

EXPERT PANEL FOR FRAGRANCE SAFETY MEETING

Minutes Virtual Meeting

September 20-23, 2020

EXPERT PANEL MEMBERS	RIFM STAFF	
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 Shannen Biserta Danielle Botelho Mihir Date Chaitra Deodhar Sanket Gadhia Kaushal Joshi Manoj Kumar Maura Lavelle	Aurelia Lapczynski Isabelle Lee Holger Moustakas Mihwa Na Gretchen Ritacco Jim Romine Dan Selechnik Gary Sullivan (9/20) Yax Thakkar

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.

2) Minutes

The minutes from the May 2020 meeting were approved with one minor change.

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.

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. While there has been an impact on the overall 2020 budget, the work at RIFM continues and the 2020 goals will be achieved.

- b) RIFM Communication update

Mr. Gary Sullivan provided an update on the RIFM Communication Plan (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 progress (See Attachment 2).

b) Safety Assessment Overview

The Panel reviewed 65 Total Safety Assessments including 84 Total materials.

c) General Comments

- i) Use of read-across for UV absorption – the Panel agreed that read across could be used for UV absorbance. UV absorbance is driven by the presence of a chromophore in the molecule and if there is no chromophore in the target or read across material, then read across can be used. Similarly, if there is a chromophore in the target and in the read-across material, then the read-across UV spectrum can be used. While it was agreed that it is very basic to run a UV absorbance; when it becomes difficult for solubility reasons or when the UV absorbance has failed after multiple attempts, then read across is justifiable.
- ii) Reporting 95th percentile use of a product type for NCSs will not occur, but will continue to report on discrete chemicals. A note will be developed to explain that the reported exposure on discrete chemicals is for the use of the chemical as such in addition to its contribution from NCSs.
- iii) Category 8 and 11 use levels – there are no exposure data on these categories. Data are needed and it is being discussed with the Aggregate team on how this can be done.

7) Update on RIFM Maximum Acceptable Concentration

a) Dr. A.M. Api Presentation

Dr. Api gave a presentation on the process involved in determining the Maximum Acceptable Concentrations (MAC) (see Attachment 3).

8) NCS Safety Assessments

a) NCS Safety Assessment publication

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 for the January meeting. In addition, they requested that any modifications suggested from the general comments also be incorporated in the manuscript where appropriate.

b) General Comments

i) Consistency between sections

The Panel recommended that there needs to be greater consistency between the sections. The summary at the beginning of the document should be considered the conclusion and each section should have a summary of that particular endpoint. The Panel requested that one safety assessment should be circulated to the Panel with changes for review.

The Panel recommended that an editorial or introduction be written in advance of the first publication of the NCS Safety Assessments.

ii) Photoallergy is not covered in the NCS SAs

In the section on phototoxicity and photoallergy, a statement is made that the material was not evaluated for photoallergy (if there are no UV absorption or data to clear the photoallergy potential). In the summary section,

it should be stated that the material is not expected to be photoallergic based on the components, but a definitive test has not been conducted.

iii) Benchmark for UV absorbance of naturals

A paper by Nishida, 2015 (Regulatory Toxicology and Pharmacology 72: 578–585) was reviewed that explains how a benchmark for UV absorbance can be used for naturals. The Panel recommended that this procedure should be explored for RIFM evaluations of NCSs. It must be ensured that the NCS is in solution. This will be further explored by Ms. G. Ritacco with Drs. Liebler, Penning, and Schultz, and a proposal will be made to the Panel in January.

iv) TTC

When the TTC approach is used, a statement will be added that the material is not genotoxic.

v) NCS Read-Across Approach

The NCS criteria document needs to be edited to include the agreement from the May 2020 Panel meeting that there can be certain conditions when read-across can be used. These conditions also need to be explained in the criteria document.

vi) Environmental Read-Across

The Panel recommended that read across principles for the environmental endpoint need to be developed further. Ms. Lapczynski will work with Drs. Date and Kumar and the RIFM Environmental Core Team to develop a draft process. This will be reviewed with the Environmental Adjunct Team and Drs. Liebler, Penning, and Schultz, and then a proposal will be made to the Panel at the January meeting.

vii) Exposure

A general statement is needed about the exposure contribution from NCSs and also a statement about the conservative use of TTC for NCSs.

d) Safety Assessment Review

A total of 22 draft NCS Safety Assessments were reviewed by the Panel (see the list below). Suggested changes were made and the Panel requested that another version be provided at the next meeting (including all the general comments as outlined above).

