
Safety Assessment of Benzyl Salicylate As Used in Cosmetics

Status: Draft Final Report for Panel Review
Release Date: March 15, 2019
Panel Meeting 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 safety assessment was prepared by Alice Akinsulie, Scientific Writer/Analyst.



Commitment & Credibility since 1976

Memorandum

To: CIR Expert Panel Members and Liaisons
From: Alice Akinsulie, Scientific Analyst/Writer
Date: March 15, 2019
Subject: Draft Final Report of the Safety Assessment of Benzyl Salicylate as Used in Cosmetics

Enclosed is the draft final report of the Safety Assessment of Benzyl Salicylate as Used in Cosmetics. (It is identified as *bensal042019rep* in the pdf document.)

At the December 2018 CIR Expert Panel (Panel) Meeting, the Panel issued a tentative report for public comment with the conclusion that Benzyl Salicylate is safe in cosmetics in the present practices of use and concentration when formulated to be non-irritating and non-sensitizing, which may be based on a quantitative risk assessment (QRA).

CIR staff have received 2019 VCRP data and the use table has been updated accordingly. According to VCRP data, Benzyl Salicylate is reported to be used in 3079 formulations, 2419 of which are leave-on products. Also, it should be noted that use concentration survey data provided by the Council on Benzyl Salicylate were reported for its functions only as a light stabilizer; however, the VCRP does not indicate the function of ingredients in cosmetic formulations, so it is not known what the intended function of Benzyl Salicylate is in any of the reported ingredient categories.

Council comments received prior to the December 2018 meeting are included in the packet (*bensal042019pcpc_1*). In addition, Council comments regarding the Tentative Report were received and addressed (*bensal042019pcpc_2*). In the comments on the Tentative Report, the Council notes that sensitization potential of a compound is not dependent on function in cosmetic products. Council suggests that the IFRA standards for Benzyl Salicylate based on a sensitization QRA should be applied for all uses in cosmetics.

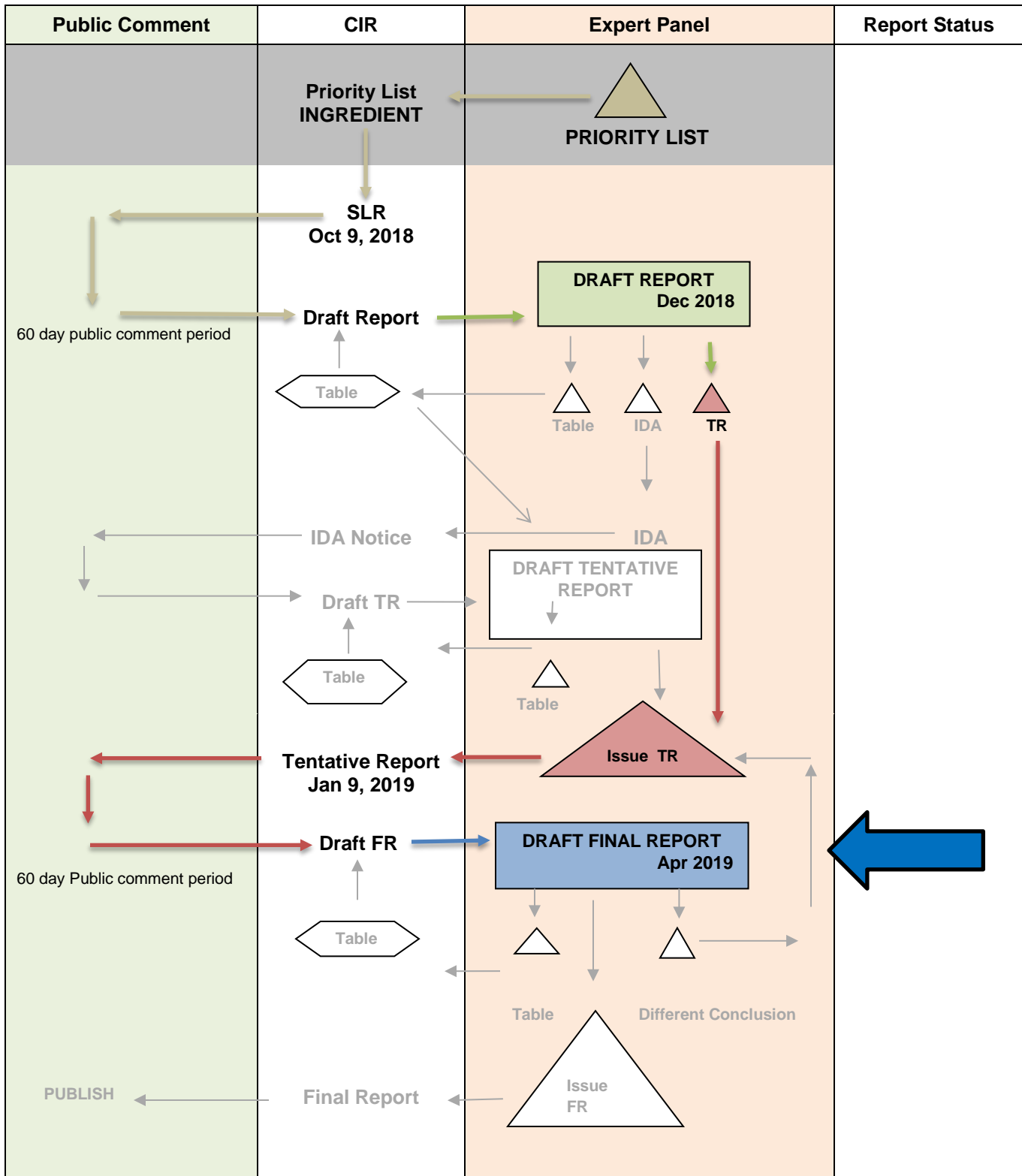
Also included in this package for your review are the CIR report history (*bensal042019hist*), flow chart (*bensal042019flow*), literature search strategy (*bensal042019strat*), ingredient data profile (*bensal042019prof*), and 2019 FDA VCRP data (*bensal042019FDA*).

The Panel should carefully review the Abstract, Discussion, and Conclusion of this safety assessment. If these are satisfactory, the Panel should issue a Final Report.

SAFETY ASSESSMENT FLOW CHART

INGREDIENT/FAMILY Benzyl Salicylate

MEETING April 2019



Benzyl Salicylate History

October 9, 2018

SLR for Benzyl Salicylate was posted.

December 2018

Panel reviewed the Draft Report; the report included penetration data, oral and dermal toxicity study, combined repeated-dose reproductive/developmental toxicity study, genotoxicity studies, skin irritation, sensitization, ocular irritation studies, clinical studies and case reports. The Panel concluded that Benzyl Salicylate is safe in cosmetics in the present practices of use and concentration described in this safety assessment when formulated to be non-irritating and non-sensitizing, which may be based on a quantitative risk assessment (QRA).

April 2019

Panel reviews the Draft Final report; Council comments received prior to the December 2018 meeting and Council comments regarding the Tentative Report were received and addressed. Also included in this iteration of the report is the 2019 VCRP which has been updated accordingly. The Panel should carefully review the Abstract, Discussion, and Conclusion of this safety assessment. If these are satisfactory, the Panel should issue a Final Report.

Benzyl Salicylate Data Profile* - April 2019 - Alice Akinsulie

				Toxicokinetics			Acute Tox			Repeated Dose Tox			DART		Genotox		Carci		Dermal Irritation			Dermal Sensitization				Ocular Irritation		Clinical Studies	
	Reported Use	Method of Mfg	Impurities	log P/log K _{ow}	Dermal Penetration	ADME	Dermal	Oral	Inhalation	Dermal	Oral	Inhalation	Dermal	Oral	In Vitro	In Vivo	Dermal	Oral	In Vitro	Animal	Human	In Vitro	Animal	Human	Phototoxicity	In Vitro	Animal	Retrospective/ Multicenter	Case Reports
Benzyl Salicylate	X	X	X	X	X		X	X		X			X		X				X	X		X	X	X	X	X	X	X	X

* "X" indicates that data were available in a category for the ingredient

Benzyl Salicylate

[illegible]

Search Terms

118-58-1
2-Hydroxybenzoic acid
Benzyl Salicylate
Benzyl Salicylate irritation
IFRA Sensitization Benzyl Salicylate
Benzyl Alcohol
Salicylic Acid
Cyclohexyl Salicylate
Benzyl Ester
Benzyl-o-hydroxybenzoate

LINKS

Search Engines

- Pubmed (- <http://www.ncbi.nlm.nih.gov/pubmed>)
- Toxnet (<https://toxnet.nlm.nih.gov/>); (includes Toxline; HSDB; ChemIDPlus; DART; IRIS; CCRIS; CPDB; GENE-TOX)
- Scifinder (<https://scifinder.cas.org/scifinder>)

appropriate qualifiers are used as necessary

search results are reviewed to identify relevant documents

Pertinent Websites

- wINCI - <http://webdictionary.personalcarecouncil.org>
- FDA databases <http://www.ecfr.gov/cgi-bin/ECFR?page=browse>
- FDA search databases: <http://www.fda.gov/ForIndustry/FDABasicsforIndustry/ucm234631.htm>;
- EAFUS: <http://www.accessdata.fda.gov/scripts/fcn/fcnavigation.cfm?rpt=eafuslisting&displayall=true>
- GRAS listing: <http://www.fda.gov/food/ingredientspackaginglabeling/gras/default.htm>
- SCOGS database: <http://www.fda.gov/food/ingredientspackaginglabeling/gras/scogs/ucm2006852.htm>
- Indirect Food Additives: <http://www.accessdata.fda.gov/scripts/fdcc/?set=IndirectAdditives>
- Drug Approvals and Database: <http://www.fda.gov/Drugs/InformationOnDrugs/default.htm>
- <http://www.fda.gov/downloads/AboutFDA/CentersOffices/CDER/UCM135688.pdf>
- FDA Orange Book: <https://www.fda.gov/Drugs/InformationOnDrugs/ucm129662.htm>
- OTC ingredient list: <https://www.fda.gov/downloads/aboutfda/centersoffices/officeofmedicalproductsandtobacco/cder/ucm135688.pdf>
- (inactive ingredients approved for drugs: <http://www.accessdata.fda.gov/scripts/cder/iig/>)
- HPVIS (EPA High-Production Volume Info Systems) - <https://ofmext.epa.gov/hpvis/HPVISlogin>
- NIOSH (National Institute for Occupational Safety and Health) - <http://www.cdc.gov/niosh/>

- NTIS (National Technical Information Service) - <http://www.ntis.gov/>
- NTP (National Toxicology Program) - <http://ntp.niehs.nih.gov/>
- Office of Dietary Supplements <https://ods.od.nih.gov/>
- FEMA (Flavor & Extract Manufacturers Association) - http://www.femaflavor.org/search/apachesolr_search/

- EU CosIng database: <http://ec.europa.eu/growth/tools-databases/cosing/>
- ECHA (European Chemicals Agency – REACH dossiers) – <http://echa.europa.eu/information-on-chemicals;jsessionid=A978100B4E4CC39C78C93A851EB3E3C7.live1>
- ECETOC (European Centre for Ecotoxicology and Toxicology of Chemicals) - <http://www.ecetoc.org>
- European Medicines Agency (EMA) - <http://www.ema.europa.eu/ema/>
- IUCLID (International Uniform Chemical Information Database) - <https://iuclid6.echa.europa.eu/search>
- OECD SIDS (Organisation for Economic Co-operation and Development Screening Info Data Sets)- <http://webnet.oecd.org/hpv/ui/Search.aspx>
- SCCS (Scientific Committee for Consumer Safety) opinions: http://ec.europa.eu/health/scientific_committees/consumer_safety/opinions/index_en.htm
- NICNAS (Australian National Industrial Chemical Notification and Assessment Scheme)- <https://www.nicnas.gov.au/>

- International Programme on Chemical Safety <http://www.inchem.org/>
- FAO (Food and Agriculture Organization of the United Nations) - <http://www.fao.org/food/food-safety-quality/scientific-advice/jecfa/jecfa-additives/en/>
- WHO (World Health Organization) technical reports - http://www.who.int/biologicals/technical_report_series/en/

- www.google.com - a general Google search should be performed for additional background information, to identify references that are available, and for other general information

Fragrance Websites, if applicable

- IFRA (International Fragrance Association) – <http://www.ifraorg.org/>
- Research Institute for Fragrance Materials (RIFM)

Benzyl Salicylate
December 3-4, 2018 Minutes
Group 1

DR. MARKS: The next report is benzyl salicylate. This is the first time we've seen this draft report. Alice? Where's Alice? Oh. Hi, Alice. Sent a memo dated November the 9th. And we have just one.

One of my questions, was this only used as a light stabilizer? But Ron and Tom, we aren't gonna discuss the ingredients, because we have one. Are there any needs for this, or can we proceed with a tentative report?

DR. SHANK: Safe as used.

DR. HILL: I did have a question. And it relates to what you just said in terms of the use. Is -- what is the highest concentration of use? Because it was conflicting information. And it seemed like, in the wave, the last piece of information that we got, the information seemed different than what I first saw. There wasn't a Wave 2 or Wave 3, but somewhere -- I think it was in the data summary or the annotated agenda. They had pulled something with the panel and they said -- let me see if I can find that.

DR. MARKS: No. I thought the irritation sensitization was fine, Ron Hill.

DR. HILL: The highest concentration of use. That's what I'm asking. What is it currently known to be?

DR. HELDRETH: It's .5 in cleansing.

MS. AKINSULIE: It's .15 in leave-on.

DR. HILL: So, 15 percent in leave-ons?

MS. AKINSULIE: Yes.

DR. HILL: Okay. Then I have issues, I think.

DR. MARKS: Well, the leave-on was .15, right?

MS. AKINSULIE: It's .15.

DR. MARKS: So, we have one percent, no sensitization with a guinea pig.

DR. HILL: I thought you said 15 percent.

MS. AKINSULIE: It's 0.15.

DR. HILL: Oh, .15 percent.

DR. MARKS: Yes.

DR. HILL: Yeah, I'm having difficulty hearing you, clear, down here.

DR. MARKS: Yeah. That's why I -- there's enough sensi --

DR. HILL: Oh, .15 percent. Okay.

DR. MARKS: Yes.

DR. HILL: Because somewhere I had -- I thought a bigger number.

DR. MARKS: Okay. Tentative report, safe conclusion.

DR. HILL: I had some discussant points that I would like to talk about. Insufficiencies.

DR. MARKS: So, you don't like a safe?

DR. HILL: Nope.

DR. MARKS: You want do insufficient?

DR. HILL: Nope. Insufficient. Commercially pertinent methods of preparation, or robust information about impurities that may be associated with the commercial production processes, or impurities representative of the commercial production pertinent to cosmetic use. So, do we have concern about inhalation toxicology, even though we're only evaluating for light stabilizing use? The intention of use has nothing to do with toxicological relevance.

The info on the basis for the observed toxicity and the acute dermal seems very incomplete. It seems like way more should be known. There's absolutely no way that cyclohexyl salicylate should be taken as a surrogate for toxicological inferences in a systemic study for this. And that's what they used in ECHA.

It's not a benzene ring, so as a leave-in group better for an ester, it's sterically occluded, where the benzyl is not. And electronically, it's not similar. There's no way it should've been used as a surrogate. That's crazy and chemically nonsensical. It'd be better to compare it to a butyl or an ethyl salicylate and go that way, which we have in the other report, some information about that. But this is benzyl.

The estrogenic activity is a thousand times less strong than estrogen, but not zero. So, at 0.15 percent, that's probably of no consequence in terms of any systemic effects. But what about in the skin?

And there's some information in the DART study; it's the uterine weight gain, I think. What do we do about that? Clearly, you can get an idea about the dose -- that concentration response. We could calculate an easy 50 of as low as 2 to 5 milligrams per kilogram per day, but we're missing amounts in that low range to be sure. And there's a U-shaped response curve that's very apparent. So, in looking at things like the MCF at 7 breast cancer cells, I think there are some tox issues that need to be looked at carefully.

Let's see. There's also a statement about GRAS status that suggests that GRAS status could be granted by somebody, which it's an association, so that can't be. I think it was the Flavor Extract Manufacturers Association that "regarded" it as GRAS.

DR. ANSELL: They maintain a GRAS list.

DR. HILL: Huh?

DR. ANSELL: They maintain a GRAS list.

DR. HILL: Yeah, but it has no weight in anything. It's not in the federal register as GRAS, is it?

DR. ANSELL: It's generally recognized as safe.

DR. HILL: Well, just because they say so doesn't convince me if we've got people using cyclohexyl as a surrogate for benzyl in the tox studies. It may be insane inference, but that doesn't make any sense at all.

DR. ANSELL: Curious as to what they think of CIR.

DR. HILL: Well, I'm not -- I don't know what they looked at, because I don't have that information. All I know is they concluded GRAS based on some information that I've never seen.

DR. ANSELL: I think that's a legitimate question, but I would not impugn their assessment.

DR. HILL: I'm not. I'm not impugning their assessment. I just don't know what it is, and on what basis they made that conclusion. Because I see some other organizations going through a great deal of science, and making a conclusion that doesn't make any scientific solid sense. So, having not seen what they looked at, and how they concluded it, I don't think I can rely on their conclusion of GRAS.

DR. SHANK: You don't have to rely on it, it's just a statement.

DR. HILL: I know it is.

DR. SLAGA: It's a statement. Yeah.

DR. HILL: All right. Well, what it says was -- okay. The way it was written bothered me, I think, more than anything else; because it sort of suggested it had some weight of regulatory something, and it doesn't.

DR. SLAGA: No, it doesn't.

DR. HILL: The way it was written suggested that to me.

DR. MARKS: Anything else, Ron Hill? Otherwise, Tom, I'll ask -- Ron brought up some, I think, carcinogenicity, but you were fine with all that. And Ron and Tom, you were fine with the other tox endpoints? And Ron Shank, you're still fine?

DR. SLAGA: I'm fine.

DR. SHANK: I'm still fine.

DR. HILL: So, if we have estrogenic effects in the skin -- because this stuff should be very dermally penetrable. And we have a lot of dermal penetration studies that aren't valid in terms of knowing what might go on in the skin, if this stuff gets in there, which it will.

DR. SLAGA: Are you worried about the estrogenic effect directly on the skin?

DR. HILL: In the skin. In the skin.

DR. SLAGA: Not going through the skin, or anything, systemically?

DR. HILL: Nope. Not systemically. Although -- yeah, if we're only at 0.15 percent, then nothing systemic.

