EXPERT PANEL FOR FRAGRANCE SAFETY MEETING

Minutes

May 20-22, 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	Danielle Botelho Kaushal Joshi Devin O'Brien Jim Romine	Maurice Whelan (5/20 morning) Brunhilde Blömeke (5/21) Jean-Pierre Lepoittevin (5/21)

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. Romine announced the upcoming retirement of Dan Salvito. Dr. Botelho announced the onboarding of Shannen Biserta as the RIFM Process Engineer and departure of Frances Belmonte (post-doc) to a position at Exponent.

2) Minutes

The minutes from the January 2019 meeting were approved.

3) Follow-Up and Informational Items

a) Follow-Up List

Dr. Botelho 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) RIFM communication update

Dr. Belsito will provide an update to RIFM Board of Directors on June 4th, 2019.

b) Update to safety assessment publication

Dr. Botelho provided Gary Sullivan's notes and metrics on publications from January through April 2019.

6) Prof. dr. Maurice Whelan, head of the Chemical Safety and Alternative Methods Unit of the Directorate for Health, Consumers and Reference Materials of the European Commission's Joint Research Centre (JRC) Presentation (Monday May 20)

Prof. Whelan presented on the use of alternatives in regulatory risk assessment applications (see Attachment 1).

7) Prof. Dr. Brunhilde Blömeke, Umwelttoxikologie/Head of the Department of Environmental Toxicology Presentation: COCAT – A HaCaT/THP-1 coculture model to estimate skin sensitization potential and potency in vitro. (Tuesday morning May 21)

Prof. Dr. Brunhilde Blömeke presented on CoCat (a coculture of HaCat and dendritic cells) plus analysis of CD86 and CD54 to predict potency and potential (see Attachment 2).

8) Dr. Jochen Buschmann Presentation Testing for Endocrine Disruptors (see Attachment 3)

9) RIFM Safety Evaluation Process

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

Dr. Botelho gave a presentation to update the progress on the safety assessment program (see Attachment 4).

b) **Update on Low Exposure Materials manuscript**

A total of 167 total materials are in the low exposure manuscript. The RIFM editing team is currently preparing the final version for submission to the journal for publication.

c) Safety Assessment Overview

The Panel reviewed 119 Safety Assessments covering 148 materials.

d) General Comments

- The Panel requested that whole paragraphs are presented on the pre-meeting calls.
- Dr. Botelho will resend September Batch 1 materials with a note to highlight the whole sentence so that the compilation can be streamlined

10) Maria Dagli Presentation

Dr. Dagli gave a presentation on carcinogenesis, thresholds, modes of action (see Attachment 5).

11) Sensitization summary on cinnamyl acetate and related esters (Tab 17)

See tab 17.

12) Review Safety Assessments Batch 1

CAS	Name	Tab	Status
81925-81-7 and 102322-83-8	5-Methyl-2-hepten-4-one	Tab 18	Approved
13877-91-3 and 3338-55-4	3,7-Dimethyl-1,3,6-octatriene	Tab 19	Approved
123-35-3	Myrcene	Tab 20	Approved
2436-90-0	Dihydromyrcene	Tab 21	Approved
1139-30-6	Caryophyllene oxide	Tab 22	Approved
7/7/2563	2-Ethoxy-4-methylphenol	Tab 23	Approved
13257-44-8	2-Nonyn-1-al dimethylacetal	Tab 24	Approved

