

EXPERT PANEL FOR FRAGRANCE SAFETY MEETING

Minutes

May 21-23, 2018

EXPERT PANEL MEMBERS		RIFM STAFF	GUESTS
Donald Belsito (Chair) Magnus Bruze G. Allen Burten, Jr. Jochen Buschmann Maria Dagli Wolfgang Dekant	Allison Fryer Daniel Liebler Trevor Penning Terry Schultz Glenn Sipes (Vice Chair) Yoshiki Tokura	Anne Marie Api Danielle Botelho Mihir Date Sanket Gadhia Leah Jones Kaushal Joshi Stephanie La Cava Aurelia Lapczynski Mihwa Na Devin O'Brien Gretchen Ritacco Jim Romine Nikaeta Sadekar Dan Salvito Gary Sullivan Yax Thakkar	David Moyler (5/22 via webinar in morning only)

1) Discussion of the Meeting Schedule and Agenda Topics

a) Completion/Signing of Conflict of Interest Statement

Dr. Belsito opened the meeting. The Conflict of Interest Statement was signed. The Elsevier Conflict of Interest form was also signed

2) Minutes

The January 2018 Expert Panel Meeting minutes were approved.

3) Follow-Up and Informational Items

a) Follow-Up List

Dr. Api reviewed the status of the items on the follow-up list; all items are either in progress and will be discussed later in the meeting or have been completed.

4) Standing Items (For Expert Panel information only; per Panel's request)

a) RIFM Publications

Dr. Api reviewed the RIFM publication list with the Panel. This is a standing item on the agenda, which provides a summary of all RIFM recent publications.

b) Dr. Romine gave a presentation to update the Panel on the RIFM IFRA White Paper, the RIFM trip to India and Dr. Romine's trip to Dubai (see Attachment 1).

5) RIFM Safety Evaluation Process

a) Presentation RIFM Safety Assessment Update and Metrics

Dr. Botelho gave a presentation to update the Panel on the progress made with the safety assessment process (see Attachment 2).

b) Presentation on Low Exposure Materials

Dr. Api gave a presentation to update the Panel on an approach to the safety assessments for low exposure materials (see Attachment 3). The Panel agreed with the proposal and made recommendations on how to present the data and what data should be included. All assumptions should be made in the paper and be transparent. The Panel suggested that with the publication, a popular press article should be targeted as well.

c) Presentation and Demonstration of Summary Table

Ms. LaCava gave a presentation to demonstrate on how to use the summary table for the safety assessments being reviewed (see Attachment 4).

d) Presentation on Update to safety assessment publication

Mr. Sullivan and Ms. Jones gave a presentation on publishing the safety assessment (see Attachment 5). The team reported that they are reviewing the publications when they go online now. The Panel stressed the need to review the galley proofs.

- e) Safety Assessment Overview (135 Safety Assessments covering 157 materials) were reviewed in three different batches. These documents were already reviewed by the Panel; the final drafts were reviewed at the meeting. The tables provide the summary from this final review.
- f) General Comments
 - i) Express the doses for phototoxicity and photoallergy studies should be in dose/unit area as well as percent.

6) Review Safety Assessments Batch 1

CAS#	Material Name	Tab	Status
68738-94-3, 68738-96-5, 68991-96-8 and 68991-97-9	Octahydro-8,8-dimethylnaphthalene-2-carbaldehyde	Tab 17	Approved
502-47-6	3,7-Dimethyl-6-octenoic acid	Tab 18	Approved
34686-67-4	cyclopentanol, 2-(2-hexen-1-yl)-;cyclopentanol, 2-(2-hexenyl)-	Tab 19	Approved
5947-36-4	2(10)-Pinen-3-ol	Tab 20	Approved
109-49-9	5-Hexen-2-one	Tab 21	Approved
689-67-8 and 3796-70-1	6,10-Dimethylundeca-5,9-dien-2-one	Tab 22	Approved
1322-58-3 and 4433-36-7	Tetrahydro-pseudo-ionone	Tab 23	Approved
67801-33-6 and 67633-95-8	3-(Hydroxymethyl)nonan-2-one	Tab 24	Approved
56973-85-4	1-(5,5-Dimethyl-1-cyclohexen-1-yl)pent-4-en-1-one	Tab 25	Approved
93-08-3	Methyl beta-naphthyl ketone	Tab 26	Approved

