

# EXPERT PANEL FOR FRAGRANCE SAFETY MEETING

## Final Minutes

May 11-13, 2022

New York City

EXPERT PANEL MEMBERS	RIFM STAFF		Guests
Donald Belsito (Chair) Magnus Bruze G. Allen Burton, Jr. Maria Dagli (Vice-Chair) Wolfgang Dekant Allison Fryer Dan Liebler Trevor Penning Terry Schultz I Glenn Sipes	Anne Marie Api Danielle Botelho Chaitra Deodhar (5/12) Kaushal Joshi (5/11) Maura Lavelle (5/12) Aurelia Lapczynski (5/12-13) Isabelle Lee (5/12) Holger Moustakas (5/12-13)	Mihwa Na (5/12) Gretchen Ritacco (5/12) Jim Romine (5/11, virtual) Nikaeta Sadekar (5/13) Dan Selechnik (5/11) Gary Sullivan (5/11) Yax Thakkar (5/13)	Tobey Marzouk (5/11) Henrik Johansson, SenzaGen (5/12, virtual) Emilia Costin, IIVS (5/12, virtual) Arno Gutleb, LIST (5/13, virtual)

### 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.

### 2) Minutes

The minutes from the January 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.

**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).

**c) Presentation by A.M. Api**

Dr. Api provided an update on the proposed animal testing policy (see Attachment 2).

**6) Presentation by T. Marzouk**

Mr. T. Marzouk reviewed various topics with the Panel including the Expert Panel's Operating Procedures, Conflict of Interest Policy, Transparency Policy, and Communications Policy. He also provided a summary of analytics regarding the Expert Panel Website and discussed the purpose, scope, and timing of an Expert Panel Self-Assessment. (See Attachment 3)

**7) RIFM Safety Evaluation Process**

**a) Presentation RIFM by D. Botelho Safety Assessment Update, Metrics, NCS timetable**

Dr. Botelho gave a presentation on the Safety Assessment program and its progress (see Attachment 4).

**b) Safety Assessment Overview**

The Panel reviewed 23 Safety Assessments including 23 materials.

**c) General Comments**

There were no general comments on the safety assessments.

**8) NCS Safety Assessments**

**a) General Comments**

- i) The Panel had a general discussion on resins that may be found in an NCS. It was agreed that as much information as possible should be shared on the composition of the resins (known unknown as well as unknown unknown). It may be that some will have to be tested for composition. One or two and may have to have analytical analyses conducted before any testing is conducted to learn if they are significantly different. The derived exposures will also have to be reviewed in detail
- ii) In the skin sensitization section for NCS, the Panel recommended that if the DST cannot be applied then the table should read "above DST".
- iii) In the skin sensitization section for NCS, if a material has the potential to autoxidize, then there should be a footnote in the table.
- iv) In the skin sensitization section for NCS, if a material has an existing MAC, then a footnote needs to be added to the table such as:

*Maximum Acceptable Concentrations (MAC) in final consumer products shall apply regardless of whether the restricted substance is added directly or indirectly to the fragrance mixture. Indirect contributions from other sources e.g. presence of natural complex substances (NCS) must be taken into account in the calculation of the levels of the restricted substance.*

