

EXPERT PANEL FOR FRAGRANCE SAFETY MEETING

Minutes

January 23-25, 2017

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) Y. Tokura	Anne Marie Api Stephanie La Cava Atish Patel Gretchen Ritacco Jim Romine Daniel Salvito	Tobey Marzouk (1/23 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 Dr. Tokura to the Panel. The Conflict of Interest Statement was signed and January 2019 dates were set.

2) Minutes

The September 2016 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.

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 RIFM recent publications.

5) Dr. Hans Merk gave a webinar presentation on Monday January 23. He provided an update on the research project in order to characterize the cutaneous CYP-dependent metabolism of cresol (see Attachment 1).

6) Legal (Monday morning January 23, 2017)

Tobey Marzouk, RIFM legal counsel, presented the Expert Panel's new website for final review (www.fragrancesafetypanel.com). Mr. Marzouk addressed the Expert Panel on a Self-Assessment in which the Panel members would be asked a series of questions that seek to identify areas of strengths and weaknesses with a goal of making the Panel better. Another topic covered was a "Self-Audit" whereby

someone outside the Panel audits and monitors whether and how well the Panel is complying with its own policies and guidelines. The Panel agreed that both the Self-Assessment and Self-Audit should be conducted. Mr. Marzouk will propose plans for conducting both.

7) Furaneol

- a) **A.M. Api and A. Patel Summary Presentation on Sensitization and Repeat Dose Data (see Attachment 2a and Attachment 2b).**

8) Review genotoxicity section

- a) OTNE, CAS 54464-57-2

The Panel concluded that summary of the genotoxicity studies and the rationale provided are sufficient. They did not recommend any additional studies.

- b) alpha-Methyl cinnamic alcohol, CAS 1504-55-8

The Panel did not recommend any additional genotoxicity studies on this material. The Ames assay should be detailed and the results interpreted according to current guidelines. In addition, a weight of evidence approach using read across materials should be added to the rationale. Data on unsubstituted cinnamic alcohols should be included along with data on substituted cinnamic alcohols.

- c) 4-Phenyl-3-buten-2-ol, CAS # 17488-65-2

After a thorough review of all the data on this material and related materials, the Panel recommended that an in vivo mouse micronucleus assay be conducted on 4-Phenyl-3-buten-2-ol.

9) RIFM Safety Evaluation Process

- a) **A. M. Api Presentation RIFM Safety Assessment Update and Metrics (see Attachment 3).**
- b) **A.M. Api Presentation Interface between RIFM Safety Assessments and IFRA Standard Setting: Process and proposed policy (see Attachment 4).**

In the past, when a sensitizer was identified by RIFM, an IFRA Standard was issued independent of the actual use of the material. In keeping with the guiding principle for other endpoints, the following change was considered by the Expert Panel for Fragrance Safety in January 2017 and determined that is was scientifically reasonable that:

- A Standard can be set if the 95th percentile aggregated exposure exceeds the limits dictated by the QRA2
- As such, Standards on materials that have 95th percentile aggregated exposure below the limits dictated by QRA2 are not necessary. However, the exposure must be updated on a regular basis.

- c) **A.M. Api Presentation NCS Safety Evaluation Strategy (see Attachment 5).**

- d) Introduction New Fragrance Materials After the 2015 Volume of Use Survey Procedure for member-generated safety assessments

Fragrance materials that are not part of the 2015 IFRA Volume of Use survey will not be part of the RIFM Safety Assessment program. Dr. Api introduced a procedure for introducing fragrance materials that are not in the Safety Assessment program. The Panel agreed to the procedure with changes. This policy will be added to the RIFM website.

- e) Template and SOP for the computational toxicity section

The Panel reviewed the template for the computational section in the safety assessments. Important changes were made to the section which will be incorporated in all the safety assessments reviewed at this Panel meeting and at future Panel meetings. The Panel agreed to the computational SOPs.

- f) Safety Assessment Overview (95 Safety Assessments covering 119 materials)

In summary, 40 materials were approved, 60 materials were approved with changes and 18 required testing or additional data.

