

EXPERT PANEL FOR FRAGRANCE SAFETY MEETING

Minutes

January 18-20, 2023

La Jolla, California

EXPERT PANEL MEMBERS	RIFM STAFF		Guests
Donald Belsito (Chair) Magnus Bruze Amanda Bryant-Friedrich G. Allen Burton, Jr. Maria Dagli (Vice-Chair) Wolfgang Dekant Allison Fryer Trevor Penning Terry Schultz I Glenn Sipes Yoshiki Tokura	Anne Marie Api Danielle Botelho Olive Chon (Virtual) Chaitra Deodhar Leah Jones Kaushal Joshi Aurelia Lapczynski (Virtual) Maura Lavelle (Virtual) Isabelle Lee (Virtual) Holger Moustakas (Virtual)	Jake Muldoon (Virtual) Gretchen Ritacco (Virtual) Nikaeta Sadekar (Virtual) Isabella Schember (Virtual) Dan Selechnik Faiz Siddiqi (Virtual) Gary Sullivan (Virtual) Yax Thakkar (Virtual)	Ellen Fritsche Sylvain Antoniotti (1/19) Tobey Marzouk (1/18) Paul Thomas (1/19) Jesse Salk (1/20) T Zanoni (1/20) A Aron (1/20) G Papoutsoglou (1/20)

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. Belsito welcomed Dr. Ellen Fritsche to the meeting.

2) Minutes

The minutes from the September 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. Api 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).

c) **Presentation by D. Botelho – Update on RIFM’s 1st Science Symposium**

Dr. Botelho provided a review on the first RIFM Science Symposium held in November 2022 (see Attachment 2).

6) Presentation by T. Marzouk

a) Website: Comments/questions/suggestions

The Panel had no comments or questions regarding the Panel’s website. Panel members are pleased with the content and maintenance of the website.

b) Expert Panel Adjunct Groups

The Expert Panel Adjunct Groups are advisors to the Panel. There are 5 adjunct groups (respiratory, reproduction, genotoxicity, environmental and immunotoxicology). The immunotoxicology adjunct group is not presently active. The adjunct groups are typically comprised of 3-6 members, who are not employees or representatives of fragrance companies, but are instead, consultants, academicians and experts in designated subject areas. The Expert Panel decided that Adjunct Group Members should be on the Expert Panel website with a short bio on each member.

The Panel requested that Mr. Marzouk develop a formal policy/guidelines regarding the Adjunct Groups for approval by the Panel with the expectation that the policy/guidelines will be available on the Panel’s website.

c) RIFM’s relationship with Elsevier

i) Use of CAS Numbers on Elsevier’s Fragrance Material Safety Assessment Center

Mr. Marzouk reported that RIFM was contacted by the American Chemical Society (ACS) CAS group because they were concerned that CAS numbers are being used to search for a RIFM Safety Assessment on the Fragrance Material Safety Assessment Center maintained by Elsevier. Mr. Marzouk responded to their initial inquiry and made clear that such use of CAS numbers was appropriate and in compliance with copyright laws. There has been no response or objection from ACS.

ii) Recent Developments

It was reported that there is a new Editor-In-Chief at Food and Chemical Toxicology - Bryan Delaney, PhD, DABT, Fellow, ATS. The RIFM Safety Assessments Managing Editor remains the same - Saura Sahu, Center for Food Safety and Applied Nutrition, USA.

d) Expert Panel Self-Assessment Survey 2023

Mr. Marzouk re-introduced conducting a self-assessment survey which had been stalled because of the pandemic. The benefit of conducting this type of survey is to review or “self assess” the Panel’s actions and to identify areas that may need to be improved.

Drs. Sipes and Api will assist Mr. Marzouk in developing questions and areas of inquiry to be included in the self-assessment. The self-assessment survey will be conducted online via Survey Monkey and will be comprised of approximately 50 questions that should take Panel Members approximately 20 minutes to complete. The plan is to have Panel Members complete the survey by June 2023 with a presentation of the results at the September Expert Panel meeting. At the January 2024 Expert Panel meeting, the Panel will identify next steps and propose further action based on the self-assessment.

- e) Questions Regarding Conflicts of Interest and other Expert Panel Policies

The Panel had no additional questions on the conflicts of interest or other concerns.

7) 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 3).

b) Safety Assessment Overview

- i) (29 Total Safety Assessments including 31 Total materials)

c) General Comments

- i) Environmental Read-Across

Ms. Lapczynski introduced a document prepared by Dr. Schultz which was shared in the Panel's agenda package. The document outlined how read-across is approached for the environmental endpoint.

- ii) Other environmental topics

Ms. Lapczynski introduced the new classification/labeling in Europe called PMT– Persistence, Mobile, Toxic. This could potentially be added to the RIFM Safety Assessment environmental section. RIFM will be evaluating how fragrance materials will be impacted by the new criteria.

- iii) Skin absorption references

The Panel recommended that when skin absorption studies are used in Maximum Acceptable Concentrations (MAC), the data should be added to the safety assessment. When calculating the Margin of Exposure (MOE), it should be conducted both with and without the use of the skin absorption data.

