

EXPERT PANEL FOR FRAGRANCE SAFETY MEETING

Minutes

May 22-24, 2017

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 I Glenn Sipes (Vice Chair) Y. Tokura	Anne Marie Api Stephanie La Cava Devin O'Brien Rahul Parakhia Atish Patel Jim Romine Suzana Theophilus	Marie Betou (5/22 only) Jean-Pierre Lepoittevin (5/22 only) Cronan McNamara (5/23 only) John O'Brien (5/23 only) Cian O'Mahony (5/23 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 and May 2019 dates were set.

2) Minutes

The January 2017 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.

5) RIFM Safety Evaluation Process

a) Expert Panel Discussion on Safety Assessments

Dr. Romine gave a presentation (Attachment 1) about the RIFM safety assessment program and the need to expedite the process. The plan is to complete 650 safety assessments in 2018 and 2019. There was a discussion on how the process could be improved to allow the Expert Panel to complete their review of these safety assessments. The Panel emphasized the need to maintain the quality of the safety assessments. The Panel agreed that for most endpoints, their maximum capacity had not been achieved

yet. Following a detailed discussion, several improvements were identified that would help streamline the process and improve efficiency (listed below).

- Have RIFM staff engage appropriate Panel members when issues come up rather than waiting for the meeting to resolve it
- Improve the sequence of safety assessment submissions to the Panel; the overview document could be improved with hyperlinks to the safety assessments and to the materials with read across. This table will serve as a map to show where the data exist and can be used as a template for each meeting. If linking to a read across material that has already been reviewed it should be noted in the table.
- Improve the way they are distributed so that the clusters are correct and the material with the data is identified
- Identify clusters and seed with best data set – Drs. Liebler, Penning and Schultz can assist in this
- Better workflow
- Better QA on safety assessment
- Panel is sometime given more information than necessary (e.g. 28-day and 90-day study; do you need both?)
- Continue to create batches around chemical functionality – drives availability of data
- Dr. Date should bundle his requests; the e-mails come in daily
- A key issue with universal agreement was to maintain the same panel of experts for the next 3 years we don't change the panel because to change the Panel will slow or reverse the process; suspend term limits until the safety assessment process is completed
- Do not make changes to the template unless necessary
- Bring BMP-D to help stream-line the Expert Panel process

Additional suggestions were considered and rejected:

- Expand on the division of labor approach was not considered because quality is important and the Panel did not want to sacrifice quality
- For endpoints with more than one Panel member, split the duties and separate authorship
- Add Panel members for endpoint where the capacity is critical
- Have Panel focus only on the high-gain safety assessment sections. Make the others high quality template standards that don't require review – No want to see it all
- Consider bundling assessment list Group Summaries
- Expand 4 meetings/year
- Create a second Panel
- Have the Expert Panel only review some safety assessments, but mechanism to decide which ones to review is not feasible
- Have only one Panel member as a primary reviewer per endpoint

While no one wanted to extend the target date for completion, it may need to be a consideration if the Panel cannot complete the review by 2020. There was also a discussion on different ways to publish the safety assessments. Some ideas for consideration were to publish with RIFM staff and "Expert Panel for Fragrance Safety" or to use a cluster to have one publication but individual materials.

The review of natural complex substances will also involve a more detailed discussion. The focus will be on typical constituents of concern. This will be brought back as a formal topic at future Panel meetings.

b) S. Theophilus Presentation RIFM Safety Assessment Update and Metrics

Dr. Theophilus gave an update on the RIFM safety assessment process (see Attachment 2).

c) General Comments

A total of **141** Safety Assessments covering **170** materials were reviewed.

- Skin Sensitization: Prediction for reactivity OECD Toolbox and Toxtree; Justification should use the same and remove CAESAR.
- Molarity: Scientifically correct to adjust for molecular weight. Should be done every time read across is used not only for esters. All calculations should be shown and will be done going forward
- Cramer Class: Move the judgment statement into the main body of Section V.1. Adjust the statement to: "*Due to potential discrepancies with the current *in silico* tools (Bhatia et al., 2015), the Cramer class of the target material was also determined using expert judgment based on the Cramer decision tree (Cramer et al., 1978). See Appendix below for further details"
- When isomer is undefined, then add it to the Section I. Identification as 7. And isomeric identification is undefined.
- Add the 95th percentile data in Table 1 when using DST to show that the levels fall below the acceptable levels. Need a boiler plate explanation of values. It is a transparency issue not a safety issue. **Notify Advisory Committee**
- Use data on esters before the alcohol, but if data on alcohol are present then add it as weight of evidence.
- For Panel Agenda Overview (e.g. tab 15) add the tab numbers to the table
- For the batch summaries, hyperlink the safety assessments in the summary table
- In the abbreviation list add a statement that when stating an effect is significant means that it is at least $p < 0.05$.