CAS#	Material Name	Expert Panel Status
5392-40-5, 106-26-3 and 141-27-5	Citral	Approved with Changes
19317-11-4	Farnesal	Approved with Changes
41448-29-7	3,7-Dimethyl-2,6-nonadien-1-al	Approved with Changes
762-26-5	5,9-Dimethyl-4,8-decadienal	Approved with Changes
24048-13-3 and 54082-68-7	2,6,10-Trimethylundeca-5,9-dienal (dihydroapofarnesal)	Approved with Changes
55722-59-3 and 55050-40-3	3,7-Dimethyl-3,6-octadienal	Approved with Changes
106-72-9	2,6-Dimethyl-5-heptenal	Approved with Changes
106-23-0 and 5949-05-3	Citronellal	Approved with Changes
71077-31-1	4,8-Dimethyl-4,9-decadienal	Approved with Changes
22418-66-2	3,7-Dimethyl-2-methylenocta-6-enal	Insufficient data – Gentox; HRIPT
141-13-9	2,6,10-Trimethyl-9-undecenal	Approved with Changes HRIPT on RA in progress
1576-95-0	(Z)-2-Penten-1-ol	Approved
928-95-0 and 2305-21-7	trans-2-Hexenol	Approved
22104-79-6	2-Nonen-1-ol	Approved
7786-44-9 and 28069-72-9	2,6-Nonadien-1-ol	Approved
85-91-6	Methyl N-methylantranilate	Approved with changes
65505-24-0	Isobutyl N-methylantranilate	Approved with changes
25628-84-6	Benzoic acid, 2-[(1-oxopropyl)amino]-, methyl ester	Approved with changes
2719-08-6	Methyl N-acetylantranilate	Approved
68480-21-7	Benzoic acid, 2-(dimethylamino)-, 2-methylpropyl ester	Approved
41270-80-8	Methyl 2-(formylamino)benzoate	Approved
65405-76-7	cis-3-Hexenyl anthranilate	Approved with changes
134-20-3	Methyl anthranilate	Approved with changes
7756-96-9	Butyl anthranilate	Approved with changes
87-25-2	Ethyl anthranilate	Approved with changes
7149-26-0	Linalyl anthranilate	Approved with changes
133-18-6	Phenylethyl anthranilate	Approved with changes
3508-98-3	2-Phenylhexanenitrile	Approved with changes
3288-99-1	(4-tert-Butylphenyl)acetonitrile	Test needed: Gentox
54089-83-7	3-Methyl-5-phenylpentanenitrile	Approved
75490-39-0	2,2,4-Trimethyl-4-phenyl-butane-nitrile	Approved
134123-93-6	Benzenepropanenitrile, 4-ethyl-.alpha.,.alpha.-dimethyl-	Approved with changes
68083-58-9	1,3-Dimethyl-3-phenylbutyl acetate	Approved with changes
151-05-3	1,1-Dimethyl-2-phenylethyl acetate	Approved
59354-71-1	1,1-Dimethyl-2-phenylethyl isobutyrate	Approved
103-07-1	2-Methyl-4-phenyl-2-butyl acetate	Approved
10031-71-7	2-Methyl-4-phenyl-2-butyl isobutyrate	Approved
7306-12-9	3-Phenyl-3-buten-1-yl acetate	Approved
122-72-5	3-Phenylpropyl acetate	Approved
10094-34-5	alpha,alpha-Dimethylphenethyl butyrate	Approved with changes
67785-77-7	alpha,alpha-Dimethylphenylethyl propionate	Approved with changes

