

EXPERT PANEL FOR FRAGRANCE SAFETY MEETING

Minutes

September 19-21, 2022

Lisbon

EXPERT PANEL MEMBERS	RIFM STAFF		Guests
Donald Belsito (Chair) Magnus Bruze G. Allen Burton, Jr. Maria Dagli (Vice-Chair) Wolfgang Dekant Allison Fryer Trevor Penning Terry Schultz Glenn Sipes	Anne Marie Api Danielle Botelho Olive Chon (Virtual, pm) Leah Jones Kaushal Joshi (Virtual, pm) Maura Lavelle (Virtual, pm) Aurelia Lapczynski (Virtual, pm) Holger Moustakas Jake Muldoon (Virtual, pm) Gretchen Ritacco (Virtual, pm)	Jim Romine Nikaeta Sadekar (5/13) Isabella Schember (Virtual, pm) Dan Selechnik (Virtual, pm) Faiz Siddiqi (Virtual, pm) Gary Sullivan (9/19, Virtual) Yax Thakkar (Virtual, pm)	Amanda Bryant-Friedrich Margarida Goncalo (9/20, pm) Daniel Joulain (9/19, pm) Tim Lindberg, SenzaGen (9/19, Virtual, pm) Andy Forreryd, SenzaGen (9/19, Virtual, pm) Heather Summers, Integral (9/20, Virtual) Christopher Stevens, Integral, (9/20, Virtual, pm)

1) Discussion of the Meeting Schedule and Agenda Topics

- a) Completion/Signing of the Conflict-of-Interest Statement

Dr. Belsito opened the meeting. The Conflict-of-Interest Statement was signed. Dr. Yoshiki Tokura sent his regrets; he was not able to attend the meeting. He attended the presentations in the afternoon sessions. Dr. Belsito welcomed Dr. Amanda Bryant-Friedrich to the meeting.

2) Minutes

The minutes from the May 2022 meeting were approved with no changes.

3) Follow-Up and Informational Items

- a) Follow-Up List

Dr. Api went through the follow-up list and provided updates on items and general comments where applicable.

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

- a) RIFM Publications

The Panel reviewed the RIFM publication list. This is a standing item on the agenda, which provides a summary of all RIFM's recent publications.

- b) RIFM Safety Assessment Publications

The Panel reviewed the RIFM safety assessment publications list. This list is an ongoing list of all the published safety assessments.

5) RIFM Communication

- a) Update on RIFM

Dr. Romine provided an overview of RIFM activities.

b) Presentation by G Sullivan, RIFM Communication and Safety Assessment Publication Update

Mr. Sullivan gave an update on the RIFM communication plans, safety assessment publications, and the Fragrance Resource Center website (see Attachment 1).

6) RIFM Safety Evaluation Process

a) Presentation RIFM by D. Botelho Safety Assessment Update and Metrics

Dr. Botelho gave a presentation on the Safety Assessment program and its progress (see Attachment 2).

- b) Safety Assessment Overview

The Panel reviewed 51 Safety Assessments including 57 materials.

- c) General Comments

- i) Materials with no chromophores

The chemistry team on the Panel introduced the topic of materials that have no chromophores and there is no possibility for UV absorbance. The recommendation is that for these types of chemicals, no UV absorption spectrum is needed. The Panel agreed with this recommendation.

- ii) Formaldehyde releasers

For several materials (Tabs 31, 44, 46, 47, 50, 51, 52, and 53), the predicted metabolism pathway identified formaldehyde as a potential metabolite. The chemists on the Panel reported that while plausible, it is improbable that the materials will form formaldehyde. They recommended that the graphics, which are very misleading because they do not provide plausibility, be removed and the wording in the safety assessment be modified. Dr. Moustakas will develop an alternative summary and will review it with the chemists on the Panel. The summary will be revised for all the materials where it was listed.

7) Presentation by Dr. Amanda Bryant-Friedrich

Dr. Bryant-Friedrich gave a presentation describing her background and research projects (see Attachment 3).

8) NCS Safety Assessments

a) Presentation by Dr. Daniel Joulain, SCBZ Conseil, Natural Complex Substances (NCS) as fragrance ingredients: technical and analytical aspects.

Dr. Daniel Joulain gave a presentation on NCS and addressed questions that the Panel had on NCS (see Attachment 4).

