

EXPERT PANEL FOR FRAGRANCE SAFETY MEETING

Minutes

August 27-29, 2018

EXPERT PANEL MEMBERS		RIFM STAFF	GUESTS
Donald Belsito (Chair) Magnus Bruze G. Allen Burten, Jr. Jochen Buschmann Maria Dagli Wolfgang Dekant	Allison Fryer Daniel Liebler Trevor Penning Terry Schultz Glenn Sipes (Vice Chair) Yoshiki Tokura	Anne Marie Api Danielle Botelho Stephanie La Cava Devin O'Brien Gretchen Ritacco (8/27-28 only) Jim Romine Dan Salvito (8/27-28 only) Nikaeta Sadekar (8/28 afternoon via webinar) Gary Sullivan (8/27 afternoon via webinar)	Hervé Groux (ImmunoSearch) (8/28 via webinar in morning) Dr Henrik Johansson and Prof. Malin Lindstedt (Tuesday afternoon) Drs. Johanna Bråred Christensson, Ann-Therese Karlberg and Ulrika Nilsson (Wednesday morning)

1) Discussion of the Meeting Schedule and Agenda Topics

a) Completion/Signing of Conflict of Interest Statement

Dr. Belsito opened the meeting. The Conflict of Interest Statement was signed. The Elsevier Conflict of Interest form was also signed

2) Minutes

The May 2018 Expert Panel Meeting minutes were approved.

3) Follow-Up and Informational Items

a) Follow-Up List

Dr. Api reviewed the status of the items on the follow-up list; all items are either in progress and will be discussed later in the meeting or have been completed.

4) Standing Items (For Expert Panel information only; per Panel's request)

a) RIFM Publications

Dr. Api reviewed the RIFM publication list with the Panel. This is a standing item on the agenda, which provides a summary of all RIFM recent publications.

5) RIFM Communication

a) White Paper and RIFM science accessible by the public

Dr. Romine gave a presentation to update the Panel on the RIFM IFRA White Paper, RIFM strategy for the future and RIFM science accessible by the public (see Attachment 1).

b) Presentation on Update to safety assessment publication via webinar

G. Sullivan gave an update on the publication of the RIFM safety assessments. The presentation was made on August 27 via webinar (see Attachment 2).

6) RIFM Safety Evaluation Process

a) Presentation RIFM Safety Assessment Update and Metrics

Dr. Botelho gave a presentation to update the Panel on the progress made with the safety assessment process (see Attachment 3).

b) Presentation on Low Exposure Materials

Dr. Api gave a presentation to update the Panel on an approach to the safety assessments for low exposure materials (see Attachment 4). The Panel reviewed the first draft of the manuscript which includes 69 fragrance materials. There are approximately 100 more low exposure fragrance materials that may be added to this manuscript. The Panel agreed with the proposal and made recommendations on how to present the data and what data should be included.

c) Safety Assessment Overview

Ms. LaCava presented the safety assessment overview for the materials being reviewed during the meeting. There are 36 Safety Assessments covering 39 materials.

d) General Comments

i) Acceptable concentration levels

Dr. Api gave examples of the presentation of data when DST, skin sensitizers and systemic levels are presented in the safety assessment. The Panel recommended the term "Maximum Acceptable Concentrations in Finished Products" when the QRA2 or DST are applied.

ii) Read Across "statistics"

Dr. Botelho presented the statistics from the recent batch of safety assessments. For the repeated dose and reproduction endpoints 23 of the 36 safety assessments used read across. Six of these 23 required additional review for read across by the Panel.

iii) Section VII (Materials found in naturals)

For some materials the list of foods where materials are found can be very long. The Panel recommended the some of the examples be listed but it does not need to be complete. An example with 5 -10 foods should be sufficient.

iv) Template regarding TTC statements – there should be a distinction between no data and insufficient data. However, in the skin sensitization section, continue to use limited data when there are data on multiple materials.

v) Propylanisole (CAS 104-45-0)

