ADMIN

Memo

Agenda

Minutes

Read-Across Resource Document

Strategy Memo: Silicates

Re-Review Summaries

- Isopropyl Lanolate
- Napthalenesulfonate

CIR EXPERT PANEL MEETING DECEMBER 9-10, 2019

Cosmetic Ingredient Review

Commitment & Credibility since 1976

MEMORANDUM

To: CIR Expert Panel Members and Liaisons
From: Bart Heldreth, Ph.D., Executive Director, Cosmetic Ingredient Review
Subject: 153rd Meeting of the CIR Expert Panel — Monday and Tuesday, December 9-10, 2019
Date: November 15, 2019

Welcome to the December 2019 CIR Expert Panel Meeting. Enclosed are the agenda and accompanying materials for the 153rd CIR Expert Panel Meeting to be held on December 9-10, 2019. The location is the same as the last meeting – The Westin Hotel, Washington, D.C. City Center, 1400 M St NW, Washington, District of Columbia, 20005. Phone: (202) 429-1700.

CIR is very excited to announce the addition of our newest Expert Panel member, Dr. Lisa Peterson. Dr. Peterson was appointed by the CIR Steering Committee to fill the vacancy on the Marks team. Welcome!

The meeting agenda includes the consideration of 15 reports advancing in the review process, including 6 final reports, 4 tentative reports, 4 draft reports, and 1 re-review. Also, on the agenda are 2 re-review summaries, a stragey memo regarding Silicates, and a new draft of the Read-Across Resource Document.

Schedule and hotel accommodations

We have reserved rooms for the nights of Sunday, December 8th and Monday, December 9th at the Westin Hotel. If you encounter travel problems, please contact Monice on her cell phone at 703-801-8156.

Team Meetings

Draft Reports - there are 4 draft reports for review. – Sufficient data to proceed or issue an IDA?

1. Coconut – This is the first time the Panel is reviewing the safety of these 9 *Cocos nucifera* (coconut)-derived ingredients. These ingredients are reported to function in cosmetics as skin-conditioning agents, while some are reported to have other functions, such as humectants, abrasives, and hair conditioning agents.

   The Panel should note that in botanical cosmetic ingredients, the term “water” refers to the aqueous solution of the steam distillate of plant parts; however, in the food industry, “coconut water” is the common term for the endosperm liquid of the coconut fruit.

   In addition to submitted concentration of use survey data, the following unpublished data were also provided: human dermal irritation and sensitization data on Cocos Nucifera (Coconut) Liquid Endosperm and method of manufacturing and specifications for Cocos Nucifera (Coconut) Fruit Extract. Additionally, comments on the Scientific Literature Review (SLR) were received from the Council and addressed.

   According to 2019 VCRP data, Cocos Nucifera (Coconut) Fruit Extract is reported to be used in 429 formulations, 222 of which are leave-on formulations. All other in-use ingredients are reported to be used in 64 formulations or less. The results of the concentration of use survey conducted by the

Council in 2019 indicate that Cocos Nucifera (Coconut) Liquid Endosperm has the highest maximum concentration of use; it is used at up to 6.5% in shampoos (non-coloring). Cocos Nucifera (Coconut) Liquid Endosperm also has the highest maximum concentration of use in dermal leave-on formulations; it is used at up to 1.5% in face and neck products. Cocos Nucifera (Coconut) Fruit Extract is reported to be used at up to 0.12% in leave-on hair products.

After reviewing these documents, if the available data are deemed sufficient to make a determination of safety, the Panel should issue a Tentative Report with a safe as used, safe with qualifications, or unsafe conclusion, and Discussion items should be identified. If the available data are insufficient, the Panel should issue an Insufficient Data Announcement (IDA), specifying the data needs therein.

2. Amino Acid Diacetates – This is the first time the Panel is reviewing the safety of Beta-Alanine Diacetic Acid and Tetrasodium Glutamate Diacetate. These *N,N*-diacetate-substituted amino acid ingredients are reported to function in cosmetics as chelating agents.

   The Council provided concentration of use survey data and human dermal irritation and sensitization data on Tetrasodium Glutamate Diacetate. Comments on the SLR were received from the Council and addressed.

