

EXPERT PANEL FOR FRAGRANCE SAFETY MEETING

Minutes

September 18-20, 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 Danielle Botelho Stephanie La Cava Aurelia Lapczynski Atish Patel Joseph Wahler	Jean-Pierre Lepoittevin (9/18 only) Hans Merk (09/18 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.

2) Minutes

The May 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) Presentation and Demonstration of Summary Table

S. La Cava demonstrated the use of the summary table distributed to the Panel with each batch. The Panel agreed with the modifications made and did not feel that a webinar was needed. In this meeting, the Panel will review 92 Safety Assessments covering 139 materials. These are divided into three batches.

General comments are as follows:

- Highlight only new data when using read across and new information – holds for genotoxicity and sensitization endpoints
- Discrepancies in molecular weights for materials and analogs should be resolved. There are two molecular weights - monoisotopic and average. The average molecular weight is more appropriate to use. Direct way is to start with molecular formula and calculate MW on the entire database.
- Mixture – use on a case by case basis. Define the material in commerce.

- BlueScreen™ Assay and cytotoxicity – it is not reasonable to dismiss effects due to cytotoxicity. Add text to clarify this. BlueScreen™ is a screening assay; delete the phrases “lower-tiered” and “higher tiered” from the template.
- Monitors at the meeting were a successful improvement; we should do this all the time.
- Having conference calls before the meeting to resolve comments was also a successful improvement.
- Need to work on building time/resources for staff to enter all the comments from the conference calls into the safety assessment before the Panel meeting packages get sent.
- Panel agreed that the Panel agenda book can be sent 1 week before the meeting.
- Moving the September 2018 meeting to the end of August will require an adjustment to the safety assessment timeline.

6) Review Safety Assessments Batch 1

CAS No.	Material Name	# of Materials	Tab	Status
Batch 1				
68527-77-5	2,4,6-Trimethyl-3-cyclohexene-1-methanol	1	Tab 11	<i>Approved</i>
67634-16-6 and 67634-17-7	3,5-Dimethylcyclohexene-1-methanol	2	Tab 12	<i>Approved</i>
15760-18-6	3-(4-Methyl-3-cyclohexenyl)butanol	1	Tab 13	<i>Approved</i>
2442-10-6	1-Octen-3-yl acetate	1	Tab 14	<i>Approved</i>
104-87-0, 529-20-4, 620-23-5, 1334-78-7	p-tolualdehyde	4	Tab 15	<i>Approved</i>
4748-78-1	4-ethylbenzaldehyde	1	Tab 16	<i>Approved with changes</i>
112-45-8	10-Undecenal	1	Tab 17	<i>Approved with changes</i>
39770-05-3	9-Decenal	1	Tab 18	<i>Approved with changes</i>
39770-04-2	8-Nonenal	1	Tab 19	<i>Approved with changes</i>
98-86-2	acetophenone	1	Tab 20	<i>Approved</i>
7764-50-3	2-methyl-5-(1-methylethenyl)cyclohexanone	1	Tab 21	<i>Approved</i>
108-11-2	4-Methyl-2-pentanol	1	Tab 22	<i>Approved</i>
108-82-7	2,6-Dimethyl-4-heptanol	1	Tab 23	<i>Approved</i>