CAS No.	Material Name	Tab	Expert Panel Status
Batch 3			
107-74-4	Hydroxycitronellol	Tab 15	Approved with changes
69486-14-2	5,8-Methano-2H-1-benzopyran-2-one, 6-ethylideneoctahydro-	Tab 16	Approved
472-66-2	2,6,6-Trimethyl-1-cyclohexen-1-acetaldehyde	Tab 17	Approved with changes
65405-84-7	4-(2,6,6-Trimethyl-2-cyclohexen)-2-methylbutanal	Tab 18	Approved with changes
66327-54-6	1-Formyl-1-methyl-4-(4-methyl-pentyl)-3-cyclohexene	Tab 19	Approved with changes
52475-86-2 and 52474-60-9	1-methyl-4-(4-methylpent-3-en-1-yl)cyclohex-3-ene-1-carbaldehyde	Tab 20	Approved with changes
27939-60-2, 68039-49-6, 67801-65-4, 68039-48-5, 35145-02-9, 36635-35-5, 68084-52-6, 68737-61-1	dimethylcyclohex-3-ene-1-carbaldehyde (isomer unspecified)	Tab 21	Approved with changes
31906-04-4 and 51414-25-6	3 and 4-(4-Hydroxy-4-methylpentyl)-3-cyclohexene-1-carboxaldehyde	Tab 22	Approved with changes
495-40-9	Butyrophenone	Tab 23	Approved with changes
122-00-9	4'-Methylacetophenone	Tab 24	Approved with changes
645-13-6	p-isopropylacetophenone	Tab 25	Approved with changes
943-27-1	1-(4-tert-butylphenyl)ethanone	Tab 26	Approved with changes
2040-10-0	4'-tert-butyl-2',6'-dimethylacetophenone	Tab 27	Approved with changes
13074-65-2	2-hexylcyclopentanone	Tab 28	Approved with changes
4819-67-4	2-pentylcyclopentan-1-one	Tab 29	Approved
137-03-1	2-heptylcyclopentanone	Tab 30	Approved
13074-63-0	3-methyl-2-pentylcyclopentan-1-one	Tab 31	Approved
65443-14-3	2,2,5-trimethyl-5-pentylcyclopentanone	Tab 32	Approved

CAS No.	Material Name	Tab	Expert Panel Status
928-91-6	4-Hexen-1-ol, (4Z)-	Tab 33	Approved
544-12-7, 928-96-1 and 928-97-2	3-Hexen-1-ol (isomer unspecified)	Tab 34	Approved
6191-71-5	(Z)-4-Hepten-1-ol	Tab 35	Approved
20125-84-2	cis-3-Octen-1-ol	Tab 36	Approved
35854-86-5	cis-6-Nonen-1-ol	Tab 37	Approved
64275-73-6	cis-5-Octen-1-ol	Tab 38	Approved
76649-25-7	3,6-Nonadien-1-ol	Tab 39	Approved
94-47-3	Phenethyl benzoate	Tab 40	Approved with changes
102-20-5	Phenethyl phenylacetate	Tab 41	Approved with changes
102-16-9	Benzyl phenylacetate	Tab 42	Approved with changes
10032-05-0	Heptanal dimethyl acetal	Tab 43	Approved with changes
14620-52-1	Dodecanal dimethyl acetal	Tab 44	Approved with changes
10022-28-3	Octanal dimethyl acetal	Tab 45	Approved with changes
7779-41-1	Decanal dimethyl acetal	Tab 46	Approved with changes
1817-90-9	benzene, (2-ethoxyethyl)-	Tab 47	Approved changes
538-86-3	Benzyl methyl ether	Tab 48	Approved with changes
68039-47-4	[2-Isopropoxyethyl]benzene	Tab 49	Approved with changes
122-73-6	Benzyl isoamyl ether	Tab 50	Approved with changes
56011-02-0	Phenylethyl isoamyl ether	Tab 51	Insufficient Data – need SABS or find better read across
128-50-7 and 35836-73-8	Nopol	Tab 52	Approved with changes
515-00-4	Myrtenol	Tab 53	Approved with changes
122760-85-4	4-Methyl-8- methylenetricyclo[3.3.1.(3,7)]decan-2-yl acetate	Tab 54	Approved with changes
1975-78-6	Decanenitrile	Tab 55	Approved with changes
2437-25-4	Dodecanenitrile	Tab 56	Approved with changes
628-73-9	Hexanenitrile	Tab 57	Approved with changes
629-63-0	Myristo nitrile	Tab 58	Approved with changes
124-12-9	Octanenitrile	Tab 59	Approved with changes
109-29-5	Hexadecanolide	Tab 60	Approved with changes
6707-60-4	12-Oxahexadecanolide	Tab 61	Approved with changes
3391-83-1	11-Oxahexadecanolide	Tab 62	Approved with changes
1725-01-5	10-Oxahexadecanolide	Tab 63	Approved with changes
28645-51-4	Oxacycloheptadec-10-ene-2-one	Tab 64	Approved with changes
7779-50-2	ω -6-Hexadecenlactone	Tab 65	Approved with changes
34902-57-3, 111879-80-2, 111879-79-9, 111879-81-3, 99219-32-6	Oxacyclohexadecen-2-one	Tab 66	Approved with changes
106-02-5	omega-Pentadecalactone	Tab 67	Approved with changes
329925-33-9	Oxacyclopentadec-10-en-2-one, 13- methyl-	Tab 68	Approved with changes
38223-29-9	Oxacyclohexadecane-2,13-dione	Tab 69	Approved with changes
54982-83-1	Ethylene dodecanedioate	Tab 70	Approved with changes
6379-73-3	4-Isopropyl-2-methoxy-1-methylbenzne	Tab 71	Approved
1076-56-8	1-Methyl-3-methoxy-4-isopropylbenzene	Tab 72	Approved
31574-44-4	2-Isopropyl-4-methylanisole	Tab 73	Approved