CAS#	Material Name	Tab	Status
941-98-0 and 1333-52-4	1-(1-Naphthyl)ethanone	Tab 27	Approved
211299-54-6	4H-4a,9-Methanoazuleno[5,6-d]-1,3-dioxole, octahydro-2,2,5,8,8,9a-hexamethyl-, (4aR,5R,7aS,9R)-	Tab 28	Approved
6413-10-1	Ethyl 2-methyl-1,3-dioxolane-2-acetate	Tab 29	Approved
6290-17-1	Ethyl 2,4-dimethyldioxolane-2-acetate	Tab 30	Approved
4747-07-3	1-Methoxyhexane	Tab 31	Approved
122795-41-9, 862111-34-0 and 31996-78-8	2-Ethyl-5-methoxybicyclo[2.2.1]heptane	Tab 32	Approved
5331-32-8	Isobornyl methyl ether	Tab 33	Approved
53018-24-9	3a,4,5,6,7,7a-Hexahydro-5-methoxy-4,7-methano-1H-indene	Tab 34	Approved
27135-90-6	3a,4,5,6,7,7a-Hexahydromethoxy-4,7-methano-1H-indene (isomer unspecified)	Tab 35	Approved
80858-47-5	[2-(Cyclohexyloxy)ethyl]benzene	Tab 36	Approved
101-84-8	Diphenyl ether	Tab 37	Approved with changes
64988-06-3	Ethyl 2-methoxybenzyl ether	Tab 38	Approved
91-16-7	1,2-Dimethoxybenzene	Tab 39	Approved
150-78-7	p-Dimethoxybenzene	Tab 40	Approved
21112-37-8	1,4-Dimethoxy-2-tert-butylbenzene	Tab 41	Approved
151-10-0	m-Dimethoxybenzene	Tab 42	Approved
4179-19-5	3,5-Dimethoxytoluene	Tab 43	Approved
105-45-3	Methyl acetoacetate	Tab 44	Approved
141-97-9	Ethyl acetoacetate	Tab 45	Approved
29214-60-6	Ethyl 2-hexylacetoacetate	Tab 46	Approved
111-81-9	Methyl undec-10-enoate	Tab 47	Approved
109-42-2	Butyl 10-undecenoate	Tab 48	Approved
110-19-0	Isobutyl acetate	Tab 49	Approved
540-42-1	Isobutyl propionate	Tab 50	Approved
539-90-2	Isobutyl butyrate	Tab 51	Approved
624-41-9	2-Methylbutyl acetate	Tab 52	Approved

CAS#	Material Name	Tab	Status
51115-64-1	2-Methylbutyl butyrate	Tab 53	Approved
105-79-3	Isobutyl hexanoate	Tab 54	Approved
547-63-7	Methyl isobutyrate	Tab 55	Approved
868-57-5	Methyl 2-methylbutyrate	Tab 56	Approved
556-24-1	Methyl isovalerate	Tab 57	Approved
97-62-1	Ethyl isobutyrate	Tab 58	Approved
7452-79-1	Ethyl 2-methylbutyrate	Tab 59	Approved
108-64-5	Ethyl isovalerate	Tab 60	Approved
2270-60-2	Methyl 3,7-dimethyl-6-octenoate	Tab 61	Approved
1617-23-8	Ethyl 2-methyl-3-pentenoate	Tab 62	Approved
97-85-8	Isobutyl isobutyrate	Tab 63	Approved with changes
589-59-3	2-Methylpropyl 3-methylbutyrate	Tab 64	Approved with changes
2445-67-2	2-Methylpropyl 2-methylbutyrate	Tab 65	Approved with changes
659-70-1	Isoamyl isovalerate	Tab 66	Approved with changes
2445-77-4	2-Methylbutyl 3-methylbutanoate	Tab 67	Approved with changes
27625-35-0	3-Methylbutyl 2-methylbutanoate	Tab 68	Approved with changes
816-73-9	Methylallyl isobutyrate	Tab 69	Approved
68039-78-1	Octahydro-4,7-methano-1H-indenemethyl formate	Tab 70	Approved
30772-69-1	Octahydro-4,7-methano-1H-indenemethyl acetate	Tab 71	Approved
6819-19-8	3-(4-Methylcyclohex-3-enyl)-3-butenyl acetate	Tab 72	Approved
2021-28-5	Ethyl 3-phenylpropionate	Tab 73	Approved
102-13-6	Isobutyl phenylacetate	Tab 74	Approved
102-19-2	Isoamyl phenylacetate	Tab 75	Approved
139-70-8 and 10486-14-3	Citronellyl phenylacetate	Tab 76	Approved with changes