- b) General Comments

- i) Full read-across justification for all the components of NCS

Dr. Moustakas presented the current read-across justification for all the components of the NCS. If the component has a published safety assessment with the read-across, the published safety assessment is provided. If the read-across has changed or has not been published, then the read-across justification is provided in the safety assessment. The Panel recommended that the word "None" in the table be replaced with "None required" or if exposure waiving is used, then DST, TTC should be added. The Panel also requested that a statement be added if there was insufficient data on components and therefore the whole NCS is being tested.

ii) Sensitization tables

The Panel agreed with the added clarifying language and the adjustments to the table. They recommended that the sensitization tables for the most potent sensitizing component and the component that is a sensitizer and is present in the highest composition should remain in the safety assessment. These tables demonstrate the transparency in the safety assessment and should address all possible scenarios. They also encouraged RIFM to have multiple webinars to explain the tables. It was agreed that if maximum acceptable concentrations are recommended for NCS, then these tables would only be present in Section X.

iii) Genotoxicity

The Panel requested that the footnote on Cramer Class in the component table be repeated in the genotoxicity table.

c) Safety Assessment Review

i) Total NCS Safety Assessments: 7

Material ID	RIFM ID	Material Name	Tab	Status
1042197	6607-G2.5	Tangerine oil	Tab 18	Insufficient Data: Genotoxicity
1048539	6607-G2.12	Tangerine oil	Tab 19	Approved with changes
1043684	6607-G2.30	Tangerine oil terpenes	Tab 20	Approved with changes
1048049	931-G2.5	Tangelo oil, expressed	Tab 21	Approved with changes
1044006	1091-G2.5	Bergamot oil, expressed	Tab 22	Insufficient Data: Genotoxicity
1043743	1091-G2.30	Bergamot oil terpenes	Tab 23	Insufficient Data: Genotoxicity
1042396	1429-G2.5	Persian lime oil, expressed	Tab 24	Insufficient Data: Genotoxicity

9) Follow-up on actions for Safety Assessment

b) Eugenyl methyl ether CAS No. 93-15-2

The Panel approved the safety assessment with changes.

c) Estragole CAS No. 140-67-0

The Panel approved the safety assessment with changes.

10) Presentation by Dr. Margarida Goncalo, Head of Department of Dermatology, Coimbra University Hospital: The burden of fragrance allergy. ACD and beyond - Tuesday, September 20

Dr. Goncalo gave a presentation on the burden of fragrance allergy (see Attachment 5).

11) Review Safety Assessments Batch 1

CAS #	Material Name	Tab	Status
1117-55-1	Hexyl octanoate	Tab 27	Approved
6259-76-3	Hexyl salicylate	Tab 28	Approved with changes
24238-95-7	1,7,7-Trimethylbicyclo[4.4.0]dec-3-yl acetate	Tab 29	Approved
74499-58-4	4,7,7-Trimethyl-2-(3-methyl-2-butenyl)bicyclo[4.1.0]heptan-3-one	Tab 30	Approved
40527-42-2	1,3-Benzodioxole, 5-(diethoxymethyl)-	Tab 31	Approved with changes
122-68-9	3-Phenylpropyl cinnamate	Tab 32	Approved
103-53-7	Phenethyl cinnamate	Tab 33	Approved
51115-63-0	Benzoic acid, 2-hydroxy-, 2-methylbutyl ester	Tab 34	Approved

CAS #	Material Name	Tab	Status
79915-74-5	Isopropoxy ethyl salicylate	Tab 35	Approved
119-36-8	Methyl salicylate	Tab 36	Approved
118-61-6	Ethyl salicylate	Tab 37	Approved
2052-14-4	Butyl salicylate	Tab 38	Approved
79-78-7	Allyl alpha-ionone	Tab 39	Approved with changes
72207-94-4	4-Acetoxy-3-ethoxybenzaldehyde	Tab 40	Approved
20665-85-4	Vanillin isobutyrate	Tab 41	Approved
85508-08-3	3-Pentenoic acid, 2-methyl-, hexyl ester	Tab 42	Approved
499-44-5	2,4,6-Cycloheptatrien-1-one, 2-hydroxy-4-(1-methylethyl)-	Tab 43	Approved
3149-28-8	Methoxypyrazine	Tab 44	Approved with changes
88-15-3	2-Acetylthiophene	Tab 45	Approved
2186-92-7	Benzene, 1-(dimethoxymethyl)-4-methoxy-	Tab 46	Approved with changes
2403-58-9	4-Methoxybenzaldehyde diethyl acetal	Tab 47	Approved with changes
90-02-8	Salicylaldehyde	Tab 48	Approved with changes
123-08-0	4-Hydroxybenzaldehyde	Tab 49	Approved with changes
2847-30-5; 68378-13-2; 25680-58-4; 63450-30-6	2-Methoxy-3-methylpyrazine	Tab 50	Approved with changes
32737-14-7	2-Methyl-3,5 or 6-ethoxypyrazine	Tab 51	Approved with changes
25773-40-4	2-Methoxy-3(5 and 6)-isopropylpyrazine	Tab 52	Approved with changes
24683-00-9	2-Isobutyl-3-methoxypyrazine	Tab 53	Approved with changes
68844-95-1	Pyrazine, 2-methoxy-3-(4-methylpentyl)-	Tab 54	Approved
24168-70-5	2-Methoxy-3-(1-methylpropyl)pyrazine	Tab 55	Approved
1072-83-9	Methyl 2-pyrrolyl ketone	Tab 56	Approved
109-08-0	2-Methylpyrazine	Tab 57	Approved