CAS No.	Material Name	Tab	Expert Panel Status
104-93-8	p-Methylanisole	Tab 74	Approved with changes
104-45-0	p-Propylanisole	Tab 75	Approved with changes
18479-58-8, 25279-09-8 and 53219-21-9	Dihydromyrcenol	Tab 76	Approved with changes
543-39-5	Myrcenol	Tab 77	Approved with changes
106-65-0	Dimethyl succinate	Tab 78	Approved with changes
1119-40-0	Pentanedioic acid, 1,5-dimethyl ester	Tab 79	Approved with changes
123-25-1	Diethyl succinate	Tab 80	Approved with changes
55719-85-2	Phenethyl tiglate	Tab 81	Approved with changes
2111-75-3	p-Mentha-1,8-dien-7-al	Tab 82	Insufficient – Genotoxicity review needed
1604-28-0	6-Methyl-3,5-heptadien-2-one	Tab 83	Approved with changes
13144-88-2	1-(2,4,4,5,5-Pentamethyl-1-cyclopenten-1-yl)ethan-1-one	Tab 84	Approved with changes
Batch 2			
19819-98-8	o-Tolyloethanol	Tab 86	Approved with changes
699-02-5	2-p-Tolyloethanol	Tab 87	Approved with changes
98-85-1	(1)-alpha-methylbenzyl alcohol	Tab 88	Approved With changes
705-73-7	alpha-propylphenethyl alcohol	Tab 89	Approved
56836-93-2	Benzenepropanol, a,b-dimethyl-	Tab 90	Approved
7779-78-4	α-isobutylphenethyl alcohol	Tab 91	Approved with changes
42822-86-6	2-Hydroxy-alpha,alpha,4-trimethylcyclohexanemethanol	Tab 92	Approved
104-57-4	Benzyl formate	Tab 93	Approved with changes
7460-74-4	2-Phenylethyl valerate	Tab 94	Approved with changes
10276-85-4	Benzyl octanoate	Tab 95	Approved with changes
10361-39-4	Benzyl valerate	Tab 96	Approved with changes
6290-37-5	Phenethyl hexanoate	Tab 97	Approved with changes
5457-70-5	Phenethyl octanoate	Tab 98	Approved with changes; May need additional Genotoxicity tests
140-26-1	Phenethyl isovalerate	Tab 99	Approved with changes
62346-96-7	2,4-Dimethylbenzyl acetate	Tab 100	Approved with changes
103-38-8	Benzyl isovalerate	Tab 101	Approved with Changes
56423-40-6	Benzyl 2-methylbutyrate	Tab 102	Approved with changes
2094-69-1	Benzyl 2,2-dimethylpropanoate	Tab 103	Approved with changes
6315-04-4	Phenethyl 2-ethylbutyrate	Tab 104	Approved with Changed
24817-51-4	Phenylethyl 2-methylbutyrate	Tab 105	Approved with changes
103-58-2	3-Phenylpropyl isobutyrate	Tab 106	Approved with changes
67662-96-8	2-Phenylethyl pivalate	Tab 107	Approved with changes
116-26-7	2,6,6-Trimethylcyclohexa-1,3-dienyl methanal	Tab 108	Approved with changes
432-25-7	2,6,6-Trimethyl-1&2-cyclohexen-1-carboxaldehyde	Tab 109	Approved with changes
3155-71-3, 68555-62-4	2-Methyl-4-(2,6,6-trimethylcyclohex-1-en-1-yl)-2-butenal	Tab 110	Approved with changes
61792-11-8	3,7-Dimethyl-2,6-nonadienenitrile	Tab 111	Approved
67019-89-0	2,6-Nonadienenitrile	Tab 112	Insufficient Data – Sensitization Read Across
22629-49-8	Tridecene-2-nitrile	Tab 113	Insufficient Data - Sensitization