7) Review Safety Assessments Batch 2

CAS#	Material Name	Tab	Status
Batch 2			
539-88-8	Ethyl levulinate	Tab 77	Approved
2408-37-9	2,2,6-Trimethylcyclohexanone	Tab 78	Approved
55739-89-4	Cyclohexanone, 2-ethyl-4,4-dimethyl-	Tab 79	Approved
2345-26-8 and 2345-24-6	Geranyl isobutyrate	Tab 80	Approved
109-20-6 and 3915-83-1	Geranyl isovalerate	Tab 81	Approved
102-17-0	Anisyl phenylacetate	Tab 82	Approved
10521-96-7	Styryl acetate	Tab 83	Approved with changes
37973-51-6 and 37973-52-7	(E)-2-Phenylpropenyl acetate	Tab 84	Approved
108-21-4	Isopropyl acetate	Tab 85	Approved
638-11-9	Isopropyl butyrate	Tab 86	Approved
67952-57-2	1,5-Dimethylhexyl acetate	Tab 87	Approved
622-45-7	Cyclohexyl acetate	Tab 88	Approved
1551-44-6	Cyclohexyl butyrate	Tab 89	Approved
40702-13-4	2-tert-Butylcyclohexyl propionate	Tab 90	Approved
123-18-2	2,6,8-Trimethylnonan-4-one	Tab 91	Approved with changes
108-10-1	4-Methyl-2-pentanone	Tab 92	Approved
541-85-5	5-Methyl-3-heptanone	Tab 93	Approved
74338-72-0	2,4,4,7-Tetramethyl-6-octen-3-one	Tab 94	Approved
68141-18-4	11-Tridecen-6-one, 8,12-dimethyl-	Tab 95	Approved
2550-26-7	Benzyl acetone	Tab 96	Approved
7403-42-1	4-Methyl-4-phenyl-2-pentanone	Tab 97	Approved with changes
4927-36-0	5-Methyl-5-phenyl-3-hexanone	Tab 98	Approved
58461-27-1	4-Hexen-1-ol, 5-methyl-2-(1-methylethenyl)-	Tab 99	Approved
18294-87-6	1-Cyclohexene-1-acetic acid	Tab 100	Approved
564-20-5	Sclareolide	Tab 101	Approved

CAS#	Material Name	Tab	Status
21280-29-5	Lactoscatone	Tab 102	Approved
40188-41-8	3,7-Dimethyloctanenitrile	Tab 103	Approved
85351-07-1	3-Methyldodecanonitrile	Tab 104	Approved
208041-98-9	2-Propyl heptanenitrile	Tab 105	Approved
69300-15-8	2-Methyldecanenitrile	Tab 106	Approved
61692-84-0 and 7779-81-9	Isobutyl 2-methylcrotonate	Tab 107	Approved
41519-18-0	Isopentyl 2-methylcrotonate (E)	Tab 108	Approved
53082-58-9	3-Methylpentyl 2-methylisocrotonate	Tab 109	Approved
24700-20-7	p-Tolyl 3-methylcrotonate	Tab 110	Approved
67801-23-4	2-Isopropyl-5-methylcyclohexyl 2-methylbut-2-enoate	Tab 111	Approved
50652-80-7	3-Methyl-2-hexenoic acid methyl ester	Tab 112	Approved
1189-09-9	trans-Methylgeranate	Tab 113	Approved
16493-96-2	2-Hexenoic acid, 2-methyl-, methyl ester, (2E)-	Tab 114	Approved
13058-12-3 and 32659-21-5	Ethyl 3,7-dimethylocta-2,6-dienoate	Tab 115	Approved

8) Update on QRA2 Implementation

a) A.M Api Presentation on QRA2

Dr. Api gave a presentation updating the Panel on QRA2 (see Attachment 6).

