragrance ingredient with an IFRA standard it should be removed from the report. If Hexyl Salicylate is left in the report, the IFRA standard should be presented in the Cosmetic Use section and the values for all product categories should be stated. The Council expects IFRA standards to be followed for all functions.

In the Cosmetic Use section, the EU regulations for salicylates and Salicylic Acid should be presented separately from the recent preliminary SCCS opinion on Salicylic Acid. The preliminary opinion has not been finalized and has not been incorporated into the EU cosmetic regulations as implied by the current presentation of this information in the CIR report. Salicylic Acid is not included in EU Annex II (list of substances which cosmetic products must not contain) as stated in the CIR report. Salicylic Acid is included in EU Annex III, the list of restricted ingredients. This needs to be corrected.

The exposure assessment that assumes use of a peel in a manner similar to a shower gel should be deleted from the report (including from the Summary). Actual exposure data (plasma concentrations of Salicylic Acid - C_{max} 0.81 µg/mL) from use of a peel product containing 30% Salicylic Acid are available. The actual data should be used. In addition to comparing plasma Salicylic Acid from the use of a peel containing 30% Salicylic Acid to an oral dose of 650 mg aspirin (C_{max} 56.4 µg/mL), the exposure from use of a peel could be compared to blood concentrations considered to be toxic (Case Reports section states that salicylism occurs at concentrations greater than 35 mg/dL and the Other Clinical Reports section states that blood concentrations >300 µg/mL should be considered toxic). The exposure studies (reference 54, 57, 59) need to be added to the Summary.

Additional Considerations

Introduction - It is not clear why Butyloctyl Salicylate and Hexyldodecyl Salicylate are not in the list of esters as they are esters, e.g., chemical class listed in the *Dictionary* is esters.

Cosmetic Use - It should be made clear that sunscreens are considered cosmetics in Europe, but are OTC drugs in the United States.

Noncosmetic Use, Ethylhexyl Salicylate - This section should state that when Ethylhexyl Salicylate is used as a sunscreen in the United States, it must be labeled Octisalate.

Dermal Penetration, Ethylhexyl Salicylate and Salicylic Acid - What does "total absorption" represent (reference14)?

Dermal Penetration, Ethylhexyl Salicylate - Was any Ethylhexl Salicylate recovered in the receptor fluid (reference 27)?

Dermal Penetration, Methyl Salicylate - What does "skin penetration" represent (reference 30)? Is it the amount just in the receptor fluid, or does it also include what was recovered in the skin?

Dermal Penetration, Salicylic Acid - What is meant by "dermal absorption" (reference 4)?

Dermal Penetration, Animal and Human, old report summaries - How long after exposure does about 10% of applied salicylates remain in the skin?

Dermal Penetration, Human, Methyl Salicylate - It is not clear what is meant by "or to very high doses" (reference 36).

ADME, Placental - The human placental perfusion study is published and should be cited to the original reference rather than the preliminary SCCS opinion.

Acute, Dermal, old report summary - What is meant by "Little acute toxicity", e.g., deaths, clinical signs?

Short-Term, Oral, Methyl Salicylate - Did the NTP really complete two 14 day studies of Methyl Salicylate in CD-1 mice? The protocols are the same and the titles of the references (43, 44) are the same.

Short-Term Oral, Sodium Salicylate, old report summary - What happened to the dogs that were treated with 10% aqueous Sodium Salicylate for 2 weeks?

Subchronic, Oral, old report summaries - Please include some indication of dose in the old report summaries. Please revise: "No treatment related observations were observed."

DART, Animal, Oral, Sodium Salicylate, last paragraph - Were the significant differences in body and tail length and mean body weight increases or decreases?

Risk Assessment - Reference 53 is the SCCNFP opinion not the preliminary SCCS opinion. The 75 mg/kg/day NOAEL was used in both opinions.

Risk Assessment, Oral, Salicylic Acid, old report summary - As a new exposure assessment is being added to this report, the summary of the exposure assessment included in the original report should be deleted.

Estrogenic Activity - Please correct: "the nature hormone estradiol"

Sensitization, In Vitro - Please identify the types of *in vitro* sensitization assays that were used (reference 74).

Sensitization, Animal - What was the EC_3 for Hexyl Salicylate (it says "very low")?

Sensitization, Human - A skin sensitization NOEL is usually called a NESIL (No Expected Sensitization Induction Level).