CAS No.	Material Name	Tab	Expert Panel Status
22629-48-7	2-Undecenitrile	Tab 114	Insufficient Data – Sensitization Read Across
29127-83-1	Nonen acid nitrile	Tab 115	Insufficient Data – Sensitization Read Across
60-12-8	Phenethyl alcohol	Tab 116	Approved with changes
122-97-4	3-Phenyl-1-propanol	Tab 117	Approved with changes
25634-93-9	2-Methyl-5-phenylpentanol	Tab 118	Approved
92368-90-6	2-Benzylheptanol	Tab 119	Approved with changes
1123-85-9	beta-Methylphenethyl alcohol	Tab 120	Approved
13351-61-6	2,2-Dimethyl-3-phenylpropanol	Tab 121	Approved with changes
103694-68-4	.beta.,.beta.,3-Trimethyl benzenepropanol	Tab 122	Approved with changes
92585-24-5	2-Methyl-4-phenylpentanol	Tab 123	Approved with changes
Batch 1			
61699-38-5	Methylcyclooctyl carbonate	Tab 126	Approved
59052-82-3	Cyclododecyl formate	Tab 127	Approved with changes
67801-64-3	Ethyl 2-tert-butylcyclohexyl carbonate	Tab 128	Approved
93981-50-1	Ethyl 2,3,6-trimethylcyclohexyl carbonate	Tab 129	Approved
31846-06-7	3-tert-Butylcyclohexyl acetate	Tab 130	Approved with changes
32210-23-4, 1900-69-2 and 10411-92-4	4-tert-Butylcyclohexyl acetate	Tab 131	Approved with changes
67874-72-0	Amylcyclohexyl acetate (mixed isomers)	Tab 132	Approved with changes
16409-45-3, 89-48-5, 2623-23-6 and 29066-34-0	Menthyl acetate (isomer unspecified)	Tab 133	Approved with changes
59259-38-0	<i>l</i> -Menthyl lactate	Tab 134	Approved
26252-11-9	Dihydro-.beta.-terpinyl acetate	Tab 135	Approved
16409-46-4	Menthyl isovalerate	Tab 136	Approved
63449-95-6	4-(Isopropyl)cyclohexyl propionate	Tab 137	Approved
68141-17-3	2-Methylundecanal dimethyl acetal	Tab 138	Approved with Changes
3842-03-3	3-Methylbutanal diethyl acetal	Tab 139	Approved with Changes
86198-35-8	1,1-Diethoxy-3,5,5-trimethylhexane	Tab 140	Approved with changes
69178-43-4	1,1-Diethoxyisooctane	Tab 141	Approved with changes
105-57-7	Acetal	Tab 142	Approved with Changes
4744-08-5	Propanal diethyl acetal	Tab 143	Approved with Changes
688-82-4	1,1-Diethoxyheptane	Tab 144	Approved with Changes
3658-93-3	1,1-Diethoxyhexane	Tab 145	Approved with Changes
2556-10-7	Acetaldehyde ethyl phenylethyl acetal	Tab 146	Approved
7493-57-4	Propyl phenethyl acetal	Tab 147	Approved
122-71-4	Acetaldehyde, diphenethyl acetal	Tab 148	Approved
1331-83-5 and 104-21-2	Anisyl acetate (isomer unspecified)	Tab 149	Approved with changes
7549-33-9	Anisyl propionate	Tab 150	Approved with changes
122-91-8	Anisyl formate	Tab 151	Approved with changes
224031-70-3, 224031-71-4	1-Spiro[4.5]dec-7-en-7-yl-4-penten-1-one, 4-Penten-1-one, 1-spiro[4.5]dec-6-en-7-yl-	Tab 152	Approved with changes
313973-37-4	1-(5,5-Dimethyl-1-cyclohexen-1-yl)pent-4-en-1-one	Tab 153	Approved with changes
23250-42-2, 23059-38-3	Trans Cyclohexanecarboxylic acid, 1,4-dimethyl-, methyl ester, trans-	Tab 154	Approved