CAS#	Material Name	Expert Panel Status
103-45-7	Phenethyl acetate	Approved
103-52-6	Phenethyl butyrate	Approved
104-62-1	Phenethyl formate	Approved
103-48-0	Phenethyl isobutyrate	Approved
122-70-3	Phenethyl propionate	Approved
6324-78-3	p-(2,2-Dimethoxyethoxy)toluene	Approved with changes
78-70-6 and 126-91-0	Linalool	Approved with changes
73018-51-6	1,6-Octadien-3-ol, 3,7-dimethyl-, acid-isomerized	Insufficient data; need characterization from industry; compositional analysis
10339-55-6	3,7-Dimethyl-1,6-nonadien-3-ol	Insufficient data - Sensitization
7212-44-4 and 40716-66-3, 142-50-7	Nerolidol (isomer unspecified)	Insufficient data - Sensitization
1113-21-9	Geranyl linalool	Insufficient data - Sensitization
18479-51-1	3,7-Dimethyloct-6-en-3-ol	Insufficient data - Sensitization
18479-49-7	3,7-Dimethyloct-1-en-3-ol	Insufficient data - Sensitization
115-18-4	2-Methyl-3-buten-2-ol	Insufficient data - Sensitization
505-32-8	Isophytol	Approved
13254-34-7	2,6-Dimethyl-2-heptanol	Approved with changes
18479-57-7	Tetrahydromyrcenol	Approved
78-69-3	Tetrahydrolinalool	Approved with changes
61789-17-1	Guaiacwood acetate	Insufficient data - Phototoxicity; Sensitization
8000-41-7, 7785-53-7, 10482-56-1 and 98-55-5	Terpineol	Approved
498-81-7 and 58985-02-7	Dihydro- α -terpineol	Approved with changes
562-74-3	3-Cyclohexen-1-ol, 4-methyl-1-(1-methylethyl)-	Approved
134769-33-8, 124071-42-7 and 124071-43-8	3,12-Tridecadienenitrile	Approved
51566-62-2	Citronellyl nitrile	Approved with changes
76-22-2, 21368-68-3, 464-48-2, 464-49-3	1,7,7-Trimethylbicyclo[2.2.1]heptan-2-one (camphor) and d,l-camphor	Insufficient data - Sensitization
1195-79-3, 4695-32-9, 7737-20-4	Perchone	Approved
16409-43-1, 4610-11-1 and 3033-23-6	Rose Oxide (Tetrahydro-4-methyl-2-(2-methylpropen-1-yl)pyran)	Approved with changes
1786-08-9	Nerol oxide	Approved with changes
13828-37-0	cis-4-(Isopropyl)cyclohexanemethanol	Approved with changes
67634-03-1	4-(Isopropyl)- β -methylcyclohexanethanol	Approved with changes
68480-15-9	Cyclohexanemethanol, 2,4-dimethyl-	Approved with changes
106-21-8	3,7-Dimethyl-1-octanol	Approved
25339-17-7	Isodecyl alcohol	Approved
123-51-3	Isoamyl alcohol	Approved
68526-85-2	Alcohols, C9-11-iso-, C10-rich	Insufficient Data – Refine exposure for respiratory
68526-86-3 and 27458-92-0	Alcohols, C11-14-iso-, C13-rich	Approved
589-35-5	3-Methyl-1-pentanol	Approved with changes
68526-84-1	Alcohols, C8-10-iso-, C9-rich	Approved
104-65-4	Cinnamyl formate	Approved with changes
103-54-8	Cinnamyl acetate	Approved with changes
103-59-3	Cinnamyl isobutyrate	Approved with changes

CAS#	Material Name	Expert Panel Status
103-56-0	Cinnamyl propionate	Approved with changes
103-61-7	Cinnamyl butyrate	Approved with changes
67801-20-1	3-Methyl-5-(2,2,3-trimethyl-3-cyclopenten-1-yl)pent-4-en-2-ol	Approved with changes
107898-54-4	3,3-Dimethyl-5-(2,2,3-trimethyl-3-cyclopenten-1-yl)-4-penten-2-ol (polysantol)	Approve with changes
65113-99-7	5-(2,2,3-Trimethyl-3-cyclopentenyl)-3-methylpentan-2-ol	Insufficient data: UV Absorption
72089-08-8	2-Methyl-4(2,2,3-trimethyl-3-cyclopentenyl)butanol	Approved with changes
28219-60-5	2-Methyl-4-(2,2,3-trimethyl-3-cyclopenten-1-yl)-2-buten-1-ol	Insufficient data: Sensitization
28219-61-6	2-Ethyl-4-(2,2,3-trimethyl-3-cyclopenten-1-yl)-2-buten-1-ol	Approved with changes
3293-47-8	Dihydro-beta-ionol	Approved
42866-91-1	p-(2,2-Dimethoxyethyl)toluene	Approved with changes
6314-97-2	Phenylacetaldehyde diethyl acetal	Approved with changes
90-87-9	2-Phenylpropionaldehyde dimethyl acetal	Approved with changes
101-48-4	Phenylacetaldehyde dimethyl acetal	Approved with changes

Highlighted Materials are those with the most data

10) Webinar Presentation by Jean-Pierre Lepoittevin PhD, January 24 9 AM Update: Development of HRMAS NMR spectroscopy in association with RHE to follow and characterize the metabolic transformation/activation of pro-haptens (see Attachment 6).