RIFM Material ID	Material Name	Tab
1042479	Petitgrain oil terpeneless, Paraguay	Tab 19
1046350	Petitgrain oil, Paraguay	Tab 20
1042877	Petitgrain lemon oil	Tab 21
1043850	Lemon oil terpenes	Tab 22
1044812	Lemon oil folded (5X)	Tab 23
1044824	Lemon oil, terpeneless	Tab 24
1046095	Petitgrain mandarin oil	Tab 25
1047027	Petitgrain bigarade oil	Tab 26
1047076	Lemon oil, distilled	Tab 27
1047462	Lemon oil, furocoumarin free	Tab 28
1047875	Lemon oil, washed	Tab 29
1048447	Lemon Oil	Tab 30
1048479	Petitgrain oil, rectified, Paraguay	Tab 31
1044371	Lime oil, cold-pressed, furocoumarin free	Tab 32
1044008	Lime oil, expressed	Tab 33

RIFM Material ID	Material Name	Tab
1047546	Lime oil distilled	Tab 34
1043741	Lime oil terpenes	Tab 35
1045266	Lime oil folded (2-5X)	Tab 36
1045071	Lemon oil, expressed	Tab 37
1048425	Lime oil, expressed, rectified	Tab 38
1048448	Lemon oil folded (10x)	Tab 39
1047461	Lime oil, terpeneless	Tab 40

9) Follow-up on actions for Safety Assessment

- a) trans-Anethole CAS No: 4180-23-8

The Panel reviewed the draft safety assessment and requested modifications to the metabolism, repeat dose, and genotoxicity sections.

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

The safety assessment was approved.

- c) Estragole CAS No. 140-67-0

The safety assessment was approved.

- d) Presentation from Y. Thakkar on Mintlactone CAS No. 13341-72-5 and Skatole 83-34-1

Mr. Thakkar gave a presentation on mintlactone and skatole (see Attachment 4). The Panel did not recommend any further testing for mintlactone. The Panel approved the approach to skatole safety assessment.

10) Presentation by Dr. Paul DeLeo – Environmental Framework update on Tuesday, September 22

Dr. Paul DeLeo gave a presentation on how the Environmental Framework will be updated (see Attachment 5). An update will be provided at the next Panel meeting.

11) Review Safety Assessments Batch 1

CAS #	Name	Tab	Status
35154-45-1	cis-3-Hexenyl isovalerate	Tab 45	Approved
120811-92-9	(3-Methoxy-2-methylpropyl)benzene	Tab 46	Approved
1319-88-6	Benzaldehyde glyceryl acetal	Tab 47	Approved with Changes
36306-87-3; 36306-86-2	3,3,5,5-Tetramethyl-4-ethoxyvinylcyclohexanone	Tab 48	Approved
38303-23-0	4,5,6,7,8,9,10,11,12,13- Decahydrocyclo dodecaoxazole	Tab 49	Approved
1209-61-6	Dihydroisocaryophyllene epoxide	Tab 50	Approved
71660-03-2	cis- and trans-p-1(7),8-Menthadien-2-yl acetate	Tab 51	Approved
7289-52-3	Decyl methyl ether	Tab 52	Approved
623-36-9	2-Methyl-2-pentenal	Tab 53	Approved
35158-25-9	2-Isopropyl-5-methyl-2-hexenal	Tab 54	Approved
116044-44-1; 116126-82-0	(2-endo,3-exo)-Ethyl 3-(1- methylethyl)bicyclo[221]hept-5-ene-2-carboxylate	Tab 55	Approved

