

EXPERT PANEL FOR FRAGRANCE SAFETY MEETING

Minutes Virtual Meeting

May 18-20, 2020

EXPERT PANEL MEMBERS	RIFM STAFF	
Donald Belsito (Chair) Magnus Bruze G. Allen Burton, Jr. Jochen Buschmann Maria Dagli 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 Leah Jones (5/18) Kaushal Joshi Manoj Kumar Maura Lavelle	Aurelia Lapczynski Isabelle Lee Holger Moustakas Mihwa Na Gretchen Ritacco Jim Romine Dan Selechnik Faiz Siddiqi (5/18) Gary Sullivan (5/18) Yax Thakkar

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 electronically.

Dr. Api introduced three new RIFM staff members: Dr. Manoj Kumar, a computational chemist and two post-doctoral fellows to the RIFM Staff – Drs. Isabelle Bell and Holger Moustakas.

2) Minutes

The minutes from the January 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) COVID-19 pandemic impact on RIFM

Dr. Romine provided an overview on the COVID-19 pandemic to RIFM. The staff has been working from home since March 12, 2020 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.

- i) COVID-19 pandemic impact on the safety assessment program – Dr. Botelho gave a presentation on the impact of the COVID-19 pandemic impact on the safety assessment program (see Attachment 1). While RIFM will meet the 2020 goals, the NCS program will be take an additional year to complete because of delays in testing. Dr. Botelho also provided an update on the safety assessment update and metrics.
- ii) COVID-19 pandemic impact on the research program – Dr. Api gave a presentation on the impact of COVID-19 pandemic impact on the RIFM research program (see Attachment 2). While some projects had to be deferred to 2021, most of the projects continue and manuscripts are being developed in all areas.

b) RIFM Communication update

Mr. Gary Sullivan provided an update on the RIFM Communication Plan (see Attachment 3).

6) Tobey Marzouk Presentation

Mr. Tobey Marzouk gave a presentation to the Expert Panel addressing several topics they wished to discuss (see Attachment 4).

7) Presentation by Prof. Wolfgang Dekant

Prof. Dekant gave a presentation titled “Approaches to human health risk assessment for chemical mixtures” (see Attachment 5).

8)

a) Presentation RIFM Safety Assessment Publications

Ms. Leah Jones and Mr. Faiz Siddiqi gave a presentation that reviewed the overall status of the safety assessment submission and publication to Food and Chemical Toxicology (see Attachment 6).

b) Safety Assessment Overview

The Panel reviewed 75 Total Safety Assessments including 86 Total materials.

c) General Comments:

- i) For 95% exposure values in the DST tables, concentrations will be expressed as $\geq 0.00xy\%$ and any number smaller than that are written in scientific notations (e.g. $9.5 \times 10^{-4}\%$).
- ii) Data on isomer unspecified lactic acid (CAS 50-21-5) was treated as target data for L-lactic acid (CAS 79-33-4). The unspecified material is considered a functional. RIFM need to determine if L-lactic is not also a functional. The unspecified and specific isomer are expected to have the same toxicity and the clarification should be made in the write up
- iii) When applying the DST and the parent material has no predicted alerts, but the metabolites have alerts, whether a reactive or non-reactive DST is applied must be made on a case by case basis with advice from the chemistry team and Panel members.

- iv) When weight of evidence is used to support a fragrance material with data from another material, the justification will appear in the read across section in a separate table.

9) Update on RIFM Maximum Acceptable Concentrations Implementation

Dr. Api detailed the process that was established at RIFM to calculate and document calculation of maximum acceptable concentrations. The procedure has significantly improved with the elimination of potential human error as much as possible.

10) Natural Complex Substances (NCSs) Safety Assessments

- a) Review general approach

The general approach that will be used to conduct a safety assessment on NCSs was reviewed by the Panel. A first draft of the criteria document for NCSs was distributed and the Panel provided some initial comments. After the comments have been addressed, the next draft will be uploaded to OneDrive for the Panel to review.

- i) **Presentation by M. Date on the NCS clustering approach** (see Attachment 7).
- ii) **Presentation by Y. Thakkar on the approach to NCSs for the genotoxicity endpoint** (see Attachment 8).

