

EXPERT PANEL FOR FRAGRANCE SAFETY MEETING

Minutes

May 15-17 2023

Tokyo, Japan

| EXPERT PANEL MEMBERS | RIFM STAFF | Guests |
|--|--|---|
| Donald Belsito (Chair) Magnus Bruze Amanda Bryant-Friedrich G. Allen Burton, Jr. Maria Dagli (Vice-Chair) Wolfgang Dekant Allison Fryer Trevor Penning I Glenn Sipes Yoshiki Tokura | Anne Marie Api Danielle Botelho Leah Jones Aurelia Lapczynski (5/16) Isabelle Lee Holger Moustakas (5/17) Gretchen Ritacco | Allison Hilberer (5/15) Andy Forreryd (5/15) |

1) Discussion of the Meeting Schedule and Agenda Topics

- a) Completion/Signing of the Conflict-of-Interest Statement

Dr. Belsito opened the meeting. The Conflict-of-Interest Statement was signed. Dr. Schultz sent his regrets for not attending the meeting.

2) Minutes

The minutes from the January 2023 meeting were approved with no changes.

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's recent publications.

- b) RIFM Safety Assessment Publications

The Panel reviewed the RIFM safety assessment publications list. This list is an ongoing list of all the published safety assessments.

5) RIFM Communication

a) Update on RIFM

Dr. Api provided an overview of RIFM activities. She gave a presentation on the RIFM New Approach Methodologies (NAMs) strategy (see Attachment 1).

b) Communications Update

Mr. Sullivan submitted a written summary update on the RIFM communication plans, safety assessment publications, and the Fragrance Resource Center website.

6) RIFM Safety Evaluation Process

a) Presentation RIFM by D. Botelho Safety Assessment Update and Metrics

Dr. Botelho gave a presentation on the progress of the safety assessment program including the safety assessment update and metrics on naturals (see Attachment 2).

b) Safety Assessment Overview

i) 20 Total Safety Assessments including 28 Total materials

c) General Comments

i) The Panel agreed that the products listed in IFRA Category 6 (oral care) should be rinse-off products when considering phototoxicity.

7) Presentations by Prof. Bruze

a) Photocontact allergy to ketoprofen and simultaneous contact allergies

Dr. Bruze gave a presentation on photoallergy reactions to ketoprofen (see Attachment 3).

b) Photocontact allergy to benzophenone

Dr. Bruze gave a presentation on photoallergy reactions to benzophenone (see Attachment 4).

8) Presentation by Dr. Isabelle Lee– low exposure to fragrance materials

Dr. Lee gave a presentation on low exposure to fragrance materials (see Attachment 5).

9) Review Safety Assessments Batch 1

| CAS # | Material Name | Tab | Status |
|--|---|--------|-----------------------|
| 94201-73-7; 149713-23-5; 149713-24-6 | Tetrahydro-4-methyl-2-phenyl-2H-pyran | Tab 22 | Approved |
| 68738-99-8 | Methyl 2-[[[2,4(or 3,5)-dimethyl-3-cyclohexen-1-yl]methylene]amino]benzoate | Tab 23 | Approved with changes |
| 67634-12-2; 68039-34-9 | Methyl 2-(((4-(4-hydroxy-4-methylpentyl)-3-cyclohexenyl)methylene)amino)benzoate; Benzoic acid, 2-[[[3-(4-hydroxy-4-methylpentyl)-3-cyclohexen-1-yl]methylene]amino],methyl ester | Tab 24 | Approved with changes |
| 54546-26-8 | 2-Butyl-4,4,6-trimethyl-1,3-dioxane | Tab 25 | Approved |
| 5552-30-7 | Cycloionone | Tab 26 | Approved |
| 87-22-9 | Phenethyl salicylate | Tab 27 | Approved |

10) Review Safety Assessments Batch 2

| CAS# | Material Name | Tab | Status |
|--|-----------------------------------|--------|-----------------------------------|
| 25152-85-6 | cis-3-Hexenyl benzoate | Tab 28 | Approved |
| 51755-85-2 | 3-(Methylthio)hexyl acetate | Tab 29 | Approved with changes |
| 67952-65-2; 2882-20-4 | Pyrazine, methyl (methylsulfide)- | Tab 30 | Insufficient data - phototoxicity |
| 94-02-0 | Ethyl benzoylacetate | Tab 31 | Approved |
| 11031-45-1; 77-42-9; 37172-32-0; 115-71-9 | Santalol | Tab 32 | Approved |
| 1009814-14-5 | Yuzunone | Tab 33 | Insufficient data - phototoxicity |
| 1124-11-4 | 2,3,5,6-Tetramethylpyrazine | Tab 34 | Insufficient data - phototoxicity |
| 1193-18-6 | 3-Methyl-2-cyclohexen-1-one | Tab 35 | Approved with changes |

11) Review Safety Assessments Batch 3

| CAS # | Material Name | Tab | Status |
|-----------------------------|---|--------|----------|
| 16356-11-9 | 1,3,5-Undecatriene | Tab 36 | Approved |
| 13623-11-5 | 2,4,5-Trimethylthiazole | Tab 37 | Approved |
| 67583-77-1 | 3,3,5-Trimethylcyclohexyl ethyl ether | Tab 38 | Approved |
| 181258-87-7; 181258-89-9 | Cyclohexane, 1-(1,1-dimethylpropyl)-4-ethoxy-, cis- | Tab 39 | Approved |
| 40910-49-4 | Acetaldehyde ethyl linalyl acetal | Tab 40 | Approved |
| 86611-09-8 | 3,5-Heptadien-1-ol, 1-acetate, (3Z,5E)- | Tab 41 | Approved |