   According to 2019 VCRP survey data, Tetrasodium Glutamate Diacetate is used in a total of 794 formulations; the majority of the uses are in bath soaps and detergents. Beta-Alanine Diacetic Acid is reported to be used in only 2 leave-on formulations: a moisturizing skin care product and “other” hair preparations. The results of the concentration of use survey conducted by the Council in 2018 indicate that Tetrasodium Glutamate Diacetate is used at up to 1%; this concentration is reported for deodorants (non-spray). No concentrations of use were reported for Beta-Alanine Diacetic Acid.

   If no further data are needed to reach a conclusion of safety, the Panel should formulate a Discussion and issue a Tentative Report. However, if additional data are required, the Panel should be prepared to identify those needs and issue an IDA.

3. Polysilicone-11 – This is the first time the Panel is reviewing the safety of Polysilicone-11. This ingredient is a crosslinked dimethylsiloxane, formed by the reaction of bis-vinyldimethicone and hydrogen dimethicone, and is reported to function as a film former in cosmetics.

   Following an intensive search of information in the published scientific literature, online databases, and other sources on this ingredient, there was insufficient information found to justify preparation of a formal SLR. Therefore, in July 2019, CIR issued a SLR Notice to Proceed (NTP) for Polysilicone-11 to alert interested parties that a safety assessment is being prepared and to request information in multiple areas, including:

   - Chemistry information, including composition and structure, method of manufacture, and impurity data
   - Toxicokinetics data relevant to routes of exposure expected with cosmetic use
   - General toxicity data
   - Developmental and reproductive toxicity data
   - Genotoxicity data
   - Carcinogenicity data
   - Dermal irritation and sensitization data
   - Inhalation toxicity data
   - Any other relevant safety information that may be available

   Since the issuing of the SLR NTP, the following unpublished data have been received and included in this packet:

   - Summary information regarding 2 human repeat insult patch tests (HRIPTs) on a leave-on product containing 9.675% Polysilicone-11 and a rinse-off product containing 19.830% Polysilicone-11
   - An in vitro tissue equivalent assay to evaluate the ocular irritation potential of a face cream containing 1.6% Polysilicone-11
   - A human cumulative irritation patch test on a face cream containing 1.6% Polysilicone-11

- Acute oral toxicity, skin irritation, eye irritation, sensitization, and genotoxicity summary information on different mixtures containing Polysilicone-11
- General method of manufacturing information
- A 48-hour patch test performed using a lipstick containing 1.8% Polysilicone-11
- A MatTek EpiOcular™ methylthiazole tetrazolium (MTT) viability assay on a test substance containing 98.5% Polysilicone-11
- A human dermal maximization assay performed to evaluate the contact-sensitization potential of a liquid blend containing 24.625% Polysilicone-11
- An HRIPT on a product containing 1.45% Polysilicone-11

After reviewing this document, if the available data are deemed sufficient to make a determination of safety, the Panel should issue a Tentative Report with a safe as used, safe with qualifications, or unsafe conclusion, and Discussion items should be identified. If the available data are insufficient, the Panel should issue an IDA, specifying the data needs therein.

4. Honey – This is the first time the Panel a safety assessment on these 7 honey derived-ingredients. In addition to information found in the published literature, the report package includes the following unpublished data that were received from the Council:
    - Use concentration data
    - Information regarding the manufacturing process, specifications, and ingredient breakdown of a tradename mixture containing 10.6% Honey Extract
    - Information regarding the manufacturing process, specifications, and ingredient breakdown of a tradename mixture containing 16.5% Honey Extract
    - An HRIPT performed on 102 subjects using a product containing 7% Honey Extract
    - Manufacturing information, heavy metal analysis, and physical and chemical properties of a Honey Extract

    Additionally, comments were provided by Council on the SLR and have been addressed. After reviewing these documents, if the available data are deemed sufficient to make a determination of safety, the Panel should issue a Tentative Report with a safe as used, safe with qualifications, or unsafe conclusion, and Discussion items should be identified. If the available data are insufficient, the Panel should issue an IDA, specifying the data needs therein.

Draft Tentative Reports – there are 4 draft tentative reports.

