

EXPERT PANEL FOR FRAGRANCE SAFETY MEETING

Minutes Virtual Meeting

May 17-20, 2021

EXPERT PANEL MEMBERS	RIFM STAFF		Guests
Donald Belsito (Chair) Magnus Bruze G. Allen Burton, Jr. Jochen Buschmann Maria Dagli (Vice-Chair) Wolfgang Dekant Allison Fryer Dan Liebler Trevor Penning Terry Schultz I Glenn Sipes Yoshiki Tokura	Anne Marie Api Danielle Botelho Mihir Date Chaitra Deodhar Leah Jones Kaushal Joshi Manoj Kumar Maura Lavelle Aurelia Lapczynski Isabelle Lee	Holger Moustakas Mihwa Na Gretchen Ritacco Jim Romine Christen Sachse- Vasquez (5/17) Dan Selechnik Gary Sullivan (5/17) Yax Thakkar	Paul DeLeo (5/19) Philipp Mayer (5/19) Karina Knudsmark Sjøholm (5/19) Heidi Birch (5/19) Anna Chérouvrier Hansson (5/20) Andy Forreryd (5/20)

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 electronically. Dr. Api welcomed Dr. Botelho back from maternity leave.

2) Minutes

The minutes from the January 2021 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 recent publications.

- b) RIFM Safety Assessment Publications

At the last meeting, it was agreed to separate safety assessment publications into a separate list. This list will be an on-going list of all the published safety assessments.

5) RIFM Communication

- a) Update on RIFM

Dr. Romine provided an overview of RIFM. The staff continues to work from home and all travel has been suspended.

- b) RIFM Communication update

Mr. Gary Sullivan provided an update on the RIFM Communication Plan (see Attachment 1).

- c) FCT Fragrance Material Safety Assessment Center

Dr. Api provided a review of the 2020 metrics for the FCT Fragrance Material Safety Assessment Resource Center (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 Safety Assessment program and progress (see Attachment 3).

- b) Safety Assessment Overview

The Panel reviewed 17 Total Safety Assessments including 19 Total materials.

- c) General Comments

- i) A statement was added to the beginning of the safety assessment to indicate that the safety assessments are reviewed every 5 years and that open access is available on the Resource Center. They are:

- (1) Version: MMDDYY. Initial publication. All fragrance materials are evaluated on a five-year rotating basis. Revised safety assessments are published if new relevant data become available. Open access to all RIFM Fragrance Ingredient Safety Assessments is here: fragrancematerialsafetyresource.elsevier.com.

- (2) Version: MMDDYY. This safety assessment is an updated version and replaces any previous versions. All fragrance materials are evaluated on a five-year rotating basis. Revised safety assessments are published if new relevant data become available. Open access to all RIFM Fragrance Ingredient Safety Assessments is here: fragrancematerialsafetyresource.elsevier.com.

7) NCS Safety Assessments

- a) NCS Safety Assessment publication

Dr. Api introduced the modifications made to the NCS safety assessment criteria document. The Panel reviewed the general approach for NCS safety assessments and edited the draft NCS Safety assessment publication. They requested that current modifications be incorporated into the next draft.

- b) Update on NCS Template

Ms. Sachse-Vasquez provided the Panel with an update and a preview of the computer-generated NCS template.

- e) Safety Assessment Review

A total of 22 draft NCS Safety Assessments were reviewed by the Panel (see the list below).

RIFM Material ID	Material Name	Tab
1042479	Petitgrain oil terpeneless, Paraguay	Tab 16
1046350	Petitgrain oil, Paraguay	Tab 17
1042877	Petitgrain lemon oil	Tab 18
1043850	Lemon oil terpenes	Tab 19
1044812	Lemon oil folded (5X)	Tab 20
1044824	Lemon oil, terpeneless	Tab 21
1046095	Petitgrain mandarin oil	Tab 22
1047027	Petitgrain bigarade oil	Tab 23
1047076	Lemon oil, distilled	Tab 24
1047462	Lemon oil, furocoumarin free	Tab 25
1047875	Lemon oil, washed	Tab 26
1048447	Lemon Oil	Tab 27
1048479	Petitgrain oil, rectified, Paraguay	Tab 28
1044371	Lime oil, cold-pressed, furocoumarin free	Tab 29
1044008	Lime oil, expressed	Tab 30
1047546	Lime oil distilled	Tab 31
1043741	Lime oil terpenes	Tab 32
1045266	Lime oil folded (2-5X)	Tab 33
1045071	Lemon oil, expressed	Tab 34
1048425	Lime oil, expressed, rectified	Tab 35
1048448	Lemon oil folded (10x)	Tab 36
1047461	Lime oil, terpeneless	Tab 37

