Safety Assessment of Avena sativa (Oat)-Derived Ingredients as Used in Cosmetics

Status: Release Date: Panel Meeting Date: Draft Final Report for Panel Review November 14, 2014 December 8-9, 2014

The 2014 Cosmetic Ingredient Review Expert Panel members are: Chairman, Wilma F. Bergfeld, M.D., F.A.C.P.; Donald V. Belsito, M.D.; Ronald A. Hill, Ph.D.; Curtis D. Klaassen, Ph.D.; Daniel C. Liebler, Ph.D.; James G. Marks, Jr., M.D.; Ronald C. Shank, Ph.D.; Thomas J. Slaga, Ph.D.; and Paul W. Snyder, D.V.M., Ph.D. The CIR Director is Lillian J. Gill, D.P.A. This report was prepared by Lillian C. Becker, Scientific Analyst/Writer.

© Cosmetic Ingredient Review

1620 L Street, NW, Suite 1200 & Washington, DC 20036-4702 & ph 202.331.0651 & fax 202.331.0088 & cirinfo@cir-safety.org



Commitment & Credibility since 1976

MEMORANDUM

To: CIR Expert Panel and Liaisons

From: Lillian C. Becker, M.S. Scientific Analyst and Writer

Date: November 14, 2014

Subject: Draft Final Report of Avena sativa (Oat)-Derived Ingredients as Used in Cosmetics

Enclosed is the draft final report for *Avena sativa* (oat)-derived ingredients.[*AvenaS_122014_Rep*] In September, 2014 the Panel issued a tentative report with the conclusion that 20 of 21 *A. sativa* (oat)-derived ingredients were safe as cosmetic ingredients in the practices of use and concentration of this safety assessment when formulated to be non-sensitizing; data are insufficient to come to a conclusion of safety for avena sativa (oat) meristem cell extract.

Concentration of use data were submitted by industry for the hydrolyzed ingredients that were added to this safety assessment in June, 2014.[*AvenaS_122014_Data1; AvenaS_122014_Data2*] This data has been incorporated. Comments from the Council have been addressed.[*AvenaS_122014_Council*]

The Panel is to examine the Abstract, Discussion, and Conclusion and determine if they reflect the Panel's thinking. Then the Panel should be prepared to issue a final report.

Avena Sativa (Oat) -Dervect Ingredients

SAFETY ASSESSMENT FLOW CHART

Dec 2014



*The CIR Staff notifies of the public of the decision not to re-open the report and prepares a draft statement for review by the Panel. After Panel review, the statement is issued to the Public.

**if Draft Amended Report (DAR) is available, the Panel may choose to review; if not, CIR staff prepares DAR for Panel Review.

History for Avena sativa-Derived Ingredients

March, 2014 – SLR posted for review

June, 2014 – Panel reviewed draft report. The Panel issued an insufficient data announcement. The additional information needed are:

(1) UV absorption and/or photo toxicity;

(2) irritation and sensitization, including the results of HRIPTs;

(3) methods of manufacture;

(4) identification of the ingredients included in this safety assessment that are also used in human food and/or animal feeds;

(5) molecular weight of the hydrolyzed ingredients; and

(6) peptide lengths of the proteins.

Hydrolyzed oat protein, hydrolyzed oat flour, and hydrolyzed oats were added to the report. Avena sativa (oat) starch was removed from the report and is included in the Plant Polysaccharide Gums report.

September, 2014 – The Panel examined the new data and issued a tentative report with a conclusion that *A. sativa*-derived ingredients were safe as cosmetic ingredients in the practices of use and concentration of this safety assessment when formulated to be non-sensitizing; data are insufficient to come to a conclusion of safety for Avena sativa (oat) meristem cell extract.

December, 2014 – The Panel is to issue a final report.

	Avena sativa-Derived Ingredient				is Data Profile for December, 2014. Writer - Lillian Becker													
	ŀ	ADME		Acute toxicity			Repeated dose Irritation			Sensitizatio								
	Dermal Penetration	${\sf Log}\;{\sf K}_{{\sf ow}}$	Use	Oral	Dermal	Inhale	Oral	Dermal	Inhale	Ocular Irritation	Dermal Irr. Animal	Dermal Irr Human	Sensitization Animal	Sensitization Human	Repro/Devel toxicity	Genotoxicity	Carcinogenicity	Phototoxicity
Avena sativa (oat) bran			х															
Avena sativa			Х															
Avena sativa (oat) flower/leaf/stem juice																		
(oat) kernel extract			х											Х				
Avena sativa (oat) kernel flour			х											Х				
Avena sativa (oat) kernel meal			Х															
Avena sativa (oat) kernel protein			х															
Avena sativa (oat) leaf extract												Р						
Avena sativa (oat) leaf/stalk extract												Ρ		Ρ				
Avena sativa (oat) leaf/stem extract												Ρ	х	Ρ		х		х
Avena sativa (oat) meal extract																		
Avena sativa (oat) meristem cell extract																		
Avena sativa (oat) peptide			Х															
Avena sativa (oat) protein extract			х															
Avena sativa (oat) seed extract Avena sativa																		
(oat) seed water Avena sativa (oat) sprout oil													х			Х		х
Avena sativa (oat) starch			х															
Avena sativa (oat) straw extract			х															
hydrolyzed oat protein			Х															
hydrolyzed oat flour			X															
nyuroryzed oats			^							1								
Colloidal oatmeal										Х		Х		Х				

X – Data on this ingredient is in the report

P – Data on plant parts that overlap/include this ingredient definition.

Search Strategy – Avena sativa-Derived Ingredients

SciFinder – CAS Nos., "Avena sativa", oats. 354 hits. Refined with "toxicity", "dermal", "skin". None useful.

ECHA – CAS Nos. 1 hit, not useful. "Avena sativa" 10 results, none useful.

PubMed - "Avena sativa" toxicity, 82 hits, none useful. "Avena sativa" dermal 3 hits.

("AVENA SATIVA (OAT)"[TW] OR "AVENA SATIVA (OAT)"[TW] OR "AVENA SATIVA"[TW] OR "AVENA SATIVA (OAT)"[TW] OR "AVENA SATIVA"[TW]), 2007 hits; AND tox*, 128 hits, 26 ordered; AND "derm*", 34 hits, 16 ordered; AND "ocular" 1 hit; AND "sensitiz*", 7 hits, 1 ordered.

FDA Poisonous Plant DB - "Avena sativa". 88 hits. Ordered ~20

Canadian Biodiverisity Information Facility – 1 reference ordered

FDA/GPO – "oat", "oats", "avena", "food ", "feed". Found a little more on FDA regulations on oats/grains.

Transcripts Avena Sativa-Derived Ingredients September, 2014

Dr. Belsito's Team

DR. BELSITO: Okay. Any other comments? So, now we're moving to *avena sativa*-derived ingredients, for which we've got a bunch of stuff in wave two. So, at the June meeting, we had an insufficient data announcement. We wanted method of manufacture. We wanted irritation and sensitization. We wanted (inaudible) absorption and/or phototoxicity. We wanted molecular weight of the hydrolyzed ingredients. We wanted fragments of the proteins, and some identification of the ingredients here that were also approved for use in human or animal food stuff.

We did get a lot of data on the hydrolyzed oats. We got data on weights of the small peptides. We got some manufacturing the hydrolyzed oats. We got some HRIPTs, in vitro toxicity. We had composition data. We got lots and lots of data. And then we got an article about oat sensitization in children with atopic dermatitis in addition to all of that.

So, I thought we had enough data to say everything but the meristem was safe, because I'm still not sure what's in the meristem. And the only other comment I had is, given the composition of the sprout oil -- I mean, I think we can keep it in this report and go safe as used, because we have composition. But wouldn't this have been something that would better have been put in the vegetable oils or plant oils that we reviewed, rather than kept in this report?

DR. LIEBLER: I agree. I also agree with keeping it in here. It's okay.

DR. BELSITO: I mean, because, otherwise -- we've already done the plant oil, so that would be, like -- this would just be dangling out there. But maybe someone can make a note that, 20 years from now, when it's time to review the plant oils, we might want to move this out into that report. Okay.

MS. BECKER: So, for the meristem, exactly what do we need?

DR. BELSITO: I would need to know the composition. I mean, what is in it? And it has no uses, right? The function is the same. So, I guess it would be covered by the other concentrations we're looking at here.

So, just some comments on the report -- on --

DR. SNYDER: Sorry. So, this has not been updated based on all that new data, right?

MS. BECKER: Not from wave two, no.

DR. SNYDER: Okay, so that eliminates a lot of my comments.

DR. BELSITO: Yeah, I mean, it may, you know -- I guess it eliminates mine. I mean, one was on page 30 of the PDF -- whether it was appropriate to put in the introduction as of this writing the essential data on method of manufacturing, but I guess (inaudible).

DR. SNYDER: -- needs to go, because we have all that data now. We have sensitization data (inaudible) because there's no data on irritation (inaudible) so --

DR. BELSITO: Yeah, okay.

DR. KLAASEN: Let's wait, then.

DR. BELSITO: On page 31 --

MS. BECKER: Before you go on with the meristem, I just want to point out it is the only one that is a humectant. Everything else is skin condition agents; some other kinds.

DR. BELSITO: Okay.

MS. BECKER: I don't know if you care, but --

DR. BELSITO: That's fine. On page -- PDF 31, the hydrolyzed wheat protein -- and when you're talking about multiple cases of allergic reactions, including type 1 -- I wasn't sure that it belonged there. It probably would -- should be put under the allergic reactions section, because it was just sort of sitting out there.

DR. ANSELL: We agree.

DR. BELSITO: In the introduction -- I mean, you're putting that in already into the introduction; should go back in --

DR. LIEBLER: Yeah, in the absence of evidence of some -- of a similar problem with oat as you have on wheat, this whole thing is perhaps not even (inaudible).

DR. BELSITO: Right.

DR. LIEBLER: You know, my suggestion was to condense, to paraphrase this in two or three sentences, but, also, it could be moved to the sensitivity section, because I don't think -- it just is too much of an unnecessary red flag to throw up right here, at this point of the report.

DR. BELSITO: Yeah, I think the whole purpose of introducing anything about hydrolyzed wheat is to get into the notion that we now understand that there needs to be a certain peptide length at which the IgE receptors can get bound. Because it's easier to measure molecular weight than it is to measure peptide length, we've decided to go with using a cutoff of molecular weight. That's the only reason we need to introduce the wheat at all, is, you know, because the, you know, amino acid structure of these hydrolyzed oat proteins is going to be different from amino acid structures of the wheat.

So, you know, I mean, it could essentially be that they don't create any problems; we're seeing that, in some atopic children, oats create problems. On the other hand, I think that, really, even as opposed to wheat, if you think about it, I mean, amino [Aveeno?] has made their name off of using oat products, and dermatologists have been recommending avena to atopic kids for years. So, their exposure to that particular company's products and to oat protein is huge.

So, one would expect that you might see some reports. As a food sensitizer, yeah, I mean, children can be, you know -- react to oat, but compared to soy, and tree nuts, and certain fruits, it's very low. And so, I mean, I'm not that concerned about this.

So, I mean, I think we're making too much of it, particularly right at the beginning of the document. And it really should go in when we introduce the concept that these can cause IgE-mediated allergic reactions. And what we found from wheat is that by eliminating size of the hydrolyzed protein, we can avoid that.

MS. BECKER: Okay.

DR. BELSITO: So, anyway, where I would move that summary from hydrolyzed wheat protein and really condense it would be on PDF page 39, where we're talking about IgA, IgG, delta top, with patients binding with components of the protein extracts, and then bring that concept in there.

DR. SNYDER: But not a complete iteration of the wheat report.

DR. BELSITO: No, no, just the concept of, you know, weight, and size, and the ability to bind IgE receptors.

DR. LIEBLER: In combination with no clinical evidence that this is --

DR. BELSITO: Right.

DR. LIEBLER: We've really got to keep it ---

DR. SNYDER: Yeah, tying it back to oats somehow.

DR. BELSITO: And then in the summary where you talk about the hydrolyzed oat -- I mean, they remain -- I think they should remain in the report. This is PDF page 41.

DR. SNYDER: In the discussion or conclusion?

DR. BELSITO: The summary.

DR. SNYDER: In summary.

DR. BELSITO: You know, again, that needs to just be moved down to where we're discussing reactions.

DR. SNYDER: So, in these -- this is the draft report? What is this? This is just a draft report, correct?

DR. GILL: This is a tentative report.

DR. SNYDER: Tentative -- I kind of don't like to have these (inaudible) the hydrolyzed

oat protein -- hydrolyzed oat protein and hydrolyzed oats and oat flour are to remain in this report -- I don't like those -- just write it the way it should be, and let us -- because that needs to come out of there now.

DR. BELSITO: Right.

MS. BECKER: Right.

DR. SNYDER: So, I don't like it when you insert those -- if these are to remain and blah, blah, blah. I mean, we can --

DR. BELSITO: Yeah, well -- yeah, exactly, because -- yeah, I got those -- that needs to come out. That paragraph in the introduction needs to come out. The paragraph further down on page 42 -- the Panel that they did on method of manufacture characterization needs to come out. Okay.

DR. LIEBLER: So, I just want to comment just a little bit further on this issue of peptide length and hydrolyzed proteins. The reason that we focused on this (inaudible) because we had data on different molecular weight structures being able to produce effects that are consistent with this hypersensitivity reaction --

DR. SNYDER: There's lots of -- tons of data suggesting that there was a sensitizer.

DR. LIEBLER: But there was -- the starting point was the sensitization reaction, as

observed --

DR. SNYDER: We don't have that with us.

DR. LIEBLER: -- clinically, as opposed to --

DR. SNYDER: We don't have that with us.

DR. LIEBLER: And I think we should be very careful about getting into sort of a cookie-cutter approach to these by saying, okay, if the hydrolyzed, you know, if the hydrolyzed protein or the peptide mix is below or above a certain length, then we have a problem -- because we don't have a problem unless we have a problem.

DR. SNYDER: Right. I think it goes to what Don was saying earlier, in that we do -- we're presented with a published report about atopic children having some issues, but that's totally not a normal population. And I wouldn't be surprised if they'd had reactions to lots of different things, but --

DR. BELSITO: They do. DR. SNYDER: Right. And so --

DR. LIEBLER: So, that -- yeah, that line of investigation and thinking was the solution to the wheat problem.

DR. SNYDER: Correct.

DR. LIEBLER: But it's not the solution to an oat problem, because there's not an oat

problem.

DR. SNYDER: Not applicable, not applicable. So, I think we can keep it really abbreviated, saying that we are aware of this (inaudible) atopic children, but that's more of an anomaly than an issue of concern to us regarding hydrolyzed --

MS. BECKER: I just wonder if any of this wheat should be in this report, period.

DR. LIEBLER: It's a fair question.

DR. GILL: Yeah, I was just going to suggest, it sounds more like a discussion issue that the Panel recognize that, you know, there may be some concern, but you didn't see that problem and just take anything discussing this out of the report.

DR. ANSELL: That would be our recommendation.

DR. LIEBLER: I think that's reasonable, too.

DR. GILL: All right.

DR. KLAASEN: And it's almost getting guilty by association, and there isn't any

association.

DR. LIEBLER: We surfaced it, and we need to dismiss it.

DR. SNYDER: Well, I think we did due diligence. We recognized there was a hydrolyzed

component. We asked to see -- make sure there was no data to suggest that there was sensitization (inaudible) proteins, derived proteins, and there's not. So, that's the end of it.

DR. KLAASEN: That part's okay, but we don't need to make -- I think it's a big mistake to say too much about the wheat.

DR. GILL: Okay.

DR. KLAASEN: And it almost makes the oat become guilty, and it's not guilty.

DR. GILL: Mm-hmm.

DR. SNYDER: And then we do have that -- we did have those 40 patients where they tested positive for IgE oat proteins, but there was no difference from the not-atopic individuals. So, I mean, we looked at it. We did due diligence. There's nothing there.

DR. BELSITO: So, not saying to -- am I understanding correctly, we're going to get all references to hydrolyzed wheat out of here, or just very minimally put it into the discussion at some point?

DR. GILL: At times, you will say just in case the issue comes up, should be acknowledged that the Panel discussed it. So, I would say put it in the discussion -- that we didn't see these issues (inaudible).

MS. BECKER: Okay, including the peptide length.

DR. LIEBLER: Right.

MS. BECKER: Okay. That's going to be difficult with the -- keeping with our practice of not introducing new information in the discussion that hasn't been mentioned in the body of the report.

DR. BELSITO: Yeah, but we've done that before, you know. We've, for instance, not asked for sensitization and data because there's been very little in the report, but we said, you know, based upon lack of clinical reports.

MS. BECKER: Okay.

DR. BELSITO: You know, I think that in the discussion, what we can say is that, you know, the Panel recognized that we're looking at hydrolyzed oat proteins; that, in the case of hydrolyzed wheat, there were issues with significant reactions. However, we have this data in the report that suggested this was not an issue with hydrolyzed oat, and you don't go into it any further.

So, we acknowledge in the discussion that we were aware of the hydrolyzed wheat issues. They're not relevant to what we're looking at here; that's all we're saying. We're not going -- we're not using the hydrolyzed wheat as an explanation --

DR. LIEBLER: (inaudible) --

DR. BELSITO: Right.

DR. LIEBLER: -- of concern here.

MS. BECKER: Okay.

DR. SNYDER: So, under that first --

DR. ANSELL: Would we have discussed wheat, had it not been in the report?

MS. BECKER: No, they brought up wheat, and I put it in for their discussion.

DR. ANSELL: Okay.

DR. SNYDER: I think that under tox studies section there, you've got two paragraphs there of which there's quite a bit of redundancy that we need to deal with. But I think that needs to be revised, based upon this discussion, right?

DR. BELSITO: Have you done that, Paul, for Lillian?

DR. SNYDER: A little bit, yeah. But I probably would revise it even more now, because of this most recent discussion.

DR. BELSITO: So --

DR. SNYDER: I mean, basically, the tox studies --

DR. BELSITO: Where are you?

DR. SNYDER: I'm at toxicological studies. It's page seven on mine, but I have a Word document. I don't --

DR. BELSITO: Okay, so toxicological studies -- what would you like to do? DR. SNYDER: I think we just need to say -- I mean, the first part's okay -- extensively in human food --DR. BELSITO: Right. DR. SNYDER: Okay, and then raise absorption -- that's all fine; I think probably just eliminate the second paragraph. DR. BELSITO: The proteins that serve --DR. SNYDER: Yeah. DR. BELSITO: So, that was the insert? DR. SNYDER: Yeah. MS. BECKER: Okay. DR. LIEBLER: That's fine. DR. SNYDER: Because I think it -- I mean, (inaudible) report -- is there any irritation/sensitization issues? And no, we have to --DR. BELSITO: You have a group that asks for which ones are fruit sources, so I think that's -- is that the basis on which this paragraph was added? MS. BECKER: A good deal of it, yes. DR. SNYDER: Because, I mean, the second paragraph repeats a lot of what's in the first. They're not absorbed through the skin. The oral exposures are much higher. DR. LIEBLER: So, I don't remember this specifically, but if the other group asks for that (inaudible) in that second paragraph --DR. SNYDER: That wasn't -- I mean, this was the one they asked for. Is this the report, or is it --DR. LIEBLER: Do you remember, Lillian? MS. BECKER: Yeah, they wanted more discussion on whether it's -- on the food. DR. BELSITO: Yeah, I mean --MS. BECKER: No, actually -- and the camellia, also. DR. BELSITO: No, but here, under our data needs, identification of the ingredients, including the safety assessments that are also used in human or animal feeds -- item six. DR. LIEBLER: So, that paragraph could actually stay -- the second paragraph under toxicological studies. DR. BELSITO: Well, maybe what we can do is highlight --DR. SNYDER: But it's just redundant --DR. BELSITO: I agree with you, Paul, I mean, but let's -- before we strike it here, let's just highlight it. And I don't want to get into a long discussion tomorrow with the other group about whether that needs to stay after we've said -- I mean, if they want it to stay, do you have a problem with it being there? Is there --DR. SNYDER: I mean, it's just two redundant paragraphs. DR. BELSITO: I understand. DR. SNYDER: Okay. So, we need (inaudible). DR. BELSITO: Let the editor revise it --DR. SNYDER: Okay. DR. BELSITO: -- you know, if the other group feels strongly that the entire paragraph --DR. SNYDER: Okav. DR. BELSITO: I'll just make a comment that we would delete (inaudible).

MS. BECKER: Or combine it with the previous paragraph.

DR. BELSITO: I don't even think you need to combine it. I agree with Paul. I had it marked for deletion; I thought it was redundant. But when I look at the data needs, I mean, we -- most of these data needs were brought up by the other Panel, not by us. Anything else, Paul?

DR. SNYDER: That's fine. DR. BELSITO: Anyone else? Okay.

Dr. Marks' Team

DR. MARKS: ...Lillian, you are here.

MS. BECKER: Yes. I made it.

DR. MARKS: Right on time, because there was nothing to (inaudible) to, you have all the final ingredients that we are reviewing, so I couldn't have done a tap dance, don't worry, when I'd get somebody to substitute for you here. Okay. The next ingredients are the --

MS. BECKER: Avena sativa.

DR. MARKS: -- avena sativa, and these are the oat-derived ingredients, in June we did an insufficient data announcement, and in Lillian's memo they are listed as six data points that we wanted. So Ron and Tom, how did -- Rons and Tom, how did you feel about what -- we've received a fair amount of data. Shall we go down one-by-one? I thought the UV absorption phototox, we did receive some -- received some data in Wave 2, and felt that was okay now.

Irritation and sensitization, okay. Leaf stem kernel and kernel extract, and flower, but interestingly if we had a conclusion that's formula to mean nonsensitizing, then maybe all the rest of the parts could be included. We'll come back to that.