DR. SLAGA: Well, the skin is well-known with having estrogen receptors, and testosterone receptors, and has a lot of influence from androgens and estrogens. But once again, it goes to the concentration. I mean, the level of the effect of estrogen going to the skin will be much higher than this estrogenic effect from this, which it's been tested and it's very, very weak.

DR. HILL: It's 100 nanomolar range. So that's 1000 times weaker than estrogen, but it's reasonably potent. 100 nanomolar is -- I mean, I've poo-pooed a lot of other estrogenic effects that are clearly bogus in our reviews, some of the parabens and so forth. But in this particular case, again, there's concentration response in a uterine weight-gain assay that clearly is consistent with that; a U-shaped response curve and, again, you can almost hang your hat on this roughly 100 nanomolar, EC 50 for estrogenic effect. So, if that happens in the skin --

DR. ANSELL: Well, there is a combined, repeat dose, repro/developmental DART study, which the RIFM reproductive group concludes a reproductive NOAEL of 30 milligrams per kilogram per day.

DR. HILL: But that was done orally, was it not?

DR. ANSELL: Yeah.

DR. SLAGA: Yes.

DR. HILL: So, as soon as you put first-pass effect in at that kind of concentration, then forget it. Don't tell me about that. If they were swamping out the systems, if they were giving substantial larger doses, in which case you'd see other effects, unfortunately, that would confound the whole thing --

DR. MARKS: So, Ron Hill, what we'll do, again, tomorrow when this ingredient is brought up, we'll have the -- I'll be seconding, presumably, a tentative report with a safe conclusion. You'll have an opportunity to raise your concerns and we'll see what the response of the other team is.

DR. HILL: And the last comment on that, about the dermal penetration is, it's got a log P of 4. So, that's right in the sweet -- I mean, if you want to make something for transdermal delivery, you give it a log P of 4, 5, 6; and the nice, small molecular weight, which it has.

DR. MARKS: Okay. Any other comments? Your concerns are duly noted.

DR. SHANK: In the acute oral toxicity studies in rats, it was reported that, before death, the rats were depressed.

DR. HILL: Yeah. I flagged that, of course.

DR. SHANK: I would like to know how they measured depression in a dying rat.

DR. SLAGA: You haven't seen a depressed rat?

DR. ANSELL: The number of cigarettes they smoked.

DR. HILL: I assumed it was referring to CNS depression and breathing suppression and -- yeah; not true depression, depression.

DR. SHANK: No, they were just, head down, and.

DR. SLAGA: Most rats are depressed living in sewers.

DR. MARKS: So, Ron Shank, you'd like that clarified, maybe adding --

DR. SHANK: No. No.

DR. SLAGA: They schlepped around in their bathrobes all day, and they get up late. And that's what they did.

DR. MARKS: Okay. Any other comments? I like that little end, final, with depressed rats. Okay

Group 2

DR. BELSITO: Okay, Benzyl Salicylate. This is the first time we're looking at this, and what do we think?

DR. LIEBLER: So, I'm coming down safe as used on this, with any caveats to be provided by Don and Jim, with respect to the skin data -- and Wilma. Otherwise, I thought the data package looked pretty good.

DR. BELSITO: Well, I'm not safe as used, formulated to be non-irritating and non-sensitizing, using QRA or another system.

DR. LIEBLER: Okay.

DR. BELSITO: Because it is a sensitizer. But I also said we have lack of absorption and we don't have any DART studies. We have negative genotox which, I guess, mitigates against carcinogenicity studies; so we don't know the absorption through the skin, and we don't have any reproductive --

DR. LIEBLER: We have a DART. There's an oral DART. Because there's a .003 milligram per kilogram per day, in oral toxicity, that I flagged.

DR. BELSITO: Where is this?

DR. LIEBLER: PDF 13.

DR. BELSITO: Did I miss that?

DR. EISENMANN: It's a new study and I shared that with Dr. Apey (phonetic) and she sent it to the FIFM adjunct reproductive panel, and they disagree with the interpretation. They considered the low dose to be a NOEL, not a LOEL.

DR. BELSITO: Okay. So, we do have a NOEL for reproductive?

DR. SNYDER: Um Hmm.

DR. BELSITO: And you're comfortable with that?

DR. SNYDER: Mm-hmm.

DR. BELSITO: So, then formulated to be non-irritating and non-sensitizing. Is everyone okay with that?

DR. KLAASSEN: Yes.

DR. LIEBLER: Yeah.

DR. EISENMANN: We're still concerned why you're reviewing this at all. I think at some point the procedures should be revisited, because, to me, you're wasting time. When an ingredient is reviewed by the RIFM expert panel, and has an IFRA standard, it doesn't seem necessary for you guys to also review it. We considered that the IFRA standard, which should apply, doesn't matter what kind of a use -- what the function is.

DR. BELSITO: Well, basically, then, I think you would need to change the regs for CIR.

DR. EISENMANN: The procedures.

DR. BELSITO: Right. Right now --

DR. EISENMANN: But would you be supportive of a change in the procedures to reflect that?

DR. BELSITO: Yeah. That's probably not up to the panel, that's up to --

DR. EISENMANN: Well, but sometimes --

DR. BELSITO: But I think it's redundant, you know, if there's a restriction that's been set worldwide, for us to relook at it.

DR. EISENMANN: Especially -- it's my understanding, you're almost -- if it's a RIFM -- is you're almost done with a re-review of it. Just the QRA 2 has to be complete on this one and then it will be done.

DR. BELSITO: Right.

DR. HELDRETH: Am I wrong in thinking that if we had an ingredient that's used for two different purposes, that the concentrations may be different, the exposure parameters, whether it's applied to the lip or around the eye, or not, between those two different types of uses, may all factor into the safety assessment?

DR. BELSITO: But that's what RIFM does with the QRA. I mean, the QRA looks at lip, looks at face, looks at shaved, unshaved. They're looking at all the same things we're looking at. They're actually setting a limit. I guess, the only question is, is their limit perceived only as a fragrance limit, and not as a limit in general?

DR. HELDRETH: That's our understanding of it. I mean, yes, maybe it makes the panel here looking at it, for a different use, very easy. But we believe, as it stands, there's no safety assessment available or limit publicized that applies to the light stabilizer function for this ingredient. While it may be seen somewhat redundant, maybe that just makes your job very easy for this ingredient. We've already come to a conclusion on this very quickly.

DR. BELSITO: Yeah. I guess it's my only concern. Because the way the RIFM documents are framed, it's as a fragrance ingredient. So, it could be misconstrued that, as a non-fragranced ingredient, it could be used differently. I think that, yeah, I mean, it certainly would be nice to --

DR. EISENMANN: That was one thing, we had an expectation that the concentration of use survey results would come to you before the report was prepared; so that you could look at how it was used, and compare it to what you've got for RIFM, and then decide whether or not it was worth to do the next step.

DR. BERGFELD: You know we never see those RIFM reports? I never included it in anything over the years. So, to reassign this to RIFM, when we have a cosmetic use, I think the regulations or administrative regs point out that factor very well. That when it's used in cosmetic product, for a specific behavior, then it should be as a cosmetic ingredient. It would be different if they were advertised, and they were available, and disseminated widely.

DR. EISENMANN: Well, they aren't available on the RIFM website now.

DR. HELDRETH: Even if we were talking about an FDA review, or some other agency review, the way that we have our procedures set up, the panel can adopt the conclusions of some other body, when it adequately covers cosmetic use of the ingredient. And they shall conduct their own evaluation of those cosmetic uses, not adequately covered by that review.

So, I don't think -- yes, RIFM's looked at it for another reason. I don't think that negates the panel looking at it; it may make your job really easy for this ingredient. But the panel should weigh in on whether or not they feel that that review adequately covers the safety of its use.

DR. BELSITO: Yeah. And it will. Because that review will put out a non-sensitizing QRA dose. So, it will essentially provide what we're saying, formulated to be non-irritating and non-sensitizing, using QRA or whatever other methodology. And then companies can then look at the RIFM report and figure out, okay, for lips, this is a limit, for underarm, this is a limit, and they have it.

DR. BERGFELD: Maybe we can begin to cite these in our reference list, as well as in our document.

DR. LIEBLER: The RIFM report, yeah. Public document.

DR. BELSITO: Yeah. They're now all publicly available online. It's just that the individual references, if they've not been published in the open literature, are available only to RIFM company members. So, if you had a question about a specific reference, within their document, that was part of the RIFM database but not publicly available unless you are a member, you wouldn't be able to get that specific information. But the actual document, the summary of that information, et cetera, is there. Just like with our documents when we're getting crossed out stuff, where it's not publicly available, just our summary is.

DR. HELDRETH: So, assuming this report goes final within the next few meetings, when it ultimately gets sent to the International Journal of Toxicology, we can include that reference to the RIFM conclusion, if it's publicly available at that point.

DR. BELSITO: If it's available. Okay.

DR. LIEBLER: So, Don, you mentioned lack of absorption data.

DR. BELSITO: Yeah.

DR. LIEBLER: So, on PDF page 12, they do have three studies listed in vitro absorption. One is with human skin, one is rat, and one is guinea pig skin, all these in vitro. The rat result was tens of percent's, up to 62 percent absorption, into a receptor fluid, under the conditions of the assay.

But then you go to guinea pig, it's in the single digit's percentage. And then in the human, it was less than 0.1 percent absorption. So that's a relationship that you would expect to hold, due to the skin thicknesses and so forth. So, I think the data is fine on absorption. It's going to be low, very low, in humans.

DR. BELSITO: Okay. So, safe as used, formulated to be non-irritating and non-sensitizing.

DR. LIEBLER: Yeah.

DR. BERGFELD: And your discussion to include the reasons for stating that?

DR. BELSITO: Well, that it can be irritating at certain doses. The data is there, and it's been reported to be a sensitizer. Let me just go through and find out where that is.

DR. LIEBLER: One thing I'd like to comment on, PDF 13, at the top under the subchronic tox, the use of a read-across analog. This is, I guess, from an ECHA report, and it's something we traditionally don't do in CIR, we do a lot in RIFM. And I think it's perfectly appropriate. This was using cyclohexyl salicylate as a read-across for Benzyl Salicylate. I think the data are appropriate and useful.

Another thing that -- again, it's just a comment not necessarily a recommendation. But another thing that we do on the RIFM panel, sometimes, when we have a molecule that has very predictable metabolism that's likely to be extensive in vivo, such as the de-esterification of this Benzyl Salicylate, where you have benzyl alcohol and salicylate, sometimes we bring in data from benzyl alcohol oral or Salicylic Acid oral, for example, to use as a weight of evidence. We do it when we have to, and I think we don't necessarily have to right now. But if we start to use analogs like this, for in vivo endpoints, particularly for oral in vivo endpoints, we can also think about taking in the likely metabolites for weight of evidence.

DR. HELDRETH: So, if we see those types of gaps, in the future in other reports, we should be thinking about maybe including the data on the metabolites?

DR. LIEBLER: Oh, yeah. It's very easy. I mean, we've kind of developed a boilerplate language to use to describe the logic for doing it. Basically, even in the absence of -- in published in vivo metabolism data, it's reasonable to use metabolism simulator programs to predict metabolites. That, together with expert annotation, I think, is very defensible and it helps to add to the weight of evidence.

DR. HELDRETH: Great. Thank you.

DR. BELSITO: On PDF 20, there's data showing that it can irritant and LLNA was a weak sensitizer, Magnusson-Kligman for guinea pig maximization, 10 percent, it sensitized, so I mean there's --

DR. BERGFELD: I know, it's in the tables as well. I thought in your discussion you might want to bring in something about it, because you're saying non-irritating, non-sensitizing, just to bring it together.

FINAL REPORT

DR. BELSITO: Again, this is the first time that we're looking at this ingredient. It's reported to function both as a fragrance and a light stabilizer, which is the reason we're looking at it as a light stabilizer. My team reviewed all of the data and felt that it was safe as used when formulated to be non-irritating and non-sensitizing, using QRA or other accepted methodologies.

DR. BERGFELD: And that's a motion?

DR. BELSITO: Yes.

DR. BERGFELD: Second?

DR. MARKS: I'll second that motion; although interestingly, we didn't pick out irritation and sensitization to be an issue in Table 4, so just to clarify that. The other I'll mention for our team, Ron Hill, you can speak up. You felt it was insufficient and I'll let you give the reasons. But I'll second the motion; that's obviously more conservative than our team felt. We felt we could move with just a safe conclusion.

DR. BERGFELD: Let's have Ron Hill respond, and then Dr. Belsito respond to that last comment.

DR. HILL: What am I responding to?

DR. BERGFELD: The benzyl salicylate, insufficient.

DR. HILL: Yeah. We know this compound has some estrogenic activity, grant you, it's a thousand-fold less potent than estrogen; but it's in the hundred nanomolar range, you can see from the information we have, with some sort of a U-shaped response versus concentration curve. While I really don't have any big concerns if it's used at relatively low concentration, if we're talking about what's the maximum listed use concentration right now?

MS. AKINSULIE: It's 0.15, in leave-on?

DR. HILL: In leave-on.

MS. AKINSULIE: And .5 in rinse-off?

DR. HILL: If it is .5 percent, then I have no concern.

DR. BERGFELD: Okay. Don, you want to respond to why non-sensitizing and non-irritating was added to your conclusion.

DR. MARKS: Yeah. I'll ask you to go to Page 24, to Table 4. And when I look under dermal irritation, basically, I see no irritation, all the way down up to a hundred percent. And if it's being used as a leave-on at 0.1 percent, I don't know. Maybe you can tell me why irritation was a concern. And then we'll move on to sensitization. But again, there was a little bit of sensitization in guinea pig, but the majority there was no sensitization.

DR. BELSITO: In terms of sensitization, that's the easiest, I think. If you go to page 21 or 22. Oh, okay, I'm sorry. Page 21, I guess. QRA for dermal sensitization, the RIFM expert panel reviewed the critical effect data of benzyl salicylate via weight of evidence approach; and came up with a no-expected sensitization induction level of the 17,700 micrograms per centimeter squared; and classified the chemical as a weak sensitizer.

DR. MARKS: How does that dose per area translate to what we have here as a 0.1 percent concentration. I mean, that's a very low concentration on leave-on.

DR. BELSITO: It's concentration. It's frequency of application. It's site of application. There are numerous factors that go into QRA. I think, simply by saying when formulated to be non-sensitizing, it may be that at the levels that are used in the product types, it will not be. There's also cumulative exposure that goes into the QRA.

Again, I think, when we get a signal that it can be a sensitizer, we need to be cognizant of a mistake we made with methylisothiazolinone. We had an HRIPT on a hundred or 200 people, at a hundred parts per million, and we said fine. But that was on the back. And the minute you started using it in wipes, we started getting a huge number of patients who were sensitized to it. That's my concern there.

In terms of the irritation, it's on Page 19. Let me see -- maybe 20. Okay, so, if you go to Page 19, and it's the -- going down the page, sort of towards the bottom of the page, the second full paragraph up from the bottom. It says, "A preliminary irritation screen was conducted on benzyl salicylate with four Hartley strain albino guinea pigs..." Yada, yada, yada. It says, "The concentration giving slight but perceptible irritation with no edema was .5 percent." And then above that, for benzyl salicylate, "The concentration of .1 percent was the lowest concentration to produce mild erythema in at least 25 percent." So, there was some indication of irritation. We know that's product-formulation specific, so I thought we needed to include that caveat.

DR. MARKS: Okay. Good. I thought the weight was in favor at low potential for irritation at this concentration. But, again, being on a conservative side, I'm fine. I'll second that if I hadn't already, your motion.

DR. BERGFELD: You did, but that's fine. Any other questions or editorials? Ron Hill and then oh, okay.

MS. AKINSULIE: I want to bring the panel's attention to the concentration of use, being that it's specifically surveyed for its function as light stabilizer. So, will the panel like to make mention, or any specific language in the discussion?

DR. HILL: I definitely would. Because returning to what I said before, and the specifics of that .5 percent, any credibility that I might have as a medicinal chemist would be lost if I don't point out that I think the cyclohexyl salicylate is a terrible and completely unreasonable circuit for systemic toxicology and benzyl salicylate. The transformation by esterases would be completely different.

In the context of the systemic toxicology, the molecular weight and the LogP of benzyl salicylate are perfect for transdermal delivery; so, there will be dermal absorption, which is why the questions that were raised with Dr. Belsito and Dr. Marks were relevant.

Also, to point out, very forcefully, that the intended root of use as a stabilizer, versus as a fragrance, versus anything else, has nothing to do with toxicological evaluation. It's just exposure and what might happen biologically with the compound. That the intended use has nothing to do with it, other than the maximum concentration of use and what it might be formulated in.

To say, well, we're assessing this for use as a light stabilizer, has nothing to do with assessing the toxicology at all, other than art of use. The systemic toxicology is not well covered, and the only assurance we have here is that's .5 percent. I still think there's a gap in that data; but because of the low concentration of use, and it has been in use a bit, I think we're okay.

DR. BERGFELD: Okay, Dan.

DR. LIEBLER: I'd like to point out that I have no credibility as a medicinal chemist; so, I was okay with this as a read across. I realize that Ron feels passionately about this, but that doesn't affect my evaluation of this. I think this appropriate for a read across.

But having said that, on the RIFM panel, we have a rule that if the three chemists can't agree on a read across, it's not going to work as a read across. Applying that rule here, it's not going to work as a read across. But since I have no credibility as a medicinal chemist, I feel free to say that I think that this is a reasonable read across for the endpoint indicated.

DR. BERGFELD: Thank you. Dr. Belsito, do you want to summarize where we are with this, and including the discussion remarks?

DR. BELSITO: Yeah, safe as used when formulated to be non-irritating and non-sensitizing. There is some irritation hints at .1 percent, which is concentration of use, clearly as a weak sensitizer; and that will impact potential sensitization depending upon product categories, frequency of use, chemotropic exposure, et cetera.

DR. BERGFELD: And that would appear in the discussion. Bart, do you want to make a comment about this CIR steering committee deals with a fragrance plus a cosmetic use? Just for the record.

DR. HELDRETH: The steering committee would only need to be involved in the process of deciding whether or not we look at an ingredient, if it was fragrance only and the panel wanted to look at it anyway. But since it has a cosmetic function, outside of fragrance, it's within the purview of the panel to make the decision.

DR. BERGFELD: Thank you. Ron Hill.

DR. HILL: On that subject, I had at least written a note that if RIFM did a thorough analysis of this, can we get that information and roll it over here? Because, again, I think, benzyl salicylate clearly has estrogenic activity. We not have only in vitro data to show that, we also have this uterine weight gain, which is almost certainly related to that and, again, demonstrates the same concentration range and U-shaped response curve.

