Safety Assessment of *Zanthoxylum piperitum*-Derived Ingredients as Used in Cosmetics

Status:	Draft Tentative Report for Panel Review
Release Date:	May 19, 2023
Panel Meeting Date:	June 12-13, 2023

The Expert Panel for Cosmetic Ingredient Safety members are Chair, Wilma F. Bergfeld, M.D., F.A.C.P.; Donald V. Belsito, M.D.; David E. Cohen, M.D.; Curtis D. Klaassen, Ph.D.; Allan E. Rettie, Ph.D.; David Ross, Ph.D.; Thomas J. Slaga, Ph.D.; Paul W. Snyder, D.V.M., Ph.D.; and Susan C. Tilton, Ph.D. The Cosmetic Ingredient Review (CIR) Executive Director is Bart Heldreth, Ph.D., and the Senior Director is Monice Fiume. This safety assessment was prepared by Wilbur Johnson, Jr., M.S., former Senior Scientific Analyst/Writer, and Regina Tucker, M.S., Scientific Analyst/Writer, CIR.

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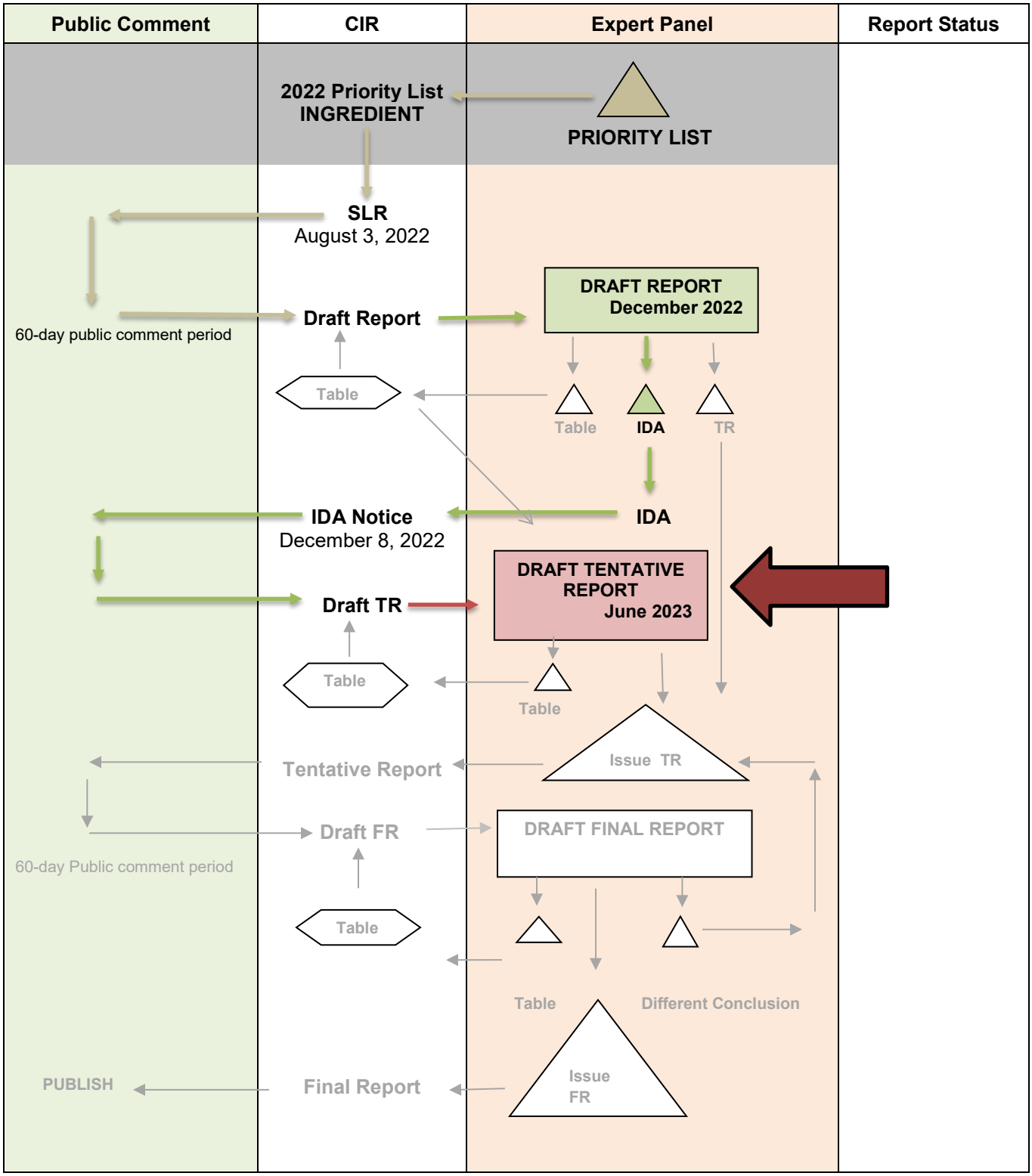
SAFETY ASSESSMENT FLOW CHART

INGREDIENT/FAMILY *Zanthoxylum piperitum* - Derived Ingredients

MEETING June 2023



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Memorandum

To: Expert Panel for Cosmetic Ingredient Safety Members and Liaisons
From: Regina Tucker M.S., Scientific Analyst/Writer, CIR
Date: May 19, 2023
Subject: Safety Assessment of *Zanthoxylum piperitum*-Derived Ingredients as Used in Cosmetics

Enclosed is a Draft Tentative Report of the Safety Assessment of *Zanthoxylum piperitum*-Derived Ingredients (identified in the pdf as *report_ZanthoxylumPiperitum_062023*) as used in cosmetics. At its initial review in December 2022, the Panel issued an Insufficient Data Announcement for the 4 *Zanthoxylum piperitum*-derived ingredients included in this report. In order to come to a conclusion of safety for these cosmetic ingredients, the following additional data are needed:

- Method of manufacture and composition Zanthoxylum Piperitum Fruit Extract and Zanthoxylum Peel Water.
- Impurities data for Zanthoxylum Piperitum Peel Water.
- Further concentration of use data, if available.

At the December 2022 meeting, Dr. Belsito provided CIR with additional published studies on *Zanthoxylum piperitum*-derived ingredients. These data, consisting primarily of additional composition details, have been incorporated into this report and are indicated by highlighting. Additional references were also identified within the provided studies as possible sources of relevant information. Most of the studies involved *Zanthoxylum piperitum*-derived ingredients that are not the subject of this review. However, they are listed on page 2 of this memo for informational purposes for the Panel. Please consider whether any are relevant for use in the report.

The following documents are also included in this packet:

- report history (*history_ZanthoxlumPiperitum_062023)*
- data profile (*dataprofile_ZanthoxlumPiperitum_062023)*
- search strategy (*search_ZanthoxlumPiperitum_062023)*
- flow chart (*flow_ZanthoxlumPiperitum_062023*)
- transcripts *(transcripts_ZanthoxylumPiperitum_062023)*

A draft Abstract and Discussion have been included in this report version. The Panel should carefully consider and discuss the data (or lack thereof), and issue a Tentative Report with a safe, safe with qualifications, insufficient data, unsafe, or split conclusion, and identify any additional items for inclusion in the Discussion.

Additional References for Consideration

- Hur JM, Park JG, Yang KH, Park JC, Park JR, Chun SS, Choi JS, Choi JW. Effect of methanol extract of *Zanthoxylum piperitum* leaves and of its compound, protocatechuic acid, on hepatic drug metabolizing enzymes and lipid peroxidation in rats. *Biosci Biotechnol Biochem*. 2003 May;67(5):945-50.

- Cho EJ, Yokozawa T, Rhyu DY, Kim SC, Shibahara N, Park JC. Study on the inhibitory effects of Korean medicinal plants and their main compounds on the 1,1-diphenyl-2-picrylhydrazyl radical. *Phytomedicine*. 2003;10(6-7):544-51.

- Gómez-Florit M, Monjo M, Ramis JM. Quercitrin for periodontal regeneration: effects on human gingival fibroblasts and mesenchymal stem cells. *Sci Rep*. 2015 Nov 12;5:16593.

- Eun-Sun Hwang, Gun-Hee Kim, Safety evaluation of *Zanthoxylum piperitum*-derived essential oil by assessing micronucleus abnormalities, mutagenicity, and chromosomal aberration, *Food Research International*, Volume 47, Issue 2, 2012, Pages 267-271.

- Jiang L, Kojima H, Yamada K, Kobayashi A, Kubota K. Isolation of some glycosides as aroma precursors in young leaves of Japanese pepper (*Zanthoxylum piperitum* DC.). *J Agric Food Chem*. 2001 Dec;49(12):5888-94.

- Li X, Kim HY, Cui HZ, Cho KW, Kang DG, Lee HS. Water extract of *Zanthoxylum piperitum* induces vascular relaxation via endothelium-dependent NO-cGMP signaling. *J Ethnopharmacol*. 2010 May 27;129(2):197-202.

- Sunohara Y, Baba Y, Matsuyama S, Fujimura K, Matsumoto H. Screening and identification of phytotoxic volatile compounds in medicinal plants and characterizations of a selected compound, eucarvone. *Protoplasma*. 2015 Jul;252(4):1047-59.

CIR History of:

Zanthoxylum piperitum- Derived Ingredients

August 2022

A Scientific Literature Review (SLR) on Zanthoxylum piperitum-Derived Ingredients was issued on August 3, 2022.

September 2022

Comments on the Scientific Literature Review were received.

Draft Report, Teams/Panel: December 05-06, 2022

Comments on the SLR and the following unpublished data, all received from the Council, have been added to the draft report that is included for the Panel's review.

- Method of manufacture and composition data on Zanthoxylum Piperitum Seed Oil
- Method of manufacture and composition data on Zanthoxylum Piperitum Peel Extract.

The Panel issued an IDA for the following 4 Zanthoxylum piperitum derived ingredients

Zanthoxylum Piperitum Fruit Extract
Zanthoxylum Piperitum Oil
Zanthoxylum Piperitum Peel Extract
Zanthoxylum Piperitum Peel Water

The additional data needed to determine safety for these cosmetics ingredients are:

- Method of manufacture for Zanthoxylum Piperitum Fruit Extract and Zanthoxylum Peel Water
- Impurities data for Zanthoxylum Piperitum Peel Water
- Further concentration of use data, if available

Draft Tentative Report, Teams/Panel June 5-6, 2023.

2023 VCRP updated.
Additional updates made based on published studies submitted by Dr. Belsito.

	***Zanthoxylum piperitum*-derived Ingredients Data Profile* –June 2023 – Wilbur Johnson/Regina Tucker**																														
						Toxico-kinetics		**Acute Tox**			**Repeated Dose Tox**			**DART**		**Genotox**		**Carci**		**Anti Carci**	**Dermal Irritation**			**Dermal Sensitization**				**Ocular Irritation**		**Clinical Studies**	
	Reported Use	**GRAS**	**Method of Mfg**	**Constituents**	**Impurities**	**Dermal Penetration**	**ADME**	**Dermal**	**Oral**	**Inhalation**	**Dermal**	**Oral**	**Inhalation**	**Dermal**	**Oral**	**In Vitro**	**In Vivo**	**Dermal**	**Oral**	**In Vitro**	**In Vitro**	**Animal**	**Human**	**In Vitro**	**Animal**	**Human**	**Phototoxicity**	**In Vitro**	**Animal**	**Case Report**	**Other Clinical Reports**
Zanthoxylum Piperitum Fruit Extract	**X**		**X**	**X**	**X**		**X**													**X**											**X**
Zanthoxylum Piperitum Oil			X	**X**	**X**																										
Zanthoxylum Piperitum Peel Extract	**X**		**X**	**X**	**X**																	*									
Zanthoxylum Piperitum Peel Water			**X**																												

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

* - indicates potentially fruit or peel

Zanthoxylum piperitum-derived Ingredients– 03/2023

Ingredient	CAS #	InfoBase	SciFinder	PubMed		FDA	EU	ECHA	IUCLID	SIDS	HPVIS	NICNAS	NTIS	NTP	WHO	FAO	ECE-TOC	Web
Zanthoxylum Piperitum Fruit Extract	97404-53-0	Yes		1/2		No	No	No	No	No	No	No	No	No	No	No	No	Yes
Zanthoxylum Piperitum Oil	97404-53-0	Yes		11/13		No	No	No	No	No	No	No	No	No	No	No	No	Yes
Zanthoxylum Piperitum Peel Extract	97404-53-0	Yes		0/0		No	No	No	No	No	No	Yes	No	No	No	No	No	Yes
Zanthoxylum Piperitum Peel Water	97404-53-0	Yes		0/0		No	No	No	No	No	No	No	No	No	No	No	No	Yes
Zanthoxylum piperitum + CAS No. 97404-53-0				24/70														Yes

Search Strategy

[*document search strategy used for SciFinder, PubMed, and Toxnet*]
[*identify total # of hits /# hits that were useful or examined for usefulness*]

LINKS

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

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

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

Botanical Websites, if applicable

Dr. Duke's https://phytochem.nal.usda.gov/phytochem/search
Taxonomy database - http://www.ncbi.nlm.nih.gov/taxonomy
GRIN (U.S. National Plant Germplasm System) - https://npgsweb.ars-grin.gov/gringlobal/taxon/taxonomysimple.aspx
Sigma Aldrich plant profiler http://www.sigmaaldrich.com/life-science/nutrition-research/learning-center/plant-profiler.html

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

Qualifiers

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

DECEMBER 2022 PANEL MEETING – INITIAL REVIEW/DRAFT REPORT

Belsito Team – December 5, 2022

DR. BELSITO: Okay. So, Zanthoxylum piperitum. There was a Wave 3 on this as well, to which I contributed. That's under -- down here. Okay.

DR. RETTIE: These abstracts mostly have to do with --

DR. BELSITO: Biological effects.

DR. RETTIE: -- a bewildering array of biological effects.

DR. BELSITO: But normally we put those in. But also, the Gwon paper had a number of references -- I think six -- to other papers that weren't included that looked at composition that I think need to be included. So if you look at the Gwon paper in the introduction, they refer specifically to --

DR. RETTIE: So, one of these that popped up here a couple of times in the abstracts here was the bone protective –

DR. BELSITO: Right.

DR. RETTIE: So I'm wondering about are there preparations where, like a gel is rubbed on your gums? And if there is, is that something that comes under this committee's purview?

DR. BELSITO: Depends upon if it were marketed as something that would improve -- that would change the structure, then it would not come under our purview, it would be considered a drug. So I would think it would be hard to come up with something that was saying that it would improve, you know, bone resorption or something and be a cosmetic.

DR. RETTIE: Under drugs then.

DR. BELSITO: Right.

MS. FIUME: So Don, for the information for a lot of it that you had forwarded; typically, what we have been doing is if these papers demonstrate this activity, we will include it under non-cosmetic use because it wasn't really affecting cosmetic safety. Is this something you'd want to see more in depth under other relevant reports or is reporting these types of activities okay under non-cosmetic use with the reference?

DR. BELSITO: Yeah, I mean, I think it can be put under non-cosmetic use, but just to know that -- because normally we look at, you know, other biological effects: immunomodulatory, anticarcinogenesis, things like that. And one of the reports was on anticarcinogenesis. So, I just thought that they were the types of things that normally we would put into a report.

DR. SNYDER: Well, certainly additional composition data should be gleaned from those.

MS. FIUME: I guess, specifically, I was talking about the papers maybe addressing rheumatoid arthritis or periodontal disease.

DR. BELSITO: Right.

MS. FIUME: We might say that these are used to address periodontal disease just with a citation and no detail, under non-cosmetic use. So, for those types, is that sufficient or would you want details somewhere in the report?

DR. BELSITO: You know, I mean, I'm fine with mentioning it, I mean, that we're aware of it. Because it is -- you know, my understanding of how we address these botanicals are obviously, there were a number of papers that we're looking at specific ingredients that were extracted. I didn't include those. But when there is information about the whole plant, because that's what we're looking at, we usually include that data.

So that's why I sent them along because those specific articles were looking at whole plant extract, not just a specific chemical from the plant. Certainly, and potentially, in levels much higher than what we're looking at.

But in the Gwon paper, the one that looks at the effect on adipocytes and weight loss, there are a number of references talking about aliphatic acid amides, terpenoids, flavonoids, alkaloids and other phenolics that I didn't have time to look into, but they may give us more information about composition, which we're really lacking here. So, I think we need to look into those.

MS. TUCKER: And so with the Gwon paper, my understanding is that you would like to see that data reflected in the non-cosmetic use section?

DR. BELSITO: Well, for the effect on adipocytes, Regina. But if you look, there's reference 13, 14, 15, 16, 17 and 18 and 19 that may shed light on composition that haven't been included in this report.

MS. TUCKER: Okay. Sure. Sure. And I do think I was able to look at one of the references on flavonoids. So, I can go back through and look at those.

DR. BELSITO: Yeah. Because right now, as it exists, this is really the first time that we're looking at this. One of the questions that CIR was asking us is whether we wanted to look at Zanthoxylum piperitum seed oil, should be included in the report. My original impression was, no, not if it only functions as a flavor or fragrance, but it is a component of the extract, as I understand it. So, I think we sort of have to look at the oil to understand the whole extract.

DR. SNYDER: The extract is GRAS, right?

DR. BELSITO: Right. So, you don't think we need to look at the oil?

DR. SNYDER: Well, I think we can add it but I don't -- I mean, that's what I had a question by, I have to see the whole report. It's a very different composition versus the fruit of the peel, which are the other original four ingredients are deriving from. So that was my only question was in regards to adding it because the composition is different.

DR. BELSITO: True. Okay.

DR. SNYDER: I mean, it's GRAS, but it's a component of the extract, which is GRAS.

DR. BELSITO: So, then don't include the oil because we're clearing systemic toxicity by saying that the fruit and the peel are GRAS?