Methods of manufacture, okay now, so page 33? Yeah. Identification about use in human food and animal feeds, and they are, so we've got that. And molecular weight of the hydrolyzed ingredients, and peptide lengths, and they are less than 3500 daltons, and less than 30 peptide lengths, so that should be okay. Is that what you read, Rons and Tom?

DR. SHANK: Yes.

DR. SLAGA: Are we sure about the molecular weights, less than 3,500?

DR. MARKS: Yes. I have 1000 average, is what I had.

DR. HILL: Yes. So although they've given an average without fully characterizing the distribution, that's the catch.

DR. SLAGA: Or what we could formulate, like we did with the weak hydrolyzed -- to be less than at molecular weight.

DR. HILL: I thought we were doing that in -- well, I thought it was proposed to do that anyway, it was supposed (inaudible), we didn't have that in the draft, but it was proposed to do that, by somebody?

MS. BECKER: That's just one of the possibilities. Yes, that's one of the possibilities. DR. HILL: Okay. I didn't dream it.

DR. SHANK: If the Panel is questioning the molecular weight of the peptides, from oat protein, hydrolsate, do we have to go back to corn protein, which we've already reviewed? And rice protein, which we've already reviewed as hydrolyzed proteins?

DR. EISENMANN: So I will remind you, you have a wheat protein out there that's safe, but that you didn't go back to, so I don't know that you want to go back to all these. Remember when you were doing the hydrolyzed wheat protein you acknowledged that you had -- that there is a weak protein itself that you have said --

DR. SHANK: The oat protein?

DR. EISENMANN: Right. The oat protein.

DR. SHANK: But then we were concerned about the hydrolyzed wheat protein, certain peptides. Now we are --

DR. EISENMANN: Because of the issues --

DR. SHANK: Now we are raising the issue with oats.

DR. EISENMANN: I mean, wheat is a food allergen, and it's got to be labeled as such. Oat is not, it's not quite the same -- I know sometimes there are issues, but there is -- there's some differences between wheat and oat, and I'm not sure you need -- necessarily need to put them in the same bucket.

DR. MARKS: Well, I was concerned --

DR. SHANK: Then why are we questioning routine hydrolysate?

DR. HILL: Because hydrolyzed food is not typically and chronically consumed, is it? I don't know --

DR. SHANK: Well, the argument was, we were concerned about wheat, hydrolyzed wheat protein because it's known people are allergic to the oat protein.

DR. HILL: Well, and then we had these reactions in Japan where people were --

DR. SHANK: For wheat?

DR. HILL: Yes.

DR. SHANK: Okay. So the people -- as far as I know, those people are not allergic to

oat protein.

DR. HILL: Okay. I get your -- I get your point here.

DR. SHANK: So why are now saying we have to have the data on oat -- hydrolyzed oat protein, and if -- it's just the molecular size of the peptide, then we have to go back to corn and rice, and whatever other hydrolysates we have reviewed. No? Yes? I'm asking --

DR. EISENMANN: I personally don't think it's necessary for you to go back to the other ones that you've reviewed.

DR. SHANK: Okay. So why is it necessary to talk about it with oat?

DR. EISENMANN: I don't know that it is necessary. You guys have said it's necessary. I mean, there are some case reports out there of people reacting, so there are -- I mean --

DR. SHANK: To oats?

DR. EISENMANN: To oats. But it's very widely used, oats. I mean colloidal oatmeal and there's a lot of oat ingredients that are widely used, and you just don't -- we haven't had the issue as what happened with wheat.

DR. MARKS: Well that was -- is my experience. In a review of the literature that was very interesting, it's a French report from 2007. I can't speak French, so I don't know how to say the author's -- either the first author or the senior author's name. This was in --

DR. HILL: Boussault? It's probably Boussault.

DR. MARKS: It was 2007. At any rate, the title is; Oat sensitization in children with atopic dermatitis; prevalence, risks and associated factors. Yeah. Boussault, is that how you say the first name?

DR. HILL: That would be my best guess.

DR. MARKS: Yeah. That's the first author. But at any rate it's really interesting, because they have a very high incidence of positive patch and prick tests to the material they tested.

DR. EISENMANN: The prick test was to pollen and not to kernel protein. It doesn't say it in there, but if you look at the paper, the prick test is to pollen, so they are testing two materials, so kind of.

DR. MARKS: Okay. But at any rate, they mentioned here, contradicts, it's higher than other published studies -- well, and no oat-sensitized child experienced any severe reactions. So I wasn't quite sure how to handle this paper, because their final sentence, they recommend not using them before the age of 2, in predisposed children, which means atopic, so they would suggest, these authors, not to use oat-derived products prior to age 2. But I felt a lot of what they did was a little bit contradictory, and I didn't know it was pollen. They said it's proteins.

So actually, I was reassured by finding -- and then if you go in and look at the colloidal oatmeal is okay in the report on page 37, that we have in this, so I was reassured with that, and I was

reassured with molecular weight, even though it's on average was much below the 3500 and now it's reassured the peptide length was a 7, less than -- which is much less than 30. And you know, perhaps, I'd put that in the discussion. I don't know how to handle this paper exactly.

DR. HILL: Well there's a response, a critique of that paper in data two, so maybe that's how to handle it.

DR. MARKS: So, option include a hydrolyzed -- Do you want to proceed? It seems like we have all the data needs now to a tentative report with a conclusion.

DR. BERGFELD: Could you restate where you are with this discussion?

DR. MARKS: Well I think we are at the point now that it appears we've -- the insufficient data, we have enough to satisfy that in our team's evaluation, and we should be able to move with a tentative report.

DR. BERGFELD: So the hydrolyzed and the non-hydrolyzed you are safe?

DR. MARKS: Well, we can get to that point. That's where next -- what is the tentative report, (inaudible)?

DR. BERGFELD: Well, in moving forward. Okay.

DR. MARKS: Exactly. And that's the way I feel, but Ron, Ron, Tom? Are all these ingredients safe?

DR. SLAGA: We have all the data needs, so I guess we could say it is.

DR. MARKS: Ron Shank?

DR. SHANK: Yes. Safe as used, recognizing that on page 34, there's a list of

oat-derived ingredients that are not used, so the usual notation on that is needed, but the others are safe as used. We got the information we asked for.

DR. MARKS: Okay, and no restrictions on the safe. That will be nice. Okay. We'll issue a tentative report that these oat-derived ingredients will have a conclusion of safe as used. And let me see. Who presents that tomorrow? I do.

SPEAKER: For everybody else, that's written.

DR. MARKS: Lillian?

MS. BECKER: How do you want to address the hydrolyzed wheat? Do you want it completely out, note the limit and peptide length, anything?

DR. MARKS: That's in the discussion.

MS. BECKER: Just in the discussion?

DR. MARKS: Ron?

DR. SHANK: Probably (inaudible). My question about the hydrolyzed protein was an aside; really, it doesn't pertain, in my opinion, to the safety of these ingredients. My point was, why are we asking for the size of the peptides for oat, what stimulated that? I think what stimulated that was the problem with wheat. So if that's the case then why don't we ask it for corn, whatever other proteins were reviewed?

MS. BECKER: So you would pick up sections on the wheat protein out of the paper?

DR. HILL: Let me address that though for a second. The sensitization that occurred with the wheat protein was pertinent to particular -- I don't know why we are getting the whistle -- pertinent to particular transformations that were occurring specifically, glutamine hydrolysis side chains. Although it was the trigger that people are allergic to wheat, the trigger was different in the sense that the past history of wheat allergy is a problem for those people who are exposed in the soak, that's been artificially treated to sensitize them.

So if a person is not allergic to wheat, it just means that whatever peptidases we have in our bodies aren't hydrolyzing the fragments, and definitely are hydrolyzing those side chains to make something that we would sensitize to. But we could still sensitize to something that was produced by the hydrolytic processes that result in the fragments of oat protein. So I think it is a reasonable question to ask to hydrolyze any protein; corn, whatever, and we get back to it.

It's a question that pertains. If people start making that same soap that they were using in Japan with hydrolyzed corn protein that's not hydrolyzed in the proper fashion, they might see the same phenomenon they saw with the wheat, based on the mechanisms that we saw for the sensitization. So I don't think we should pair it out, if we are going to include hydrolyzed wheat -- oat proteins in this repeat [report?].

DR. MARKS: Now the other -- looking at comments from the previous June meeting, Dianne had suggested separating out the kernel, bran, flower, meal protein seed, and oat components; and not include the flower, leaf and stem juice, leaf extract, leaf stalk extract, and leaf stem extract. And the (inaudible) stem cell extract about oat.

Our team, do we still feel, with all these we can go safe? I mean, I'm not sure why the others were eliminated. We certainly have leaf stem extract with sensitization data that indicates that it's fine. Can we read across to these others?

DR. HILL: My response to those specifically, is I remember, it was if we were leaving them in, and I wanted to see the method of manufacture, of some indication of how the extractions happen for all the ones that we were going to --

DR. MARKS: Okay.

DR. HILL: -- conclude to be safe. Or we can insufficient for these because of that, at the end. And I haven't cross-checked that list carefully to make sure I've got everyone.

DR. MARKS: Ron Shank? Tom? For tomorrow I -- just to make sure we are not surprised by a suggestion, and we aren't getting rid of them, which obviously --

SPEAKER: Not getting rid of them.

DR. MARKS: -- but the question was, should they be insufficient or not? And I think it was -- method of manufacture, we have enough data.

DR. HILL: I didn't look to see if we have that data and information on all of them, and I'm not sure that we do, so I need to crosscheck that. I'm sorry.

DR. MARKS: So, still, tomorrow, I'll move that we -- for the all ingredients, safe as used? DR. SLAGA: Safe as used.

MS. FIUME: Dr. Marks?

DR. MARKS: Yes.

MS. FIUME: Because these are botanicals, I think we've generally been putting -- when formulated to be nonsensitizing because of the constituents of concern, as part of our standard conclusion for botanicals. Is that not correct?

DR. BERGFELD: We are including it in the discussion rather than the conclusion.

DR. MARKS: No. It's been in the conclusion but I think that --

MS. FIUME: Grape came back because it wasn't in the conclusion.

DR. BERGFELD: Okay. I stand corrected.

DR. MARKS: So, usually that occurs -- now that would be reassuring based on this French article where they talk about sensitization, and that would take care of also the issue with hydrolyzed. Yeah? As I recall oftentimes we identify components of the plant ingredient that are sensitizers, and that was put it so that if multiple plants -- I assume there were components in here, but I quite frankly don't recall. But Ron, and Ron and Tom, how do you like that? With putting in formulated to be nonsensitizing?

DR. SHANK: That's fine.

DR. SLAGA: Yeah. I agree too.

DR. HILL: I wonder how industries' take on that would be though, because that requires demonstration of nonsensitizing; doesn't it? And why would we have to do that for a lot of these ingredients?

DR. MARKS: But if the only concern that Dan had on some of those others was mainly sensitization. Were there any other concerns on these other parts of this plant concerning systemic

toxicity, wheat pro or carcin? None of those, so that would actually also address the issue of, well, if there is any concern about not having irritation and sensitization studies, we've covered what (inaudible) --

MS. FIUME: And part of the rationale for including that in the conclusion is not only to address this ingredient, but it's also been formulated to (inaudible) to any other botanicals that could be added to those components.

DR. MARKS: Right. Okay. Thank you, Monice. So, I will move that we issue a tentative report tomorrow, with safe as used when formulated to be nonsensitizing. Thanks, Monice, for bringing that up.

DR. HILL: Just to bring up all of your multiple staff writers in the room, this is an example of boilerplate that needed to be glanced at a little, so there's language in the -- about inhalation and it says, the adverse effects reported using high doses of respirable particles in the inhalation studies. We don't have any inhalation studies.

DR. MARKS: Okay. Well we'll let -- that's an editorial. DR. HILL: Absolutely.

Day 2

DR. BERGFELD: ...Now we're moving on to the report's advancing to the next level and Dr. Marks has the first one, I believe is oats, *Avena sativa*.

DR. MARKS: So in June, these oat derived ingredients were assessed and an insufficient data notice or announcement was issued with a sixth request. Our team felt that these were addressed by what we have received since June and so we move to issue a tentative report, safe as used when formulated to be non-sensitizing for these oat derived ingredients.

DR. BELSITO: Are you including the meristem, for which we have no composition?

DR. MARKS: Yes. Our team didn't specifically pick that out as a need even, with the unsufficient data, so you want to clarify that Don, fine. We can react to that.

DR. BELSITO: What we had asked for composition of the ingredients. We got no composition of the meristem so --

DR. HILL: We raised that in discussion yesterday too, and I never did get to 100 percent comfort level, so --

DR. MARKS: So I can withdraw that motion and if you want to put insufficient data for that particular ingredient?

DR. BELSITO: Yeah, I'd also, I believe had no uses, so we were going insufficient for meristem for composition and concentration of use, but the other as safe.

DR. BERGFELD: So we have a first and second basically, just a modified motion.

DR. BELSITO: Correct.

DR. BERGFELD: All right. Any other comments? Ron Hill?

DR. HILL: He has some.

DR. BERGFELD: Don, sorry.

DR. BELSITO: Well I just thought that we had extensively revised the report, particularly in terms of the number of times the hydrolyzed wheat issue came into the report and exactly where it came into the report. But otherwise, and on page 35 of the pdf, we thought that that paragraph, the second, third paragraph under toxicological studies, just above dermal affects, could be completely deleted. It's basically a redundant paragraph to the paragraph above it. And then there were a number of comments throughout that about if hydrolyzed oat protein and flour were to remain in, all of those paragraphs need to come out, so there's an amount of -- there's extensive editing that needs to be done. But you know, all of them are safe as used when formulated to be non-sensitizing, except for the

meristem that needs composition and concentration of use.

DR. BERGFELD: Ron Hill, did you have a comment, or was it covered?

DR. HILL: No. No, I had a question but that's why we'll get --

DR. BERGFELD: Okay.

DR. HILL: In the discussion, it's on page 42, and it's the paragraph that starts with, because final product formulations may, et cetera, et cetera, et cetera, I just wondered -- it's the language dealing with quercetin, whether that actually, particularly the last couple of sentences' words I wrote here, does that get it? Does it say what we really want to say with regard to that?

DR. KLAASSEN: This is in the discussion?

DR. HILL: It's in the discussion and it's --

DR. BELSITO: 42 of the pdf, second paragraph.

DR. HILL: It's page 42 of the pdf and it's the second full paragraph.

DR. SNYDER: That's just our standards cumulative issue that we put in for botanicals, right? That when there's an ingredient of concern --

DR. HILL: It says we had these results however consistently negative in oral Gen-O tox [genotox] tests using mice and rats. Then it simply says, when formulating products manufacturers should avoid reach levels of this plant constituent that may cause sensitization or other adverse health effects. And can people make decisions based on that language? Is there anything else that needs to be added to that? Because it's so vague that we should take it out? I guess I'm --

DR. BERGFELD: Paul, did you have a comment?

DR. HILL: And this is not the final final, right? This is a draft?

DR. SNYDER: Yeah, I think it's just our normal warning that when you have a constituent of concern, that you have to be aware that when you start to create final product formulations, that you may get a cumulative effect. It may reach levels that may be a concern. And so I think that's just our standard language.

DR. HILL: I just wanted to raise the issue before we have it one more time. We will have it one more time, correct?

DR. MARKS: Yeah, so this is issuing a tentative report.

DR. HILL: I wanted to raise that so people would pay attention for next version.

DR. BERGFELD: Any other comments? Jim, do you have some?

DR. MARKS: I was just going to say, Ron Hill, we should see the draft final report the

next time.

DR. HILL: Just one last comment -- our team thought that the sprout oil should go in the plant oil document, in fact if that is ever revisited.

DR. BELSITO: Right.

DR. BERGFELD: Anything else? If no, let's call the question. All those in favor of safe, with the exclusion of the one ingredient, thank you, unanimous.

Safety Assessment of Avena sativa (Oat)-Derived Ingredients as Used in Cosmetics

Status: Release Date: Panel Meeting Date: Draft Final Report for Panel Review November 14, 2014 December 8-9, 2014

The 2014 Cosmetic Ingredient Review Expert Panel members are: Chairman, Wilma F. Bergfeld, M.D., F.A.C.P.; Donald V. Belsito, M.D.; Ronald A. Hill, Ph.D.; Curtis D. Klaassen, Ph.D.; Daniel C. Liebler, Ph.D.; James G. Marks, Jr., M.D.; Ronald C. Shank, Ph.D.; Thomas J. Slaga, Ph.D.; and Paul W. Snyder, D.V.M., Ph.D. The CIR Director is Lillian J. Gill, D.P.A. This report was prepared by Lillian C. Becker, Scientific Analyst/Writer.

© Cosmetic Ingredient Review

1620 L Street, NW, Suite 1200 & Washington, DC 20036-4702 & ph 202.331.0651 & fax 202.331.0088 & cirinfo@cir-safety.org

ABSTRACT

This is a safety assessment of *Avena sativa* (oat)-derived ingredients. The functions of these ingredients in cosmetics include: abrasives, antioxidant, skin-conditioning agents, absorbents, and bulking agents. The Panel reviewed relevant animal and human data related to the ingredient. Because final product formulations may contain multiple botanicals, each 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 *A. sativa*-derived ingredients, the Panel was concerned about the presence of quercetin in cosmetics. The Panel also stated that industry should use good manufacturing practices to limit impurities. The Panel concluded that most *A. sativa* (oat)-derived ingredients are safe as cosmetic ingredients in the practices of use and concentration described this safety assessment when formulated to be non-sensitizing; data are insufficient to come to a conclusion of safety for avena sativa (oat) meristem cell extract.

INTRODUCTION

This is a review of the available scientific literature and unpublished data provided by industry relevant for assessing the safety of *Avena sativa* (oat)-derived ingredients as used in cosmetics. The functions of these ingredients in cosmetics include: abrasives, antioxidant, skin-conditioning agents, absorbents, and bulking agents (Table 1). The 21 ingredients included in this report are:

Avena sativa (oat) bran	Avena sativa (oat) meristem cell
Avena sativa (oat) bran extract	extract
Avena sativa (oat) flower/leaf/stem juice	Avena sativa (oat) peptide
Avena sativa (oat) kernel extract	Avena sativa (oat) protein extract
Avena sativa (oat) kernel flour	Avena sativa (oat) seed extract
Avena sativa (oat) kernel meal	Avena sativa (oat) seed water
Avena sativa (oat) kernel protein	Avena sativa (oat) sprout oil
Avena sativa (oat) leaf extract	Avena sativa (oat) straw extract
Avena sativa (oat) leaf/stalk extract	Hydrolyzed oat flour
Avena sativa (oat) leaf/stem extract	Hydrolyzed oat protein
Avena sativa (oat) meal extract	Hydrolyzed oats

The *International Cosmetic Dictionary and Handbook*¹ defines colloidal oatmeal as finely ground oatmeal; the definition does not specify the species of oat from which it is derived. Therefore, any oat species (ie, *A. abyssinica*, *A. byzantine*, *A. nuda*, and *A. strigosa*) may be used to manufacture this cosmetic ingredient. However, some information on colloidal oatmeal does specify the source species. Therefore, when the colloidal oatmeal is derived from *A. sativa*, the data are included in this report for read-across.

The U.S. Pharmacopeia Convention (USP) defines colloidal oatmeal as derived from only *A. sativa* or *A. byzantina*; the USP definition does not include *A. nuda* or *A. strigosa*. The USP indicates that oats used to make colloidal oatmeal must meet U.S. standards for No.1 or 2 grade oats (ie, 97% or 94% undamaged oats, respectively) and may contain, singly or in combination, not more than 25% wild oats and other grains for which standards have been established under the U.S. Grain Standards Act.² [7CFR810.1001] When included in over-the-counter drugs, colloidal oatmeal is the name used for oat ingredients.

Even though "avena sativa" is not included in the names of the hydrolyzed oat flour or hydrolyzed oats, the Dictionary does specify that these ingredients are derived from the *A. sativa* plant, therefore appropriate for inclusion in this report.¹

Avena sativa (oat) kernel oil was reviewed by the Cosmetic Ingredient Review (CIR) Expert Panel (Panel) in 2011 and the Panel concluded that it was safe as used in cosmetics.³ The Panel also previously reviewed the safety of α -amino acids, animal- and plant-derived amino acids, hydrolyzed collagen, hydrolyzed corn protein, and triticum vulgare (wheat) gluten and concluded that these ingredients are safe as used in cosmetic products.⁴⁻¹⁰

Oats are included in the list of food grains and feed grains established under the United States Grain Standards Act.[7CFR810.101] *A. sativa* grains are used extensively in both animal feed and human food and the plant parts are used in animal feed, resulting in much larger oral exposures than would result from cosmetic uses. Therefore, the systemic toxicity potential of these cosmetic ingredients is not the focus of this report. Data on the potential for reproductive toxicity and genotoxicity are presented, but the primary focus of this report is on the potential of these ingredients to cause irritation and sensitization.

CHEMISTRY

Definition and Description

The definitions and functions of Avena sativa (oat)-derived ingredients are provided in Table 1.

A. sativa is a member of the *Gramineae* (grass) family.¹¹ The plant is an annual grass that grows up to 1.5 meters tall. The stems are smooth and may be tufted or solitary, and erect or bent at the base. The leaves are non-auriculate and green, with the sheaths rounded on the back. The cluster of flowers is a diffuse panicle with 2 to 3 florets, which can be either all bisexual or mostly bisexual with the distal one or two flowers reduced in size and either male or sterile. The grain is tightly enclosed in the hard lemma and palea. The seed size varies with cultivar (plant strain) and commonly yields approximately 30 000 seeds per kilogram of harvested plants.

