

EXPERT PANEL FOR FRAGRANCE SAFETY MEETING

DRAFT Minutes

September 19-21, 2016

EXPERT PANEL MEMBERS		RIFM STAFF	GUESTS
Donald Belsito (Chair) Magnus Bruze G. Allen Burten, Jr. Jochen Buschmann Peter Calow Maria Dagli	Wolfgang Dekant Allison Fryer Daniel Liebler Trevor Penning Terry Schultz I. Glenn Sipes (Vice Chair)	Anne Marie Api Danielle Botelho Daveda Browne Mihir Date Chaitra Deodhar Kaushal Joshi Stephanie La Cava Aurelia Lapczynski Devin O'Brien Rahul Parakhia Atish Patel Gretchen Ritacco Jim Romine Daniel Salvito Sai Yee Tsang Yax Thakkar Joseph Wahler	Yoshiki Tokura (9/19-20 only) R. Panettieri, Jr. (9/20 pm only) J. Jude (9/20 pm only) Tobey Marzouk (9/21 am only)

1) Discussion of the Meeting Schedule and Agenda Topics

- a) Completion/Signing of Conflict of Interest Statement

Dr. Belsito opened the meeting and welcomed the guests. The Conflict of Interest Statement was signed.

2) Minutes

The September 2015 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. A new format for this list was discussed and approved.

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 the publications. The Panel suggested that this document be shared with the Board of Directors.

5) Presentation by Yoshiki Tokura, MD, PhD, Editor-in-Chief, Journal of Dermatological Science, Professor and Chairman, Department of Dermatology. Hamamatsu University School of Medicine- Assessments of photoallergenicity of chemicals (see Attachment 1)

6) Allylalkoxybenzene Derivatives

a) Methyl Eugenol

i) Drs. Atish Patel and Joseph Wahler gave a summary presentation on the genotoxicity and repeat dose data on methyl eugenol (see Attachment 2).

7) RIFM Safety Evaluation Process

a) A. M Api Presentation RIFM Safety Assessment Update and Metrics (see Attachment 3)

b) Safety Assessment General Items

i) Presentation by Gretchen Ritacco - Photoallergy assessment (see Attachment 4)

ii) Skin absorption data

Dr. Patel will revise the skin absorption template to explain when evaporative loss is observed in skin absorption studies. explanation.

iii) Presentation by D. Botelho and M. Date - Use of metabolism data for local respiratory endpoint (see Attachment 5)

The Panel advised that metabolism data can be used as read across for the local respiratory endpoint if the metabolism is simple and efficient. Use of metabolism data for esters may be useful.

iv) Template and SOP for the computational toxicity section

The Panel reviewed the templates for the read across justifications and the standard operating procedures (SOP) for clustering and read across. Some modifications were recommended, which Dr. Date will implement. The SOP for clustering and read across is still being refined and will be reviewed again at the next Panel meeting.

v) Updates to templates

The staff presented the updates to their respective endpoint templates.

c) Safety Assessment Overview (69 Safety Assessments covering 94 materials)

CAS #	Material Name	Panel Decision
138-86-3, 5989-54-8, 5989-27-5 (mixture)	dl-Limonene (racemic), l-limonene, d-limonene	Approved with Changes
586-62-9	Terpinolene	Approved
29350-67-2	4-Isopropyl-1-methylcyclohexene	Approved with changes
99-85-4, 99-86-5, 4221-98-1, 99-83-2, 555-10-2 and 1329-99-3	p-Mentha-1,4-diene	Approved with changes
1205-17-0	α-Methyl-1,3-benzodioxole-5-propionaldehyde	Approved
55418-52-5	4-(3,4-Methylenedioxyphenyl)-2-butanone	Approved
115-95-7	Linalyl acetate	Approved with changes
2306-78-7 and 56001-43-5	Nerolidyl acetate (isomer unspecified)	Approved
144-39-8	Linalyl propionate	Approved with changes
61931-80-4	3,7-Dimethyl-1,6-nonadien-3-yl acetate	Approved
78-35-3	Linalyl isobutyrate	Approved
78-36-4	Linalyl butyrate	Approved
1118-27-0	Linalyl isovalerate	Approved
7779-23-9	Linalyl hexanoate	Approved
1118-39-4	Myrcenyl acetate	Approved

