EXPERT PANEL FOR FRAGRANCE SAFETY MEETING

FINAL Minutes

September 23-25, 2019

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) Yoshiki Tokura	Anne Marie Api Shannen Biserta Danielle Botelho Mihir Date Chaitra Deodhar Sanket Gadhia Leah Jones (9/23) Kaushal Joshi Aurelia Lapczynski Maura Lavelle	Mihwa Na Dan Selechnik Gretchen Ritacco Jim Romine (9/24-25) Francisco Rodriguez Ropero Nikaeta Sadekar Faiz Siddiqi (9/23) Gary Sullivan (9/23) Yax Thakkar	Frank Gerberick (Webinar 9/24) Tobey Marzouk (9/25) Shawn Blythe (9/25) James McKim (9/25) Christopher Borgert (9/23)

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. Dr. Api announced the departure of Devin O'Brien and Sai Yee Tsang. New RIFM staff members were introduced and welcomed to the Panel meeting.

2) Minutes

The minutes from the May 2019 meeting were approved.

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) **Mr. Gary Sullivan Presentation Update to safety assessment publication**

Mr. Sullivan gave a presentation on the progress made with publishing safety assessments and provided an update on the RIFM communications strategy and plan (see Attachment 1).

6) Dr. Christopher J. Borgert, President & Principal Scientist, Applied Pharmacology and Toxicology, Inc. Presentation on Endocrine Disruptors (Monday September 23)

Dr. Borgert gave a presentation on the science of endocrine disruptors (see Attachment 2).

7) RIFM Safety Evaluation Process

a) **Presentation RIFM Safety Assessment Update and Metrics**

Dr. Botelho provided an update on the safety assessment program (see Attachment 3).

b) Update on Low Exposure Materials manuscript

Dr. Api provided an update on the low exposure manuscript. It is finalized and will be submitted for publication this month.

c) Safety Assessment Overview

During the Panel meeting a total of 98 Safety Assessments including 117 fragrance materials were reviewed.

d) General Comments

i) **Presentation by S. Gadhia on comparison of dermal absorption**

Dr. Gadhia gave a presentation comparing dermal absorption in rats and humans (see Attachment 4). The Panel recommended in vitro rat skin absorption studies for geraniol and hexyl cinnamic aldehyde. The Panel suggested the clusters be reviewed for additional skin absorption data. There was no objection to pursuing development of a model to predict rat skin absorption, but there may only be enough data to provide dermal absorption ranges.

e) Geraniol & Nerol Updated Assessments

i) Geraniol CAS 106-24-1 - Approved with Changes

ii) Nerol CAS 106-25-2 - Approved with Changes

(1) Geraniol and Nerol Read Across - Approved with Changes

(a) Geranyl acetate, CAS 105-87-3

(b) dl-Citronellol, CAS 106-22-9

(c) Phytol, CAS 150-86-7

(d) 2,6,10-Trimethylundeca-5,9-dienol, CAS 24048-14-4

(e) Farnesol, CAS 4602-84-0

(f) Geranyl crotonate, CAS 56172-46-4

(g) Geranyl tiglate, CAS 7785-33-3

8) NCS Safety Assessments

a) Review general approach

Dr. Botelho gave an overview presentation on the general approach to safety assessments on natural complex substances. This was followed by presentations from endpoint toxicologists – Y. Thakkar (genotoxicity), G. Ritacco (phototoxicity), M. Na (sensitization), S. Gadhia (repeat dose and reproduction), N. Sadekar (respiratory), A. Lapczynski (environmental) and M. Date (computational chemistry) (see Attachment 5). The first drafts on 3 safety assessments were previewed - Petitgrain oil Terpeneless, Paraguay, Petitgrain oil terpenes, Paraguay, Petitgrain oil, Paraguay.

b) General proposals for NCS Safety Assessments

- Appropriate sections using sample information instead of the matrix data will state so in their section. It has been agreed upon with the fragrance industry members present at the 2018 NCS Workshop that so long as the sample is 80% similar, then it is sufficiently similar to the matrix data.

- Dr. Api will be submitting a draft proposal to Elsevier for feedback post-September Expert Panel meeting
- RIFM will always prioritize testing the whole oil, and will only test NCSs with a RIFM ID.
- The environmental endpoint will always need to evaluate NCSs on a component basis. It was agreed that for components without a RIFM ID that will need testing for this endpoint, a sample will be acquired from a trusted vendor; however, search for available open-source data will be conducted first.
- The same level of study detail as the other components will be required.
- Once you get to the component level, they will be treated as discrete materials, and use the same read-across rules as previously applied by the Panel.