I'm not suggesting it's a huge red flag, but whatever analysis RIFM already did, why should we reinvent the wheel? Can we get that information, pull it over to indicate why they set the limits that they set? Ours at .5 percent are already lower, I believe.

DR. BERGFELD: Monice has a response, yeah?

MS. FIUME: Alice did a thorough search and she did request the information from RIFM; and so, RIFM did submit any information that they had. Some of it can be used, some of it can't based on the sponsor. There was a published paper -- I believe it was actually two published papers -- that are also in this report, that have a lot of the RIFM data.

DR. HILL: And they're in there as references, because I didn't catch that?

MS. FIUME: Yes.

MS. AKINSULIE: Yes, as a primary reference.

DR. HILL: What references are they? I will look. I'll figure it out. Never mind.

MS. FIUME: They're five and six, to be clear. One is Belsito and the other is Lapczynski. I think the clarification Alice may have been looking for, is for language, for the discussion, regarding the light stabilizer use from the concentration of use survey.

The VCRP data, we have no idea what those data were that were submitted. I think the concern may have been, does the panel want any language stating that there's a high number of uses, for these ingredients, two of which are some type of fragrance? Whereas, the concentration of use is purely for the light -- was asked specifically for the light stabilizer functions. So, did any mention of that need to be made in the discussion, to know that there may be a discrepancy between the uses reported to VCRP, versus the concentration of use data that were submitted?

DR. BERGFELD: Ron Hill, you want to respond to that?

DR. HILL: I would say we would at least have to say, in the discussion, we're assessing the safety up to .5 percent. It doesn't matter what the use is.

DR. BERGFELD: I think in the summary, and also in the description of use, it says a light stabilizer; so, it is in the document itself.

DR. HILL: I'm not suggesting we have to put a limit in the conclusion or anything.

DR. BERGFELD: Okay. Tom?

DR. SLAGA: Yes. Ron brought up about the estrogenic effect, which is very low. First of all, the amount of the compound is very low dose, and its estrogenic effect is 1000th of what estrogen would be. There's more circulating -- the skin has both estrogenic and androgenic receptors in it, and they have a lot of influence from estrogens and androgens; and that would overwhelm whatever this compound would do.

DR. HILL: I agree, and that's an important piece of information.

DR. SLAGA: That could be put into question if people have a concern about the estrogen.

DR. HILL: But, again, it relates to the concentration, because if you put 4 percent concentration of a dermally penetrable substance on there, versus .5 percent, we're going to be looking at a different picture. Because concentration drives diffusion rate across the skin direct proportion.

DR. BERGFELD: That can be added to the discussion, and I think that Alice has captured that. All right, we're going to call for the question. All those in favor of the safe conclusion. Thank you. Unanimous.

Safety Assessment of Benzyl Salicylate As Used in Cosmetics

Status: Draft Final Report for Panel Review
Release Date: March 15, 2019
Panel Meeting 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 safety assessment was prepared by Alice Akinsulie, Scientific Writer/Analyst.

ABSTRACT

The Cosmetic Ingredient Review (CIR) Expert Panel (Panel) assessed the safety of Benzyl Salicylate, which is reported to function as a fragrance ingredient and light stabilizer. The Panel reviewed the available data to determine the safety of this ingredient. The Panel concluded that Benzyl Salicylate is 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).

INTRODUCTION

This is a safety assessment of Benzyl Salicylate as used in cosmetic formulations. According to the web-based *International Cosmetic Ingredient Dictionary and Handbook* (wINCI; *Dictionary*), this ingredient is reported to function in cosmetics as a fragrance ingredient and light stabilizer.¹

CIR Procedures state that fragrance ingredients may be excluded from evaluation by the Panel if their safety is being determined by the Research Institute for Fragrance Materials (RIFM), and a fragrance ingredient is defined therein as an ingredient that is only known to function as a fragrance in cosmetic formulations. Accordingly, as an ingredient assessed by the RIFM for its fragrance use, but not as a light stabilizer, Benzyl Salicylate does not qualify for such exclusion. An earlier safety assessment by the Panel addressed the safety of benzyl alcohol, benzoic acid and its salts (i.e. benzyl benzoate, calcium benzoate, magnesium benzoate, and potassium benzoate).² The Panel concluded that these ingredients were “safe as used in cosmetic products.” The Panel is concurrently reviewing the safety of salicylic acid and 18 salicylates, and at the December 2018 meeting, issued a Revised Tentative Amended Report with the conclusion that salicylic acid and 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.”³ Both reports are available on the CIR website (<https://www.cir-safety.org/ingredients>).

This safety assessment includes relevant published and unpublished data that are available for each endpoint that is evaluated. Published data are identified by conducting an exhaustive search of the world’s literature. A listing of the search engines and websites that are used and the sources that are typically explored, as well as the endpoints that CIR typically evaluates, is provided 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 are provided by the cosmetics industry, as well as by other interested parties.

Much of the data were obtained from the Research Institute for Fragrance Materials (RIFM) Expert Panel review.^{4,5} Additionally, some chemical and toxicological data on Benzyl Salicylate included in this safety assessment were obtained from data submitted to the European Chemical Agency (ECHA) by companies as part of the Registration, Evaluation, Authorization and Restriction of Chemicals (REACH).⁶ To address some toxicological endpoints of Benzyl Salicylate as part of the REACH registration, cyclohexyl salicylate was proposed to share structural similarities and ‘mechanistic action’ similarities, which are both general and endpoint specific, such that read-across is justified. Accordingly, toxicological data on cyclohexyl salicylate (not a cosmetic ingredient) is included herein for the purposes of read-across, as proposed in the ECHA dossier. When appropriate, information from these summary documents has been included in this report, and is cited to these sources. Toxicology data from an earlier CIR safety assessment on benzyl alcohol are also included in this safety assessment for read-across.⁷

CHEMISTRY

Definition and Structure

Benzyl Salicylate (CAS No. 118-58-1) is the ester of benzyl alcohol and salicylic acid.¹ It conforms to the formula that is depicted in Figure 1. As some of the data obtained from ECHA for Benzyl Salicylate (Figure 1), have been read-across from cyclohexyl salicylate,⁶ the inference source structure is also included below (Figure 2).

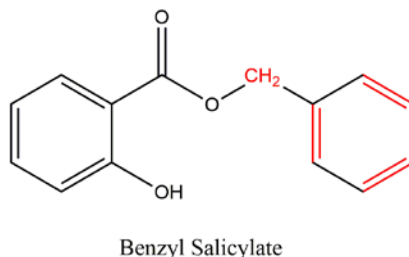
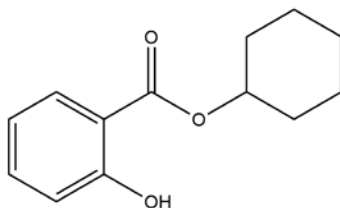


Figure 1. Benzyl Salicylate



cyclohexyl salicylate

Figure 2. cyclohexyl salicylate

Physical and Chemical Properties

Benzyl Salicylate is a colorless to pale yellow liquid.⁶ The freezing point of Benzyl Salicylate was determined to be less than -50 °C. The solubility of Benzyl Salicylate in water at 20°C is 8.8 mg/L. Other pertinent physical and chemical properties of Benzyl Salicylate are presented in Table 1.

Method of Manufacture

A synthetic methodology for manufacturing Benzyl Salicylate reported that Benzyl Salicylate can be synthesized by homogeneous reaction of sodium salicylate with benzyl chloride, with a stoichiometric ratio of 2.5:1, in dimethylformamide (DMF) at 100°C, for 2.5 h.⁸

Impurities

Impurity data were not discovered in the published literature, and unpublished data were not submitted. However according to the United States Pharmacopeial (USP) Convention's Food Ingredients Expert Committee, Benzyl Salicylate must not be less than 98% of C₁₄H₁₂O₃ in food.⁹

Natural Occurrence

Benzyl Salicylate can be found in ylang-ylang oil (5.2%), carnation oil (3.9%), and tuberose absolute (2.6%).¹⁰

USE

Cosmetic

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

According to information supplied to the FDA in 2019 by industry as part of the VCRP, Benzyl Salicylate is reported to be used in 3079 formulations, 2419 of which are leave-on products (Table 2).¹¹ Additionally, 949 of those uses are in fragrance-type formulations. However, the VCRP does not indicate the function of ingredients in cosmetic formulations, so it is not known what the intended function of Benzyl Salicylate is in any of the reported ingredient categories.

In 2016, the Council conducted a survey of the maximum use concentrations of Benzyl Salicylate, but only for the function of light stabilizer.¹² According to the survey, the greatest concentration of use of Benzyl Salicylate as a light stabilizer is up to 0.5% in skin cleansing preparations, and the greatest leave-on use concentration for this function is up to 0.15% Benzyl Salicylate in "other" makeup preparations.

According to VCRP data, Benzyl Salicylate is used in formulations that are applied near the eye, that can be incidentally ingested, and that come in contact with mucous membranes; no concentration of use data were provided for these use-types.¹¹ Additionally, in the VCRP, Benzyl Salicylate is reported to be used in spray formulations (56 hair sprays, for example) and could possibly be inhaled. 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 < 10 µm compared with pump sprays.¹³ Therefore, most droplets/particles incidentally inhaled from cosmetic sprays would be deposited in the nasopharyngeal and thoracic regions of the respiratory tract and would not be respirable (i.e., they would not enter the lungs) to any appreciable amount. Benzyl Salicylate is also reported in the VCRP to be used in powder formulations, such as face powders (34 reported uses). 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.¹⁴⁻¹⁶

The International Fragrance Association (IFRA) has recommended restriction limits for the use of Benzyl Salicylate based on the weight of evidence evaluation of the sensitization data and therefore classified Benzyl Salicylate as a weak sensitizer.¹⁷ The IFRA Standard limits range from a maximum of 0.5% Benzyl Salicylate in lip products to a maximum of 12.8% in oral care products; additional finished product use categories and standard limits are listed in Table 3.

According to the European Union, Benzyl Salicylate may be used in cosmetics and personal care products, but its presence must be indicated when its concentration exceeds 0.001% in leave-on products and 0.01% in rinse-off products.¹⁸

Non-Cosmetic

In the US, Benzyl Salicylate has been approved as a direct food additive for use as a synthetic flavoring substance by the FDA [21 CFR 172.515]. It should be used in the minimum quantity required to produce the intended effect, and otherwise in accordance with all the principles of good manufacturing practice. In addition, Benzyl Salicylate has been granted generally recognized as safe (GRAS) status as a flavoring ingredient by the Flavor and Extract Manufacturers Association.¹⁹

TOXICOKINETIC STUDIES

Dermal Penetration

In Vitro

The penetration of Benzyl Salicylate through human epidermis was studied using a glass chamber.²⁰ Benzyl Salicylate (0.2 mL) was applied to a sample of human lower abdominal cadaver skin for 72 hours. The chamber was kept at 21°C and 55% relative humidity. The upper surface of the skin was fixed to a glass tube and then placed inside one arm of a U-shaped glass chamber. The experiment was repeated six times. Benzyl Salicylate penetrated the epidermis very slightly. It was reported that 0.031% \pm 0.004% of the chemical traversed the skin.

In an in vitro percutaneous absorption study, [¹⁴C]-Benzyl Salicylate at 1%, 3%, and 10% in ethanol was applied to excised intact skin of a naked rat for 30 seconds at a dose of 120 μ g, 360 μ g or 1200 μ g active substance/cm².⁵ Unabsorbed Benzyl Salicylate was removed from the skin surface at 1, 6, 16, and 24 hours after application and absorption was measured at intervals, i.e. after 6, 16, 24, hours. An estimated 62.7, 58.8, and 40.3% of 1, 3, and 10% of Benzyl Salicylate migrated into the receptor fluid and was recovered in the chamber liquid, respectively. When the same test was conducted using guinea pig skin, after 16 hours, 3.5, 1.7, and 0.9% of the solution migrated through the skin into the receptor fluid for the 1, 3, and 10% concentrations, respectively.

TOXICOLOGICAL STUDIES

Acute Toxicity Studies

Dermal

In an acute dermal toxicity study, Benzyl Salicylate (neat) was applied to the clipped area of three albino rabbits at doses of 5, 10, or 20 g/kg and held in close contact with the skin under a plastic wrap and bandages for an exposure period of 24 hours.⁵ Animals were observed for seven days. No effects were observed at 5 g/kg. One of three rabbits at the 10 g/kg level and two of the three at the 20 g/kg level died. No significant gross pathology was noted in animals that died during the study; however, a low hemoglobin value was noted for the animal treated at the 20 g/kg level. The acute dermal LD₅₀ of Benzyl Salicylate was calculated to be 14.15 g/kg.

Oral

Three groups of 6 rats were dosed by gavage with 1.25, 2.5, or 5.0 g/kg Benzyl Salicylate.⁵ The LD₅₀ was reported to be 2.23 g/kg. Rats were observed for a 7-day period. At 1.25 g/kg, no deaths (0/6) were observed; 4/6 deaths were observed at 2.5 g/kg and all (6/6) animals died at 5.0 g/kg. The principal toxic effect observed before death was depression.

Short-Term Toxicity Studies

Oral

In a combined repeated-dose reproductive/developmental screening toxicity test, Benzyl Salicylate was administered to 9 week old male and female Sprague-Dawley rats (5 per sex) via gavage at 0 (corn oil), 250, 500, or 1000 mg/kg/day for 14 days.²¹ All animals died in the 1000 mg/kg/day treatment group and one female died in the 500 mg/kg/day treatment group. Significant decreases in the body and thymus weights and significant increases in the liver weights and aspartate aminotransferase (AST) were observed in both sexes in the 500 mg/kg/day treatment group. Slight decreases in glucose and thymus absolute weights were also observed in males in the 250 mg/kg/day treatment group. The considered tolerable dose

was 250 mg/kg/day. Based on the results of the 14-day dose-range finding study (described earlier), it was determined that the doses used in the DART study are 30, 100 and 300 mg/kg/day, respectively. Reproductive and developmental toxicity data are summarized in the DART section.

Subchronic Toxicity Studies

Oral

Cyclohexyl Salicylate (read-across for Benzyl Salicylate)

Repeated-dose toxicity data were not available for Benzyl Salicylate. However, ECHA identified a read-across source material. In a 90-day study conducted using cyclohexyl salicylate, 10 females and 10 male rats were administered the test substance via gavage at doses of 0 (vehicle control), 40, 120, and 360 mg/kg bw/day in arachis oil.⁶ The total volume administered was 5 mL/kg in all dose groups. An additional five male and female rats served as the recovery animals in the control and the high-dose group during a 29-day recovery period without oral treatment. The no-observable-adverse-effect-level (NOAEL) in this oral repeated dose toxicity study was 360 mg/kg bw/day. There were no adverse systemic effects on rats in this study.

Benzyl alcohol (read-across for Benzyl Salicylate)

Benzyl alcohol was administered in corn oil to groups of 10 male and 10 female B6C3F1 mice at doses of 0, 50, 100, 200, 400, and 800 mg/kg bw by gavage, five days a week for 13 weeks.⁷ Animals were observed twice daily for signs of toxicity and mortality. Deaths of five mice were attributed to rupture caused by the gavage procedure. The final mean body weight of males at 800 mg/kg bw was 5% lower than that of controls; the final mean body weight of female mice at this dose was 5% lower than that of controls. Both male and female mice at the high dose showed staggering during the first and second weeks of the study. No treatment related histopathological effects were observed.

When benzyl alcohol was administered in corn oil to groups of 10 male and 10 female Fischer 344 rats by gavage at doses of 0, 50, 100, 200, 400, and 800 mg/kg bw, five days per week for 13 weeks, eight males and two females at 800 mg/kg bw, one female at 400 mg/kg bw, one male at 200 mg/kg bw and one female in the control group died after treatment.⁷ The deaths of five rats were attributed to gavage error. Aside from these, 4/10 male rats and one female of the 800 mg/kg group, as well as one female of the 400 mg/kg group and one male of the 200 mg/kg group died on study. At 800 mg/kg bw, signs of neurotoxicity were observed, and animals had blood around the mouth and nose. After 13 weeks, the body weights of males and females at the high dose were 7 and 5 % lower than those of the controls, and histopathological examination showed some treatment-related histopathological effects including necrosis of the dentate gyrus of the hippocampus, skeletal muscle necrosis, nephrosis of the kidney, thymic congestion, haemorrhage, and atrophy. Lesions were not observed at lower doses; therefore, treatment-related effects (mortality and neurotoxicity) were only observed at the high dose (800 mg/kg-day).

Chronic Toxicity Studies

Benzyl alcohol (read-across for Benzyl Salicylate)

Groups of 100 F344/N rats (50 per sex) were dosed with 200 or 400 mg/kg benzyl alcohol in corn oil, 5 days per week for 103 weeks.⁷ Mean body weights were comparable among dosed and vehicle control rats throughout the study. A number of accidental deaths were due to gavage errors in female rats of both dose groups (17 deaths, low-dose; 13 deaths, high-dose) and in males of the 400 mg/kg group (14 deaths). At the end of the study, 17 female rats survived from each of the dose groups compared to 35 female vehicle control; 27 low-dose males and 24 high dose males survived, compared to 28 male vehicle controls. Clinical signs of sialodacryoadenitis virus (cervical swelling, pink eyes, and red exudate around eyes) were observed in dosed and vehicle-control rats.

Groups of 100 B6C3F1 mice were dosed with 100 or 200 mg/kg benzyl alcohol following the same schedule as the previous study.⁷ Mice were unintentionally given α -methylbenzyl alcohol for 4 days during week 80 with no observed toxicological syndromes. Animals were observed twice daily for signs of toxicity. Mean body weight was compared among dosed and vehicle control mice throughout the study. Survival of female vehicle controls was significantly lower than that of the high-dose group after week 74 (female; vehicle control, 26/50; low dose, 32/50; high dose, 36/50). Corpora amylacea (foci of mineralization in the thalamus) was observed at an increased incidence in high-dose mice (male: vehicle control, 15/49; low dose, 21/48; high dose, 22/05; female 14/50; 15/48; 25/50), but was noted to be a common and spontaneously occurring lesion.