Physical and Chemical Properties

The solid components of an alcohol extract of ground and macerated *A. sativa* seeds were reported to have a relative molecular mass of 1000 to 10 000 Da, as characterized by ultrafiltration.¹² The average molecular weight of small peptides for a batch of hydrolyzed oats was reported to be 1365 Da.¹³ The average molecular weight for hydrolyzed oats was reported to be approximately 1000 Da.^{13,14}

The high concentration of starch and β -glucan in colloidal oatmeal has a water-holding function; phenols have antioxidant and anti-inflammatory activity and are reported to act as ultraviolet absorbers.¹⁵ The cleansing activity of oat is from the saponins.

Some of the flavonoid constituents with phenolic structures strongly absorb A-band ultraviolet radiation (UVA) in the 320- to 370- nm range.¹⁶

CONSTITUENTS OF AVENA SATIVA

As in all plants, there are large numbers of constituents that make up *A. sativa* grains and other plant parts. Table 2 presents an overview of the constituent groups and subgroups. The constituent groups include:

Amino acids - Oats are rich in the amino acid lysine, approximately 4%.¹⁷ Other amino acids, including (-) threonine have also been identified as constituents by a supplier in a characterization of hydrolyzed oat protein.

Avenacins and Avenacosides – These are saponins. Avenacosides are biologically inactive until they are converted to antifungal monodesmosidic saponins (26-desglucoavenacosides A and B) in response to tissue damage.¹⁸ The stem and leaves contain bidesmosidic steroidal saponins (eg, avenacosides A and B); triterpenoid saponins and avenacin have been also reported in the root.¹⁸⁻²²

Enzymes – There are multiple enzymes found in A. sativa.^{23,24}

Carbohydrates - Mucilage (β -glucan), 3%-4% sugar (glucose, fructose), β -glucan, pentosans, saccharose, kestose, neokestose, bifurcose, neobifurcose, and acid galactoarabinoxylan have been reported.²⁰ Starch is the most abundant component of the oat grain, which is approximately 25%-30% amylose.^{20,25} Polysaccharide carbohydrates include starches and β -glucan.^{26,27} Carbohydrates mostly consist of araban and xylan gums.²⁸

Flavonoids – The following flavonoids have been isolated from *A. sativa* bran: kaempferol 3-*O*-(2",3"-di-*E*-*p*-coumaroyl)-α-L-rhamnopyranoside; kaempferol 3-*O*-(3"-*E*-*p*-coumaroyl)-α-L-rhamnopyranoside; kaempferol 3-*O*-(2"-*O*-*E*-*p*-coumaroyl)-β-D -glucopyranoside; kaempferol 3-*O*-β-D-glucopyranoside; kaempferol 7-*O*-α-L-rhamnopyranoside; linarin; tilianin; myricitrin; quercitrin; kaempferol 3-*O*-rutinoside; rutin; tricin 7-*O*-β-D-glucopyranoside; tricin; kaempferol; and luteolin.²⁹

The total flavonoid content in the *n*-hexane extract of an *A*. sativa whole plant was 40.72 ± 4.81 mg/g, and was 77.59 ± 6.71 mg/g in an ethyl acetate extract.³⁰ No flavonoids were detected in an ethanol or a water extract.

The stem and leaves are rich in apigenin and luteolin flavonoids (i.e., *C*-glycosylflavones), tricin flavones, and flavonolignans.³¹

Lipids – A. sativa contains higher levels of lipids, particularly those containing a high content of unsaturated fatty acids, than other cereal-type grains. The most abundant lipids are unsaturated triglycerides.^{32,33} The lipid content depends on genetic and environmental factors. The methods of extraction and analysis result in differences in the lipid content of the extracts.

Various lipids, like steryl esters, partial glycerides, free fatty acids, glycolipids, and phospholipids, were identified in oats.^{20,34}

A. sativa starches contain lipids ranging from 1% to 3%, present in the starch possibly as amylose–lipid complexes.³³

Phenolic compounds – At various growth stages, *A. sativa* has been found to contain a large number of phenolic compounds, including all major classes, in addition to avenanthramides: benzoic and cinnamic acids, quinones, flavones, flavonols, chalcones, flavanones, anthocyanidines, and aminophenolics.¹⁶ *A. sativa* oat flour contains the glyceryl esters of hydroxycinnamic, ferulic, *p*-coumaric, and caffeic acids.³⁵ Antioxidant activity is attributed to the presence of phenolic esters.^{16,36} *A. sativa* also contains various compounds with antioxidant activity, which serves to help protect the lipids from oxidation.¹⁶ Avenanthramides are soluble, phenolic compounds that are minor components of *A. sativa* (0.03% by weight).^{37,38,39} They have powerful anti-oxidative activity. They also have anti-inflammatory properties.⁴⁰ The stem and leaves contain phenolic compounds.^{31,41,42}

The total phenol content of the *n*-hexane extract of an *A*. sativa whole plant extract was $26.10 \pm 2.31 \text{ mg/g}$, $75.79 \pm 4.02 \text{ mg/g}$ in an ethyl acetate extract, $39.34 \pm 0.78 \text{ mg/g}$ in an ethanol extract, and $46.02 \pm 0.07 \text{ mg/g}$ in a water extract.³⁰

Proteins – *A. sativa* has a high level of total protein compared to other grasses.^{43,44} The primary storage protein is globulin.⁴³ The proteins in the stem and leaves include membrane proteins and soluble proteins of chloroplasts.¹⁸

Sterols - Sterols, sterylglycosides, acylated sterylglycosides, and steroidal saponins are present in oat leaves. The sterol moeities consisted mainly of sitosterol, stigmasterol, cholesterol, cholesterol, Δ^5 -avenasterol, Δ^7 -avenasterol, campesterol, campeslenol, lophenol, stigmastenol, Δ^7 -stigmasterol, and Δ^7 -cholesterol.^{20,45}

Vitamins and minerals – A. sativa contains a variety of minerals and vitamins.⁴⁴ These include vitamin E, mostly as α -tocopherol, which is a major antioxidant component in crude oat lipids. β - and γ -tocopherol are present in minor amounts.²⁴

CONSTITUENTS OF CONCERN

Quercetin – Quercetin has been reported to be in the hay of *A. sativa* at 310 ppm.⁴⁶ This constituent was positive for genotoxicity in an Ames assay.⁴⁷ It was also consistently positive in in-vitro tests of genotoxicity, and in some in-vivo studies via i.p. injections in mice and rats, but was consistently negative in oral-exposure genotoxicity tests using mice and rats.⁴⁸

CHARACTERIZATION OF AVENA SATIVA-DERIVED INGREDIENTS

Constituents of *A. sativa* plants may or may not be present in the ingredients, depending on cultivation conditions and manufacturing process.

A supplier reported that avena sativa (oat) kernel extract was reported to contain sugars at 91.0%, mineral ashes at 2.7%, proteins at 0.7%, polyphenols at 0.02%, and unidentified materials at 5.6%.⁴⁹ Glucose was identified as the only carbohydrate in the kernel extract.⁵⁰ The monosaccharides consist of 3.3% with MW of 180, polysaccharides with MW 25 000–300 000 are 91.9% of the carbohydrates, and polysaccharides with MW >300 000 are 4.9%.

The molecular weights of the peptides in hydrolyzed oat protein were reported to be 2000-4000.⁵¹ Hydrolyzed oat protein contained 25.2% glutamic acid in a characterization by a supplier (Table 3).

The composition of an avena sativa (oat) leaf/stem extract was reported to be: sugars, minimum 60%; flavonoids, 7%-10%; saponins, 1%.⁵²

The composition of avena sativa (oat) sprout oil (100%) was reported to contain glycerides of fatty acid residues consisting of 43% linoleic acid, 37% oleic acid, and 14% palmitic acid.⁵² This is similar to avena sativa (oat) kernel oil (linoleic acid, 22.8%-43.1%; oleic acid, 31.4%-51.26%; palmitic acid, 13.9%-18.82%).³

Method of Manufacture

Many solvents are used singly, serially, or in combination to make avena sativa (oat) kernel extract including ethanol, water and glycerin.

Avena sativa (oat) kernel extract can be manufactured by extracting the milled oat kernels with ethyl alcohol and water.⁵³ The ethyl alcohol is distilled off and the remaining extract is formulated in glycerin and water with potassium sorbate.

A supplier reported that in the manufacturing of avena sativa (oat) kernel extract, oat kernels, glycerin, and water are macerated for several days followed by draining and pressing.⁵⁴ The product is sterilized and packaged. Samples are sent for final analysis before being released for use.

Another supplier reports that avena sativa (oat) kernel extract is manufactured by solubilizing powdered *A. sativa* kernels in water followed by enzymatic hydrolysis.⁵⁵ The product is heated then filtered. Proteins are extracted by adsorption on an adjuvant. The soluble phase is concentrated, filtered and sterilized.

Avena sativa (oat) kernel flour is manufactured from dehulled, cleaned high quality oats processed under sanitary conditions.⁵⁶ Good manufacturing practices according to 21 CFR 110 and current USP Monographs are followed. There are no other ingredients used in the process.

To extract proteins from oat kernels, a first extract was prepared from dried grains (200 g) by extracting the grains twice with sodium hydroxide pH 8 (1 L) for 1 h at room temperature. After centrifugation, the supernatant was precipitated with hydrochloric acid (pH 5.4) and centrifuged. The precipitate was suspended in water, dialyzed overnight at 4°C using 6000-8000 Da molecular-weight cut-off dialysis bags, and lyophilized. A second extract was obtained from dried grains (40 g) by extracting with 200 mL 70% ethanol for 1 h at boiling temperature. This extract was then centrifuged and the precipitate dried. The second extract (2 g) was combined with the first one (1 g) to obtain the grain-protein extract.

It was reported by industry that to produce avena sativa (oat) leaf/stem extract, plantlets (young or small plants) are extracted with 80% acetone and water.⁵² The resulting medium is filtered and concentrated to 0.9-1 volume for 1 kg of engaged plant. After filtration of the aqueous concentrate, the extract is concentrated, filtered, and sterilized by filtration. It is further concentrated up to 40%-50% of dried extract. The medium is then stabilized and dried with maltodextrin. The resulting composition of the extract is: avena sativa (oat) leaf/stem extract, 75%; maltodextrin = 25%.

To produce protein-free extracts of *A. sativa*, young plants were air-dried and ground.⁵⁷ A 200-g sample of the dried, ground plant was extracted with 2 L acetone/water 80:20 (v/v) under constant agitation and refluxed for 1 h. After filtration, the extract was concentrated to eliminate the acetone and precipitate lipophilic compounds. Filtration and drying

produced a beige powder (yield 11.3%). An aliquot of the extract (2 g) was subjected to chromatography. Four fractions of eluent were collected by successive elution with 10 mL 25% methanol (fraction 1), 10 mL 50% methanol (fraction 2), and 20 mL 100% methanol (fraction 3). The same operation was repeated 3 times and the corresponding fractions were pooled to obtain 4 g of fraction 1, 0.58 g of fraction 2, and 0.27 g of fraction 3.

For the preparation of *A. sativa* plantlet-protein extract, fresh oat plantlets were homogenized in a buffered extraction containing Tris acetate, 100 mM pH 7.5/lithium chloride, 50 mM/dithiothreitol 20 mM/sodium dodecyl sulfate 40 g/L, 3M urea, and 1M thiourea, followed by a 1-hour maceration at room temperature. After filtration, the extracted fraction was purified by precipitation from acetone.

In the kernel-protein and plant-protein extracts above, protein concentrations were determined as 20% (w/w) and 40% (w/w), respectively. Analysis of the protein-free plant extract by silver nitrate protein staining showed no protein (limit of detection of 0.3 ppm).⁵⁷

In another procedure to produce extracts (information was unclear on the exact plant parts and the solvents used) without detectable proteins, young (prior to earing or the start of developing seeds) *A. sativa* plants are dried and crushed.⁵⁸ An extraction is performed with stirring for 1 h. The extract is filtered and the residue is rinsed. The filtrate is then concentrated, delipidated, and dried yielding an extract in powder form containing 2% to 15% flavonoids and 0.2% to 2% avenacosides A and B.

To manufacture avena sativa (oat) sprout oil, the oil is extracted from oat sprouts with acetone and the extract is filtrated. ⁵² The oil is then concentrated, followed by a final filtration.

The oatflake raw material used in the manufacture of hydrolyzed oats is food grade; the resulting hydrolyzed oats are not used in human food.¹³

Hydrolyzed oats is manufactured by mixing the oatflake with water then hydrolysis by enzymes.⁵⁹ The mixture is then filtered and evaporated. The liquid is spray dried to create a powder form. The products are analyzed and packed.

Another manufacturer reports that the manufacturing process entails enzyme hydrolysis of oats, followed by purification steps that include enzyme denaturation, filtration, evaporation, and preservation.¹⁴ The sodium hydroxide, enzymes, oats, potassium sorbate and disodium EDTA (ethylene diamine tetra acetic acid) are food grade. It is not known if the hydrochloric acid and sodium benzoate are also food grade.

Impurities

Analysis of an avena sativa (oat) leaf/stem extract and an avena sativa (oat) sprout oil (100%) showed that allergens listed in EU regulation 1223/2009⁶⁰ were below detection level as measured by gas chromagraphy-mass spectrometry (GC-MS); heavy metals (As, Cd, Cu, Fe, Hg, Ni, Pb, Zn, Ag, Ba, Se, Sb, Cr, and Co) totaled <20 ppm and that pesticide concentrations were compliant with EU Pharmacopeia^{61,52}

There were no detectable proteins (limit of detection of enzyme-linked immunesorbent assay [ELISA] less than 0.5 ppm protein) in an extract of young *A. sativa* plants (solvent(s) not specified).⁵⁸

Fusarium avenaceum, Pseudodiscosia avenae, and *Sclerospora macrospora* are among the species of fungi known to infect oat plants, including *A. sativa*.¹⁷ Two of five oat-based cereals tested positive for the mycotoxin deoxynivalenol (DON) at a concentration of 2.6 and $1.3 \mu g/g$ cereal.⁶² Three of these products tested positive for zearalenone (ZEA) at an average concentration of 16 ng/g cereal. Aflatoxin B₁ (AFB₁) was not detected in these samples. The mycotoxins DON, 3-acetyl DON (3AcDON), nivalenol, neosolaniol, T-2 triol, T-2 toxin, and HT-2 toxin (HT-2) were detected in samples of recently harvested oats (species/varieties not provided).⁶³ Samples were obtained from both conventional and organic farms. In *A. sativa* bran samples (n=30) collected from grocery stores and health food stores in Spain, ZEA was detected in 17% of the samples, DON in 17%, and ochratoxin A (OTA) in 20%.⁶⁴

Cadmium content in fresh *A. sativa* grown in Finland ranged from 0.008 to 0.120 mg/kg dry weight.⁶⁵ There was no difference in cadmium content between conventionally and organically grown crops. Nitrogen fertilization increased cadmium content. Cadmium content may vary by strain and may exceed the safe level for human consumption set by the European Commission (0.1 mg/kg fresh mass).⁶⁶

USE

Cosmetic

The *A. sativa* (oat)-derived ingredients were reported to function in cosmetics as abrasives, antioxidant, skinconditioning agents, absorbents, and bulking agents.¹

Data on ingredient usage are provided to the Food and Drug Administration (FDA) Voluntary Cosmetic Registration Program (VCRP; Table 4).⁶⁷ A survey was conducted by the Personal Care Products Council (Council) of the maximum use concentrations for these ingredients.⁶⁸⁻⁷⁰

Avena sativa (oat) kernel extract has the most reported uses, with 499 in cosmetic products. Avena sativa (oat) kernel extract also has the highest reported use concentration of 25% in face and neck products.^{67,68}

There were no reported uses for:

Avena sativa (oat) flower/leaf/stem juice Avena sativa (oat) leaf/stalk extract Avena sativa (oat) leaf/stem extract Avena sativa (oat) meristem cell extract Avena sativa (oat) seed extract Avena sativa (oat) seed water Avena sativa (oat) sprout oil

Avena sativa (oat) kernel extract was reported to be used in face and neck spray products in concentrations up to 0.0025% and avena sativa (oat) kernel protein in pump hair sprays up to 0.001%. In practice, 95% to 99% of the droplets/particles released from cosmetic sprays have aerodynamic equivalent diameters >10 μ m, with propellant sprays yielding a greater fraction of droplets/particles below 10 μ m compared with pump sprays.⁷¹⁻⁷⁴ Therefore, most droplets/particles incidentally inhaled from cosmetic sprays would be deposited in the nasopharyngeal and bronchial regions and would not be respirable (ie, they would not enter the lungs) to any appreciable amount.^{71,73}

Non-Cosmetic

A. sativa-containing products are used medically as dermal moisturizers and to treat itchy skin due to dryness, chicken pox, poison ivy/oak/sumac, and insect bites.⁷⁵ They are also used to treat acne.

Colloidal oatmeal, including that derived from *A. sativa*, is used in dermatological practice as an adjunctive therapy to treat many pruritic skin conditions such as cercarial dermatitis (swimmer's itch), chicken pox, poison ivy, oak and sumac, insect bites, winter itch, atopic dermatitis, dry skin, allergic or irritant contact dermatitis, and ichthyosis.^{38,39,76-81} Other indications for colloidal oatmeal products include prickly heat, hives, sunburn and rashes. It is regulated for these uses by the FDA as an over-the-counter (OTC) drug, and can be included in tub baths at a minimum concentration of 0.003% when combined with mineral oil.[21 CFR347.10(f), 21 CFR347.10(o)] Colloidal oatmeal is to be used in footbaths at a minimum concentration of 0.25%.[21CFR347.20]

For agricultural purposes, the FDA specifies that oats grain consists of 50% or more of oats (*Avena sativa* L. and A. *byzantina C*. Koch) and may contain, singly or in combination, not more than 25% of wild oats and other grains for which standards have been established under the United States Grain Standards Act.[7 CFR 810.1001]

The FDA defines the following foods derived from oats:

Oat bran - Oat bran is produced by grinding clean oat groats (hulled kernels) or rolled oats and separating the resulting oat flour into fractions such that the oat bran fraction is not more than 50% of the original starting material and provides at least 5.5% (dry weight basis [dwb]) β -glucan soluble fiber and a total dietary fiber content of 16% (dwb), and such that at least one-third of the total dietary fiber is soluble fiber.[21 CFR 101.81]

Rolled oats - Rolled oats, also known as oatmeal, produced from 100% dehulled, clean oat groats by steaming, cutting, rolling, and flaking, provide at least 4% (dwb) β -glucan soluble fiber and total dietary fiber content of at least 10%.

Whole oat flour - Whole oat flour is produced from 100% dehulled, clean oat groats by steaming and grinding, such that there is no significant loss of oat bran in the final product, and provides at least 4% (dwb) β -glucan soluble fiber and total dietary fiber content of at least 10% (dwb).

Oatrim - The soluble fraction of α -amylase-hydrolyzed oat bran or whole oat flour. Oatrim is produced from either oat bran, as defined in paragraph (c)(2)(ii)(A)(1) of 21 CFR 101.81 or whole oat flour, as defined in paragraph (c)(2)(ii)(A)(3), by solubilizing the starch in the starting material using an α -amylase-hydrolysis process, followed centrifugation to remove the insoluble components consisting of a high portion of protein, lipid, insoluble dietary fiber, and the majority of the flavor and color components of the starting material. The FDA regulation specifies that oatrim shall have a β -glucan soluble fiber content up to 10% (dwb) and not less than that of the starting material (dwb).[21 CFR 101.81]

TOXICOKINETICS

Since these ingredients are complex mixtures, data on the toxicokinetics of *A. sativa*-derived ingredients would not be practical. However, since these ingredients are consumed as food and feed, exposure to the components of these ingredients in cosmetics is expected to be lower than dietary exposure.

TOXICOLOGICAL STUDIES

A. sativa oats and other plant parts are used extensively in human food, as well as in animal feed resulting in much larger systemic oral exposures than would result from cosmetic uses. Thus, the potential for systemic effects, other than sensitization, are not discussed in detail in this report. The primary focus of this report is on the potential for irritation and sensitization.

DERMAL EFFECTS

Overview of Dermal Effects

The dermal effects of colloidal oatmeal derived from *A. sativa* have been attributed to the anti-inflammatory and antipruritic properties of the avenanthramides. These constituents have been shown to reduce oxazolone-induced contact hypersensitivity, resiniferatoxin-induced neurogenic inflammation, and induced histamine-mediated itch.⁸² In vitro,

avenanthramides reduced histamine release from mast cells stimulated by substance P. The buffering property of colloidal oatmeal (the pH of the skin surface is important for preservation of skin barrier function) was demonstrated when treatment with colloidal oatmeal reduced the elevated pH of diseased skin (eg, eczematous or pruritic) and alkali-treated normal skin to within the normal range. Other reported skin-barrier-related effects include the formation of a protective moisturizing barrier by the proteins and polysaccharides in colloidal oatmeal, which reduced transepidermal water loss (TEWL). Colloidal oatmeal has also been shown to act as an emollient, humectant and occlusive on the skin.⁸³ The application of *A. sativa* extracts to sodium lauryl sulfate (SLS)-treated skin has been reported to reduce irritation, demonstrating the anti-inflammatory effects of oats and suggesting potential benefits for the skin barrier.⁸⁴ *A. sativa* extracts reportedly inhibited the phospholipase A2 (PLA2)-dependent mobilization of arachidonic acid from phospholipids in cultured human keratinocytes.⁸⁵ This extract also inhibited the formation of eicosanoids, expression of cytosolic phospholipase PLA2, and formation of metabolites of prostacyclin in keratinocytes, all of which are implicated in the regulation of inflammation. An *A. sativa* extract oligomer reduced vasodilation induced by vasoactive intestinal peptide (VIP) in human skin samples.⁸⁶ Treatment with the oligomer reduced edema and mean surface of dilated vessels. It has also been reported that colloidal *A. sativa* extracts (both ethanol and phosphate buffer; with and without boiling) inhibited the activity of prostaglandin synthase of bull seminal vesicles.¹²

In Vitro

When fibroblasts from cosmetic surgery patients were incubated with *A. sativa* whole-young-plant extract (0.05%; solvent not provided), there was an increase in the proliferation of the cells and extension of a neoepithelium compared to untreated cells.⁸⁷ There were no differences in the number of basal layers up to day 20 post exposure, and then there were more layers observed in the treated cells on day 22. The dermal equivalent was created in a petri dish by combining the dermal fibroblasts with collagen type I. A punch biopsy from skin left over from surgery was used as the source of epidermal cells, which were then placed on the dermal equivalent, where a multilayered epidermis developed.