8) Follow-up on actions for Safety Assessment

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

The Panel approved the safety assessment on eugenyl methyl ether. The editing team will review it and Dr. Sipes will review it one last time before it is submitted for publication.

c) Estragole CAS No. 140-67-0

The Panel approved the safety assessment on estragole. The editing team will review it and ensure it is comparable to the one on Eugenyl methyl ether CAS No. 93-15-2. Dr. Sipes will review it one last time before it is submitted for publication.

9) Rose Ketones

Dr. Api introduced the background on the materials known as the rose ketones (see Attachment 4). Mr. Thakkar provided the background on the genotoxicity data on the materials (see Attachment 5).

CAS	Name	Other name	Tab	Status
23726-92-3; 23726-91-2; 35044-68-9	(Z)-beta-1-(2,6,6-Trimethyl-1-cyclohexen-1-yl)-2-buten-1-one	cis-beta-Damascone	Tab 47	Approved

CAS	Name	Other name	Tab	Status
23696-85-7; 23726-93-4; 59739-63-8	1-(2,6,6-Trimethylcyclohexa-1,3-dienyl)-2-buten-1-one	Damascenone	Tab 48	Approved
57378-68-4; 71048-82-3	delta-1-(2,6,6-Trimethyl-3-cyclohexen-1-yl)-2-buten-1-one	delta-Damascone	Tab 49	Approved
39872-57-6; 70266-48-7; 33673-71-1	(E)-1-(2,4,4-Trimethyl-2-cyclohexen-1-yl)-2-buten-1-one	E alpha-Isodamascone	Tab 50	Approved
43052-87-5; 24720-09-0; 23726-94-5	alpha-1-(2,6,6-Trimethyl-2-cyclohexen-1-yl)-2-buten-1-one	alpha-Damascone	Tab 51	Insufficient data - genotoxicity
35087-49-1	1-(2,2-Dimethyl-6-methylenecyclohexyl)but-2-en-1-one	gamma-Damascone	Tab 52	Approved

10) Paul DeLeo – Environmental Framework2 update on Wednesday (5/19; 8:30)

Dr. DeLeo provided an update on the work encompassing the RIFM Environmental Framework2 document (see Attachment 6). Another call will be scheduled with Drs. Burton, Schultz, Dagli, DeLeo and the environmental adjunct group for a more detailed discussion on the proposal. Dr. Burton suggested that a second publication may be useful to demonstrate the results from the environmental framework2 document with extreme examples.

11) Philipp Mayer, Technical University of Denmark (DTU) – How to determine the persistence of UVCBs – combining degradation testing with constituent specific analysis. Presentation on Wednesday (5/19; 9:30) (Tab 53)

Drs. Philipp Mayer, Karina Knudsmark Sjøholm and Heidi Birch gave a presentation on a research proposal to develop a method to determine the persistence of UVCBs – combining degradation testing with constituent specific analysis (see Attachment 7).

12) Photoirritation IFRA Standards

Dr. Api gave a presentation on the proposed changes to IFRA Standards on materials that are known to be photoirritants. The Panel endorsed the proposal to establish a limit for those rinse-off products that are exposed to the sun (Categories 7A, 8, 9, 10A 10B) (see Attachment 8). In addition, she presented a possible change in the IFRA Standards for dermal sensitizers.