DEVELOPMENTAL AND REPRODUCTIVE TOXICITY (DART) STUDIES

Oral

Following a short term screening assessment described above, Sprague–Dawley rats were administered Benzyl Salicylate dissolved in corn oil once daily via gavage at levels of 0 (control), 30, 100, or 300 mg/kg/day using a dosing volume of 5 mL/kg.²¹ Males (n = 12 per group) were dosed for 14 days prior to mating and a further 28 days during mating,

giving a total of 42 dosing days. Females in the mating group (n = 12 per treatment group) were dosed for 14 days prior to mating and then through mating and gestation until postpartum day 4, giving a total of 41 to 46 days of dosing, while females in the non-mating group (n=10 per treatment group) were dosed for 42 days. In total, 5 males and 5 non-mated females in the control and high-dose groups were left untreated for 14 days as a recovery period.

In terms of reproductive/developmental toxicity, Benzyl Salicylate was not found to have any effects on fertility or implantation, or to cause severe maternal toxicity. However, at the end of the recovery period, males in the 300 mg/kg/day treatment group had significantly greater relative weights of the kidney and seminal vesicle, as well as a greater relative thymus weight. By contrast, non-mated females in the 300 mg/kg/day treatment group exhibited a significantly lower absolute brain weight than the control group. Also, marked embryotoxicity was observed in the form of early embryonic resorption in 6/12 females in the 300 mg/kg/day treatment group, and dead offspring exhibited neural tube defects. Offspring of rats that had been administered 30 or 100 mg/kg/day exhibited lower body weights on PND 0 or 4. Based on the developmental toxicity, the lowest-observable-adverse-effect-level (LOAEL) of Benzyl Salicylate was 30 mg/kg/day.

GENOTOXICITY

In Vitro

The genotoxicity of Benzyl Salicylate was evaluated in an Ames test, in the presence and absence of exogenous metabolic activation, using the following *Salmonella typhimurium* strains: TA98, TA100, TA1535, and TA1537, and/or TA97.²² Benzyl Salicylate, at doses of 3.3 to 333 µg/plate in dimethyl sulfoxide (DMSO), did not produce any mutagenic effects with or without metabolic activation.

Chinese hamster lung fibroblastic cells (CHL), at doses of 0 - 170 µg/mL, were used to evaluate the cytogenetic toxicity of Benzyl Salicylate.²¹ Using the 6 hour direct method, 50 µL of the test chemical solution was added to the 60 mm dishes on day 3 after seeding and left for 6 hours; cells were then washed and cultured for 18 hours. With 24 hours continuous treatment, 50 µL of negative control (DMSO) or test article solution was added on day 3 after seeding. In the metabolic activation method, 833 µL of S9 mix and 50 µL of test article solution were added on day 3 after seeding and were treated similarly as the 6 hour direct method. Appropriate positive controls were used. All of the Benzyl Salicylate treatment groups had ≤ 1.0% structural aberrations and ≤ 1.3% polyploidy, and exhibited no significant differences in the frequencies of chromosomal aberrations from the negative controls or dose-dependency. No significant increases in chromosomal aberrations were seen at these doses.

In Vivo

In vivo genotoxic studies of Benzyl Salicylate were not found in the published literature, and unpublished data were not provided.

CARCINOGENICITY STUDIES

Carcinogenicity studies of Benzyl Salicylate were not found in the published literature, and unpublished data were not provided.

OTHER RELEVANT STUDIES

Estrogen Activity

Benzyl Salicylate was tested in assays using the estrogen responsive MCF-7 human breast cancer cell line to determine its estrogenic effects on breast cancer cells in vitro.²³ Benzyl Salicylate (98% purity) in ethanol and diluted 1 in 10,000 (v/v) into culture medium increased the growth of estrogen-dependent MCF-7 human breast cancer cells at 10⁻⁴ M, an effect which could be inhibited by the anti-estrogen fulvestrant, suggesting involvement in an ER-mediated mechanism; however, concentrations are not detrimental to proliferation of MCF-7 cells.

In order to examine the estrogenic activities of plasticizers used in tissue conditioners, plasticizers, including Benzyl Salicylate, were evaluated by the E-screen test using MCF-7 cells.²⁴ Seven plasticizers and two metabolites, including Benzyl Salicylate (97% purity), were diluted with DMSO and a medium containing 5% bovine serum at concentrations ranging from 10⁻⁹ to 10⁻⁴ M. The samples included 0.1% DMSO. The estrogenic activities and liquid compositions of the four commercial tissue conditioners were examined by high-performance liquid chromatography. The negative control was the cell culture medium including 0.1% DMSO. Benzyl Salicylate increased proliferation of MCF-7 breast cancer cells at 10⁻⁵ M (22.8 mg/L), however it had opposite effect at 10⁻⁴ M (22.8 mg/L). At a concentration of 10⁻⁵ M, Benzyl Salicylate significantly increased proliferation of MCF-7 cells (p < 0.05).

The estrogenic potential of Benzyl Salicylate was evaluated using an in vitro human estrogen receptor hERα-coactivator recruiting assay and in an in vivo immature rodent uterotrophic bioassay.²⁵ The estrogen receptor agonist activity of the salicylate esters (SEs) was measured using a ligand-dependent coactivator recruiting assay with glutathione S-transferase (GST)-tagged hERα – ligand binding domain (LBD). Stock solutions of test chemicals were subjected to a 10-fold serial dilution with DMSO to prepare eight concentrations in the range of 10⁻³ to 10⁻¹⁰ M. The binding affinities of the

tested chemicals for hER α were expressed as the absorbance at 405 nm (bone alkaline phosphatase (BAP) activity). The wells with only DMSO added were used as background values for this assay. Benzyl Salicylate exhibited obvious dose-dependent increases with a maximal acceptable daily exposure of 0.0294 ppm. The immature rodent uterotrophic assay showed that the uterine weights were significantly increased in mice that received 11.1, 33.3, 100, and 300 mg/kg/day. Benzyl Salicylate was intragastrically administered for 3 days, beginning on postnatal day (PND) 21; the corresponding uterine weights were 114%, 118%, 138%, and 119% of vehicle control, respectively. The uterine weights were also significantly increased at a dose-dependent manner in rats who were given 11.1, 33.3, and 100 mg/kg/day Benzyl Salicylate by intragastric administration for 3 days, beginning on PND 21. The mean uterine weights in rats given 11.1, 33.3 and 100 mg/kg/day Benzyl Salicylate were higher than the uterine weights of rats given 1 μ g/kg/day 7 β -estradiol (E2), but lower than the uterine weights of rats given 5 μ g/kg/day E2.

DERMAL IRRITATION AND SENSITIZATION

The skin irritation and sensitization studies summarized below are presented in greater detail in Table 4.

Irritation

In a preliminary test, 0.025 mL of Benzyl Salicylate (concentration not specified) was applied with a pipette to the clipped flank of 6 to 8 male and female outbred Himalayan white-spotted guinea pigs.²⁶ The concentration of 0.1% was the lowest concentration to produce mild erythema in at least 25% of the animals, and this dose was selected as the minimal irritating concentration after one application. The skin irritation potential of Benzyl Salicylate was then evaluated in the induction phase of an Open Epicutaneous Test (OET). Benzyl Salicylate (0.1 mL) was applied to clipped flank of 6 to 8 male and female outbred Himalayan white spotted guinea pigs. The minimal irritating concentration after 21 applications was 0.1% (vehicle not specified). A preliminary irritation screen was conducted to determine the Injection Challenge Concentration (ICC) of Benzyl Salicylate using four inbred Hartley albino guinea pigs.²⁷ Benzyl Salicylate (0.1 mL) was administered via intradermal injection (unspecified vehicle) at a range of concentrations. The concentration giving slight but perceptible irritation with no edema was 0.5% and it was selected as the ICC. In a modified Draize sensitization study, the irritation potential of Benzyl Salicylate (0.1 mL) was evaluated in four inbred Hartley albino guinea pigs to determine the Application Challenge Concentration (ACC).²⁷ The highest concentration causing no irritation was 2%, and it was selected as the ACC. A 4-hour semi-occlusive patch test was conducted on four female New Zealand white albino rabbits.²⁸ No irritation was observed when Benzyl Salicylate (0.5 mL neat) was applied to intact dorsal skin. No irritation was observed in a 24-hour closed patch test conducted using three albino rabbits.⁴ As a part of an acute dermal LD₅₀ study, irritation was not observed with neat Benzyl Salicylate at 5, 10, or 20 g/kg when applied to a clipped area and held in contact with the skin for 24 hours under occlusion.⁵ No irritation was observed in a maximization pre-test when 30% Benzyl Salicylate in petrolatum was administered in a closed patch test on the volar forearms of five subjects for 48 hours.⁵ Two irritant reactions were observed in a maximization pre-test study when 30% Benzyl Salicylate in petrolatum was applied under occlusion to the backs of 22 male subjects. No irritation was observed in a patch test conducted on 30 subjects when administered 0.2 mL Benzyl Salicylate (neat) to the upper outer arm for up to 4 hours.²⁸ Benzyl Salicylate at 5% in petrolatum caused no irritation when applied to the upper arms of 12 male and 13 female subjects.⁵ Five positive reactions were observed when 0.2% Benzyl Salicylate in 99% ethanol was applied under occlusion for 24 to 48 hour to the upper inside of the arm of 313 subjects.²⁹ Irritation was not observed when a 24 to 72 hour closed patch with 2% Benzyl Salicylate in unguentum simplex (a simple ointment containing 5 parts olive oil and 2 parts white wax) was applied to the upper inside arm of 30 subjects. In a 48-hour closed patch test conducted in five subjects, 20% Benzyl Salicylate in petrolatum applied to the back of each subject produced no irritation.

Sensitization

In a local lymph node assay (LLNA) performed to assess the sensitization capacity of Benzyl Salicylate, 4 female CBA/JN mice were administered 25 μ l of Benzyl Salicylate topically at 10% in 4:1 acetone/olive oil vehicle to the left and right ear lobe for three days.⁵ The estimated concentration required to produce a three-fold increase in lymphocyte proliferation (EC3) was determined to be 1.5% (375 μ g/cm²), and Benzyl Salicylate was categorized as a weak sensitizer. Benzyl Salicylate was considered a sensitizer in an LLNA in which 4 female CBA/Ca mice were treated with 25 μ l of the chemical at 2.5, 5, 10, 25, or 50% w/v in 1:3 ethanol:diethyl phthalate vehicle.⁵ Sensitization was observed at all concentration in a maximization test conducted in 8 test and 8 control female albino Dunkin-Hartley guinea pigs.⁵ Sensitization was observed in a guinea pig maximization test (number of animal not specified) conducted using 10% Benzyl Salicylate for both induction and challenge phase.⁵ A maximization test on 10 Hartley guinea pigs per dose using 1% Benzyl Salicylate in ethanol and 100% dermally administered revealed no sensitization reactions.³⁰ Five of 20 animals revealed sensitization reactions in a study in which 10% Benzyl Salicylate in liquid paraffin and FCA was intradermally injected in the shoulder of 4-week old female Hartley strain guinea pigs (20 per group).³¹ Twenty-four hours later, 50% Benzyl Salicylate in white petrolatum was applied for 48 hours with adhesive bandage. Two weeks after the topical application, Benzyl Salicylate at 5%, 10%, and 20% in white petrolatum was applied. Two reactions were observed at 20%. 'questionable' reactions were observed in three (3/20) animals at 5%, five (5/20) animals at 10%, and four (4/20) animals at

20%. Results were negative in a maximization test conducted using outbred Himalayan white-spotted guinea pigs.²⁶ In another maximization test, 10% Benzyl Salicylate in liquid paraffin and 30% Benzyl Salicylate in ethanol were administered to 10 female Hartley albino guinea pigs.³² During the first challenge, positive reactions were observed at 48 and 72 hours for all doses. At the second challenge, positive reactions were observed with 0.03% at 24 hours and all concentrations at 48 and 72 hours. No sensitization was produced in a guinea pig open epicutaneous test (OET) using Benzyl Salicylate at 30% for both induction and challenge (vehicle not specified).⁵ In an OET conducted in guinea pigs, there was no reaction to 10% Benzyl Salicylate in a 21 daily open application study. In a closed epicutaneous test (CET) in guinea pigs, 30% Benzyl Salicylate (vehicle not provided) was not a sensitizer.⁵ Sensitization was observed in a cumulative contact enhancement test (CCET) conducted in 10 female Hartley albino guinea pigs when induced for 24 hours with an occlusive patch containing 30% Benzyl Salicylate in ethanol.³² Sensitization was evaluated in groups of ten Pirbright guinea pigs using a modified FCA method.³³ Benzyl Salicylate at 10% was a moderate sensitizer.

In a quantitative risk assessment (QRA) for dermal sensitization, the RIFM Expert Panel reviewed the critical effect data for Benzyl Salicylate via a weight of evidence (WoE) approach.¹⁷ IFRA reported a no expected sensitization induction level (NESIL) of 17,700 µg/cm² based on a human maximization test, and therefore classified the chemical as a weak sensitizer. No sensitization was observed in a human repeated insult patch test (HRIPT) when 0.3 mL of 15% Benzyl Salicylate in 3:1 DEP:EtOH was applied to the left side of the back of 29 male and 72 female subjects via an adhesive patch for 24 hours.⁵ No sensitization was observed in 17 male and 18 female volunteers when patch tested with 0.5 mL aliquot of 10% Benzyl Salicylate in alcohol SDA 39 C for 24 hours. No sensitization was observed when 0.5 mL of 5% Benzyl Salicylate in dimethyl phthalate was applied to absorbent patches and administered to the inner surface of the left deltoid area of eight male and female volunteers for 48 hours. Another HRIPT was performed in 101 volunteers (29 males and 72 females) induced with 0.3 mL of Benzyl Salicylate for 2 weeks. Under the conditions of the study, 15% Benzyl Salicylate in 3:1 DEP:EtOH did not induce dermal sensitization. No sensitization was observed when 35 subjects (17 males and 18 females) completed an HRIPT with 10% Benzyl Salicylate (0.5mL) in alcohol SDA 39C under semi-occlusion for 24 hours. No sensitization was observed when 52 volunteers using a modified Draize method were patch tested with an aliquot of 5 mL of 5% Benzyl Salicylate in dimethyl phthalate for 48 hours (ten induction patches). In five maximization tests each using 25 human subjects, Benzyl Salicylate was administered at 20 to 30 % in petrolatum. Reactions were observed in two of the five studies, affecting 2/25 and 1/25 subjects at 20%. No positive reactions were reported at 30%.

Cross-Reactivity

To evaluate the potential for cross-reactivity, an HRIPT was conducted on 103 subjects (29 male and 74 females).⁵ Subjects were administered 30% hexyl salicylate in ethanol:diethyl phthalate (3:1 DEP:ethanol), and challenged with 15% Benzyl Salicylate in 3:1 DEP:ethanol. No cross-reactions were observed.

Phototoxicity/Photosensitization

Phototoxicity and photoallergy studies summarized below are presented in Table 5.

No phototoxic effects were observed in a study conducted on groups of hairless mice (6/group), when administered twenty µl of 100% Benzyl Salicylate and 25% Benzyl Salicylate in methanol.⁵ No phototoxic responses were observed in an open application of 5%, 10%, and 30% Benzyl Salicylate in acetone tested on five female albino Dunkin-Hartley guinea pigs. Mixed results were found in another study conducted on Himalayan white spotted guinea pigs (10 per dose) when 0.025 mL of Benzyl Salicylate at 1% or 3% in ethanol with 2% DMSO. No reactions were observed with 1% Benzyl Salicylate, however with 3%, phototoxic reactions were observed in 10/10 animals. No phototoxic effects were observed when 20 (10 per sex) adult albino Dunkin Hartley guinea pigs were administered a single application of 0.5 mL of 10% Benzyl Salicylate in absolute ethanol under an occlusive patch. No photoallergic reactions were observed in a photoallergy study conducted on 25 adult albino Dunkin-Hartley guinea pigs when administered 0.5 mL of Benzyl Salicylate at 10% in absolute ethanol. In human studies, no phototoxic reactions were observed in six female subjects administered 0.025 mL/2 cm² of 3% and 10% Benzyl Salicylate in 1:1 ethanol/acetone.

OCULAR IRRITATION STUDIES

In Vitro

In a bovine corneal opacity permeability (BCOP) study conducted according to Organization for Economic Co-operation and Development test guideline (OECD TG) 437, 0.75 mL undiluted Benzyl Salicylate was applied to isolated bovine corneas for 10 minutes, followed by rinsing and further 120-minute incubation. An irritancy score of 0/5 was reported and it was concluded that the Benzyl Salicylate is not predicted to be an ocular corrosive or severe irritant.³⁴

Animal

The potential for Benzyl Salicylate to induce ocular irritation was evaluated following the instillation of 0.1 mL of 10% Benzyl Salicylate in SD alcohol 39-C into the right eye of three albino rabbits; the left eye of each animal served as an untreated control.⁵ The animals were observed for 10 days. Mild conjunctival irritation was observed in all three rabbits and corneal opacity was observed in one rabbit. All effects were reversed within seven days. Benzyl Salicylate was determined to be irritating.

CLINICAL STUDIES

Retrospective and Multicenter Studies

Incidence of sensitivity to Benzyl Salicylate was evaluated in a perfume screening series in 241 consecutive patients (180 females and 61 males) from October 1981 to June 1983.³⁵ Patients were patch-tested for sensitivity to fragrances in a perfume screening series using the Finn Chamber technique. Reactions to 2% Benzyl Salicylate in paraffin were observed in 6/241 patients and were characterized by erythema and edema. Five female and 1 male patients (2.5% incidence) had a positive reaction to Benzyl Salicylate.

To identify the specific fragrance chemicals responsible for allergic reactions to perfumes, patch tests to several screening sets of fragrance materials were performed on 20 perfume-sensitive patients during a one-year period (1975).³⁶ Patches were applied to the back of each patient for 48 hours. Readings were made at the time of removal or 24 hours after removal. Patients were instructed to return if an additional delayed reaction occurred. Benzyl Salicylate at 2% gave a positive reaction in 2/20 patients. All the fragrance allergens were tested on 50 control patients, with negative results.