CAS #	Material Name	Panel Decision
115-99-1	Linalyl formate	Approved
24851-98-7	Methyl dihydrojasmonate	Approved
37172-53-5	Methyl hexyl oxo cyclopentanone carboxylate	Approved
1211-29-6 and 39924-52-2	Methyl jasmonate	Approved with changes
40942-73-2	3-(2-Oxopropyl)-2-pentylcyclopentanone	Insufficient data - sensitization
104-54-1	Cinnamyl alcohol	Approved with changes
17488-65-2	4-Phenyl-3-buten-2-ol	Insufficient data - genotoxicity
1504-55-8	α -Methylcinnamic alcohol	Insufficient data - genotoxicity
621-82-9 , 140-10-3	Cinnamic acid	Approved with changes
103-82-2	Phenylacetic acid	Approved with changes
501-52-0	3-Phenylpropionic acid	Approved with changes
25225-08-5	l-Cyclocitronellene formate	Approved with changes
25225-10-9	d-Cyclocitronellene acetate	Approved
93917-67-0	.alpha.,.gamma.,.gamma.-Trimethylcyclohexylpropyl acetate	Approved with changes – verify exposure data
13487-27-9	.alpha.-Methylcyclohexylmethyl acetate	Approved with changes
63449-88-7	1-Cyclohexylethyl butyrate	Approved
106-22-9 , 7540-51-4, 141-25-3, 1117-61-9, 26489-01-0 and 6812-78-8	dl-Citronellol	Approved with changes
106-24-1 and 106-25-2	Geraniol	Approved with changes
4602-84-0	Farnesol	Approved
24048-14-4	2,6,10-Trimethylundeca-5,9-dienol	Approved
150-86-7 and 7541-49-3	Phytol	Approved with changes
556-82-1	3-Methyl-2-buten-1-ol	Approved
15323-35-0	5-Acetyl-1,1,2,3,3,6-hexamethylindan	Insufficient Data – phototoxicity
13171-00-1	4-Acetyl-6-t-butyl-1,1-dimethylindan	Insufficient Data - phototoxicity
68140-48-7	5-Acetyl-3-isopropyl-1,1,2,6-tetramethylindane	Approved
21145-77-7 (identical to CAS# 1506-02-1)	6-Acetyl-1,1,2,4,4,7-hexamethyltetraline	Approved with changes
94-62-2	Piperine	Insufficient data – UV absorption
475-20-7	Longifolene	Approved
514-51-2	beta-Patchoulene	Approved with changes
11028-42-5 and 469-61-4, 546-28-1	Cedrene and alpha- cedrene and beta cedrene	Approved
88-84-6 , 3691-12-1 and 3691-11-0	beta-Guaiene	Approved
1135-66-6	Isolongifolene	Approved with changes – verify exposure data
23787-90-8 , 29461-13-0 and 29461-14-1 (mixture)	Isolongifolanone (isolongifolene ketone)	Approved
639-99-6	Elemol	Approved
65114-03-6	α ,2,2,3-tetramethylcyclopent-3-ene-1-butyraldehyde	Approved
111-80-8	Methyl 2-nonynoate	Approved with changes
111-12-6	Methyl 2-octynoate	Approved with changes

CAS #	Material Name	Panel Decision
40379-24-6 and 58430-94-7	Isononyl acetate (isomer unspecified)	Approved with changes
69103-23-7	Isotridecyl acetate	Approved with changes
65155-45-5	Isononyl propionate	Approved
110-45-2	Isoamyl formate	Approved
123-92-2	Isoamyl acetate	Approved with changes
105-68-0	Isoamyl propionate	Approved with changes
106-27-4	Isoamyl butyrate	Approved with changes
2050-09-1	3-Methylbutyl valerate	Approved
2035-99-6	Isoamyl octanoate	Approved
2198-61-0	Isoamyl hexanoate	Approved with changes
20780-49-8	3,7-Dimethyl-1-octanyl acetate	Approved
108419-32-5	Acetic acid, C7-9-branched alkyl esters, C8-rich	Approved
108419-33-6	Acetic acid, C8-10-branched alkyl esters, C9-rich	Approved
2050-01-3	3-Methylbutyl 2-methylpropanoate	Approved
100-47-0	Benzonitrile	Insufficient data - sensitization
874-90-8	p-Methoxybenzotrile	Approved
13816-33-6	Cuminy nitrile	Approved

8) IDEA Update

a) QRA 2016 Implementation Update

Dr. Api provided an update on the work being done to implement QRA2 for the next IFRA Amendment to the Code of Practice.

b) IDEA Working Group Meeting on evaluating effectiveness of QRA

Dr. Api discussed a draft proposal for a study to investigate the effectiveness of the QRA. The Panel offered suggestions to the protocol.