- b) Safety Assessment Review

The Panel reviewed the safety assessments for three NCSs and some general comments were made.

- i) Each section should have a summary statement
- ii) In the skin sensitization tables, add that the exposure was derived by Creme RIFM Aggregate Exposure Model in footnote b
- iii) Rewrite the sentence in the disclaimer about chemical components that will be evaluated >0.1% and <1%
- iv) In the skin sensitization tables, provide the highest concentration component and the strongest sensitizer if they are not the same
- v) In the skin sensitization tables, include the name of the component along with the CAS Number

The following drafts were evaluated by the Panel. The Panel requested that updated drafts are provided at the next meeting after the recommended changes are made to the draft safety assessments.

- i) 1042479 Petitgrain oil Terpeneless, Paraguay
- ii) 1043739 Petitgrain oil terpenes, Paraguay
- iii) 1046350 Petitgrain oil, Paraguay

11) Review Safety Assessments Batch 1

CAS	Name	Tab	Status
1618-26-4	bis-(Methylthio)methane	Tab 21	Approved with changes
156679-39-9; 156324-78-6	Carbonic acid, 2-hydroxyethyl 5-methyl-2-(1-methylethyl)cyclohexyl ester	Tab 22	Approved
260781-16-6; 156324-82-2	Carbonic acid, 2-hydroxypropyl (1R,2S,5R)-5-methyl-2-(1-methylethyl) cyclohexyl ester	Tab 23	Approved
2179-57-9	Allyl disulfide	Tab 24	Approved with changes

CAS	Name	Tab	Status
3390-12-30	Acetaldehyde cyclic propylene glycol acetal	Tab 25	Approved with changes
68133-76-6	3-Hexenyl 2-oxopropionate	Tab 26	Approved with changes
3943-74-6	Methyl vanillate	Tab 27	Approved with changes
53834-70-1; 20053-88-7	(e)-3,7-dimethylocta-1,5,7-trien-3-ol;(5e)-3,7-dimethylocta-1,5,7-trien-3-ol;1305;1,5,7-octatrien-3-ol, 3,7-dimethyl-, (5e)-	Tab 28	Approved with changes
70851-61-5	5-(cis-3-Hexenyl)dihydro-5-methyl-2(3H)furanone	Tab 29	Approved with changes
63095-33-0	(Z)-5-(3-Hexenyl)dihydrofuran-2(3H)-one	Tab 30	Approved with changes
97384-48-0	2-Benzyl-2-methylbut-3-enenitrile	Tab 31	Approved
75975-83-6	Caryophyllene acetylated	Tab 32	Approved
67633-96-9	cis-3-Hexenyl methyl carbonate	Tab 33	Approved
83-34-1	Skatole	Tab 34	Insufficient Data - genotoxicity
1125-21-9	2,6,6-Trimethylcyclohex-2-ene-1,4-dione	Tab 35	Approved with changes
91-61-2	p-Methyltetrahydroquinoline	Tab 36	Insufficient Data - genotoxicity
123-07-9	p-Ethylphenol	Tab 37	Approved with changes
16491-24-0	2,4-Hexadienyl isobutyrate	Tab 38	Approved with changes
4219-24-3; 1775-43-5; 1577-18-0	3-Hexenoic acid; cis-3-Hexenoic acid; 3-Hexenoic acid, (3E)-	Tab 39	Approved with changes
72881-27-7	5- and 6-Decenoic acid	Tab 40	Approved with changes
102-60-3	2-Propanol, 1,1',1',1'-(1,2-ethanediyldinitrilo)tetrakis-	Tab 41	Approved
136954-25-1	3-Acetylmercaptohexyl acetate	Tab 42	Approved
156472-94-5	(+/-) Ethyl 3-mercaptoputyrate	Tab 43	Approved with changes
888021-82-7	(+/-)-Ethyl 3-mercapto-2-methylbutanoate	Tab 44	Approved with changes
1576-78-9	cis-3-Heptenyl acetate	Tab 45	Approved
13049-88-2	cis-3-Nonenyl acetate	Tab 46	Approved
1670-47-9	cyclohexanone diethyl ketal	Tab 47	Approved with changes
7785-64-0; 7785-66-2	Butyl 2-methylcrotonate (Z); Butyl 2-methylcrotonate	Tab 48	Approved with changes
16930-96-4	Hexyl tiglate	Tab 49	Approved with changes
97-64-3; 687-47-8	Ethyl lactate; Ethyl (L)-lactate	Tab 50	Approved