CAS No.	Material Name	# of Materials	Tab	Status
70214-77-6	6,8-Dimethylnonan-2-ol	1	Tab 24	<i>Approved</i>
87118-95-4 , 862107-86-6 and 81787-06-6	3,4,5,6,6-Pentamethylheptan-2-ol	3	Tab 25	<i>Approved</i>
123-17-1	4-Nonanol, 2,6,8-trimethyl-	1	Tab 26	<i>Approved with changes</i>
1569-60-4	2-Methyl-2-hepten-6-ol	1	Tab 27	<i>Approved</i>
81782-77-6	4-Methyl-3-decen-5-ol	1	Tab 28	<i>Approved</i>
67845-50-5	4,8-Dimethyl-3-7-nonadien-2-ol	1	Tab 29	<i>Approved</i>
1335-09-7	Methylheptenol	1	Tab 30	<i>Approved with changes</i>
536-59-4	p-Mentha-1,8-dien-7-ol	1	Tab 31	<i>Approved with changes</i>
104864-90-6	2-Methyl-4-(2,2,3-trimethyl-3-cyclopenten-1-yl)-4-penten-1-ol	1	Tab 32	<i>Insufficient Data</i>
7070-15-7	exo-2-[(1,7,7-Trimethylbicyclo[2.2.1]hept-2-yl)oxy]ethanol	1	Tab 33	<i>Insufficient Data</i>
128119-70-0	1-Propanol, 2-methyl-3-[(1,7,7-trimethylbicyclo[2.2.1]hept-2-yl)oxy]-	1	Tab 34	<i>Insufficient Data</i>
143-28-2	(Z)-Octadec-9-enol	1	Tab 35	<i>Approved</i>
101-85-9	α -Amylcinnamyl alcohol	1	Tab 36	<i>Approved</i>
116-02-9 and 933-48-2	3,5,5-Trimethylcyclohexanol	2	Tab 37	<i>Approved with changes</i>
470-99-5	Isophorol	1	Tab 38	<i>Approved</i>
13380-89-7	Octahydro-4,7-methano-1H-indene-5-ol	1	Tab 39	<i>Approved</i>
79771-15-6	4,7-Methano-1H-inden-5-ol, 3a,4,5,6,7,7a-hexahydrodimethyl-	1	Tab 40	<i>Approved with changes</i>
77-53-2	Cedrol	1	Tab 41	<i>Approved with changes</i>
472-97-9 , 56747-96-7 and 4586-22-5	β -Caryophyllene alcohol	3	Tab 42	<i>Approved</i>
13419-69-7	trans-2-Hexenoic acid	1	Tab 43	<i>Approved</i>

CAS No.	Material Name	# of Materials	Tab	Status
459-80-3	Geranic acid	1	Tab 44	<i>Approved with changes</i>
80-59-1	2-Methyl-trans-2-butenoic acid	1	Tab 45	<i>Approved</i>
16957-70-3 and 3142-72-1	2-Methyl-2-pentenoic acid	2	Tab 46	<i>Approved</i>
3213-73-8	3,3,5-Trimethylcyclohexaneacetic acid	1	Tab 47	<i>Approved</i>
98-89-5	Cyclohexanecarboxylic acid	1	Tab 48	<i>Approved</i>

7) RIFM Safety Evaluation Process

a) Webinar Presentation by Mathias Kirchmer, BPM-D (Tab 49)

M. Kirchmer gave a presentation on the progress made on improvements to the process (see Attachment 01).

b) Presentation RIFM Safety Assessment Update and Metrics

Dr. Api presented the safety assessment update and metrics prepared by Dr. Romine (see Attachment 02).

c) Presentation on Safety Assessment Timing

Ms. LaCava provided the Panel with safety assessment timing. Moving the September meeting to the end of August will require an adjustment to the safety assessment timeline. The Panel agreed that the agenda books can be sent out one week before the meeting.

d) General Comments

i) Revised Abstract/Summary Template

Panel agreed to the modified template (see Attachment 03 - 51 revised)

ii) RIFM Guidelines for Sensitizers

Panel agreed with the Guidelines for sensitizers and the revised template for the summary section, human health safety assessment table for skin sensitization and Section X, 1.

8) Review Safety Assessments Batch 2

CAS No.	Material Name	# of Materials	Tab	Status
Batch 2				
120-51-4	Benzyl benzoate	1	Tab 53	<i>Approved with changes</i>
103-41-3	Benzyl cinnamate	1	Tab 54	<i>Approved</i>
6485-40-1, 99-49-0, 2244-16-8	d-Carvone	3	Tab 55	<i>Approved</i>
103-95-7	2-methyl-3-(p-isopropylphenyl)propionaldehyde	1	Tab 56	<i>Approved with changes</i>