DR. SNYDER: Well, no, the extract, yeah. Yeah, I do -- I have extract as GRAS. I don't know if that just means the fruit or the peel extract.

DR. BELSITO: Well, it later on goes to say --

DR. RETTIE: I found this one very difficult to work through with all the different types of extracts that were discussed.

DR. BELSITO: Right.

DR. RETTIE: Even getting to the point for the peel extract, where there were I think three extract procedures provided. And I just had no idea which one was relevant to the products that we were --

DR. BELSITO: It's a huge problem for this panel, Allan, and also for, you know, the fragrance panel. Because depending upon what you extract these plants with, it can result in something totally different as you see.

DR. RETTIE: And they used t-butyl ether for one, set of extracts, methanol for another. And you would expect -- and the composition tables reflect a different composition for those two extractions. But then there's a third one, a butylene glycolic extract. And there was there no information about the constituents that one peels over that. So what would you do with that?

MS. FIUME: You can split the conclusion based on solvent. I think we've done that in the past.

DR. RETTIE: Can we get the information about the 12 peel extracts that are in use, and know which extraction process they refer to? Or if all of them cover? Can we get that info?

MS. FIUME: It can definitely be asked for. And when the writer knows what the solvent is, we do try and include that in the text in parentheses.

DR. BELSITO: But before we get into that, is the decision of our group not to include the oil because it's only a flavoring fragrance? Is that what we want to do?

DR. SNYDER: Yes. And it's a significant different composition.

DR. BELSITO: Okay.

MS. TUCKER: So the decision is not to add the seed oil --

DR. BELSITO: For us.

MS. TUCKER: -- in part due to the composition?

DR. BELSITO: So we're going to delete that from the list of the ingredients we're reviewing. Not only because of the composition, but simply because it's a fragrance flavoring and that's not our purview.

MS. TUCKER: Thank you. So, on my end I just would like to make sure that I have everything reflected. The data that you submitted, Dr. Belsito, I'm going to place that data appropriately throughout the document so that the information is reflected for the panel. And we're not adding the seed oil, in part, because of the composition and it's not in our purview. Thus far, is there anything that I'm missing?

DR. BELSITO: Yeah. We're still going through it.

MS. TUCKER: No problem. Got you.

DR. RETTIE: One of the ingredients is peel water.

DR. BELSITO: Right.

DR. RETTIE: And I wondered if -- what did I write here. Is peel water covered by the --

DR. SNYDER: By the extract.

DR. RETTIE: -- by the more aqueous extract? Is that the moisture that we saw in another one, in the water?

DR. BELSITO: Yeah. Sometimes you get information on that by the description of the material because we have no method of manufacture, right?

DR. RETTIE: I don't think we have any information on composition on peel water.

DR. BELSITO: Right.

DR. RETTIE: We have an ethanolic peel extract. I'm not sure we have much in the way of composition for that one.

DR. BELSITO: Yeah. What we have on peel water is, it's the aqueous solution of the steam distillate obtained from the peel. And for the peel extract, we have it's the extract of the peels. And the information we have on the extracts were all with organic solvents, not with water. So one would expect that the water might be very different from the peel extracts, no?

DR. RETTIE: Well, even at the level of the organic extracts, if you look at the composition table for the fruit pericarp ethyl acetate extracts, it's a listing of half-a-dozen dodecatrienamides that are not reflected in the more limiting general acetate components of everything else. So, it just all seems to be up in the air as far as composition is concerned. I couldn't easily move from one to the other to feel like I knew what was going on.

DR. BELSITO: Okay. But we're looking at whole plant and from what I can gather --

DR. SNYDER: With a max use of .0022 percent.

DR. RETTIE: Yes.

DR. BELSITO: The fruit and the peel are both food uses. Correct?

DR. SNYDER: Yes.

DR. BELSITO: And so they're GRAS. So that normally gets rid of tox endpoints.

DR. RETTIE: Yeah.

DR. BELSITO: So then you're looking at sensitization and irritation.

DR. SNYDER: And 2 percent on the extract.

DR. BELSITO: Right. But I had a question about that. The data was not published on that. And why aren't my notes connecting to the areas -- so the data on the sensitization was not published. So, we don't know if this included the fruit and the peel or just the fruit. Is that correct? Because I tried looking for it.

So, this was a super critical carbon dioxide extract of Zanthoxylum piperitum. It was 2 percent HRIPT. It was just a comment. If it was in the report that you saw, what was -- was it the fruit, the whole plant? Do you know, Regina?

DR. SNYDER: Food extract, peel extract or the whole thing?

MS. FIUME: So Regina, I think this is referring back to your question in the intro for the NICNAS report, is that it's unclear, right?

MS. TUCKER: Yes. So, it was unclear. It just says the extract, so we don't know which extract it was.

DR. BELSITO: Okay.

MS. FIUME: So, we've noted that in the introduction.

DR. BELSITO: So, it should be noted here too.

MS. TUCKER: Okay.

DR. SNYDER: Unspecified.

DR. BELSITO: Right. So, does that help our sensitization or are we asking for additional sensitization?

DR. SNYDER: That's at 2 percent and we're at .00.

DR. BELSITO: Right.

DR. SNYDER: .01 for the fruit and .002 for the peel max, so I would think that would be sufficient. The composition is similar.

DR. BELSITO: Well, we're going to go with formulated to be non-sensitizing because it has terpenes, right?

DR. SNYDER: Yes.

DR. BELSITO: So, I thought in the discussion, first of all, we need the botanical and respiratory boilerplates. That it's GRAS, so you know we have some tox endpoints but we feel they're cleared by the GRAS status. We're eliminating the oil. We have sensitization on an extract. We're not exactly certain what it's an extract of, but it was done at two percent and max use concentration is at --

DR. SNYDER: .01 for peel.

DR. BELSITO: .01. And I guess we could go insufficient for ocular toxicity, but I don't think so since we only ask for it if available. It has terpenes, so it needs to be formulated when non-sensitizing. So, my question was can we go ahead where the safe as used or does the manufacture and composition, for the fruit and peel, really bother you? I didn't think so because of the GRAS status for these, but.

DR. RETTIE: It only bothered me because the composition data was all over the place for the different ingredients. I was flailing around thinking what to do.

DR. BELSITO: So, then let's go back to the tables which we're being asked to look at here.

DR. SNYDER: Use tables.

DR. BELSITO: Use tables. And quite honestly, I think both tables are extremely useful. First, it's helpful for me to look for certain endpoints and the second, to see specific areas of use. But in this case, I was really shocked by the fact that they were getting use in only one of the body and hand spray for the fruit extract.

You know, has this happened before where we're assuming that -- I mean, there are 70 moisturizing products out there and we have no reported concentration of use. There are 52 face and neck, we have no reported concentrations of use. Without that kind of table, I wouldn't know how poor the response from industry is. This is disturbing. Has this happened before and we've not been made aware of it or?

DR. EISENMANN: It happens all the time because I'm only surveying the people that will respond to the surveys. I mean, I've tried to reach out to -- it's not ICMAD anymore, but that group and I just don't get many responses.

MS. KOWCZ: IBA.

DR. EISENMANN: Yeah.

DR. BELSITO: I'm sorry, I didn't hear you.

DR. EISENMANN: Independent Beauty Association is what they are now. I've tried reaching out to them to get them to participate also.

MS. KOWCZ: That would be good.

DR. EISENMANN: I could only get some smaller companies, I really don't get much of a response from them, if any.

I mean, as we go, it's getting more and more that I get -- you know, the high use ingredients, yeah, I get a reasonable response. But these ingredients that have fewer uses, a lot of our companies are not using them, so I don't get a response.

DR. BELSITO: But they don't have fewer uses. In the case of the fruit extract, I mean, the majority of uses, we have no reported concentration.

DR. EISENMANN: It's just the companies that -- I mean, there's plenty of companies that participate in VCRP that aren't our members.

DR. RETTIE: So, we can't evaluate those maximum concentration of use in .01 percent reported for an extract when there are no reports for substitutes.

DR. BELSITO: So, how does this work? When we say safe as used, when it's used in 70 moisturizing products and we don't know the concentration, does that mean it's safe as used up to .01 percent because that's the highest concentration?

DR. SNYDER: That's what it means.

MS. FIUME: Yeah. Because it's as reported in this document.

DR. SNYDER: As reported.

MS. FIUME: I mean, we can add a paragraph in, if you'd like, to state that this is the only concentration of use reported and therefore that's what is being considered for the conclusion. But that's what our conclusion means.

DR. SNYDER: What's more alarming to me were there were 180 uses and only six reported at .1 percent.

DR. BELSITO: That's what I mean. That's the vast majority we don't know what they're being used at.

DR. SNYDER: Right. I mean, I wish there was a way we can combine the two tables because I'm so used to looking at the old tables of what data needs I'm going to look for in the report. But this new table format is hugely informative and it has made me aware of just what Don brought up, I couldn't see that before.

DR. BELSITO: Yeah, I mean the old table are good because they tell us, okay, this is what I'm looking for, for tox endpoints. This is what I'm looking for, for sensitization, irritation endpoints to clear this and I can do it very quickly as opposed to the new tables where --

DR. SNYDER: Yeah, because the leave-on and rinse off is the first thing I go to.

DR. BELSITO: Right.

DR. SNYDER: Because I look for the max concentration for leave-on. And then that by fault tells me where I want to go for tox data and for sensitization data.

DR. BELSITO: Right.

MS. FIUME: So my concern was based on how products have changed, we include that, but we don't know -- I don't feel confident that it's truth because every shampoo is being listed, and every conditioner is being listed, as a rinse off --

DR. BELSITO: As a rinse off. And there are dry shampoos.

MS. FIUME: -- and non-aerosol. Right. So, that's where -- I mean, obviously, you know, I took up the torch of trying to change tables because I was concerned that we weren't capturing the information correctly. That's why I tried to add at least a likely exposure site so that the area of skin, but --

DR. SNYDER: Well, in doing so, you brought to our attention another deficiency.

MS. FIUME: I just don't know how to accurately capture the true leave-on concentration, which is what would be the one that would concern me because if we only have shampoos and it's used at 40 percent, we're capturing that as a rinse-off, but it may not be. Or if it's conditioner -- I should say a conditioner. It may not be.

DR. BELSITO: Right. But just like you say, it's not possible, or it may be a spray but it's not specified, you could do another footnote to say that it's reported as a shampoo use, presumed to be rinse off but not verified or something like that.

MS. FIUME: Would a good compromise be rather than -- I don't know if that would give you any information. Let's say we could identify the possible types of spray, powder, leave-on/rinse off, but then if we don't include a concentration, then that's not giving you any information either.

DR. BELSITO: Right. No, I mean, it's just that the old tables, you know, what you're hearing from Paul and I is that they set our mind to look at specific tox endpoints with those in mind. Knowing that, you know, particularly with shampoos, so now we need to then look at a shampoo and also think about, well what if it's not diluted? But the other table is nice, draws attention to the fact that --

DR. SNYDER: We don't have a lot of data.

DR. BELSITO: -- we don't have a lot of data.

DR. EISENMANN: One thing to note, when I do send out the surveys, I have been including that shampoos are listed as rinse off. So sometimes people put dry shampoos into other hair care products rather than shampoo.

I mean, but that can't guarantee what they're telling me, though, because I don't have access to their database. So I don't really know for sure, you know, how everybody classifies their products. But I do let them know how CIR has been putting it as rinse off versus leave-on. Whether or not they pay attention to that, I don't know that.

DR. SNYDER: I mean, the top table, you look at it and it says leave-on 157 uses, .01 percent and six uses at .022. But then when I looked at the bottom table, I was just struck by that concentration of use represented so few of those ingredients. And I've never looked it that way previously.

MS. FIUME: We've had discrepancies between VCRP and concentration of use. This is the first one that I can recall that there's only been one concentration of use reported for something that has so many uses. It may have happened once before because that's where we even tried to call it out -- in text -- saying even though this has the highest, you know, use report in the VCRP, this is the only use reported in the concentration of use survey.

DR. SNYDER: I think that needs to be in the discussion with the data that we're looking at.

DR. RETTIE: It seems to me some consolidation of Tables 8 and 9 might be considered, where you mostly have everything in Table 9 but you just add this first part here, this leave on and rinse off section gets incorporated in there at the top. And maybe, you just mentioned the maximum concentration of reported use up there as well.

DR. BELSITO: But what Monice is saying, is that the concern that has been building with her over time, is that very frequently she's just guesstimating that it's a rinse off when she doesn't actually know that it's a rinse off. And therefore, there could be inaccuracies in the table. But I think for us, it is helpful, and we would know that -- I guess we don't know from looking at categories, but then we would know from Table 2 the range for shampoos, non-coloring.

DR. SNYDER: Does it have to be an either or, could we have both?

DR. BELSITO: No. That's what I was saying.

DR. SNYDER: I didn't think of that until you said that. I mean, I hate to give people more work.

MS. FIUME: This is the second time where I've tried to streamline. The writers are going to want to strangle me at some point because I'm like, we can give them this option, which is better. And they both went, eh. It's whatever provides the best information for you as you review it is what we want.

DR. BELSITO: Yeah. I think in this case, when you look at it, you go down to shampoos, we don't have any reported concentrations. So I mean, if it's used in higher than .01 in a shampoo, whether it's a leave-on or a rinse off, that's what we're looking at.

You know, my major concern is, and I think we need to craft some language for the discussion, simply saying that -- and this table brings it out very nicely -- that where there are reported uses and we have no information on concentration, our assumption is those reported uses aren't exceeding .01 percent. And that should go into every discussion that we write. Just like we have a botanical boilerplate, we have a respiratory boilerplate.

DR. SNYDER: Yeah, I had a note that it could say in the conclusion, you know, that as we say --

DR. BELSITO: Safe as used.

DR. SNYDER: In this instance, I feel a little uncomfortable with that because that gives a false -- somewhat of a false pretense that it's -- we have a lot of uses.

DR. BELSITO: Yeah, because we don't know what the use concentrations are in a huge number of products.

DR. SNYDER: It far exceeds what I would be comfortable with, especially in those other product categories.

DR. RETTIE: So the phrase, safe as used at maximum concentration of .01 percent --

DR. BELSITO: Yeah, we used to do that for when we had sensitization endpoints, you know, that -- we would just go with the highest endpoint that we have. And then we used to do it for irritation, but we definitely got rid of it for irritation because irritation is all going to be about how it's formulated. So you can formulate to be non-irritating. Like lactic acid is irritating, but if you put into formulation and it's a lactate salt.

DR. RETTIE: It's non-irritating.

DR. BELSITO: Yeah. So, where are we going here? They're GRAS, so we don't need systemic toxicity.

DR. RETTIE: But are you also saying that because it's GRAS you're happier with wiggle room on the method of manufacture?

DR. BELSITO: Yeah.

DR. RETTIE: Okay. That's a new one for me.

DR. BELSITO: That's sort of how we've been operating.

DR. SNYDER: Yeah, the botanicals are just unique. We're still blazing the trails so to speak.

DR. BELSITO: But I see your point, Allan, because extracting them is very different from eating a whole plant.

DR. RETTIE: Yes, sir. Concentrating lipophilic component with methyl t-butyl ether definitely were different. Just eating the plant, those things are (inaudible).

DR. BELSITO: So, what are you suggesting? I mean, we rely on you for this type of stuff.

DR. RETTIE: I prefer more information on the method of manufacture. Ask for that and then we can run it through.

DR. BELSITO: Okay. So, a little more information on manufacturing and composition of the fruit and peel ingredients.

DR. RETTIE: And we are missing any kind of composition for the peel water, although we might be able to guess what that is from the methanolic extracts of the peel water, so maybe we don't need that.

DR. BELSITO: We're going insufficient.

DR. SNYDER: We ask for whatever we want.

DR. BELSITO: We ask for whatever we want.

DR. RETTIE: Okay, MOM for the peel water as well.

DR. BELSITO: So more information on manufacturing and composition for fruit peel and peel water.

DR. RETTIE: Did you decide on ocular irritation or only if it's available?

DR. BELSITO: Yeah. We're going to hold off on systemic endpoints at this time? Okay.

DR. RETTIE: There's just a place in the text where there's a reference to constituent sanshool and shamshoolamite (phonetic). It might be samshoolamite (phonetic). I was curious why either of those didn't turn up in any of the composition tables since they seem to be the most important systemic components after oral at least. Did you see anything about that?

MS. TUCKER: I didn't see anything about that. And what I had -- I reported it as it was. So, if it wasn't reflected in that manner, that meant that's not what was available in the data.

DR. RETTIE: Okay. I was just interested in them because it seemed that they were more like the capsaicin compounds that might cause irritation. The only other note I had was that there's some LogP data that's --

MS. TUCKER: Could you repeat that? I'm sorry.

DR. RETTIE: There's some LogP data that presented in the text. As it stands, I think it's maybe a little misleading because they just cherry-picked a few of the compounds a few of the terpenes. So I don't know, maybe that could be refined.

MS. TUCKER: Refined. Okay. I noticed that. Thank you.

DR. BELSITO: What's the issue with the LogP data, Allan? I missed that. I'm sorry.

DR. RETTIE: Oh. The table divides petition coefficient ranges from 2.9 to 3.9 and from 4.2 to 4.4. But those are described that they're specifically for the aliphatic terpene constituents and the aliphatic cyclic constituents. But there's a whole range of compounds in here that there's no information for and it would be likely impossible to get it. So I rather wondered what the value was of printing the LogP, or specifying the LogP, for those particular constituents. It might be as simple as to leave it out. I don't know what to do.

I mean, it does say, I guess, clearly, that these things are going to get dermally absorbed because they're small and they've got an appropriate lipophilicity. So maybe it's just as fair to even then specify the way that you've done. That's all I have.

DR. BELSITO: And that's in which table, Allan?

DR. RETTIE: That's on Table 2. Right above it, it estimates the water solubility from a ridiculously low number to a number of two grams per liter. So that's definitely not being captured by the LogP values in the line below it. So it's just a little disconnect.