9) Review Safety Assessments – Batch 3

CAS#	Material Name	Tab	Status
Batch 3			
2396-78-3; 13894-62-7	Methyl 3-hexenoate	Tab 116	Approved
41654-15-3	Methyl cis-5-octenoate	Tab 117	Approved
13481-87-3	Methyl 3-nonenoate	Tab 118	Approved
26553-46-8; 2396-83-0	Ethyl (E)hex-3-enoate	Tab 119	Approved
78989-37-4; 34495-71-1	4-Octenoic acid, ethyl ester, (4E)-	Tab 120	Approved
606-45-1; 121-98-2	Methyl o-methoxybenzoate	Tab 121	Approved with changes

CAS#	Material Name	Tab	Status
66576-71-4	Isopropyl 2-methylbutyrate	Tab 122	Approved
6784-08-3	4,7,7-Trimethyl-6-thiabicyclo[3.2.1]oct-3-ene	Tab 123	Approved
53767-93-4	Dihydromyrcenyl acetate	Tab 124	Approved
72214-23-4	Ocimenyl acetate	Tab 125	Approved
97-63-2	Ethyl methacrylate	Tab 126	Approved
97-88-1	Butyl methacrylate	Tab 127	Approved
4802-20-4	Cyclohexaneethanethiol, 3-mercapto-b,4-dimethyl-	Tab 128	Approved
67715-80-4; 59323-76-1; 59324-17-3	2-Methyl-4-propyl-1,3-oxathiane; cis-2-Methyl-4-propyl-1,3-oxathiane; trans-2-Methyl-4-propyl-1,3-oxathiane	Tab 129	Approved
13532-18-8	Methyl 3-methylthiopropionate	Tab 130	Approved
13327-56-5	Ethyl 3-methylthiopropionate	Tab 131	Approved
2432-51-1	Methyl thiobutyrate	Tab 132	Approved
34322-06-0	S-Isopropyl 3-methylthiobutyrate	Tab 133	Approved
2432-91-9	S-2-Butyl 3-methylbutanethioate	Tab 134	Approved
34365-79-2	S-1-Methylethyl 3-methylbut-2-enethioate	Tab 135	Approved
68084-04-8; 21690-43-7	3-(4-Methyl-3-pentenyl)-3-cyclohexene-1-carbonitrile; 3-Cyclohexene-1-carbonitrile, 4-(4-methyl-3-pentenyl)-	Tab 136	Approved
1438-94-4	N-Furfurylpyrrole	Tab 137	Approved with changes
137-00-8	4-Methyl-5-thiazoleethanol	Tab 138	Approved
24295-03-2	2-Acetylthiazole	Tab 139	Approved
2525-16-8	Methyl 3,4,5,6-tetrahydro-7H-azepin-2-yl ether	Tab 140	Approved
93-04-9	beta-Naphthyl methyl ether	Tab 141	Approved
93-18-5	beta-Naphthyl ethyl ether	Tab 142	Approved
2173-57-1	beta-Naphthyl isobutyl ether	Tab 143	Approved
104-55-2	Cinnamaldehyde	Tab 144	Insufficient data - phototoxicity
101-39-3	alpha-Methylcinnamaldehyde	Tab 145	Insufficient data - phototoxicity
84697-09-6	p-Methyl-alpha-amyl cinnamic aldehyde	Tab 146	Approved with changes
3487-99-8	Amyl cinnamate	Tab 147	Approved

CAS#	Material Name	Tab	Status
7779-65-9	Isoamyl cinnamate	Tab 148	Approved
122-67-8	Isobutyl cinnamate	Tab 149	Approved

10) Human Health Research Projects

a) Epidemiology

i) Validation of Clinical Relevance Algorithm

Dr. Bruze reported that the draft manuscript is written; Dr. Api needs to add information for completion and it will be circulated to the Panel dermatologists for comment. The paper has been submitted for discussion at the upcoming European Society for Contact Dermatitis in 2018.

b) Update on RIFM TTC Research

Dr. Api provided an update on the oral TTC research project. A manuscript is in preparation and submission is scheduled for Q4 2018. Dr. Botelho provided an update on the inhalation TTC research project.

c) Update on RIFM Genotoxicity Research Projects

Dr. Joshi and Mr. Thakkar gave a presentation on the RIFM genotoxicity research projects (see Attachment 7).

11) Safety Assessment approach to Naturals Complex Substances (NCSs)

a) Presentation overall approach

Dr. Salvito gave a presentation on the overall approach to the NCS safety assessment (see Attachment 8).

b) NCS component matrix

Dr. David Moyler gave a presentation via webinar to the Panel. Dr. Moyler explained the technical aspects of the IFRA-IOFI NCS Matrix (see Attachment 9).