**b) Safety Assessment Review**

- i) The Total NCS Safety Assessments: 19

RIFM Material ID	Material Name	Tab	Status
1045267	Mandarin oil	Tab 21	Insufficient Data - Genotoxicity (whole NCS testing)
1043377	Grapefruit oil	Tab 22	Insufficient Data – Genotoxicity (whole NCS testing); Environmental component testing (2 missing structures); Photo study review
1048498	Grapefruit essence oil	Tab 23	Insufficient Data – Environmental component testing
1048499	Grapefruit oil	Tab 24	Insufficient Data – Environmental component testing
1043849	Grapefruit oil terpenes	Tab 25	Approved with changes
1043338	Mandarin oil, terpenes	Tab 26	Approved with changes
1045027	Citrus junos oil	Tab 27	Insufficient Data – Environmental component testing
1043340	Citron oil	Tab 28	Approved with changes
1048531	Orange flower, bitter, CO2 extract	Tab 29	Insufficient Data – High percentage resin Photo testing needed Genotoxicity testing Not Supported List no sample
1042471	Orange blossoms absolute	Tab 30	Insufficient Data – High percentage resin Genotoxicity testing
1047553	Orange oil, bitter	Tab 31	Insufficient Data – Genotoxicity testing
1046367	Orange flower oil, bitter (Neroli and Neroli bigarade)	Tab 32	Insufficient Data – Genotoxicity testing Environmental component testing
1044055	Orange flower water absolute	Tab 33	Insufficient Data – Genotoxicity testing
1045269	Orange peel, sweet oil	Tab 34	Insufficient Data – Genotoxicity testing
1043886	Orange sweet, Valencia oil	Tab 35	Approved with changes
1043970	Orange essence oil	Tab 36	Approved with changes
1048532	Orange flower, bitter, concrete	Tab 37	Insufficient Data – High Non-volatile percentage Genotoxicity testing
1044817	Orange leaf absolute (aka Petitgrain bigarade absolute)	Tab 38	Insufficient Data – Genotoxicity testing
1043685	Orange oil, sweet terpenes	Tab 39	Approved with changes

### 9) Presentation by K. Joshi and D. Selechnik – estimating reproduction NOAEL

Drs. Joshi and Selechnik gave a presentation on developmental and reproductive toxicity (DART) Point of Departure (PoD) extrapolation (see Attachment 5). They addressed the questions that the Panel presented during the January 2022 meeting. The Reproduction Adjunct Team reviewed the method and overall it seems like a practical approach to deriving a NOAEL. All five Adjunct group members agreed to use this approach for RIFM Safety Assessment. One Adjunct group member thought it would be best to use this method only by deferring it to an uncertainty factor of 10. The Panel recommended that If the tool supports a decrease of the uncertainty factor to 3, the conditions would need to be reviewed extensively by the Panel and the Reproduction

Adjunct Team. Rational approach and conservative; will proceed with writing up the safety assessments for the three examples provided.

### 10) Presentation by M. Bruze - the possible significance of systemic exposure to sensitizers and deteriorating pain in those with chronic pain in joints and muscles

Prof. Bruze gave a presentation on the possible significance of systemic exposure to sensitizers and deteriorating pain in those with chronic pain in joints and muscles (see Attachment 6).

### 11) Presentation by A. Lapczynski – OTNE update

Ms. Lapczynski gave a presentation on the species sensitivity assessment on the fragrance ingredient, 1-(1,2,3,4,5,6,7,8-Octahydro-2,3,8,8-tetramethyl-2-naphthalenyl)ethenone, CAS No: 54464-57-2 (OTNE) (see Attachment 7).

### 12) Review Safety Assessments Batch 1

CAS #	Material Name	Tab	Status
319002-92-1	Propyl (2S)-2-(1,1-dimethylpropoxy)-propanoate	Tab 41	Approved
100-06-1	Acetanisole	Tab 42	Approved with Changes
113486-29-6	3-Methyl-2,4-nonedione	Tab 43	Approved with Changes
1963-36-6	p-Methoxycinnamaldehyde	Tab 44	Insufficient Data - Photo
72987-59-8	Ethanol, 2-(4-methylphenoxy)-1-(2-phenylethoxy)-	Tab 45	Approved
92-52-4	Biphenyl	Tab 46	Approved
1438-91-1	Furfuryl methyl sulfide	Tab 47	Approved
94248-38-1	[(3a,4,5,6,7,7a-Hexahydro-4,7-methano-1H-inden-5(or 6)-yl)oxy]acetaldehyde	Tab 48	Approved with Changes
68039-38-3	Citronellyl crotonate	Tab 49	Approved with Changes
689-89-4	Methyl sorbate	Tab 50	Approved
3025-30-7	Ethyl trans-2,cis-4-decadienoate	Tab 51	Insufficient Data - Skin
136954-20-6	3-Mercaptohexyl acetate	Tab 52	Approved
22717-57-3	Benzoic acid, 2-hydroxy-5-methyl-, methyl ester	Tab 53	Approved with Changes
81-14-1	Musk ketone	Tab 54	Approved with Changes