13019-22-2	9-Decen-1-ol	Tab 25	Insufficient data - skin sens
112-43-6	Undecen-1-ol	Tab 26	Insufficient data - skin sens
118562-73-5	Cyclododecaneethanol, .beta.-methyl-	Tab 27	Approved
929625-08-1	2-(2,2,7,7-Tetramethyltricyclo[6.2.1.01,6]undec-5-en-5-yl)propan-1-ol	Tab 28	Insufficient data - skin sens
55066-48-3	3-Methyl-5-phenylpentanol	Tab 29	Approved
93-28-7	eugenyl acetate	Tab 30	Approved
100-42-5	Styrene	Tab 31	Approved with Changes
28664-35-9	4,5-Dimethyl-3-hydroxy-2,5-dihydrofuran-2-one	Tab 32	Approved
3658-77-3	4-Hydroxy-2,5-dimethyl-3(2H)-furanone	Tab 33	Approved
27538-09-6 and 27538-10-9	2-Ethyl-4-hydroxy-5-methyl-3(2H)-furanone	Tab 34	Approved with Changes - DONE
2785-89-9	4-Ethylguaiacol	Tab 35	Approved
13794-73-5	Isocedranone	Tab 36	Approved
25966-79-4	3-Thujopsanone	Tab 37	Approved
629-19-6	Dipropyl disulfide	Tab 38	Approved
37677-14-8 and 52475-89-5	Isohexenyl cyclohexenyl carboxaldehyde	Tab 39	Approved
56107-04-1	3-(p-tert-Butylphenyl)-2-methylpropanol (Lysmerol)	Tab 40	Approved with Changes
2035-93-0	4-methyl-4-phenylpentan-2-ol;benzenepropanol, α,γ,γ-trimethyl-;2-pentanol, 4-methyl-4-phenyl-;benzenepropanol, α, γ,γ-trimethyl-	Tab 41	Approved
123-76-2	Levulinic acid	Tab 42	Approved
28043-10-9	Methyl 2,6,6-trimethylcyclohex-2-ene-1-carboxylate	Tab 43	Approved

815580-59-7; 540734-22-3	3-Cyclohexene-1-carboxylic acid, 2,6,6-trimethyl-, methyl ester	Tab 44	Approved
57934-97-1 and 77851-07-1	Ethyl 2-ethyl-6,6-dimethylcyclohex-2-ene-1-carboxylate	Tab 45	Approved
94333-50-3	Ethyl 2-ethyl-3,6,6-trimethylcyclohexenecarboxylate	Tab 46	Approved
138-22-7	Butyl lactate	Tab 47	Approved
65405-69-8	Cyclohexyl cyclopent-2-ene-1-acetate	Tab 48	Approved
87-91-2	Diethyl tartrate	Tab 49	Approved
33885-51-7	6,6-Dimethylbicyclo[3.1.1]hept-2-ene-2-propionaldehyde	Tab 50	Approved
68527-82-2	Octane, 1,1-bis(octyloxy)-	Tab 51	Approved
7779-94-4	Hydroxycitronellal diethyl acetal	Tab 52	Approved with changes
1708-34-5	2-Hexyl-1,3-dioxolane	Tab 53	Approved
358331-95-0; 357650-26-1; 847144-75-6	5,6,7-Trimethylocta-2,5-dien-4-one	Tab 54	Approved
68922-12-3 and 68141-16-2	10-Dodecen-3-one, 5-hydroxy-7,11-dimethyl-	Tab 55	Approved
108-94-1	Cyclohexanone	Tab 56	Approved with Changes - DONE
28940-11-6	7-Methyl-2H-benzo-1,5-dioxepin-3(4H)-one	Tab 57	Insufficient data
34131-98-1	6-Isopropyl-2(1H)-octahydronaphthalenone	Tab 58	Approved
30640-46-1; 1489-56-1; 1888-90-0; 1489-57-2	Methyl cyclohexadiene (mixture of isomers)	Tab 59	Approved with Changes
39212-23-2	4-Hydroxy-3-methyloctanoic acid lactone	Tab 60	Approved

33673-62-0	Dihydro-4-methyl-5-pentylfuran-2(3H)-one	Tab 61	Approved
67663-01-8	(+/-) 3-Methyl-gamma-decalactone	Tab 62	Approved
7011-83-8	gamma-Methyldecalactone	Tab 63	Approved