Non-Human

AVENA SATIVA WHOLE PLANT EXTRACT

In a wound-healing experiment using the *n*-hexane, ethyl acetate, ethanol, and water extracts of whole *A. sativa* plants, there were no adverse effects to Sprague-Dawley rats (n = 6+) and Swiss albino mice (n = 6+) when the extracts (1%, 0.5 g in an ointment base) were administered to wounds daily for 9 days.³⁰ The ethanol extract increased wound healing activity, the other extracts did not. The rats and mice were anesthetized and either two incisions along either side of the backbone or biopsy punches were performed. The extracts were administered to the wounds once per day for 9 days. The rats and mice were killed and the wounds excised. The healing of the incisions was measured by tensile strength across the wound and the healing of the punches was measured by area of healing.

Human

COLLOIDAL OATMEAL

In a blind study of acute burn patients (n = 35), a shower/bath oil containing colloidal oatmeal (5% in liquid paraffin), resulted in no adverse effects.⁸⁸ The group using colloidal oatmeal had reduced itchiness compared to the group using paraffin oil alone. The subjects showered or bathed with the test material or the same product without the colloidal oatmeal for 30 days. Patients who had been admitted to intensive care were excluded from this study.

Complete or marked itch relief was reported by over 71% of the subjects (n = 139; aged 21 to 91) suffering from pruritic dermatoses when colloidal oatmeal was used as a bath and regular cleanser for 3 months.⁷⁹

Pediatric subjects (n = 152) presenting with atopic dermatitis, contact dermatitis, fungus infections, or seborrheic dermatitis who were administered baths with colloidal oatmeal in an oil exhibited improved soothing and cleansing effects, with no irritation, compared to standard therapy.⁷⁷

REPRODUCTIVE AND DEVELOPMENTAL TOXICITY

Data on the reproductive and developmental toxicity of *A. sativa* (oat)-derived ingredients were not found in the published literature, nor were unpublished data provided.

Anti-Estrogenic Activity

When 23-24-day-old female rats (n = 5-10) were subcutaneously injected with any of 3 *A. sativa* hay extracts (0.15 mL in olive oil) and 0.05 μ g estradiol, uterine weights were less than in the rats injected with estradiol alone.⁸⁹ This result was consistent when the extraction solvent was ether, the chloroform-extract fraction of the ether extract, or the fraction obtained from the ether extract passed over an alumina column and eluted with chloroform. The extracts were processed by first extracting ground *A. sativa* hay with HCl followed by precipitation with ethanol. The solids were filtered out and discarded. The ethanol was evaporated and the remaining aqueous phase was extracted with ether in a separating funnel. The residue was then extracted with chloroform.

GENOTOXICITY

AVENA SATIVA (OAT) LEAF/STEM EXTRACT

In the Ames test performed following the Organization for Economic Cooperation and Development (OECD) 471 Guideline using *Salmonella typhimurium* (strains TA98, TA100, TA102, TA1535 and TA 1537), avena sativa (oat) leaf/stem extract (concentration not specified) was not mutagenic with or without metabolic activation.⁵²

Avena sativa (oat) leaf/stem extract (concentration not specified) was not mutagenic in a micronucleus test on mouse lymphoma cells (L5178Y/TK+/-) following OECD 487 guideline.⁵² The test material did not exhibit an in vitro intrinsic genotoxic potential in conditions of this study with or without metabolic activation.

AVENA SATIVA (OAT) SPROUT OIL

In 2 in vitro assays, avena sativa (oat) sprout oil (concentration not specified) was not mutagenic.⁵² In a Fluctuation Ames test, the test material was not mutagenic with or without metabolic activation system. In a micronucleus test, performed in accordance with OECD 487 guidelines, on Chinese hamster ovary (CHO) cells, the test substance did not demonstrate intrinsic genotoxic potential up to 1500 ppm without metabolic activation and up to 150 ppm with metabolic activation.

CARCINOGENICITY

Data on the carcinogenicity of *A. sativa* (oat)-derived ingredients were not found in the published literature, nor were unpublished data provided.

IRRITATION AND SENSITIZATION Dermal Irritation

Human

In a series of cumulative irritation tests (total n=1717), it was concluded that multiple products containing various *A*. *sativa* (oat)-derived ingredients (Table 5) were not irritants (Table 6).⁹⁰ The maximum irritation score was 0.326% (non-irritant score=2.9%-5.0%). The test substances (100%) were administered under semi-occlusion 3 times per week for 2 weeks. Patches were left in place for 48 or 72 h. Times of observations were not provided. The concentrations of *A*. *sativa*-derived ingredients ranged from 0.00002%-1% except for colloidal oatmeal which ranged up to 43.3%. This information was presented in aggregate and the individual studies on the individual ingredient-containing products were not provided.

In another series of dermal studies of 10 moisturizing products that contain *A. sativa* (oat)-derived ingredients (up to 1%) on subjects with various dermal issues, there were few adverse events and it was concluded in all tests that the test substance was well tolerated (Table 7).⁹¹ Most of these products contained multiple *A. sativa*-derived ingredients. Adverse events included burning rash and burning itching. There were no adverse events in subjects with diabetes or in babies and children.

AVENA SATIVA (OAT) PLANT EXTRACT

When a cream containing an extract of young *A. sativa* plants (information not clear on the type of extract, e.g., avena sativa (oat) leaf/stalk extract and/or avena sativa (oat) leaf/stem extract; concentration, amount applied, and extract solvent not provided) was administered to female subjects (n = 16) with dry skin, there were no signs of irritation.⁵⁸ Sixty-three percent of the subjects used for this study had sensitive skin and 81% had sensitive eyes. The cream was administered to one or the other elbow fold twice daily for 4 days, then once more on day 5. The cream was also applied to one side of the face once daily.

In another study of the same product, no irritation was observed when the cream was administered to the tapestripped skin of subjects (n=19). Both elbow folds were stripped 6 times and the test material administered 72 h later to one of the stripped sites. The test material was administered twice per day for 4 days, and once on the fifth day. The sites were examined for erythema, pruritus, heat, tingling, and burning on days 4, 5, 6, and 7. All subjects exhibited moderate to intense erythema after tape-stripping prior to administration of the test material. No erythema was observed in 14 subjects by day 4 or in any subject by day 8. No subjects exhibited any symptoms of a reaction.⁵⁸

When an emollient containing an extract of young *A. sativa* plants (concentration not specified), in addition to separately administered topical corticosteroids of both high- or moderate-potency, was administered to infant subjects (<12 month old; n=78, control=70) with moderate to severe atopic dermatitis, the tolerance evaluation was good to very good in 89% of the subjects at day 21 and 94% at day 42 for *A. sativa* emmollient.⁹² Three adverse events that were possibly treatment-related were reported as mild and 3 as moderate. Two were severe and treatment was discontinued. All of the adverse events resolved spontaneously. Further details about the adverse events were not provided. The amount of high-potency corticosteroids used by the parents on the subjects that were also administered the emollient reduced over time while the amount of moderate-potency corticosteroids did not.

The information was not clear on the type of extract, eg, avena sativa (oat) leaf/stalk extract and/or avena sativa (oat) leaf/stem extract that was in the emollient. The control group only administered the corticosteroids and the test group administered the corticosteroids and the emollient containing the *A. sativa* extract. The test substances were administered

twice daily; the parents of the emollient group were instructed to administer the test substance "...in sufficient amount on the dry, non-inflammatory areas of the skin, over the whole body" for 21 days. The parents were supplied with 2 bottles of the emollient (400-mL each). The corticosteroids (high- or moderate-potency) were administered by the parents to the subjects as needed to treat the atopic dermatitis. The unused portions of the corticosteroids were returned for weighing. The subjects were evaluated on days 1, 21, and 42.⁹²

COLLOIDAL OATMEAL

In 12 use safety studies of various personal care products containing *A. sativa* colloidal oatmeal, there was a low percentage of subjects (0–10.9%) who exhibited irritation and it was concluded that these products had a low potential for irritation (Table 8).⁹³ The concentrations of colloidal oatmeal were not provided. The products tested were a shower and bath oil, cream, moisturizing oil, shower gel, night cream, conditioning shampoo, body lotion, liquid hand wash, face and eye cleansing lotion (two products), facial exfoliating cleanser, intimate wash, and baby milk. Assessments, conducted by a dermatologist, included visual examination of skin dryness and appearance of the skin, as well as tactile evaluation of skin roughness. A 10-cm visual analog scale was used, where 0 represented "none" and 10 was "severe". The subjects self-assessed using a questionnaire with a five-point scale. Measurements were made on the treated body areas (leg and inner forearm), as well as on an untreated area on the mid-thigh, which served as a control site. Clinical assessments were performed only on the treated leg and on the control area.

There were no adverse effects reported for children (aged < 14 years) with mild atopic dermatitis who used 5 different baby products (n=55, 29, 75, 37, and 67) containing colloidal oatmeal (concentrations not specified) for 12 weeks.⁹⁴ Evaluation of their skin conditions were: improved in 201/263 cases after 3 months of treatment (in 153/263 after 2 weeks), remained unchanged in 60/263 (in 108/263 after 2 weeks), and deteriorated in 2/263.

No adverse effects were observed or reported by the subjects (n=54) with various dry skin conditions in an efficacy study of moisturizing lotion containing colloidal oatmeal (concentration not specified).^{20,95} Improvement of cutaneous lesions including erythema, scaling, scratching lesions, lichenification, and pruritus was reported in 52 out of 54 subjects. The lotion was used as the only treatment once a day for 3 weeks. Patients were allowed to use neutral cleansing daily.

In Vitro

AVENA SATIVA (OAT) LEAF/STEM EXTRACT

Avena sativa (oat) leaf/stem extract (100%) was rated as non-irritant in a Reconstructed Human Epidermis Model test (RHE Skinethic).⁵²

HYDROLYZED OATS

In an in vitro toxicity test using the MATREX system, hydrolyzed oats (100%) was not predicted to be a dermal irritant.⁹⁶ At 1%, 10%, and 100% the viability after 1 h was 97%, 121%, and 120%, respectively, compared to controls. Propylene glycol and morpholine served as the positive and negative controls, respectively. The test used a 3-dimensional construct of living cells on a collagen matrix that was to mimic human skin. Viability of the cells was measured photometrically after administration of tetrazolium salt (MTT).

In an in vitro toxicity test using the EpiDerm Skin Model, hydrolyzed oats (100%) was not predicted to be a dermal irritant.⁹⁷ At 1, 4.5, and 20 h the viability was 104%, 79%, and 99%, respectively, compared to controls. Triton X 100 served as the control. The test used human keratinocytes. Viability of the cells was measure by photometrically after administration of MTT.

Dermal Sensitization

Non-Human

AVENA SATIVA (OAT) LEAF/STEM EXTRACT

In a Local Lymph Node Assay (LLNA), using non-gravid female mice (n=5), of dermally administered avena sativa (oat) leaf/stem extract (1%, 10%, 25%, 50%, 70% in diluted propylene glycol/water, 50/50), the stimulation indexes were 0.7, 0.6, 0.9, 1.8, 4.4, respectively.⁵² The test substance was not a sensitizer at all concentrations except at 70% (SI \geq 3). The EC₃ was 59%.

AVENA SATIVA (OAT) SPROUT OIL

An LLNA of avena sativa (oat) sprout oil (2%, 10%, 30%, 100%) did not induce delayed contact hypersensitivity when dermally administered to female CBA mice (n=4) for 3 consecutive days.⁵² The protocol followed those in OECD 429 guidelines.

Human

In a series of repeated insult patch test (HRIPT; total n=5725), it was concluded that multiple products containing various *A. sativa*-derived ingredients (Table 5) were not sensitizing (Table 6).⁹⁰ Only 2 subjects had confirmed allergic responses to products containing 0.001% and 1% colloidal oatmeal. The follow-up data for these subjects was lost. The test

substance (100%) was administered under occlusion 3 times per week for 3 weeks for a total of 9. Patches were left in place for 24-72 h. After a 2-week rest period, a new patch was administered for 24 h. Times of observation were not provided. The concentrations of *A. sativa*-derived ingredients ranged from 0.00002%-1% except for colloidal oatmeal which ranged up to 43.3%. This information was presented in aggregate and the individual studies on the individual ingredient-containing products were not provided.

AVENA SATIVA (OAT) KERNEL EXTRACT

A paste mask product containing avena sativa (oat) kernel extract (25%) was not sensitizing in a double blind HRIPT (n=111).⁹⁸ No responses were observed at any phase of the study. The test material (150 μ L) was administered, under semi-occlusion, 3 days/week for 3 weeks and removed after 24 h. The challenge was administered on the fourth week of the study.

AVENA SATIVA (OAT) KERNEL FLOUR

A face powder containing avena sativa (oat) kernel flour (1%) was not sensitizing in an HRIPT (n=51).⁹⁹ In the induction phase, the test material was administered to the backs of the subjects and the patches left in place for 24 h. This was repeated 9 times consecutively. The test sites were observed immediately upon removal of the patch, or on the Monday following the removal of the patch on a Saturday. After a 2-week rest, the test material was administered to a naïve site, and was left in place for 24 h. The challenge site was observed at removal and at 48 and 72 h.

In an HRIPT (n=56) following the same procedure as the face powder, a blush containing avena sativa (oat) kernel flour (1%) was not sensitizing.¹⁰⁰

A body lotion that contained avena sativa (oat) kernel flour (0.1%) was not sensitizing in an HRIPT (n=93).¹⁰¹ One subject exhibited transient, low level (± 1) reactions accompanied by dryness, and another subject exhibited dryness. In the induction phase, 0.2 g of the test material was administered to the skin in the scapular region under occlusion. Induction exposure was repeated 9 times for 24 h each. The challenge was 0.2 g of the test material administered to a naïve site for 24 h. The test site was observed at 24, 48, 72, and 96 h after the challenge patch was removed.

HYDROLYZED OATS

Hydrolyzed oats (100%; 0.2 mL) was not sensitizing in an HRIPT (n=52).¹⁰² There were no signs of irritation or sensitization during the test. The test substance was administered to the scapular region under occlusion Monday, Wednesday, and Friday for 10 applications. All patches were removed after 24 h. After approximately 14 days of rest, the challenge patch was administered to a naïve site on the volar forearm.

OTHER AVENA SATIVA-DERIVED INGREDIENTS

In a use study of a cream and soap containing an extract of young *A. sativa* plants, subjects (n=8 females, 4 males) with a history of cereal-sensitized atopic dermatitis did not develop immediate or delayed-type hypersensitivity in response to the products after using them for 21 days.¹⁰³ The cream contained 12% and the soap contained 3% of the extract. Prior to and after the 21-day use study, none of the subjects displayed positive reactions in patch tests and skin prick tests of 5 fractions of the extract used in the products or the study cream. Total serum *A.sativa* IgE levels analyzed before and after the use study did not change.

In the first 10 days of the use study of the cream and soap, open application tests, prick tests, and IgE tests of the *A*. *sativa* extracts (colloidal 5%, phenolic 5%, acetonic 5%, enzyme-hydrolyzed phenolic 5%, acetonic 5%) and the cream were conducted on all subjects. During these 10 days, the subjects used their own cream and soap (ingredients unknown). On day 11, the test cream was administered to one half of each body. The vehicle cream, without the *A*. *sativa* extract, was administered to the other half of each body. The subjects showered 4 h later using the test soap. The subjects then used the cream containing the extract twice per day and showered with the soap once per day for a total of 21 days. The patch test and a skin prick tests were repeated after the use part of the experiment, and total IgE and *A*. *sativa*-specific IgE were measured.¹⁰³

In a group of children (under 15 years of age) referred for allergy testing (n=150 females, 152 males), 14.6% had positive results in a patch test of the *A. sativa* young-plant extract described above (1%, 3%, and 5%).¹⁰⁴ Sixteen of 44 subjects tested positive at 5%, 6 each for 3% and 5%, and 22 subjects reacted to all three concentrations.

In a skin prick test of the subjects in the previous study, 19.2% had positive reactions to oat pollen. Sensitization was observed in a total of 32.5% of the subjects demonstrated by either the patch or skin prick test; only four subjects tested positive in both tests. Sensitization decreased with the age of the subjects.

The authors concluded that the prevalence of sensitivity to *A. sativa* was higher than expected and could possibly be attributed to the prevalent use of cosmetics that contain some form of *A. sativa*. In a history survey of 67 of the subjects, no connection was found between sensitization and clinical signs (asthma, hay fever, atopic dermatitis severity); home location; proximity of cereal production; consumption of oats; skin prick test results to grass, cereal pollen or wheat pollen; or oat- or wheat-specific IgE. In the patch test, 100% of the subjects that had not used products containing *A. sativa* tested negative; only 66.7% of those that had used product containing *A. sativa* had negative results (p=0.0068).¹⁰⁴

There were no signs of irritation or sensitization in a human repeat insult patch test (HRIPT; n=104) of a cream containing *A. sativa* (concentration not provided; 50 μ L).⁵⁸ The test material was administered in a Finn chamber on days 1, 3, 5, 8, 10, 12, 15, 17, and 19 for 48 or 72 h. Two weeks later, the challenge patch was left on a naïve site for 48 h.

COLLOIDAL OATMEAL

Children (n = 65; 6 months to 2 years of age) that were atopic or non-atopic, with and without previous exposure to *A. sativa* colloidal oatmeal, did not show signs of immediate or urticarial allergic reactions to either of two bath products containing *A. sativa* colloidal oatmeal at the expected use concentration (0.007% in water) or at an elevated concentration (0.7% in water).¹⁰⁵ These subjects were also non-reactive to *A. sativa* colloidal oat flour (0.7% and 0.007% in water). The subjects were exposed to the bath products for 15 min. There were no reactions. Then a patch test using a pair of Finn chambers (50 μ L) for each test substance and concentration was conducted. One of each pair of chambers was removed and the test sites observed after 24 h, the second set was removed after 48 h. The skin under both sets of chambers was examined at 72 and 96 h after removal.

Of children (n = 302) with atopic dermatitis, 14.6% and 19.2% tested positive in a patch test and a skin prick test of *A. sativa* colloidal oatmeal.¹⁰⁴ Of those sensitized, 15.6% (5 of 32) and 28% (7 of 25) tested positive in an oral food challenge and a repeated open application test. Children with atopic dermatitis that were referred for allergy testing were administered patch tests and skin prick tests of oat proteins (1%, 3% and 5%) and the European standard series sensitization tests were performed. Subjects found to be sensitized to *A. sativa* colloidal oatmeal were administered an oral food challenge and repeated open application test. Children under 2 years of age were more likely to have a positive patch test than the older children. Thirty-two percent of the subjects who used *A. sativa* creams had oat-positive patch tests, while none of the nonusers exhibited sensitivity. The authors noted that *A. sativa* sensitization in children with atopic dermatitis was higher than expected. This may be the result of repeated applications of cosmetics containing *A. sativa* on the damaged epidermal barrier of these subjects. The authors suggested that topical creams containing *A. sativa* proteins should be avoided in infants with atopic dermatitis.

In 12 HRIPTs (total n=2291) performed using 12 skin care products containing *A. sativa* colloidal oatmeal, the products did not produce signs of sensitization (Table 9).⁹³ The test substances comprised 3 lotions, 2 face creams, 1 serum product, 2 cleansing lotions, 1 exfoliating cleanser, 2 baby products (1 cream and 1 cleanser), and 1 hand cream. The concentrations of colloidal oatmeal in the products were not specified. Overall, 23 subjects experienced a reaction. A total of 34 transient low-level grade \pm reactions (ie, faint, minimal erythema) were observed, including 1 subject with 8 consecutive faint erythema readings, 6 transient low-level grade 1 reactions in 6 subjects, and mild erythema in 1 subject. In the challenge period, 17 subjects had the following reactions: 18 transient low-level grade \pm reactions were not confirmed in subsequent patch tests on 2 of the subjects. The other subjects' reactions were confirmed for the complete product.

Photo-irritation and Phototoxicity

A. sativa has been reported to cause photosensitization when consumed by cattle, goats, pigs, and sheep.¹⁰⁶ No further information was provided.

In a series of phototoxicity tests (total n=485) and photoallergy tests (total n=1233), it was concluded that multiple products containing various *A. sativa*-derived ingredients (Table 5) were not phototoxic or photoallergenic (Table 6).⁹⁰ The maximum irritation score was 0.326% (non-irritant score=2.9%-5.0%). The concentrations of *A. sativa* (oat)-derived ingredients ranged from 0.00002\%-1% except for colloidal oatmeal which ranged up to 43.3%. This information was presented in aggregate and the individual studies on the individual ingredient-containing products were not provided.

In the phototoxicity test, the finished products were administered (100%) under occlusion on 2 sites on the subjects' back for 24 h. The patches were removed and one of the test sites exposed to UVA light (wavelengths and times not provided). Times of observation were not provided.