9) Review Safety Assessments Batch 1

CAS	Name	Tab	Status
33885-52-8	alpha,alpha,6,6-Tetramethylbicyclo[3.1.1]hept-2-ene-2-propionaldehyde	Tab 30	Approved
1193-81-3	1-Cyclohexylethanol	Tab 31	Approved
10528-67-3	alpha-methyl-cyclohexanepropanol	Tab 32	Approved
79771-15-6; 94248-21-2	4,7-Methano-1H-inden-5-ol, 3a,4,5,6,7,7a-hexahydrodimethyl-	Tab 33	Approved
61444-38-0	cis-3-Hexenyl cis-3-hexenoate	Tab 34	Approved
68922-14-5; 108419-35-8; 84712-50-5	1-Nonanol, 2,4,6,8-tetramethyl-,acetate	Tab 35	Approved
104468-21-6	2,2-Dimethyl-3-methyl-3-butenyl propanoate	Tab 36	Approved
15848-49-4	2-Cyclopentene-1-acetic acid, ethyl ester	Tab 37	Approved
607-88-5	p-Cresyl salicylate	Tab 38	Approved
627-93-0	Dimethyl adipate	Tab 39	Approved
104986-28-9	Hexanoic acid, 6-(acetyloxy)-, ethyl ester	Tab 40	Approved
1984-60-7	2-Hydroxyethyl phenoxyacetate	Tab 41	Approved
774-55-0	1-(5,6,7,8-tetrahydro-2-naphthalenyl)ethanone	Tab 42	Approved
68259-33-6	1-[5(Or 6)-Methyl-7(or 8)-(1-methylethyl)bicyclo[2.2.2]oct-5-en-2-yl]ethan-1-one	Tab 43	Approved
14576-08-0	4-(1-Methoxy-1-methylethyl)-1-methylcyclohexene	Tab 44	Insufficient Data – REP/DART needs SABS
69103-20-4	2,2-Dimethyl-3-(3-methyl-2,4-pentadienyl)oxirane	Tab 45	Approved
131766-73-9	Tetrahydro-4-methyl-2-propyl-2H-pyran-4-yl acetate	Tab 46	Approved

CAS	Name	Tab	Status
68480-11-5	Decahydrospiro[furan-2(3H),5'-[4,7]methano[5H]indene]	Tab 47	Approved
22457-23-4	5-Methyl-3-heptanone oxime	Tab 48	Approved with changes
996-97-4	N,N-Diethyloctamide	Tab 49	Approved with Changes potential Insufficient Data – sensitization
852379-28-3	N-p-Benzeneacetonitrilementhanecarboxamide	Tab 50	Approved
1374760-95-8	2-(4-Methylphenoxy)-N-(1H-pyrazol-3-yl)-N-(thiophen-2-ylmethyl)acetamide	Tab 51	Approved
107-85-7	Isopentylamine	Tab 52	Approved
98-52-2; 21862-63-5	4-tert-Butylcyclohexanol	Tab 53	Approved
68133-79-9	2-(3,7-Dimethyl-2,6-octadienyl)cyclopentanone	Tab 54	Approved
5320-75-2	Cinnamyl benzoate	Tab 55	Approved
2444-46-4	Nonanoyl 4-hydroxy-3-methoxybenzylamide	Tab 56	Insufficeint data – sensitization; functional ingredient?
67634-25-7; 67634-26-8	3,5-Dimethylcyclohex-3-ene-1-methyl acetate	Tab 57	Approved
142-62-1	Hexanoic acid	Tab 58	Approved
124-07-2	Octanoic acid	Tab 59	Approved
112-05-0	Nonanoic acid	Tab 60	Approved
334-48-5	Decanoic acid	Tab 61	Approved
143-07-7	Lauric acid	Tab 62	Approved
57576-09-7	Isopulegyl acetate	Tab 63	Approved
20777-49-5	Dihydrocarvyl acetate	Tab 64	Approved
19089-92-0	n-Hexyl 2-butenoate	Tab 65	Approved
7392-19-0; 13837-56-4	2,2,6-Trimethyl-6-vinyltetrahydropyran	Tab 66	Approved

10) Review Safety Assessments Batch 2

CAS	Name	Tab	Status
21722-83-8	Cyclohexaneethyl acetate	Tab 67	Approved
67634-22-4	2,4-Dimethylcyclohexylmethyl acetate	Tab 68	Approved
236391-76-7	Acetic acid, (1-oxopropoxy)-, 1-(3,3-dimethylcyclohexyl)ethyl ester	Tab 69	Approved