CAS #	Name	Tab	Status
68966-86-9	Methyl 4(or 1)-isopropyl-1(or 4)-methylbicyclo[222]oct-5-ene-2-carboxylate	Tab 56	Approved
69103-24-8	Isodecyl acetate	Tab 57	Approved with Changes
197098-61-6	2,5,7-Octatrien-1-ol, 2,6-dimethyl-, 1-acetate	Tab 58	Approved
111-03-5	Glyceryl monooleate	Tab 59	Approved
72429-08-4	3,4,4a,5,8,8a(Or 3,4,4a,7,8,8a)-Hexahydro-3,3,6,7-tetramethyl-1H-2-benzopyran	Tab 60	Approved
106-44-5	p-Cresol	Tab 61	Approved
1319-77-3	Cresol (mixed isomers)	Tab 62	Approved
95-48-7	o-Cresol	Tab 63	Approved
495-62-5; 502-61-4; 18794-84-8; 17627-44-0; 495-61-4	Bisabolene	Tab 64	Approved
89-82-7; 15932-80-6; 3391-90-0	Pulegone	Tab 65	Approved with Changes
4437-51-8	3,4-Hexanedione	Tab 66	Approved
96-04-8	2,3-Heptanedione	Tab 67	Approved
5422-34-4	N-Lactoyl ethanolamine	Tab 68	Approved
62439-42-3	Heptanal, 6-hydroxy-2,6-dimethyl-	Tab 69	Approved
5988-91-0	Tetrahydrogeranial	Tab 70	Approved
58475-04-0	(+/-)-4-Ethylactanal	Tab 71	Awaiting UV
7492-70-8	Butyl butyryllactate	Tab 72	Approved
2520-60-7	2-Prenylcyclopentanone	Tab 73	Approved
502-72-7	Cyclopentadecanone	Tab 74	Approved
2550-52-9	Cyclohexadecanone	Tab 75	Approved
541-91-3	3-Methyl-1-cyclopentadecanone	Tab 76	Approved
67801-45-0	trans-3-Heptenyl 2-methylpropanoate	Tab 77	Approved

12) RIFM Research Projects

a) Eugenol Threshold Study

Prof. Bruze reported that Dr. Robert Ofenloch (Research Associate | post-doctoral fellow at University Hospital Heidelberg) is working on drafting a manuscript on the Eugenol study. Dr. Api has contacted Dr. Ofenloch and he reported that he would begin working on the manuscript in the summer.

b) Presentation by S. Gadhia on the skin absorption projects, iTTC, IonTox

Dr. Gadhia presented on the various research projects he is working on (see Attachment 6).

c) Presentation by M. Date/M. Kumar on read-across2 paper

Drs. Date and Kumar presented on the read-across2 paper (see Attachment 7). An outline of the manuscript was presented.

d) Presentation by K Joshi on the reproduction research program

Dr. Joshi presented on the various research projects he is working on (see Attachment 8).

e) Presentation by G. Ritacco on photosensitization research projects

Ms. Ritacco presented on the various research projects she is working on (see Attachment 9).

f) Presentation by N. Sadekar on the respiratory research program

Dr. Nikaeta Sadekar gave a presentation on the RIFM respiratory research program (See Attachment 10). The Panel reviewed the list of confirmed respiratory sensitizers or a gold standard list. The Panel reviewed and approved the IIVS hPLCS proposal.

g) Presentation by M. Lavelle on HRIPT protocol update

Ms. Lavelle presented on the HRIPT project she is working (See Attachment 11).