In the photoallergy tests, the finished products (100%) were administered on 2 sites on the subjects' upper back for 24 h. Following removal of the patch, one site was exposed to UVA and UVB light (wavelengths and times not provided). This was repeated twice per week for 3 weeks. After a 2-week rest, 2 more patches were administered for 24 h followed by the irradiation of one site with UVA light. Observation times were not provided. The subjects' skin was classified as having Fitzpatrick skin types I, II, or III.⁹⁰

AVENA SATIVA (OAT) LEAF/STEM EXTRACT

In a guinea pig maximization assay, avena sativa (oat) leaf/stem extract was not a photo-irritant up to 70% but was a slight photosensitizer (class II).⁵² No further details were provided.

In Vitro

AVENA SATIVA (OAT) SPROUT OIL

Avena sativa (oat) sprout oil (100%) was not phototoxic in a human Epidermis Model test (RHE SkinethicTM) in the presence or absence of UV.⁵² In an in vitro 3T3 phototoxicity assay, the test substance was not phototoxic. The test has performed according to OECD 432 guidelines. No further details were provided.

Ocular Irritation

Human

In a series of human ocular tests (total n=490), it was concluded that multiple products containing various *A. sativa*-derived ingredients (Table 5) were not ocular irritants (Table 6).⁹⁰ The concentrations of *A. sativa*-derived ingredients ranged from 0.00002%-1% except for colloidal oatmeal which ranged up to 43.3%. In vitro testing was conducted before these finished products were administered to humans. Irritation was determined by the measurement of lacrimation, stinging, and bulbar and palpebral redness. This information was presented in aggregate and the individual studies on the individual ingredient-containing products were not provided.

COLLOIDAL OATMEAL

In two use studies of a face and eye cleansing lotion containing *A. sativa* colloidal oatmeal (concentration not provided), the products caused little or no ocular irritation (Table 8).⁹³

In Vitro

AVENA SATIVA (OAT) LEAF/STEM EXTRACT

In a human corneal Epithelium (HCE) test, avena sativa (oat) leaf/stem extract was not predicted to be an irritant at 10% and 100%.⁵² Negligible cytotoxicity was observed in a neutral red uptake assay. The extract (100%) was predicted to be slightly irritating in a Hen's Egg Test – Chorioallantoic Membrane (HET-CAM) Test.

AVENA SATIVA (OAT) SPROUT OIL

In an HCE test, avena sativa (oat) sprout oil was not predicted to be an irritant at 10% and 100%.⁵² Negligible cytotoxicity was observed in a neutral red uptake assay. The extract (100%) was predicted to be slightly irritating in a HET-CAM Test.

TYPE I AND IV HYPERSENSITIVITY

The binding of IgE in the sera of 40 adult atopic dermatitis patients (35 with severe, chronic atopic dermatitis, 4 with urticaria, and 1 with rhinitis) to proteins from oats (species and source not specified) and other grains in immunoblotting experiments was evaluated.¹⁰⁷ The sera of 35 of the 40 patients tested positive for IgE binding to oat proteins in the radioallergosorbent test (RAST). Four non-atopic subjects served as controls.

The authors prepared an acidic extract and a neutral extract from milled oats ("oat flour" or, essentially, colloidal oatmeal) and other milled grains, then, for each grain, mixed equal amounts of the acidic extract and the neutral extract for immunoblotting. They separated the components of the mixed extract of each grain by sodium dodecyl sulfate-polyacrylamide gel electrophoresis (SDS-PAGE), and transferred the resultant protein bands to nitrocellulose sheets. The sera of 33 of the 40 patients bound to one or more of 10 protein bands of the oat extract mixture, including a 66 kDa protein, designated by the authors as the major allergen, and a 23 kDa and a 42 kDa protein, designated as "intermediate allergens." The remaining 7 proteins were designated minor allergens. The sera of the 5 patients with negative RAST results tested positive in the immunoblotting experiment, and the sera of the 7 patients with negative immunoblotting results were positive in the RAST. The oat allergens appeared to cross-react only weakly with the wheat, rye and barley allergens in this experiment. The authors stated that their results reveal the potential for proteins from oats and other grains to induce IgE-mediated type 1 immediate hypersensitivity reactions in adult atopic dermatitis patients. However, establishing a relationship between exposures to these substances and clinical allergic responses would require controlled elimination diet and challenge studies and characterization of the stability of the potential allergens after heating and in the gastro-intestinal tract.¹⁰⁷

The same authors examined the potential for IgA and IgG from the same 40 adult atopic dermatitis patients to bind to the components of the protein extracts of the same grains, including oats.¹⁰⁸ They found that the immunoblotting binding patterns of IgA and IgG in the sera of the patients were indistinguishable from the binding patterns of these antibodies in the sera of the non-atopic controls, in contrast to the binding patterns of IgE, which were clearly different for the atopic patients compared to the non-atopic controls.

In a review of oat and wheat contact allergens, the authors note that different results among the studies of sensitization and contact dermatitis may be due to several factors such as study population, type of allergy tests, and type and concentration of allergens.¹⁰⁹ Although prick tests and serologic tests for antigen-specific IgE to oat are useful in detecting immediate reactions such as contact urticaria, patch testing may detect delayed reactions manifesting as contact dermatitis or flares of atopic dermatitis. Patch testing with oat proteins and extracts should be performed more frequently, especially in

atopic children. It may help identify cutaneous sensitization and contact dermatitis, which may be the cause of flares in patients with atopic dermatitis.

Studies in the report on hydrolyzed wheat protein showed that hydrolysates with weight-average MW of approximately 3000 or less exhibit no potential to elicit hypersensitivity reactions in sensitized individuals, in contrast to hydrolysates with weight-average MWs >10,000.¹¹⁰ Substantial experimental results support the theory that a polypeptide must be at least 30 amino acids long (ie, MW approximately 3570, assuming an average of 119 /amino acid) to have the two IgE-binding epitopes needed to elicit Type 1 hypersensitivity reactions.

The manufacturing process of personal care products may function like cooking in that it destroys the protein structure to the point that the allergen loses the capacity to bind IgE and cause a type I response. However, T cells can react to short peptide sequences and may still elicit a type IV response even in finished products.¹¹¹ This means that type IV sensitivity may not be recognized when screening patients selected for antigen-specific IgE with skin prick tests or serologic tests.

It has been demonstrated that there are allergenic proteins in crude and refined peanut oil.¹¹² These proteins are the same size as 2 allergens previously described in peanut protein extracts.

CASE STUDIES

A 4-month old infant with atopic dermatitis and allergy to cow's milk tested positive in patch-tests (++) for sensitization to oats (species not specified) and exhibited a sensitization to wheat, which the child had never ingested.¹¹³ The authors suggested that, although sensitization to wheat in utero could not be eliminated, most likely the infant developed a cross-sensitization to wheat during exposure to a cream containing oats. At 1 year old, the child had results for the patch-test to wheat identical to the results at 4 months of age and remained on an eviction diet.

Three children (14 months, 2 years, and 14 years of age) with atopic dermatitis had positive patch tests for oatmeal extract (species not specified).¹¹⁴ The children all had histories of bathing with a product that contained an oatmeal extract. The eczema worsened after such baths. None of the subjects had a history of consuming oats.

A 3-year-old girl presented with an atopic dermatitis event on her arm and hands after using a moisturizer cream containing the young *A. sativa* plant extract.¹¹⁵ Serum IgE levels were elevated and a standard prick test was positive for *Dermatophagoides farina* and *D. pteronyssinus*. The subject had a family and personal history of other atopic maladies such as hay fever and rhinitis. Standard patch testing was positive for the cream at days 2 and 3 (++, ++). She was patch tested further with the ingredients of the cream (provided by the manufacturer) and was positive for the plant extract at days 2 and 3 (++, ++) but not for the zinc oxide and Vaseline® oil. The atopic dermatitis did not reoccur when she no longer used the product.

A 7-year-old girl presented with swollen lesions where an oat cream had been applied after bathing.¹¹⁶ The lesions appeared 15 min after application. She had a history of IgE-mediated allergic rhinoconjunctivitis, allergic asthma, and atopic dermatitis syndrome from the age of 3. The lesions were only on the application sites and resolved in less than 1 h without treatment. Skin tests were positive for grass, rice and oat pollens, and were negative for the other pneumoallergens and foods. An open patch test was positive, and swollen lesions were apparent on the right forearm 10 min after the cream was administered, which resolved 30 min after administration of oral cetirizine. The oat-specific IgE assay was positive (0.76 kU/L) and negative for the other cereals. The girl ate foods containing oats with no adverse effects.

A 33-year-old female presented with a persistent rash that had linear streaks of eczema, mostly on the forearm, the sides of her face and neck, and less so on her waist and ankles.¹¹⁷ The rash started 3 weeks after beginning a job weighing bird feeds that included oats. Patch test of the seeds had a ++ reaction to crushed oats at 48 h and + at 96 h. She also had a ++ reaction to bran at 96 h. The rash resolved when the subject avoided working with oats and bran. The rash reoccurred when she measured out oats and bran on two subsequent occasions.

A 33-year-old woman presented with atopic eczema and allergic rhinoconjunctivitis.¹¹⁸ She had a history of type 1 hypersensitivity reactions to dust mites, cats, dogs, malassezia, nuts, shrimp, lobster, and asparagus. She had used a moisturizer made for atopic and very dry skin, and contained *A. sativa* extract, for 1 year. The reaction began to appear approximately 6 months after she began using the moisturizer. The reaction faded a few hours after application. The subject noted that she experienced itching and swelling of the lips and pruritic, erythematous papules and patchy lesions on her trunk after eating breads containing oatmeal.

The patch test of the moisturizer was negative but the prick test was positive. Her total serum IgE was slightly elevated. Further analysis of her serum revealed immunoreactivity to a "casual" *A. sativa* extract but not another *A. sativa* extract with the proteins removed. The sera of three other cereal-sensitized subjects were tested with five different *A. sativa* extracts, one without proteins. Two subjects reacted to all of the extracts; the third did not react to any.¹¹⁸

SUMMARY

This is a safety assessment of 21 *A. sativa*-derived cosmetic ingredients. These ingredients function as abrasives, antioxidant, skin-conditioning agents, absorbents, and bulking agents. This safety assessment does not include colloidal oatmeal as the definition does not restrict the species of oats used to *A. sativa*. However, data from colloidal oatmeal that were confirmed to be derived from this species were included for read-across purposes.

Multiple fungi and their toxins have been reported in the plant, seed, dried hay, and/or in processed oat cereals. Avena sativa (oat) kernel extract has the most reported uses, with 499 in cosmetic products and the highest reported use concentration of 25% in face and neck products.

Dermal, anti-inflammatory and buffering effects have been attributed to *A. sativa*. Increased proliferation was observed in dermal cells incubated in extract of the whole plant of *A. sativa*. Dermal administration of a whole plant ethanol extract of *A. sativa* increased wound healing activity in rats and mice. There were no adverse effects when products containing colloidal oatmeal were used on subjects with damaged skin.

Female rats subcutaneously injected with any of 3 *A. sativa* hay extracts (0.15 mL) and estradiol had reduced uterine weights compared to rats injected with estradiol alone.

Avena sativa (oat) leaf/stem extract was not mutagenic with or without metabolic activation in an Ames test and a micronucleus test. Avena sativa (oat) sprout oil was not mutagenic with or without metabolic activation in a fluctuation Ames test and a micronucleus test.

In a series of cumulative irritation tests (total n=1717), it was concluded that multiple products containing various *A*. *sativa*-derived ingredients were not irritants. The concentrations of *A*. *sativa*-derived ingredients ranged from 0.00002%-1% except for colloidal oatmeal which ranged up to 43.3%.

Avena sativa (oat) leaf/stem extract and Avena sativa (oat) sprout oil at 100% was rated as non-irritant in a RHE test. Creams containing an extract of the entire young *A. sativa* plant were not irritating when administered to the intact and tape-stripped skin of human subjects for up to 5 days. In 12 use safety studies of various personal care products containing colloidal oatmeal (concentrations not specified), there were a low percentage of subjects (0–10.9%) who had positive reactions and it was concluded that these products had a low potential to cause irritation. An emollient containing an extract of young *A. sativa* plants, in addition to topical corticosteroids, administered to 78 infant subjects with moderate to severe atopic dermatitis was mostly well tolerated with 3 mild, 3 moderate, and 2 severe adverse events.

In a series of human ocular tests, it was concluded that multiple products containing various *A. sativa*-derived ingredients were not ocular irritants. Two use studies of a face and eye cleansing lotion containing colloidal oatmeal caused little or no ocular irritation. There were no adverse effects reported in children with mild atopic dermatitis who used several baby products containing colloidal oatmeal for 12 weeks.

Avena sativa (oat) leaf/stem extract and Avena sativa (oat) sprout extract were not predicted to be ocular irritants at 10% and 100%. Negligible cytotoxicity was observed in a neutral red uptake assay. The extracts at 100% were predicted to be slightly irritating in a HET-CAM test.

In an LLNA using mice of avena sativa (oat) leaf/stem extract, the EC_3 was 59%. Avena sativa (oat) sprout oil up to 100% did not induce delayed contact hypersensitivity when dermally administered to mice on 3 consecutive days.

A paste mask product containing 25% avena sativa (oat) kernel extract was not sensitizing in a double blind human repeat insult patch tests.

A face powder containing 1% avena sativa (oat) kernel flour, a blush containing 1% avena sativa (oat) kernel flour, and a body lotion containing 0.1% avena sativa (oat) kernel flour were not sensitizing in HRIPTs.

The use of a cream and soap containing the extract of young *A. sativa* plants (12%, and 3%, respectively) for 21 days did not result in hypersensitivity. In a patch test of children referred for allergy testing, 14.6% tested positive for a young plant extract of *A. sativa* at 1%, 3% or 5%. In a skin prick test of the same subjects, 19.2% had positive reactions to *A. sativa* pollen. An HRIPT of a cream containing an extract of the entire *A. sativa* plant (concentration not provided) was negative in 104 subjects. In HRIPTs performed of skin care products containing *A. sativa* colloidal oatmeal (concentration not provided), the products did not yield signs of sensitization. In a series of HRIPTs (total n=5725), it was concluded that multiple products containing various *A. sativa*-derived ingredients were not sensitizing; the concentrations of *A. sativa*-derived ingredients ranged from 0.00002%-1% except for colloidal oatmeal which ranged up to 43.3%.

The sera of 33 of the 40 patients tested positive for IgE binding to oat proteins in a RAST. The immunoblotting binding patterns of IgA and IgG in the sera of the patients were indistinguishable from the binding patterns of these antibodies in the sera of the non-atopic controls, in contrast to the binding patterns of IgE.

In a series of phototoxicity and photoallergy tests it was concluded that multiple products containing various *A*. *sativa*-derived ingredients were not phototoxic or photoallergenic; the concentrations of *A*. *sativa*-derived ingredients ranged from 0.00002%-1% except for colloidal oatmeal which ranged up to 43.3%. In a guinea pig maximization assay, avena sativa (oat) leaf/stem extract was not a photo-irritant up to 70% but was a slight photosensitizer. Avena sativa (oat) sprout oil at 100% was not phototoxic in a RHE SkinethicTM test in presence or absence of UV.

There are several reported cases of atopic dermatitis as a result of using products containing A. sativa ingredients.

DISCUSSION

The Panel acknowledged that *A. sativa* grains are used extensively in both animal feed and human food and the plant parts are used in animal feed, resulting in much larger oral exposures than would result from cosmetic uses. Therefore, the Panel was not concerned about the systemic toxicity potential of most of these cosmetic ingredients. There were no available data on the composition or concentration of use for avena sativa (oat) meristem cell extract. Because potential differences may exist between the meristem cells and the other ingredients for which data were provided, the Panel stated that

composition and concentration of use data for avena sativa (oat) meristem cell extract were needed to come to a conclusion on safety.

The Panel expressed concern about pesticide residues and heavy metals that may be present in botanical ingredients. They stressed that the cosmetics industry should continue to use current good manufacturing practices (cGMP) to limit impurities. The Panel noted that aflatoxins have been detected in *A. sativa* plants, seeds, dried hay, and/or in processed oat cereals. They recognized the U.S. Department of Agriculture (USDA) designation of ≤ 15 ppb as corresponding to "negative" aflatoxin content and concluded that aflatoxins will not be present at levels of toxicological concern in *A. sativa*-derived ingredients.

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. For *A. sativa*-derived ingredients, the Panel was concerned about the presence of quercetin in cosmetics, which was positive for genotoxicity in an Ames assay, consistently positive in in-vitro tests of genotoxicity, and in some in-vivo studies via ip injections in mice and rats. Therefore, when formulating products, manufacturers should avoid reaching levels of this plant constituent, and any other constituent, that may cause sensitization or other adverse health effects.

The Panel discussed the issue of incidental inhalation exposure from face and neck spray products, body and hand creams, lotions, and powders. There were no inhalation toxicity data available. These ingredients are reportedly used at concentrations up to 0.0025% in cosmetic products that may be aerosolized and up to 0.01% in other products that may become airborne. The Panel noted that 95%–99% of droplets/particles would not be respirable to any appreciable amount. Furthermore, these ingredients are not likely to cause any direct toxic effects in the upper respiratory tract, based on data that shows that these ingredients are not irritants. Coupled with the small actual exposure in the breathing zone and the concentrations at which the ingredients are used, the available information indicates that incidental inhalation would not be a significant route of exposure that might lead to local respiratory or systemic effects. The Panel considered other data available to characterize the potential for *A. sativa*-derived ingredients as food for humans and feed for animals. They also noted little or no dermal irritation or sensitization, ocular irritation, and the absence of genotoxicity in Ames tests and micronucleous tests. A detailed discussion and summary of the Panel's approach to evaluating incidental inhalation exposures to ingredients in cosmetic products is available at <u>http://www.cir-safety.org/cir-findings</u>.

The Panel discussed the potential for these ingredients to cause Type 1 reactions in individuals. In the previous report for hydrolyzed wheat protein, the Panel limited the size of proteins to 3500 or less. The data provided for this assessment indicate that the ingredients in this report do not have the properties required to induce Type 1 hypersensitivity, thus the Panel concluded that these products had a low potential to cause sensitivity. Additionally, the Panel was not as concerned about the potential for protein in *A. sativa*-derived ingredients to cause Type I reactions because, compared to wheat, soy, eggs, and nuts, oats are not considered to be a major food allergen.

CONCLUSION

The CIR Expert Panel concluded that the following ingredients are safe in the present practices of use and concentration described in this safety assessment in cosmetics when formulated to be non-sensitizing:

avena sativa (oat) bran	avena sativa (oat) meal extract
avena sativa (oat) bran extract	avena sativa (oat) peptide
avena sativa (oat) flower/leaf/stem juice*	avena sativa (oat) protein extract
avena sativa (oat) kernel extract	avena sativa (oat) seed extract*
avena sativa (oat) kernel flour	avena sativa (oat) seed water*
avena sativa (oat) kernel meal	avena sativa (oat) sprout oil*
avena sativa (oat) kernel protein	avena sativa (oat) straw extract
avena sativa (oat) leaf extract	hydrolyzed oat protein
avena sativa (oat) leaf/stalk extract*	hydrolyzed oat flour
avena sativa (oat) leaf/stem extract*	hydrolyzed oats

Based on the data included in this report, the CIR Expert Panel concluded that the available data or information are insufficient to come to a conclusion on the safety of avena sativa (oat) meristem cell extract.

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

TABLES

Table 1.	Definition an	d function	of A	sativa-derived	l ingredients ¹
Lanc L.	Deminition an	u runcuon	0171.	sunva-activee	i ingreurents.

Ingredient	Definition	Function
Avena sativa (oat) bran	The broken coat of the kernels of oats, Avena sativa.	Abrasive, absorbent, bulking agent
Avena sativa (oat) bran extract	The extract of the bran of Avena sativa	Skin-conditioning agents – miscellaneous
Avena sativa (oat) flower/leaf/stem juice	The juice expressed from the flowers, leaves and stems of <i>Avena sativa</i> .	Skin-conditioning agents – miscellaneous
Avena sativa (oat) kernel extract 84012-26-0	The extract of the kernels of Avena sativa.	Antioxidant; skin-conditioning agent – emollient; skin-conditioning agent – miscellaneous
Avena sativa (oat) kernel flour 134134-86-4	A powder obtained by the fine grinding of the kernels of oats, <i>Avena sativa</i> .	Abrasive, absorbent, bulking agent; viscosity increasing agent – aqueous
Avena sativa (oat) kernel meal	A coarse meal obtained by the grinding of the kernels of oats, Avena sativa	Abrasive, absorbent, bulking agent
Avena sativa (oat) kernel protein	A protein obtained from the kernels of oats, <i>Avena sativa</i> .	Film former; hair conditioning agent; skin- conditioning agent – miscellaneous
Avena sativa (oat) leaf extract	The extract of the leaves of Avena sativa.	Cosmetic astringent
Avena sativa (oat) leaf/stalk extract	The extract of the leaves and stalks of <i>Avena</i> sativa.	Skin-conditioning agent – miscellaneous
Avena sativa (oat) leaf/stem extract	The extract of leaves and stems of Avena sativa.	Skin-conditioning agent – miscellaneous
Avena sativa (oat) meal extract	The extract of the meal of Avena sativa.	Skin-conditioning agent – miscellaneous
Avena sativa (oat) meristem cell extract	The extract of the cultured meristem cells ¹ of <i>Avena sativa</i> .	Skin-conditioning agent – humectant
Avena sativa (oat) peptide 151661-87-9	The peptide fraction isolated from Avena Sativa (Oat) Protein Extract by ultra-membrane filtration.	Film former; hair conditioning agent; skin- conditioning agent – miscellaneous
Avena sativa (oat) protein extract	The extract of Avena Sativa (Oat) Kernel Protein.	Skin-conditioning agent – miscellaneous
Avena sativa (oat) seed extract	The extract of the seeds of the oat, Avena sativa.	Hair conditioning agent; skin-conditioning agent - miscellaneous
Avena sativa (oat) seed water	An aqueous solution of the steam distillates obtained from the seeds of <i>Avena sativa</i>	Solvent
Avena sativa (oat) sprout oil	The oil obtained from the sprouts of Avena sativa.	Skin-conditioning agent – miscellaneous
Avena sativa (oat) straw extract	The extract of the straw of Avena sativa.	Skin-conditioning agent – miscellaneous
Hydrolyzed oat flour	The hydrolysate of avena sativa (oat) kernel flour derived by acid, enzyme, or other method of hydrolysis.	Hair conditioning agent; skin-conditioning agent – miscellaneous
Hydrolyzed oat protein	The hydrolysate of oat protein derived by acid, enzyme, or other method of hydrolysis.	Hair conditioning agent; skin-conditioning agent - miscellaneous
Hydrolyzed oats	The hydrolysate of oats, <i>Avena sativa</i> , derived by acid, enzyme, or other method of hydrolysis.	Hair conditioning agent; skin-conditioning agent - miscellaneous

¹ The meristem is the tissue in most plants containing undifferentiated cells (meristematic cells), found in zones of the plant where growth can take place.