The Panel will also evaluate the use of read-across for skin absorption data.

8) Presentation by Dr. Ellen Fritsche, Group of Sphere Models and Risk Assessment, IUF - Leibniz Research Institute of Environmental Medicine - NAMs for Acute and Developmental Neurotoxicity Evaluation in Light of European Union Projects

Dr. Fritsche gave a presentation on numerous research projects that she has contributed to (see Attachment 4).

9) Presentation by Dr. Terry Schultz: Metabolism-based read-across: Where we are and where we are going?

Dr. Schultz gave a presentation on metabolism based read-across (see Attachment 5).

10) Presentation by Prof. Bruze

a) Basics on skin hazardous factors and contact dermatitis

Prof. Bruze gave a presentation on the basics on skin hazardous factors and contact dermatitis (see Attachment 6).

11) Review Carvone

Drs. Joshi and Selechnik gave a presentation on the reproduction data on L-Carvone (see Attachment 7). The Panel suggested that the report on the OECD 414 Developmental Toxicity study be reviewed to learn if there were any maternal effects. It should be brought back to the Reproduction Adjunct Group and then the Expert Panel for final review.

12) Presentation by Sylvain Antoniotti on January 19

Dr. Antoniotti gave a presentation introducing the Cote D'Azur University program and the analytical work his group is doing (see Attachment 8).

13) Review Safety Assessments Batch 1

CAS #	Material Name	Tab	Status
94-30-4	Ethyl p-anisate	Tab 19	Approved
7335-26-4	Ethyl 2-methoxybenzoate	Tab 20	Approved
4707-47-5	Methyl atrarate	Tab 21	Approved with changes
33662-58-7	Methyl 2,4-dihydroxy-m-toluate	Tab 22	Approved
27593-23-3	5-Hydroxy-2,4-decadienoic acid delta-lactone	Tab 23	Approved
698-10-2	5-Ethyl-3-hydroxy-4-methyl-2(5H)-furanone	Tab 24	Approved
292605-05-1	3-Hexene, 1-[(2-methyl-2-propenyl)oxy]-(3Z)-	Tab 25	Approved
94-48-4	Geranyl benzoate	Tab 26	Approved with changes
100520-15-8	1,3-Cyclohexadiene-1-carboxylic acid, 4,6,6-trimethyl-, ethyl ester	Tab 27	Approved
69-72-7	2-Hydroxybenzoic acid	Tab 28	Approved with changes
555-10-2	beta-Phellandrene	Tab 29	Approved
10444-50-5	Citral propylene glycol acetal	Tab 30	Approved
499-75-2	Carvacrol	Tab 31	Approved
950919-28-5	2H-1,5-Benzodioxepin-3(4H)-one, 7-(1-methylethyl)-	Tab 32	Approved
103-26-4	Methyl cinnamate	Tab 33	Insufficient Data (UV Spectrum)
103-36-6	Ethyl cinnamate	Tab 34	Insufficient Data (UV Spectrum)
18309-32-5; 80-57-9; 1196-01-6	dextro-Verbenone	Tab 35	Approved
1866-31-5	Allyl cinnamate	Tab 36	Approved

14) Review Safety Assessments Batch 2

CAS#	Material Name	Tab	Status
498-02-2	4'-Hydroxy-3'-methoxyacetophenone	Tab 37	Approved
6939-35-1	3,4-Dihydro-5-methylnaphthalen-1(2H)-one	Tab 38	Approved

CAS#	Material Name	Tab	Status
54440-17-4	2,3,3-Trimethylindanone	Tab 39	Approved
98-01-1	Furfural	Tab 40	Approved with changes
620-02-0	5-Methylfurfural	Tab 41	Approved with changes
68555-63-5	2-Methyl-3-(1-oxopropoxy)-4H-pyran-4-one	Tab 42	Approved with changes
78417-28-4	Ethyl 2,4,7-decatrienoate	Tab 43	Approved
5205-11-8	3-Methyl-2-butenyl benzoate	Tab 44	Approved with changes
102-22-7	Geranyl phenylacetate	Tab 45	Insufficient Data Skin Sensitization
42436-07-7	3-Hexenyl phenylacetate	Tab 46	Insufficient Data Skin Sensitization
3608-11-5	Acetylcarene	Tab 47	Approved

15) Review Safety Assessments Maintenance Batch

CAS#	Material Name	Tab	Status
13074-65-2	2-Hexylcyclopentanone	Tab 49	Approved with changes
65443-14-3	2,2,5-Trimethyl-5-pentylcyclopentanone	Tab 50	Approved with changes
72881-27-7	5- and 6-Decenoic acid	Tab 51	Approved
29350-67-2	4-Isopropyl-1-methylcyclohexene	Tab 52	Approved with changes
23726-92-3; 23726-91-2; 35044-68-9	(Z)-beta-1-(2,6,6-Trimethyl-1-cyclohexen-1-yl)-2-buten-1-one	Tab 53	Approved with changes
39872-57-6; 70266-48-7; 33673-71-1	(E)-1-(2,4,4-Trimethyl-2-cyclohexen-1-yl)-2-buten-1-one	Tab 54	Approved with changes
43052-87-5; 24720-09-0; 23726-94-5	alpha-1-(2,6,6-Trimethyl-2-cyclohexen-1-yl)-2-buten-1-one	Tab 55	Insufficient Data Genotoxicity
16409-43-1; 4610-11-1; 3033-23-6	Tetrahydro-4-methyl-2-(2-methylpropen-1-yl)pyran	No Tab	Approved with changes