The Panel concluded that:

- RIFM should publish the compositional analysis of the NCSs being evaluated in safety assessments down to at least 0.1%. If for some reason this is not achievable, then publishing the composition down to all components at 1% or great assuming that any substances that have known adverse effect regardless of the compositional level.
- Considering the data quality criteria presented, RIFM and the Panel will need to review the underlying data for the summary composition of an NCS; i.e., the MIS sheets.
- We will need to define terms such as folded, rectified, etc. This will help clarify which materials can be grouped together based on their botany, composition, and processing.
- How does (or when will) RIFM have access to the next matrix revision?
- There are many materials that are still not in the matrix; can the NCS TF provide timing of when that may be completed.
- It would be good to learn of the 758 materials that have data – what is the number of fragrance materials in the RIFM palette (e.g. 902) with breakdown in DRF 1, 2, 3, 4?
- Understanding that RIFM may start the SA process before the matrix is completed, RIFM, based on NCSs that are grouped together for the SAs, may be able to prioritize materials for additional compositional information to develop new analytical data. Is this prioritization helpful? How long would it take to develop additional data?
- Are there any low volume materials that can be eliminated?
- While the DRF classifications are helpful, the panel suggested a well described (qualitative) approach to data quality description we would be more appropriate for the published SAs.

c) NCS Safety Assessment Approach

The RIFM staff reviewed the approach to safety assessments for Natural Complex Substances (NCSs). The first presentation was on the genotoxicity endpoint by Dr. Joshi and Mr. Thakkar (see Attachment 10). This was followed by presentations from Ms. O'Brien who presented on the approach to the sensitization endpoint (see Attachment 11). Ms. Lapczynski presented the approach for the environmental endpoint (see Attachment 12). Ms. Ritacco presented on phototoxicity/photoallergy endpoints (see Attachment 13); there is a plan for phototoxicity evaluation. If the NCS absorbs in the UVA range and no photoallergy data are available and no evidence of photoallergy is available in the literature, then a statement will be placed in the safety assessment that reads "While the material absorbs in the UVA range, there is no clinical evidence that the material is a photoallergen. The material has not be fully evaluated for photoallergenicity, but when in vitro assays are validated, the material will be tested." Dr. Sadekar presented on the respiratory endpoint (see Attachment 14). Dr. Api presented the repeat dose, developmental and reproduction endpoints (see Attachment 15).

The Panel accepted the overall approaches to each of the endpoints.

12) Future Meeting Dates

• Monday – Wednesday	Aug. 27-29, 2018	Stockholm
• Monday – Wednesday	Jan. 28-30, 2019	Miami, FL
• Monday – Wednesday	May 20-22, 2019	Rome
• Monday – Wednesday	Sept. 23-25, 2019	New Jersey
• Monday – Wednesday	Jan. 20-22, 2020	Delhi, India
• Monday – Wednesday	May 18-20, 2020	Chicago
• Monday – Wednesday	Sept. 21-23, 2020	New Jersey

Respectfully submitted,



Anne Marie Api, PhD
Vice President, Human Health Sciences
(August 27, 2018)

Attachment 1:	Dr. Romine presentation on the RIFM IFRA White Paper
Attachment 2:	Dr. Botelho presentation on the safety assessment process
Attachment 3:	Dr. Api presentation on an approach to the safety assessments for low exposure materials
Attachment 4:	Ms. LaCava presentation to demonstrate use of summary table for the safety assessments
Attachment 5:	Mr. Sullivan presentation on publishing the safety assessment
Attachment 6:	Dr. Api presentation updating the Panel on QRA2
Attachment 7:	Dr. Joshi and Mr. Thakkar presentation on the RIFM genotoxicity research projects
Attachment 8:	Dr. Salvito presentation on overall approach to the NCS safety assessment

- Attachment 9: Dr. David Moyler gave a presentation via webinar on the technical aspects of the IFRA-IOFI NCS Matrix
- Attachment 10: Presentation by Dr. Joshi and Mr. Thakkar on NCS genotoxicity endpoint
- Attachment 11: Presentation by Ms. O'Brien on NCS sensitization endpoint
- Attachment 12: Presentation by Ms. Lapczynski on NCS environmental endpoint
- Attachment 13: Presentation by Ms. Ritacco on NCS phototoxicity/photoallergy endpoints
- Attachment 14: Presentation by Dr. Sadekar on NCS respiratory endpoint
- Attachment 15: Presentation by Dr. Api on NCS repeat dose and reproduction endpoints