Fractions	Subfractions	Main components	Plant part(s)
Oat starch	Carbohydrates	Amylose and amylopectin	Groats, flours, endosperm
	Lipids	Lysophospholipids and free fatty acids	Seed, bran, hull, endosperm
	Proteins	Peptides, amino acids, etc.	Groat, endosperm
	Inorganics	Calcium, magnesium, potassium	Hull, ash
Non starch	Monosaccharides	Glucose, xylose, arabinose, galactose,	Hull, bran
polysaccharides		mannose, uronic acid, fucose, rhamnose	
	Polysaccharides	B-glucan	Groats, endosperm
Phenolic compounds	Hydroxy benzoic acids and	<i>p</i> -Hydroxybenzaldehyde, <i>p</i> -hydroxyphenyl	Whole oats, groats, hulls, flour,
	aldehydes	acetic acid, p -hydroxybenzoic acid,	trolled oats, wholemeal, kernels
		salicylic acid, vanillin, vanillic acid,	
		syringic acid, protocatechuic acid, cinnamic	
		acid, p -coumaric acid, o -coumaric acid,	
	A	caffeic acid, ferulic acid, sinapic acid	Lance and built flamm ach the
	Avenanthramides	Avenanthramide 2, Avenanthramide A,	Leaves, groats, nulls, llour, whole
		Avenanthramide E, Avenanthramide B,	oatmeai
		Avenanthramide E, Avenantinanide D, Z-	
	Phanolic glucosidas	2 Methowybydroguinone glucosides	Opt spedlings, debulled opts
	Thenone glucosides	<i>n</i> -hydroxybenzoic acid-4- <i>Q</i> -h-d-glucoside	Out securings, denuned outs
		vanillic acid-4- <i>O</i> -b-d-glucoside, <i>o</i> -coumaric	
		acid-4- <i>O</i> -b-d-glucoside, ferulic acid-4- <i>O</i> -b-	
		d-glucoside	
Flavonoid	Aglycones	2',4,4',6' -tetrahydroxy-3-	Oat kernel, whole plant
		methoxychalcone, apigenin, luteolin, tricin,	
		leucodelphinidin, homo-eriodictyol	
	Glycosyl flavones	Isovetexin, vitexin-rhamnoside, vicenin-2,	Leaves, stem, florets, whole
		isoswertisin-rhamnoside, isoorientin,	plant, seedlings, kernel
		isoorientin-rhamnoside, luteolin glucosides,	
		isoorientin-glucoside, isoscoparin,	
		tricinarabinoside,	
		tricin-glucoside, tricin-arabinose,	
	A 1	salcolin A, salcolin B	
Lignans	Agrycones	Phoresinol, medioresinol, syringaresinol,	Oat nour, oat bran, kernel, Huli
		matairesinol	
Sanonin	Glucosides	Avenacin A and B	Roots kernels
Phenylpropanoid	Ferulovl and caffeovl	Hexocosanols octacosanol hexacosadiols	Oat flour kernel bran
<i>n</i> -alkanol esters	r eruloyr and earleoyr	hexacosanoic acid Octacosanoic acid and	Out nour, kerner, brun
in unumor esters		mixed esters	
Oat protein	Globulins	Globulin, glutelin, and albumin	Groat, kernel, hull, flakes
	Prolamins	Avenins	Seed, bran, groat
	Albumins	Limit dextrinase, Nuatigenin 3β-	Oat leaves, seeds, flakes, groat
		glucosyltransferase, Sterol 3β-	
		glucosyltransferase	
		More common: enzymes include lipase,	
		lipoxygenase, and lipoperoxidase	
	Peptides	Avenothionin alpha	
		Avenothionin beta	
Oat lipids	Triacylglycerol	Oil contents 3–9%; Hybrid varieties of oats	Seeds, bran, endosperm
		have triacylglycerol content as high as 18%	01
	Free fatty acids	Fatty acids	Oat bran, oat oil
	Phospholipids and Glycolipids		Opt good logyog opt sil
Minerals	Oxylipins	Potassium phosphorus magnasium	Ash hull bran
minerais		rotassium, phosphorus, magnesium,	Asii, iluii, braii
		copper	
Vitamins		Vitamin E (tocols) niacin pantothenic acid	Bran
v nullillio		thiamin vitamin B6 riboflavin folic acid	Dim
		biotin, choline	

Table 2. Major constituent groups found in A. sativa.

Amino acid	g Amino acids/100g
Lysine	4.0
Hystidine	2.2
Arginine	6.5
Aspartic acid	7.9
Threonine	3.2
Serine	4.5
Glutamic acid	25.2
Proline	6.1
Cystine	2.3
Glycine	5.1
Alanine	4.5
Valine	5.5
Methionine	2.6
Isoleucine	4.0
Leucine	7.2
Tyrosine	3.3
Phenylananine	5.4

Table 3. Typic	al amino acid
composition of hydro	lyzed oat protein ⁵¹

Use type	Uses	Maximum Concentration	Uses	Maximum Concentration	Uses	Maximum Concentration	Uses	Maximum Concentration
ese type	0303	(70)	Avena s	ativa (oat) bran	Avena sa	tiva (oat) kernel	Avena sat	tiva (oat) kernel
	Avena sa	ativa (oat) bran		extract		extract		flour
Total/range	35	0.0072-2.5	6	0.2	499	0.00001-25	122	0.001-20
Duration of use								
Leave-on	17	0.0072	4	0.02	411	0.000016-25	84	0.01-20
Rinse-off	18	2.5	1	NR	86	0.00001-1	36	0.1-5
Diluted for (bath) use	NR	NR	1	NR	2	NR	2	NR
Exposure type ^a								
Eye area	NR	0.0072	NR	NR	33	0.00006-0.13	NR	NR
Incidental ingestion	2	NR	NR	NR	NR	0.24	NR	NR
Incidental Inhalation-sprays	8 ^b ; 2 ^d	NR	2 ^b ; 1 ^d	NR	271 ^b ; 80 ^d	0.0006-0.14 ^b ; 0.0025	21 ^b ; 20 ^d	0.01-3 ^d
Incidental inhalation-powders	13 ^c ; 2 ^d	NR	2 ^c ; 1 ^d	0.02 ^c	270 ^c ; 80 ^d	5; 0.005°	41°; 20 ^d	5; 0.01-3 ^d
Dermal contact	27	0.0072-2.5	6	0.02	473	0.000016-25	115	0.01-20
Deodorant (underarm)	NR	NR	NR	NR	NR	NR	NR	NR
Hair-noncoloring	6	NR	NR	NR	24	0.00001-0.05	7	0.001-3.2
Hair-coloring	NR	NR	NR	NR	NR	0.00006	NR	NR
Nail	NR	NR	NR	NR	1	NR	NR	NR
Mucous Membrane	7	2.5	1	NR	26	0.0051-1	14	NR
Baby	11	NR	NR	NR	10	NR	7	NR

 Table 4. Frequency of use according to duration and exposure of A. sativa-derived ingredients.

		Maximum		Maximum		Maximum	<u> </u>	Maximum
		Concentration		Concentration		Concentration		Concentration
Use type	Uses	(%)	Uses	(%)	Uses	(%)	Uses	(%)
	Avena sa	ativa (oat) kernel	Avena sa	tiva (oat) kernel	Avena sa	ativa (oat) leaf	Avena sa	ativa (oat) meal
		meal		protein	e	extract		extract
Total/range	21	1	29	0.001-5.2	3	NR	22	0.0001-0.005
Duration of use								
Leave-on	4	NR	22	0.001	3	NR	13	0.001-0.0025
Rinse-off	14	1	7	0.001-5.2	NR	NR	9	0.0001-0.005
Diluted for (bath)	3	NR	NR	NR	NR	NR	NR	0.005
use	5	T III	INIX	I	THE	T KK	THX .	0.005
Exposure type								
Eye area	NR	NR	4	NR	NR	NR	NR	NR
Incidental	NR	NR	NR		NR	NR	NR	NR
ingestion	1.11	T III	1.11		1.11	T III	1111	T III
Incidental	2^{d}	NR	14 ^b : 3 ^d	0.001	3 ^b	NR	7 ^b : 5 ^d	NR
Inhalation-sprays			, -		-			
Incidental	2^{d}	NR	12 ^c : 3 ^d	NR	3°	NR	7 ^c : 5 ^d	NR
inhalation-powders						ND		0.0001.0.005
Dermal contact	21	1	22	5.2	3	NR	20	0.0001-0.005
Deodorant	NR	NR	NR	NR	NR	NR	NR	NR
(underarm)	ND	ND	7	0.001	ND	ND	2	ND
Hair-noncoloring	NK	NK		0.001	NR	NK	2	NK
Hair-coloring	NK	NK	NR	NR	NR	NK	NR	NK
Nail	NK	NR	NR	NR	NR	NR	NR	NR
Mucous Membrane	11	1	1	5.2	NR	NR	4	0.001-0.005
Baby	NR	NR	NR	NR	NR	NR	NR	NR

T-11. 4 E	· C · · · · · · · 1'		1		7.68.70
Table 4. Frequency	/ of use accordin	g to duration an	a exposure of A.	<i>sativa</i> -derived ingredients.	.,,.

	Aven	a sativa (oat) peptide	Avena s protei	Avena sativa (oat) protein extract		Avena sativa (oat) straw extract		ed oat flour
Total/range	5	0.0026-0.33	4	1.5	2	0.001	7	NR
Duration of use								
Leave-on	2	0.013-0.33	2	NR	2	0.001	4	NR
Rinse-off	3	0.0026-0.013	2	1.5	NR	NR	3	NR
Diluted for (bath) use	NR	NR	NR	NR	NR	NR	NR	NR
Exposure type								
Eye area	1	0.33	NR	NR	NR	NR	NR	NR
Incidental ingestion	NR	NR	NR	NR	NR	NR	NR	NR
Incidental Inhalation-sprays	1 ^b	0.013 ^b	1 ^b ; 1 ^d	1.5 ^b	2 ^b	NR	1 ^b ; 1 ^d	NR
Incidental inhalation-powders	1°	NR	1°; 1 ^d	NR	2°	NR	1°; 1 ^d	NR
Dermal contact	3	0.013-0.33	4	NR	NR	0.001	7	NR
Deodorant (underarm)	NR	NR	NR	NR	NR	NR	NR	NR
Hair-noncoloring	2	0.0026-0.013	NR	NR	NR	NR	NR	NR
Hair-coloring	NR	NR	NR	NR	NR	NR	NR	NR
Nail	NR	NR	NR	NR	NR	NR	NR	NR
Mucous Membrane	NR	NR	NR	NR	NR	NR	NR	NR
Baby	NR	NR	NR	NR	NR	NR	NR	NR

Table 4. Fr	equency of	use according to	duration and e	exposure of A	sativa-derived	ingredients 67,68,70
I abit 7 , 11	cquene y or	use according to	uuranon anu c	Aposule of <i>I</i> .	<i>sunva</i> -ucriveu	ingiculents.

		Maximum Concentration		Maximum		Maximum Concentration		Maximum
Use type	Uses	(%)	Uses	(%)	Uses	(%)	Uses	(%)
¥.	Hydroly	zed oat protein	Hyd	rolyzed oats				
Total/range	76	0.0001-0.6	38	0.075-0.27		-		-
Duration of use								
Leave-on	39	0.0001-0.21	25	0.075				
Rinse-off	37	0.0026-0.6	12	0.27				
Diluted for (bath) use	NR	NR	1	NR				
Exposure type								
Eye area	1	0.18	4	NR				
Incidental ingestion	NR	NR	NR	NR				
Incidental Inhalation-sprays	17 ^b ; 7 ^d ; 3	NR	10 ^b ; 8 ^d	NR				
Incidental inhalation-powders	5 ^c ; 7 ^d	0.0075-0.21 ^c	9°; 8 ^d	0.075 ^c				
Dermal contact	28	0.0075-0.6	30	0.075-0.27				
Deodorant (underarm)	NR	NR	NR	NR				
Hair-noncoloring	44	0.0026-0.025	5	NR				
Hair-coloring	NR	0.0052	2	NR				
Nail	4	0.0001	NR	NR				
Mucous Membrane	12	NR	2	NR				
Baby	NR	NR	2	NR				

NR = Not Reported; Totals = Rinse-off + Leave-on Product Uses.

Note: Because each ingredient may be used in cosmetics with multiple exposure types, the sum of all exposure type uses may not equal the sum total uses.

^a 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.

^b It is possible these products <u>may</u> be sprays, but it is not specified whether the reported uses are sprays.

^e-It is possible these products <u>may</u> be powders, but it is not specified whether the reported uses are powders.

^d Not specified whether a powder or a spray, so this information is captured for both categories of incidental inhalation.

^e Pump spray.

Ingredient	Concentration range
Avena sativa (oat) kernel extract	0.00002-0.799
Avena sativa (oat) kernel flour	0.1-1
Avena sativa (oat) leaf extract	0.081
Avena sativa (oat) peptide	0.0075
Avena sativa (oat) straw extract	0.02
Hydrolyzed oat flour	0.5-1
Hydrolyzed oat protein	0.0015-0.5
Hydrolyzed oats	0.0025-0.025
Colloidal oatmeal*	0.001-43.3
Avena sativa (oat) kernel oil*	0.01-0.52
Potassium palmitoyl hydrolyzed oat protein*	0.0025-0.003

Table 5. Ranges of concentrations of *A. sativa*-derived ingredients in cosmetic products used in various tests summarized in Table 6.⁹⁰

*Not an ingredients in this report but included here for read-across purposed.

Table 6. Summary information (of irritation and sensitization tests	of various cosmetic	products containing A. sati	va-derived
ingredients. Concentration range	s of these ingredients are provide	d in Table 5. This inf	formation was presented in	aggregate
and the	individual studies on the individ	al products were not	provided. ⁹⁰	

	and the marrie	idal staales on the me	in riddai prodaets wer	e not provided.	
	Cumulative irritation tests	Phototoxicity tests	Photoallergenicity tests	HRIPT	Human Ocular Test
Number of cosmetic products tested ¹	61	45	39	31	49
n	1717	485	1233	5725	490
Results	Max score % of irritation 0.326%. Irritation response for non-irritant=2.9%- 5.00%	0 subjects showed signs of phototoxicity	0 subjects showed a photoallergenic response	2 subjects had confirmed allergic response ²	There were no signs of ocular irritation
Conclusion	Non-irritant	Non-phototoxic	Non-photoallergenic	Non-allergenic	Not an ocular irritant
	A (* 1 * 1* 1* 1*)	1.6 0.000020/	10/ / 6 11 1 1 /	1 1 1 1 1	12 20/

¹ The concentrations of *A*. sativa-derived ingredients ranged from 0.00002%-1% except for colloidal oatmeal which ranged up to 43.3%. ² Only 2 subjects had confirmed allergic responses to products containing 0.001% and 1% colloidal oatmeal.

								0.1
Toble 7 Uumon	irritation t	acts of pro	duate con	toining A	antina a	laring	ingradianta	11
i able /. numan	πηπαιιόη υ	ests of Dru	Juucis com	tanning A.	sauva-c	lenveu	ingreatents.	

Test product; ingredients,			
concentration	n	Protocol/duration	Results
Moisturizing cream; avena sativa (oat) kernel flour, 1.0%; avena sativa (oat) kernel extract, 0.00033%; avena sativa (oat) kernel oil, 0.5%	21 with mild to moderate atopic dermatitis	Used twice/d for 2 weeks on arms, legs, and torso	1 burning rash, well tolerated otherwise
Moisturizing cream; avena sativa (oat) kernel flour, 1.0%; avena sativa (oat) kernel extract, 0.00033%; avena sativa (oat) kernel oil, 0.5%	45 with atopic dermatitis-severe dryness, mild to moderate itch	Used for 4 weeks on half the body. Another moisturizer without <i>A. sativa</i> - derived ingredients.	No product-related adverse effects. Well tolerated.
Moisturizing cream; avena sativa (oat) kernel flour, 1.0%; avena sativa (oat) kernel extract, 0.00033%; avena sativa (oat) kernel oil, 0.5%	23 babies and children with mild to moderate atopic dermatitis (2 months-8 yr)	Used twice/d for 4 weeks on arms, legs, and torso	1 mild burning itching, well tolerated otherwise
Moisturizing cream; avena sativa (oat) kernel flour, 1.0%; avena sativa (oat) kernel extract, 0.00033%; avena sativa (oat) kernel oil, 0.5%	30 with mild to moderate hand eczema	Used 4 times/d for 3 weeks	No adverse effects
Moisturizing cream; avena sativa (oat) kernel flour, 1.0%; avena sativa (oat) kernel extract, 0.00033%; avena sativa (oat) kernel oil, 0.5%	1607 babies and children with mild to moderate atopic dermatitis (2 months – 16 yr).	Used twice/d for 8 weeks	Adverse effects reported by 2.4%, none determined to be product-related; well tolerated
Lotion; avena sativa (oat) kernel flour, 1.0%	19 women with dry, ashy skin	Used twice/d for 2 weeks	No adverse effects
Lotion; avena sativa oat kernel flour, 1.0% and moisturizing cream; avena sativa (oat] kernel flour, 1.0%; avena sativa (oat) kernel extract, 0.00011%; avena sativa (oat) k)rnel oil, 0.5%	46 with diabetes	Used for 4 weeks in a bilateral study	No product-related adverse events; well tolerated
Lotion; avena sativa (oat) kernel flour, 1.0%	50 female with moderate to extreme dryness of the lower legs	Used twice/d for 21 days followed by a 13-day regression	No adverse effects
Moisturizing lotion; avena sativa (oat) kernel flour, 1.0%; avena sativa (oat) kernel extract, 0.00011%; avena sativa (oat) kernel oil, 0.5%	29 female with bilateral itch and moderate to severe dry skin on both lower legs	Used twice/d for 14 days on lower legs	No adverse effects
Moisturizing lotion; 1.0% avena sativa (oat) kernel flour, 0.00011% avena sativa (oat) kernel extract, 0.5% avena sativa (oat) kernel oil	11 female	Randomized blind study on intact and abraded skin under occlusion comparing 2 ointments and a saline control. One administration to the volar surface of the forearm, abraded site covered with a bandage until abrasion no longer apparent. Dermal irritation graded daily.	No adverse effects; no differences in irritation compared to control.