DR. BELSITO: Yeah. I see what you're saying. So let me recap where we are so far. We're going insufficient with these, despite their GRAS use, for more information on manufacturing composition for the fruit, the peel and the peel water.

At this point, we're not asking for any additional tox endpoints. We have the HRIPT at 2 percent. We're going to go formulated to be non-sensitizing anyway, so we're okay there. And that's basically our own insufficiency, that is manufacture and composition, correct?

And then in the discussion, the botanical and respiratory boilerplates, ocular irritation, if available, because it has eye uses, discussed the sensitizer so formulated to be non-sensitizing. And introduce boilerplate language to say that we're assuming that in the multiple product categories, for where we have no concentration of use, that the maximum is at 0.1 percent.

DR. SNYDER: And in that discussion, Don, if you look at Table 2 and Table 3 on page 17 --

DR. BELSITO: Yeah.

DR. SNYDER: So, Table 2 is that supercritical carbon dioxide extract of which we have nothing on.

DR. BELSITO: Right.

DR. SNYDER: And then Table 3 is of an extract not otherwise specified. So, that composition data is not on that same supercritical carbon dioxide extract -- or now down below it does say that.

DR. RETTIE: The next line.

DR. SNYDER: Oh, below. I see it now. Okay. So we have -- the data we have on is the extract we know the least about. We don't know what it's an extract of.

DR. RETTIE: The rest of the report goes to some lengths to define fruit extract and pericarp and everything, but what is the ZP extract?

DR. SNYDER: So Table 2 and Table 3, we don't know whether that's a --

DR. BELSITO: That's what I was asking.

DR. SNYDER: -- seed or a fruit or -- yeah. I just noticed that, yeah. So we may not have any properties or composition data on what's actually being used. If this doesn't represent the peel or the fruit, then we essentially have no data, other than Table 4, I guess, we got some fruit, pericarp.

DR. RETTIE: Table 1 defines -- gives definitions of structures, but it misses the definition of the ZP extract.

DR. BELSITO: And it almost looks like that could be the one that was used for the HRIPT, right, because that was a supercritical extract as well.

DR. SNYDER: Yes.

DR. BELSITO: Looking at the composition of this, I almost wonder if it's not the oil that they're looking at because it's going to be highly fragranced. If it's 30 to 50 percent linalyl acetate, 10 to 20 percent linalool, 5 to 10 percent limonene, those are all fragrances.

DR. SNYDER: Almost probably certainly is.

DR. BELSITO: Yes.

DR. SNYDER: Which is even less informative to us.

MS. TUCKER: It's simply identified in the NICNAS document as -- the marketing name is Pepper Sichuan Extract. The chemical name is Zanthoxylum Piperitum Extract. But that was the only information that's given. I don't think there's a clear definition anywhere of what it is.

DR. EISENMANN: But generally, CO2 extracts are very similar to the essential oils.

DR. SNYDER: Yep.

DR. BELSITO: Which we've said we're taking out of this report.

MS. FIUME: The peel oil will remain. The seed oil is not being added is what I thought.

DR. BELSITO: Yes.

MS. FIUME: The peel oil was exiting in the report, the seed oil was a possible addition.

DR. BELSITO: Okay.

DR. RETTIE: I'm sorry, you said peel oil, specifically?

DR. BELSITO: Seed oil.

DR. RETTIE: Oh, seed oil.

DR. BELSITO: Seed oil is not.

MS. FIUME: Oh, I'm sorry, the oil in general, which is obtained from the fruit and fruit pericarp, is in the report as it currently stands.

DR. BELSITO: So, Zanthoxylum piperitum oil is the oil from the fruit and pericarp.

MS. FIUME: Yes. And there is a CAS number in the NICNAS document, but all four ingredients have the same generic CAS number, including the oil. The oil and the extracts all have the same generic CAS number.

DR. RETTIE: To your point, comparing Table 3 and Table and 5, constituents, as you said, very similar from the CO2 extract to the oil itself. Heavy in linalool, linalyl acetate and limonene, in both.

MS. FIUME: So then those data may actually be on the oil and not one of the extracts?

DR. RETTIE: Might be.

MS. FIUME: Which would mean then there's no sensitization data on the extract, just possibly on the oil.

DR. BELSITO: But it says here in Table 1 that the Zanthoxylum piperitum oil is only a fragrance ingredient.

MS. FIUME: It is, but we don't have any clarification from RIFM that's it's under review.

DR. BELSITO: It's not.

MS. FIUME: So, if it's not, then we go forward with it in our documents, which is what we've been doing --

DR. BELSITO: Okay.

DR. SNYDER: We state that in the intro.

MS. FIUME: Yes.

DR. BELSITO: Okay. So then we are including the oil. Then why aren't we including the seed oil?

MS. FIUME: So it's at the panel's discretion. Right now, as it stands, the four ingredients in the report are fruit or peel. So I don't know if -- I don't know enough about it to know if the fruit -- when you're looking at the extract of the fruit, does that include the seed? But it's up to the panel if they want to include it.

It originally was not because it appeared to be a different plant part, but the panel is more than welcome to include it if you want. And what is the piece of data that we have? It was method of manufacture and composition of the seed oil. And that's on PDF Page 26.

If you decide to include the seed oil, that is data that would be added into the report. Currently, it's not in the report. I'm correct in assuming that, right, Regina? It's probably not in the report.

MS. TUCKER: No, it's not.

MS. FIUME: Do we know, is the seed oil in use in the VCRP?

DR. SNYDER: Supposedly only as a fragrance.

MS. FIUME: It's function -- I'm just wanting to see if it has a reported use in the VCRP.

DR. BELSITO: But also the oil is supposedly (inaudible).

DR. SNYDER: And we don't have any use data on it.

DR. BELSITO: Right.

DR. RETTIE: So, for the extract of the seed and the seed oil, it doesn't specify but I'm assuming that it's alcohol with water extract based on what's in the bottom of the table on PDF 26. Seed oil and alcohol and water.

DR. BELSITO: Right.

DR. RETTIE: But they're three separate ingredients or?

DR. BELSITO: No. It says it's the raw material added with alcohol/water mixture. That's how I read it. It's soaked, it's extracted, it's filtered, it's concentrated and that's what's left.

DR. RETTIE: So it's soaked in alcohol and water.

DR. BELSITO: Yeah.

DR. RETTIE: And that's the extract.

DR. BELSITO: That's how I read the table.

DR. RETTIE: That's how I read it too. So, it's a highly aqueous extract. It's not really an oil, at the end the day. It's an extract of the seed of it. It's got a very different composition from the seed oil.

DR. EISENMANN: And this is what the company has requested as a name. It doesn't mean that's what they'll get as a name.

DR. BELSITO: They're requesting?

DR. EISENMANN: That's what it looks like to me that they haven't -- it says trade name requested. So in other words, this hasn't received an official INCI name yet. And I don't know if it's in the process, I'll check with Joanne (phonetic) when we get back. So it might be called an extract, but if the INCI Committee gets to it they might call it an extract instead of an oil.

DR. RETTIE: Because there's no destination here.

DR. EISENMANN: Correct. Which would be an essential oil. Right.

DR. RETTIE: It's just an aqueous.

DR. EISENMANN: Right.

DR. BELSITO: So, the seed oil is currently not listed in the INCI dictionary?

DR. EISENMANN: Correct, as far as I know. Or is it?

MS. FIUME: I believe -- let me double-check. Because I think I just looked up the definition there.

DR. EISENMANN: It could be that this company doesn't have their name listed.

MS. FIUME: The seed oil is in the INCI dictionary. There are no reported uses in the VCRP. I think it's a brand new name based on the monograph ID, it's like, 37,000. And Carol, because this is your data -- industry -- you understand it better. With the nomenclature, does it mean that this is actually -- they're requesting it as a mixture to be submitted? Is the data actually on a mixture?

DR. EISENMANN: Yeah. The data -- they're requesting the name be the oil, alcohol and water. So if you put the material in, you have to put all three on your label.

DR. BELSITO: I am confused.

DR. RETTIE: I spent more time on this one than I did with all of the others.

MS. FIUME: The writers always are as well. I think this comes down -- well, to me, it's more clearcut with the extract when I'm looking at the data, where a lot of times the extract is one small part of botanical and a huge part of solvent. Based on this manufacturing process --

DR. SNYDER: All extracts.

MS. FIUME: -- the trade name is seed oil. But that trade name actually refers to a mixture of the seed oil, alcohol and water. Now, within that mixture is 98 percent of the seed, 1.4 percent alcohol and .7 percent water. So it's essentially a seed.

DR. RETTIE: A seed oil. Yeah. The alcohol and water is just coming along for the ride because they were residual in the final prep.

MS. FIUME: But as far as composition, it doesn't go anything -- it gives the composition of the mixture but not the composition of the botanical ingredient itself.

DR. SNYDER: Right. Right.

MS. KOWCZ: Since this the first review, can I just suggest that we will ask for everything that Dr. Belsito just asked for? And then we can get more information, as much as we can, but I wouldn't hope for too much. We can find out from the INCI Committee, they have not, obviously, looked at this because the name has not been branded. So, we'll find out whatever we can to help the panel.

MS. FIUME: But as the report goes forward, for right now, then Dr. Belsito exclude the seed oil as an ingredient and go with the four that are currently in the report until more information is received?

DR. BELSITO: Well, I mean, I think what Alex is saying is putting the seed oil in and request from the INCI committee where they're going.

MS. KOWCZ: Right. Exactly. Where they're going and what have they found. Maybe they have more information than we have right now. I mean, that's the best we can do, Monice, at this point.

MS. FIUME: But what I'm saying is the seed oil is not currently included in the report. It's been requested to be included.

MS. KOWCZ: Well, it's in your trade name requesting.

DR. EISENMANN: That's the problem, though, that the seed oil that you've got information on is probably not a seed oil, as defined in the dictionary. Because the dictionary does define it as an essential oil.

MS. KOWCZ: Yeah. And from the method of manufacture, it doesn't look like it is.

DR. EISENMANN: Right. The method of manufacture of the one we've gotten information doesn't look like that's what it is, even though that's their suggested name for it. So, you can include the seed oil, but it would not be -- you'd be making sure that the oil you're reviewing is the essential oil and not that water/alcohol extract.

DR. BELSITO: Okay. So, if we ask for seed oil, it would not really be the product that we have this method of manufacturing on that they're calling a seed oil, because it clearly is not being manufactured to produce oil?

MS. KOWCZ: Exactly. You're absolutely right.

DR. BELSITO: So, this company is asking for their product to be listed in the dictionary. We don't know how the INCI Committee will list it. So, do we even want to consider -- and they're coming to us to ask us to include this product in our consideration.

So, we can say we are not going to look at seed oil; however, we will look to see what the INCI committee calls this material. Is that fair? Is that what you're requesting, Alex?

MS. KOWCZ: Right. That's what I think would be very helpful here.

DR. SNYDER: I think what it comes down to is this review covers the fruit and the peel. We would have to then open it for the seed.

MS. KOWCZ: Yes.

DR. SNYDER: Irrespective of the INCI, right? So it would be the three components: the seed, the peel and the fruit. We have enough data on the fruit and the peel. And so, irrespective of the oil or whatever, we need data on the seed in order to consider

anything related to the seed. We could say the seed is safe as used and then that whole nomenclature doesn't matter, right? Because if we get data on the seed extract, composition of the seed and -- right?

MS. FIUME: Yes. But two factors to consider are we don't have that information currently, the ingredient is not in use and you would be adding an ingredient that has no information and no use in expanding your IDA based on that.

DR. BELSITO: If we were to include seed oil?

MS. FIUME: Seed oil, yes.

DR. BELSITO: So, but what I'm hearing Alex asking for is to say we are not including seed oil. So, that is what you're saying. But we will await the INCI nomenclature committee's decision about this specific extract -- which they're calling a seed oil that doesn't appear to be a seed oil to us -- to determine whether to include it in this report.

MS. KOWCZ: If that's suitable for you and if it's acceptable to you. I think that's the best way to go.

DR. BELSITO: Yeah. Okay. So, await INCI --

DR. SNYDER: Clarification.

DR. BELSITO: -- nomenclature clarification for alcohol, water, seed extract. Is that a seed oil or not? And we're not including seed oil. Okay.

So, what I have in discussion, botanical and respiratory boilerplates. It's GRAS but we're concerned by the lack of manufacturing -- or the discrepancies and what is the final outcome of extraction methods. So, we would like to know more about the method manufacturing.

It does contain sensitizers, so would be formulated to be non-sensitizing. ocular toxicity, if available. And construct some boilerplate language that we're aware that there are multiple product categories without concentration, but we're assuming max concentration as reported in this document to be 0.1 percent across all categories.

MS. KOWCZ: (Inaudible).

DR. BELSITO: Yeah.

MS. FIUME: And then Don, I wasn't sure if this was an additional consideration for a need, in that it's not clear what's being called Zanthoxylum piperitum extract in that document. Did I understand it may actually be the oil or possibly could be the oil?

DR. BELSITO: The supercritical extract, yes.

DR. RETTIE: It could be the fruit, couldn't it? It could be the whole --

MS. FIUME: It could be -- okay. So, I just didn't know if anything was needed on the fruit extract or peel as far as sensitization goes. But it sounds like what is there is acceptable.

DR. SNYDER: Well, we like that Table 1, or whatever it is, to define the supercritical carbon dioxide extract.

DR. BELSITO: Yeah.

DR. RETTIE: To define just the extract.

DR. SNYDER: Yeah, what is that?

DR. RETTIE: Because it doesn't have anything in front to extract other than the --

DR. BELSITO: But we know from NICNAS that it's not further specified.

MS. FIUME: Right.

DR. BELSITO: So, we're not going to get that information, that's the problem. So, if we're not going to get the information, do we then need sensitization and irritation? I mean, sensitization is almost like a no-brainer. It's like asking for sensitization on a hair dye, which is exempt, because we're going to say when formulated to be non-sensitizing because it has terpenes.

Given the concentration of use and what I've seen from ingredients in these so far, I'm not that concerned about irritation. Because what do we have, we have .1 percent max for the extract.

DR. SNYDER: .01.

DR. BELSITO: .01 max for the fruit extract.

DR. SNYDER: .0022.

DR. BELSITO: And .0022, right, for the peel extract.

MS. FIUME: I just wanted to make sure because it would be -- just to avoid a second IDA, I was just adding for clarification. But as long as it's all good, then that's fine.

DR. BELSITO: Just run that by me again, Monice, what the question is.

MS. FIUME: I wasn't sure if the sensitization data that were in there were now sufficient, based on some of the conversations. But it appears that they are.

DR. BELSITO: Yeah, because I mean, I think, if you look at the supercritical extract, it almost looks like it's a fragrance. I mean, that's where you'd expect the sensitizers to be coming from. And if anything, they'd be in lower concentrations in other extracts. And what was the max concentration for that peel extract, Paul?

DR. SNYDER: .01. The fruit is .01, the peel is .0022. Zero, zero, two, two.

DR. BELSITO: Thank you. Okay. Anything more on this?

DR. SNYDER: That only represents six of 180 uses.

DR. BELSITO: Yeah, I know. That's why we have this boilerplate that we're assuming the max concentration is .01 percent for the fruit extract and .0022 percent for the peel.

DR. SNYDER: So, did you get your answer regarding the frequency of use table?

MS. FIUME: Include it all. I did, I did, loud and clear.

DR. BELSITO: Yeah. I think both are very helpful.

DR. SNYDER: I second that.

DR. RETTIE: Just to clean it up, and for my own education, can we go back to the dermal irritation and sensitization?

DR. BELSITO: Sure.

DR. RETTIE: Because I have written down here that we would ask for them all except for the fruit extract. At the end of the day it's a bit of a no-brainer since we have a boilerplate that says that they are going to be formulated to be non-sensitizing.

DR. BELSITO: Right.

DR. RETTIE: I suppose that's for (inaudible)?

DR. BELSITO: Yeah. I mean, you know, it's 2 percent of the supercritical dioxide extract. And I'm looking at Table 2 where we have the composition of it. It's pretty clear that that extract is probably a fragrance, given the high level of fragrances in there. And those are really going to be your sensitizers and then you bring it down to .01 percent.

DR. RETTIE: Yeah.

DR. BELSITO: So, I think we're pretty clear there.

DR. RETTIE: Yeah.

DR. BELSITO: Okay. Let me hit the save button and clear off of this.

Cohen Team – December 5, 2022

DR. COHEN: Let's close it and move on to the *Zanthoxylum Piperitum*, or Japanese pepper. This is a draft report and it's the first time we're reviewing it. The safety assessment is for four derived products. It's used as a skin conditioning agent and -- was that right? Did I have that right? Yeah.

The fruit extract is reported to be used in 180 products and its max use is 0.01 percent in a body spray. And the peel extract at 0.01 percent and this is used in one baby product.

Not in this report is the seed oil, which has no reported uses. And the seed oil is reported to function as a fragrancing ingredient and flavoring agent. And the seed oil is a volatile oil with apparently very different composition than what we're looking at. So, we're asked whether we should include this seed oil in this report and maybe we'll tackle that question first.

I had very mixed feelings about it. If it's just functioning as a fragrance this would fall under RIFM, right?

DR. ROSS: That was my sense of it.

DR. HELDRETH: Yes.

DR. BERGFELD: But you can always mention why you're not including it. Which is the fragrance.

DR. TILTON: Yeah. If it's not under the purview of this group, it seems different enough to not include it.

DR. HELDRETH: Right. What we usually do for ingredients that are listed either as fragrance only or fragrance and flavoring agent, if there are reported uses, we will look to RIFM and ask them is this on your radar to do? Because sometimes it just may

not be something they're going to look at. If they are planning to look at it or have looked at it, then, again, like you'd mentioned, we consider it outside of our purview and let them handle it.