1. Vanilla – At the June 2019 meeting, the Panel issued an IDA for this ingredient group. The Panel requested the following data on Vanilla Planifolia Flower Extract:

    - Composition
    - Method of manufacture and impurities
    - Concentration of use
    - 28-day dermal toxicity
        - Depending on the results, other toxicological endpoints may be needed (e.g., genotoxicity and DART)

    To date, there has been no response to the above data requests. However, a summary of the HRIPT on a leave-on product containing 0.02% Vanilla Planifolia Fruit Extract was received from the Council. In spite of the insufficient data determination for Vanilla Planifolia Flower Extract, the Panel agreed that the available data are supportive of the safety of the remaining ingredients.

    After reviewing these documents, the Panel should issue a Tentative Report with a safe as used, safe with qualifications, unsafe, or insufficient data conclusion (or a split conclusion). Additionally, Discussion items should be identified.

2. Caprylhydroxamic Acid – At the June 2019 meeting, the Panel found that the data were insufficient to determine the safety of this ingredient as used in cosmetics.

Several HRIPTs were included in the Draft Report that described testing with varying concentrations of Caprylhydroxamic Acid. Although the test results are largely negative, there were some alerts for sensitization in HRIPTs on formulations containing less than the maximum reported use concentration of Caprylhydroxamic Acid. Because the potential for sensitization could not be ruled out completely based on the reactions observed in the HRIPTs, and because of the reported reactions to Caprylhydroxamic Acid in a reformulated moisturizer in Finland and the absence of a local lymph node assay or guinea pig maximization test to demonstrate a lack of sensitization potential, the following were requested:

- Human repeated insult patch test at maximum use concentrations
  - the Panel has requested that the study includes a minimum of 100 subjects, preferably with Fitzpatrick skin types 1-4
- A quantitative risk assessment (QRA) should be performed, and a no-expected-sensitization-induction-level (NESIL) should be determined

The CIR has been made aware that an HRIPT has been commissioned, but a study report (and therefore, a NESIL) has not yet been received. Dermal penetration data were submitted to the Panel in Wave 2 of the June meeting. This information has been added to the report.

Because the Panel is aware that requested data are expected to be forthcoming in the near future, the Panel has the option to table this review until the data are received. However, if this option is chosen, the Panel is asked to set a schedule for when the report will return for their consideration. Alternatively, the Panel can formulate a tentative conclusion and issue a Tentative Report for public comment, and if appropriate, re-evaluate the conclusion when the requested data are received.

3. Glycerin Ethoxylates – At the June 2019 meeting, the Panel issued an IDA for method of manufacture, impurities, and inhalation toxicity data. Since then, the following unpublished data were received and have been incorporated into the document:

   Glycereth-26
   - Certificate of Analysis
   - Safety testing summary (includes acute oral, ocular irritation, and dermal irritation studies)
   - Topical application EpiOcular™ ocular irritation assay
   - Summary of an HRIPT on product containing 3%

   Glycereth-7
   - Summary of an HRIPT on product containing 0.68%

   The Panel should carefully consider and discuss the data (or lack thereof), ensure that the draft Abstract and Discussion presented in this report are in-line with their thinking, and issue a Tentative Report with a safe, safe with qualifications, unsafe, insufficient data, or split conclusion.

4. Soy – At the June 2019 Panel meeting, an IDA was issued. In order to make a conclusion of safety on these ingredients, the Panel requested sensitization data on either Glycine Max or Glycine Soja (Soybean) Seed Extract at the current maximum use concentration of 2%. In addition, the Panel requested data identifying the composition, method of manufacture, or general characteristics of the callus-derived ingredients.

   The current report package includes the following unpublished data that were received from the Council since the previous iteration of this report.

   - An HRIPT on a skin care preparation containing 0.198% Glycine Soja (Soybean) Seed Extract
   - A summary of an HRIPT on a leave-on product containing 3% Glycine Soja (Soybean) Seed Extract

The Panel should carefully consider and discuss the data (or lack thereof), ensure that the Abstract and draft Discussion presented in this report are in-line with their thinking, and issue a Tentative Report with a safe, safe with qualifications, unsafe, insufficient data, or split conclusion.

Draft Final Reports - there are 6 draft final reports for consideration (including 2 amended reports). After reviewing these drafts, especially the rationales provided in the Discussion sections, the Panel should issue them as Final Reports, as appropriate.

1. MIPA – At the September 2019 meeting, the Panel issued a Tentative Report with the conclusion that these 14 alkyl amide MIPA ingredients are safe in cosmetics in the present practices of use and concentration described in this safety assessment when formulated to be non-irritating.