Computational Analyses/Predictions - This section concerns sensitization and should be presented after the Sensitization section rather than the Phototoxicity/Photosensitization section.

Summary - Please add the conclusion for MEA-Salicylate to the Summary.

When discussing dermal penetration what is meant by "relatively low"?

Please correct "Amyl Acetate" to "Amyl Salicylate"

Personal Care Products Council
Committed to Safety, Quality & Innovation

Memorandum

TO: Bart Heldreth, Ph.D.
Executive Director - Cosmetic Ingredient Review (CIR)

FROM: Alexandra Kowcz, MS, MBA
Industry Liaison to the CIR Expert Panel

DATE: January 22, 2019

SUBJECT: Revised Tentative Report: Amended Safety Assessment of Salicylic Acid and Salicylates as Used in Cosmetics (release date January 8, 2019)

The Council respectfully submits the following comments on the revised tentative report, Amended Safety Assessment of Salicylic Acid and Salicylates as Used in Cosmetics.

Key Issues

Somewhere in this report e.g., Cosmetic or Non-Cosmetic Use section, please state that when used as a sunscreen in the United States, Ethylhexyl Salicylate must be on the label as Octisalate (International Nonproprietary Name [INN name]).

Cosmetic Use - The EU Commission has not yet added the recent SCCS opinion on Salicylic Acid into the cosmetic regulations. Therefore, the statements "This opinion is not applicable to oral products such as toothpaste and mouthwash; sprayable products that could lead to exposure of the consumer's lung by inhalation are also excluded." should not be presented with the regulation. The statement concerning "A preliminary opinion on Salicylic Acid..." in the paragraph on Ethylhexyl Salicylate is not correct. The recent SCCS opinion on Salicylic Acid only applies to Salicylic Acid and not the salts or esters of Salicylic Acid.

In the presentation of the EU regulation of salicylates as preservatives (Annex V item 3) the CIR report currently states: "For use other than as a colorant, See Annex IV, No. 143." This is not correct. It should state: "For use other than a preservative, see Annex III No. 98."

DART, Animal, Oral, Ethylhexyl Salicylate - Please look more closely at the ECHA dossiers for Ethylhexyl Salicylate (reference 28) and Butyloctyl Salicylate (reference 45). The same developmental toxicity study on Ethylhexyl Salicylate is presented in both dossiers. The study described in both dossiers was done in 2012 (report completed in 2013), done in the same strain of rats, at the same doses, and the room numbers are the same. The results of the studies, e.g., 1 maternal death at the high dose, are also the same. Therefore, there

was only one study on Ethylhexyl Salicylate that is being used to support both Ethylhexyl Salicylate and Butyloctyl Salicylate. This study only needs to be presented once in the CIR report (it is currently presented twice cited to both dossiers).

Risk Assessment, Summary, Discussion - Stating that the risk assessment for Butyloctyl Salicylate in lipstick "was performed because the maximum use concentration of 35.9% Butyloctyl Salicylate exceeds IFRA's 1% concentration limit (relative to sensitization potential) for Butyloctyl Salicylate in lip products" suggests that Butyloctyl Salicylate is a sensitizer. The available data do not provide any evidence that Butyloctyl Salicylate is a sensitizer. In addition, the risk assessment being completed concerns systemic toxicity rather than sensitization. The systemic toxicity risk assessment for Butyloctyl Salicylate should be completed because 35.9% Butyloctyl Salicylate was the highest use concentration reported and because of the potential to be metabolized to Salicylic Acid.

Additional Considerations

Introduction - The Dictionary definitions of Butyloctyl and Hexyldodecyl Salicylate differ from the other salicylate esters only because the definitions were written at different times. Although it does not say so in the definitions, Butyloctyl and Hexyldodecyl Salicylates are esters (see Chemical Class field for these ingredients). The definitions of the other esters were written before there was also a chemical class field in the Dictionary database, so the class needed to be stated in the definition. For the purposes of the Introduction of the CIR report, it is not necessary to call Butyloctyl and Hexyldecyl Salicylates "compounds". These two esters can be included with the other salicylate esters in this report.

The SCCS opinion on Salicylic Acid was finalized on December 21, 2018. It should no longer be called a "preliminary opinion."

Chemical and Physical Properties - It is not clear what is meant by "These esters". Are all the esters included in this report liquids (the physical form of all the esters is not included in Table 2)?

