EXPERT PANEL FOR FRAGRANCE SAFETY MEETING

Minutes

May 20-22, 2024

Edinburgh

EXPERT PANEL MEMBERS	RIFM STAFF		Guests
Donald Belsito (Chair) Magnus Bruze Amanda Bryant-Friedrich (virtual) G. Allen Burton, Jr. Maria Dagli (Vice-Chair) Wolfgang Dekant Allison Fryer Debra Laskin Trevor Penning I Glenn Sipes	Anne Marie Api Adrianna Bartlett (Virtual) Danielle Botelho Olive Chon (Virtual) Sam Crotty (Virtual) Chaitra Deodhar (Virtual) Leah Jones Kaushal Joshi (Virtual Aurelia Lapczynski Maura Lavelle (Virtual) Isabelle Lee (Virtual)	Holger Moustakas (Virtual) Jake Muldoon (Virtual) Gretchen Ritacco Nikaeta Sadekar (Virtual) Isabella Schember (Virtual) Faiz Siddiqi (Virtual) Gary Sullivan (Virtual) Yax Thakkar (Virtual)	Sylvain Antoniottti (May 21) Mark Cronin Elena Gimenez (May 21) Sally Ibbotson (May 22) Philippe Meyer (May21) Aldert Piersma Kristin Schirmir (May 21, 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.

2) Minutes

The minutes from the January 2024 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 (see Attachment 1).

b) Communications Update

Mr. Sullivan and Siddiqi and Ms. Chon provided an update on the RIFM communication plans, safety assessment publications, and the Fragrance Resource Center website (see Attachment 2).

6) RIFM Safety Evaluation Process

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

Dr. Botelho gave a presentation on the progress of the safety assessment program including the safety assessment update and metrics on naturals (see Attachment 3)

b) Safety Assessment Overview

i) (13 Total Safety Assessments including 13 Total materials)

c) General Comments

i) Low exposure materials that may require additional data (e.g., 104037-85-6; 127459-79-4)

The Panel reviewed several materials with low exposure that may require additional data. It was recommended that prior to testing, the exposure should be verified. Dr. Api pointed out that that some of the materials may be functional ingredients and this should be confirmed before any testing is conducted.

ii) NCS components that reach 95% composition with the same Cramer Classification

The Panel agreed that if a NCS components are in the same Cramer Classification and a minimum of 95% of components are known, then the Cramer Classification of the NCS is the same as those of the components. If the components are less than 95% known, then the Cramer Class should be the most conservative classification (Cramer Class 3).

iii) Materials without a chromophore

Dr. Bryant-Friedrich talked to the Panel about chromophores in chemicals and predicting whether the material can absorb.

iv) ROS Assay results language final reports (database and safety assessments)

The Expert Panel approved the language that will be used in the safety assessments when the ROS Assay data are available for a fragrance ingredient.

Positive ROS assay result:

The available data suggests that the ROS assay is highly sensitive to predicting direct in vivo phototoxicants (photoirritants and photoallergens). However, it shows low specificity, resulting in a high percentage of outcomes incorrectly classified as positive (false positives). This result does not conclusively determine photoirritation or photoallergy. Positive, weakly positive, and inconclusive results in ROS assay conducted under appropriate conditions would require proceeding to the next level of photosafety testing in an in vitro test system*.

*Japanese photosafety guidance for Quasi-Drugs and Cosmetic Products (2022)

Negative ROS assay result:

The available data suggests that the ROS assay is highly sensitive to predicting direct in vivo phototoxicants (photoirritants and photoallergens). However, it shows low specificity, resulting in a high percentage of outcomes incorrectly classified as positive (false positives). As such, a negative ROS assay is a true negative, and therefore, this material is not a concern for photoirritation and photoallergy. Therefore, it would not require further photosafety testing*.

*Japanese photosafety guidance for Quasi-Drugs and Cosmetic Products (2022)

7) Presentation Dr. Mark Cronin

Dr. Cronin gave a presentation on machine learning and how it will fit into a safety assessment process (see Attachment 4).

8) Reproduction Toxicity

a) Presentation by Dr. Aldert Piersma

Dr. Piersma gave a presentation on the next generation of reproductive toxicology (see Attachment 5).

b) Presentation by K. Joshi, A. Bartlett, F. Siddiqi

Drs. Joshi and Bartlett and Mr. Siddiqi gave a presentation updating the Panel on the RIFM summary of all reproductive/fertility data (see Attachment 6).