Table 8. Use safety tests of personal care products containing colloidal oatmeal derived from A. sativa. The concentration
of the colloidal oatmeal in these products was not provided. ⁹³

Test		n; Skin/hair type, skin/eye sensitivity (if				
material	Date/country	applicable)	Application	Results		
		Derm	al			
Shower and bath oil	December 2006, UK	53/60 completed; dry, very dry body skin. Skin sensitivity: 19% not sensitive, 47% a little sensitive, 23% sensitive, 11% very sensitive. Age 18–55 yrs. Female	Use product on 7 consecutive days instead of usual shower product	Adverse reaction: 3.8%, 2/53. 1 moderate, 1 slight.		
Cream moisturizing oil	December 2006, UK	56/60 completed; dry, normal to dry body skin; Skin sensitivity: 23% not sensitive, 52% a little sensitive, 21% sensitive, 4% very sensitive. Age 18–55 yrs. Female	Use product once a day on 7 consecutive days instead of usual body moisturizer	Adverse reaction: 3.6%. 2/56. 1 severe, 1 moderate.		
Shower gel	August 2006, UK	59/60 completed; dry, sensitive body skin. Skin sensitivity not indicated. Age 20–50 yrs. Female	Use product on 7 consecutive days instead of usual shower product	Adverse reaction: 3.4%. 2/59 (two moderate)		
Night cream	April–May 2009, UK	64/70 completed; facial skin: normal, dry, normal to dry, normal to greasy, normal/dry/greasy. Skin sensitivity: 5% not sensitive, 61% a little sensitive, 30% sensitive, 5% very sensitive. Age 25–49 yrs. Female	Use product on 28 consecutive days instead of usual night-time moisturizer	Adverse reaction: 10.9%. 7/64. 5 subjects with slight to moderate reactions, 1 subject with moderate to severe reactions, and 1 subject with severe reactions.		
Conditioning shampoo	January– February 2007. UK	55/60 completed (30/sex); all hair types. Age 18–55 yrs	Use product on 10 occasions, no use of conditioner	Adverse reaction: 3.6%. 2/55 (two moderate)		
Body lotion	November– December 2006, UK	57/60 completed; dry, normal to dry body skin. Skin sensitivity: 12% not sensitive, 39% a little sensitive, 19% sensitive, 30% very sensitive. Age 18–55 yrs. Female	Use product on 7 consecutive days as frequently as required	Adverse reaction: 0%		
Liquid hand wash	October 2006, UK	58/60 completed; dry, normal to dry, very dry hand skin. Skin sensitivity: 12% not sensitive, 55% a little sensitive, 22% sensitive, 10% very sensitive. Age 18–55 yrs. Female	Use product on 7 consecutive days as frequently as required instead of usual hand wash product	Adverse reaction: 5.2%. 3/58 (1 slight and 2 moderate)		
Facial exfoliating cleanser	March–April 2009, Bulgaria	60/62 completed; normal, mixed oily, oily, mixed dry, dry skin. Sensitive skin 100%, history of atopy 32%. 2 withdrew consent. Age 18–60 yrs. Female	Use product 1x/day on face and neck for 3 weeks	Safety evaluation: Adverse reactions observed by dermatologist: 0/60. Adverse reaction reported by subjects: 3/60.		
Intimate wash	January 2007, Germany	60/60 completed; 48% healthy skin, 17% dry skin, 2% sensitive skin, 33% atopic dermatitis/eczema-free interval. Age 18–58 yrs. Female	Use product at least 1 ×/day for 4 weeks. Subsequent occlusive patch test with 1%, 2%, 5% dilutions, inner forearm for 24 hours	After 4 weeks: adverse reaction: 0. Patch test: no reaction at any concentration.		
Baby milk	January 2007, Germany	20/20 adults (6 male, 14 female) completed; 25% normal skin, 20% dry skin, 20% sensitive skin, 35% atopic dermatitis/eczema free interval. Age 21–47 yrs. 30/30 children (11 male, 19 female) completed; 27% normal skin, 20% dry skin, 17% sensitive skin, 37% atopic dermatitis/eczema free interval. Age 8 months - 4 yrs.	Use product at least 2 ×/day for 4 weeks. Subsequent occlusive patch test with adults only (undiluted), inner forearm for 24 h	After 4 weeks: adverse reaction: 0. Patch test: no reaction.		
		Ocula	r			
Face and eye cleansing lotion	September 2009, Poland	22/22 completed; normally sensitive eyes. Age 18–70 yrs. Female	Use product 2 ×/day on face including eye area and neck for 3 weeks	Clinical signs: 0%		
Face and eye cleansing lotion	September 2009, Poland	21/22 completed; normally sensitive eyes. Age 18–60 yrs. Female	Use product 2 ×/day on face including eye area and neck for 3 weeks	Clinical signs: 14%. 3/21 (possibly attributable to product and for 2 subjects only on 1 eye)		

Table 9.	HRIPTs of personal	care products	that contain co	olloidal oatmea	l derived from A	A. sativa.'	The concentra	ation of the
		colloidal o	batmeal in eacl	h product was i	not provided. ⁹³			

Test material	Date, country	n and description	Application	Results
Lotion	June–July 2005,	207/245 completed. 66	Occlusive	No reaction during induction phase or challenge phase.
	US	male, 141 female. Age		Conclusion: no potential for dermal irritation or sensitization
Lotion	December 2001	18-70 years.	Occlusive	Induction phases 1 transiant low layer + respection in 1 subject (1-11
Lotion	Jecember 2001– January 2002	209/220 completed. 55	Occlusive	nhace: 3 low-level + reactions in one subject (A8, 72, 96 h): 1 level 1
	January 2002, US	18_69 years		edema reaction (72 h) 1 transient low-level reaction (1 ^a) in 1 subject (96
	00	10 07 years.		h). Remarks: test material did induce an edematous reaction indicative of
				dermal sensitization in 1 human subject. This reaction was not confirmed
				by a second patch testing. Conclusion: no potential of the product for
			~ .	dermal sensitization
Lotion SPF	July–August	193/221 completed. 55	Semi-	No reaction during induction phase or challenge phase. Conclusion: no
15	2001, US	18_69 years	occlusive	potential for dermal initiation or sensitization
Cleansing	February-April	206/227 completed. 66	Semi-	Induction phase: 2 transient low-level \pm reactions in 1 subject (readings 1,
lotion	2005, US	male, 140 female. Age	occlusive	2^{a}); 3 transient low-level ± reactions in 1subject (readings $7-9^{a}$).
		18–70 years.		Challenge: no reactions. Conclusion: no potential for dermal irritation or
	E 1 4 1	102/212 1 1 1 40	0.1.1	sensitization.
Cleansing	February–April	183/213 completed. 48	Occlusive	Induction phase: 1 transient low-level \pm reaction in 2 subjects (readings 6, 8 b); 2 transient low level \pm reactions in 2 subjects (readings 4, 5 ^a); 4 low
1011011	2000, US	18–69 years		(1) a finite constraint the section $(1 \times 1; 3 \times +)$ in 1 subjects (readings 4, 5); 4 low level transient reactions $(1 \times 1; 3 \times +)$ in 1 subject (readings $2-5^{a}$)
		io of journ		Challenge phase: 1 transient low-level reaction (\pm) in 4 subject (claungs 2 \pm),
				\times 48 h); 2 transient low-level reactions (1; ±) in 1 subject (48, 72 h).
	D 1 0007	000/04/0 1 1 70	<u> </u>	Conclusion: no potential for dermal irritation or sensitization.
Cream	December 2005–	223/240 completed. 59	Occlusive	No reaction during induction phase. Challenge phase: I transient low- lowal reaction $(+)$ in 1 subject (48 h): 2 transient low loval + reactions in 1
	US	18–69 years		subject (48, 72 h). Conclusion: no potential for dermal irritation or
	0.0	io of journ		sensitization.
Night cream	July-August	217/240 completed. 68	Semi-	Induction phase: 1 transient low-level \pm reaction in 2 subjects (readings
	2006, US	male, 149 female.	occlusive	2^{a}). Challenge phase: 2 transient low-level \pm reactions in 1 subject (48, 72
Sorum	July August	Aged 18–70 years.	Sami	h). Conclusion: no potential for dermal irritation or sensitization.
Serum	2006. US	male, 149 female, Age	occlusive	9. 9 ^a): one transient low-level reaction (1 ^a) in one subjects (reading 5 ^a): 2
		18–70 years.		transient low-level reactions $(1; \pm)$ in 1 subject (readings 5, 6 ^a). Challenge
				phase: 1 level 1 + edema reaction (48 h), 2 low-level transient reactions
				(1 ^a) in 1 subject (24, 72 h); 2 transient low-level reactions (1; \pm) in 1
				subject (48, 72 h). Remark: test material did induce an edematous reaction indicative of dermal sensitization in 1 human subject: reaction
				not confirmed by a second patch test. Conclusion: no potential of the
				product for dermal sensitization
Baby cream	February-March	109/114 completed. 13	Semi-	Induction phase: 1 mild erythema (1 ^a) in 1 subject (reading 3 ^a). Challenge
	2009, Romania	male, 96 female. Age	occlusive	phase: no reaction. Conclusion: no potential for dermal irritation or
Hand cream	May_June 2002	$1\delta - 10$ years. 201/240 completed 50	Semi	Sensitization. Induction phase: 2 transient low-level reactions $(1^{a_1} \pm)$ in one subject
	US	male, 142 female. Age	occlusive	(readings 3, 4 ^a); 8 low-level reactions (\pm) in 1 subject (readings 2–9 ^a).
		18–70 years.		Challenge phase: 1 transient low-level reaction (\pm) in 1 subject (72 h); 3
		-		level 1 + edema reactions in 1 subject (48, 72, 96 h). Remarks: test
				material did induce an edematous reaction indicative of dermal
				sensitization in 1 human subject; reaction confirmed with the finished
				doubtful.
Exfoliating	March-May	109/114 completed. 23	2% dilution;	No reaction during induction phase or challenge phase. Conclusion: no
cleanser	2009, Romania	male, 86 female. Age	semi-	potential for dermal irritation or sensitization
XX7 1 /1 1	•	18–68 years.	occlusive	
wash (head-	August– September 2007	216/245 completed. 59 male 157 female Age	8% dilution;	Induction phase: I transient low-level \pm reaction in 3 subjects (readings 2, 7, 7 ^a): I transient low-level reaction (1 ^a) in 1 subject (reading 2 ^a): 2
10-1007	US	18–70 years.	occlusive	transient low-level reactions $(1^{\circ}, \pm)$ in 1 subject (reading 2), 2
				Challenge phase: 2 transient low-level reactions $(1^{a}; \pm)$ in 2 subjects (48,
				72 hours); three transient low-level reactions $(2 \times 1; 1 \times \pm)$ in one subject
				(48, 72, 96 h). Conclusion: no potential for dermal irritation or
				sensitization.

^a 0 = no reaction; 10 = severe reaction.

REFERENCES

- 1. Nikitakis, J and Breslawec HP. International Cosmetic Ingredient Dictionary and Handbook. 15 ed. Washington, DC: Personal Care Products Council, 2014.
- U.S. Department of Agriculture. Oats. Chapter: 7. In: Grain Inspection Handbook. Vol. II. Washington, DC: U.S. Department of Agriculture; 2013:1-30.
- Burnett, C, Fiume, M, Bergfeld, WF, Belsito, DV, Hill, RA, Klaassen, CD, Liebler, DC, Marks Jr, JG, Shank, RC, Slaga, TJ, and Snyder, PW. Final Report: Plant-derived fatty acid oils as used in cosmetics. Washington, DC, Cosmetic Ingedient Review. 3-4-2011. pp. 1-100.
- Burnett, C, Heldreth, B, Bergfeld, WF, Belsito, DV, Klaassen, CD, Liebel, F, Hill, RA, Marks Jr, JG, Shank, RC, Slaga, TJ, Snyder, PW, and Andersen, FA. Safety assessment of α-amino acids as used in cosmetics. Washington, DC, Cosmetic Ingredient Review (CIR). 2012.
- Andersen, FA, Bergfeld, WF, Belsito, DV, Klaassen, CD, Marks Jr, JG, Shank, RC, Slaga, TJ, and Snyder, PW. Final report of the safety assessment of cosmetic ingredient derived from zea mays (corn). *International Journal of Toxicology*. 2011;25(Suppl 2):1-89.
- 6. Elder, RL. Final report on the safety assessment of hydrolyzed collogen. Journal of the American College of Toxicology. 1985;4(5):199-221.
- Burnett, C, Heldreth, B, Bergfeld, WF, Belsito, DV, Klaassen, CD, Liebler, DC, Hill, RA, Marks Jr, JG, Shank, RC, Slaga, TJ, Snyder, PW, and Andersen, FA. Safety assessment of animal- and plant-derived amino acids as used in cosmetics. Washington, DC, Cosmetic Ingredient Review (CIR). 2013.
- 8. Elder, RL. Final report of the safety assessment for wheat germ glycerides and wheat gluten. *Journal of Environmental Pathology and Toxicology*. 1980;4(4):5-17.
- Andersen, FA. Annual review of cosmetic ingredient safety assessments 2004/2005. International Journal of Toxicology. 2006;26(Suppl. 2):1-89.
- Andersen, FA. Annual review of cosmetic ingredient safety assessments 2001/2002. International Journal of Toxicology. 2003;22(Suppl. 1):1-35.
- 11. Suttie, JM. Avena sativa L.; Gramineae. http://www.fao.org/ag/AGPC/doc/Gbase/DATA/Pf000466.HTM.
- 12. Saeed, SA, Butt, NM, McDonald-Gibson, WJ, and Collier, HOJ. Inhibitor(s) of prostaglandin biosynthesis in extracts of oat (*Avena sativa*) seeds. *Biochemical Society Transactions*. 1981;9:444.
- 13. Personal Care Products Council. 8-7-2014. Hydrolyzed Oats. Unpublished data submitted by Personal Care Products Council.
- 14. Croda Inc. 2014. Product information CROMOIST 025-LQ-(WD) and HYDROA VENA HPO-LQ(WD) (Hydrolyzed Oats). Unpublished data submitted by Personal Care Products Council.
- 15. Kurtz, ES and Wallo, W. Colloidal oatmeal: history, chemistry, and clinical properties. Journal of Drugs in Dermatology. 2007;6(2):167-170.
- Collins, FW. Oat phenolics: Structure, occurrence and function. Webster, FH. In: Oats: Chemistry and Technology. St. Paul, Minnesota: American Association of Cereal Chemists, Inc.; 1986:227-291.
- Purdue University Center for New Crops & Plants Products. Avena sativa L. Poaceae, Common oats. <u>http://www.hort.purdue.edu/newcrop/duke_energy/Avena_sativa.html</u>. Date Accessed 2-26-2014.
- 18. Osbourn, AE. Preformed antimicrobial componenets and plant defense against fungal attack. Plant Cell. 1996;8(10):1821-1831.
- 19. Osbourn, AE. Saponins in cereals. Phytochemistry. 2003;62(1):1-4.
- 20. Singh, R, De, S, and Belkheir, A. Avena sativa (oat), a potential neutraceutical and therapeutic agent: An overview. Critical Reviews in Food Science and Nutrition. 2013;53(2):126-144.
- 21. Tschesche, R, Tauscher, M, Fehlhaber, HW, and Wulff, G. Avenacosid A, ein bisdesmosidisches Steroidsaponin aus Avena sativa. Chemische Berichte. 1969;102:2072-2082.
- 22. Tschesche, R and Lauven, P. Avenacosid B ein zweites bidesmosidishes Steroidsaponin aus Avena sativa. Chemische Berichte. 1971;104:3549-3555.
- 23. Giannopolitis, CN and Ries, SK. Superoxide dismutases. I. Occurrence in higher plants. Plant Physiology. 1977;59:309-314.
- 24. Youngs, VL. Oat lipids and lipid-related enzymes. Chapter: 8. Webster, FH. In: *Oats: Chemistry and Technology*. St. Paul, Minnesota: American Association of Cereal Chemists, Inc.; 1986:205-226.

- Webster, FH. Whole-grain oats and oat product. Marquart, L, Slavin, JL, and Fulcher, RG. In: Whole-Grain Foods in Health and Disease. St. Paul, MN: American Association of Cereal Chemists; 2002:83-123.
- 26. Paton, D. Oat starch. I. Extraction, purification and pasting properties. Staerke. 1977;29:149-153.
- Wood, PJ. Oat β-glucan: Structure location and properties. Chapter: 6. Webster, FH. In: Oat: Chemistry and Technology. St. Paul, Minnesota: American Association of Cereal Chemists, Inc.; 1986:121-152.
- MacArthur-Grant, LA. Sugars and nonstarchy polysaccharides in oats. Chapter: 4. Webster, FH. In: Oats: Chemistry and Technology. St. Paul, Minnesota: American Association of Cereal Chemists, Inc.; 1986:75-92.
- Zhang, W-K, Xu, J-K, Zhang, L, and Du, G-H. Flavanoids from the bran of Avena sativa. Chinese Journal of Natural Medicines. 2012;10(2):110-114.
- Küpeli Akkol, E, Süntar, I, Erdogan Orhan, I, Keles, H, Kan, A, and Çoksari, G. Assessment of dermal wound healing and *in vitro* antioxidant properties of Avena sativa L. Journal of Cereal Science. 2011;53(3):285-290.
- Chopin, J, Dellamonica, G, Bouillant, ML, Besset, A, Popovici, G, and Veissenboeck, G. C-Glycosylflavones from Avena sativa L. Phytochemistry. 1977;16:2041-2043.
- 32. Aman, P and Hellelman, K. Analysis of starch and other main constituents of cereal grains. *Swedish Journal of Agricultural Research*. 1984;14:135-139.
- 33. Zhou, M, Robards, K, Glennie-Holmes, M, and Helliwell, S. Oat lipids. Journal of the American Oil Chemists' Society. 1999;7(2):159-169.
- Hutchinson, JB and Martin, HF. The chemical composition of oats. 1. The oil and the free fatty acid content of oats and groats. *Journal of Agricultural Science*. 1955;45:411-418.
- 35. Emmons, CL and Peterson, DM. Antioxidant activety and phenolic contents of oat groats and hulls. Cereal Chemistry. 1999;76:902-906.
- 36. Graf, E. Antioxidant potential of ferulic acid. Free Radical Biology & Medicine. 1992;13:435-448.
- Pazyar, N, Yaghoobi, R, Kazerouni, A, and Feily, A. Oatmeal in dermatology: a brief review. Indian Journal of Dermatology, Venereology, and Leprology. 2012;78(2):142-145.
- Cerio, R, Dohil, M, Downie, J, Magina, S, Mahé, E, and Stratigos, AJ. Mechanism of action and clinical benefits of colloidal oitmeal for dermatolagic practice. *Journal of Drugs in Dermatology*. 2010;9(9):1116-1120.
- Fowler, JF, Nebus, J, Wallo, W, and Eichenfield, LF. Colloidal oatmeal formulations as adjunct treatments in atopic dermatitis. *Journal of Drugs* in Dermatology. 2012;11(7):804-807.
- Sur, R, Nigam, A, Grote, D, Liebel, F, and Southall, MD. Avenanthramides, polyphenols from oats, exhibit anti-inflammatory and anti-itch activity. Archives of Dermatological Research. 2008;300(10):569-574.
- 41. Popovici, G, Weissenboeck, G, Bouillant, ML, Dellamonica, G, and Chopin, J. Isolation and characterization of flavonoids from *Avena sativa* L. *Zeitschrift Fur Pflanzenzuchtung-Journal Of Plant Breeding*. 1977;85:103-115.
- 42. Wenzig, E, Kunert, O, Ferreira D, Schmid, M, Schuhly, W, Bauer, R, and Hiermann, A. Flavonolignans from *Avena sativa*. *Journal of Natural Products*. 2005;68(2):289-292.
- Peterson, DM and Brinegar, AC. Oat storage proteins. Chapter: 7. Webster, FH. In: Oats: Chemistry and Technology. St. Paul, Minnesota: American Association of Cereal Chemists, Inc.; 1986:153-204.
- 44. Lockhart, HB and Hurt, HD. Nutrition of oats. Webster, FH. In: *Oats: Chemistry and Technology*. St. Paul, Minnesota: American Association of Cereal Chemists, Inc.; 1986:292-310.
- 45. Eichenberger, W and Urban, B. Sterols in seeds and leaves of oats (Avena sativa L.). Plant Cell Reports. 1984;3(6):226-229.
- Duke, JA. Dr. Duke's phytochemical and ethnobotanical databases Avean sativa L.- Poaceae. <u>http://sun.ars-grin.gov:8080/npgspub/xsql/duke/plantdisp.xsql?taxon=144</u>. Date Accessed 11-27-2013.
- Poginsky B, Westendorf N, Prosenc N, Kuppe M, and Marquardt H. St. John's wort (*Hypericum perforatum* L.). Genotoxicity induced by quercetin content. *Deutsche Apotheker Zeitung*. 1988;128:13464-13466.
- Harwood M, Danielewska-Nikiel B, Borzelleca JF, Flamm GW, Williams GM, and Lines TC. A critical review of the data related to the safety of quercetin and lack of evidene of *in vivo* toxicity, including lack of genotoxic/carcinogenic properties. *Food and Chemical Toxicology*. 2007;45(11):2179-2205.

- 49. Silab. 2007. Characterization and detailed quantification of dry matter of OSILIFT® (Avena Sativa (Oat) Kernel Extract). Unpublished data submitted by Personal Care Products Council.
- Silab. 2007. Characterization of OSILIFT® carbohydrates (Avena Sativa (Oat) Kernel Extract). Unpublished data submitted by Personal Care Products Council.
- 51. Personal Care Products Council. 7-25-2014. Hydrolyzed Oat Protein. Unpublished data submitted by Personal Care Products Council. 1 pages.
- Plantes and Industries. 2014. Summary of studies on Avena Sativa (Oat) Leaf/Stem Extract and Avena Sativa (Oat) Sprout Oil. Unpublished data submitted by Personal Care Products Council.
- 53. Personal Care Products Council. 7-28-2014. Avena Sativa (Oat) Kernel Extract. Unpublished data submitted by Personal Care Products Council. 1 pages.
- 54. Gattefossé. 2014. Manufacturing flow chart Vegetol® Oat ME 166 Hydro (Avena Sativa (Oat) Kernel Extract). Unpublished data submitted by Personal Care Products Council.
- 55. Silab. 2008. Process data OSILIFT® BIO (water and Avena Sativa (Oat) Kernel Extract). Unpublished data submitted by Personal Care Products Council.
- Anonymous. 2014. Avena Sativa Oat Kernel Flour- Processing and quality systems. Unpublished data submitted by Personal Care Products Council.
- Mandeau, A, Aries, MF, Boé, JF, Brenk, M, Crebassa-Trinqueros, V, Vaissière, C, Teysseyre, V, and Bieber, T. Rhealba® oat plantlet extract: evidence of protein-free content and assessment of regulatory activity on immune inflammatory mediators. *Planta Medica*. 2011;77(9):900-906.
- Pierre Fabre. Scientific Report: Rhealba® Oat Plantlets. A-Derma, Avoine Rhealba®. 2010. dermoapo.no/produkter/a_derma/linker/content_1/text_2957f752-4376-43d8-8f1b-4f1bea492ba1/1356723884261/ds_exomega_ang.pdf. Report No. Réf. 479005 - Réf. 479002 - 01/10. pp. 1-44.
- 59. Anonymous. 2014. Method of manufacture: Hydrolyzed oats. Unpublished data submitted by Personal Care Products Council.
- European Parliment and the Council of European Union. Regulation (EC) No 1223/2009 of the European Parliment and of the Council of 30 November 2009 on cosmetic products (recast). European Union. 12-22-2009. <u>http://eur-lex.europa.eu/legalcontent/EN/TXT/PDF/?uri=CELEX:32009R1223&from=en</u>. Date Accessed 7-31-2014.pp. 1-151.
- 61. European Parliment and the Council of European Union. European Pharmacopoeia. 8 ed. 2014.
- Abouzied, MM, Azcona, JI, Braselton WE, and Pestka JJ. Immunochemical assessment of mycotoxins in 1989 grain foods: Evidence for deoxynivalenol (vomitoxin) contamination. *Applied and Environmental Microbiology*. 1991;57(3):672-677.
- 63. Edwards, SG. Fusarium mycotoxin content of UK organic and conventional oats. Food Additives and Contaminants. 2009;26(7):1063-1069.
- 64. Vidal, A, Marín, S, Ramos, AJ, Cano-Sancho, G, and Sanchis, V. Determination of aflatoxinsm deoxynivalenol, ochratoxin A and zearalenone in wheat and oat based bran supplements sold in the Spanish market. *Food and Chemical Toxicology*. 2013;53(March):133-138.
- Eurola, M, Hietaniem, V, Kontituri, M, Tuuri, H, Pihlava, J-M, Saastamoinen, M, Rantanen, O, Kangas, A, and Niskanen, M. Cadmium contents of oats (*Avena sativa* L.) in officialt variety organic cultivation, and nitrogen fertilization trials during 1997-1999. *Journal of Agriculture and Food Chemistry*. 2003;51(9):2608-2614.
- 66. Tanhuanpää, P, Kalendar, R, Schulman, AH, and Kiviharju, E. A major gene for grain cadmium accumulation in oat (*Avena sativa* L.). *Genome*. 2007;50(6):588-594.
- 67. Food and Drug Administration (FDA). Frequency of use of cosmetic ingredients. FDA Database. Washington, DC: FDA.
- 68. Personal Care Products Council. 2-3-2014. Concentration of Use information: Avena sativa-Derived Ingredients. Unpublished data submitted by Personal Care Products Council.
- 69. Personal Care Products Council. 9-24-2012. Concentration of Use by FDA Product Category: Hydrolyzed Proteins. 17 pages.
- Personal Care Products Council. 2014. Concentration of Use by FDA Product Category: Hydrolyzed Proteins. Unpublished data submitted by Personal Care Products Council. 17 pages.
- Bremmer HJ, Prud'homme de Lodder LCH, and van Engelen JGM. Cosmetics Fact Sheet: To assess the risks for the consumer; Updated version for ConsExpo 4. 2006. <u>http://www.rivm.nl/bibliotheek/rapporten/320104001.pdf</u>. Date Accessed 8-24-2011. Report No. RIVM 320104001/2006. pp. 1-77.