13) Review Safety Assessments Batch 1

CAS #	Material Name	Tab	Status
13481-09-9	Tetrahydro-2-(p-tolyloxy)-2H-pyrane	Tab 54	Approved
57500-00-2	Methyl furfuryl disulfide	Tab 55	Approved
14049-11-7	Linalool oxide pyranoid	Tab 56	Approved
32764-98-0	Tetrahydro-6-(3-pentenyl)-2H-pyran-2-one	Tab 57	Approved
25524-95-2; 34686-71-0	5-Hydroxy-7-decenoic acid delta-lactone	Tab 58	Approved

14) Use of weight of evidence in read across

Dr. Date presented a weight of evidence approach being used in read-across for fragrance materials (see Attachment 9). Drs. Liebler, Penning and Schultz provided additional rationale for this methodology refinement.

15) Review Safety Assessments Batch 2

CAS#	Material Name	Tab	Status
532-32-1	Sodium benzoate	Tab 59	Approved
80118-10-1	1,3-Dimethyl-3-butenyl salicylate	Tab 60	Approved
54088-65-2	5-Heptenenitrile, 2,6-dimethyl-	Tab 61	Approved
10402-33-2	Eugenyl phenylacetate	Tab 62	Approved with changes
3558-60-9	Methyl phenethyl ether	Tab 63	Approved
18492-65-4	4-Heptenal diethyl acetal	Tab 64	Approved
97-45-0	Carvyl propionate	Tab 65	Approved
100-66-3	Anisole	Tab 66	Approved

16) Review Safety Assessments Batch 3

CAS#	Material Name	Tab	Status
123-15-9	2-Methylpentanal	Tab 67	Approved
37064-20-3	Propyl 2-methylbutyrate	Tab 68	Approved
110-54-3	n-Hexane	Tab 69	Approved
2548-87-0; 2363-89-5	trans-2-Octenal	Tab 70	Approved

17) Review Safety Assessments Maintenance Batch (Tab 71)

Ms. Jones introduced a new document that summarizes the status including any modifications made to the safety assessments undergoing a review. RIFM Safety Assessments are dynamic documents, and are reevaluated on a rolling five-year basis to help ensure safe conditions of use. When a Safety Assessment is updated and published, only the most up-to-date version will be available on this resource center. (Previous versions of the safety assessments will always be available on the Food and Chemical Toxicology site or from Science Direct.)

The list below provides the status of some of the materials in the maintenance review process for this meeting. The other materials either do not require an update or any issues have been resolved prior to the meeting.

CAS#	Material Name	Tab	Status
1725-01-5	10-Oxahexadecanolide	Tab 72	Approved with changes
3391-83-1	11-Oxahexadecanolide	Tab 73	Approved with changes
6707-60-4	12-Oxahexadecanolide	Tab 74	Approved with changes
28645-51-4; 63286-42-0	Oxacycloheptadec-10-ene-2-one	Tab 75	Approved with changes
7492-67-3	Citronelloyacetaldehyde	Tab 76	Approved
10032-13-0	Hexyl isovalerate	Tab 77	Approved
10032-15-2	Hexyl 2-methylbutyrate	Tab 78	Approved
109-15-9	Octyl isobutyrate	Tab 79	Approved
2349-07-7	Hexyl isobutyrate	Tab 80	Approved
7786-58-5	Octyl isovalerate	Tab 81	Approved

CAS#	Material Name	Tab	Status
41270-80-8	Methyl 2-(formylamino)benzoate	Tab 82	Insufficient Data - photoallergy
53767-93-4	Dihydromyrcenyl acetate	Tab 83	Approved with changes
87731-18-8; 84681-92-5	Cyclooct-4-en-1-yl methyl carbonate	Tab 84	Approved
586-62-9	Terpinolene	Tab 85	Approved with changes
4927-36-0	5-Methyl-5-phenyl-3-hexanone	Tab 86	Insufficient Data- skin sensitization

18) RIFM Research Projects

a) Overview on research programs

Dr. Api provided an overview of the research programs being conducted at RIFM (see Attachment 10).

b) Epidemiology

Prof. Bruze reported that there are a few more manuscripts in preparation from the EDEN Epidemiology study, however, the EDEN group has been unable to meet.

i) Eugenol Threshold Study

Prof. Bruze reported that he and Dr. Robert Ofenloch (Research Associate, post-doctoral fellow at University Hospital Heidelberg) have drafted a manuscript on the eugenol study. The manuscript has been forwarded to RIFM and co-authors.