9) alpha-Damascone (alpha-1-(2,6,6-Trimethyl-2-cyclohexen-1-yl)-2-buten-1-one; CAS 43052-87-5; RIFM ID: 1298)

Mr. Yax Thakkar gave a presentation summarizing the genotoxicity data on alpha-Damascone (alpha-1-(2,6,6-Trimethyl-2-cyclohexen-1-yl)-2-buten-1-one (see Attachment 7). The Panel recommended additional studies on alpha-damascone and metabolism studies on both alpha- and delta-damascone.

10) NCS Safety Assessments

i) Total NCS Safety Assessments: 10

Material ID	RIFM ID	Material Name	Tab	Status
1046798	310-E2.1	Clary sage absolute	**Tab 21**	Insufficient data; Environmental testing on 2 components
1046841	310-E2.12	Clary sage oil	**Tab 22**	Insufficient data; Environmental testing on 3 components
1046832	311-E2.12	Sage Dalmatian oil	**Tab 23**	Insufficient data; Environmental testing on 3 components
1042440	479-E2.12	Sage oil, Spanish	**Tab 24**	Approved
1046842	696-E2.12	Savory summer oil	**Tab 25**	Insufficient data; Skin Sensitization for carvacrol component
1044251	1181-E2.12	Savory winter oil	**Tab 26**	Approved
1048330	583-F2.1	Clove bud absolute	**Tab 27**	Approved
1045568	583-F2.12	Clove bud oil	**Tab 28**	Insufficient data; Environmental 1 component
1044593	583-E2.12	Clove leaf oil	**Tab 29**	Insufficient data; Environmental 1 component
1044413	583-L2.12	Clove stem oil	**Tab 30**	Insufficient data; Environmental 1 component

11) Review Safety Assessments Batch 1

CAS#	Material Name	Tab	Status
7549-37-3	Citral dimethyl acetal	**Tab 31**	Insufficient data; Phototoxicity and Skin Sensitization (need RA or testing)
7492-66-2	Citral diethyl acetal	**Tab 32**	Insufficient data; Phototoxicity
122-69-0	Cinnamyl cinnamate	**Tab 33**	Approved
104-20-1	4-(p-Methoxyphenyl)-2-butanone	**Tab 34**	Approved
122-84-9	1-(p-Methoxyphenyl)-2-propanone	**Tab 35**	Approved

12) Review Safety Assessments Batch 2

CAS#	Material Name	Tab	Status
1129-47-1	Propanoic acid, 2-methyl-, cyclohexyl ester	**Tab 36**	Approved
3289-28-9	Ethyl cyclohexanecarboxylate	**Tab 37**	Approved
54889-63-3	1,4-Bis(ethoxymethyl)cyclohexane	**Tab 38**	Approved
1247790-47-1	3,6-dimethylheptan-2-ol;711;2-heptanol, 3, 6-dimethyl-	**Tab 39**	Approved
41890-92-0	3,7-Dimethyl-7-methoxyoctan-2-ol	**Tab 40**	Approved
18374-76-0	Rotundone	**Tab 41**	Approved
2601-13-0	2-Methylbutyl hexanoate	**Tab 42**	Approved
55066-54-1	Bicyclo[2.2.1]heptan-2-ol, 1,3,3-trimethyl-, benzoate	**Tab 43**	Approved

13) Review Safety Assessments Maintenance Batch

CAS#	Material Name	Tab	Status
1335-09-7	Methylheptenol	**Tab 45**	Approved
2270-60-2	Methyl 3,7-dimethyl-6-octenoate	**Tab 46**	Approved
41199-19-3; 643-53-8; 670-24-6; 71832-76-3	1,2,3,4,4a,5,6,7-Octahydro-2,5,5-trimethyl-2-naphthalenol	**Tab 47**	Approved with changes
42288-75-5	Cyclohexyl phenylacetate	**Tab 48**	Approved
87118-95-4; 81787-06-6; 862107-86-6	3,4,5,6,6-Pentamethylheptan-2-ol	**Tab 49**	Approved

14) Presentation Dr. Sylvain Antoniotti, Director, Institute for Innovation and Partnerships Flavour Fragrance Cosmetics, Université Cote d'Azur – Tuesday, May 21 10:00

Dr. Antoniotti provided an update on the NCS constituent analyses he and his colleagues are conducting for RIFM (see Attachment 8).

15) Presentation Dr. Sally H. Ibbotson, Professor (Clinical) School of Medicine, University of Dundee "Topical photoallergy in the current clinical setting" – Wednesday, May 22 9:00

Dr. Ibbotson gave a presentation on photoallergy in the current clinical setting (see Attachment 9).