- 72. Johnsen MA. The Influence of Particle Size. Spray Technology and Marketing. 2004;14(11):24-27.
- Rothe H, Fautz R, Gerber E, Neumann L, Rettinger K, Schuh W, and Gronewold C. Special aspects of cosmetic spray safety evaluations: Principles on inhalation risk assessment. *Toxicol Lett.* 8-28-2011;205(2):97-104.
- Rothe H. Special aspects of cosmetic spray safety evaluation. 2011. Unpublished information presented to the 26 September CIR Expert Panel. Washington D.C.
- 75. Physician's Desk Reference for Nonprescription Drugs. 15 ed. Montvale, NJ: Medical Economics Data Production Co., 1994.
- 76. Centers for Disease Control and Prevention. Chickenpox (Varicella). http://www.cdc.gov/chickenpox/index.html. Date Accessed 2-25-2014.
- 77. Dick LA. Colloidal emollient bath in pediatric dermatoses. Archives of Pediatrics. 1958;75:506-508.
- 78. Dick LA. Colloidal emmolient baths in geriatric dermatoses. Skin. 1962;1:89-91.
- 79. Grais, ML. Role of colloidal oatmeal in dermatological teatment of the aged. AMA Archives of Dermatology and Syphilology. 1953;68:402-407.
- 80. O'Brasky, L. Management of extensive dry skin conditions. Connecticut Medicine. 1959;23:20-21.
- 81. Smith GC. The treatment of various dermatoses associated with dry skin. Journal of the South Carolina Medical Association. 1958;54:282-283.
- 82. Schmaus, G, Herrmann, M, and Joppe, H. Oat avenanthramides: New activites to reduce itch sensations in skin. 10-24-2004. Orlando, FL.
- Wallo, W, Nebus, J, and Nystrand, G. Agents with adjunctive potential in atopic dermatitis. 65th Annual Meeting of the American Academy of Dermatology, 02/02/2007. 2007. Washington, DC.
- Vie, K, Cours-Darne, S, Vienne, MP, Boyer F, Fabre B, and Dupuy P. Modulat ing effects of oatmeal extracts in the sodium lau ryl sulfate skin irritancy model. *Skin Pharmacology and Applied Skin Physiology*. 2002;15(2):120-124.
- Aries, MF, Vaissiere, C, and Pinelli, E. Avena rhealba® inhibits A23187-stimulated arachidonic acid mobilization, eicosanoid release, and cPLA2 expression in human keratinocytes: Potential in cutaneous inflammatory disorders. *Biological & Parmaceurtical Bulletin*. 2005;28(4):601-606.
- Boisnic, S, Branchet-Gumila, MC, and Coutanceau, C. Inhibitory effect of oatmeal extract oligomer on vasoactive intestinal peptide-induced inflammation in surviving human skin. *International Journal of Tissue Reactions*. 2003;25(2):41-46.
- Boisnic, S, Branchet, MC, and Ermosilla, V. Healing effect of a spray containing Rhealba® oat colloidal extract in an *in vitro* reconstitution model of skin. *International Journal of Tissue Reactions*. 2005;27(3):83-89.
- Matheson, JD, Clayton, J, and Muller, MJ. The reduction of itch during burn wound healing. Journal of Burn Care & Rehabilitation. 2001;22:76-81.
- 89. Adler, JH. Antioestrogenic activity in Fahli clover hay and oat hay. Acta Endocrinology. 1965;49:90-96.
- Anonymous. 2014. Summary of clinical studies concerning the safety of products containing oat-derived ingredients. Unpublished data submitted by Personal Care Products Council.
- 91. Anonymous. 2014. Avena Sativa (Oat) CIR Review. Unpublished data submitted by Personal Care Products Council.
- 92. Grimalt, R, Mengeaud, V, and Cambazard, F. The steroid-sparing effect of an emollient therapy in infants with atopic dermatitis: A randomized controlled study. *Dermatology*. 2007;214(1):61-67.
- Criquet, M, Roure, R, Dayan, L, Nollent, V, and Bertin, C. Safety and efficacy of personal care products containing colloidal oatmeal. *Clinical, Cosmetic and Investigative Dermatology*. 2012;5:183-193.
- Camplone, G, Arcangeli, F, Bonifazi, E, Gelmetti, C, Menni, S, Mulas, P, Paradisi, M, and Patrizi, A. The use of colloidal oatmeal products in the care of children with mild atopic dermatitis. *European Journal of Pediatric Dermatology*. 2004;14:157-160.
- 95. Pacifico, A, de Angelis, L, Fargnoli, MC, DeFelice, C, Chimenti, S, and Peris, K. Clinical trial on Aveeno Skin Relief Moisturizing Lotion in patients with itching accompanied by skin lesions and xerosis. *The Journal of Applied Research*. 2005;5(2):325-330.
- Consumer Product Testing. 1993. The MATREX[™] in vitro toxicity testing system: Hydrolyzed Oats. Unpublished data submitted by Personal Care Products Council.
- 97. Consumer Product Testing. 1998. The MatTek Corporation EpiDerm[™] skin model in vitro toxicity testing system: Hydrolyzed Oats. Unpublished data submitted by Personal Care Products Council.

- Product Investigations Inc. 2003. Determination of the irritating and sensitizing propensities of a paste mask product containing 25% Avena Sativa (Oat) Kernel Extract. Unpublished data submitted by Personal Care Products Council.
- Clinical Research Laboratories Inc. 2007. Repeated insult patch test on a face powder containing 1% Avena Sativa (Oat) Kernel Flour. Unpublished data submitted by Personal Care Products Council.
- Clinical Research Laboratories Inc. 2007. Repeated insult patch test on a blush containing 1% Avena Sativa (Oat) Kernel Flour. Unpublished data submitted by Personal Care Products Council.
- 101. Harrison Research Laboratories Inc. 1998. Summary of a human repeated insult patch test of a body lotion containing 0.1% Avena Sativa (Oat) Kernel Flour. Unpublished data submitted by Personal Care Products Council. 2 pages.
- 102. Consumer Product Testing. 1993. Repeat insult patch test: Hydrolyzed Oats. Unpublished data submitted by Personal Care Products Council.
- Goujon, C, Jean-Decoster, C, Dahel, K, Bottigioli, D, Lahbari, F, Nicolas, J-F, and Schmitt, A-M. Tolerance of oat-based topical products in cereal-sensitized adults with atopic dermatisis. *Dermatology*. 2009;218:327-333.
- Boussault, P, Léauté-Labrèze, C, Saubusse, E, Maurice-Tison, S, Perromat, M, Roul, S, Sarrat, A, Taïeb, A, and Boralevi, F. Oat sensitization in children with atopic dermatitis: Prevalence, risks and associated factors. *Allergy*. 2007;62(11):1251-1256.
- Pigatto, P, Bigardi, A, Caputo, R, Angelini, G, Foti, C, Grandolfo, M, and Rizer, RL. An evaluation of the allergic contact dermatitis potential of colloidal grain suspensions. *American Journal of Contact Dermatitis*. 1997;8(4):207-209.
- 106. Rowe LD. Photosesitization problems in livestock. Veterinary Clinics of North America: Food Animal Practice. 1989;5(2):301-323.
- Varjonen, E, Savolainen, J, Mattila, L, and Kalimo, K. IgE-binding components of wheat, rye, barley and oats recognized by immunoblotting analysis with sera from adult atopic dermatitis patients. *Clinical and Experimental Allergy*. 1994;22(5):481-489.
- Varjonen, E, Kalimo, K, Savolainen, J, and Vainio, E. IgA and IgG binding components of wheat, rye, barley and oats recognized by immunoblotting analysis with sera from adult atopic dermatitis patients. *International Archives of Allergy and Immunology*. 1996;111(1):55-63.
- 109. Pootongkam, S and Nedorost, S. Oat and wheat as contact allergens in personal care products. Dermatitis. 2013;24(6):291-295.
- 110. Burnett, C, Heldreth, B, Bergfeld, WF, Belsito, DV, Hill, RA, Klaassen, CD, Liebel, F, Marks Jr, JG, Shank, RC, Slaga, TJ, and Snyder, PW. Safety assessment of hydrolyzed wheat protein and hydrolyzed wheat gluten as used in cosmetics. Washington, DC, Cosmetic Ingredient Review. 2014. pp. 1-17.
- 111. Bohle, B, Zwöfer, B, Heratizadeh, A, Jahn-Schmid, B, Antonia, YD, Alter, M, Keller, W, Zuidmeer, L, van Ree, R, Werfel, T, and Ebner, C. Cooking birch pollen-related food: divergent consequences for IgE- and T cell-mediated reactivity in vitro and in vivo. *Journal of Allergy and Clinical Immunology*. 2006;118(1):242-249.
- Olszewski, A, Pons, L, Moutété, F, Aimone-Gastin, I, Kanny, G, Moneret-Vautrin, DA, and Guéant, JL. Isolation and characterization of proteic allergens in refined peanut oil. *Clinical and Experimental Allergy*. 1998;28(7):850-859.
- Codreanu, F, Morisset, M, Cordebar, V, Kanny, G, and Moneret-Vautrin, DA. Risk of allergy to food proteins in topical medicinal agents and cosmetics. *European Annals of allergy and Clinical Immunology*. 2006;38(4):126-130.
- 114. Riboldi, A, Pigatto, PD, Altomare, GF, and Gibelli, E. Contact allergic dermatitis from oatmeal. Contact Dermatitis. 1988;18:316-317.
- 115. Pazzaglia, M, Jorizzo, M, Parente, G, and Tosti, A. Allergic contact dermatitis due to avena extract. Contact Dermatitis. 2000;42(6):364.
- 116. de Pax Arranz, S, Pérez Montero, A, Zapatero Remón, M, and Martínez Molero, I. Allergic conact urticaria to oatmeal. 57. 2002;(1215).
- 117. Dempster, JG. Contact dermatitis from bran and oats. Contact Dermatitis. 1981;7(2):12.
- 118. Vansina, S, Debilde, D, Morren, M-A, and Goossens, A. Sensitizing oat extracts in cosmetic creams: Is there an alternative? *Contact Dermatitis*. 2010;63(3):169-171.
- 119. Mahmood, K, Saliou, C, and Wallo, W. Nutrient-rich botanicals in skin health Focus on Avena sativa. Chapter: 16. Watson, RR and Zibadi, S. In: Bioactive Dietary Factors and Plant Extracts in Dermatology. New York: Springer Science + Business Media; 2013:153-168.



Memorandum

- TO: Lillian Gill, D.P.A. Director - COSMETIC INGREDIENT REVIEW (CIR)
- **FROM:** Beth A. Lange, Ph.D. Industry Liaison to the CIR Expert Panel
- **DATE:** October 3, 2014
- SUBJECT: Concentration of Use by FDA Product Category: Hydrolyzed Oat Ingredients

Concentration of Use by FDA Product Category*

Hydrolyzed Oat Flour	Hydrolyzed Oats	Hydrolyzed Oat Protein
Ingredient	Product Category	Maximum Concentration of Use
Hydrolyzed Oats	Skin cleansing (cold creams, cleansing lotions, liquids and pads)	0.27%
Hydrolyzed Oats	Body and hand products not spray	0.075%
Hydrolyzed Oat Protein	Eye lotion	0.18%
Hydrolyzed Oat Protein	Hair conditioners	0.0052-0.025%
Hydrolyzed Oat Protein	Rinses (noncoloring)	0.0052%
Hydrolyzed Oat Protein	Shampoos (noncoloring)	0.0026-0.0052%
Hydrolyzed Oat Protein	Tonics, dressings and other hair grooming aids	0.0028-0.013%
Hydrolyzed Oat Protein	Other hair preparations (noncoloring)	0.0026%
Hydrolyzed Oat Protein	Hair tints	0.0052%
Hydrolyzed Oat Protein	Basecoats and undercoats (manicuring preparations)	0.0001%
Hydrolyzed Oat Protein	Skin cleansing (cold creams, cleansing lotions, liquids and pads)	0.6%
Hydrolyzed Oat Protein	Face and neck products	
	not spray	0.0075-0.21%
Hydrolyzed Oat Protein	Body and hand products	
	not spray	0.013%

*Ingredients included in the title of the table but not found in the table were included in the concentration of use survey, but no uses were reported.

Information collected in 2014 Table prepared October 2, 2014



Memorandum

TO: Lillian Gill, D.P.A. Director - COSMETIC INGREDIENT REVIEW (CIR)

FROM: Beth A. Lange, Ph.D. Industry Liaison to the CIR Expert Panel

DATE: September 24, 2014

SUBJECT: Comments on the Tentative Report: Safety Assessment of *Avena sativa*-Derived Ingredients as Used in Cosmetics

Key Issues

<u>The conclusion in the tentative report is wrong</u>. The CIR Expert Panel did not say that Avena Sativa (Oat) Meristem Extract is: "not safe for use as a cosmetic ingredient." As stated in the post-meeting announcement: "The Panel concluded that there is insufficient data to come to a conclusion on the safety of avena sativa (oat) meristem cell extract. The additional data needed are (1) composition, and (2) concentration of use." The conclusion for the meristem extract in the tentative report needs to be stated very clearly as an "insufficient data" conclusion. It is very unfortunate that a tentative report has been posted on the CIR website with the incorrect conclusion.

This insufficient data conclusion for the meristem extract and the data needs still need to be added to the Discussion section.

The Abstract still has to be written for this tentative report.

- The difference between the subsections "Constituents" and "Characterization" is not clear. Molecular weight ranges of cosmetic ingredients are presented in both sections. Rather than having two sections, perhaps there should be subsections under "Constituents" for constituents of the plant, and constituents/descriptions of the cosmetic ingredients.
- The section about Type I sensitization should be about Type I sensitization and not include information about Type IV reactions.
- The information about protein size and Type I sensitization in the last paragraph of the Discussion section needs to be presented elsewhere in the report so that the appropriate primary references can be provided in this report.
- The Discussion should also note that the CIR Expert Panel was not as concerned about the potential for protein in oat-derived ingredients to cause Type I reactions because

compared to wheat, soy, eggs, and nuts, oats are not considered to be a major food allergen.

Additional Comments

p.1, Introduction - Please delete "as" in the first sentence of the Introduction.

In the Introduction, it would be helpful to note that Colloidal Oatmeal is the labeling name of the ingredient in OTC drug products in the United States, and to explain how to tell the difference between products containing Colloidal Oatmeal that are drugs, compared to products that are cosmetics. Drug products will include a drug facts panel and indicate a condition which the product is intended to treat.

- p.3 Please cite the CIR report on plant oils and state that the composition of the sprout oil is similar to the kernel oil.
- p.3 At the start of the Method of Manufacture section, it would be helpful to state that many solvents are used to make Avena Sativa (Oat) Kernel Extract including ethanol, water and glycerin.
- p.4 In the Impurities section, it is not clear what the values presented after the abbreviations for the mycotoxins represent. The reader should not have to guess the meaning of these values. What were the levels of these mycotoxins that were detected?
- p.4 At the start of the Use section, it is not clear what is meant by "These ingredients" "The oat-derived ingredients" would at least be more specific.
- p.5 Both the Toxicokinetics and the first paragraph to the Toxicological Studies sections states "rates of dermal absorption and metabolism" since there is nothing in the report about dermal absorption and metabolism of the components, it is not necessary to state this twice. The speculation about rates of absorption from the digestive tract compared to the skin should be deleted from the first paragraph under Toxicological Studies. It would be better to say that because oats are used as food, exposure to the components of oats is expected to be lower compared to use of oat-derived ingredients in cosmetic products.
- p.7 The protocol of the study described in reference 91 is not clear. How many products were tested? Were the oat-derived ingredients and the corticosteroids in the same product? What were the adverse events that occurred?
- p.8 How was the sprout oil administered to mice (reference 49)?
- p.9 The presentation of the study described in reference 102 is very confusing. How many times were IgE levels measured? It is stated twice that IgE was measured before and after the use study but was there more than one use study use of the subjects own products followed by use of the test products?
- p.9 How many chambers were used per child in the study described in reference 104? What is meant by a "set of chambers"? Please revise: "One set of chambers was removed and observed..." - it is likely that the skin, rather than the chambers was "observed".
- p.10 When describing the photoxicity tests, please used "finished products" rather than "test substances". As the tests were completed on multiple subjects, please use "subjects" rather than "subject's". The way it is currently written (subject's), only one subject had Fitzpatrick skin types I, II or III.

- p.10 In the Ocular Irritation section, please correct "HRIPT" to "HOT". Please changed "test substances" to "products".
- p.12, Summary Please correct "had increase proliferation"
- p.13, Table 9 Please indicate that the prick tests were done with oat pollen rather than the plant extract. As oat pollen is not a source of cosmetic ingredients, please consider deleting Table 9 from the report.
- p.13 The following sentence does not make sense. "The Panel discussed the issue of incidental inhalation exposure from face and neck spray products, avena sativa (oat) kernel protein, hydrolyzed oat protein, and body and hand creams lotions, and powders." There is no information in the report on particle sizes of these ingredients it is particle size of products that is being discussed.
- Table 1 Avena Sativa (Oat) Kernel Oil needs to be deleted from Table 1 as it is no longer in this report.
- Table 2 The column headings of this table do not make sense with the information in this table. For example, lipids are not a "subclass" of oat starch, "monosaccharides" are not a subclass of polysaccharides, and "phospholipids and glycolipids" are not free fatty acids.

Why are a number of enzymes presented with albumins?

Table 4 - In the heading, please delete: "The Council conducted a survey of the concentration of use for most of the ingredients in this report."

Avena Sativa (Oat) Bran - Only one concentration was reported for this ingredient, 0.02% in a face and neck product (not spray). Therefore, the 0.2% value in the Total/range row needs to be corrected to -0.02%.

Avena Sativa (Oat) Kernel Extract - In the Council survey, the 0.14% concentration was associated with skin fresheners. The CIR protocol does not include skin fresheners in the powder row.

Avena Sativa (Oat) Kernel Flour - In the Council survey, 5% Avena Sativa (Oat) Kernel Powder was reported to be used in face powders. Why is there an NR in the powder row for this ingredient?

Avena Sativa (Oat) Kernel Protein - The Council indicated that the product containing 0.001% was a pump spray. Therefore, it should have the footnote "e" not "b, d".

Avena Sativa (Oat) Peptide - The Council survey included use at 0.0026% in shampoo, and 0.013% in hair grooming products. Why is there an NR in the Hair-noncoloring row?

Avena Sativa (Oat) Protein Extract - The 1.5% concentration was in a skin cleansing product. Therefore, this concentration should be in the rinse-off rather than the leave-on row.

Avena Sativa (Oat) Starch is not in this report and needs to be deleted from this table. Delete the last blank section of the table.

Table 5 - Although it needs to be designated as "Not an ingredient in this report", the products tested also may have contained Avena Sativa (Oat) Kernel Oil at a concentration of 0.01-0.52%. This needs to be added to Table 5.

Table 6 - In the title of Table 6, please delete "individual ingredient containing". It is likely that many of the products tested contained more than one oat-derived ingredient.

Table 7 - Please correct "product-relate".

Correct "[oat]" to "(oat)".

Delete "no adverse effects" from the protocol column as it is also stated in the results column.

Reference 11 - Was this reference translated from German?

Reference 20 - Correct "Ceral"

Reference 28 - Correct "cerial"

Reference 44 - When was Dr. Duke's data base accessed?

Reference 82 - This reference is not complete.

Reference 96 - Please correct "mode" to "model"