

# EXPERT PANEL FOR FRAGRANCE SAFETY MEETING

## Minutes

September 19-21, 2016

| EXPERT PANEL MEMBERS   |  | RIFM STAFF  | GUESTS   |
|--|--|---|--|
| Donald Belsito (Chair)<br>Magnus Bruze<br>G. Allen Burten, Jr.<br>Jochen Buschmann<br>Peter Calow<br>Maria Dagli | Wolfgang Dekant<br>Allison Fryer<br>Daniel Liebler<br>Trevor Penning<br>Terry Schultz<br>I. Glenn Sipes (Vice Chair) | Anne Marie Api<br>Danielle Botelho<br>Daveda Browne<br>Mihir Date<br>Chaitra Deodhar<br>Kaushal Joshi<br>Stephanie La Cava<br>Aurelia Lapczynski<br>Devin O'Brien<br>Rahul Parakhia<br>Atish Patel<br>Gretchen Ritacco<br>Jim Romine<br>Daniel Salvito<br>Sai Yee Tsang<br>Yax Thakkar<br>Joseph Wahler | Yoshiki Tokura (9/19-20 only)<br>R. Panettieri, Jr. (9/20 pm only)<br>J. Jude (9/20 pm only)<br>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        |
|--|---|-----------------------|
| <b>138-86-3</b> , 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 |
| <b>99-85-4</b> , 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 |
| <b>2306-78-7</b> 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              |

| CAS #  | Material Name   | Panel Decision                               |
|--|---|--|
| 78-36-4  | Linalyl butyrate  | Approved                                     |
| 1118-27-0  | Linalyl isovalerate                                       | Approved                                     |
| 7779-23-9  | Linalyl hexanoate   | Approved                                     |
| 1118-39-4  | Myrcenyl acetate  | Approved                                     |
| 115-99-1   | Linalyl formate   | Approved                                     |
| 24851-98-7   | Methyl dihydrojasmonate                                   | Approved                                     |
| 37172-53-5   | Methyl hexyl oxo cyclopentanone carboxylate               | Approved                                     |
| <b>1211-29-6</b> 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  | $\alpha$ -Methylcinnamic alcohol                          | Insufficient data - genotoxicity             |
| <b>621-82-9</b> , 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                                     |
| <b>106-22-9</b> , 7540-51-4, 141-25-3, 1117-61-9, 26489-01-0 and 6812-78-8 | dl-Citronellol  | Approved with changes                        |
| <b>106-24-1</b> and 106-25-2   | Geraniol  | Approved with changes                        |
| 4602-84-0  | Farnesol  | Approved                                     |
| 24048-14-4   | 2,6,10-Trimethylundeca-5,9-dienol                         | Approved                                     |
| <b>150-86-7</b> 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                                     |
| <b>21145-77-7</b><br>(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                        |
| <b>11028-42-5</b> and 469-61-4, 546-28-1                                   | Cedrene and alpha- cedrene and beta cedrene               | Approved                                     |
| <b>88-84-6</b> , 3691-12-1 and 3691-11-0                                   | beta-Guaiene  | Approved                                     |
| 1135-66-6  | Isolongifolene  | Approved with changes – verify exposure data |
| <b>23787-90-8</b> , 29461-13-0 and 29461-14-1 (mixture)                    | Isolongifolanone (isolongifolene ketone)                  | Approved                                     |



| CAS #                     | Material Name  | Panel Decision                    |
|---------------------------|--|-----------------------------------|
| 639-99-6                  | Elemol   | Approved                          |
| 65114-03-6                | $\alpha$ ,2,2,3-tetramethylcyclopent-3-ene-1-butylaldehyde | Approved                          |
| 111-80-8                  | Methyl 2-nonynoate   | Approved with changes             |
| 111-12-6                  | Methyl 2-octynoate   | Approved with changes             |
| 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                | Cumynyl 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.

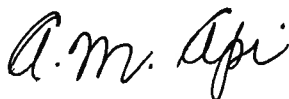
#### **12) Legal (Wednesday morning September 21, 2016)**

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**

- |                      |                   |                 |
|----------------------|-------------------|-----------------|
| • 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 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