As a general rule, for reproduction (and genotoxicity) the most relevant dose is the oral route because the systemic dose is the most important dose. As such, if an oral and dermal study are available, the margin of exposure should be based on the oral study. There may be exceptions if there are data to show that the dermal study will be more appropriate (e.g. toxicokinetic data are available to show much less bioavailability from the dermal route).

vi) Genotoxicity

There were comments on which concentration to use in the safety assessment document. Usually a concentration range finding study is conducted to determine the cytotoxicity potential. The range-finding study usually has very high concentrations. Based on the range finding study the concentrations for the definitive study are selected. When reporting doses, the doses used in the definitive study should be reported and not the doses used in the range finding study.

7) 5471-51-2 4-(p-Hydroxyphenyl)-2-butanone (Raspberry ketone)

Ms. Ritacco gave a presentation summarizing the depigmentation data on 4-(p-Hydroxyphenyl)-2-butanone (Raspberry ketone) (see Attachment 5). A NOAEL of 10% in the minipig was observed. The Panel

suggested using a safety factor of 10 which results in a maximum acceptable concentration of 1% in the final product. The safety assessment was approved with this one change.

8) Webinar Presentation on SENS-IS by Hervé Groux (ImmunoSearch) (Tuesday morning)

Dr. Hervé Groux (ImmunoSearch) gave a presentation via webinar on Tuesday morning, August 28 (see Attachment 6).

9) Review Safety Assessments Batch 1

CAS	Name	Tab	Status
7492-67-3	Citronelloxyacetaldehyde	Tab 25	Approved
4430-31-3	Octahydrocoumarin	Tab 26	Approved with changes
93-16-3	Isoeugenyl methyl ether	Tab 27	Insufficient Data - sensitization
15373-31-6	2,2,3-Trimethylcyclopent-3-enylacetonitrile	Tab 28	Approved
20780-48-7 and 68480-08-0	Tetrahydrolinalyl acetate; 2,6-Dimethyl-2-octyl acetate	Tab 29	Approved
111-79-5	Methyl 2-nonenoate	Tab 30	Approved with changes
623-70-1 and 10544-63-5	Ethyl trans-2-butenoate	Tab 31	Approved
22874-79-9	Octyl crotonate	Tab 32	Approved
544-40-1	Butyl sulfide	Tab 33	Approved
64-19-7	Acetic acid	Tab 34	Approved
79-09-4	Propionic acid	Tab 35	Approved
107-92-6	Butyric acid	Tab 36	Approved

10) Presentation by Dr. Bruze – Thoughts on the HRIPT

Dr. Bruze gave a presentation on thoughts on the HRIPT (see Attachment 7). The Expert Panel recommended changes to the RIFM HRIPT protocol:

Challenge conc dose in mg/cm²

Challenge occlusion time to 48 hours

Reading days: D2, D3/4 and D7

Define what constitutes a positive challenge reaction

Rechallenge

Use test

Dr. Bruze provided data that will be published soon to show that a significant number of reactions are missed when a 24-hour challenge vs a 48-hour challenge period are used (20/36 patients had 24 Hr. = 48 Hr. readings; 13/36 patients had 24 Hr. < 48 Hr. readings and 3/36 patients had 24 Hr. > 48 Hr. readings).

The HRIPT induction with 24-hour applications is not in question, but the challenge is similar to the patch test conducted by dermatologists and this portion of the HRIPT should follow the international guidelines for patch testing (ICDRG, ESCD). As such, the recommendation is to change the HRIPT challenge application to a 48-hour challenge application and to conduct readings at D2, D3/4 and D7. The Politano and Api paper does not define a positive challenge. (Dr. Api reported that the rechallenge positive was defined which is the same definition as the challenge, but it should have been defined.) A rechallenge and use test are difficult to do with appropriate number of subjects. Dr. Api reported that RIFM has not conducted either in a very long time; the results from the HRIPT have been accepted as final with the challenge results. The Panel considered these changes and improvements appropriate because they are based on advancements in the science related to skin sensitization.. Dr. Api reported that running both protocols (on random materials) for a period of time may be an appropriate next step. The HRIPT data collected since the mid-1980s have been collated and a paper is in preparation. A refinement to the protocol may be suggested in that paper.

