

EXPERT PANEL FOR FRAGRANCE SAFETY MEETING

Minutes Virtual Meeting

January 24-27, 2022

EXPERT PANEL MEMBERS	RIFM STAFF		Guests
Donald Belsito (Chair) Magnus Bruze G. Allen Burton, Jr. Maria Dagli (Vice-Chair) Wolfgang Dekant Allison Fryer Dan Liebler Trevor Penning Terry Schultz I Glenn Sipes Yoshiki Tokura	Anne Marie Api Danielle Botelho Olive Chon (1/24) Chaitra Deodhar Leah Jones Kaushal Joshi Manoj Kumar Maura Lavelle Aurelia Lapczynski (1/24-26)	Isabelle Lee Holger Moustakas Mihwa Na Gretchen Ritacco Jim Romine Christen Sachse- Vasquez (1/27) Dan Selechnik Yax Thakkar	Martyn Chilton (1/25) Hannah Jones (1/27) Paul Thomas (1/26)

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 electronically.

2) Minutes

The minutes from the September 2021 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. Romine provided an overview of RIFM (see Attachment 1).

b) Presentation by A.M. Api

Dr. Api provided an update on the proposed animal testing policy (see Attachment 2).

6) RIFM Safety Evaluation Process

a) Presentation RIFM by D. Botelho Safety Assessment Update, Metrics, NCS timetable

Dr. Botelho gave a presentation on the Safety Assessment program and progress (see Attachment 3).

b) Safety Assessment Overview

The Panel reviewed 22 Safety Assessments including 24 materials.

c) General Comments

There were no general comments on the safety assessments.

7) NCS Safety Assessments

a) Demonstration of NCS template – Christen Sachse-Vasquez (Thursday, Jan. 27)

8) Follow-up on actions for Safety Assessment

a) Eugenyl methyl ether CAS No. 93-15-2 and Estragole CAS No. 140-67-0

A virtual meeting was held on January 11, 2022, between the members of the Expert Panels for Fragrance Safety and the FEMA Expert Panel to discuss the data on alkoxybenzenes. After the meeting, the RIFM and FEMA staff discussed the differences in the derived benchmark doses (BMDL10) for methyl eugenol and estragole. Dr. Selechnik gave a presentation to report on the results (see Attachment 4). The Panel wanted to review the Van den berg et al., 2011 and Miller et al., 1983 papers again in more detail. The Panel agrees that a joint publication with the FEMA Expert Panel is needed to detail the limitations of the estragole data and to agree on the BMDL10 value.

9) Presentation by K. Joshi and D. Selechnik – estimating reproduction NOAEL

Drs. Joshi and Selechnik gave a presentation on developmental and reproductive toxicity (DART) Point of Departure (PoD) extrapolation (see Tab 18 in the Panel agenda items). This method of estimating the DART decision tree (Wu et al., 2013) can be useful in informing the appropriate magnitude of a database uncertainty factor to account for a missing reproductive and/or developmental toxicity study when repeat dose data are available (Blackburn et al., 2015). In principle, the Panel agreed with the approach. However, they would like to know the opinion of the Reproduction Adjunct Team and get their feedback during the next Panel meeting. In addition, they would like to review a few examples of when this approach may be used. The Panel wanted to learn more about the basis for the safety factors that are used.

10) Furocoumarin proposal

At the January 2022 meeting of the Expert Panel for Fragrance Safety, a proposal for a draft policy for IFRA Standards on citrus oils and other natural complex substances (NCS) containing furocoumarins was reviewed. Furocoumarins are natural constituents of citrus oils and some other NCS that are used as ingredients in fragrance creations. They are not used and should not be used as such as direct fragrance ingredients. The draft policy limits the total furocoumarins by limiting 7 marker furocoumarins (Bergamottin, Byacangelicol, epoxy-Bergamottin, Isopimpinellin, 5-Methoxypsoralen [5-MOP, Bergapten], 8-Methoxypsoralen [8-MOP, Methoxsalen, Xanthotoxin] and Oxypeucedanin). In principle, the Expert Panel agreed with the proposal, but had the following comments and suggestions:

- The category of “Sun protection and bronzing products” should be more explicit. Lip products and products applied to the face (e.g., facial creams and make-up) may have the same sun exposure as sun protection products. These products should be included in this category
- The Panel would like to see a summary table of the data (with species, doses in mg/cm², UVA dose, and the occlusion time clearly identified) that are used to support the proposal.
- The Panel agrees that Bergamottin does not have to be included as a marker because the material does not exhibit photoirritation potential.