CAS	Name	Tab	Status
5533-03-9	Methyl vanillyl ether	Tab 70	Approved
13184-86-6	Vanillyl ethyl ether	Tab 71	Approved
82654-98-6	Vanillyl butyl ether	Tab 72	Approved
1815-99-2	pyridine, 4-decyl-	Tab 73	Approved
72403-67-9	Myraldyl acetate	Tab 74	Approved
68683-20-5	Menthadiene-7-methyl formate	Tab 75	Insufficient data – photoallergy
1330-20-7	Xylene (mixed)	Tab 76	Insufficient data - Sensitization
99-87-6	p-Cymene	Tab 77	Insufficient data - Sensitization
98-51-1	4-tert-Butyltoluene	Tab 78	Insufficient data - Sensitization
97-42-7; 1205-42-1	Carvyl acetate	Tab 79	Approved
6728-26-3; 16635-54-4; 505-57-7	trans-2-Hexenal	Tab 80	Insufficient data - Sensitization
119-84-6	Dihydrocoumarin	Tab 81	Insufficient data - Sensitization
7780-06-5	Isopropyl cinnamate	Tab 82	Approved
4674-50-4	Nootkatone	Tab 83	Approved with changes
1049017-63-1; 1049017-68-6	3-Cyclohexene-1-carboxaldehyde, 1-ethenyl-	Tab 84	Approved
10138-32-6	(±)-Bicyclo[2.2.1]hept-5-ene-2-carboxylic acid, ethyl ester	Tab 85	Approved
194934-66-2	6,10-Dodecadienal, 3,7,11-trimethyl-, (3S,6E)-	Tab 86	Approved
2120-70-9	Phenoxyacetaldehyde	Tab 87	Approved
111-84-2	Nonane	Tab 88	Approved
124-18-5	Decane	Tab 89	Approved
1120-21-4	Undecane	Tab 90	Approved
112-40-3	Dodecane	Tab 91	Approved
71078-31-4	1-Oxaspiro[4.5]deca-3,6-diene, 2,6,9,10-tetramethyl-	Tab 92	Approved
79893-63-3	1-Oxaspiro[4.5]deca-3,6-diene, 6-ethyl-2,10,10-trimethyl-	Tab 93	Approved
89079-92-5	1-Oxaspiro[4.5]deca-3,6-diene, 2,7-dimethyl-10-(1-methylethyl)-	Tab 94	Approved
109-94-4	Ethyl formate	Tab 95	Approved
141-78-6	Ethyl acetate	Tab 96	Approved with changes

CAS	Name	Tab	Status
623-42-7	Methyl butyrate	Tab 97	Approved with changes
105-37-3	Ethyl propionate	Tab 98	Approved with changes
109-60-4	Propyl acetate	Tab 99	Approved with changes
624-24-8	Methyl valerate	Tab 100	Approved with changes
105-54-4	Ethyl butyrate	Tab 101	Approved with changes
106-36-5	Propyl propionate	Tab 102	Approved
123-86-4	Butyl acetate	Tab 103	Approved
539-82-2	Ethyl valerate	Tab 104	Approved with changes
105-66-8	Propyl butyrate	Tab 105	Approved with changes
628-63-7	Pentyl acetate	Tab 106	Approved
109-21-7	Butyl butyrate	Tab 107	Approved
540-18-1	Amyl butyrate	Tab 108	Approved
2173-56-0	Amyl valerate	Tab 109	Approved
1365-19-1; 60047-17-8	Linalool oxide	Tab 110	Approved
60763-41-9	alpha-Amyl cinnamic aldehyde diethyl acetal	Tab 111	Approved
91-87-2	alpha-Amylcinnamaldehyde dimethyl acetal	Tab 112	Approved
2349-07-7	Hexyl isobutyrate	Tab 113	Approved
10032-15-2	Hexyl 2-methylbutyrate	Tab 114	Approved
10032-13-0	Hexyl isovalerate	Tab 115	Approved
109-15-9	Octyl isobutyrate	Tab 116	Approved
7786-58-5	Octyl isovalerate	Tab 117	Approved
14436-32-9	9-Decenoic acid	Tab 118	Approved
112-38-9	10-Undecenoic acid	Tab 119	Approved
10458-14-7; 1074-95-9; 1196-31-2; 14073-97-3; 491-07-6; 89-80-5	Menthone	Tab 120	Approved
499-70-7; 59471-80-6	p-Menthan-2-one	Tab 121	Approved
1078-95-1	Pinocarvyl acetate	Tab 122	Approved