11) Review Safety Assessments Batch 2

CAS	Name	Tab	Status
544-63-8	Myristic acid	Tab 37	Approved
57-11-4	Stearic acid	Tab 38	Approved
503-74-2	Isovaleric acid	Tab 39	Approved
116-53-0	2-Methylbutyric acid	Tab 40	Approved
4621-04-9	4-Isopropylcyclohexanol	Tab 41	Approved
830322-14-0	Cyclohexanol,4-(3-methylbutyl)-	Tab 42	Approved
1191-16-8	3-Methyl-2-butenyl acetate	Tab 43	Approved
93-51-6	2-Methoxy-4-methylphenol	Tab 44	Approved with changes
3209-13-0	3-Methoxy-5-cresol	Tab 45	Approved
546-80-5 and 471-15-8	α -Thujone	Tab 46	Approved
13466-78-9	delta-3-Carene	Tab 47	Approved

12) Safety Assessment Approach to Natural Complex Substances (NCSs)

a) Presentation by D. Salvito: Update on the NCS Project

Dr. Salvito provided an update from the NCS Workshop that was held in May 2018 (see Attachment 8). The Panel agreed that compositional ranges are needed in the publication in order for the publication to have credibility. The Panel would like to refine the disclaimer that is drafted. Components that are CMRs, sensitizers, photoallergens, phototoxins, will be listed if they are in the NCS below 1% - 0.01%.

13) Presentation by Dr Henrik Johansson and Prof. Malin Lindstedt: Respiratory and Skin Sensitizer Predictions in SenzaGen (Tuesday afternoon)

Dr Henrik Johansson and Prof. Malin Lindstedt gave a presentation on Tuesday, August 28 in the afternoon on Respiratory and Skin Sensitizer Predictions in SenzaGen (see Attachment 9). The Panel recommended that this assay be explored in more detail.

14) Update on QRA2 Implementation

a) A.M Api Presentation on QRA2

Dr. Api gave a presentation updating the Panel on QRA2 (see Attachment 10).

15) Presentation by N. Sadekar – Respiratory Research Projects (Tuesday afternoon webinar)

Dr. Nikaeta Sadekar gave a presentation that reviewed the outcome from the respiratory workshop in May 2018. She also reviewed the two proposals for future work, which were given to the Panel for review and also reviewed by the RIFM Respiratory Core Team and Adjunct Group (see Attachment 11). The first proposal is on using lysine and cysteine reactivity data for the identification of respiratory sensitizers. The second proposal is investigating whether the tool compounds effect ILC2 alarmins in human precision cut lung slices. The Panel recommended that the next step should be a comprehensive literature review on respiratory sensitizers. This document will be used to develop a list of gold standards for respiratory sensitizers for future work. They agreed that the first phase of the human precision cut lung slices project should proceed. The proposal on using lysine and cysteine reactivity data for the identification of respiratory sensitizers should only be started after the review is completed and the DPRA should be run on the materials at the same time in the same laboratory. The Panel also recommended that the GARDAir assay be investigated.

16) Review Safety Assessments – Batch 3

CAS	Name	Tab	Status
106-70-7	Methyl hexanoate	Tab 54	Approved
123-66-0	Ethyl hexanoate	Tab 55	Approved
111-11-5	Methyl octanoate	Tab 56	Approved
106-30-9	Ethyl heptanoate	Tab 57	Approved
106-32-1	Ethyl octanoate	Tab 58	Approved
110-42-9	Methyl decanoate	Tab 59	Approved
123-29-5	Ethyl nonanoate	Tab 60	Approved
540-07-8	Amyl hexanoate	Tab 61	Approved
110-38-3	Ethyl decanoate	Tab 62	Approved
36431-72-8	Theaspirane	Tab 63	Approved
2109-22-0	2-Cyclohexylpropanal	Tab 64	Approved
70788-30-6	1-(2,2,6-Trimethylcyclohexyl)-3-hexanol	Tab 65	Approved