### 13) Review Safety Assessments Batch 2

CAS#	Material Name	Tab	Status
1504-74-1	o-Methoxycinnamaldehyde	Tab 55	Approved with Changes
17909-77-2	2,6-Dimethyl-10-methylene-2,6,11-dodecatrienal	Tab 56	Approved with Changes
5406-58-6	2,5,5-Trimethyl-2-phenyl-1,3-dioxane	Tab 57	Approved with Changes
20770-40-5	Citronellyl 3-methyl-2-butenate	Tab 58	Approved with Changes
24717-85-9	Citronellyl tiglate	Tab 59	Approved with Changes
67845-42-5	Citronellal methylanthranilate Schiff base	Tab 60	Approved
14735-72-9	Benzoic acid, 2-(((4-methoxyphenyl)methylene)amino)-,methyl ester	Tab 61	Approved with Changes
118635-60-2	2,11-Dodecadienal, (E)- (9CI)	Tab 62	Approved with Changes

CAS#	Material Name	Tab	Status
554-12-1	Methyl propionate	Tab 63	Approved

#### 14) Review Safety Assessments Maintenance Batch (Tab 64)

CAS#	Material Name	Tab	Status
31501-11-8	cis-3-Hexenyl hexanoate	Tab 65	Approved with changes
55418-52-5	4-(3,4-Methylenedioxyphenyl)-2-butanone	Tab 66	Approved with changes
7492-44-6	alpha-Butylcinnamaldehyde	Tab 67	Approved with changes
10458-14-7; 491-07-6; 14073-97-3; 1074-95-9; 1196-31-2; 89-80-5	Menthone	Tab 68	Approved with changes
109-94-4	Ethyl formate	Tab 69	Approved
7779-81-9; 61692-84-0	Isobutyl angelate	Tab 70	Approved with changes
41519-18-0	Isopentyl 2-methylcrotonate (E)	Tab 71	Approved with changes
53082-58-9	3-Methylpentyl 2-methylisocrotonate	Tab 72	Approved with changes
67633-94-7	Phenylacetaldehyde 2,4-dihydroxy-2-methylpentane acetal	Tab 73	Approved with changes

#### 15) RIFM Research Projects

##### a) Presentation on research programs

Dr. Api gave a presentation on the progress of the various research projects (see Attachment 8).

##### b) Epidemiology

Prof. Bruze reported that there are no updates from the EDEN Epidemiology study because they have been unable to meet.

##### i) Eugenol Threshold Study

Prof. Bruze and Dr. Robert Ofenloch (Research Associate, post-doctoral fellow at University Hospital Heidelberg) recently addressed the comments on the manuscript on the eugenol study. Dr. Belsito expressed an interest to review the final edited version again. Dr. Api will then circulate to the RIFM Advisory Committee and will share any final comments with Prof. Bruze and Dr. Ofenloch.

##### c) Read-across2 and NCS Cluster manuscripts

Drs. Liebler, Penning, and Schultz met with Dr. Moustakas on the final edits for the read-across2 manuscript. Another final draft is anticipated in June 2021.

Dr. Moustakas will draft the first version of the NCS cluster paper. This manuscript is still being targeted for completion in 2022.

##### d) Skin Sensitization Research Projects

##### i) Presentation by I. Lee and H. Moustakas on epoxide research update May 12

Drs. Lee and Moustakas provided an update on the epoxide research program, the progress made and the plans for the project (see Attachment 9).