CAS	Name	Tab	Status
20279-51-0	Hexyl 2-hydroxypropionate	Tab 51	Approved
258823-39-1	(+/-)2-Mercapto-2-methylpentan-1-ol	Tab 52	Approved with changes

12) Review Safety Assessments Batch 2

CAS	Name	Tab	Status
90-42-6	2-Cyclohexylcyclohexanone	Tab 53	Approved with changes
86-26-0	o-Phenyl anisole	Tab 54	Approved with changes
76917-23-2; 56767-18-1	2,6-Octadienal, (2E,6Z)-	Tab 55	Approved
21662-22-6	2,7-Nonadienal, (2E,7Z)	Tab 56	Approved
52711-52-1	2,7-Decadienal, (2E,7Z)-	Tab 57	Approved
21662-13-5	2-trans-6-cis-Dodecadialenal	Tab 58	Approved
78-84-2	Isobutyraldehyde	Tab 59	Approved with changes
96-17-3	2-Methylbutyraldehyde	Tab 60	Approved with changes
590-86-3	3-Methylbutyraldehyde	Tab 61	Approved with changes
67859-96-5	3,3,5-Trimethylcyclohexyl acetate	Tab 62	Approved
79-33-4	L-Lactic acid (2-hydroxy propionic acid)	Tab 63	Approved
1195-92-2; 203719-53-3	d-8-p-Menthene-1,2-epoxide	Tab 64	Approved with changes
489-84-9	7-Isopropyl-1,4-dimethylazulene	Tab 65	Approved with changes
3387-41-5	Sabinene	Tab 66	Approved with changes
144761-91-1	Benzoic acid, 2-[(1-hydroxy-3-phenylbutyl)amino], methyl ester	Tab 67	Approved
101-81-5	Diphenylmethane	Tab 68	Approved with changes
108766-16-1	l-Menthyl (R,S)-3-hydroxybutyrate	Tab 69	Approved
505-10-2	3-(Methylthio)propanol	Tab 70	Approved
25905-14-0	Lavandulyl acetate	Tab 71	Approved with changes

13) Safety assessment on 108-95-2 Phenol

Dr. Gadhia gave a presentation on the safety assessment on phenol (see Attachment 9). The safety assessment was approved with changes.

14) Review Safety Assessments Batch 3

CAS	Name	Tab	Status
112-63-0	Methyl linoleate	Tab 72	Approved with changes
301-00-8	Methyl linoleate (48%) methyl linolenate (52%) mixture	Tab 73	Approved with changes
544-35-4	Ethyl linoleate	Tab 74	Approved with changes
198404-98-7	Cyclopropanemethanol, 1-methyl-2-[(1,2,2-trimethylbicyclo[3.1.0]hex-3-yl)methyl]-	Tab 75	Approved with changes
108-39-4	m-Cresol	Tab 76	Approved with changes
1120363-98-5	(+/-)-5-Isopropyl-2,6-diethyl-2-methyltetrahydro-2H-pyran	Tab 77	Approved with changes
1181244-95-0	Cyclopropanemethanol, 1-methyl-2-[[[(1R,3R)-2,2,3-trimethylcyclopentyl]methyl]-, (1R,2R)-	Tab 78	Approved with changes
1801275-25-1	2,7-Decadienenitrile	Tab 79	Approved
1801275-26-2	2,7-Decadienenitrile, (2E,7Z)-	Tab 80	Approved
1958026-97-5	2,10-Tetradecadienenitrile, (2E,10Z)-	Tab 81	Approved
1891-67-4	2,?6-?Octadienal, 3,?6,?7-?trimethyl-	Tab 82	Approved
74-93-1	Methyl mercaptan	Tab 83	Approved with changes
68555-58-8	3-Methyl-2-butenyl salicylate	Tab 84	Approved
103-93-5	p-Tolyl isobutyrate	Tab 85	Approved with changes
18368-91-7; 67952-68-5; 137255-07-3	2-Ethyl-1,3,3-trimethyl-2-norbornanol; Ethyl-1,3,3-trimethylbicyclo[2.2.1]heptan-2-ol	Tab 86	Approved with changes
2396-85-2	Methyl trans-2-octenoate	Tab 87	Approved with changes
51100-54-0	1-decen-3-ol	Tab 88	Approved with changes
53399-81-8	Ethyl 2-methyl-4-pentenoate	Tab 89	Approved with changes
626-93-7	2-Hexanol	Tab 90	Approved
589-98-0	3-Octanol	Tab 91	Approved
628-99-9	2-Nonanol	Tab 92	Approved
1653-30-1	2-Undecanol	Tab 93	Approved
33079-56-0	1,2-Cyclopentanedione, 3,4,4-trimethyl-	Tab 94	Approved with changes