11) IDEA Update

a) QRA Implementation Update

Dr. Api reported that implementation of QRA2 will begin with the 49th Amendment to the IFRA Code of Practice in 2017. All existing Standards based on sensitization will be converted to QRA2 Standards. They will also all be reviewed for systemic toxicity.

b) IDEA Working Group Meeting on evaluating effectiveness of QRA

Another IDEA Working Group meeting will occur in February. The aim is to develop a method for evaluating the effectiveness of the QRA.

12) Human Health Research Projects

a) Epidemiology

i) Validation of Clinical Relevance Algorithm

Prof. Bruze reported that European Dermato-Epidemiology Network (EDEN) is working on a summary of the clinical relevance validation study.

b) Elicitation Threshold Study on Eugenol

The Panel reviewed preliminary data on this study. They asked for an analysis of the correlation between the strength of the reaction and the repeated open application test results. They also recommended that statistical analyses be conducted on the results.

c) Respiratory Research Program

i) Webinar Presentation by D Botelho on use of MPPD in Safety Assessment Process (see Attachment 7)

The Panel agreed that MPPD (Multiple-Path Particle Dosimetry) model can be used to refine inhalation exposure when necessary. Drs. Api and Botelho will work with Creme Global to incorporate this into the Creme RIFM Aggregate Exposure Model.

d) Photoallergy Research Project

i) **Presentation by G. Ritacco (see Attachment 8)**

ii) **Presentation on in vitro/in vivo photoallergy studies – Doug Learn, Charles River Laboratories (see Attachment 9)**

The Panel recommended the photoallergy research project proceed. Drs. Belsito, Bruze and Tokura will review the protocols in detail and offer suggestions.

13) Environmental Program Update

a) **D. Salvito Presentation on Environmental Program Update (see Attachment 10)**

14) IFRA Standards

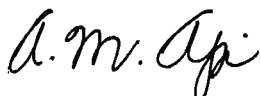
a) Furfural

The Panel recommended that the NOAEL be derived by using the benchmark dose (BMD) technique based on the liver effects in rats from the 13-week NTP study. There was no dose response in the NTP 2-year carcinogenicity study and therefore the Panel did not recommend using BMD or deriving a T25 value. Once the BMD is obtained, it will be shared with the panel for setting the IFRA Standard on furfural.

15) Future Meeting Dates

- | | | |
|----------------------|-------------------|-----------------|
| • Monday – Wednesday | May 22-24, 2017 | Dublin |
| • Monday – Wednesday | Sept. 18-20, 2017 | Berlin |
| • Monday – Wednesday | Jan. 22-24, 2018 | Miami, FL |
| • Monday – Wednesday | May 21-23, 2018 | RIFM |
| • Monday – Wednesday | Sept. 17-19, 2018 | Europe – Paris? |
| • Monday – Wednesday | Jan. 28-30, 2019 | Miami, FL |

Respectfully submitted,



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

Attachment 1: Presentation by webinar from Dr. Hans Merk on Monday January 23: Update on the research project to characterize the cutaneous CYP-dependent metabolism of creosol

Attachment 2a: Presentation by Atish Patel - Repeat Dose Data on furaneol

Attachment 2b: Presentation by Anne Marie Api - Sensitization Data on furaneol

Attachment 3: Presentation by A. M. Api - RIFM Safety Assessment Update and Metrics

- Attachment 4: Presentation by A. M. Api – Interface between RIFM Safety Assessments and IFRA Standard Setting: Process and Alternative Policy
- Attachment 5: Presentation by A. M. Api – NCS Safety Evaluation Strategy
- Attachment 6: Presentation by webinar by Jean-Pierre Lepoittevin PhD, January 24 9 AM Update: Development of HRMAS NMR spectroscopy in association with RHE to follow and characterize the metabolic transformation/activation of pro-haptens
- Attachment 7: Presentation by D. Botelho - use of MPPD in Safety Assessment Process
- Attachment 8: Presentation by G. Ritacco - Photoallergy Research Project
- Attachment 9: Presentation by webinar by Doug Learn, Charles River Laboratories on in vitro/in vivo photoallergy studies
- Attachment 10: Presentation by D. Salvito - Update on the Environmental Program