   The ECHA data have been clarified in this version of the report, specifically in regard to substances that were provided as read-across sources. These data are incorporated into the CIR safety assessment because the Panel determined that the data that ECHA used for read-across were applicable to fulfill the data needs for the missing data endpoints on these alkyl amide MIPA ingredients. The CIR staff did not include information from the CIR report on diethanolamides in the current assessment of alkyl amide MIPA ingredients because, at the April meeting, the Panel decided to not include those data.

   The Panel should review the Abstract, Discussion, and Conclusion and issue a Final Report.

2. Pomegranate – At the September meeting, the Panel concluded that the data were insufficient to support a determination of safety for the 18 *Punica granatum*-derived ingredients. The Panel's data needs were:

   - A no-observed-effect-level (NOEL) for skin lightening effects for all ingredients
   - Method of manufacturing with special regard to solvent-type used for the extracts
   - For Punica Granatum Bark Extract, Punica Granatum Bark/Fruit Extract, Punica Granatum Callus Culture Extract, Punica Granatum Flower Extract, Punica Granatum Fruit/Root/Stem Powder, Punica Granatum Leaf Cell Extract, and Punica Granatum Peel Extract
     - Composition and impurities data
     - Systemic toxicity data
     - Dermal irritation and sensitization data

   Since the September Panel meeting, CIR has received method of manufacturing and specifications data for Punica Granatum Fruit Extract, which have been incorporated into the report. No other data have been received.

   The Panel should carefully review the Abstract, Discussion, and Conclusion of this safety assessment. If these are satisfactory, then the Panel should issue a Final Report.

3. MCI/MI – At the September 2019 meeting, the Panel tentatively concluded that the ingredient mixture MCI/MI is safe in cosmetics when formulated to be non-sensitizing, based on the results of a QRA or similar methodology; however, at no point should concentrations exceed 7.5 ppm in leave-on products or 15 ppm in rinse-off products.

   The Panel also concluded that the data are insufficient to support the safety of MCI/MI in products that may be incidentally inhaled. The Panel requested an inhalation study of at least 3 months in duration that is in accordance with the OECD TG 413. This request is in response to reports of adverse events observed in infants following inhalation exposure to humidifier disinfectants that contained this preservative mixture.

   No additional data have been received. Comments from the Council on the Draft Tentative Amended Report that were received before the September meeting, and those on the Tentative Amended Report, have been considered and are included in this report package. CIR staff have also received comments from the CIR Science and Support Committee (CIR SSC) regarding the report's current conclusion, which the Panel should also review.

The Panel should carefully consider the Abstract, Discussion, and Conclusion presented in this report. If these are satisfactory, the Panel should issue a Final Amended Report.

4. Mannitol – At the September 2019 meeting, the Panel concluded that these 3 sugar alcohols are safe in the present practices of use and concentration described in the safety assessment. The safety of these ingredients was supported by a lack of evidence of systemic toxicity, sensitization, irritation, and adverse clinical reports.

   The Panel should carefully consider the Abstract, Discussion, and Conclusion presented in this report. If these are satisfactory, the Panel should issue a Final Report.

5. Palm – At the September 2019 meeting, the Panel issued a Tentative Report with the following conclusions: Euterpe Oleracea Fruit Extract, Euterpe Oleracea Juice, and Euterpe Oleracea Pulp Powder are safe in cosmetics in the present practices of use and concentration described in the safety assessment when formulated to be non-sensitizing. The Panel further concluded that the available data are insufficient to support a conclusion of safety for 5 ingredients under intended conditions of use in cosmetic formulations. The data needs on these 5 ingredients are listed below.

   Euterpe Edulis Fruit Extract and Euterpe Edulis Juice Extract
   - Method of manufacture
   - Skin irritation and sensitization

   Euterpe Oleracea Seed Powder and Hydrolyzed Euterpe Oleracea Fruit
   - Method of manufacture

   Euterpe Oleracea Palm Heart Extract
   - Skin irritation and sensitization

   To date, there has been no response to the above data requests. The Panel should carefully consider the Abstract, Discussion, and Conclusion presented in this report. If these are satisfactory, the Panel should issue a Final Report.