15) RIFM Research Projects

a) Overview on research programs

Dr. Api postponed her overview of research programs until the next meeting. Attached is the presentation for information (see Attachment 10).

b) Epidemiology

Prof. Bruze was very sad to inform the Panel that Prof. Thomas Diepgen had passed away on March 27, 2020 in Heidelberg succumbing to a chronic disease that he had endured bravely. There were no further updates on the epidemiology project.

c) Eugenol Threshold Study

Prof. Bruze reported that Dr. Robert Ofenloch (Research Associate | post-doctoral fellow at University Hospital Heidelberg) is interested in 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.

d) Presentation by Y. Thakkar And H. Moustakas

Mr. Y. Thakkar and Dr. H. Moustakas gave presentations on the genotoxicity research projects (see Attachments 11 and 12).

e) Presentation by M. Na

Dr. Na gave a presentation on the on skin sensitization research projects (see Attachment 13).

f) Presentation by A. Lapczynski on the environmental research projects

Ms. Lapczynski gave a presentation on the on environmental research projects (see Attachment 14).

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

This presentation was deferred to the September 2020 meeting.

h) Outline of second read across paper

An outline is being developed and will be shared with the Panel before the next meeting.

i) Presentation by K. Joshi on reproduction research program

This presentation was deferred to the September 2020 meeting.

j) Presentation by G. Ritacco on photosensitization research projects

This presentation was deferred to the September 2020 meeting.

k) Respiratory research program

This presentation was deferred to the September 2020 meeting.

16) Expert Panel Operating Procedures

a) Elect Chair/Vice-Chair

Dr. Dagli was voted in as Vice-Chair of the Panel.

17) Expert Panel Executive Session

The Expert Panel held an executive session.

18) Future Meeting Dates

• Monday – Wednesday	Sept. 20-23, 2020	Virtual Meeting
• Wednesday – Friday	Jan. 20-22, 2021	Puerto Rico
• Monday – Wednesday	May 30-June 2, 2021	Lisbon
• Monday – Wednesday	Sept. 20-22, 2021	New Jersey
• Monday-Wednesday	Jan. 24-26, 2022	Miami

Respectfully submitted,

Anne Marie Api

Anne Marie Api, PhD
Vice President

Attachment 1:	Presentation: Dr. Danielle Botelho
Attachment 2	Presentation: Dr. Anne Marie Api
Attachment 3:	Presentation: Mr. Gary Sullivan
Attachment 4:	Presentation: Mr. Tobey Marzouk
Attachment 5:	Presentation: Dr. Wolfgang Dekant
Attachment 6:	Presentation: Ms. Leah Jones and Mr. Faiz Siddiqi
Attachment 7:	Presentation: Dr. Mihir Date
Attachment 8:	Presentation: Mr. Y. Thakkar
Attachment 9:	Presentation: Dr. Sanket Gadhia
Attachment 10:	Presentation: Dr. Anne Marie Api
Attachment 11:	Presentation: Mr. Y. Thakkar
Attachment 12:	Presentation: Dr. H. Moustakas
Attachment 13:	Presentation: Dr. Mihwa Na
Attachment 14:	Presentation: Ms. Aurelia Lapczynski