In an assessment of the hypersensitization potential of Benzyl Salicylate initiated in 1979, data from 10,538 patch tests utilizing a wide range of Benzyl Salicylate concentrations in 8430 different subjects were evaluated.³⁷ Results were reported from a total of 6291 patch tests on personal care and household products in which the applied concentrations of Benzyl Salicylate ranged from 1×10^{-6} to 2×10^{-10} %. Vehicles used in the test included water, ethanol petroleum, dimethylphthalate, and mineral oil. Exposure to these products did not induce sensitization or identify pre-existing Benzyl Salicylate reactivity in any of the subjects. No elicited or induced sensitization reaction was observed in 3164 tests on personal products containing a mixture of 3×10^{-6} to 2×10^{-1} % Benzyl Salicylate. No sensitization reaction was observed in 3127 tests in household products containing 1×10^{-6} to 2×10^{-1} % Benzyl Salicylate. No sensitization was observed in 3217 HRIPTs evaluated in fragrances containing a mixture of 8×10^{-3} to 1.0% Benzyl Salicylate. No sensitization was observed in 20 occluded patch tests in product blends containing 6×10^{-3} to 8×10^{-3} % Benzyl Salicylate. In another blend containing 5×10^{-6} to 5×10^{-3} % Benzyl Salicylate, no sensitization was observed in 975 tests. The study authors indicated that Benzyl Salicylate has a very low potential to induce hypersensitivity or to elicit reactions attributable to preexisting sensitization.

To determine the prevalence and risk factors of responses to selected fragrance materials in patients with suspected fragrance allergy, 167 patients were patch tested with selected fragrance substances in 7 centers worldwide.³⁸ Benzyl Salicylate was applied to Finn chambers and placed on the upper back. Fifteen to 45 minutes were allowed between the initial patch test removal and the first reading. The patch test sites were evaluated using the North American Contact Dermatitis Research Group modification. The patients were tested with Benzyl Salicylate at 2 and 5%. Benzyl Salicylate, at 2% in petrolatum, produced irritant reactions in 5 patients and allergic reactions in 3% of the patients. At 5%, irritant reactions were observed in 8 of the patients and allergic reactions were observed in 4.8% of the patients. Benzyl Salicylate was a more common cause of positive patch test reactions in Japan than in Europe or the US.

Over a 64-month period (September 1977 to August 1983), twelve dermatologists from various sections of the US studied a total of 713 out of an estimated total of 13,216 patients with contact dermatitis.³⁹ The patients were evaluated using standard patch tests with numerous cosmetic products and specific ingredients, including Benzyl Salicylate. When such data were not available for an ingredient, the dermatologists performed the patch tests at an empirically determined concentration utilizing controls to exclude irritancy where possible. Patch tests were done on some products and ingredients without dilution; others were suspended in petrolatum or another appropriate, inert material. Shampoos were generally tested at 1% to 4% in water. Patch tests were applied to the upper back for 48 hours. The result of the study identified 713 patients with cutaneous reactions to cosmetic products. In 578 cases, allergic reactions were observed. In one subject Benzyl Salicylate was one of the causative ingredients as judged by patch testing.

To study the frequency of sensitization to 26 fragrance compounds qualified as allergens by the European Union, a total of 21,325 dermatitis patients were patch tested with Benzyl Salicylate (0.1%), from January 2003 to December 2004.⁴⁰ Benzyl Salicylate at 1% showed a positive reaction in 2/2041 patients. The calculated frequency of allergic reactions, standardized for age and sex was also 0.1% with the 95% confidence interval (95% CI). The authors classified Benzyl Salicylate as a "very rare allergen."

In a trial intended to evaluate the delayed hypersensitivity to Benzyl Salicylate brought out by UV exposure, fifteen patients, age 9 to 62 years, applied a trade name mixture (containing 1% Oxsoralen with acetone, 71% alcohol, and propylene glycol (concentration not specified)) to vitiliginous areas of the right forearm and hand, and a trade name mixture in a vehicle containing more than 5% Benzyl Salicylate to the left forearm and hand.⁴¹ The patients used the medications from 2 to 20 months. Control patients applied a 6% Benzyl Salicylate solution to make it similar to the test article. The control test article contained Benzyl Salicylate (6%), chloroform (20%), hexadecyl alcohol (1%), liquid petrolatum (20%), and isopropyl alcohol (53%). Fourteen subjects applied the solution containing 6% Benzyl Salicylate to their left volar forearms twice daily for six weeks. To test the stability of Benzyl Salicylate to UV, 1% solution in xylene was irradiated for six hours with a fluorescent sunlamp. The absorption spectra of the irradiated and non-irradiated Benzyl Salicylate solutions were compared on a spectrophotometer. All 15 subjects developed the expected moderate erythema, while six developed severe erythema and itching on the side treated with trade name mixture and Benzyl Salicylate. In patch tests on 14 controls, Benzyl Salicylate produced only one positive reaction. Delayed hypersensitivity to Benzyl Salicylate was enhanced by the phototoxic effects of test product.

Photoallergy

Summary data from four clinical reports demonstrated no photoallergic reactions.⁵ No photoallergic reactions were observed when a photopatch test that was conducted in 482 patients with 2% Benzyl Salicylate in petrolatum. Photopatch testing was conducted on 386 patients with suspected contact dermatitis from cosmetic and toiletry products. A photopatch test was conducted in two subjects with 10% Benzyl Salicylate in dimethylphthalate. No photoallergic reactions were observed. Benzyl Salicylate at 2% in petrolatum was photopatch tested in 706 patients with contact dermatitis. No photoallergic reactions were observed.

Case Reports

A case report described the incidence of a 74 year old woman who presented with a two month history of worsening non-pruritic pigmented patches over the face.⁴² Patch tests were performed with standard series, cosmetic series, and the patient's own products using the inert quadrate (IQ) chamber. Patches were removed from the back after day 2 and readings were performed on day 3. The patch tests showed positive reactions to colophonium, nickel sulfate, potassium dichromate 0.5 %, fragrance mix I, and Benzyl Salicylate. The patient also showed a positive reaction to her own face wash, which contained Benzyl Salicylate. In addition, the positive reactions to Benzyl Salicylate and the face wash showed a similar appearance of brownish hyperpigmentation.

A 60-year old woman presented with an 11-month history of chronic eyelid erythema and swelling with slight pruritus.⁴³ On examination, weak edema and erythema were observed in the upper and lower eyelids, with a bilateral and symmetrical distribution. The patient was patch tested with an exposure time of two days, using two different allergen series (Spanish Standard Patch Test Series supplemented with further allergens and another cosmetics and fragrance series), and readings were performed on days 2 and 4. On Day 4, a weak positive reaction to Benzyl Salicylate in 10% petrolatum was observed in both series.

A 70 year old woman was presented with a history of facial dermatitis with scaly erythematous plaques affecting the upper and lower eyelids and extending to both infraorbital regions. The patient had come into contact with several hair products that contained Benzyl Salicylate.⁴⁴ The patient was patch tested with the Spanish Contact Dermatitis Research Group (GEIDAC) baseline series. The patch tests were applied on the upper back for 2 days. Readings were performed on day 3 and day 7. Patch test results were positive on day 3 and day 7 for 10% Benzyl Salicylate in petrolatum.

SUMMARY

This is a review of the safety of Benzyl Salicylate as used in cosmetics. According to the *Dictionary*, this ingredient is an ester of benzyl alcohol and salicylic acid, and is reported to function in cosmetics as a fragrance ingredient and light stabilizer. According to 2019 VCRP data, Benzyl Salicylate is used in a total of 3079 cosmetic formulations, 433 of which are in perfumes (spray). The results of a concentration of use survey provided in 2016 indicate that Benzyl Salicylate, as a light stabilizer, is used at concentrations up to 0.15 % in leave-on products and up to 0.5% in rinse-off products.

For fragrance use, IFRA has a suggested use concentration of Benzyl Salicylate dependent on product type. Limitations include 12.8% for oral care products and a limit of 0.5% for lip products. According to the European Union, Benzyl Salicylate may be used in cosmetics and personal care products, but its presence must be indicated when its concentration exceeds 0.001% in leave-on products and 0.01% in rinse-off products.

Benzyl Salicylate has been approved as a direct food additive for use as a synthetic flavoring substance by the US FDA. Benzyl Salicylate has been granted GRAS status as a flavoring ingredient by the Flavor and Extract Manufacturers Association

In a skin penetration study, 0.2 mL of Benzyl Salicylate was administered to the human epidermis using a glass chamber; it was reported that $0.031\% \pm 0.004\%$ of the chemical traversed the skin. In an in vitro absorption study in which 1, 3, and 10% Benzyl Salicylate in ethanol was applied to naked rat skin, the amount that migrated into receptor fluid was measured to be 62.7, 58.8, and 40.3%, respectively. When the same test was conducted in guinea pig, 3.5, 1.7, and 0.9% of the solution migrated through the skin into the receptor fluid for the 1, 3, and 10% concentrations, respectively.

Studies involving acute dermal and oral toxicity of Benzyl Salicylate reported low toxicity levels. The acute dermal LD₅₀ of Benzyl Salicylate was calculated to be 14.15 g/kg in rabbits. The LD₅₀ for Benzyl Salicylate was reported to be 2230 mg/kg bw when three groups of 6 rats were dosed with 1.25, 2.5, or 5.0 g/kg Benzyl Salicylate by gavage and observed for a 7-day period. At 1.25 g/kg, no deaths (0/6) were observed; 4/6 deaths were observed at 2.5 g/kg and all (6/6) animals died at 5.0 g/kg.

In a combined repeated dose and reproductive/developmental screening toxicity test, male and female and rats (5 per sex) were administered Benzyl Salicylate by gavage at 0 (corn oil), 250, 500, or 1000 mg/kg/day for 14 days. All animals died in the 1000 mg/kg/day treatment group and one female died in the 500 mg/kg/day treatment group. Significant decreases in the body and thymus weights and significant increases in the liver weights and aspartate aminotransferase (AST) were observed in both sexes in the 500 mg/kg/day treatment group. Slight decreases in glucose and thymus absolute weights were also observed in males in the 250 mg/kg/day treatment group. The considered tolerable dose was 250 mg/kg/day.

In a 90-day oral repeated dose toxicity study, rats were administered cyclohexyl salicylate (used for read-across to Benzyl Salicylate) at doses of 0 (vehicle control), 40, 120, and 360 mg/kg bw/day; the total volume of administered formulation was 5 mL/kg in all dose groups. No adverse systemic effects were observed, and the NOAEL was 360 mg/kg bw/day.

Following a short-term screening assessment described above, Sprague-Dawley rats were administered Benzyl Salicylate dissolved in corn oil once daily via gavage at levels of 0 (control), 30, 100, or 300 mg/kg/day using a dosing volume of 5 mL/kg. Females in the mating group (n = 12 per treatment group) were dosed for 14 days prior to mating and then through mating and gestation until postpartum day 4, giving a total of 41 to 46 days of dosing, while females in the non-mating group (n=10 per treatment group) were dosed for 42 days. Based on reproductive/developmental toxicity study, Benzyl Salicylate was not found to have any effects on fertility or implantation, or to cause severe maternal toxicity. However, males in the 300 mg/kg/day treatment group had significantly greater relative weights of the kidney and non-mated females in the 300 mg/kg/day treatment group exhibited a significantly lower brain weight. Also, marked embryotoxicity was observed in the form of early embryonic resorption in the 300 mg/kg/day treatment group, and dead offspring exhibited neural tube defects. Offspring of rats that had been administered 30 or 100 mg/kg/day exhibited lower body weights on PND 0 or 4. The LOAEL of Benzyl Salicylate was 30 mg/kg/day.

An Ames test of Benzyl Salicylate, in *S. typhimurium* strains TA98, TA100, TA1535, and TA1537, and/or TA97 did not produce any mutagenic effects, with or without metabolic activation. Benzyl Salicylate was found to be non-genotoxic in vitro based on the chromosomal aberration test using Chinese hamster lung cells.

Benzyl Salicylate tested in an assay using estrogen responsive MCF-7 human breast cancer cell line produced estrogenic responses and increased the proliferation of MCF-7 cells at 10^{-4} M. In order to examine the estrogenic activities of plasticizers used in tissue conditioners, plasticizers including Benzyl Salicylate were evaluated in vitro and evaluated by the E-screen test using MCF-7 cells. Benzyl Salicylate increased proliferation of MCF-7 breast cancer cells at 10^{-5} M (22.8 mg/L). In an in vivo study evaluating estrogenic potential of Benzyl Salicylate, estrogenic activities were observed in rat and mouse uterotrophic assays almost in all concentrations tested. The immature rodent uterotrophic assay showed that the uterine weights were significantly increased in mice who received 1.1, 33.3, 100, and 300 mg/kg/day.

In a preliminary test, 0.025 mL of Benzyl Salicylate was applied with a pipette to the clipped skin on the flank of 6 to 8 male and female outbred Himalayan white-spotted guinea pigs. The concentration of 0.1% was the lowest concentration to produce mild erythema in at least 25% of the animals and this dose was selected as the minimal irritating concentration after one application. The skin irritation potential of Benzyl Salicylate was evaluated in the induction phase of an OET. Benzyl Salicylate (0.1 mL) was applied to clipped flank of 6 to 8 male and female outbred Himalayan white spotted guinea pigs. The minimal irritating concentration after 21 applications was 0.1% (vehicle not specified). In a preliminary irritation screen conducted to determine the ICC of Benzyl Salicylate using four inbred Hartley albino guinea pigs, Benzyl Salicylate (0.1 mL) administered at a range of concentration gave slight but perceptible irritation with no edema tested at 0.5% and it was selected as the ICC. In a modified Draize sensitization study, the irritation potential of Benzyl Salicylate was evaluated in four inbred Hartley albino guinea pigs to determine the ACC. The highest concentration causing no irritation was 2% and it was selected as the ACC. No irritation was observed in a 4-hour semi-occlusive patch test was conducted on four female New Zealand white albino rabbits. No irritation was observed in a 24-hour closed patch test conducted using three Albino rabbits. As a part of an acute dermal LD₅₀ study, irritation was not observed with neat Benzyl Salicylate at 5, 10, or 20 g/kg

when applied to a clipped area and held in contact with the skin for 24 hours under occlusion. No irritation was observed in maximization pre-test when 30% Benzyl Salicylate in petrolatum was administered in a closed patch test on the volar forearms of 5 subjects for 48 hours. Two irritant reactions were observed in a maximization pre-test study conducted when 30% Benzyl Salicylate in petrolatum was applied under occlusion to the backs of 22 male subjects. No irritation was observed in a patch test conducted on 30 subjects administered 0.2 mL Benzyl Salicylate (neat) to the upper outer arm for up to 4 hours. Benzyl Salicylate at 5% in petrolatum caused no irritation when applied to the upper arms of 12 male and 13 female subjects.⁵ Reactions were scored after 1 and 24 hours. Five positive reactions were observed when 0.2% Benzyl Salicylate in 99% ethanol was applied under occlusion for 24 to 48 h to the upper inside of arm of 313 subjects. Irritation was not observed when a 24- to 72-hour closed patch with 2% Benzyl Salicylate in unguentum simplex (a simple ointment containing 5 parts olive oil and 2 parts white wax) was applied to the upper inside of arm of 30 male and female subjects. In a 48-hour closed patch test conducted in five male and female subjects, 20% Benzyl Salicylate in petrolatum applied to the back of each subject produced no irritation.

In an LLNA performed to assess the sensitization capacity of Benzyl Salicylate, 4 female CBA/JN mice were administered 25 µl of Benzyl Salicylate topically at 10% in 4:1 acetone/olive oil vehicle to the left and right ear lobe for three days. Benzyl Salicylate was categorized as a weak sensitizer. Benzyl Salicylate was considered a weak sensitizer in another LLNA in which 4 female CBA/Ca mice were treated with 25 µl of the chemical at 2.5, 5, 10, 25, or 50% w/v in 1:3 ethanol:diethyl phthalate vehicle. Sensitization was observed at all concentrations in a maximization test on Benzyl Salicylate was conducted in Dunkin-Hartley guinea pigs. Sensitization was observed in a guinea pig maximization test conducted using 10% Benzyl Salicylate for both induction and challenge phase. A maximization test on 10 Hartley guinea pigs per dose using 1% Benzyl Salicylate in ethanol and 100% dermally administered revealed no sensitization reactions. Five of 20 animals revealed sensitization reactions in a study in which 10% Benzyl Salicylate in liquid paraffin and FCA was intradermally injected in the shoulder of 4-week old female Hartley strain guinea pigs (20 per group). 'Questionable' reactions were observed in three (3/20) animals at 5%, five (5/20) animals at 10%, and four (4/20) animals at 20%.

Results were negative in a maximization test conducted using outbred Himalayan white-spotted guinea pigs. In another maximization test, 10% Benzyl Salicylate in liquid paraffin and 30% Benzyl Salicylate in ethanol were administered to 10 female Hartley albino guinea pigs. At first challenge, no reactions were observed at 24 h, but positive reactions were observed at 48 and 72 h for all doses. At the second challenge, positive reactions were observed with 0.03% at 24 h and all concentrations at 48 and 72 h. No sensitization was produced in a guinea pig open epicutaneous test (OET) using Benzyl Salicylate at 30% for both induction and challenge (vehicle not specified). An OET conducted in guinea pigs exhibited no reaction to 10% Benzyl Salicylate in a 21 daily open application study. In a CET in guinea pigs, 30% Benzyl Salicylate (vehicle not provided) was not a sensitizer. Sensitization was observed in a CCET conducted in 10 female Hartley albino guinea pigs when induced for 24 hours with an occlusive patch containing 30% Benzyl Salicylate in ethanol. Sensitization was evaluated in groups of ten Pirbright guinea pigs using a modified FCA method. Benzyl Salicylate at 10% was a moderate sensitizer. In a QRA for dermal sensitization, the RIFM Expert Panel reviewed the critical effect data for Benzyl Salicylate via a WoE approach. IFRA reported a NESIL of 17,700 µg/cm² based on a human maximization test, and therefore classified the chemical as a weak sensitizer.

In five maximization tests using 25 human subjects, Benzyl Salicylate was administered at 20 to 30 % in petrolatum. Reactions were observed in two of the five studies, affecting 2/25 and 1/25 subjects at 20%. No positive reactions were reported at 30%. In another study, 15% Benzyl Salicylate in 3:1 diethyl phthalate: ethanol did not induce dermal sensitization in an HRIPT conducted on 101 subjects (29 males and 72 females). No sensitization reactions were observed when 35 subjects completed an HRIPT with 10% benzyl salicylate in alcohol SDA 39C. No sensitization reactions were observed when 52 volunteers were administered an aliquot of 5 ml of 5% benzyl salicylate in dimethyl phthalate. No sensitization was observed in an associated HRIPT study involving 8 male and female subjects when administered 0.5 mL of 5% Benzyl Salicylate in dimethyl phthalate. To evaluate the potential for cross-reactivity, an HRIPT was conducted on 103 subjects (29 male and 74 females). No cross-reactions were observed in subjects administered 30% hexyl salicylate in 3:1 DEP:ethanol, and cross-challenged with 15% Benzyl Salicylate in 3:1 DEP:ethanol.