9) Human Health Research Projects

a) Epidemiology

i) Validation of Clinical Relevance Algorithm

Prof. Bruze has reviewed the draft report on the validation of the clinical relevance algorithm. Dr. Api will follow-up with Prof. Diepgen to obtain a revised draft report.

b) Elicitation Threshold Study on Eugenol

Dr. Api provided an update on this study. There are six centers participating in the study. All six centers have completed the study and the data were transferred to Dr. Diepgen for analysis. A draft report was not available yet.

c) Respiratory Research Program

i) **Presentation by Reynold A. Panettieri, Jr., M.D. and Joseph Jude, PhD - Human Precision Cut Lung Slices: A platform to assess environmental toxicity - Tuesday afternoon September 20, 2016 (see Attachment 6).**

10) Environmental Program Update

Ms. A. Lapczynski and Dr. D. Salvito provided an update on the environmental program (see Attachment 7).

11) IFRA Standards

a) Isophorone

The Panel reviewed the data on isophorone. The dose response for preputial gland carcinoma was identified as the critical effect for deriving an oral exposure threshold. Thus, the NOAEL for preputial gland carcinoma from the 2-year US-NTP carcinogenicity study was determined to be 250 mg/kg/day. The U.S. Environmental Protection Agency (EPA) reported that over a life-time, an individual could consume 40 micrograms per liter ($\mu\text{g/L}$) (0.04 mg/L) isophorone and would have no more than a one-in-a-million increased chance of developing cancer as a direct result of ingesting water containing this chemical. According to the EPA, drinking water consumption is 2 Liters/day. As such, $40 \mu\text{g/L} \times 2\text{L/day}$ consumption = 80 $\mu\text{g/person/day}$. Using a 60 kg bodyweight/person the Reference Dose (RfD) can be derived for humans as, $80/60 = 1.33 \mu\text{g/kg/day}$. This dose was used in the Creme RIFM Model to derive the acceptable safe use of 0.0013% in the final product.

12) Legal (Wednesday morning September 21, 2016)

Tobey Marzouk, RIFM legal counsel, presented a revised draft of the Expert Panel's Vision and Mission Statements. These statements were finalized and approved at the meeting. Revised Conflict of Interest Statement and revised Operating Guidelines were also reviewed and approved. The Expert Panel's transparency Policy was reviewed and approved. There was a demonstration of a beta version of the new Expert Panel website. More details will be added to the website and another demonstration will be given at the next meeting.

13) Future Meeting Dates

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| • Monday – Wednesday | Jan. 23-25, 2017 | Miami, FL |
| • Monday – Wednesday | May 22-24, 2017 | Dublin |
| • Monday – Wednesday | Sept. 18-20, 2017 | Europe |
| • Monday – Wednesday | Jan. 22-24, 2018 | Miami, FL |
| • Monday – Wednesday | May 21-23, 2018 | RIFM |
| • Monday – Wednesday | Sept. 17-19, 2018 | Europe – Paris? |

Respectfully submitted,

Anne Marie Api, PhD
Vice President Human Health Sciences
(date finalized)

- Attachment 1: Presentation by Yoshiki Tokura, MD, PhD, Editor-in-Chief, Journal of Dermatological Science, Professor and Chairman, Department of Dermatology. Hamamatsu University School of Medicine- Assessments of photoallergenicity of chemicals
- Attachment 2: Presentation by Atish Patel and Joseph Wahler - the genotoxicity and repeat dose data on methyl eugenol
- Attachment 3: Presentation by A. M Api - RIFM Safety Assessment Update and Metrics
- Attachment 4: Presentation by G. Ritacco - Photoallergy assessment
- Attachment 5: Presentation by D. Botelho and M. Date - Use of metabolism data for local respiratory endpoint
- Attachment 6: Presentation by Reynold A. Panettieri, Jr., M.D. and Joseph Jude, PhD - Human Precision Cut Lung Slices: A platform to assess environmental toxicity
- Attachment 7: Presentation by A. Lapczynski and D. Salvito- Update on the Environmental Program