But if there are uses and they're not interested in looking at it, then it just kind of gets falling to the wayside with nobody addressing it. Often in those cases, they'll pick the ingredient up anyway. But I don't think there's any reported uses here, so.

DR. COHEN: My concern, why I was torn on this, is we don't have method of manufacturing on the fruit extract, and the fruit extract apparently has the pericarp in it. And I can't imagine a circumstance where they're mashing the fruit up and no seeds get in.

DR. HELDRETH: Right.

DR. COHEN: Right. And we don't have method of manufacturing so I don't even know how they deseed this thing before it goes into it. So that was my torn part of it is. I can't tell you -- I mean, we know what the definitions are, we just never know -- like with olives, what's the method of manufacturing for this thing?

And if seeds ultimately get in, then we should look at the seed oil because it's going to change the toxicology of the fruit extract. So, I don't know. I'm not really sure.

DR. HELDRETH: I think the primary concern here is this is -- the seed oil is listed as a volatile oil, essentially kind of like an essential oils thing.

And the components of it are going to be very different from the rest of the extracts from the plant, and I'm not sure how well they'll relate overall even if we take the entire plant and crush it up. How much of that is going to be made up of this concentrated extract from the seed. Because even within the seed, how much of the entire seed's composition is this volatile oil? I imagine it's quite small. Probably takes many, many seeds to get a small vial of this oil.

So, I'm not sure the composition is of significant concentration to be comparable. And that's why we very often exclude essential oils or volatile oils from our reports, as long as they're not in use or somebody else is looking at it.

DR. COHEN: We're just assuming the definition and method of manufacturing are going to match?

DR. HELDRETH: Yes.

DR. COHEN: Okay. So, are we a no on this?

DR. TILTON: Yes.

DR. ROSS: A no or a yes?

DR. COHEN: Are we a no on including the oil?

DR. ROSS: Yes. I'm a no on including the oil.

DR. COHEN: Yes. We have no bananas. Tom, what do you think? I think you're on mute. Tom?

DR. SLAGA: Which ingredient?

DR. COHEN: Yeah. So, the question was do we include the seed oil in this assessment or not?

DR. BERGFELD: He needs to know the ingredient.

DR. SLAGA: This is the draft report for the Zanthoxylum?

DR. COHEN: Yes, Piperitum. Yes.

DR. SLAGA: We just have a little data on the fruit extract, the rest of them we have -- essentially, we need everything.

DR. COHEN: Hold on one second.

DR. ROSS: Can I make a comment?

DR. COHEN: Please.

DR. ROSS: I think Tom is correct in that. But I think the critical issue here is how the different extracts compare. So, you've got a lot of data here with the supercritical CO2 ZP extract. And so, how does that compare to the actual fruit extract which is GRAS and the peel extract?

There's some composition tables in the back, they all look pretty different. The Australian safety assessment was done essentially with the super critical CO2 ZP extract.

So, if their equivalent -- if that's equivalent to the fruit extract, for example, that would be the first question, then I think that we're in good shape. Because there's a lot of data with the super critical CO2 extract.

So, for example, we have dermal irritation and sensitization, David, with the super critical CO2 extract at 2 percent. Is that extract

different to the fruit extract? I don't know the answer to that.

DR. COHEN: I don't know the answer, right. And we don't ha- -- we're not provided the data to answer that question.

DR. ROSS: Yeah. And I don't know if anyone in the audience can help with that description. It doesn't look that way. And I expect they'll be a lot of discussion on this tomorrow with respect to --

DR. COHEN: It's interesting. I ultimately concluded that this would possibly be safe when formulated to be non-sensitizing. It's got a lot of sensitizers in it.

DR. ROSS: Yeah.

DR. COHEN: Right. So, the fact that the patch that the HRIPT was well below max use, it seemed strange for us not to address the fact that it's got linalool and limonene in very high concentrations.

DR. ROSS: Yeah.

DR. COHEN: So, I would go ahead with -- I think we might've had enough for safe when formulated to be non-sensitizing, but I'm still hung up on how they're making the fruit extract.

DR. ROSS: Yeah.

DR. BERGFELD: Fruit or food, did you say?

DR. COHEN: Fruit. The fruit extract.

DR. ROSS: I don't think we have an HRIPT with the fruit extract. It's with the super critical CO2 extract, is it not?

DR. COHEN: Fruit extract. One second. I'm looking at the table.

DR. ROSS: Yeah, let's look at the table.

DR. COHEN: The table.

DR. TILTON: I was reading those as being synonymous, but --

DR. ROSS: I did first time through. I went back in, and I thought I wish I hadn't reopened this because this makes it really complicated.

DR. COHEN: But it says the extract. Right. It's your super critical carbon dioxide extract.

DR. ROSS: Well, I think so. Let's look at the table. Where is this table?

DR. COHEN: It's at the top.

DR. ROSS: Yeah. Genotox.

DR. COHEN: The third wave had some articles on safety.

DR. ROSS: I'm not finding it there. So, it is in the text?

DR. COHEN: This one.

DR. ROSS: Oh. That.

DR. COHEN: You see?

DR. ROSS: Yeah. Now I have.

DR. COHEN: I think I would've gone straight to safe when formulated to be non-sensitizing if I just had confirmation that it was prepared the way the definition is.

DR. ROSS: Yeah. I would've needed some indication that that CO2 -- super critical CO2 extract -- was the same.

DR. COHEN: So, what are we going to ask for?

DR. ROSS: Comparison of the fruit extract with the super critical CO2 extract.

DR. TILTON: In terms of method of manufacturing?

DR. ROSS: Composition.

DR. TILTON: Composition.

DR. COHEN: Composition. And we're okay with the method of manufacturing for -- I had, we need method of manufacturing for the fruit extract -- peel water. Do we have that?

DR. ROSS: You've got composition of impurities on the peel and you've got.

DR. COHEN: Peel extract, not peel water.

DR. ROSS: You've got peel extract.

DR. COHEN: Yeah.

MS. TUCKER: You don't have the method of manufacturing on the fruit, the peel and the peel water.

DR. ROSS: I think you have on the peel extract.

DR. COHEN: It says we have it on the peel extract. It doesn't look like we have it on the fruit extract or the peel water. And we don't have impurities on the peel water.

DR. ROSS: It looks like you've got method of manufacture on the peel water. It's whether or not you think it's sufficient enough. If you look at the text, it's at the top of --

DR. COHEN: Actually, we do have it.

DR. ROSS: -- Page 13.

MS. TUCKER: 13.

DR. ROSS: And you've got the peel extract.

DR. COHEN: I think the table needs to just be updated.

DR. ROSS: Yeah. And you just really need the fruit extract.

DR. COHEN: We need the method of manufacturing for the fruit extract?

DR. ROSS: Yeah, and you need that composition comparison with that super critical CO2 extract. The Australian document didn't address that.

DR. COHEN: Okay. So, we need method of manufacturing for the fruit extract and some comparison of the fruit extract and the super critical CO2 extract regarding composition?

DR. ROSS: Yep.

DR. COHEN: Okay. Just some scenarios now. The Belsito team comes back and similar, or they come back safe as used then we'll open up the conversation for this because I think this can go either way.

DR. ROSS: I mean, this composition discussion could go on all day, I think, because right now we just don't know.

DR. COHEN: Okay. We don't need to get wrapped around the axel on this.

DR. TILTON: I mean, I had grouped the peel extract and peel water --

DR. COHEN: Together?

DR. TILTON: -- separate from the fruit and so there's

DR. ROSS: It looks separate, yeah.

DR. TILTON: -- insufficient data there in terms of irritation and sensitization, acute toxicity. There's really no toxicity data for the peel.

DR. COHEN: Okay, wait, that's --

DR. ROSS: That was Tom's point that there's nothing on the peel. Right, Tom?

DR. HELDRETH: He's muted again.

DR. COHEN: You're muted, Tom. We're talking about the peel.

DR. SLAGA: You're talking about the peel?

DR. ROSS: Yeah.

DR. COHEN: Yeah. But, you know, am I incorrect to read that the oil and the extract, wouldn't they have the peel?

DR. BERGFELD: It says whole plant.

DR. COHEN: And it's the whole fruit, at least, right? So, I lumped them all together.

DR. SLAGA: The peel would be part of the fruit, wouldn't it?

DR. COHEN: Yeah, because the oil comes from the fruit and the pericarp.

DR. ROSS: I think it would be -- I mean, I've got a note here, we've got to decide if the peel extract is a part of the fruit extract or

the super critical CO2 extract. And if it's not, then we would need to ask for all the data. But if it is, then I think you're in decent shape.

DR. COHEN: Why wouldn't we assume the peel is part of the fruit?

DR. ROSS: Well, if you look at Table 7.

DR. COHEN: Table 7.

DR. ROSS: You've got -- and I hate to get into the weeds here, because I mean, it's -- again, as I said, we could go on all day with this but if you look at composition data on the peel extract and look at those major constituents, it's mainly limonene and phellandrene.

DR. COHEN: Right. And a lot of it.

DR. ROSS: Yeah. And then you go back, for example, I think it's Table 3. Yeah, and there's the composition data on the ZP extracts -- Zanthoxylum Piperitum extract -- and that's going to be the CO2 extract. And that is fair amount of limonene but quite different. So, when you look, the peel extract and the -- if you compare Tables 3 and 7 they do look different.

DR. COHEN: The thing is, would these be different enough if we were just looking at two cultivars of the same -- you know what I mean, of the same fruit? What is shockingly different here? I see what you mean. I guess table --

DR. HELDRETH: So, if we're looking at these constituents of concern in the compositions, and we see the linalyl acetate of 50 percent in Table 3 and then -- I forget --

DR. COHEN: Table 7.

DR. ROSS: Limonene.

DR. HELDRETH: Table 7 was -- limonene was --

DR. COHEN: 44 percent.

DR. HELDRETH: 44 percent. Are those still concerning when the max use concentration is 0.01 percent?

DR. COHEN: No, and we might advocate for a formulate to not be sensitizing.

DR. HELDRETH: Right.

DR. COHEN: That's why I wasn't so concerned about those differences.

DR. HELDRETH: Right.

DR. COHEN: But the point is procedural that they're different. All right, so why --

DR. BERGFELD: We could discuss it in the discussion.

DR. COHEN: Why don't we close it at -- wait, but actually, Susan, I don't think I addressed -- no, no, we did. This was the issue with the peel. This is the peel. So, we're making some assumptions that the peel is part of the fruit. That's how I did it, but we --

DR. SLAGA: It has to be from the fruit. It's a good assumption.

DR. COHEN: I'm just looking. Yeah. The oil comes from the fruit and the fruit pericarp. But we don't know what the extract is.

DR. ROSS: I think the problem is, you've got that CO2 extract for the dermal sensitization, right, which is at 2 percent, which is great.

DR. COHEN: Yes.

DR. ROSS: But you have nothing on the actual fruit extract. So, if they're equivalent then you don't have to worry about --

DR. COHEN: I was thinking that that super critical was the fruit extract.

DR. ROSS: I was, too, initially but.

DR. COHEN: And it changed your mind because of the constituents?

DR. ROSS: Well, there's no definition in here that one is equivalent to the other. In fact, there's some comments in there that they may be different. I think that was in the preamble from the staff.

MS. TUCKER: That's correct because there was -- with what NICNAS provided, we don't exactly know what the extract was referring to.

DR. ROSS: Yeah, I agree with you. I went back to that study and it did not.

MS. TUCKER: Yeah, it doesn't say. So, we just know it's an extract. We don't know whether or not it is the peel extract or the

fruit extract.

DR. ROSS: Yep.

MS. TUCKER: It's not defined.

DR. ROSS: So, if you knew that the fruit extract was equivalent to that CO2 extract, dermal irritation and sensitization is taken care of.

DR. BERGFELD: Can you go back to the unpublished data and check with the provider? Ask the question?

DR. HELDRETH: Well, it came from the NICNAS document. And Regina has gleaned through it and it's not there -- that information. So, we would have to get back to the submitter that sent it to NICNAS, and I'm not sure we can follow that trail all the way back.

DR. COHEN: So, what are we really worried about?

DR. ROSS: Composition of the two extracts.

DR. BERGFELD: Sensitization.

DR. COHEN: Right. But we know there are sensitizers in here. So, whether there's different levels of these sensitizers in there, okay, we'll accept that, that there's a lot of them in there. We have very low max use, right. And we will -- we might -- I don't know what the Belsito team will submit. But if we put it not be sensitizing, what haven't we covered by that? What's the worst scenario?

If we have very low concentration max use, we know there are known sensitizers in there, we're going to caveat with a finding. What do you anticipate we will find that could create a problem?

DR. ROSS: I'm not sure how anyone formulates it to be non-sensitizing if they don't know what's in it.

DR. COHEN: Well, they'll do --

DR. ROSS: Do the actual test.

DR. COHEN: Yeah, they do the test.

DR. HELDRETH: So, with botanicals when we have a non-sensitizing caveat, the idea is that with the ingredient by itself, at the maximum use concentration in a formulation, does not induce or elicit a sensitization response. But that potentially, multiple ingredients with the same constituents of concern added to a single formulation, might exceed a threshold to cause sensitization, either induction or elicitation.

And that's what the formulated to be non-sensitizing means. It means avoid that aggregate buildup of concentration sensitizers in your formulation.

DR. COHEN: Bart, that's predicated on non-botanical, right?

DR. HELDRETH: That's just for botanicals.

DR. BERGFELD: No --

DR. COHEN: Just for botanicals?

DR. ROSS: So, could we go that way?

DR. BERGFELD: That's what David's proposing.

DR. COHEN: Yeah. That we cleared this, or get close to clear it, and ask for method of manufacturing and ask for some clarification on the super critical versus the fruit extract. But I'd like to hear -- I'm open to clearing it.

DR. ROSS: Yeah.

DR. COHEN: Tom, what was your -- before the conversation, what was your conclusion on it?

DR. SLAGA: Well, I had that we had sufficient data with the fruit extract, which would include the peel and the peel water. And the only thing that I wasn't quite sure, but I thought we reviewed it before, is the oil. But I may be wrong.

I didn't think we need method of manufacturing. I basically would go that it's used in such small amounts that it would be safe as used. The ingredients.

DR. COHEN: Okay.

DR. SLAGA: I mean, that's what I had initially now, and I've heard all of the additional. I wasn't sure absolutely about the sensitization, but in some cases we formulated to be non-sensitizing and -- if there is an issue there.

DR. COHEN: So, Bart, industry gets formulated to be non-sensitizing. From an operational standpoint, they're going to

formulate this with their best guess of levels of sensitizers. And then they're going to do an HRIPT on the product? They don't have -- I'm just say- --

DR. HELDRETH: I mean, I can't speak for industry, industry can speak up on that. They have at their disposal, they could do an HRIPT, guinea pig maximization test. Use some of these new alternative approach methods. Use the QRT 2.0 way to clear it. There's numerous ways they could mitigate any risk of sensitization there.

But if this is the only ingredient that they're putting in their formulation, that has any potential sensitizers, they're already going to be in good shape without doing any testing.

DR. BERGFELD: Well, you could always put in your discussion of the back to the mixed -- any mixtures might add to the --

DR. HELDRETH: Well, that's why we have the caveat, the non-sensitizing.

DR. COHEN: Yeah, and that was the issue. The seed oil, if it's fragrance, it probably has high concentrations. So, the very same chemicals, they're next-door neighbors in the fruit so -- okay. I think we know what to do from here, right?

DR. ROSS: We do?

DR. COHEN: I do. I do. I think we're going to either be presented with a safe as used, safe as used to not be sensitizing, or an IDA with probably very similar things than what we have. I don't think there's going to be an infinite number of -- but we'll see. But I think we're very comfortable with the data ambiguities we have right now, and we'll talk them through.

DR. ROSS: I think that's a good segue.

DR. SLAGA: Right.

DR. COHEN: Okay.

DR. BJERKE: Dr. Cohen, one thing to consider, too, is the way, like in Europe, they approach limonene and linalool and some of these constituents for labeling. So, for a rinse off, if it's less than 100 parts per million it doesn't need to be on the label. For a leave on, if it's less than ten parts per million it doesn't need to be on the label. So, when you're talking about low concentrations that's another consideration that you can think about.

DR. COHEN: So, this, if it's at -- I've got to go --

DR. BJERKE: So, 0.01 percent would be a hundred parts per million.

DR. COHEN: A hundred parts per million and for leave on it'd be --

DR. BJERKE: It'd be ten.

DR. COHEN: So, this could be 40 parts per million based on the constituents for linalool/limonene, 40 or 50 parts per million. So, it's a legit caveat in the conclusion.

DR. BERGFELD: On the discussion.

DR. COHEN: Both, right?

DR. HELDRETH: Both.

DR. COHEN: Yeah. That's helpful. Okay.

DR. ROSS: Yeah, thank you.

DR. COHEN: That's very helpful. All right. We have a lot of dodecyl's to talk about here.

Full Panel – December 6, 2022

DR. COHEN: Zanthoxylum piperitum, this is a draft report and it's the first time we're reviewing this. The safety assessment has four ingredients and it's used as a skin conditioning agent. The Fruit Extract is reported to be used in 180 products. And we have max use of 0.01 percent in a body spray and hand product. We have the Peel Extract at 0.01 percent in a body and hand product as well.

As for the Piperitum Seed Oil, there were no reported uses in the VCRP, we don't know the concentration, and it's reported to function as a fragrance and flavoring agent. And there was a presumption that the Seed Oil is a volatile oil likely to be different in composition than some of the other ingredients. We went back and forth on whether to include this in our report and we elected not to, but we'd like to discuss that further.

We have a fairly good portfolio on these items. The extract is GRAS. We have HRIPT at 2 percent. And, so our motion is in consideration for future possible safe as used when formulated to be non-sensitizing. Our present motion is an insufficient data announcement with needs of method of manufacturing for the Fruit Extract and Peel Water, and impurities on the Peel Water.