The phototoxic potential of 20 µl of 100% Benzyl Salicylate and 25% Benzyl Salicylate in methanol resulted in no phototoxic effects when exposed to 6 groups of hairless mice. In another study, 5%, 10%, and 30% Benzyl Salicylate in acetone administered to five female albino Hartley-Dunkin guinea pigs, caused no phototoxic effects. No irritation was observed at 5%, however irritation was observed at 10% and 30% in 5 female albino Hartley-Dunkin guinea pigs. Benzyl Salicylate (0.025 mL) at 1%, with 2% DMSO revealed no evidence of phototoxicity, however phototoxic reactions were observed in 10/10 animals administered 0.025 mL of Benzyl Salicylate 3% in ethanol with 2% DMSO. No phototoxic effect were observed when twenty (10/sex) adult albino Dunkin Hartley guinea pigs were administered 0.5mL of 10% Benzyl Salicylate in absolute ethanol. No photosensitization reactions were observed when Dunkin-Hartley guinea pigs (25/group) were administered 10% Benzyl Salicylate in ethanol.

No phototoxic reactions were observed in a test conducted on six female subjects when administered 0.025 mL/2 cm² of 3% and 10% Benzyl Salicylate in 1:1 ethanol/acetone.

The ocular irritation potential of 0.75 mL undiluted Benzyl Salicylate was evaluated using a BCOP study according to OECD TG 437. An irritancy score of 0/5 was reported and it was concluded that the Benzyl Salicylate is not an ocular corrosive or severe irritant. Irritation was evaluated following the instillation of 0.1 mL of 10% Benzyl Salicylate in SD alcohol 39-C into the right eye of three albino rabbits. Mild conjunctival irritation was observed in all three rabbits and corneal opacity was observed in one rabbit

In a patch test conducted in 241 patients from October 1981 to June 1983, sensitivity to 2% Benzyl Salicylate in paraffin was observed in 6/241 patients and was characterized by erythema and edema. Five female and 1 male patients (2.5% incidence) had a positive reaction to Benzyl Salicylate. Benzyl Salicylate at 2% gave a positive reaction in 2/20 patients when patch tested with several fragrance materials during a one-year period (1975). In 10,503 patch tests of consumer products containing < 2% Benzyl Salicylate, no reactions were directly attributed to Benzyl Salicylate. In a world-wide multicenter study to investigate fragrance sensitization in 167 patients with suspected fragrance allergies, allergic reaction were observed in eight and 5 patients tested with 2% and 5% Benzyl Salicylate, respectively. Over a 64-month period (September 15, 1977 to August 31, 1983), twelve dermatologists from various sections of the US studied a total of 713 out of an estimated total of 13,216 patients with contact dermatitis. Of 713 cosmetic dermatitis patients, one (0.14%) reacted to Benzyl Salicylate (concentration not reported). In 578 cases of eczema patients known to be sensitized to cosmetics, one (0.17%) tested positive to Benzyl Salicylate. To study the frequency of sensitization to 26 fragrances including Benzyl Salicylate, patch tests were conducted during 4 periods of 6 months, from 1 January 2003 to 31 December 2004, in a total of 21 325 patients. The study reported 2 positive reactions to 1% Benzyl Salicylate in 2041 (0.1%) patients. In a study to evaluate the delayed hypersensitivity to Benzyl Salicylate, Benzyl Salicylate caused severe pruritus in six of 15 patients who applied a trade name mixture (containing 1% Oxsoralen with acetone, 71% alcohol, and propylene glycol (concentration not specified)) in a vehicle containing more than 5% Benzyl Salicylate. Delayed hypersensitivity to Benzyl Salicylate was enhanced by the phototoxic effects of the same lotion. Only one of 14 control patients reacted to Benzyl Salicylate.

No photoallergic reactions were observed when several photopatch tests were conducted in 482 patients with 2% Benzyl Salicylate in petrolatum. Another photopatch test in two subjects with 10% Benzyl Salicylate in dimethylphthalate showed no photoallergic reactions. Benzyl Salicylate at 2% in petrolatum tested in 706 patients with contact dermatitis resulted in no photoallergic reactions. No photoallergic reactions were observed when 386 subjects with suspected contact dermatitis were administered Benzyl Salicylate at 2% in petrolatum.

DISCUSSION

This report reviews the safety of Benzyl Salicylate, which is reported to function in cosmetics as a fragrance ingredient and light stabilizer. Use concentration survey data provided by the Council on Benzyl Salicylate were only reported for its use as a light stabilizer. However, the VCRP does not indicate the function of ingredients in cosmetic formulations, so it is not known what the intended function of Benzyl Salicylate is in any of the ingredient categories reported in the VCRP.

The Panel noted the potential for Benzyl Salicylate to bind to and interact with endocrine receptors of the skin. However, taking into consideration that the low concentrations of use and lack of dermal absorption would prevent effective systemic exposure, the potential for mimicking human estrogen, by binding to the cell's normal estrogen receptor location, was considered irrelevant to cosmetic safety.

The Panel recognized several positive sensitization studies as well as the outcome of a QRA for dermal sensitization. Consequently, the Panel noted that the potential for induction of skin sensitization varies depending on a number of factors, including formulation, frequency of use, and duration of exposure. The Panel noted that the induction of skin sensitization is not dependent on function in cosmetic products, but it does vary depending on the area of product application, and should be assessed 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 Benzyl Salicylate, and thus specified that products containing Benzyl Salicylate must be formulated to be non-irritating.

CONCLUSION

The CIR Expert Panel concluded that Benzyl Salicylate is safe in cosmetics in the present practices of use and concentration described in this safety assessment when formulated to be non-irritating and non-sensitizing, which may be based on a quantitative risk assessment (QRA).

TABLES**Table 1.** Physical and Chemical Properties

Property	Value	Reference
Physical Form	Liquid	6
Color	Colorless to pale yellow	6
Odor	Floral, Jasmine-like, Balsamic, mushroom-like	6
Molecular Weight (g/mol)	228.5	45
Density/Specific Gravity ()	1.181 ± 0.001	6
Viscosity (mm ² /s at 20 ± 0.5 °C)	17.0 ± 0.5	6
(mm ² /s at 40 ± 0.5 °C)	7.1 ± 0.5	
Vapor pressure (@ 25 °C)	0.01	6
Melting Point (°C)	122.1 ± 0.2	6
Boiling Point (°C)	322	6
Water Solubility (mg/L)	8.8	6
log K _{ow}	4.0	6
Disassociation constants (pKa @ 25 °C)	9.82	6
UV Absorption (λ) (nm)	200 - 340	4

Table 2. Frequency (2019) and concentration of use (2016**) for Benzyl Salicylate^{11,12}

	# of Uses ¹¹	Max Conc of Use (%) ¹² **
Totals*	3079	0.0036-0.5
<i>Duration of Use</i>		
<i>Leave-On</i>	2419	0.019-0.15
<i>Rinse-Off</i>	628	0.0036-0.5
<i>Diluted for (Bath) Use</i>	32	NR
<i>Exposure Type</i>		
Eye Area	25	NR
Incidental Ingestion	28	NR
Incidental Inhalation-Spray	976;562 ^a ;492 ^b	NR
Incidental Inhalation-Powder	62;492 ^b	NR
Dermal Contact	2525	0.0036-0.5
Deodorant (underarm)	77 ^a	NR
Hair - Non-Coloring	490	0.0065
Hair-Coloring	19	NR
Nail	16	NR
Mucous Membrane	324	NR
Baby Products	2	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.

** The Council concentration of use survey was only for the light stabilizer function

^a It is possible these products are sprays, but it is not specified whether the reported uses are sprays.

^b Not specified whether a spray or a powder, but it is possible the use can be as a spray or a powder, therefore the information is captured in both categories.

NR – no reported use

Table 3. IFRA Standard: Benzyl Salicylate in finished products¹⁷

Category	Standard limits
Category 1	0.5% in lip products
Category 2	0.7% in deodorants / antiperspirants
Category 3	2.7% in hydroalcohols for shaved skin; baby lotion; eye area products
Category 4	8% in hydroalcohols for unshaved skin; body products; hair sprays
Category 5	4.2% in baby powder; face products; hair treatments
Category 6	12.8% in oral care products
Category 7	1.3% in wipes; feminine hygiene
Category 8	2% in eye makeup removers; powders; hair grooming; hair dyes; nail products
Category 9	5% in rinse-off products; shampoos; conditioners; bath products; shaving products
Category 10	2.5% in hard surface cleaners
Category 11	Includes all non-skin contact or incidental skin contact products. Due to the negligible skin contact from these types of products there is no justification for a restriction of the concentration of this fragrance ingredient in the finished product.

IFRA - International Fragrance Association

*42nd Amendment to the IFRA QRA Category (2007)

*The RIFM Expert Panel reviewed the critical effect data for Benzyl Salicylate and, based on the weight of evidence, established the No Expected Sensitization Induction Level (NESIL) as 17,700 µg/cm².

*The Category Consumer Exposure Level (mg/cm²/day) is driven by the product type in that category with the combined highest consumer exposure level and highest Sensitization Assessment Factor (SAF)

Table 4. Dermal irritation and sensitization studies on Benzyl Salicylate

Concentration/Dose/vehicle	Test Population	Procedure	Results	Reference
<i>Irritation Animal</i>				
0.03 – 100% Benzyl Salicylate	6 to 8 male and female outbred Himalayan white-spotted guinea pigs	Pre-test for OET; a single application of Benzyl Salicylate (vehicle not specified) was administered for 24 hours.	At 0.03%, no irritation was observed. The concentration of 0.1% was the lowest concentration to produce mild erythema in at least 25% of the animals and this dose was selected as the minimal irritating concentration after one application	²⁶
0.03 –100% Benzyl Salicylate	6 to 8 male and female outbred Himalayan white spotted guinea pigs	Induction phase of OET; Benzyl Salicylate was applied daily for 21 days (vehicle not specified)	0.03%: no irritation. Minimal irritating concentration was observed after 21 applications at 0.1%.	²⁶
0.1 mL of Benzyl Salicylate in an unspecified vehicle at a range of concentrations	4 inbred Hartley strain albino guinea pigs (same sex)	As a part of a modified Draize sensitization study, a preliminary irritation screen was conducted to determine the ICC and ACC. Animals were administered intradermal injections of 0.1 mL aliquots of Benzyl Salicylate on shaved flanks in an unspecified vehicle. Reactions were read 24 hours after injection.	The concentration giving slight but perceptible irritation with no edema was 0.5% and it was selected as the Challenge Concentration (ICC). The highest concentration causing no irritation was 2% and it was selected as the Application Challenge Concentration (ACC)	²⁷
0.5 mL of Benzyl Salicylate (neat)	4 New Zealand white albino rabbits	4-hour semi-occlusive patch test	No irritation was observed	²⁸
0.5 mL aliquot of 10% Benzyl Salicylate in SD alcohol 39-C	3 Albino Rabbits; Sex not reported	24-h closed patch test	No irritation was observed	⁴
Benzyl Salicylate at 5, 10 or 20 g/kg (neat)	Rabbit	LD ₅₀ study for 24 hours under occlusion	No irritation was observed	⁴
<i>Irritation- Human</i>				
0.2 mL of Benzyl Salicylate (neat)	30 subjects	4 hour closed patch test	No irritation was observed	²⁸
0.2% Benzyl Salicylate in 99% ethanol	313 subjects	24 - 48 hour closed patch test	Five (5/313) positive reactions were observed	²⁹
2% Benzyl Salicylate in unguentum simplex (A simple ointment containing 5 parts olive oil and 2 parts white wax)	30 male and female subjects	24 - 72 hour closed patch	No irritation observed	⁵
5% in petrolatum	12 male and 13 female subjects	24 hour closed patch test	No irritation was observed	⁵
20% Benzyl Salicylate in petrolatum	5 male and female subjects	48 hour closed patch test	No irritation observed	²⁹
30% Benzyl Salicylate in petrolatum	5 subjects	maximization pre-test study	No irritation was observed	⁵
30% Benzyl Salicylate in petrolatum	22 male subjects	maximization pre-test	Two irritant reaction (2/22)	⁵

Table 4. Dermal irritation and sensitization studies on Benzyl Salicylate

Concentration/Dose/vehicle	Test Population	Procedure	Results	Reference
<i>Sensitization- Animal</i>				
10% Benzyl Salicylate in FCA for induction; 5%, 10%, and 20% in acetone for challenge	8 test and 8 control female albino Hartley-Dunkin guinea pigs	GPMT <u>Induction</u> consisted of a two-stage procedure. In the first stage, three intradermal injections (0.1 mL each) were administered to the clipped shoulder region of each animal. The injections consisted of Freund's Complete Adjuvant (FCA) plus distilled water (1:1); 10% Benzyl Salicylate in FCA; and 10% Benzyl Salicylate in FCA with distilled water (1:1). The second stage was a 48-hour topical application made seven days later to the same area on the shoulder. The shoulder was treated with 10% sodium lauryl sulfate (SLS) in petrolatum. <u>Challenge</u> test was performed by applying 0.02 mL of 5%, 10% and 20% Benzyl Salicylate in acetone to each site.	Sensitization was observed at all concentrations	⁵
10% Benzyl Salicylate for induction and challenge	Guinea pigs (sex and number not specified)	GPMT	Sensitization was observed	⁵
1% Benzyl Salicylate in ethanol intradermally and 100% dermally	10 Hartley guinea pigs/dose	Magnusson-Kligman GPMT <u>Induction</u> : a patch containing 0.2 mL of the test solution was applied for 24 hours under closed conditions and repeated every other day over a period of 2 weeks. An untreated group acted as a control. In combination with this procedure, 0.1ml FCA was administered intradermally on each side of the application unit on day 3 and 7 before the initial patch and before the initial 2 nd , 3 rd , and 4 th patch application. <u>Challenge</u> : was performed with 0.01 mL to the lateral part of the animal on the 11th day.	No sensitization reactions were observed	³⁰
Benzyl Salicylate at 10% in liquid paraffin for intradermal induction; 50% in white petrolatum for topical induction; 5%, 10% and 20% in white petrolatum for challenge	Four week old female Hartley strain guinea pigs (20/group)	GPMT Benzyl Salicylate at 10% in liquid paraffin and FCA was intradermally injected in the shoulder region of each animal. Five days after the intradermal injections 10% SLS in petrolatum was topically applied to the same region. Twenty-four hours later, 50% Benzyl Salicylate in white petrolatum was applied for 48 hours with impermeable tape and adhesive bandage. Two weeks after the topical application, Benzyl Salicylate at 5%, 10% and 20% in white petrolatum was applied on the backs of the animals.	No sensitization at 5% and 10%; Sensitization were observed in 2/20 at 20%	⁵
Intradermal induction: 5% Benzyl Salicylate in FCA Topical induction: 25% Benzyl Salicylate in petrolatum Topical Challenge: sub-irritant concentration (< 0.1%) in petrolatum	Himalayan white-spotted male and female guinea pigs (numbers not specified)	GPMT <u>Induction</u> : was via two intradermal injections on day 0. On day 8, 25% Benzyl Salicylate in petrolatum was applied to a clipped area on the neck for 48 hours under occlusion. <u>Challenge</u> : conducted on day 21 was with a 24 hours occluded patch	No sensitization reactions were observed	²⁶

Table 4. Dermal irritation and sensitization studies on Benzyl Salicylate

Concentration/Dose/vehicle	Test Population	Procedure	Results	Reference
Intradermal induction: 10% in liquid paraffin Topical induction: 30% in ethanol Topical Challenge: 0.003%, 0.01%, or 0.03% in ethanol	10 female Hartley albino guinea pigs	GPMT <u>Induction</u> was via intradermal injection of 10% Benzyl Salicylate in liquid paraffin and a 48-hour occlusive patch with 30% Benzyl Salicylate in ethanol. The animals were <u>challenged</u> twice with Benzyl Salicylate at 0.003%, 0.01%, and 0.03% in ethanol. The second challenge was conducted three weeks after the first challenge.	At first challenge, no reactions were observed at 24 hours, but positive reactions were observed at 48 and 72 hours at all doses. At the second challenge, positive reactions were observed with 0.03% at 24 hours and all concentrations at 48 and 72 hours.	³²
Induction and challenge: 30% Benzyl Salicylate (vehicle not specified)	6 to 8 male and female guinea pigs	A guinea pig OET; Daily applications of 0.1 mL Benzyl Salicylate (undiluted or progressively diluted solutions) were made for 3 weeks to a clipped 8.0 cm ² area on the flank of each guinea pig. Ten control animals were either left untreated or treated with 0.1 mL of the vehicle for 21 days. <u>Challenge</u> : Both the test and control animals were treated on days 21 and 35 on the opposite flank with 30% Benzyl Salicylate.	No sensitization reactions were observed	⁵
Induction and challenge: 10% Benzyl Salicylate (vehicle not specified)	Guinea pigs (6 to 8 males and females)	A guinea pig OET consisted of 21 daily open applications to the shaved flank of 6–8 guinea pigs per group. Open challenge applications were made on days 21 and 35	No sensitization reactions were observed	⁵
Induction and challenge: 0.03 - 100% Benzyl Salicylate (vehicle not specified)	Himalayan white spotted guinea pigs (6 to 8 males and females)	In an OET, test animals received 21 daily open applications of 0.1 mL of undiluted and progressively diluted solutions of Benzyl Salicylate applied to clipped flank. Guinea pigs were challenged by an open application of 0.025 mL Benzyl Salicylate to a skin area measuring 2 cm ² on the contralateral flank on days 21 and 35.	0.03%: minimum eliciting concentration 30%: minimum sensitizing concentration	³⁶
Induction: 30% (vehicle not specified) Challenge: 1% (vehicle not specified)	Guinea pigs (20, sex not specified)	In a CET <u>Induction</u> : 30% Benzyl Salicylate (vehicle not provided) under occlusion for 48 hours on the shaved nape. The same procedure was repeated three times per week for two weeks. Following a 2-week rest period and challenge with 1% Benzyl Salicylate for 48 hours.	Sensitization observed in 3/20	⁵
30% Benzyl Salicylate in ethanol for induction; 1%, 3%, and 10% in ethanol for challenge	10 female Hartley albino guinea pigs	In a CCET, guinea pigs were administered 30% Benzyl Salicylate in ethanol applied to each test animal in 24-hour occlusive patch. The animals were challenged twice (2nd challenge was conducted 3 weeks after the 1st challenge) with 1%, 3% and 10% Benzyl Salicylate in ethanol.	At 1% concentration, one positive (1/10) reaction was observed at 24 hours, while no reactions were observed at 48 or 72 hours in both challenges. At 3%, positive reactions (3/10) were observed at 24 hours of the first challenge and (2/10) were observed at 24 and 48 hours in both challenges. At 10%, positive reactions were observed at 24, 48 and 72 hours in both challenges.	³²
Induction: 3%, 10%, 30%, and 100% topically Challenge: concentration not specified topically	Pirbright and Hartley albino guinea pigs (6–10/group)	In a CCET the application of test article were repeated every other day over a period of 2 weeks. Eleven days after the final induction patch, a challenge was performed.	10%: no reactions 30%: sensitization in 3/6 Pirbright guinea pigs 100%: sensitization in 1/10 Hartley guinea pigs	³⁰