16) RIFM Research Projects

a) Overview of research programs

Dr. Api proposed to have an orientation for new Panel members to the RIFM safety assessment process as well as the RIFM Research Program. In addition, it was proposed that all RIFM research programs be reviewed at the September meeting and therefore limit external speakers and focus on the RIFM staff. The Panel agreed to both proposals.

b) Epidemiology

Prof Bruze reported that EDEN is planning to submit another paper on psoriasis. As part of IDEA an extended surveillance study is planned.

c) Chemistry

i) Chemical Signature paper

Dr. Muldoon discussed the plans for the publication of the chemical signature manuscript.

d) Environmental Research Program Update

i) **Presentation by Dr. Philippe Meyer Presentation**

Dr. Meyer provided an update on the RIFM funded research project on the environmental persistence research project on NCS and their constituent analyses (see Attachment 10).

ii) **Presentation by Dr. Kristin Schirmir (Eawag, Zurich)**

Dr. Schirmir presented a potential research project that will use fish cell lines as a substitute for fish testing (see Attachment 11).

iii) **Presentation by Aurelia Lapczynski – Environmental Research Update**

Ms. Laczynski gave an update on the environmental research program (see Attachment 12).

e) Skin Sensitization Research Projects

i) **Presentation by Isabelle Lee/Holger Moustakas on epoxide research update – Wednesday May 22 3:30**

Drs. Lee and Moustakas gave an update on skin sensitization chemistry research (see Attachment 13).

f) Phototoxicity and Photoallergy

i) **Presentation by Dr. Elena Gimenez**

Dr. Elena Gimenez presented a potential research project on the development of an innovative EPR-ST/SC methodology in sun-exposed RHE models, to provide information on the mechanisms responsible for photosensitivity to fragrance allergens in sun exposed individuals, by determining if they are correlated to a common radical species or to specific radicals formed in the skin (see Attachment 14).

g) Genotoxicity

i) Presentation Target Tissue Exposure Model for Genotoxicity by Yax Thakkar

Mr. Yax Thakkar gave a presentation on a potential target tissue exposure model for genotoxicity (see Attachment 15). The Panel supported the work being done and encouraged the work on positive controls to be completed and once done, a publication is envisioned for publication. The SAM Model is being updated to a new computer platform. The Panel encouraged RIFM to review the SAM Model since new skin absorption data are available.

17) New Expert Panel Members

Dr. Terry Schultz has announced his intention to retire from the Panel at the end of 2024. Dr. Glenn Sipes announced that he plans to retire from the Panel in 2025. Drs. Cronin and Piersma were invited to join the Panel and they both accepted.

18) Panel Executive Session

The Expert Panel held an Executive Session.

19) Future Meeting Dates

a)	Wednesday-Friday,	September 25-27, 2024,	NYC, New Jersey
b)	Monday-Wednesday,	January 27-29, 2025	Puerto Rico
c)	Tuesday-Thursday,	June 3-5, 2025	NYC
d)	Monday-Wednesday,	September 29-October 1, 2025	Cannes/Grasse France
e)	Monday-Wednesday,	January 26-28, 2026	TBD
f)	Monday-Wednesday,	May 18-20, 2026	NYC

Respectfully submitted,

Anne Marie Api, Ph.D., ATS
President

Attachment 1:	Presentation: Dr. Anne Marie Api
Attachment 2:	Presentation: Mr. Gary Sullivan, Mr. Faiz Siddiq, Ms. Oliv Chon
Attachment 3:	Presentation: Dr. Danielle Botelho
Attachment 4:	Presentation: Dr. Mark Cronin
Attachment 5:	Presentation: Dr. Aldert Piersma
Attachment 6:	Presentation: Drs. Kaushal Joshi and Arianna Bartlett and Mr. Faiz Siddiqi
Attachment 7:	Presentation: Mr. Yax Thakkar
Attachment 8:	Presentation: Dr. Sylvain Antoniotti
Attachment 9:	Presentation: Dr. Sally H. Ibbotson
Attachment 10:	Presentation: Dr. Philippe Meyer
Attachment 11:	Presentation: Dr. Kristin Schirmir
Attachment 12:	Presentation: Ms. Aurelia Lapczynski
Attachment 13:	Presentation: Drs. Isabelle Lee and Holger Moustakas
Attachment 14:	Presentation: Dr. Elena Gimenez
Attachment 15:	Presentation: Mr. Yax Thakkar