11) Review Safety Assessments Batch 1

CAS #	Material Name	Tab	Status
285977-85-7	1h-indende-2-methanol, 2,3-dihydro-2,5-dimethyl-	Tab 22	Approved
84560-00-9	2-pentylcyclopentan-1-ol;2-pentylcyclopentanol;cyclopentanol, 2-pentyl-	Tab 23	Approved
591-12-8	4-Hydroxy-3-pentenoic acid lactone	Tab 24	Approved
1073-29-6	o-(Methylthio)-phenol	Tab 25	Approved
15111-96-3	p-Mentha-1,8-dien-7-yl acetate	Tab 26	Approved
1195-32-0	p,alpha-Dimethylstyrene	Tab 27	Approved
110-89-4	Piperidine	Tab 28	Approved
4728-82-9	Allyl cyclohexaneacetate	Tab 29	Approved
2986-54-1	Methoxycyclododecane	Tab 30	Approved
179911-08-1	N-Ethyl-N-(3-methylphenyl)propionamide	Tab 31	Approved with changes
53767-86-5	7-Methoxy-3,7-dimethyloct-1-ene	Tab 32	Approved with changes
23550-40-5	4-(Methylthio)-4-methyl-2-pentanone	Tab 33	Approved

12) Review Safety Assessments Batch 2

CAS#	Material Name	Tab	Status
25485-88-5	Cyclohexyl salicylate	Tab 34	Approved
27113-22-0	1-(4-Hydroxy-3-methoxyphenyl)decan-3-one	Tab 35	Approved with changes
28588-74-1	2-Methyl-3-furanthiol	Tab 36	Approved
513-86-0	Acetoin	Tab 37	Approved
60066-88-8	beta-Sinensal	Tab 38	Approved
67634-00-8; 67634-01-9	Allyl (3-methylbutoxy)acetate	Tab 39	Approved with changes
68132-80-9; 71500-37-3	Allyl trimethylhexanoate	Tab 40	Approved with changes
7493-74-5	Allyl phenoxyacetate	Tab 41	Approved
90-05-1	Guaiacol	Tab 42	Approved
91-10-1	2,6-Dimethoxyphenol	Tab 43	Approved

13) Review Safety Assessments Maintenance Batch (Tab 44)

CAS#	Material Name	Tab	Status
74499-60-8	1-(1,2,3,4-Tetrahydro-4,4-dimethyl-1-naphthyl)propan-1-one	Tab 45	Approved
25304-14-7	1-(3,3-Dimethylcyclohexyl)ethan-1-one	Tab 46	Approved
123-11-5	p-methoxybenzaldehyde	Tab 47	Approved

14) RIFM Research Projects

a) Epidemiology

Prof. Bruze reported that there are no updates from the EDEN Epidemiology study because they have not been unable to meet.

i) Eugenol Threshold Study

Prof. Bruze and Dr. Robert Ofenloch (Research Associate, post-doctoral fellow at University Hospital Heidelberg) recently addressed the comments on the manuscript on the eugenol study. After this version of the manuscript has been reviewed, it will be returned to them.

b) Report from M. Kumar/H. Moustakas on read-across2 and NCS Cluster manuscripts

Dr. Liebler reported that he is editing the latest draft of the read-across2 paper and will circulate it to the other authors. He noted that the manuscript is too long and needs to be edited. This manuscript will be given a higher priority for publication than the NCS cluster manuscript.

Drs. Kumar and Moustakas will draft the first version of the NCS cluster paper. This manuscript is still being targeted for completion in 2022.

c) Skin Sensitization Research Projects

i) Presentation by M. Lavelle on HRIPT protocol updates

Ms. Lavelle gave a presentation to update the Panel on the status of the modified HRIPT protocols (see Attachment 5). The Panel concluded that the reaction observed in one panelist during the irritation pre-screen to L-Piperitone is a pre-sensitization reaction; no other reactions were observed. The full study can begin as planned.

ii) Presentation by M. Na on GARDSkin assay results

Dr. Na provided an update on the GARDSkin assay results (see Attachment 6). The Panel felt that this model is promising and work should continue.

iii) Presentation by I. Lee and H. Moustakas on epoxide research update

Drs. Lee and Moustakas provided an introduction to the epoxide research program, the progress made and the plans for the project (see Attachment 7). The Panel felt that this model is promising and work should continue. Dr. Schultz volunteered to help in the initial review of identifying appropriate and relevant materials to test.