DR. BERGFELD: And that's your motion?

DR. COHEN: That's our motion.

DR. BERGFELD: Is there a second or discussion?

DR. BELSITO: We had method of manufacturing more information, for just Fruit Peel and Peel Water.

DR. COHEN: Fruit Peel, hold on a second.

DR. BERGFELD: Are you agreeing to the insufficiency, though?

DR. BELSITO: Yes, it's insufficient.

DR. BERGFELD: Okay.

DR. BELSITO: We also agreed not to do the Seed Oil, but there was information on a product that was called Seed Oil that was actually an alcohol water seed extract that's awaiting nomenclature from the INCI committee. That may or may not be able to be included in this report.

DR. COHEN: So, Don, why did we go back and forth? The fruits are very small apparently.

DR. BELSITO: Um-hmm.

DR. COHEN: And, it was unclear, since the oil, as obtained from the fruit and the pericarp, you know, how efficient is the extraction of the seed in this thing. And will we have any Seed Oil in there. But we went under the assumption that we'll get method of manufacturing for the extract. That's the most used item. And we don't clearly have method of manufacturing, even though we have the definition of what the Fruit Extract is.

I found like when we'll review some other ones, what the definitions are and how the methods of manufacturing play out, don't always come together in parallel. So, before drawing any conclusions on what we think the Fruit Extract is, we'd like actually method of manufacturing on the Fruit Extract.

DR. BELSITO: I mean, that's fine, we're going insufficient.

DR. COHEN: Yeah.

DR. BELSITO: But you don't want manufacturing on the Fruit Peel; you said Fruit Extract and Fruit Water.

DR. SNYDER: Peel water.

DR. BELSITO: Peel water.

DR. COHEN: We have method of manufacturing on Peel Extract and Peel Water, right?

MS. TUCKER: Not peel water.

DR. COHEN: No? Peel Water is an aqueous solution of the steam distillate of the peel. Let's just make sure we're -- so we had method of manufacturing for Fruit Extract and Peel Water, and impurities on the Peel Water.

DR. BELSITO: Okay. I mean, I see what you're going at, the Peel Extract there. Okay.

DR. COHEN: Is that --

DR. BERGFELD: So, you've both agreed it's insufficient.

DR. BELSITO: Yeah.

DR. BERGFELD: Now you've agreed on the needs, is that correct?

DR. BELSITO: Yeah. It's fine.

DR. ROSS: Could I just ask?

DR. BERGFELD: Sure, David.

DR. ROSS: Did your team have any discussion on the equivalence of Zanthoxylum piperitum liquids CO2 extract versus the Fruit Extract?

DR. BELSITO: We thought that CO2 extract was likely a fragrance, based upon the composition.

DR. ROSS: Yeah. So we talked quite a bit about the fact that the dermal and sensitization data was done with the CO2 extract. And we were trying to equate that to the Fruit Extract. But maybe the method of manufacture of the Fruit Extract would inform us about how to perceive that.

DR. BELSITO: But I think the sensitizing component of that extraction, the CO2, looking at the ingredients that were present, that would be much more sensitizing than anything else coming out of the fruit, you know, very high concentrations of tropines.

DR. RETTIE: Dave, are you referring to the fruit pericarp ethyl acetate extract?

DR. ROSS: No, I think the CO2 extract was used for the dermal and sensitization data and some of the genotox data.

DR. RETTIE: Yeah. So, what was the other one that you were --

DR. ROSS: Just the Fruit Extract itself. So we were trying to equate those two, you know, there was no details. The Australian safety assessment used the CO2 extract.

DR. BELSITO: The NICNAS, yes.

DR. ROSS: Yeah.

DR. RETTIE: So we don't know what the Fruit Extract is?

DR. ROSS: Exactly.

DR. COHEN: That's why we want method of manufacture.

DR. BELSITO: That's fine.

DR. COHEN: We're not sure what we're looking at. And then, the oil has a lot of fragrance sensitizers.

DR. RETTIE: It does.

DR. COHEN: So, even though we saw the HRIPT at 2 percent was negative, we were still polarizing to formulate to not be sensitizing.

DR. BELSITO: You'd have to do it.

DR. COHEN: Yeah, well, we would agree on that. We'll just get the further data and finish this.

DR. BELSITO: Yeah, fine.

DR. RETTIE: Yes.

DR. BERGFELD: So, may I call the question then? All those in favor of an insufficient data report? Unanimous again. And the needs -- are we clear on what is needed?

MS. TUCKER: Yes, the method of manufacture for the -- are we asking for the Fruit Extract and the Peel Water, and impurities on the Peel Water?

DR. COHEN: Exactly, yeah.

MS. TUCKER: Okay, thank you. All are noted.

DR. BERGFELD: Thank you.

DR. BELSITO: And, this would actually be a good document to discuss the Use Tables. We really didn't go back and forth on this. We thought that both tables were very helpful. The old line tables were helping us to quickly set where we wanted to look for upper limits and lower limits. And the other tables to point out the number of product categories that exist where we're not getting reported concentrations.

With that in mind, however, our conclusions are always safe as used as described in the safety assessment. So, if we're getting only one concentration on one product line, that means that that concentration is the upper limit for everything else that hasn't been reported. So, we liked seeing both of them. We thought that was helpful.

DR. BERGFELD: I think there was some question about the Journal taking two such tables. Monice, did you ever resolve that, or Bart?

MS. FIUME: I don't think we discussed it with the Journal. I think if it was okay with the Panel, we could probably work on the format of the table a bit so that it may all be able to be placed on one table. Or, somehow consolidate it so that it gives you all the information you want. So I'd like to work on that.

DR. BERGFELD: Okay.

DR. RETTIE: Seems like a consolidation was a good way to go because only a small amount of information really needed to be transferred into the enlarged tables to give us everything.

DR. BERGFELD: David Cohen?

DR. COHEN: Yeah, on the team we had a very broad standard deviation of opinions, so even though our mean and median opinion would be the same as yours. There are some that liked the new tables, some liked the old tables, some liked both tables. And it didn't completely depend on which report we looked at, but it was maybe slight variation there. So, if we can have both tables that would be great.

I feel, Don, what you mentioned that the report kind of anchors on the max use of the only thing we have. It's come up more times recently than it has in the past. And, it has created some issues for us if we know products were being used on the lips, or on the eyes, and we have max use of a body lotion. And we're using that data and it may not so easily carry over.

DR. BERGFELD: Well, it seems that there's a unanimous agreement that it will have both tables in every document, and good luck consolidating them.

MS. FIUME: Thank you.

Safety Assessment of *Zanthoxylum piperitum*-Derived Ingredients as Used in Cosmetics

Status: Draft Tentative Report for Panel Review
Release Date: May 19, 2023
Panel Meeting Date: June 12-13, 2023

The Expert Panel for Cosmetic Ingredient Safety members are Chair, Wilma F. Bergfeld, M.D., F.A.C.P.; Donald V. Belsito, M.D.; David E. Cohen, M.D.; Curtis D. Klaassen, Ph.D.; Allan E. Rettie, Ph.D.; David Ross, Ph.D.; Thomas J. Slaga, Ph.D.; Paul W. Snyder, D.V.M., Ph.D.; and Susan C. Tilton, Ph.D. The Cosmetic Ingredient Review (CIR) Executive Director is Bart Heldreth, Ph.D., and the Senior Director is Monice Fiume. This safety assessment was prepared by Wilbur Johnson, Jr., M.S., former Senior Scientific Analyst/Writer, and Regina Tucker, M.S., Scientific Analyst/Writer, CIR.

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ABBREVIATIONS

AICIS	Australian Industrial Chemicals Introduction Scheme
BoNT/A	botulinum toxin type A
CFR	Code of Federal Regulations
cGMP	current good manufacturing practices
CIR	Cosmetic Ingredient Review
CPSC	Consumer Product Safety Commission
Council	Personal Care Products Council
Da	Daltons
DMSO	dimethyl sulfoxide
FDA	Food and Drug Administration
FEMA	Flavor and Extract Manufacturers Association
GC-MS	gas chromatography-mass spectrometry
GRAS	generally recognized as safe
HRIPT	human repeated insult patch test
MS/MS	tandem mass spectrometry
MTT	3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyl-2H-tetrazolium bromide
MW	molecular weight
NICNAS	National Industrial Chemicals Notification and Assessment Scheme
OECD	Organization for Economic Co-operation and Development
Panel	Expert Panel for Cosmetic Ingredient Safety
RC	relative content
RIFM	Research Institute for Fragrance Materials
TG	test guideline
US	United States
VCRP	Voluntary Cosmetic Registration Program
wINCI; *Dictionary*	web-based *International Cosmetic Ingredient Dictionary and Handbook*

DRAFT ABSTRACT

The Expert Panel for Cosmetic Ingredient Safety (Panel) assessed the safety of 4 *Zanthoxylum piperitum*-derived ingredients as used in cosmetic formulations. These ingredients are reported to function in cosmetics as skin conditioning agents, skin protectants, cosmetic biocides, cosmetic astringents, and fragrance ingredients in cosmetic products. *Zanthoxylum piperitum*-derived ingredients comprise, in part, constituents that may cause adverse effects. Because final product formulations may contain multiple botanicals, each possibly containing similar constituents of concern, formulators are advised to be aware of these constituents and to avoid reaching levels that may be hazardous to consumers. With *Zanthoxylum piperitum*-derived ingredients, the Panel was concerned about the presence of potential sensitizers (e.g., linalool and limonene) in cosmetics. Additionally, industry should continue to use good manufacturing practices to minimize impurities, such as heavy metals and pesticide residues, in cosmetic formulations. The Panel considered the available data and concluded **[**TBD**]**..

INTRODUCTION

The safety of the following 4 *Zanthoxylum piperitum*-derived ingredients as used in cosmetics is reviewed in this safety assessment.

Zanthoxylum Piperitum Fruit Extract
Zanthoxylum Piperitum Oil
Zanthoxylum Piperitum Peel Extract
Zanthoxylum Piperitum Peel Water

According to the web-based *International Cosmetic Ingredient Dictionary and Handbook* (wINCI; *Dictionary*), collectively, the *Zanthoxylum piperitum*-derived ingredients are reported to function as skin conditioning agents, skin protectants, cosmetic biocides, cosmetic astringents, and fragrance ingredients in cosmetic products (See Table 1).[1] The Expert Panel for Cosmetic Ingredient Safety (Panel) routinely does not review ingredients that function only as fragrance ingredients, because, as fragrances, the evaluation of the safety of these ingredients is the purview of the Research Institute for Fragrance Materials (RIFM). However, although Zanthoxylum Piperitum Oil is only reported to function as a fragrance ingredient in cosmetics, the safety of this ingredient was neither previously nor currently the subject of review by RIFM; thus, it is included in this review.

These *Zanthoxylum piperitum*-derived ingredients may contain hundreds of constituents, some of which may have the potential to cause toxic effects. In this assessment, the Panel will review the potential toxicity of each of the *Zanthoxylum piperitum*-derived ingredients as a whole, complex mixture; toxicity from single components may not predict the potential toxicity of botanical ingredients.

This safety assessment includes relevant published and unpublished data that are available for each endpoint that is evaluated. The published data in this document were identified by conducting an exhaustive search of the world's literature; this search was last conducted March 2023. A list of the search engines and websites that are used, and the sources that are typically explored, as well as the endpoints that the Panel typically evaluates, is available on the Cosmetic Ingredient Review (CIR) website (https://www.cir-safety.org/supplementaldoc/preliminary-search-engines-and-websites; https://www.cir-safety.org/supplementaldoc/cir-report-format-outline). Unpublished data may be provided by the cosmetics industry, as well as by other interested parties and is included and summarized, where appropriate.

An assessment report on *Zanthoxylum piperitum* extract has been published by the National Industrial Chemicals Notification and Assessment Scheme (NICNAS; now known as the Australian Industrial Chemicals Introduction Scheme (AICIS)).[2] Because the ingredient in that assessment is identified as *Zanthoxylum piperitum* extract, it is possible that the data could pertain to either Zanthoxylum Piperitum Fruit Extract or Zanthoxylum Piperitum Peel Extract; although, it is not clear which ingredient is being reviewed specifically, these data are included in this review and may inform safety. Please note that this source provides summaries of information generated by industry, and it is those summary data that are reported in this safety assessment when this source is cited.

The names of the ingredients in this report are written in accordance with the INCI naming conventions, i.e., capitalized without italics or abbreviations. When referring to the genus and species from which the ingredients are derived, the standard taxonomic practice of using italics is followed (e.g., *Zanthoxylum piperitum*). It is often not known how the substance being tested in a study compares to the cosmetic ingredient. In the report text, if it is known that the material being tested is a cosmetic ingredient, the INCI naming convention will be used (e.g., Zanthoxylum Piperitum Fruit Extract). However, if it is not known that the test substance is the same as the cosmetic ingredient, the taxonomic naming conventions (e.g., a *Zanthoxylum piperitum* extract) will be used.

CHEMISTRY

Definition and Plant Identification

All of the *Zanthoxylum piperitum*-derived ingredients named in this assessment have the generic CAS No. 97404-53-0.[1] The definitions for the *Zanthoxylum piperitum*-derived ingredients are presented in Table 1.

Zanthoxylum piperitum (common names, Japanese pepper and Sichuan pepper)[1] is native to East Asia and prevalent in Japan.[3] It bears a tiny red fruit between August and September. The fruit includes the pericarp, which is a portion of the fruit that surrounds the seeds.

Chemical Properties

According to a submission to NICNAS, a *Zanthoxylum piperitum* extract (plant part not specified) has an average molecular weight (MW) of constituents equivalent to < 500 Daltons (Da) and a water solubility value of 5.69 mg/l - 1.56 g/l.[2] These and other properties are presented in Table 2.

Method of Manufacture

Zanthoxylum Fruit Extract

A powdered extract of *Zanthoxylum piperitum* was prepared from 100 g of *Zanthoxylum* fruit.[4] It was extracted by reflux with 1 l of 50% ethanol for 4 h. The extract was concentrated under decompression and powdered by freeze drying at -80°C for 72 h. Eleven grams of *Zanthoxylum piperitum* were obtained, resulting in 11% final yield of *Zanthoxylum piperitum*.

Two additional studies describe the manufacturing methods of *Zanthoxylum piperitum* fruit extract from dried fruit. In one instance, 100 g of *Zanthoxylum piperitum* fruit was soaked in 50% ethanol (1 l) at room temperature for 24 h.[5] The ethanol extract was filtered through filter paper and concentrated in a rotary vacuum evaporator for 30 min to remove the ethanolic base. The concentrated extracts were then freeze-dried. In the second study the dried fruits (1 kg) were soaked in 70% ethanol (10 l) at room temperature for 12 h.[6] The ethanol extract was filtered through filter paper, and concentrated under a vacuum at 40°C. The concentrated extracts were then freeze-dried and stored at -20°C until use.

Zanthoxylum Piperitum Oil

In some cases, the definition of the ingredients, as given in the *Dictionary*, provides insight as to the method of manufacture. According to the *Dictionary*, Zanthoxylum Piperitum Oil is the oil obtained from the fruit and fruit pericarp of *Zanthoxylum piperitum*.[1]

Zanthoxylum Piperitum Peel Extract

Zanthoxylum Piperitum Peel Extract can be manufactured by extracting dried raw material with an ethanol solution (70%/vol), and afterwards allowing it to settle as a sediment.[7] The sediment is then filtrated and adjusted before being packaged. Zanthoxylum Piperitum Peel Extract can also be prepared by extracting the dried raw material with 1,3-butylene glycolic solution (50%/vol), and allowing it to deposit as a sediment. This sediment is again then filtrated and adjusted before being packaged.

The peel of *Zanthoxylum piperitum* fruit was extracted with purified water at 100°C for 1 h.[8] The soluble extract was then separated from the insoluble waste and concentrated by removal of water under reduced pressure. Spray drying was used to generate dried extract powder.

Zanthoxylum Piperitum Peel Water

According to the *Dictionary*, Zanthoxylum Piperitum Peel Water is the aqueous solution of the steam distillate obtained from the peel of *Zanthoxylum piperitum*.[1]

Composition/Impurities

There are more than 50 sanshools present in the *Zanthoxylum* genus.[9] The main pungent components of *Zanthoxylum piperitum* fruit are sanshool and sanshoolamide.[10] Sanshoamide, a component from the fresh unripe fruits of *Zanthoxylum piperitum*, has also been reported as a component.[11]

Zanthoxylum piperitum extract

According to NICNAS, the degree of purity of a *Zanthoxylum piperitum* extract (supercritical carbon dioxide extract, plant part not specified) is 100%, and it does not contain any additives/adjuvants.[2] The three constituents present at the highest concentrations in the *Zanthoxylum piperitum* extract tested are: linalyl acetate at 30 — 50% %, linalool at 10 — 20% and limonene at 5 — 10% , accounting for 56.13% (ranging from 45 — 80%) of the composition of the *Zanthoxylum piperitum* extract. Composition data on *Zanthoxylum piperitum* extract from the NICNAS report is included in Table 3.[2]

Zanthoxylum Piperitum Fruit Extract

One study identified the following constituents of *Zanthoxylum piperitum* pericarp steam distillate: carveol, β-caryophyllene oxide, 1,8-cineole, citronellal, citronellol, citronellyl acetate, α-copaene, cuminaldehyde, cuminyl alcohol, *p*-cymene, geranyl acetate, limonene, linalool, linalool oxide, β-myrcene, α-pinene, β-pinene, piperitone, and, α-terpineol.[12]*Zanthoxylum piperitum* pericarp extract was analyzed, its amides were isolated independently, and its composition was examined. [13,14] The highest composition of the pericarp was noted to be hydroxy-α-sanshool (1.89% of dry weight) and (6*RS*,11*SR*)-6,11-dihydroxy-*N*-(2-hydroxy-2- methylpropyl)-2,7,9-dodecatrienamide (0.41% composition). Details from

these studies are summarized in Table 4. Composition data on the extract from the dried pericarp and seed are also provided in Table 5, where it's shown that α-tocopherol had the highest composition in the dried pericarp at 3.2 mg/100g dry weight.