6. Capryloyl Salicylic Acid – At the September 2019 meeting, the Panel issued a Tentative Amended Report with the following conclusion on this ingredient: the Panel concluded that the data were insufficient to support a determination of safety for Capryloyl Salicylic Acid under intended conditions of use in cosmetic formulations. The data needs to assess the safety of this ingredient are listed below:
   - Impurities
   - Phototoxicity

   To date, there has been no response to the above data requests. The Panel should carefully consider the Abstract, Discussion, and Conclusion presented in this report. If these are satisfactory, the Panel should issue a Final Amended Report.

Re-Review – there is 1 Re-Review. Do the data, or other changes since prior review, warrant re-opening?

1. Methicones – The CIR Expert Panel first published a safety assessment of these 20 ingredients in 2003. The Panel considered it unlikely for any of these polymers to be absorbed into the skin due to their large molecular weights and low concentrations of use; hence, the Panel concluded that these ingredients are safe as used in cosmetic products.

   The Panel reached this conclusion in spite of having limited inhalation exposure data. However, relatively few ingredients were used in aerosol formulations at the time, and the Panel was informed that formulations containing these ingredients would not likely be inhaled. In particular, it was stated that expected particle sizes would primarily be in the range of 60 to 80 microns, and less than 1% would be under 10 microns.

   In accordance with CIR Procedures, because it has been at least 15 years since the original safety

assessment was published, the Panel should again consider whether the safety assessment of Stearoxy Dimethicone, Dimethicone, Methicone, Amino Bispropyl Dimethicone, Aminopropyl Dimethicone, Amodimethicone, Amodimethicone Hydroxystearate, Behenoxy Dimethicone, C24-28 Alkyl Methicone, C30-45 Alkyl Methicone, C30-45 Alkyl Dimethicone, Cetearyl Methicone, Cetyl Dimethicone, Dimethoxysilyl Ethylenediaminopropyl Dimethicone, Hexyl Methicone, Hydroxypropyldimethicone, Stearamidopropyl Dimethicone, Stearyl Dimethicone, Stearyl Methicone, and Vinyl Dimethicone should be re-opened. An exhaustive search of the world's literature was performed for studies dated 1998 forward. A brief synopsis of the relevant new data is enclosed.

Frequency and concentration of use have generally increased for these ingredients, with some of the increases being quite significant. Particularly, the frequency of use of Dimethicone has increased from 1659 uses in 1998, to 12,934 uses in 2019. The reported maximum concentration of use of Dimethicone also increased, from 80% to 85%. Also, although the concentration of use of Methicone actually decreased, the number of uses increased, from none reported in 1998 to 600 uses reported in 2019. Current and historical frequency of use and concentration data have been provided for your review.

Furthermore, the number of products that could be incidentally inhaled (potential sprays or powders) has increased, especially in Amodimethicone (3 in 1998 to 191 in 2019), Cetearyl Methicone (not reported in 1998 to 40 in 2019), Cetyl Dimethicone (6 in 1998 to 44 in 2019), Dimethicone (56 in 1998 to 114 in 2019), and Methicone (not reported in 1998 to 22 in 2019). Of note, the reported use and maximum concentration in formulations near the eye has also increased for Dimethicone, with 1822 uses and 37.8% (compared to 111 uses in 1998 and 13% in 1999), for Methicone with 160 uses (compared to not reported in 1998), and for Cetyl Dimethicone with 58 uses (compared to 5 uses in 1998). Three ingredients were not reported to be in use, while one ingredient was not surveyed. The results of the concentration of use survey conducted by the Council (collected in 2018; updated in 2019) and 2019 FDA VCRP data are included with this submission.

If, upon review of the new studies and/or updated use data, the Panel determines that a re-review is warranted, a full draft amended report will be presented at an upcoming meeting.

Administrative Items - there are 2 re-review summaries, 1 strategy memo, and 1 resource document.

Re-Review Summaries - The Panel considered the re-review of these ingredients at the June 2019 meeting, and determined that these reports should not be re-opened. The re-review summaries are included for Panel review:

1. Naphthalenesulfonate
2. Isopropyl Lanolate

Strategy Memo

1. Silicates – In June 2018, the Panel considered the re-review of the CIR Final Report on the safety assessment of various silicates, which was published in 2003. This re-review proposed the addition of 14 possible "add-on" ingredients that had not yet been looked at by CIR; Potassium Silicate, Sodium Metasilicate, and Sodium Silicate from the safety assessment published in 2005; and 6 ingredients from the Safety Assessment of Silica and Related Cosmetic Ingredients that was finalized in 2009. The Panel voted to re-open the 2003 review of the 17 ingredients and include 23 additional ingredients.