13) Review Safety Assessments Batch 2

CAS	Name	Tab	Status
3391-86-4; 3687-48-7	**1-Octen-3-ol**; (R)-(-)-1-Octen-3-ol	Tab 64	Approved
1322-17-4	1,3-Nonanediol acetate (mixed esters)	Tab 65	Approved
141-92-4	Hydroxycitronellal dimethyl acetal	Tab 66	Approved with Changes
5182-36-5	2,4,6-Trimethyl-4-phenyl-1,3-dioxane	Tab 67	Approved with Changes
1373821-23-8	4H-1,3-Benzodioxin, hexahydro-4-methyl-2-(phenylmethyl)-	Tab 68	Approved
326-61-4	Piperonyl acetate	Tab 69	Insufficient Data - Rep Dose/DART testing
617-35-6	Ethyl pyruvate	Tab 70	Approved
1447712-18-6	2-Cyclohexen-1-one, 2-methyl-5-propyl-	Tab 71	Approved
83863-64-3	7,9-Dimethylspiro[5.5]undecan-3-one	Tab 72	Approved
92015-65-1	2(3H)-Benzofuranone, hexahydro-3,6-dimethyl-	Tab 73	Approved
68228-06-8	4-Methyl-1-oxaspiro[5.5]undecene	Tab 74	Approved
13679-86-2	5-Isopropenyl-2-methyl-2-vinyltetrahydrofuran	Tab 75	Approved
22047-25-2	Acetylpyrazine	Tab 76	Approved
19096-86-7	Cyclohexanone,5-methyl-2-(1-methylethyl)-,oxime	Tab 77	Approved with Changes - DONE

847565-09-7	N-(2-(Pyridin-2-yl)ethyl)-3-p-menthanecarboxamide	Tab 78	Approved
1643-20-5	Dodecyldimethylamine oxide	Tab 79	Approved
1392276-61-7	Acetonitrile, 2-(2,4,4-trimethylcyclopentylidene)-	Tab 80	Insufficient data skin sens
42075-45-6	Methyl 2-methylthiobutyrate	Tab 81	Approved
68398-18-5; 68921-26-6	**4,7,7-Trimethyl-6-thiabicyclo[3.2.1]octane**; Cyclohexene, 1-methyl-4-(1-methylethenyl)-, sulfurized	Tab 82	Approved
943723-15-7; 93939-86-7; 85633-07-4; 85700-01-2; 85700-02-3; 85633-08-5	**5,8-Methano-2H-1-benzopyran, 6(or 7)-ethylideneoctahydro-, [4aR,5S,8S,8aS(or 4aR,5R,8S,8aR)]-rel-**; 6-Ethylideneoctahydro-5,8-methano-2H-benzo-1-pyran; 5,8-Methano-2H-1-benzopyran, 6-ethylideneoctahydro-, (4aalpha,5beta,7Z,8beta,8aalpha)-5,8-Methano-2H-1-benzopyran, 6-ethylideneoctahydro-, (4aalpha,5beta,7E,8beta,8aalpha)-; 5,?8-?Methano-?2H-?1-?benzopyran, 6-?ethylideneoctahydro-?, (4aα,?5β,?6E,?8β,?8aα)?-; 5,8-Methano-2H-1-benzopyran, 6-ethylideneoctahydro-, (4aalpha,5beta,6Z,8beta,8aalpha)-	Tab 83	Approved
1245725-35-2	Cyclopentanol, 2-?methyl-?5-?(1-?methylethyl)?-?, 1-?propanoate	Tab 84	Approved
2230-87-7	Cyclohexanol, 5-methyl-2-(1-methylethyl)-, acetate, (1a,2a,5b)-	Tab 85	Approved
1266606-26-1	Butanoic acid, 2-?methyl-?5-?(1-?methylethyl)?cyclopentyl ester	Tab 86	Approved