c) Read-across2 and NCS Cluster manuscripts

d) Skin Sensitization Research Projects

i) **Presentation by I. Bell on the NESIL manuscript**

Dr. Lee presented the work conducted to describe the process RIFM uses to establish No Effect Sensitization Induction Levels (NESIL) for fragrance materials. The manuscript will be shared with the Panel for review soon. The paper details the procedure currently used and it is recognized this is may change as new alternative methodologies become available (see Attachment 11).

ii) **Presentation by M. Na**

Dr. Na presented on several skin sensitization research projects. She gave an update on the weight of evidence categorization project (see Attachment 12). The manuscript on this project was reviewed by the Panel and will be submitted for peer-reviewed publication shortly. She also provided an update on the SENS-IS project see Attachment 13). A manuscript on this work is in preparation. Finally, a proposal for a new project investigating the data on weak sensitizers in the LLNA assay was detailed. The Panel supported continuing this project (see Attachment 14).

iii) **Presentation by A.M. Api and M. Na on the Implementation of a dermal sensitization threshold (DST) concept for risk assessment: structure-based DST and mixture DST**

Dr. Na reviewed the two publications by Nishijo et al., 2019. This work was previously presented to the Panel in 2019. Dr. Na introduced the collaborative work being done by RIFM with Kao scientists on mixture DST and determining a cell responsive mixture NESIL (see Attachment 15). The Panel expressed interest in this method and believe it can be a great step forward for evaluating NCS. The next step is to test the method with a few different NCS where the components and the skin sensitization potential of the components are known.

iv) **Presentation by GARDSkin on assay and M. Na present preliminary results – 5/20 8:30**

Drs. Anna Chérourvier Hansson and Andy Forreryd, SENZA GEN gave an introduction to the GARDSkin assay and the preliminary results from the pilot assay (see Attachment 16). The research project will be expanded to

include additional fragrance materials. Dr. Na also presented a comparison of the GardSkin assay results with the SENS-IS results for the pilot study materials (see Attachment 17).

e) Presentation by H. Moustakas on genotoxicity tool

Dr. Moustakas gave a presentation of the RIFM genotoxicity tool which is available through the RIFM Database. The Panel commended the work done on this useful tool.

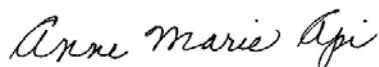
f) Presentation by N. Sadekar on the Respiratory Irritation Project - update

Dr. Sadekar gave an update on the respiratory irritation project (see Attachment 18).

19) Future Meeting Dates

- Monday – Wednesday, Sept. 20-22, 2021 Virtual
- Monday-Wednesday Jan. 24-26, 2022 Virtual
- Monday – Wednesday, May 16-18, 2022 Lisbon
- Monday – Wednesday, Sept. 19-21, 2022 New Jersey
- Wednesday - Friday Jan. 18-20, 2023 Puerto Rico?
- Monday - Wednesday May 15-17, 2023 Europe

Respectfully submitted,



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

- Attachment 1: Presentation: Mr. Gary Sullivan
- Attachment 2: Presentation: Dr. Anne Marie Api
- Attachment 3: Presentation: Dr. Danielle Botelho
- Attachment 4: Presentation: Dr. Anne Marie Api
- Attachment 5: Presentation: Mr. Yax Thakkar
- Attachment 6: Presentation: Dr. Paul DeLeo
- Attachment 7: Presentation: Drs. Philipp Mayer and Karina Knudsmark Sjøholm
- Attachment 8: Presentation: Dr. Anne Marie Api
- Attachment 9: Presentation: Dr. Mihir Date
- Attachment 10: Presentation: Dr. Anne Marie Api
- Attachment 11: Presentation: Dr. Isabelle Lee
- Attachment 12: Presentation: Dr. Mihwa Na
- Attachment 13: Presentation: Dr. Mihwa Na
- Attachment 14: Presentation: Dr. Mihwa Na
- Attachment 15: Presentation: Dr. Mihwa Na
- Attachment 16: Presentation: Dr. Andy Forreryd
- Attachment 17: Presentation: Dr. Mihwa Na
- Attachment 18: Presentation: Dr. Nikaeta Sadekar