CAS No.	Material Name	# of Materials	Tab	Status
103-50-4	Dibenzyl ether	1	Tab 57	Approved
86803-90-9	Methoxy dicyclopentadiene carboxaldehyde (Scentenal)	1	Tab 58	Approved with changes
5462-06-6	4-Methoxy- α -methylbenzenepropanal	1	Tab 59	Approved
6658-48-6	p-Isobutyl- α -methyl hydrocinnamaldehyde	1	Tab 60	Approved with changes
68922-13-4	3-Methyl-2-(pentyloxy)cyclopent-2-en-1-one	1	Tab 61	Approved
16251-77-7	3-Phenylbutanal	1	Tab 62	Approved
93-53-8	2-Phenylpropionaldehyde	1	Tab 63	Approved
22029-76-1 and 25312-34-9	β -Ionol	2	Tab 64	Approved
79-69-6, 54992-91-5, 79-70-9	α -Irone	3	Tab 65	Approved
67801-38-1	4-(2,4,6-Trimethyl-3-cyclohexen-1-yl)-3-buten-2-one	1	Tab 66	Approved
1335-46-2, 7779-30-8, 27-51-5, 127-43-5, 79-89-0, 127-42-4, 1335-94-0, 68555-94-2,	Methyl ionone (mixture of isomers)	8	Tab 67	Approved
31499-72-6, 17283-81-7, 13720-12-2	Dihydro- β -ionone	3	Tab 68	Approved with changes
23726-92-3, 23726-91-2, 35044-68-9	(Z)- β -1-(2,6,6-Trimethyl-1-cyclohexen-1-yl)-2-buten-1-one	3	Tab 69	Approved
57378-68-4, 71048-82-3, 35087-49-1	δ -1-(2,6,6-Trimethyl-3-cyclohexen-1-yl)-2-buten-1-one	3	Tab 70	Approved
39872-57-6, 33673-71-1, 70266-48-7	(E)-1-(2,4,4-Trimethyl-2-cyclohexen-1-yl)-2-buten-1-one	3	Tab 71	Approved
43052-87-5, 23726-94-5, 24720-09-0	α -1-(2,6,6-Trimethyl-2-cyclohexen-1-yl)-2-buten-1-one	3	Tab 72	Approved

9) Presentation on Skin P450 Research by Hans Merk & Lepoittevin, Update & proposal

Professors Merk and Lepoittevin joined the meeting on Monday September 18 for a presentation on the skin P450 Research project supported by RIFM and carried out by Prof. Merk with analytical work

conducted by Prof. Lepoittevin. Prof. Merk made a presentation for an additional project for consideration (See Attachment 04).

10) Presentation on Coumarin by A. Patel

Dr. Patel gave a presentation on coumarin (see Attachment 05 and 06). The Panel reviewed the safety assessment where all the data are summarized and several review papers were also provided for their review.

In principle, the Panel agreed with the conclusions of the Felter et al., 2006 paper. It was agreed that based on a weight of evidence, the No Observed Adverse Effect Level (NOAEL) is 16 mg/kg/day. For the reference dose, they requested a margin exposure of 100 be used, thus the reference dose is 0.16 mg/kg/day that the safety assessment be drafted with the appropriate scientific rationale.

11) Update on QRA2 Implementation

a) A.M Api Presentation on QRA2

Dr. Api gave a presentation on the implementation of QRA2 and systemic toxicity for materials that require risk management measures. This will result in some modifications of the safety assessment for materials that will require risk management. These were reviewed and agreed upon by the Panel.

12) Review Safety Assessments – Batch 3

CAS No.	Material Name	# of Materials	Tab	Status
Batch 3				
23696-85-7, 23726-93-4, 59739-63-8	1-(2,6,6-Trimethylcyclohexa-1,3-dienyl)-2-buten-1-one	3	Tab 79	Approved with changes
4826-62-4, 20407-84-5	2-Dodecenal	2	Tab 80	Approved with changes
3913-71-1, 3913-81-3	2-Decenal	2	Tab 81	Approved with changes
2548-87-0, 2363-89-5	trans-2-Octenal	2	Tab 82	Approved with changes
18829-56-6, 2463-53-8, 60784-31-8	2-Nonenal	3	Tab 83	Approved with changes
1337-83-3, 2463-77-6, 53448-07-0	Undecenal	3	Tab 84	Approved with changes
7774-82-5, 7069-41-2	2-Tridecenal	2	Tab 85	Approved with changes
557-48-2	Nona-2-trans-6-cis-dienal	1	Tab 86	Approved with changes
1335-66-6, 1423-46-7, 67634-07-5	Isocyclocitral	3	Tab 87	Approved