52557-97-8	Methyl 3,3-dimethylbicyclo[221]heptane-2-carboxylate	Tab 87	Approved
67845-30-1	8-Isopropyl-6-methylbicyclo[2.2.2]oct-5-ene-2-carbaldehyde	Tab 88	Approved
68259-31-4	5(Or 6)-Methyl-7(or 8)-(1-methylethyl)bicyclo[2.2.2]oct-5-ene-2-carbaldehyde	Tab 89	Approved
120-72-9	Indole	Tab 90	Approved
93963-23-6	Ethanone, 1-?(1,?2,?3,?4,?5,?6,?7,?8-?octahydro-?3,?8,?8-?trimethyl-?2-?naphthalenyl)?-	Tab 91	Approved with Changes - DONE
54464-57-2; 68155-66-8; 68155-67-9	**1-(1,2,3,4,5,6,7,8-Octahydro-2,3,8,8-tetramethyl-2-naphthalenyl)ethanone**; 1-(1,2,3,5,6,7,8,8a-Octahydro-2,3,8,8-tetramethyl-2-naphthyl)ethan-1-one; 1-(1,2,3,4,6,7,8,8a-Octahydro-2,3,8,8-tetramethyl-2-naphthyl)ethan-1-one	Tab 92	Insufficient data - Environmental
188570-78-7	Cyclopropanecarboxylic acid, (3Z)-3-hexenyl ester	Tab 93	Approved
93-29-8	isoeugenyl acetate	Tab 94	Approved
63767-86-2	alpha-Methyl-4-(1-methylethyl)-cyclohexanemethanol	Tab 95	Approved
60241-52-3	cyclohexanepropanol, a-ethyl-2,2,6-trimethyl-	Tab 96	Approved
139504-68-0	1-(2-tert.-Butyl cyclohexyloxy)-2-butanol	Tab 97	Approved
32974-92-8	2-Acetyl-3-ethylpyrazine	Tab 98	Insufficient data - Phototox - need strategy to address Pall.

23787-80-6	2-Acetyl-3-methylpyrazine	Tab 99	Insufficient data - Phototox - need strategy to address Pall.
13678-59-6	2-Methyl-5-(methylthio)furan	Tab 100	Insufficient data - Phototox - need strategy to address Pall.
3526-75-8	1.alpha.,5.alpha.-Dihydroguaiol	Tab 101	Approved
57-10-3	Palmitic acid	Tab 102	Approved
64-18-6	Formic acid	Tab 103	Approved
5421-17-0	Hexyl phenylacetate	Tab 104	Approved
63449-68-3	beta-Naphthyl anthranilate	Tab 105	Approved
4312-99-6	1-Octen-3-one	Tab 106	Approved
36267-71-7	5,7-Dihydro-2-methylthieno(3,4-d)pyrimidine	Tab 107	Approved
140-39-6	*p*-Tolyl acetate	Tab 108	Approved

14) Update on QRA2 Implementation

a) **A.M Api Presentation on QRA2**

Dr. Api provided an update on the QRA2 methodology via webinar (see Attachment 6).

15) Review Safety Assessments – Batch 3

CAS	Name	Tab	Status
93-15-2	Eugenyl methyl ether	Tab 109	Approved with Changes
7784-67-0	Isoeugenyl ethyl ether	Tab 110	Approved
6032-29-7	2-pentanol	Tab 111	Approved
14765-30-1	2-sec-Butylcyclohexanone	Tab 112	Approved
10461-98-0	alpha-Cyclohexylidene benzeneacetonitrile	Tab 113	Approved
916887-53-1	2-Cyclohexylidene-2-o-tolylacetonitrile	Tab 114	Approved
5405-41-4	Ethyl 3-hydroxybutyrate	Tab 115	Approved