CAS No.	Material Name	Tab	Expert Panel Status
22471-55-2	Cyclonexanecarboxylic acid, 2,2,6-trimethyl-, ethyl ester, (1R,6S)-rel-	Tab 155	Approved
2511-00-4	Cyclohexaneacetic acid, alpha-methyl-, ethyl ester	Tab 156	Insufficient Data; Genotoxicity
211018-1-	2-(3-Phenylpropyl)pyridine	Tab 157	Approved with changes
2057-49-0	4-(3-Phenylpropyl)pyridine	Tab 158	Approved with changes

Bolded Materials are those with the most data

6) Webinar Presentation by Jean-Pierre Lepoittevin PhD, January 24 9 AM Update: Development of HRMAS NMR spectroscopy in association with RHE to follow and characterize the metabolic transformation/activation of pro-haptens (see Attachment 3).

7) IDEA Update

a) QRA Implementation Update

Dr. Api reported that implementation of QRA2 will begin with the 49th Amendment to the IFRA Code of Practice in 2017. All existing Standards based on sensitization will be converted to QRA2 Standards. They will also all be reviewed for systemic toxicity.

b) IDEA Working Group Meeting on evaluating effectiveness of QRA

Another IDEA Working Group meeting will occur in February. The aim is to develop a method for evaluating the effectiveness of the QRA.

8) Human Health Research Projects

a) Epidemiology

i) Validation of Clinical Relevance Algorithm

The study is completed and the draft paper is in progress and should be completed by the end of the year.

b) Elicitation Threshold Study on Eugenol

Dr. Api reported that an updated report has been received. It is under review. It was noted that no induction of sensitization was observed in the negative control group with QRA2 levels. It was recommended that a conference call be organized with the study coordinator. A comparison with moderate/strong sensitizers (e.g. cinnamic aldehyde and isoeugenol) is needed.

9) Process and proposed policy Board Update

Dr. Api presented the results from the recent Board meeting on a policy update (see Attachment 4)

10) Introduction New Fragrance Materials After the 2016 Volume of Use Survey Procedure for member-generated safety assessments

Dr. Api presented the results from the final version of the procedures for new fragrance materials after the 2016 Volume of Use Survey for member-generated safety assessments (see Attachment 5)

11) Presentation by Creme Global on Tuesday May 23, 2017

Drs. Cian O'Mahony, John O'Brien and Cronan McNamara joined the Panel on Tuesday afternoon (May 23). Dr. O'Mahony gave a presentation on the RIFM Creme Aggregate Exposure Model (see Attachment 6). This was followed by a tour of the Creme Global offices.

12) IFRA Standards

13) Future Meeting Dates

- | | | |
|----------------------|-------------------|-----------------------|
| • Monday – Wednesday | Sept. 18-20, 2017 | Berlin |
| • Monday – Wednesday | Jan. 22-24, 2018 | Miami, FL |
| • Monday – Wednesday | May 21-23, 2018 | RIFM |
| • Monday – Wednesday | Sept. 17-19, 2018 | Europe – Paris, Rome? |
| • Monday – Wednesday | Jan. 28-30, 2019 | Miami, FL |
| • Monday – Wednesday | May 20-22, 2019 | Europe – Stockholm? |

Respectfully submitted,



Anne Marie Api, PhD
Science Fellow Human Health Sciences
(date finalized)

- Attachment 1: Presentation by webinar from J. Romine on the safety assessment process
- Attachment 2: Presentation by S. Theophilus - RIFM Safety Assessment Update and Metrics
- Attachment 3: Presentation by webinar by Jean-Pierre Lepoittevin PhD, January 24 9 AM Update: Development of HRMAS NMR spectroscopy in association with RHE to follow and characterize the metabolic transformation/activation of pro-haptens
- Attachment 4: Presentation by A. M. Api – Board policy update
- Attachment 5: Presentation by A. M. Api – Introduction New Fragrance Materials After the 2016 Volume of Use Survey Procedure for member-generated safety assessments
- Attachment 6: Presentation by C. O 'Mahony – Creme RIFM Aggregate Exposure Model