13) Review Safety Assessments Batch 2

CAS#	Material Name	Tab	Status
744251-93-2	N-3,7-Dimethyl-2,6-octadienylcyclopropylcarboxamide	Tab 81	Approved
108-93-0	Cyclohexanol	Tab 82	Approved
41547-22-2	cis-5-Octenal	Tab 83	Approved
79-42-5	2-Mercaptopropionic acid	Tab 84	Approved
624-92-0	Dimethyl disulfide	Tab 85	Approved
81783-01-9	2,4,4,7-Tetramethylnona-6,8-diene-3-one-oxime	Tab 86	Approved
98-53-3	p-tert-Butylcyclohexanone	Tab 87	Approved
1728-46-7	2-tert-Butylcyclohexanone	Tab 88	Approved
81752-87-6	Methyl-2,2-dimethyl-6-methylene-1-cyclohexanecarboxylate	Tab 89	Approved
75147-23-8	1,5-Dimethylbicyclo[3.2.1]octan-8-one-oxime	Tab 90	Approved with Changes
16874-34-3	2-Furancarboxylic acid, tetrahydro-, ethyl ester	Tab 91	Approved with Changes
2705-87-5	Allyl cyclohexanepropionate	Tab 92	Approved
259854-70-1; 259854-71-2	5-Cyclotetradecen-1-one, 3-methyl-,(5E)-	Tab 93	Approved with Changes
35720-57-1; 14595-54-1	4-Cyclopentadecen-1-one	Tab 94	Approved with Changes
88642-03-9; 5365-06-0; 2550-59-6; 3100-36-5; 5120-20-7; 854373-71-0; 854373-70-9	Cyclohexadecenone	Tab 95	Approved with Changes
82356-51-2	3-Methylcyclopentadecenone	Tab 96	Approved with Changes
37609-25-9	5-Cyclohexadecen-1-one	Tab 97	Approved with Changes
63314-79-4	3-Methyl-5-cyclopentadecen-1-one	Tab 98	Approved with Changes
542-46-1	9-Cycloheptadecen-1-one	Tab 99	Approved with Changes
121251-67-0; 121251-68-1	Spiro[bicyclo[4.1.0]heptane-2,5'-[1,3]dioxane], 2',2',3,7,7-pentamethyl-, (1.alpha.,3.alpha.,6.alpha.)-	Tab 100	Approved
1958027-16-1	4,8-Undecadienal, (4Z,8E)-	Tab 101	Approved
1958027-35-4	4,8-Decadienal, (4Z,8Z)-	Tab 102	Approved
1882830-62-7	4,8-Undecadienal, (4Z,8Z)-	Tab 103	Approved

CAS#	Material Name	Tab	Status
1801275-28-4	4,9-Dodecadienal, (4Z,9Z)-	Tab 104	Approved

14) Review Safety Assessments Batch 3

CAS#	Material Name	Tab	Status
3208-16-0	2-Ethylfuran	Tab 105	Approved
1968-40-7	Ethyl 4-pentenoate	Tab 106	Approved
675-09-2	4,6-Dimethyl-2H-pyran-2-one	Tab 107	Approved
621-23-8	Benzene, 1,3,5-trimethoxy-	Tab 108	Approved
3268-49-3	3-(Methylthio)propionaldehyde	Tab 109	Approved
40596-76-7 ; 379693-55-7	4,8-Dimethyl-7-nonen-2-ol	Tab 110	Approved
111-66-0	1-Octene	Tab 111	Approved with Changes
5405-58-3	Acetaldehyde dihexyl acetal	Tab 112	Approved with Changes

15) Panel Executive Session

The Expert Panel held an executive session.

16) Future Meeting Dates

- Tuesday – Friday, Jan. 19-22, 2021 Virtual
- Monday – Wednesday, May 17-19, 2021 Virtual
- Monday – Wednesday, Sept. 20-22, 2021 New Jersey?
- Monday-Wednesday Jan. 24-26, 2022 Miami
- Monday – Wednesday, May 16-18, 2022 Europe
- Monday – Wednesday, Sept. 19-21, 2022 New Jersey

Respectfully submitted,



Anne Marie Api, PhD
Vice President

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| Attachment 1: | Presentation: Mr. Gary Sullivan |
| Attachment 2: | Presentation: Dr. Danielle Botelho |
| Attachment 3: | Presentation: Dr. Anne Marie Api |
| Attachment 4: | Presentation: Mr. Yax Thakkar |
| Attachment 5: | Presentation: Dr. Paul DeLeo |
| Attachment 6: | Presentation: Dr. S. Gadhia |
| Attachment 7: | Presentation: Drs. Mihir Date/ Kumar Manoj |
| Attachment 8: | Presentation: Dr. Kaushal Joshi |

Attachment 9: Presentation: Ms. Gretchen Ritacco
Attachment 10: Presentation: Dr. Nikaeta Sadekar
Attachment 11: Presentation: Ms. Maura Lavelle