CAS	Name	Tab	Status
60335-71-9; 60335-74-2	3,6-Dihydro-4-methyl-2-phenyl-2H-pyran	Tab 123	Approved
1197-01-9	p-alpha,alpha-Trimethylbenzyl alcohol	Tab 124	Approved
1759-28-0	4-Methyl-5-vinylthiazole	Tab 125	Insufficient data - phototoxicity
76649-17-7	2-Pentenoic acid, 2-methyl-, (3Z)-3-hexen-1-yl ester	Tab 126	Approved
67883-79-8; 84060-80-0	cis-3-Hexenyl tiglate	Tab 127	Approved

11) Presentation by J McKim (Iontox) - Multiple Organ Integrated In Vitro Model for Studying Repeated Dose Toxicity (Wednesday morning)

Dr. McKim provided an overview on the Multiple Organ Integrated In Vitro Model for Studying Repeated Dose Toxicity (see Attachment 6).

12) RIFM Research Projects

a) Epidemiology

Dr. Bruze reported on the work being done by EDEN on the epidemiology study. Many publications are still being written on non-fragrance ingredients. The manuscript on the validation of clinical relevance algorithm was published in 2019.

b) Draft Blue Screen manuscript

The draft BlueScreen manuscript was distributed. Mr. Thakkar gave an update on the draft Blue Screen manuscript. Any comments should be sent to him in the next 2 weeks.

c) Read Across manuscript

The read across manuscript was distributed. Dr. Date gave an update on the draft manuscript. Dr. Schultz will send comments in the next 2 weeks and Dr. Date will provide an update to some tables. The final manuscript will be circulated to the Panel.

d) **Dr. Frank Gerberick Presentation on QRA for NCSs including a DST for HPCs (Tuesday morning)**

Dr. Gerberick reported on a QRA methodology for NCSs developed by Kao scientists included a DST for high potency chemicals (HPCs). RIFM is collaborating with Kao on these methodologies (see Attachment 7).

e) **Presentation by M. Na on the kinetics DPRA project and the recategorization of skin sensitizers**

Dr. Na provided an update on several skin sensitization research projects (see Attachment 8).

f) **Presentation by A. Lapczynski on environmental framework and research projects**

Ms. Lapczynski provided an update on several environmental research projects (see Attachment 9).

g) **Presentation by Y. Tokura on Phototoxicity and photoallergenicity assessments of chemicals**

Dr. Tokura gave a presentation on in vitro testing paradigms for phototoxicity and photoallergy testing (see Attachment 10).

h) **Presentation by F. Rodriguez Ropero on plans to use artificial intelligence**

Dr. Rodriquez Ropero gave a presentation on plans to use artificial intelligence in read across (see Attachment 11).

13) Presentation by S Blythe – Industry Trends (Wednesday morning)

Mr. Blythe gave a presentation on industry trends (see Attachment 12).

14) Expert Panel Executive Session

The Expert Panel held an executive session.

15) Future Meeting Dates

• Monday – Wednesday	Jan. 20-22, 2020	Delhi, India
• Thursday	Jan. 23, 2020	INFOX in India - Delhi, India
• Monday – Wednesday	May 18-20, 2020	Chicago
• Monday – Wednesday	Sept. 21-23, 2020	New Jersey
• Wednesday – Friday	Jan. 20-22, 2021	Puerto Rico?
• Monday – Wednesday	May 31-June 2, 2021	Lisbon
• Monday – Wednesday	Sept. 20-22, 2021	New Jersey

Respectfully submitted,

Anne Marie Api

Anne Marie Api, PhD
Vice President

Attachment 1:	Presentation: Mr. Gary Sullivan
Attachment 2	Presentation: Dr. Christopher Borgert
Attachment 3:	Presentation: Dr. Danielle Botelho
Attachment 4:	Presentation: Dr. Sanket Gadhia
Attachment 5:	Presentation: Staff presentations on NCS
Attachment 6:	Presentation: Dr. Jim McKim
Attachment 7:	Presentation: Dr. Frank Gerberick
Attachment 8:	Presentation: Dr. Mihwa Na
Attachment 9:	Presentation: Ms. Aurelia Lapczynski
Attachment 10:	Presentation: Dr. Yoshiki Tokura
Attachment 11:	Presentation: Dr. Francisco Rodriguez Ropero
Attachment 12:	Presentation: Mr. Shawn Blythe