CAS No.	Material Name	# of Materials	Tab	Status
100-52-7	Benzaldehyde	1	Tab 88	Approved with changes
122-03-2	Cuminaldehyde	1	Tab 89	Approved
40654-82-8	Methyl-4-phenylbutyraldehyde	1	Tab 90	Approved with changes
55066-49-4	beta-methyl-benzenepentanal	1	Tab 91	Approved
122-78-1	phenylacetaldehyde	1	Tab 92	Approved
104-53-0	3-phenylpropionaldehyde	1	Tab 93	Approved
104-09-6	p-tolylacetaldehyde	1	Tab 94	Approved
68844-97-3	Benzeneacetaldehyde, 3,4-dimethyl-	1	Tab 95	Approved
4395-92-0	p-Isopropyl phenylacetaldehyde	1	Tab 96	Approved
7775-00-0	3-(p-Isopropylphenyl)propionaldehyde	1	Tab 97	Approved with changes
41496-43-9	2-Methyl-3-tolylpropionaldehyde	1	Tab 98	Approved
67634-15-5, 67634-14-4	3-(o-Ethylphenyl)-2,2-dimethylpropionaldehyde	2	Tab 99	Approved with changes
300371-33-9	2,3-Dihydro-1,1-dimethyl-1H-indene-ar-propanal	1	Tab 100	Approved with changes
99-75-2	Methyl p-methylbenzoate	1	Tab 101	Insufficient Data
93-58-3	Methyl benzoate	1	Tab 102	Approved with changes
93-89-0	Ethyl benzoate	1	Tab 103	Approved with changes
136-60-7	Butyl benzoate	1	Tab 104	Approved with changes
2049-96-9	Pentyl benzoate	1	Tab 105	Approved with changes
6789-88-4	Hexyl benzoate	1	Tab 106	Approved with changes
120-50-3	Isobutyl benzoate	1	Tab 107	Approved with changes

CAS No.	Material Name	# of Materials	Tab	Status
101-41-7	Methyl phenylacetate	1	Tab 108	Approved with changes
101-97-3	Ethyl phenylacetate	1	Tab 109	Approved with changes
5137-52-0	Pentyl phenylacetate	1	Tab 110	Approved with changes
122-43-0	butyl phenylacetate	1	Tab 111	Approved with changes
122-99-6	2-Phenoxyethanol	1	Tab 112	Approved with changes

13) Human Health Research Projects

a) Epidemiology

Prof. Bruze reported that the manuscript on the study of the validation of clinical relevance algorithm from the EDEN study is still being drafted.

b) Elicitation Threshold Study on Eugenol

Dr. Api reported that Prof. Diepgen was asked to revise the draft report and provide all the raw data in the report.

14) Presentation by A. Lapczynski – Environmental Research Project

Ms. Lapczynski gave an update on the bioaccumulation research project (see Attachment 07).

15) Presentation by D. Botelho – Respiratory Research Projects

Dr. Botelho gave an update on the respiratory research projects (see Attachment 08). A

16) Presentation by T. Schultz – Naturals Complex Substances – Chemistry Blocks

Dr. Schultz gave an introductory presentation on conducting safety assessments on natural complex substances. This process is still being developed and more information will be reviewed by the Panel in the future (see Attachment 09)

17) Presentation RIFM TTC Research by D. Botelho and A. Patel

Drs. Patel and Botelho gave presentations on the RIFM oral and respiratory TTC research projects, respectively (see Attachment 10 and 11). The goal is to have manuscripts available in early 2018.

18) Future Meeting Dates

- Monday – Wednesday Jan. 22-24, 2018 Miami, FL
- Monday – Wednesday May 21-23, 2018 New Jersey
- 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

Respectfully submitted,



Anne Marie Api, PhD
Vice President, Human Health Sciences
(January 22, 2018)

Attachment 1:	M. Kirchmer presentation on the progress made on improvements to the process
Attachment 2:	Presentation on the safety assessment update and metrics prepared by Dr. Romine
Attachment 3:	Modified template for the summary section
Attachment 4:	Presentation on Skin P450 Research by Profs. Hans Merk & Lepoittevin, Update & proposal
Attachments 5 & 6:	Presentation on Coumarin by Dr. A. Patel
Attachment 7:	Presentation by Ms. Lapczynski the bioaccumulation research project
Attachment 8:	Presentation by Dr. D. Botelho on the respiratory research projects
Attachment 9:	Presentation by Dr. T. Schultz on Naturals Complex Substances – Chemistry Blocks
Attachment 10:	Presentation by Dr. A. Patel on the oral TTC research project
Attachment 11:	Presentation by Dr. D. Botelho on the respiratory TTC research project