12) Review Safety Assessments Batch 2

CAS#	Material Name	Tab	Status
5910-89-4	2,3-Dimethylpyrazine	Tab 58	Approved
108-50-9	2,6-Dimethylpyrazine	Tab 59	Approved
123-32-0	2,5-Dimethylpyrazine	Tab 60	Approved
15707-23-0	2-Ethyl-3-methylpyrazine	Tab 61	Approved
13360-64-0	2-Ethyl-5-methylpyrazine	Tab 62	Approved
15707-24-1	2,3-Diethylpyrazine	Tab 63	Approved
13925-06-9	2-Isobutyl-3-methylpyrazine	Tab 64	Approved
13708-12-8	5-Methylquinoxaline	Tab 65	Approved with changes
118-60-5	Ethyl hexyl salicylate	Tab 66	Approved with changes
120-14-9	Veratraldehyde	Tab 67	Approved
118-71-8	Maltol	Tab 68	Insufficient Data: Photoirritation
4940-11-8	Ethyl maltol	Tab 69	Insufficient Data: Photoirritation
14667-55-1	2,3,5-Trimethylpyrazine	Tab 70	Approved
13925-07-0; 13360-65-1; 27043-05-6	3-Ethyl-2,6-dimethylpyrazine	Tab 71	Approved with changes

CAS#	Material Name	Tab	Status
18138-04-0	2,3-Diethyl-5-methylpyrazine	Tab 72	Approved

13) Review Safety Assessments Batch 3

CAS#	Material Name	Tab	Status
1885-38-7; 4360-47-8	Cinnamyl nitrile	Tab 73	Approved
34413-35-9	5,6,7,8-Tetrahydroquinoxaline	Tab 74	Approved
23747-48-0	5H-5-Methyl-6,7-dihydrocyclopenta(b)pyrazine	Tab 75	Approved
2524-52-9	2-pyridinecarboxylic acid, ethyl ester	Tab 76	Approved
80417-97-6	2(4H)-Benzofuranone, 5,6-dihydro-3,6-dimethyl-	Tab 77	Approved

14) Review Safety Assessments Maintenance Batch

CAS#	Material Name	Tab	Status
7785-64-0	Butyl 2-methylcrotonate (Z)	Tab 79	Approved
16930-96-4	Hexyl tiglate	Tab 80	Approved
127-91-3	beta-Pinene	Tab 81	Approved
79-92-5	Camphene	Tab 82	Approved
87-19-4	Isobutyl salicylate	Tab 83	Approved
87-20-7	Isoamyl salicylate	Tab 84	Approved
2050-08-0	Amyl salicylate	Tab 85	Approved
4112-89-4	Guaiacyl phenylacetate	Tab 86	Approved
135-02-4	o-Methoxybenzaldehyde	Tab 87	Approved
68133-76-6	3-Hexenyl 2-oxopropionate	Tab 88	Approved
95-41-0	Dihydroisojasmone	Tab 89	Approved with changes
122-91-8	Anisyl formate	Tab 90	Approved with changes
1331-83-5	Anisyl acetate (isomer unspecified)	Tab 91	Approved with changes
7549-33-9	Anisyl propionate	Tab 92	Approved with changes
8000-41-7	Terpineol	Tab 93	Approved
10519-12-7	Decahydro-beta-naphthyl formate	Tab 94	Approved
10519-11-6	Decahydro-beta-naphthyl acetate	Tab 95	Approved
28940-11-6	7-Methyl-2H-benzo-1,5-dioxepin-3(4H)-one	Tab 96	Approved
1113-21-9	Geranyl linalool	Tab 97	Approved
98-52-2; 21862-63-5	4-tert-Butylcyclohexanol	Tab 98	Approved

15) RIFM Research Projects

a) Presentation by A.M. Api - Overview of RIFM research programs

Dr. Api gave a presentation that reviewed all the research projects underway at RIFM (see Attachment 6). The Panel thanked the RIFM staff for all the hard work they have done. It is an impressive body of work.