17) Human Health Research Projects

- a) Epidemiology
 - i) Validation of Clinical Relevance Algorithm

Dr. Bruze reported that the draft publication on the validation study is available. He also reported that there will be four presentations at ESCD from the epidemiology study (not on fragrances, but other materials).

b) Presentation by D. O'Brien on RIFM Dermal Sensitization Research Project Update

Devin O'Brien gave a presentation updating the Panel on the RIFM Dermal Sensitization Research Program (see Attachment 12).

c) Presentation by G. Ritacco – Photoallergy Research Project and review for potent photoallergens – is there a NOAEL?

Gretchen Ritacco gave a presentation on the plans for the photoallergy research project and a review of potent photoallergens (see Attachment 13).

- d) Update on RIFM TTC Research

Dr. Api updated the Panel on the oral TTC research program. A manuscript is being developed. Dr. Botelho updated the Panel on the respiratory research program.

18) Presentation by Johanna Bråred Christensson, Ann-Therese Karlberg, Ulrika Nilsson - Oxidized Linalool and Oxidized Limonene

Drs. Johanna Bråred Christensson, Ann-Therese Karlberg and Ulrika Nilsson updated the Panel on their work on oxidized linalool and oxidized limonene (see Attachment 14, 15 and 16).

19) IFRA Standards

- a) Geranyl Nitrile

The Panel recommended that a reasonable proposal is to keep the level of geranyl nitrile below the TTC level for genotoxicity (0.0025 ug/kg/day in the final product).

20) Future Meeting Dates

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| • Monday – Wednesday | Jan. 28-30, 2019 | Miami, FL |
| • Monday – Wednesday | May 20-22, 2019 | Rome |
| • Monday – Wednesday | Sept. 23-25, 2019 | New Jersey |
| • Monday – Wednesday | Jan. 20-22, 2020 | Delhi, India |
| • Thursday | Jan. 23, 2020 | INFOX, India (?) |
| • Monday – Wednesday | May 18-20, 2020 | Chicago |
| • Monday – Wednesday | Sept. 21-23, 2020 | New Jersey |
| • Wednesday-Friday | Jan. 20-22, 2021 | Puerto Rico (?) |

Respectfully submitted,



Anne Marie Api, PhD
Vice President, Human Health Sciences
(finalized: January 28, 2019)

- Attachment 1: Dr. Romine presentation on the RIFM IFRA White Paper, strategy and communication
- Attachment 2: Mr. Gary Sullivan presentation on publication of RIFM safety assessments
- Attachment 3: Dr. Botelho presentation on the safety assessment process
- Attachment 4: Dr. Api presentation on an approach to the safety assessments for low exposure materials
- Attachment 5: Ms. Ritacco presentation on 4-(p-Hydroxyphenyl)-2-butanone
- Attachment 6: Dr. Hervé Groux (ImmunoSearch) presentation on SENS-IS
- Attachment 7: Dr. Bruze presentation on thoughts on the HRIPT
- Attachment 8: Dr. Salvito presentation on overall approach to the NCS safety assessment
- Attachment 9: Dr. Henrik Johansson presentation on respiratory and skin sensitizer predictions in SenzaGen
- Attachment 10: Dr. Api presentation updating the Panel on QRA2
- Attachment 11: Presentation by Dr. Sadekar on respiratory research project proposals
- Attachment 12: Presentation by Ms. O'Brien on sensitization research projects
- Attachment 13: Presentation by Ms. Ritacco on phototoxicity/photoallergy research projects
- Attachment 14: Presentation by Dr. Johanna Bråred Christensson
- Attachment 15: Presentation by Dr. Ulrika Nilsson
- Attachment 16: Presentation by Dr. Ann-Therese Karlberg