In another study, the total polyphenol and flavonoid content of *Zanthoxylum piperitum* fruit extract was 742.8 ± 3.97 mg gallic acid equivalents/g and 486.8 ± 7.08 mg quercetin equivalents/g, respectively.[6] Flavone was the major component of *Zanthoxylum piperitum* fruit extract although the individual polyphenols and flavonoids were not specified. The dried fruit extract has reported concentrations of 40.342 ± 0.13 and 23.209 ± 0.04 µg/ml for hyperoside and quercitrin, respectively. The relative standard deviations of both compounds was less than 8.07%.[5] Additional composition data on a *Zanthoxylum piperitum* fruit extract are found in Table 6 and Table 7.

Zanthoxylum Piperitum Oil

Composition data on *Zanthoxylum piperitum* fruit oil are found in Table 8.[15] Volatile components of *Zanthoxylum piperitum* fruit oil from the ripe fruit include hydrocarbons, alcohols, aldehydes, and esters, primarily D-limonene (11.5%), geraniol (11.0%), citronellal (16.2%), and geranyl acetate (40.1%).[16] (Percent composition was calculated by adding all the totals of the relative content (RC) and dividing individual RC). Another study identified similar constituents of *Zanthoxylum piperitum* fruit oil. However, the main component was limonene (37.99%) with minor amounts of sabinene (13.30%), and β-myrcene (7.17%), constituting almost 59% of all the volatile constituents.[17] Data on the major components of *Zanthoxylum piperitum* oil (from whole plant) are found in Table 9.[16]

Zanthoxylum Piperitum Peel Extract

The composition of Zanthoxylum Piperitum Peel Extract from an ethanol solvent contains triterpene and tannin (% composition not specified).[7] Impurities of this extract include heavy metals, not more than 20 ppm, and arsenic, not more than 2 ppm. The composition of the extract from the 1,3-butylene glycolic solution yield triperpenoids (% composition not mentioned) along with heavy metals, no more than 10 ppm and arsenic, no more than 2 ppm.

The volatile compounds from the skin of the mature fruit of *Zanthoxylum piperitum* extracted with methyl *t*-butyl ether were analyzed with gas chromatography – mass spectrometry (GC-MS).[3] The composition can be found in Table 10.

The composition of a methanolic extract of a *Zanthoxylum piperitum* peel was determined.[18] The results, obtained using GC-MS, are also shown in Table 10.

USE

Cosmetic

The safety of the cosmetic ingredients 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 these ingredients in cosmetics, and does not cover their use in airbrush delivery systems. Data are submitted by the cosmetic industry via the FDA's Voluntary Cosmetic Registration Program (VCRP) database (frequency of use) and in response to a survey conducted by the Personal Care Products Council (Council) (maximum use concentrations). The data are provided by cosmetic product categories, based on 21CFR Part 720. For most cosmetic product categories, 21CFR Part 720 does not indicate type of application and, therefore, airbrush application is not considered. Airbrush delivery systems are within the purview of the US Consumer Product Safety Commission (CPSC), while ingredients, as used in airbrush delivery systems, are within the jurisdiction of the FDA. Airbrush delivery system use for cosmetic application has not been evaluated by the CPSC, nor has the use of cosmetic ingredients in airbrush technology been evaluated by the FDA. Moreover, no consumer habits and practices data or particle size data are publicly available to evaluate the exposure associated with this use type, thereby preempting the ability to evaluate risk or safety.

According to 2023 VCRP data, Zanthoxylum Piperitum Fruit Extract is reported to be used in 183 cosmetic products (Table 11).[19] Although this ingredient has the highest reported frequency of use for the ingredients in this group, and it is used in numerous product categories in the VCRP, the results of a concentration of use survey provided by the Council in 2021 only report concentration of use data for Zanthoxylum Piperitum Fruit Extract in one product category; according to the survey, it is used at a maximum use concentration up to 0.01% in spray body and hand products.[20] Zanthoxylum Piperitum Peel Extract is the only other ingredient in this report that is reported to be in use; it is reported to be used in 19 formulations at maximum use concentrations up to 0.0022%. According to VCRP and Council survey data, 2 of the 4 ingredients, i.e., Zanthoxylum Piperitum Oil and Zanthoxylum Piperitum Peel Water, are not currently in use in cosmetic products (Table 12).

Cosmetic products containing *Zanthoxylum piperitum*-derived ingredients may incidentally come in contact with the eyes or mucous membranes (concentration data for these formulation-types not provided). It should be noted that Zanthoxylum Piperitum Fruit Extract is reported to be used in 5 baby products (use concentration not provided). Additionally, some of the ingredients are used in cosmetic sprays and powders, and could possibly be inhaled; for example, Zanthoxylum Piperitum Fruit Extract and Zanthoxylum Piperitum Peel Extract are reported to be used in products that are known to be sprayed (up to 0.01% in body and hand products and up to 0.0000018% in night products, respectively), and Zanthoxylum Piperitum Peel Extract is reported to be used in face powders at a maximum use concentration of 0.0000022%. In practice, as stated in the Panel's respiratory exposure resource document (https://www.cir-safety.org/cir-findings), most

droplets /particles incidentally inhaled from cosmetic sprays would be deposited in the nasopharyngeal and tracheobronchial regions and would not be respirable (i.e., they would not enter the lungs) to any appreciable amount. 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.

Although products containing some of these ingredients may be marketed for use with airbrush delivery systems, this information is not available from the VCRP or the Council survey. Without information regarding the frequency and concentrations of use of these ingredients (and without consumer habits and practices data or particle size data related to this use technology), the data are insufficient to evaluate the exposure resulting from cosmetics applied via airbrush delivery systems.

The *Zanthoxylum piperitum*-derived ingredients are not restricted from use in any way under the rules governing cosmetic products in the European Union.[21]

Non-Cosmetic

Zanthoxylum piperitum extract appears on the Flavor and Extract Manufacturers Association's (FEMA) list of flavoring ingredients that are classified as generally recognized as safe (GRAS), under the 1958 food additives amendment to the US Federal Food, Drug, and Cosmetics Act.[22]

As a result of its lemon-like aroma and pungent taste, Japanese pepper (Rutaceae, *Zanthoxylum piperitum*) is commonly used in Japanese dishes as a spice and for seasoning to mask unpleasant odors that arise from fish and meat ingredients.[3] Specifically, the fresh young leaves of the plant, as well as the fruit pericarp, are used as spices in Japanese cuisine.[10] According to another source, fruit peels and leaves of *Zanthoxylum piperitum* (Rutaceae) have been used in Japan for centuries as spices to preserve foods.[18]

Zanthoxylum piperitum is among the Korean medicinal plants (Korean salad plants), so named due to their content of purported bioactive compounds, mainly antioxidant phenolics.[23] *Zanthoxylum piperitum* fruit extract has been indicated to alleviate rheumatoid arthritis, inhibit alveolar bone loss, reduce weight gain, decrease adipocytes and adipose tissue mass, and act as a therapeutic agent for osteoporosis.[4-6,24]

TOXICOKINETIC STUDIES

Dermal Penetration

Zanthoxylum piperitum extract

NICNAS noted that given the low molecular weight of the components of *Zanthoxylum piperitum* extract (supercritical carbon dioxide extract, < 500 Da; plant part not specified), its water solubility (5.69 mg/l – 1.56 g/l), and a log P_{ow} of 2.9 – 4.4, there is potential for *Zanthoxylum piperitum* extract to cross biological membranes.[2]

Absorption, Distribution, Metabolism, and Excretion

Zanthoxylum Piperitum Fruit Extract

The pharmacokinetics of a mixture containing *Zanthoxylum piperitum* fruit was studied using 16 subjects (fasted).[25] The mixture had the following composition: *Zanthoxylum piperitum* fruit, ginger, ginseng, and maltose. A randomized, open-label, three-arm, three-period protocol was used. The mixture was administered orally to each subject in doses of 2.5, 5, and 10 g. Blood samples were collected just before and at the following intervals after administration: 0.25, 0.5, 1, 2, 3, 4, 8, 12, 24, and 48 h. Plasma fractions were stored prior to analysis by high performance liquid chromatography. Of the 6 compounds measured, hydroxy-α-sanshool, a constituent of *Zanthoxylum piperitum* fruit, had the highest plasma concentration. The plasma concentration of hydroxy-α-sanshool reached the maximum concentration within 30 min after administration. Its median half-life was 1.6 to 1.7 h, indicating rapid absorption and elimination. The maximum concentration of hydroxy-α-sanshool in the plasma was 0.76 to 2.66 µM.

TOXICOLOGICAL STUDIES

Acute Toxicity Studies

Oral

Data on the acute toxicity of *Zanthoxylum piperitum*-derived ingredients reviewed in this safety assessment were not found in the published literature, nor were these data submitted.

Short-Term, Subchronic, and Chronic Toxicity Studies

Data on the short-term, subchronic, and chronic toxicity of *Zanthoxylum piperitum*-derived ingredients reviewed in this safety assessment were not found in the published literature, nor were these data submitted.

DEVELOPMENTAL AND REPRODUCTIVE TOXICITY STUDIES

Data on the developmental and reproductive toxicity of *Zanthoxylum piperitum*-derived ingredients reviewed in this safety assessment were not found in the published literature, nor were these data submitted.

GENOTOXICITY STUDIES

The genotoxicity studies summarized below are presented in Table 13.

In the Ames test (Organisation for Economic Co-operation and Development test guideline (OECD TG) 471), a *Zanthoxylum piperitum* extract (carbon dioxide extract, in acetone; plant part not specified) was evaluated using the following bacterial strains: *Salmonella typhimurium* strains TA1535, TA1537, TA98, and TA100, and *Escherichia coli* strain WP2uvrA.[2] At concentrations up to 5000 µg/plate (with and without metabolic activation), results were negative. The genotoxicity of a *Zanthoxylum piperitum* extract (supercritical carbon dioxide extract, in DMSO) in human lymphocytes was evaluated in the mammalian cell micronucleus test (OECD TG 487). The test concentrations were up to 640 µg/ml (without metabolic activation) and up to 320 µg/ml (with metabolic activation). Results indicated that the test substance was neither clastogenic nor aneugenic in the presence or absence of metabolic activation.

CARCINOGENICITY STUDIES

Data on the carcinogenicity of *Zanthoxylum piperitum*-derived ingredients reviewed in this safety assessment were not found in the published literature, nor were these data submitted.

ANTI-CARCINOGENICITY STUDIES

Zanthoxylum Piperitum Fruit Extract

A *Zanthoxylum piperitum* fruit extract and its ability to induce autophagic cell death was examined.[8] Using phase-contrast microscopy, cells were treated for 24 h with 200 µg/ml of a *Zanthoxylum piperitum* fruit extract, and vacuoles were observed in the cytoplasm. Cell proliferation assays were performed after 48 h of treatment, and proliferation in at least 3 cell lines was inhibited. In a human colorectal cell line, after 72 h of treatment, the viability and number of cancer cells was reduced. To further confirm the induction of autophagy, Western blot analysis was performed to analyze the conversion of cytosolic LC3-1 into LC3 II in DLD-1 cells. This demonstrated autophagic activity. Quantitative RT-qPCR and Western blot were also utilized to examine the ability of an essential protein to prevent a *Zanthoxylum piperitum* fruit extract from inducing autophagic cell death. The phosphorylation of c-Jun-N-terminal kinase in 6 different types of cancer cells was also measured via Western blot analysis. To explore the effect of a *Zanthoxylum piperitum* fruit extract on normal cells, a rat intestinal cell line was treated with *Zanthoxylum piperitum* fruit extract and examined. *Zanthoxylum piperitum* fruit extract appears to induce JNK-dependent autophagic cell death.

OTHER RELEVANT STUDIES

Cytotoxicity

Zanthoxylum piperitum extract

Zanthoxylum piperitum extract and its ability to display anti-cancer activity by inducing apoptosis in human cell lines was examined on human cancer cell lines (Calu-6 for human pulmonary carcinoma and SMU-601 for human gastric carcinoma) was measured using the 3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyl-2H-tetrazolium bromide (MTT) assay.[23] Serial dilutions of *Zanthoxylum piperitum* extract (dried methanol extract) were prepared by dissolving the extract in DMSO, followed by dilution with medium to yield the following final concentrations: 25, 50, 100, 200, 400, and 800 µg/ml. Optical density was recorded using a micro plate reader at 540 nm. Distilled water served as the positive control, and DMSO served as the solvent control. Controls and samples were assayed in duplicate for each concentration and replicated three times for each cell line. Cytotoxicity was obtained by comparing absorbance between the samples and the control. The values obtained were then used to calculate the concentration of *Zanthoxylum piperitum* extract required to cause a 50% reduction (IC_{50}, in µg/ml) in growth (cell number) for each cell line. In the Calu-6 cell line, the IC_{50} value for *Zanthoxylum piperitum* extract was 470.4 ± 13.1 µg/ml. In the SMU-601 cell line, the IC_{50} value for *Zanthoxylum piperitum* extract was 349.0 ± 9.1 µg/ml. Additionally, a dose-dependent inhibition of cell proliferation was observed in this study.

DERMAL IRRITATION AND SENSITIZATION STUDIES

Human

Zanthoxylum piperitum extract

The skin sensitization potential of 2% *Zanthoxylum piperitum* extract (super critical carbon dioxide extract; plant part not specified) in ethanol: diethyl phthalate (1:3 w/w) was evaluated in a human repeated-insult patch test (HRIPT) involving 110 subjects.[2] Two different samples of the test substance were tested on each subject. During induction, the test substance (on a 3.62 cm^2 occlusive patch) was applied to the same location on the back of each subject 3 times per week for a total of 9

applications. Test sites were examined for dermal irritation at each visit prior to re-application of the test substance. Approximately 10 to 21 d after the final visit of the induction phase, the challenge phase was initiated. The test substance was applied for ~ 24 h to a new site on the back. Test sites were examined for signs of dermal irritation or sensitization. The test substance did not elicit skin irritation or sensitization during the challenge phase and was classified as a non-sensitizer.

OCULAR IRRITATION STUDIES

Data on the ocular irritation potential of the *Zanthoxylum piperitum*-derived ingredients reviewed in this safety assessment were not found in the published literature, nor were these data submitted.

CLINICAL STUDIES

The mechanisms, components, synergistic effects, and topical effects of a *Zanthoxylum piperitum* fruit extract were all examined in one study to determine methods to reduce wrinkles non-invasively via mechanisms similar to botulinum toxin type A (BoNT/A) injection.[26] Two in vitro assays (a co-cultured cell-based muscle contraction assay and a muscle contraction assay in *Caenorhabditis elegans*) were performed and *Zanthoxylum piperitum* was identified as a BoNT/A-like reagent that induced a 27.7% decrease in muscle contraction rates in concentration of 1000 ppm. A test performed with the Neurotransmitter Transporter Uptake Assay Kit with modifications to assess the ability of *Zanthoxylum piperitum* fruit extract to regulate signal transduction in neurons indicated that muscle contraction is inhibited by attenuating electric signal transduction in presynaptic neurons. Furthermore, two components of a *Zanthoxylum piperitum* fruit extract, quercitrin and hyperoside, were examined for their role in muscle contraction. Quercitrin was found to be responsible for muscle contraction inhibition.

Finally, the effect of topical treatment of a *Zanthoxylum piperitum* fruit extract on facial wrinkles was determined. Twenty-four women aged 38 and older were initially included in the trial. Twenty-three completed the study. The study was randomized, double-blinded, and placebo-controlled. The participants were divided into a placebo group (n = 8), a *Zanthoxylum piperitum* fruit extract-treated group (n = 7, 60 ppm), and a *Zanthoxylum piperitum* fruit extract (60 ppm) with acetyl hexapeptide-8 (50 ppm)-treated group (n = 8). Lateral canthal rhytides were evaluated after daily application for 0, 4, 8, and 12 wk using a 3D skin imaging system. Compared to placebo treatment, *Zanthoxylum piperitum* fruit extract treatment for 12 wk ameliorated lateral canthal rhytides. The topical treatment of *Zanthoxylum piperitum* fruit extract improved the appearance of lateral canthal rhytides by 11.4%. It was also determined that *Zanthoxylum piperitum* fruit extract and acetyl hexapeptide-8 have synergistic effects on wrinkle improvement.

SUMMARY

The safety of the following 4 *Zanthoxylum piperitum*-derived ingredients as used in cosmetics is reviewed in this safety assessment: Zanthoxylum Piperitum Fruit Extract, Zanthoxylum Piperitum Oil, Zanthoxylum Piperitum Peel Extract, and Zanthoxylum Piperitum Peel Water. According to the *Dictionary*, collectively, the *Zanthoxylum piperitum*-derived ingredients are reported to function as skin conditioning agents, skin protectants, cosmetic biocides, cosmetic astringents, and fragrance ingredients in cosmetic products.

Zanthoxylum piperitum (i.e., Japanese pepper; Rutaceae) is native to East Asia and prevalent in Japan. It bears a tiny red fruit between August and September. The available composition data indicate that *Zanthoxylum piperitum*-derived ingredients consist of numerous volatile aromatic and aliphatic hydrocarbons.

According to 2023 VCRP data, Zanthoxylum Piperitum Fruit Extract is reported to be used in 183 cosmetic products. The results of a concentration of use survey provided by the Council in 2021 only reported maximum use concentration data for Zanthoxylum Piperitum Fruit Extract in one product category (i.e., at up to 0.01% in body and hand spray products). Zanthoxylum Piperitum Peel Extract is the only other ingredient in this report for which use concentration data are being reported; this ingredient is being used at maximum use concentrations of up to 0.0022%.