Dermal Penetration, In Vitro, Methyl Salicylate - Please include the identity of the receptor fluid used in the study of Methyl Salicylate in human skin (reference 32).

Dermal Penetration, In Vitro, Salicylic Acid - Please state the units (likely "%") after 50.09.

Dermal Penetration, Animal, Methyl Salicylate - The *in vitro* study in hairless mouse skin should be moved to the *in vitro* subsection.

Dermal Penetration, Human, Ethylhexyl Salicylate - In the study in 9 volunteers (reference 37), the INCI name is only used for Ethylhexyl Salicylate, while the INN names are used for the other sunscreen ingredients. If the INN name for Ethylhexyl Salicylate is not presented earlier in the report, it should be stated in this section. Please indicate if the amount of sunscreen absorbed was the amount of sunscreen recovered in the urine.

Dermal Penetration, Human, Hexyl Salicylate - The title of reference 30 is: "Prediction of ultraviolet filters used in sunscreen formulations". Since Hexyl Salicylate is not a UV filter, did these investigators really study Hexyl Salicylate? As it states that they studied "some salicylate esters", what esters did they study in addition to Hexyl Salicylate?

ADME, Animal, Dermal, Methyl Salicylate - The description of the methods (reference 31) states that the rats were killed at 6 hours after dosing. The results ("At 0.5-1 hr after application.... the presence of salicylate in contralateral dermal tissue") suggest that rats were also killed at earlier time points.

ADME, Human, Oral, Salicylic Acid - The information cited to the SCCS opinion (reference 4) is not a summary of a specific study. It is a general discussion of the ADME of Salicylic Acid in humans. This information is covered by older studies summarized in the original CIR report and is not needed. If it is left in the report, the following sentence should be deleted: "Further details relating to the study protocol were not provided."

Short-term, Oral, Salicylic Acid, old report summary - Were the "changes" in liver and plasma enzymes increases or decreases?

Subchronic, Dermal, Salicylic Acid - Please correct: "anriskd"

Subchronic, Inhalation, Methyl Salicylate - Units of "mg/m^3" should be called concentration rather than dose.

DART, In Vitro, Salicylic Acid, old report summary - In the *in vitro* sperm exposure study, what compound was used (it says: "The effect of Salicylic Acid..." but the concentrations are stated as "salicylate").

DART, Animal, Oral, Salicylic Acid, old report summary - The summary paragraph only reports effect levels. Were any NO(A)ELs identified?

DART, Animal, Oral, Sodium Salicylate - Did any adverse effects occur at 30 mg/kg/day in rats treated on gestation days 6-15? In the study in A/Jax mice, were the dams or offspring killed at 24 hours?

Estrogenic Activity - It is not necessary to define the prediction confidence twice in the same paragraph.

Irritation, Animal, Dermal, old report summary - Please include the species used in the study of Butyloctyl Salicylate.

Summary - Please correct: "diluted to containing 0.25% Salicylic Acid"

The paragraph describing the risk assessment presented after the DART summary paragraph should be deleted as the risk assessment is also presented at the end of the Summary. The paragraph describing the risk assessment should make it clear that actual exposure measurements were used for the 30% peel product.

Discussion - The risk assessment summary in the Discussion should also make it clear that actual exposure measurements were used for the 30% peel product.

Table 4, Irritation - Please correct: "As semiocclusive patch..."

The Results column of the 14-day rabbit study of Salicylic Acid still needs to be completed. It ends with: "was irritating to the skin of."

If the HRIPTs of formulations containing up to 1.5% Salicylic Acid (reference 5) are left in the irritation section of this table, the results section should mention irritation rather than sensitization (currently says "No skin sensitization").

Table 4, Sensitization, Human - Please check the 52 subject sensitization study of Butyloctyl Salicylate (reference 45) again. The Test Protocol column says "site not stated". The study says: "The upper back between the scapulae served as the treatment area."

Table 5, In Vitro - In the *in vitro* phototoxicity test, the Test Protocol (PIF >1 potential phototoxic; MPE >0.1 predicted to be phototoxic) disagrees with the results column (PIF = 1.756 and 1.043; MPE = 0.109) phototoxicity results were classified as negative. Is this correct?

Table 5, Animal - Since the study of Hexyl Salicylate in hairless mice included a positive control, the Results should be more detailed than: "No reactions were observed." Presumably, exposure to 8-methoxypsoralen plus light resulted in reactions. If it did not the study would not be considered acceptable.

Please correct: "w2 intergreen"