16) RIFM Research Projects

a) Epidemiology

Dr. Bruze reported that there has been no activity by the EDEN group.

b) Threshold study on eugenol

Dr. Bruze reported that the manuscript on the threshold study on eugenol was submitted to Contact Dermatitis and reviewer comments were received. The comments were addressed and the manuscript was re-submitted.

Dr. Bruze also reported on work he is doing under the IDEA project.

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

Dr. Moustakas gave a presentation to update the Panel on the research projects being conducted (see Attachment 9).

i) Status read-across2 paper

Dr. Moustakas reported that the read-across2 paper was published at the end of 2022. The Panel congratulated all the authors.

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.

d) Skin Sensitization Research Projects

i) **Presentation by I. Lee on the reproducibility of GARDSkin dose response study**

Dr. Lee provided an update on the reproducibility of GARDSkin dose response study (see Attachment 10).

ii) **Presentation by M. Lavelle on the CNIH data – comparison of 2 protocols -Jan**

Ms. Lavelle gave a presentation on the CNIH project which compared two different protocols (see Attachment 11). This work is being written for publication.

e) **Environmental Research Projects**

i) **Presentation by Dr. Paul Thomas, KREATIS – update on CHANCES2 Project**

Dr. Thomas provided an update on the RIFM sponsored CHANCES2 Project (see Attachment 12).

f) **Genotoxicity Research Projects**

i) **Presentation by ICEM- Ottawa on 3D skin mutagenesis assay**

Representatives from TwinStrand Biosciences (Jesse Salk, T Zanoni, A Aron, G Papoutsoglou) gave a presentation on their work on the 3D skin mutagenesis assay (see Attachment 13). The Panel agreed that the pilot study should proceed.

g) **Repeat Dose**

i) **Presentation by Dr. Selechnik presentation on IONTOX model**

Dr. Selechnik provided an update on the IONTOX model (see Attachment 14). He reported that there are more data being collected. The Panel had some valuable questions and requested additional information. It was suggested that Dr. McKim be invited to a future Panel meeting.

h) **Reproduction**

i) **Presentation by Drs. Joshi on reproduction summary data**

Dr. Joshi gave a presentation on the reproduction summary project at RIFM (see Attachment 15).

i) **Presentation by N. Sadekar on respiratory irritation project proposal**

Dr. Sadekar presented a proposal for the next phase of the respiratory irritation project (see Attachment 16). The Panel agreed the research should proceed with consideration on the cost/benefit of conducting ciliary beat frequency analyses.

17) NCS Safety Assessments

a) **General Comments**

i) **NCS updates**

Ms. Jones provided an update on the NCS safety assessments that were reviewed by the Expert Panel but required additional testing. The information was also provided in the Panel package. After testing is completed and reviewed by the Panel, the NCS safety assessments will be submitted for publication.

ii) **Environmental comment on NCS with low percentage waxes**

Ms. Lapczynski presented phrasing for NCS with low percentage of waxes. The Panel agreed with the proposed wording.

18) New Expert Panel Members

The Panel discussed potential new Panel members.

19) Panel Executive Session

The Panel held an Executive Session.

20) Future Meeting Dates

- 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 San Diego, CA
- Monday-Wednesday, May 20-22, 2024 Edinburgh
- Monday-Wednesday, September 23-25, 2024 New Jersey
- Monday-Wednesday, January 27-29, 2025 San Diego, CA

Respectfully submitted,



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

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| Attachment 1: | Presentation: Mr. Gary Sullivan |
| Attachment 2: | Presentation: Dr. Danielle Botelho |
| Attachment 3: | Presentation: Dr. Danielle Botelho |
| Attachment 4: | Presentation: Dr. Ellen Fritsche |
| Attachment 5: | Presentation: Dr. Terry Schultz |
| Attachment 6: | Presentation: Dr. Magnus Bruze |
| Attachment 7: | Presentation: Drs. Kaushal Joshi and Dan Selechnik |
| Attachment 8: | Presentation: Dr. Sylvain Antoniotti |
| Attachment 9: | Presentation: Dr. Holger Moustakas |
| Attachment 10: | Presentation: Dr. Isabelle Lee |
| Attachment 11: | Presentation: Ms. Maura Lavelle |
| Attachment 12: | Presentation: Dr. Paul Thomas |
| Attachment 13: | Presentation: Mr. Yax Thakkar and TwinStrand |
| Attachment 14: | Presentation: Dr. Dan Selechnik |
| Attachment 15: | Presentation: Dr. Kaushal Joshi |
| Attachment 16: | Presentation: Dr. Nikaeta Sadekar |