iv) Presentation by Martyn Chilton on DST project - Tuesday, January 25 at 8:30 AM

Dr. Chilton (Lhasa Limited) provided an update on a collaborative project between Lhasa Limited and RIFM on updating the Dermal Sensitization Thresholds (see Attachment 8). This was very well received and the Panel will review the draft manuscript on the project.

d) Environmental Research Projects

i) Presentation by A. Lapczynski – update on Eco-TTC and biodegradation projects

Ms. Aurelia Lapczynski provided an update on several environmental research projects including the eco-TTC and biodegradation projects (see Attachment 9).

ii) Presentation by Paul Thomas on CHANCES2 project Wednesday, January 26 at 8:30 AM

Dr. Paul Thomas provided an update on the CHANCES2 project (see Attachment 10). This work will be presented at the SETAC meeting later this year. The Panel agreed that the chronic daphnia study should be conducted and they agreed to proceed with the next phase of the program which will include testing another fragrance ingredient.

e) **Respiratory Research Projects**

i) **Presentation by N. Sadekar - Respiratory Research Program Update**

Dr. Sadekar provided an update on the respiratory research projects (see Attachment 11). She also provided an update on the use of the MPPD Model, which is an assessment model developed to study the uptake of vapors and deposition of aerosol particulate/droplet components using a computational model of the nasal and lung airways of humans and rats (see Attachment 12).

f) **Genotoxicity**

i) **Presentation by Hannah Jones, Certara on the biosimulation software Simcyp (Thursday, January 27 at 8:30 AM)**

Mr. Thakkar provided an introduction on the role that physiological-based pharmacokinetic modeling and simulation (PBPK) could have in genotoxicity testing (see Attachment 13). Dr. Hanna Jones, Simcyp, Certara explained how the Simcyp Population-based Simulator works (see Attachment 14). The Panel recommended that the proposed project of selecting 10 fragrance materials with in vivo studies is a good beginning to evaluate how the model may be useful.

15) 3-Acetyl-2,5-dimethylfuran (CAS#10599-70-9)

Mr. Thakkar gave a presentation on the genotoxicity data available on 3-Acetyl-2,5-dimethylfuran (CAS#10599-70-9) (see Attachment 15). The Panel suggested that more details on the studies are needed. They also recommended that the Genotoxicity Adjunct Group be consulted.

16) New Expert Panel Members

The Panel discussed the possibility of adding new experts to the Panel, however, they felt it would be best to wait for an in-person meeting.

17) Panel Executive Session

No executive session was required.

18) Future Meeting Dates

- Wednesday - Friday, May (10)-13, 2022 New Jersey
 - SETAC Europe (Copenhagen) May 15-19, 2022
- Monday – Wednesday, Sept. 19-21, 2022 Portugal?
- Wednesday - Friday, Jan. 18-20, 2023 Puerto Rico?
- Monday - Wednesday, May 15-17, 2023 Europe/Tokyo?
 - May 10-13, 2023 ISID (International Societies for Investigative Dermatology), Tokyo, Japan
- Monday – Wednesday, September 25-27, 2023 New Jersey
- Monday-Wednesday, Jan. 22-24, 2024 Miami/Puerto Rico?

Respectfully submitted,



Anne Marie Api, Ph.D., ATS
Vice President

Attachment 1:	Presentation: Dr. James Romine
Attachment 2:	Presentation: Dr. Anne Marie Api
Attachment 3:	Presentation: Dr. Danielle Botelho
Attachment 4:	Presentation: Dr. Dan Selechnik
Attachment 5:	Presentation: Ms. Maura Lavelle
Attachment 6:	Presentation: Dr. Mihwa Na
Attachment 7:	Presentation: Drs. Isabelle Lee and Holger Moustakas
Attachment 8:	Presentation: Dr. Martyn Chilton
Attachment 9:	Presentation: Ms. Aurelia Lapczynski
Attachment 10:	Presentation: Dr. Paul Thomas
Attachment 11:	Presentation: Ms. Gretchen Ritacco
Attachment 12:	Presentation: Dr. Nikaeta Sadekar
Attachment 13:	Presentation: Mr. Yax Thakkar
Attachment 14:	Presentation: Dr. Hannah Jones
Attachment 15:	Presentation: Mr. Yax Thakkar