##### e) Presentation by G.-Emilia Costin, Ph.D., M.B.A., ATS, ERT: in vitro depigmentation assay May 12 at 1:30 PM

Dr. Costin (Institute for In Vitro Sciences) gave a presentation on in vitro pre-clinical efficacy testing strategies of compounds with the potential to modulate skin tone (see Attachment 10).

**f) Presentation from SenzaGen on PhotoGard Assay May 12**

Dr. Henrik Johansson (Chief Scientist, SenzaGen AB) gave a presentation on the PhotoGARD assay (see Attachment 11).

**g) Presentation by N. Sadekar on respiratory research projects on May 13**

Dr. Sadekar provided an update on the respiratory research projects (see Attachment 12).

**i) Presentation by Prof. A. Gutleb May 13, 9:00 AM (Tab 74)**

Dr. Arno Gutleb, Luxemburg Institute of Science and Technology (LIST) gave a virtual presentation on a 3D alveolar in vitro model for the prediction of chemical respiratory sensitizers and irritants (see Attachment 13).

**16) Furocoumarin proposal**

At the January 2022 meeting of the Expert Panel for Fragrance Safety, a proposal for a draft policy for IFRA Standards on citrus oils and other natural complex substances (NCS) containing furocoumarins was reviewed. A modified draft was reviewed by the Panel, and they agreed with the changes made.

**17) Naphtho[2,1-b]furan, dodecahydro-3a,6,6,9a-tetramethyl-, (3aR,5aS,9aS,9bR)- CAS No: 6790-58-5**

The Panel reviewed the skin sensitization data on Naphtho[2,1-b]furan, dodecahydro-3a,6,6,9a-tetramethyl-, (3aR,5aS,9aS,9bR)-, CAS No: 6790-58-5. While autoxidation was predicted, it is a very conservative tool and the Panel advised that autoxidation is unlikely to occur. Based on the data available, they suggested that a CNIH can be conducted at 6000 µg/cm<sup>2</sup>.

**18) Eucalyptol CAS No. 470-82-6**

The Panel reviewed the skin sensitization data on Eucalyptol, CAS No: 470-82-6. Based on the data available, they suggested that a CNIH can be conducted at 7000 µg/cm<sup>2</sup>.

**19) New Expert Panel Members**

The Panel discussed potential new Panel members.

**20) Panel Executive Session**

The Panel had a closed executive session.

**21) Future Meeting Dates**

- Monday – Wednesday, Sept. 19-21, 2022 Portugal
- Wednesday - Friday, Jan. 18-20, 2023 Puerto Rico/Florida
- Monday - Wednesday, May 15-17, 2023 Tokyo
  - May 10-13, 2023 ISID (International Societies for Investigative Dermatology), Tokyo, Japan
  - **RIFM Satellite Symposia May 10, 2023 – 9 AM-12 PM, Keio Plaza Hotel, Tokyo**
- Monday – Wednesday, September 25-27, 2023 New Jersey
- Monday-Wednesday, Jan. 22-24, 2024 Florida

• Monday-Wednesday,

May 20-22, 2024

Edinburgh

Respectfully submitted,



Anne Marie Api, Ph.D., ATS  
Vice President

Attachment 1:	Presentation: Mr. Gary Sullivan
Attachment 2:	Presentation: Dr. Anne Marie Api
Attachment 3:	Presentation: Mr. Tobey Marzouk
Attachment 4:	Presentation: Dr. Danielle Botelho
Attachment 5:	Presentation: Drs. Dan Selechnik and Kaushal Joshi
Attachment 6:	Presentation: Prof. Magnus Bruze
Attachment 7:	Presentation: Ms. Aurelia Lapczynski
Attachment 8:	Presentation: Dr. Anne Marie Api
Attachment 9:	Presentation: Drs. Isabelle Lee and Holger Moustakas
Attachment 10:	Presentation: Dr. G. Emilia Costin, IIVS
Attachment 11:	Presentation: Dr. Henrik Johansson, SenzaGen
Attachment 12:	Presentation: Dr. Nikaeta Sadekar
Attachment 13:	Presentation: Dr. Arno Gutleb, LIST