b) Epidemiology

No new update from the EDEN Fragrance Group. Dr. Luigi Naldi is now leading that group.

i) Eugenol Threshold Study

Dr. Api reported Dr. Belsito had additional comments on the manuscript but there were no further comments from the RIFM Advisory Committee. Dr. Bruze reported that the manuscript was submitted to Contact Dermatitis for publication.

c) Presentation by H. Moustakas on read-across2 and NCS Cluster manuscripts

i) Read-across2 paper

Dr. Moustakas explained that the second read-across paper is completed and has been submitted for publication. The paper explains the rules for each endpoint and how it governs the read-across. He reviewed the paper with the Panel and provided examples of many of the rules outlined in the paper.

ii) Outline of NCS Clustering paper

Dr. Moustakas provided an update on the plans for the NCS clustering manuscript. The goal is to submit the paper in 2023. The goal is to explain how the NCS were grouped to make the safety assessment more efficient to complete. The citrus family may be used as an example of how the principles outlined were used.

d) Skin Sensitization Research Projects

i) Epoxide research update

Dr. Moustakas provided an update on the epoxide research project. The selected materials are being tested in the Sens-IS assay. It will help determine if the materials are more reactive and therefore have more potential for sensitization. This will help refine the read-across rules for these materials.

e) **Environmental Research Projects**

i) Framework2 - Presentation by Heather Summers and Christopher Stevens, Integral, Tuesday afternoon, 2 PM

Dr. Heather Summers and Christopher Stevens (Integral) and Ms. Aurelia Lapczynski (RIFM) joined the Panel meeting virtually on Tuesday to provide a detailed review of the update to the Framework document (Framework2). The Panel agreed to the overall approach and requested that the group prepare a manuscript for peer-reviewed publication. They encouraged them to have a few examples of how the Framework will work.

f) Presentation from SenzaGen on PhotoGard Assay - Monday, September 19

Drs. Tim Lindberg and Andy Forreryd, SenzaGen gave a virtual presentation on Monday, September 19 on the research they have conducted on the PhotoGard Assay (see Attachment 7).

g) Presentation by N. Sadekar on respiratory tools – MPPD

Dr. Sadekar gave a presentation on the use of the MPPD Model to refine inhalation exposure (see Attachment 8). Dr. Schultz recommended that the chemistry experts review the material and the other fragrance materials in the class to determine if the other materials in the cluster have similar classifications. This can all be added as support for the classification of the material and use of a refined exposure in the TTC. Dr. Moustakas will follow up on this review. Dr. Sadekar will draft the rationale for the safety assessment and review it with the Panel.

h) Presentation by Y. Thakkar on Certara PBPK results

Mr. Thakkar gave a presentation on the Certara PBPK Model (see Attachment 9).

16) New Expert Panel Members

The Panel discussed potential new Panel members.

17) Panel Executive Session

The Panel held an Executive Session and agreed to invite Dr. Amanda Bryant-Friedrich to join the Expert Panel for Fragrance Safety. Dr. Bryant-Friedrich agreed.

18) Future Meeting Dates

- Wednesday - Friday, Jan. 18-20, 2023 San Diego
- Monday - Wednesday, May 15-17, 2023 Tokyo
 - May 10-13, 2023 ISID (International Societies for Investigative Dermatology), Tokyo, Japan
 - May 13, 2023 ISID RIFM Satellite symposium, 4:30-7:00pm, May 13, Eminence Room, Keio Plaza Hotel in Tokyo, Japan
- Monday – Wednesday, September 25-27, 2023 New Jersey
- Monday-Wednesday, Jan. 22-24, 2024 Miami/Puerto Rico
- Monday-Wednesday, May 20-22, 2024 Edinburgh
- Monday-Wednesday, September 23-25, 2024 New Jersey

Respectfully submitted,



Anne Marie Api, Ph.D., ATS

Vice President

- | | |
|---------------|---|
| Attachment 1: | Presentation: Mr. Gary Sullivan |
| Attachment 2: | Presentation: Dr. Danielle Botelho |
| Attachment 3: | Presentation: Dr. Amanda Bryant-Friedrich |
| Attachment 4: | Presentation: Dr. Daniel Joulain |
| Attachment 5: | Presentation: Dr. Margarida Goncalo |
| Attachment 6: | Presentation: Dr. Anne Marie Api |
| Attachment 7: | Presentation: Drs. Tim Lindberg and Andy Forreryd, SenzaGen |
| Attachment 8: | Presentation: Dr. Nikaeta Sadekar |
| Attachment 9: | Presentation: Mr. Yax Thakkar |