21188-58-9	Methyl 3-hydroxyhexanoate	Tab 116	Approved
2305-25-1	Ethyl 3-hydroxyhexanoate	Tab 117	Approved
2555-49-9	Ethyl phenoxyacetate	Tab 118	Approved
67633-94-7	Phenylacetaldehyde 2,4-dihydroxy-2-methylpentane acetal	Tab 119	Approved
33941-99-0	2-Methyl-4-phenyl-1,3-dioxolane	Tab 120	Approved
104-67-6	gamma-Undecalactone	Tab 121	Approved
99-48-9; 2102-59-2; 1197-07-5	Carveol	Tab 122	Approved with Changes
40203-73-4	Methyl cyclopentylideneacetate	Tab 123	Approved
94-46-2	Isoamyl benzoate	Tab 124	Approved
947-05-7	Oxacyclotridecan-2-one	Tab 125	Approved
51755-83-0	3-Mercaptohexanol	Tab 126	Approved
96-48-0	4-Hydroxybutanoic acid lactone	Tab 127	Approved
614-34-6	p-Cresyl benzoate	Tab 128	Approved
2206-94-2	Benzenemethanol, alpha-methylene-, acetate	Tab 129	Approved
118-93-4	2-Hydroxyacetophenone	Tab 130	Approved with Changes
13477-62-8	Tetrahydro-2-isobutyl-4-methyl-2H-pyrane	Tab 131	Approved
78-93-3	2-Butanone	Tab 132	Approved with Changes
140-67-0	Estragole	Tab 133	Approved with Changes
104-46-1; 25679-28-1; 4180-23-8	Anethole (isomer unspecified)	Tab 134	Approved with Changes

501-92-8	4-Allylphenol	Tab 135	Approved with Changes -bring back with 14 day study and TTC WoE
1122-62-9	2-Acetylpyridine	Tab 136	Approved

16) Human Health Research Projects

a) Epidemiology

i) Validation of Clinical Relevance Algorithm **MB**

b) Eugenol Elicitation Threshold draft report

Dr. Api provided an update on the eugenol elicitation threshold draft report. There had been no response from the authors. As such the additional analyses may have to be done in a manuscript by RIFM.

c) **Presentation by D. O'Brien on RIFM Dermal Sensitization Research Project Update**

Ms. O'Brien gave an update on the RIFM Dermal Sensitization Research Project Update (see Attachment 7).

d) **Presentation by Prof. Jean-Pierre Lepoittevin, Laboratoire de Dermatochimie, Institut Le Bel - Development of HRMAS NMR spectroscopy in association with RHE to follow and characterize the metabolic transformation/activation of pro-haptens Research Project (Tuesday afternoon May 21)**

Prof. Prof. Jean-Pierre Lepoittevin gave an update on the Development of HRMAS NMR spectroscopy in association with RHE to follow and characterize the metabolic transformation/activation of pro-haptens project (see Attachment 8).

e) **Presentation by K. Joshi - Use of the EpiDermTM 3D reconstructed skin micronucleus assay to address misleading positive results from in vitro genotoxicity assays for fragrance materials**

Dr. Joshi presented an update on the Use of the EpiDermTM 3D reconstructed skin micronucleus assay to address misleading positive results from in vitro genotoxicity assays for fragrance materials (see Attachment 9).

17) 2,3-Butanedione

The panel recommended an *in vivo* comet on 2,3-Heptanedione.

18) Estragole

The panel will review the Safety Assessment on Estragole.

19) Future Meeting Dates

• Monday – Wednesday	Sept. 23-25, 2019	New Jersey
• 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 30-June 2, 2021	Lisbon

Respectfully submitted,

Danielle Botelho, PhD
Safety Assessment Manager

Attachment 1:	Prof. Whelan presentation
Attachment 2	Prof. Brunhilde Biomeke presentation
Attachment 3:	Dr. Buschmann presentation
Attachment 4:	Dr. Botelho presentation on the safety assessment process
Attachment 5:	Dr. Dagli presentation
Attachment 6:	Dr. Api presentation
Attachment 7:	Ms. O'Brien presentation
Attachment 8:	Prof. Lepoittevin presentation
Attachment 9:	Dr. Joshi presentation