Zanthoxylum piperitum extract appears on the FEMA list of flavoring ingredients that are classified as GRAS under the 1958 food additives amendment to the US Federal Food, Drug, and Cosmetics Act.

NICNAS noted that given the low molecular weight of the components of *Zanthoxylum piperitum* extract (supercritical carbon dioxide extract, < 500 Da, plant part not specified), its water solubility (5.69 mg/l - 1.56 g/l), and a log P_{ow} of 2.9 - 4.4, there is potential for *Zanthoxylum piperitum* extract to cross biological membranes.

The pharmacokinetics of a mixture containing *Zanthoxylum piperitum* fruit was studied using 16 subjects (fasted). The mixture was administered orally to each subject in doses up to 10 g. Hydroxy-α-sanshool, a constituent of *Zanthoxylum piperitum* fruit, had the highest plasma concentration (maximum concentration range: 0.76 to 2.66 µM). Its median half-life was 1.6 to 1.7 h, indicating rapid absorption and elimination.

A *Zanthoxylum piperitum* extract (supercritical carbon dioxide extract, in acetone, plant part not specified) was not mutagenic in an Ames test when tested at concentrations of up to 5000 µg/plate, with or without metabolic activation. Results were also negative in an in vitro micronucleus test, whereby human lymphocytes were incubated with *Zanthoxylum piperitum* extract (supercritical carbon dioxide extract, in DMSO, plant part not specified) at concentrations up to 640 µg/ml

(without metabolic activation) and up to 320 µg/ml (with metabolic activation). Neither a statistically nor biologically significant increase in the number of micronucleated cells was observed, and the test substance was neither clastogenic nor aneugenic to human lymphocytes.

The ability of a *Zanthoxylum piperitum* fruit extract to induce autophagic cell death was studied. Using phase-contrast microscopy, cells were treated for 24 h with 200 µg/ml of the *Zanthoxylum piperitum* fruit extract, and vacuoles were observed in the cytoplasm. Cell proliferation in at least 3 cell lines was inhibited. In a human colorectal cell line, the viability and number of cancer cells was reduced. The phosphorylation of c-Jun-N-terminal kinase in 6 different types of cancer cells was also measured. *Zanthoxylum piperitum* fruit extract appears to induce JNK-dependent autophagic cell death.

Apoptosis of *Zanthoxylum piperitum* extract in human cancer cell lines (Calu-6 for human pulmonary carcinoma and SMU-601 for human gastric carcinoma) was measured using the MTT assay to evaluate anti-cancer activity potential. The following concentrations (in DMSO) were tested: 25, 50, 100, 200, 400, and 800 µg/ml. In the Calu-6 cell line, the IC_{50} value for *Zanthoxylum piperitum* extract was 470.4 ± 13.1 µg/ml. In the SMU-601 cell line, the IC_{50} value for *Zanthoxylum piperitum extract* was 349.0 ± 9.1 µg/ml. Additionally, a dose-dependent inhibition of cell proliferation was observed.

The skin sensitization potential of 2% *Zanthoxylum piperitum* extract (supercritical carbon dioxide extract, plant part not specified) in ethanol: diethyl phthalate (1:3 w/w) was evaluated in an HRIPT involving 110 subjects. During induction, the test substance (on a 3.62 cm^2 occlusive patch) was applied repeatedly to the back. At challenge, the test substance was applied for ~ 24 h to a new site on the back. The test substance induced neither skin irritation nor sensitization.

The mechanisms, components, synergistic effects, and topical effects of a *Zanthoxylum piperitum* fruit extract were examined in one study to determine methods to reduce wrinkles non-invasively via mechanisms similar to BoNT/A injection. The *Zanthoxylum piperitum* fruit extract was identified as a wrinkle-reducing reagent and showed decreased lateral canthal rhytides in humans.

DRAFT DISCUSSION

[Note: This Discussion is in the draft form, and changes will be made following the Panel meeting.]

This assessment reviews the safety of 4 *Zanthoxylum piperitum*-derived ingredients as used in cosmetic formulations. The Panel concluded [TBD].

Though an HRIPT of *Zanthoxylum piperitum* extract (super critical carbon dioxide extract; plant part not specified) in ethanol at 2% deemed the ingredient neither a sensitizer nor an irritant, because the final product formulations may contain multiple botanicals, each possibly containing similar constituents of concern, formulators are advised to be aware of these constituents and to avoid reaching levels that may be hazardous to consumers. For *Zanthoxylum piperitum*-derived ingredients, the Panel was concerned about the presence of terpenes (e.g., linalool and limonene) in cosmetics, which could result in sensitization reactions. Therefore, when formulating products, manufacturers should avoid reaching levels of plant constituents that may cause sensitization or other adverse health effects. The Panel expressed concern about pesticide residues, heavy metals, and other plant species that may be present in botanical ingredients. They stressed that the cosmetics industry should continue to use current good manufacturing practices (cGMPs) to limit impurities in cosmetic formulations.

Finally, The Panel discussed the issue of incidental inhalation exposure resulting from these ingredients (for example, Zanthoxylum Piperitum Peel Extract is reported to be used at up to 0.0000022 % in face powders). Inhalation toxicity data were not available. However, the Panel noted that in aerosol products, the majority of droplets/particles would not be respirable to any appreciable amount. Furthermore, droplets/particles deposited in the nasopharyngeal or tracheobronchial regions of the respiratory tract present no toxicological concerns based on the chemical and biological properties of these ingredients. Coupled with the small actual exposure in the breathing zone and the low concentrations at which these ingredients are used (or expected to be used) in potentially inhaled products, the available information indicates that incidental inhalation would not be a significant route of exposure that might lead to local respiratory or systemic effects. A detailed discussion and summary of the Panel's approach to evaluating incidental inhalation exposures to ingredients in cosmetic products is available at https://www.cir-safety.org/cir-findings.

The Panel's respiratory exposure resource document (see link above) notes that airbrush technology presents a potential safety concern, and that no data are available for consumer habits and practices thereof. As a result of deficiencies in these critical data needs, the safety of cosmetic ingredients applied by airbrush delivery systems cannot be assessed by the Panel. Therefore, the Panel has found the data insufficient to support the safe use of cosmetic ingredients applied via an airbrush delivery system.

CONCLUSION

To be determined.

TABLES

Table 1. Definitions and reported functions of the ingredients in this safety assessment.[1]

Ingredient/CAS No.	Definition & Structures	Function(s)
Zanthoxylum Piperitum Fruit Extract 97404-53-0 (generic)	Zanthoxylum Piperitum Fruit Extract is the extract of the fruit of *Zanthoxylum piperitum.*	Skin-Conditioning Agents - Miscellaneous
Zanthoxylum Piperitum Oil 97404-53-0 (generic)	Zanthoxylum Piperitum Oil is the oil obtained from the fruit and fruit pericarp of *Zanthoxylum piperitum*.	Fragrance Ingredients
Zanthoxylum Piperitum Peel Extract 97404-53-0 (generic)	Zanthoxylum Piperitum Peel Extract is the extract of the peels of *Zanthoxylum piperitum*.	Cosmetic Biocides
Zanthoxylum Piperitum Peel Water 97404-53-0 (generic)	Zanthoxylum Piperitum Peel Water is the aqueous solution of the steam distillate obtained from the peel of *Zanthoxylum piperitum*.	Cosmetic Astringents; Fragrance Ingredients; Skin Protectants; Skin-Conditioning Agents - Miscellaneous

Table 2. Chemical properties of a *Zanthoxylum piperitum* extract (supercritical carbon dioxide)[2]

Property	Value
Physical Form (@ 20ºC and 101.3 kPa)	liquid
Molecular weight (Da; average of constituents)	< 500
Density (g/ml)	0.8984 – 0.9284
Water solubility (g/l)	0.00569 – 1.56 (estimated)
Partition coefficient (log P_{ow})	2.9 – 3.9 (aliphatic terpene constituents) (estimated) 4.2 - 4.4 (aliphatic cyclic constituents) (estimated)
Vapor pressure (kPa, @ 24 °C)	0.0249
Melting point (°C)	< -20 – 156 (based on primary constituents)
Boiling point (°C)	176 – 421 (based on primary constituents)
Flash point (ºC, @ 101.3 kPa)	39

Table 3. Composition data on a *Zanthoxylum piperitum* extract[2]

***Zanthoxylum piperitum* extract (supercritical carbon dioxide extract)**	
Constituents	***Percent composition***
linalyl acetate	30 - 50
linalool	10 - 20
limonene	5 - 10
3-cyclohexene-1-methanol, α, α,4-trimethyl-, 1-acetate	1 – 5
bicyclo [3.1.0] hexan-2-ol, 2-methyl-5-(1- methylethyl)-, 2- acetate; bicyclo [3.1.0]hexan-2-ol, 2-methyl-5-(1- methylethyl)-, 2- acetate, (1*R*,2*S*,5*S*)- *rel*-	5 - 15
2,6,8,10-dodecatetraenamide, *N*-(2-hydroxy-2- methyl propyl)-, (2*E*,6*E*,8*E*,10*E*)-	1 - 10

Table 4. Composition data on *Zanthoxylum piperitum* fruit pericarp[13,14]

***Zanthoxylum piperitum* fruit (fruit pericarp ethyl acetate extract)**			
Constituents	**Quantity (mg)**	**% composition***	**% of dry weight****
(6RS) -(2E,7E,9E)-6-hydroxy-*N*-(2-hydroxy-2-methylpropyl)-11-oxo-2,7,9-dodecatrienamide	5.4	0.13%	
(11RS)- (2E,7E,9E)-11-hydroxy-*N*-(2-hydroxy-2-methyl-propyl)-6-oxo-2,7,9-dodecatrienamide	4.8	0.11%	
(10RS,11SR)-dihydroxy-*N*-(2-hydroxy-2-methylpropyl)-2,6,8-dodecatrienamide	10.1	0.24%	
(10RS,11RS) -(2E,6Z,8E)- dihydroxy-*N*-(2-hydroxy-2-methylpropyl)-2,6,8-dodecatrienamide	4	0.10%	
(6RS,11SR)-6,11-dihydroxy-*N*-(2-hydroxy-2- methylpropyl)-2,7,9-dodecatrienamide)	17.2	0.41%	
(6RS,11RS) -(2E,7E,9E)-6,11-dihydroxy-*N*-(2-hydroxy-2- methylpropyl)-2,7,9-dodecatrienamide)	9.5	0.23%	
α-shanshool			0.32
γ-shanshool			0.21
hydroxy-γ-shanshool			0.08
hydroxy-α-shanshool			1.89

* percent composition calculated from 4.2 grams of extract

** percent of dry weight pericarp (37 – 150 g pericarp used in this experiment)

Table 5. Composition data on *Zanthoxylum piperitum* extract from dried pericarp and seed[27]

Constituents	Dried Pericarp Content (mg/100g dw)	Seed Content (mg/100g dw)
Hydrocarbons		
α-tocopherol	3.2	0.12
β-tocopherol	0.12	
δ-tocopherol	.35	2.8
δ-tocopherol	.27	

Table 6. Composition data on *Zanthoxylum piperitum* fruit extract.[24]

Compounds	Area (%)*
myrcene	1.49
3(5)-[[1,2-dihydroxy-3-propoxy]methyl]-4hydroxy-1h-pyrazole-5(3)-carboxamide	0.09
β-phellandrene	4.28
hex-3-yne	0.10
3-hydroxycyclohexanone	0.06
isopropyl hexanoate	0.12
terpinolene	0.59
vinylcyclooctane	0.07
2-tetradecynoic acid	0.10
citronellal	2.75
3-hydroxy-2,3-dihydromaltol	0.67
pulegol	0.29
octanoic acid	0.24
(e)-4-undecenal	0.10
4-isopropyl-2-cyclohexenone	1.04
citronellol	1.20
(e)-beta-ocimene	0.39
3,7-dimethylocta-2,6-dien-1-ol	0.65
spiro[4.4]nona-1,3-diene, 1,2-dimethyl-	0.21
piperitone	0.41
nonanoic acid	0.42
8,8-dimethoxy-2,6-dimethyloct-2-ene	0.98
p-isopropylbenzyl formate	0.40
citronellic acid	0.55
α-terpinene	0.24
2,6-octadiene, 2,6-dimethyl-	1.60
terpinyl propionate	0.43
geranyl acetate	4.60
3-methylcyclohexene	0.21
1,4-dimethyl-4beta-methoxy-2,5cyclohexadien-1α-ol	0.33
2-propenoic acid, 3-phenyl-, methyl ester	0.49
6-methylenespiro[4.5]decane	0.07
β-caryophyllene	0.67
bergamotane	0.09
3-methyl-4,7-dioxo-oct-2-enal	0.30
2,6-dimethyl-3,5,7-octatriene-2-ol, z,z-	0.24
2-dodecenoic acid	0.12
1,6,10-dodecatrien-3-ol, 3,7,11-trimethyl-	0.35
1-methyldecahydronaphthalene	0.46
cadina-1(10),4-diene	0.34
2-(4-methylcyclohexyl)prop-2-en-1-ol	0.42
tetradec-13-enal	0.24
9-octadecenoic acid	0.15
1,2-di-but-2-enyl-cyclohexane	0.10
4,12,12-trimethyl-9-methylene-5oxatricyclo[8.2.0.04,6]dodecane	0.11
3,4-*o*-isopropylidene-d-galactose	0.08
2-hexenoic acid, 6-cyclohexyl-	0.22
heptadec-8-ene	0.35
octane	0.35
myristic acid	0.44
D-(-)-kinic acid	1.35
nonadecanoic acid	0.35
10-bromoundecanoic acid	0.77
stearic acid	0.23
cysteamine s-sulfate	1.27

Table 6. Composition data on *Zanthoxylum piperitum* fruit extract.[24]

Compounds	Area (%)*
limonene dioxide	0.23
2,6-dimethyl-4-nitro-3-phenyl-cyclohexanone	0.26
methyl palmitate	0.46
2,6-dimethyl-1,3,6-heptatriene	0.68
palmitic acid	2.65
neral	1.58
2-methyl-6-methylene-1,7-octadien-3-one	0.75
bis(3-benzyl-2,4pentanedionato)palladium(ii)	1.03
pentamethylbenzenesulfonyl chloride	6.52
myrtenal	3.77
n,n-dimethyl-2-phenylethen-1-amine	20.61
allyl(chloromethyl)dimethylsilane	7.64
cyclohexene, 4-(4-ethylcyclohexyl)-1-pentyl-	1.64
3-epicycloeucalenol	1.09
2,5-furandione, 3-dodecenyl-	0.61
1-cinnamyl-3-methylindole-2-carbaldehyde	1.35
glyceryl palmitate	4.82
2-methyl-z,z-3,13-octadecadienol	0.37
pentadeca-2,3,6,9,12,13-hexaen-8-one, 2,5,5,11,11,14-hexamethyl-	0.51
6-(3,4-dimethoxy-phenyl)-8-ethoxy-1,3-dimethyl-cyclohepta[c]furan-4-one	1.04
monoolein	2.02
cyclohexene, 4-(4-ethylcyclohexyl)-1-pentyl-	1.56
cedrane-8,13-diol	0.12
26,27-dinorergosta-5,23-dien-3β-ol	0.18
cholest-4-en-3-one, 14-methyl-	0.07
(+)-sesamolin	0.08
5,5'-[tetrahydro-1h,3h-furo[3,4-c]furan-1,4-diylbis(oxy)]bis(2h-1,3-benzodioxole)	0.32
campesterol	0.12
stigmasta-5,22-dien-3-ol	0.06
clionasterol	0.15

* Peak area in GC-MS

Table 7. Composition data on *Zanthoxylum piperitum* fruit extract in 50% methanol [4]

Constituents	**MS/MS product ions***
adenosine	136.0625, 119.0357
quinic acid	111.0454, 83.0519, 69.0382, 95.0510
phenylalanine	120.0818, 103.0562, 149.0598, 131.0486
neochlorogenic acid	163.0399, 145.0292, 135.0451, 117.0349
procyanidin b1	127.0393, 409.0886, 287.0541
chlorogenic acid	163.0398, 145.0294, 135.0449, 117.0344
procyanidin b2	127.0404, 139.0407, 409.0897, 427.0983
magnoflorine	297.1112, 265.0851, 282.0878, 58.0690
epicatechine	139.0398, 123.0450, 147.0445, 161.0603, 207.0652
3-o-feruloylquinic acid	177.0548, 145.0288, 117.0343
rutin	303.0505, 465.1005, 129.0556, 85.0310
procyanidin b4	127.0403, 409.0878, 287.0529
hyperoside	303.0494, 229.0497, 257.0430, 91.0413
isoquercetin	303.0494, 229.0484, 145.0498, 85.0310
quercetin	229.0500, 257.0422, 201.0625, 285.0370
kaempferol	287.0551, 153.0185
astragalin	287.0546, 153.0209, 85.0299, 97.0323
isorhamnetin-3-o-galactorhamnoside	317.0648, 479.1149, 129.0554
quercitrin	303.0494, 85.0316, 71.0522, 129.0552
hesperidin	303.0855, 153.0184, 465.1347, 413.1184, 195.0285
kaempferol-3-o-α-l-rhamnoside	287.0550, 129.0554, 85.0308, 71.0519
hydroxyl-sanshool	105.0705, 91.0562,139.1002
unknown1	234.1490, 182.1179, 121.0662,278.1748
unknown2	284.2216, 302.2326, 266.2114, 248.2008
unknown3	105.0713, 117.0706, 145.1012
unknown4	128.0629, 143.0863, 121.0661, 119.0867
unknown5	262.1794, 105.0710, 149.0961, 95.0508
unknown6	117.0708, 145.0654, 115.0550, 159.0803
unknown7	347.0750, 332.0515
unknown8	369.0563, 329.0842, 613.1490

* Product ions via tandem mass spectrometry

Table 8. Composition data on a *Zanthoxylum piperitum* fruit oil[15,28]