Table 4. Dermal irritation and sensitization studies on Benzyl Salicylate

Concentration/Dose/vehicle	Test Population	Procedure	Results	Reference
Induction: 100% Challenge: 50% topically	30 tortoise shell guinea pigs	In a CCET, animals were shaved and 24 hours occluded patch with Benzyl Salicylate (neat) was applied. Patches were applied every third day for 2 weeks (maximum, 4 applications). An injection of FCA was intradermally administered before the third patch. An untreated group of five animals was used as a control. <u>Challenge:</u> After 11 days, 0.01 mL aliquot of 50% Benzyl Salicylate in ethanol was applied to a previously untreated site once daily for 1 to 3 days.	Sensitization reactions were observed in 13/30 animals	46
10% Benzyl Salicylate in FCA for intradermal induction; 10% in acetone for challenge	10 Pirbright guinea pigs	In a modified FCAT, a total of 4.5 mg of Benzyl Salicylate (10%) was administered and challenged by applying 0.05 mL of 10% Benzyl Salicylate in acetone onto the clipped, shaved right flank.	Benzyl Salicylate at 10% was a moderate sensitizer	33
50% Benzyl Salicylate in FCA for induction application; 0.1% for challenge application	Himalayan white spotted guinea pigs (6 to 8 males and females)	FCAT was conducted using induction via five intradermal injections of 0.1 mL of a 50:50 mixture of Benzyl Salicylate and FCA into the neck <u>Challenge:</u> A 24 hour closed patch challenge application was conducted on days 21 and 35 <0.1% (vehicle not specified)	No reactions were observed	26
Intradermal induction: 1% in saline Intradermal challenge: 0.1% in saline Topical challenge: 10% in petrolatum	20 Pirbright White Strain guinea pigs (10/sex).	Optimization test; test population received one intracutaneous injection of 0.1% Benzyl Salicylate in saline. Benzyl Salicylate was incorporated at the same concentration in a mixture of FCA and physiological saline (adjuvant/saline, 1:1 v/v). The animals were challenged with 0.1% Benzyl Salicylate in saline at week 6 (intradermally) and at week 8 (epidermal challenge)	One (1/20) reaction was observed after the intradermal challenge, and seven (7/20) reactions were observed after the epidermal challenge	47
Induction: 30% Benzyl Salicylate in ethanol Challenge: 1%, 3%, or 10% in ethanol	10 Female Hartley guinea pigs	Delayed contact hypersensitivity assay using the AP2 test method; Two induction applications were administered via intradermal injection with FCA and a occluded patch with 30% Benzyl Salicylate in ethanol. Two open challenge applications were administered with 1%, 3% and 10% Benzyl Salicylate in ethanol. A third challenge application was made with 0.003%, 0.01% and 0.03% Benzyl Salicylate in ethanol.	Sensitization was observed at all three challenges	5
25µl of 10% Benzyl Salicylate in 4:1 acetone: olive oil	4 Female CBA/JN mice/group	In an LLNA, test article was applied to the dorsal surface of ear. The procedure was repeated daily for three consecutive days. Three days after the third application, all test subjects were injected via the tail vein with 250 µl of phosphate buffered saline (PBS) containing 20 µCi of 2.0 Ci/mmol specific activity 3H-methyl thymidine.	Benzyl Salicylate was categorized as a weak sensitizer. The EC3 value was calculated to be 1.5% (375 µl /cm ²)	5
25µl of 2.5%, 5.0%, 10%, 25%, and 50% Benzyl Salicylate in 3:1DEP:ethanol	4 Female CBA/Ca mice/group	Evaluated in an LLNA; Test article was applied to the dorsal surface of each ear and three days after the third application, all animals were injected via the tail vein with 250µl of phosphate buffered saline (PBS) containing 20 µCi of 2.0 Ci/mmol specific activity 3H-methyl thymidine.	Overall, Benzyl Salicylate was found to be a skin sensitizer. The EC3 value was calculated to be 2.9% (725 µl /cm ²)	5

Table 4. Dermal irritation and sensitization studies on Benzyl Salicylate

Concentration/Dose/vehicle	Test Population	Procedure	Results	Reference
0.5% Benzyl Salicylate for intradermal induction; 0.5% for intradermal challenge and 2% for dermal challenge (vehicle not specified)	Hartley albino guinea pigs (4 or 6 of each sex, 10 total)	In a Draize (Modified) test, a 0.1 ml aliquot of 1.25% Benzyl Salicylate, at 2.5 times the ICC (injection challenge concentration: 0.5%), was injected intradermally at four sites. The animals were challenged 14 days later by an intradermal injection of 0.1 ml Benzyl Salicylate into one flank and a topical open application of Benzyl Salicylate on the other flank at the respective ICC of 0.5% and ACC at 2% (vehicle not provided).	No sensitization	27
0.1% in isotonic saline for intradermal induction; 0.1% in isotonic saline for challenge	Himalayan white spotted guinea pigs (6–8 males and females)	Draize (Modified); Induction consisted of ten intradermal injections on alternate days with a dose of 0.05 mL of 0.1% Benzyl Salicylate in isotonic saline. Test subjects were challenged on days 35 and 49 with an intradermal injection of 0.05 mL of 0.1% Benzyl Salicylate in saline. Control test subjects were also challenged intradermally on days 35 and 49 with Benzyl Salicylate	No sensitization	26
Sensitization- Human				
0.3mL of 15% Benzyl Salicylate (3:1) DEP:EtOH	29 males and 72 females subjects	HRIPT; adhesive patch (25mm) was applied to the left side of the back of each subject. Patches remained in place for 24 hours. Nine induction patches were completed over a period of approximately three weeks. After a 2-week rest period, challenge patches were applied to a virgin site on the back and kept in place for 24 h.	No sensitization was observed	5
0.5mL of Benzyl Salicylate in SD alcohol 39-C	17 male and 18 female subjects	HRIPT; test article was applied on a test patch and administered to the upper arms of the subjects for 24 hours. Nine applications were made during the induction phase and reactions were scored 48 hours after application. After a 2-week rest period, a 24-hour challenge application was made to the same site and to a virgin site in the same manner as the induction applications	No sensitization was observed	5
0.5 mL of 5% Benzyl Salicylate in dimethyl phthalate.	8 male and female subjects	HRIPT; 0.5mL of 5% Benzyl Salicylate in dimethyl phthalate was applied to absorbent patches and applied to the inner surface of the left deltoid area for 48 hours. Reactions were read at 24 and 48 hours.	No sensitization was observed	5
10% Benzyl Salicylate in SD alcohol 39-C	35 subjects	HRIPT; Patches remained in place for approximately 24 hours. Nine induction patches were completed over a 3-week period. After a 2-week rest period, a 24-hour challenge application was made to the same site and to a virgin site in the same manner as the induction applications.	No sensitization reactions	5
5% Benzyl Salicylate in dimethyl phthalate	52 subjects	HRIPT using a modified Draize method. Patch was then applied to the inner surface of the right deltoid area of each. The patches remained in place for 48 hours. A series of ten induction patches were applied. The challenge patches were applied after a 2-week rest period in the same manner as the induction patches except they were applied in duplicate, one set to the inner surface of each deltoid area. Patches remained in place for 48 hours.	No sensitization reactions	5

Table 4. Dermal irritation and sensitization studies on Benzyl Salicylate

Concentration/Dose/vehicle	Test Population	Procedure	Results	Reference
20% Benzyl Salicylate in petrolatum	25 male and female subjects	MAX; application was under occlusion to the same site on the volar forearms of all subjects for five alternate day, 48 hours. After a 14-day rest period, a challenge patch was applied under occlusion and reactions were read at 48 and 96 hours.	Sensitization was observed in two (2/25) subjects	⁵
20% Benzyl Salicylate in petrolatum	25 subjects	MAX; application was under occlusion to the volar forearms of all subjects for five alternate day, 48-hour periods. The patch site was pre-treated for 24 hours with 5% aqueous SLS under occlusion. Following a 10 to 14-day rest period, a challenge patch of Benzyl Salicylate was applied to fresh sites for 48 hours under occlusion.	One (1/25) sensitization reaction was observed	⁵
30% Benzyl Salicylate in petrolatum	25 male and female subjects	MAX; application was under occlusion to the same site on the volar forearms of each subject for five alternate days, 48-hour periods. Patch sites were pre-treated for 24 hours with 5% aqueous sodium lauryl sulfate (SLS) under occlusion. After a rest period, a challenge patch was applied under occlusion and challenge sites were read 24 hours later.	No sensitization reactions	⁵
30% Benzyl Salicylate in petrolatum	25 male subjects	MAX; application was under occlusion for five alternate days, 48 hours. Each application was preceded by 24-hour occlusive applications of 5% aqueous SLS. Following a 10-day rest period, challenge patches of Benzyl Salicylate were applied to fresh sites on the backs of each subject under occlusion for 48 hours.	No sensitization reactions	⁵
30% Benzyl Salicylate in petrolatum	22 male subjects	MAX; application under occlusion to the same site on the forearms of all subjects for five alternate days, 48-hour periods. Following a 10 to 14-day rest period, a challenge patch was applied to a fresh site for 48 hours under occlusion.	No sensitization reactions	⁵

Abbreviations: ACC= application challenge concentration; CCET = cumulative contact enhancement test; CET = closed epicutaneous test; DEP:EtOH = Ethanol:diethyl phthalate; FCA = Freund's Complete Adjuvant; FCAT = Freund's complete adjuvant test; GPMT = guinea pig maximization test; HRIPT = human repeat insult patch test; ICC = injection challenge concentration; LLNA = Local lymph node assay; MAX = human maximization test; OET = open epicutaneous test; PBS = phosphate buffered saline; SLS = sodium lauryl sulfate.

Table 5. Phototoxicity and Photoallergy studies on Benzyl Salicylate

Concentration/Dose	Test Population	Procedure	Results	Reference
ANIMAL				
20 µl aliquot of 100% Benzyl Salicylate and 25% Benzyl Salicylate in methanol	Skh:hairless mice (6/group)	The test material was applied to 5cm ² site on the back of each animal. Thirty minutes later, the first group was exposed to a florescent black light (a bank of 6 Sylvania F40T12BL PUVA lamps with a broadband output of 350 nm) for one hour and at a distance of 0.65m to provide a measure dose of 200 RB units. One RB corresponds to ~0.068 mJ/cm ² . ⁴⁸ The second group was irradiated one meter from a simulated sunlight (6.5 kw xenon light source) for one hour providing a dose of 200 RB units. The areas were examined at 4, 24, 48, 72 and 96 hours.	No phototoxic effects were observed.	⁵
0.02 mL of Benzyl Salicylate at 5%, 10% or 30% in acetone	Five female albino Dunkin Hartley guinea pigs	Test material was applied to clipped skin sites and irradiated with 13 J/cm ² UV light (UV-A black light 300 – 400 nm, max 360 nm) at 10cm for 60 minutes. Reactions were graded according to Draize at 24 and 48 hours after application.	No phototoxic effects were observed	⁵
0.025mL aliquot of Benzyl Salicylate as 1% or 3% in ethanol, with 2% DMSO	Himalayan white spotted guinea pigs (10/dose)	Test material was applied to 2 cm ² skin on the left flank of the animals. Thirty minutes after the application, the sites on the left flank were irradiated with 20 J/cm ² UV light (320 – 400 nm, energy 1 · 10 ⁴ ergs/cm ²), at 10 cm from the animal. Sites on the right side were not irradiated and served as controls.	No reactions were observed with 1% Benzyl Salicylate. However, phototoxic reaction were observed in 10/10 animals administered 3% Benzyl Salicylate	⁵
0.5mL of 10% Benzyl Salicylate in absolute ethanol	Twenty (10/sex) adult albino Dunkin Hartley guinea pigs weighing 300 to 400g.	A single application of the test material was applied under an occlusive patch for 90 minutes on the anterior part of the back. Irradiation was carried out using a system of fluorescent lamps with continuous spectrum emission. Radiation emitted by these lamps was principally in the UVA range (wavelength from 4000 to 315 nm) and in the UVB range (wavelength from 315 to 290 nm). The two lamps used were placed 10 cm from the back of each animal and irradiated for 5 min. The total radiation dose was 12.5 J/cm ² and the rage of UVB was 1%.	No phototoxic effects were observed	⁵
10% Benzyl Salicylate in ethanol	Dunkin Hartley guinea pigs (25/group)	Photoallergy (sensitization) test; 4 topical application of 0.5 mL of Benzyl Salicylate in absolute ethanol was applied and challenged with 0.5 mL of 10% Benzyl Salicylate in absolute ethanol	No photosensitization reactions were observed	⁵
HUMAN				
0.025 mL/2cm2 aliquot of 3% and 10% Benzyl Salicylate in 1:1 ethanol/acetone	Six female subjects	Test article was applied to the left and right side on the back of each subject. The right test side served as control. The test sites were exposed to non-erythrogenic UV-A radiation at 1, 2.5, 5, 10 and 20 J/cm2. The light source was a bank of four blacklight fluorescent tubes with an emission spectrum of 320 – 400 nm housed in a reflector unit.	No phototoxic responses were observed.	⁵

Abbreviations: PUVA = psoralen ultra violet A; RB = ~0.068 mJ/cm²; UV- A = ultraviolet A; UV-B = ultraviolet B

REFERENCES

1. Nikitakis, J and Kowcz A. Web-Based Ingredient Dictionary (wINCI): Benzyl Salicylate. <https://online.personalcarecouncil.org/jsp/IngredientDetail.jsp?monoid=291>. Washington, DC. Last Updated 2018. Date Accessed 4-20-2018.
2. Johnson W and Bergfeld WF et al. Safety Assessment of Benzyl Alcohol, Benzoic Acid and its Salts, and Benzyl Benzoate. *International Journal of Toxicology*. 2017;36(3):5S-30S.
3. Johnson W, Zhu J, and Bergfeld WF, et al. Amended Safety Assessment of Salicylic Acid and Salicylates as Used in Cosmetics. <https://www.cir-safety.org/ingredients>. Last Updated 2018.
4. Belsito D, Bickers D, Bruze M, et al. A toxicologic and dermatologic assessment of salicylates when used as fragrance ingredients. *Food and Chemical Toxicology*. 2007;45:318-361.
5. Lapczynski A, McGinty L, Jones L, et al. Fragrance material review on Benzyl Salicylate. *Food and Chemical Toxicology*. 2007;45:S362-S380.
6. European Chemical Agency(ECHA). REACH registration dossier: Benzyl Salicylate (CAS 118-58-1). <https://echa.europa.eu/de/registration-dossier/-/registered-dossier/16100>. Last Updated 2018. Date Accessed 8-16-2018.
7. Andersen FA (ed). Final report on the Safety Assessment of Benzyl Alcohol, Benzoic Acid, and Sodium Benzoate. *International Journal of Toxicology*. 2001;20(3):23-50.
8. Yu-wen L and Cui-li M. Green synthesis of Benzyl Salicylate. *Zhongguo Shipin Tianji*. 2014;(4):58-60.
9. United States Pharmacopeial Convention. Food Chemicals Codex. Tenth ed. Rockville, MD: The United States Pharmacopeial Convention, 2016.
10. Tisserand, R and Young, R. Essential Oil Safety: A Guide for Health Care Professionals. 2nd ed. Churchill Livingstone Elsevier, 2014.
11. U.S. Food and Drug Administration (FDA) Center for Food Safety & Applied Nutrition (CFSAN). Voluntary Cosmetic Registration Program (VCRP) - Frequency of Use of Cosmetic Ingredients. 2019. Obtained under the Freedom of Information Act from CFSAN; requested as "Frequency of Use Data" received 2019.
12. Personal Care Products Council. 2016. Concentration of Use by FDA Product Category: Benzyl Salicylate. Unpublished data submitted by Personal Care Products Council.
13. Rothe H, Fautz R, Gerber E, et al. Special aspects of cosmetic spray safety evaluations: Principles on inhalation risk assessment. *Toxicol Lett*. 8-28-2011;205(2):97-104. PM:21669261.
14. CIR Science and Support Committee of the Personal Care Products Council (CIR SSC). 11-3-2015. Cosmetic Powder Exposure. Unpublished data submitted by the Personal Care Products Council.
15. Aylott RI, Byrne GA, Middleton J, et al. Normal use levels of respirable cosmetic talc: preliminary study. *Int J Cosmet Sci*. 1979;1(3):177-186. PM:19467066.
16. Russell RS, Merz RD, Sherman WT, et al. The determination of respirable particles in talcum powder. *Food Cosmet Toxicol*. 1979;17(2):117-122. PM:478394.
17. IFRA Standards. International Fragrance Association (IFRA). [file:///C:/Users/aaa/Downloads/23153_STRS_2013_06_11_Benzyl_salicylate%20\(2\).pdf](file:///C:/Users/aaa/Downloads/23153_STRS_2013_06_11_Benzyl_salicylate%20(2).pdf). Last Updated 2018. Date Accessed 5-18-2018.
18. European Commission (EC). Annex III; List of substances which cosmetic products must not contain except subject to the restrictions laid down. http://ec.europa.eu/growth/tools-databases/cosing/pdf/COSING_Annex%20III_v2.pdf. Last Updated 2018. Date Accessed 5-28-2018.
19. Adams T.B, Cohen S.M, Doull J, et al. The FEMA GRAS assessment of hydroxyl- and alkoxy-substituted benzyl derivatives used as flavor ingredients. *Food and Chemical Toxicology*. 2005;43:1241-1271.