12) Review Safety Assessments Maintenance Batch (Tab 42)

| CAS# | Material Name | Tab | Status |
|-----------------------------|--|--------|---------------------------------------|
| 3720-16-9 | 3-Methyl-5-propyl-2-cyclohexen-1-one | Tab 43 | Approved with changes |
| 6790-58-5; 3738-00-9 | Naphtho[2,1-b]furan, dodecahydro-3a,6,6,9a-tetramethyl-, (3aR,5aS,9aS,9bR)- | Tab 44 | Insufficient data; skin sensitization |
| 338735-71-0; 351343-77-6 | 8H-Indeno(4,5-B)furan,2,3,3a,4,5,5a,6,7,8a,9-decahydro-2,6,6,7,8,8-hexamethyl Mixture of isomers | Tab 45 | Insufficient data; skin sensitization |
| 476332-65-7; 647828-16-8 | 2H-Indeno[4,5b] furan, decahydro-2,2,6,6,7,8,8-heptamethyl | Tab 46 | Insufficient data; skin sensitization |

The Panel reviewed several groups of materials with conflicting data on dermal sensitization and made recommendations on how to draft the safety assessments. They also reviewed the CNIH data on allyl(cyclohexyloxy) acetate (CAS #68901-15-5). Reactions were observed late in the induction phase. In the absence of any additional testing, it must be assumed that the reactions were sensitization. The Panel recommended that the subjects who reacted should be asked to return for a 48 hour patch test with a dilution series of the material. The protocol will be reviewed by the Panel before the study commences.

13) RIFM Research Projects

- a) Overview on research programs

Dr. Api provided an overview on the research programs conducted by RIFM.

b) Epidemiology

Dr. Bruze reported that the EDEN group has not been active due to the pandemic. However, they will meet on June 12 to continue their evaluation of all the data from the study.

c) Eugenol Threshold Study

Dr. Bruze reported that the manuscript on the threshold study on eugenol was accepted by Contact Dermatitis.

d) Skin Sensitization Research Projects

i) **Presentations by Andy Forreryd, PhD and Isabelle Lee, PhD**

Dr. Forreryd (SenzaGen) presented data on the development of the Gard Dose Response Assay and the photoGard Assay (see Attachment 6). Dr. Lee presented an analysis of the Gard Dose Response Assay (see Attachment 7). An update on epoxide research was deferred to the next meeting.

e) Phototoxicity and Photoallergy

i) **Presentation on RIFM SenzaGen Photoallergy Research, Andy Forreryd, PhD, SenzaGen**

Dr. Forreryd (SenzaGen) presented data on the development of the Gard Dose Response Assay and the photoGard Assay (see Attachment 6).

ii) **Presentation by Allison Hilberer, M.S., DABT, Senior Toxicologist, Institute For In Vitro Sciences, Inc. (IIVS)**

Ms. Hilberer, Institute For In Vitro Sciences, Inc. (IIVS), gave a presentation on the work the IIVS has done on developing Photo-DPRA, Photo-Keratinosens and photo-HCLAT (See Attachment 8).

iii) **Presentation by G. Ritacco on the RIFM photoallergy projects**

Ms. Ritacco gave a presentation on the RIFM photoallergy projects (see Attachment 9).

f) **Presentation by A. Lapczynski on an in vitro environmental assay**

Ms. Lapczynski gave a presentation on the new Hyalella Azteca BCF test (see Attachment 10).

g) **Presentation on RIFM Grouping and Read-Across by Holger Moustakas, PhD**

Dr. Moustakas gave a presentation on the RIFM grouping and read across approach (see Attachment 11).

14) New Expert Panel Members

The Panel discussed potential new Panel members.

15) Panel Executive Session

The Panel held an Executive Session.

16) Future Meeting Dates

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|-----------------------|-----------------------|----------------|
| • Monday – Wednesday, | September 25-27, 2023 | New Jersey |
| • Monday-Wednesday, | Jan. 22-24, 2024 | San Diego, CA |
| • Monday-Wednesday, | May 20-22, 2024 | Edinburgh |
| • Monday-Wednesday, | September 23-25, 2024 | New Jersey |
| • Monday-Wednesday, | January 27-29, 2025 | San Diego, CA |
| • Monday-Wednesday, | May 19-21, 2025 | Warsaw, Poland |

Respectfully submitted,



Anne Marie Api, Ph.D., ATS
President

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| Attachment 1: | Presentation: Dr. Anne Marie Api |
| Attachment 2: | Presentation: Dr. Danielle Botelho |
| Attachment 3: | Presentation: Dr. Magnus Bruze |
| Attachment 4: | Presentation: Dr. Magnus Bruze |
| Attachment 5: | Presentation: Dr. Isabelle Lee |
| Attachment 6: | Presentation: Dr. Andy Forreryd |
| Attachment 7: | Presentation: Dr. Isabelle Lee |
| Attachment 8: | Presentation: Ms. Allison Hilberer. |
| Attachment 9: | Presentation: Ms. Gretchen Ritacco |
| Attachment 10: | Presentation: Ms. Aurelia Lapczynski |
| Attachment 11: | Presentation: Dr. Holger Moustakas |