	Ripe Fruit	Dried Pericarp
Constituents	**Relative Content***	**Relative Content***
Hydrocarbons		
aromadendrene	0.01	-
2-carene	0.01	trace
β-caryophyllene	0.23	0.08
α-copaene	-	trace
β-cubebene	0.02	0.01
p-cymene	trace	trace
decane	0.01	trace
β-elemene	0.02	0.01
p-ethyltoluene	0.01	trace
(*E, E*)-α-farnesene	-	0.03
germacrene D	0.23	0.12
α-humulene	0.06	0.01
isomer of farnesene	-	0.01
D-limonene	6.04	5.55
(E)-β-ocimene	0.01	0.01
p-mentha-1,4,8-triene	0.02	0.01
4-methyldecane	-	-
myrcene	0.92	0.83
(Z)-β-ocimene	0.02	trace
(*E*)-β-ocimene	0.01	0.01
β-phellandrene	3.64	3.35
α-pinene	0.02	0.01
β-pinene	0.01	0.01
sabinene	0.03	0.03
α-selinene	0.02	-
β-selinene	0.01	-
α-terpinene	trace	trace
γ-terpinene	-	trace
terpinolene	-	trace
toluene	0.01	-
undecane	0.08	0.01
camphene		
α-phellandrene		
α-calacorene		
calamenene		
γ-cadinene		
δ-cadinene		
α-muurolene		
γ_2-cadinene		
Alcohols		
8-acetoxylinalool	0.06	0.06
benzyl alcohol	-	trace
bisabolol	0.10	0.12
δ-cadinol	trace	0.11
(*E*)-carveol	0.01	0.01
(*Z*)-carveol	0.01	0.01
citronellol	0.28	0.05
3,7-dimethyl-1,5-octadiene-3,7-diol	0.01	0.01
elemol	0.11	0.03
endo-1-bourbonanol	0.05	0.03
β-eudesmol	0.02	0.01
geraniol	5.81	1.67
(Z)-3-hexenol	-	trace
1-hydroxylinallol	0.06	0.06
isopulegol	0.05	0.05
ledol	0.01	trace
linalool	0.44	0.15
p-mentha-(E)-2,8(9)-dienol	-	0.01
4-(1-methylethyl) benzenemethanol	0.04	0.01
1-methyl-4-(1-methylethyl) 2-cyclohexen-1-ol	0.12	0.05
2-methylpropanol	-	trace
myrtenol	0.02	0.01
piperitol	0.04	0.01
1,2-propanediol	-	0.34
spathulenol	0.03	0.01
terpinen-4-ol	0.03	0.01
1-terpineol	0.06	0.03
α-terpineol	0.01	0.05

Table 8. Composition data on a *Zanthoxylum piperitum* fruit oil[15,28]

	Ripe Fruit	Dried Pericarp
Constituents	**Relative Content***	**Relative Content***
δ-terpineol	0.03	0.01
trans-2,8-p-menthadien-1-ol		
cis-2,8-*p*-menthadien-1-ol		
methyl chavicol		
limonen-4-ol		
β-caryophylenne alcohol		
cuminalcohol		
1(7),8-*p*-menthadien-trans-2-ol		
nerolidol		
Aldehydes		
citronellal	8.55	1.36
4-ethylbenzaldehyde	-	-
geranial	1.79	0.06
(*E*,*E*)-2,4-hexadienal	0.01	trace
neral	0.31	0.04
perillaldehyde		
cuminaldehyde		
phellandral		
Esters		
cinnamyl acetate	0.02	0.01
citronellyl acetate	0.11	0.07
ethyl hexanoate	0.01	-
geranyl acetate	21.10	3.33
geranyl butyrate	0.03	0.02
isobutyl hexanoate	0.09	0.02
linalyl acetate	0.33	0.33
methyl benzoate	0.01	-
methyl cinnamate	0.56	0.16
methyl hexanoate	0.01	-
neryl acetate	0.02	-
α-terpinenyl acetate	0.12	0.12
isobutyl isovarelate		
isobutyl caproate		
Ketones		
cryptone		0.06
1-(3,4-dimethylphenyl) ethanone	0.03	Trace
isomer of ethylacetophenone	0.03	0.01
piperitone	0.31	0.08
valeranone	0.04	0.03
dihydrocarvone		
carvone		
Acids		
acetic acid	0.02	Trace
heptanoic acid	0.01	0.01
hexanoic acid		0.02
3-hexenoic acid	0.04	0.01
octanoic acid	0.01	0.01
Others		
caryophyllene oxide	0.02	0.01
1,8-cineole	0.15	-
2,5-dihydro-3-methyl furan	0.02	Trace
β-terpinen-3,4-oxide		
trans and cis Limonen-1,2-oxide		
terpinolene-4,8-oxide		

* = Relative content; average values calculated by comparing the peak are area of each compound with that of the internal standard, which is assigned the numerical value of 1, $n = 3$

- Quantity unlisted

Table 9. Composition data on a *Zanthoxylum piperitum* whole plant oil [16]

Constituents	***Percent composition***
citronellal	7.1
citronellyl acetate	-
cryptone	8.5
cuminal	6.2
geranyl acetate	15.3
limonene	18.0
linalool	-
β-myrcene	-
phellandral	5.2
β-phellandrene	-

Table 10. Composition data on *Zanthoxylum piperitum* peel extract [3,18]

***Zanthoxylum piperitum* fruit peel extract (methyl *t*-butyl ether extract) [3]**	
Constituents	**Percent composition**
β-caryophyllene	1.1%
citronellal	1.9%
D-limonene	44.3%
β-phellandrene	24.8%
volatile terpenes	0.012 (fresh weight)
***Zanthoxylum piperitum* fruit peel extract (methanol extract) [18]**	
Constituents	**Quantity (mg)**
3-*O*-caffeoylquinic acid	24.6
4-*O*-caffeoylquinic acid	8.3
(+)-catechin	10.1
(-)-epicatechin	27.8
procyanidin B1	14.2
procyanidin B2	24.7
procyanidin B4	17.6
hyperin	27.2
quercitrin	3.7
proanthocyanidin	2.10

Table 11. Frequency (2023) and concentrations of use (2021) according to duration and exposure[19,20]

	Zanthoxylum Piperitum Fruit Extract		Zanthoxylum Piperitum Peel Extract	
	# of Uses	Max Conc of Use (%)	# of Uses	Max Conc of Use (%)
Totals	**183**	**0.01**	**19**	**0.0000018-0.0022**
summarized by likely duration and exposure*				
Duration of Use				
Leave-On	*159*	*0.01*	*11*	*0.0000018-0.0022*
Rinse-Off	*24*	*NR*	*8*	*0.0022*
Diluted for (Bath) Use	*NR*	*NR*	*NR*	*NR*
Exposure Type **				
Eye Area	4	NR	NR	NR
Incidental Ingestion	NR	NR	NR	NR
Incidental Inhalation-Spray	81[a];51[c]	0.01	1;3 [a]	0.0000018
Incidental Inhalation-Powder	51[c]	NR	NR	0.0000022; 0.0022[b]
Dermal Contact	174	0.01	10	0.0000018-0.0022
Deodorant (underarm)	NR	NR	NR	NR
Hair - Non-Coloring	7	NR	9	NR
Hair-Coloring	NR	NR	NR	NR
Nail	NR	NR	NR	NR
Mucous Membrane	6	NR	1	NR
Baby Products	5	NR	NR	NR
as reported by product category				
Baby Products				
Baby Lotions/Oils/Powders/Creams	2	NR		
Other Baby Products	3	NR		
Eye Makeup Preparations				
Eye Lotion	3	NR		
Other Eye Makeup Preparations	1	NR		
Hair Preparations (non-coloring)				
Hair Conditioner			2	NR
Shampoos (non-coloring)	4	NR	3	NR
Tonics, Dressings, and Other Hair Grooming Aids	3	NR		
Other Hair Preparations			4	NR
Makeup Preparations				
Face Powders			NR	0.0000022
Foundations			3	0.0022
Makeup Bases	2	NR		
Personal Cleanliness Products				
Bath Soaps and Detergents	1	NR	1	NR
Douches	2	NR		
Other Personal Cleanliness Products	3	NR		
Skin Care Preparations				
Cleansing	13	NR	1	0.0022
Face and Neck (exc shave)	45	NR	NR	0.0022 (not spray)
Body and Hand (exc shave)	6	0.01 (spray)	NR	0.0022 (not spray)
Moisturizing	72	NR	3	0.0022 (not spray)
Night	3	NR	NR	0.0000018 (spray)
Paste Masks (mud packs)	1	NR	1	NR
Skin Fresheners	3	NR	1	NR
Other Skin Care Preparations	16	NR		
Suntan Preparations				
Suntan Gels, Creams, and Liquids			NR	0.00022 (not spray)

NR – not reported

*likely duration and exposure is derived based on product category (see Use Categorization https://www.cir-safety.org/cir-findings); because each ingredient may be used in cosmetics with multiple exposure types, the sum of all exposure types may not equal the sum of total uses.

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

[b] It is possible these products are powders, but it is not specified whether the reported uses are powders.

[c] 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

Table 12. *Zanthoxylum piperitum*-derived ingredients with no reported uses[19,20]

Zanthoxylum Piperitum Oil
Zanthoxylum Piperitum Peel Water

Table 13. Genotoxicity studies[2]

Test Article	Concentration/Dose	Vehicle	Test System	Procedure	Results
IN VITRO					
Zanthoxylum piperitum extract (carbon dioxide extract)	0, 1.5, 5, 15, 50, 150, 500, 1500 and 5000 µg/plate	acetone	*S. typhimurium* strains TA1535, TA1537, TA98, and TA100, and *E. coli* strain WP2uvrA (tests 1 and 2). *S. typhimurium* strains TA100 and TA1537 (test 3)	Doses with and without metabolic activation (tests 1 and 2). Doses without metabolic activation (test 3). Positive controls with metabolic activation: 2-aminoanthracene and benzo[a]pyrene. Positive controls without metabolic activation: 9-aminoacridine and 4-nitroquinoline-1-oxide	No biologically relevant increases in frequency of revertant colonies for any bacterial strain, either with or without metabolic activation. Two instances of slight increase in revertants (in different tests). These findings not dose-related and were not considered biologically relevant because they were within the range of historical negative controls. Test substance classified as non-genotoxic
Zanthoxylum piperitum extract (carbon dioxide extract)	Concentrations up to 260 µg/ml and up to 640 µg/ml (without metabolic activation). Concentrations up to 320 µg/ml (with metabolic activation)	DMSO	Human lymphocytes	Mammalian cell micronucleus test (OECD TG 487).	Inhibition of the cytokinesis block proliferation index at all test conditions. No statistically- or biologically significant increase in number of micronucleated cells with or without metabolic activation. Negative and positive controls performed as expected. Test substance not clastogenic or aneugenic to human lymphocytes

REFERENCES

1. Nikitakis J, Kowcz A, (eds). *International Cosmetic Ingredient Dictionary and Handbook*, Online Version (wINCI). https://incipedia.personalcarecouncil.org/winci/. Last Updated 2023. Accessed April 2023.

2. National Industrial Chemicals Notification and Assessment Scheme (NICNAS). Public Report: *Zanthoxylum piperitum* extract. File No. LTD/2126. https://www.industrialchemicals.gov.au/sites/default/files/LTD2126%20Public%20Report%20PDF.pdf. Last Updated 2020. Accessed October 4, 2021.

3. Fujita Y, Koeduka T, Aida M, Suzuki H, Iijima Y, Matsui K. Biosynthesis of volatile terpenes that accumulate in the secretory cavities of young leaves of Japanese pepper (*Zanthoxylum piperitum*): Isolation and functional characterization of monoterpene and sesquiterpene synthase genes. *Plant Biotechnol (Tokyo)*. 2017;34 (1):17-28.

4. Kim MH, Lee H, Ha IJ, Yang WM. *Zanthoxylum piperitum* alleviates the bone loss in osteoporosis via inhibition of RANKL-induced c-fos/NFATc1/NF-κB pathway. *Phytomedicine*. 2021;80:153397.

5. Kim MH, Lee HJ, Park JC, Hong J, Yang WM. *Zanthoxylum piperitum* reversed alveolar bone loss of periodontitis via regulation of bone remodeling-related factors. *J Ethnopharmacol*. 2017;195:137-142.

6. Gwon SY, Ahn JY, Kim TW, Ha TY. *Zanthoxylum piperitum* DC ethanol extract suppresses fat accumulation in adipocytes and high fat diet-induced obese mice by regulating adipogenesis. *J Nutr Sci Vitaminol (Tokyo)*. 2012;58(6):393-401.

7. Anonymous. 2022. Method of manufacture and composition Zanthoxylum Piperitum Peel Extract. Unpublished data submitted by the Personal Care Products Council on October 11, 2022.

8. Nozaki R, Kono T, Bochimoto H, et al. *Zanthoxylum* fruit extract from Japanese pepper promotes autophagic cell death in cancer cells. *Oncotarget*. 2016;7(43):70437-70446.

9. Chen K, Xue L, Li Q, et al. Quantitative structure-pungency landscape of sanshool dietary components from *Zanthoxylum* species. *Food Chem*. 2021;363:130286.

10. Yanase E, Ohno M, Harakawa H, Nakatsuka S. Isolation of *N,N*-dimethyl and *N*-methylserotonin 5-O-β-glucosides from immature *Zanthoxylum piperitum* seeds. *Biosci Biotechnol Biochem* 2010;74(9):1951-1952.

11. Aihara T. On the principales of *Xanthoxylum piperitum* DC. The structure of sanshoamide. *Society of Japan Pharmacy*. 1951;71 (10) 1112-1115.

12. Hieu TT, Kim SI, Ahn YJ. Toxicity of *Zanthoxylum piperitum* and *Zanthoxylum armatum* oil constituents and related compounds to *Stomoxys calcitrans* (Diptera: Muscidae). *J Med Entomol*. 2012 49(5):1084-1091.

13. Hatano T, Inada K, Ogawa TO, Ito H, Yoshida T. Aliphatic acid amides of the fruits of *Zanthoxylum piperitum*. *Phytochemistry*. 2004;65(18):2599-2604.

14. Yasuda Ichiro, Takeya Koichi, Itokawa Hideji. Distribution of unsaturated aliphatic acid amides in Japanese *Zanthoxylum* species. *Phytochemistry*. 1982;Volume 21, Issue 6:Pages 1295-1298.

15. Jiang L, Kubota K. Differences in the volatile components and their odor characteristics of green and ripe fruits and dried pericarp of Japanese pepper (*Xanthoxylum piperitum* DC). *J Agric Food Chem*. 2004;52(13):4197 - 4203.

16. Choi SI, Chang KM, Lee YS, Kim GH. Antibacterial activity of essential oils from *Zanthoxylum piperitum* A.P. DC. and *Zanthoxylum schinifolium*. *Food Sci Biotechnol*. 2008;17 (1):195-198.

17. Choochote W, Chaithong U, Kamsuk K, et al. Repellent activity of selected essential oils against *Aedes aegypti*. *Fitoterapia*. 2007;78(5):359-364.

18. Kusuda M, Inada K, Ogawa TO, et al. Polyphenolic constituent structures of *Zanthoxylum piperitum* fruit and the antibacterial effects of its polymeric procyanidin on methicillin-resistant *Staphylococcus aureus*. *Biosci Biotechnol Biochem*. 2006;70(6):1423-1431.

19. U.S. Food and Drug Administration Center for Food Safety & Applied Nutrition (CFSAN). Voluntary Cosmetic Registration Program - Frequency of Use of Cosmetic Ingredients. College Park, MD2023. Obtained under the Freedom of Information Act from CFSAN; requested as "Frequency of Use Data" January 4, 2023; received February 2, 2023.

20. Personal Care Products Council. 2021 Concentration of use by FDA product category: 2022 draft priorities - *Zanthoxylum piperitum*-derived ingredients. Unpublished data submitted by the Personal Care Products Council on July 7, 2021.

21. European Commission. Cosing database; following Cosmetic Regulation (EC) No. 1223/2009. https://ec.europa.eu/growth/tools-databases/cosing. Last Updated 2023. Accessed April 2023.

22. Expert Panel of the Flavor and Extract Manufacturers Association. GRAS Flavoring Substances 26. 2013. https://www.femaflavor.org/sites/default/files/26.%20GRAS%20Substances%20%284728-4778%29.pdf Accessed May 16, 2022.

23. Chon SU, Heo BG, Park YS, Kim DK, Gorinstein S. Total phenolics level, antioxidant activities and cytotoxicity of young sprouts of some traditional Korean salad plants. *Plant Foods Hum Nutr*. 2009;64(1):25-31.

24. Oh K, Adnan M, Cho D. Uncovering mechanisms of *Zanthoxylum piperitum* fruits for the alleviation of rheumatoid arthritis based on network pharmacology. *Biology (Basel)*. 2021;10(8).

25. Munekage M, Kitagawa H, Ichikawa K, et al . Pharmacokinetics of daikenchuto, a traditional Japanese medicine (kampo) after single oral administration to healthy Japanese volunteers. *Drug Metab Dispos*. 2011;39(10):1784-1788.

26. Hwang W, Kim D, Kwon OS, Kim YS, Ahn B, Kang NG. Topical application of *Zanthoxylum piperitum* extract improves lateral canthal rhytides by inhibiting muscle contractions. *Sci Rep*. 2020;10(1):21514.

27. Hisatomi E, Matsui M, Kubota K, Kobayashi A. Antioxidative activity in the pericarp and seed of Japanese pepper (*Xanthoxylum piperitum* DC). *J Agric Food Chem*. 2000;48(10):4924-4928.

28. Sakai T, Yoshihara K, Hirose Y. Constituents of fruit oil from Japanese pepper. *Bull Chem Soc Jpn*. 1968;41(8):1945-1950.