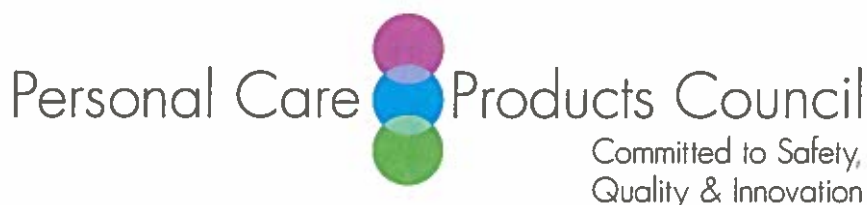
20. Jimbo Y. Penetration of fragrance compounds through human epidermis. *Journal of Dermatology*. 1983;10:229-239.
21. Igarashi T, Takashima H, Takabe M, et al. Initial hazard assessment of Benzyl Salicylate: In vitro genotoxicity test and combined repeated-dose and reproductive/developmental toxicity screening tests in rats. *Regulatory Toxicology and Pharmacology*. 10-20-0018;100:105-117.
22. Zeiger E, Anderson B, Haworth S, et al. *Salmonella* Mutagenicity Tests: 111. Results From the Testing of 255 Chemicals. *Environmental Mutagenesis*. 1987;9(9):1-110.
23. Charles AK and Darbre PD. **Oestrogenic activity of benzyl salicylate, benzyl benzoate and butylphenylmethylpropional (Lilial) in MCF7 human breast cancer cells *in vitro***. *Journal of Applied Toxicology*. 2009;29(5):422-434.
24. Hashimoto Y, Kawaguchi M, Miyazaki K, et al. Estrogenic activity of tissue conditioners in vitro. *Dental Materials*. 2003;19:341-346.
25. Zhang Z, Jia C, Hu Y, et al. The estrogenic potential of salicylate esters and their possible risks in food and cosmetics. *Toxicology Letters*. 2012;(209):146-153.
26. Klecak G, Geleick H, and Frey JR. Screening of fragrance materials for allergenicity in the guinea. I. Comparison of four testing methods. *Journal of the Society of Cosmetic Chemists*. 1977;28:53-64.
27. Sharp DW. The sensitization potential of some perfume ingredients tested using a modified Draize procedure. *Toxicology*. 1978;9:261-271.
28. Basketter DA, York M, McFadden JP, et al. Determination of skin irritation potential in the human 4-h patch test. *Contact Dermatitis*. 2004;51(1):1-4.
29. Fujii T, Furukawa S, and Suzuki S. Studies on compounded perfumes for toilet goods. On the non-irritative compounded perfumes for soaps. *Yukugaku*. 1972;21:904-908.
30. Tsuchiya S, Kondo M, Okamoto K, et al. Studies on contact hypersensitivity in the guinea pig. The cumulative contact enhancement test. *Contact Dermatitis*. 1982;8:246-255.
31. Kozuka T, Hayashi H, Hiroyama H, et al. Allergenicity of fragrance materials: collaborative study of the Second Research Group of the Japanese Society for Cutaneous Health. *Environmental Dermatology*. 1996;3:326-335.
32. Kashima R, Oyake Y, Okada J, et al. Studies of new short-period method for delayed contact hypersensitivity assay in guinea pig. *Contact Dermatitis*. 1993;28:235-242.
33. Hausen BM and Wollenweber E. Propolis allergy. (III). Sensitization studies with minor constituents. *Contact Dermatitis*. 1988;19(4):296-303.
34. European Commission. European Chemicals Agency (ECHA): Benzyl Salicylate. <https://echa.europa.eu/registration-dossier/-/registered-dossier/16100/4/8>. Last Updated 2018. Date Accessed 4-20-2018.
35. Ferguson J and Shama S. Cinnamic aldehyde test concentration. *Contact Dermatitis*. 1984;10:191-192.
36. Larsen WG. Perfume Dermatitis. A Study of 20 patients. *Archives of Dermatology*. 1977;113:623-626.
37. Kohrman K.A, Booman K.A, Dorsky J, et al. Benzyl Salicylate: A survey of consumer patch-test sensitization. *Food and Chemical Toxicology*. 1983;21(6):741-744.
38. Larsen W, Nakayama H, Lindberg M, et al. Fragrance contact dermatitis. A worldwide multicentre investigation (Part I) . *American Journal of Contact Dermatitis*. 1996;7(2):77-83.
39. Adams RM and Maibach H.I. A five-year study of cosmetic reactions. *Journal of the American Academy of Dermatology*. 1985;13:1062-1069.
40. Schnuch A, Uter W, Geier J, et al. Sensitization to 26 fragrances to be labelled according to the current European regulation. Results of the IVDK and review of the literature. *Contact Dermatitis*. 2007;57(1):1-10.
41. Kahn G. Intensified Contact Sensitization to Benzyl Salicylate. Phototoxic Effects of Topical Psoralen Therapy. *Archives of Dermatology*. 1971;103(5):497-500.

42. Alagappan U, Tay YK, and Lim SP. Pigmented Contact Dermatitis Secondary to Benzyl Salicylate. *Acta Dermato Venereologica*. 2013;93:590
43. Fernandez-Canga P, Ruiz-Gonzalez I, Varas-Meis E, et al. Contact allergy to Benzyl Salicylate. *Contact Dermatitis*. 2017;76:296-321.
44. Tous-Romero F, Prieto-Barrios M, Andres-Lencina JJ, et al. Allergic contact dermatitis cause by Benzyl Salicylate in hair products. *Contact Dermatitis*. 2018;1-2.
45. Benzyl Salicylate; 118-58-1. https://pubchem.ncbi.nlm.nih.gov/compound/benzyl_salicylate#section=Top. Last Updated 2018. Date Accessed 8-11-2018.
46. Imokawa G and Kawai M. Differential hypermelanosis by allergic contact dermatitis. *Journal of Investigative Dermatology*. 1987;89:540-546.
47. Maurer T, Weirich E, and Hess R. The optimization test in the guinea pig in relation to other predictive sensitization methods. *Toxicology*. 1980;15:163-171.
48. Fears TR, Bird CC, Guerry D, et al. Average Midrange Ultraviolet Radiation Flux and Time Outdoors Predict Melanoma Risk. *Cancer Research*. 2002;62(14):3992-3996.

2019 VCRP data**BENZYL SALICYLATE**

01A - Baby Shampoos	1
01C - Other Baby Products	1
02A - Bath Oils, Tablets, and Salts	18
02B - Bubble Baths	6
02D - Other Bath Preparations	8
03B - Eyeliner	1
03D - Eye Lotion	17
03E - Eye Makeup Remover	1
03G - Other Eye Makeup Preparations	6
04A - Cologne and Toilet waters	362
04B - Perfumes	433
04C - Powders (dusting and talcum, excluding aftershave talc)	28
04D - Sachets	1
04E - Other Fragrance Preparation	125
05A - Hair Conditioner	119
05B - Hair Spray (aerosol fixatives)	56
05C - Hair Straighteners	4
05D - Permanent Waves	1
05E - Rinses (non-coloring)	3
05F - Shampoos (non-coloring)	107
05G - Tonics, Dressings, and Other Hair Grooming Aids	153
05H - Wave Sets	5
05I - Other Hair Preparations	41
06D - Hair Shampoos (coloring)	9
06H - Other Hair Coloring Preparation	10
07A - Blushers (all types)	3
07B - Face Powders	34
07C - Foundations	7
07E - Lipstick	27
07F - Makeup Bases	3
07I - Other Makeup Preparations	12
08B - Cuticle Softeners	5
08C - Nail Creams and Lotions	2
08E - Nail Polish and Enamel	3
08F - Nail Polish and Enamel Removers	1
08G - Other Manicuring Preparations	5
09C - Other Oral Hygiene Products	1
10A - Bath Soaps and Detergents	147
10B - Deodorants (underarm)	77
10C - Douches	1
10D - Feminine Deodorants	1
10E - Other Personal Cleanliness Products	115
11A - Aftershave Lotion	28
11B - Beard Softeners	1
11D - Preshave Lotions (all types)	1

11E - Shaving Cream	3
11F - Shaving Soap	1
11G - Other Shaving Preparation Products	9
12A - Cleansing	71
12C - Face and Neck (exc shave)	197
12D - Body and Hand (exc shave)	293
12E - Foot Powders and Sprays	1
12F - Moisturizing	337
12G - Night	42
12H - Paste Masks (mud packs)	18
12I - Skin Fresheners	11
12J - Other Skin Care Preps	87
13A - Suntan Gels, Creams, and Liquids	1
13B - Indoor Tanning Preparations	13
13C - Other Suntan Preparations	5



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 28, 2018

SUBJECT: Draft Report: Safety Assessment of Benzyl Salicylate 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 report, Safety Assessment of Benzyl Salicylate as Used in Cosmetics.

Key Issues

Introduction - As the intent of the CIR procedures is to prevent duplication of effort, the CIR Expert Panel can exercise their discretion to determine whether or not the review of Benzyl Salicylate, primarily used as a fragrance ingredient in cosmetic products, should continue.

Short-Term - The description of the dose-range finding study (14 day study in rats) (reference 20) is not correct. The methods describe the 14 day study (250, 500 or 1000 mg/kg/day), but the results are from the 41-46 day study (30, 100 or 300 mg/kg/day).

DART; Summary - More details of the combined repeated-dose reproductive/developmental toxicity study should be included in the CIR report. Only the Summary describes the effects observed at 30 and 100 mg/kg/day. The only significant effect observed in the offspring at 30 mg/kg/day was lower body weights compared to controls at PND 4. It is questionable as to whether or not the lower offspring body weights should be considered an adverse effect. Although, the study authors indicated that a D-value is like a DNEL, this assessment followed the Japanese process for hazard assessment and did not use the process from REACH as suggested in the DART section of the CIR report. The Japanese hazard assessment process should not be included in the CIR report.

Phototoxicity/Photosensitization, Summary - Details of the light exposure for each study (animal and human) should be stated in the text and the Summary. The studies summarized in the Photoallergy subsection under Case Reports should be moved to the Phototoxicity/Photosensitization section and be added to Table 5.

Clinical Studies; Summary - As the IFRA standards were revised in 2007, and the EU required labeling of Benzyl Salicylate above certain levels in 2003, it would be very helpful to state the time frame of each clinical study in both the text and the Summary.

Additional Considerations

Introduction - If only the RIFM reviews were used to obtain information from RIFM about Benzyl Salicylate, it is misleading to state: "Additionally, data were obtained from the Research Institute for Fragrance Materials (RIFM) Expert Panel review."

Method of Manufacture - Please do not imply that there may be a "cosmetic industry-specific" method of manufacture. This ingredient used in cosmetics is not made in a different manner than this ingredient used in food or other applications.

Cosmetic Use - The RIFM use information should be added to this section. Please revise "Benzyl Salicylate is used formulations". It would be helpful to state that potential sensitization is the basis of the IFRA standard.

Dermal Penetration - If available, the amount of Benzyl Salicylate recovered in the skin should also be stated. The identity of the receptor fluid should be stated as it impacts the amount that will penetrate.

Genotoxicity, In Vitro - Please state the concentrations used in the study in Chinese hamster lung fibroblasts (see table 1 in reference 20).

Estrogen Activity - Please define "BAP activity".

Clinical Studies, third paragraph (reference 37) - Please add units to all concentrations, or indicate that the values in the paragraph are all (likely %).

Clinical Studies, fourth paragraph (reference 38); Summary - It is not clear why irritant reactions are given as number of patients and sensitization reactions are given as a percentage, when these values are actually the same for the number of subjects tested, e.g., 5 of 167 patients is 3%. In contrast to the Clinical Studies section, the Summary states the number for sensitization reactions. How did they reach the conclusion that "Benzyl Salicylate was a more common cause of positive patch test reactions in Japan than in Europe or the US"?

Clinical Studies, last paragraph (reference 40) - It is not clear what is meant by test product. Is this the product containing oxisoralen?

Summary - The description of the dermal penetration study using guinea pig skin only states one result (0.9%) when three concentrations were tested.

The summary of acute studies states: "when test substances were applied". What other substances were applied?

The description of the combined repeated-dose and reproductive/developmental toxicity screening test says: "non-mating rats". As the rats were mated in this study, this is not correct. The only effect noted at 30 mg/kg/day was offspring body weight lower than controls on PND 4. Although this may be considered an effect on development, it does not suggest "teratogenicity".

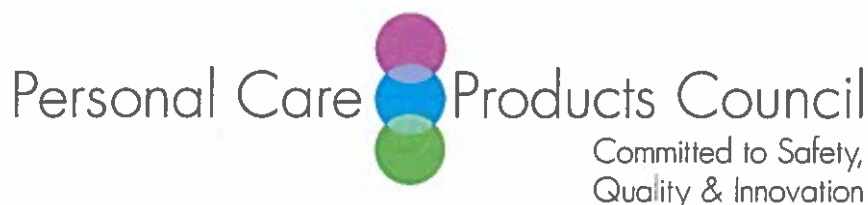
The Summary states: "The NOAEL for developmental effects in the pups was 180 mg/kg bw/day." Where did this come from as it is not stated earlier in the report.

Uterotrophic assays are not *in vitro* studies as stated in the Summary.

Please correct "Harley" albino guinea pigs

References are generally not included in the Summary (a 6 is in the paragraph on human sensitization studies).

Table 3 - This table should indicate the NESIL on which the IFRA limits were developed.



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 25, 2019

SUBJECT: Tentative Report: Safety Assessment of Benzyl Salicylate as Used in Cosmetics
(release date January 9, 2019)

The Council respectfully submits the following comments on the tentative report, Safety Assessment of Benzyl Salicylate as Used in Cosmetics.

Key Issues

DART - The description of the combined repeated-dose and reproductive/developmental toxicity study in rats is incomplete. Only effects at the high dose (300 mg/kg/day) are described. The DART section should also discuss observations at 30 and 100 mg/kg/day. The only significant effect noted at the low dose was lower pup weights on PND 4. Although the study authors considered this to be an adverse effect, it is not always considered an adverse effect.

This study was completed by Japan's National Institute of Health Sciences. The abstract says: "toxicity tests and hazard classification were conducted for screening assessment under the Japanese Chemical Substances Control Law." Therefore, it is not clear why the CIR report is referring to the EU REACH regulations.

Summary - The Summary should reflect the information presented earlier in the report and not present new information. For example, the Acute section includes one dermal study in rabbits, and one oral study in rats. In contrast the following sentences in the Summary suggests that there was also a dermal rat study: "The LD₅₀ for Benzyl Salicylate was >2000 mg/kg bw when 1.25, 2.5, or 5 g/kg Benzyl Salicylate was applied via a semi occlusive patch in three groups of rats. No clinical signs were observed after patch removal." Where is this study coming from as it is not presented earlier in the report?

The Summary presents the combined repeated dose and reproductive and developmental toxicity study (30, 100 and 300 mg/kg/day) twice, introduces new information about this study (lower body weights in offspring at 30 and 100 mg/kg/day) and does not present the

dose-range finding study (250, 500 or 1000 mg/kg/day) that is described in the Short-Term section.

Summaries of CIR reports generally do not include information from old reports. Does the information on benzyl alcohol belong in the Summary? This type of information is often included in tables in CIR reports.

Please revise the following sentence: "The phototoxic potential of 20 µl of 100% Benzyl Salicylate and 25% Benzyl Salicylate in methanol exposed to 6 groups of hairless mice resulted in no phototoxic effects." The Phototoxicity section describes two groups of mice in this study, with 6 mice/group (not 6 groups of mice as stated in the Summary). It would also be helpful to structure the sentence to indicate that the mice were exposed to Benzyl Salicylate rather than the Benzyl Salicylate was exposed to mice.

Discussion - What were the "other components of the skin" to which Benzyl Salicylate bound? This is not mentioned earlier in the report.

It would be helpful if the Discussion noted that sensitization potential of a compound is not dependent on function in cosmetic products. The IFRA standards for Benzyl Salicylate based on a sensitization QRA should be applied for all uses in cosmetics.

Additional Considerations

Cosmetic Use, Summary - As stated in a footnote to Table 3, the IFRA NESIL is based on a weight of evidence evaluation of the sensitization data. Therefore, in the Cosmetic Use section, it is not correct to state that it is based on a maximization test.

Dermal Penetration, In Vitro - As the composition of the receptor fluid influences dermal penetration, please identify the receptor fluid for the *in vitro* dermal penetration studies (references 20 and 7).

Subchronic, Oral, Benzyl Alcohol, old report summary - The first paragraph appears to be about a study in mice. Therefore, "Deaths of five rats..." needs to be corrected. In the second paragraph, please correct: "deaths of fives rats..."

Estrogen Effects - If the investigators (reference 23) looked for androgenic effects, theses studies should be described and the heading Estrogen Activity should be changed to Endocrine Activity. If they did not look for androgenic effects, "androgenic effects" should be deleted.

Irritation - How many subjects were used in the maximization pre-test with 30% Benzyl Salicylate (reference 7)?

Sensitization, Animal - What concentration was used for topical application in the maximization study in 8 test and 8 control Dunkin-Hartley guinea pigs?

How many positive reactions were observed in guinea pigs treated with 10% at 24, 48 and 72 hours?

Sensitization, Human - If available, mg/cm² doses and/or patch size (in addition to concentration) should be stated for the human sensitization studies.

Cross-Reactivity, Summary - This section says the subjects were induced with “hexyl salicylate”. In contrast, the Summary states that the subjects were induced with “cyclohexyl salicylate”. Which compound was studied?

Phototoxicity/Photosensitization, Table 5 - The table number needs to be added to the sentence that refers to the table. The study in humans should be added to Table 5. If this study is not added to Table 5, the sentence indicating that the studies are presented in the table should be moved after the Animal subheading.

Please provide references and a description of the light exposure for the studies in Dunkin Hartley guinea pigs (20 in the phototoxicity test; 25 in the photosensitization study).

Retrospective and Multicenter Studies - Is reference 36 the correct reference for the perfume screening study in 241 patients? The title given in the reference section is: “Cinnamic aldehyde test concentration”.

Retrospective and Multicenter Studies, Summary - The section summarizing retrospective and multicenter studies describes a study with Oxsoralen, while the Summary describes a study with trioxsalen. Are these supposed to be the same study?

Clinical Studies, Photoallergy - The light exposure should be described.

Summary - What species was used in a maximization pre-test in which 30% Benzyl Salicylate was administered in closed patch for 48 hours?

Table 4, Sensitization, Animal - In the description of reference 30, it is not clear that there was an intradermal injection. The first column describes an intradermal concentration, but the Procedure column only describes dermal induction patches.

Table 4, Sensitization, Human - If available, please provide patch sizes or mg/cm² doses. In the first study in this section, it is not clear why the duration of “approximately three weeks” needs to be stated twice. In the second study, please correct: “administrated”

Table 5 - The time of examination and the method of grading should be in the Procedure column not the Results column. Hartley Dunkin needs to be corrected to Dunkin Hartley. The light exposure should be stated for each study in this table.