   In subsequent meetings (April 2019 and September 2019), the Panel decided to split off Silica and Hydrated Silica into a report separate from the remaining 38 ingredients due to concerns over ingredient sourcing and potential constituents/impurities from the sourcing. The Panel tentatively determined that the data were insufficient to support safety of the outstanding 38 ingredients, although the conclusions of safety for the re-reviewed ingredients still stand officially (safe as used). The Panel charged CIR staff to propose sensible grouping of the remaining ingredients into reports for new re-reviews. Please consider the groupings provided in the memo. Alternatively, the Panel may propose their own groupings.

Precedents Document

1. Read-Across – The Panel first reviewed this document at the June 2017 meeting, and agreed that it would be a living document, constantly growing with the advancement of the related sciences and regulatory acceptance.

   The updated Document includes a read-across framework to provide a rationale for supporting the scientific justification of read-across in CIR safety assessments. While the framework is designed to encompass the approaches most frequently encountered during the evaluation of cosmetic ingredients under assessment, each read-across case is unique. Therefore, it is intended to be understood as a living framework for analysis, rather than a series of steps to be followed mechanically.

   The framework focuses on the crucial scientific aspects of the examination of read-across approaches. Algorithms for read-across predictions of skin sensitization and mutagenicity are presented in a figure as examples to demonstrate the application of OECD QSAR Toolbox workflow within the proposed framework. In addition, the format of read-across justification table in CIR reports was revised to promote scientific confidence associated with a read-across prediction, taking into consideration more aspects of the target chemical in terms of structural, physicochemical, and biological similarities as well as mechanisms of action across different toxicity endpoints.

   The Panel should carefully review the strategy for structuring and reporting read-across, the proposed algorithms and the updated justification table in the Document. The Panel should determine whether the read-across framework is scientifically sound and feasible in the scope and decision context of CIR safety assessment, and determine how, and to what extent, the attached draft Document should be revised further.

Full Panel Meeting

Please remember, the breakfast buffet will open at 8:00 am and the meeting starts at 8:30 am on day 1 and on day 2.

The Panel will consider the 6 reports to be issued as final safety assessments, followed by the remaining reports advancing in the process (including the tentative reports, draft reports, and re-reviews), re-review summaries, strategy memo, and a precedents document. It is likely that the full Panel session will conclude before lunch on day 2; so, please plan your travel accordingly.

Have a safe journey!

Agenda
153rd Cosmetic Ingredient Review Expert Panel Meeting
December 9th - 10th, 2019

The Westin Hotel
1400 M Street, NW,
Washington, District of Columbia, 20005

Monday, December 9th

8:00 am	**CONTINENTAL BREAKFAST**	
8:30 am	**WELCOME TO THE 153rd EXPERT PANEL TEAM MEETINGS**	**Drs. Bergfeld/Heldreth**
8:45 am	**TEAM MEETINGS**	**Drs. Marks/Belsito**

Dr. Marks Team*		**Dr. Belsito Team**	
Admin (JZ)	Read-Across	FR (CB)	Pomegranate
FR (PC)	Mannitol	FAR (CB)	MCI/MI
DR (PC)	Polysilicone-11	DR (CB)	Coconut
DR (PC)	Honey	DR (CB)	Amino Acid Diacetates
TR (PC)	Soy	RRsum (CB)	Napthalenesulfonate
FR (WJ)	Palm	SM (CB)	Silicates
FAR (WJ)	Capryloyl Salicylic Acid	FR (MF)	MIPA
TR (WJ)	Vanilla	TR (MF)	Caprylhydroxamic Acid
TR (PR)	Glycerin Ethoxylates	RRsum (MF)	Isopropyl Lanolate
RR (PR)	Methicones	FR (PC)	Mannitol
FR (CB)	Pomegranate	DR (PC)	Polysilicone-11
FAR (CB)	MCI/MI	DR (PC)	Honey
DR (CB)	Coconut	TR (PC)	Soy
DR (CB)	Amino Acid Diacetates	FR (WJ)	Palm
RRsum (CB)	Napthalenesulfonate	FAR (WJ)	Capryloyl Salicylic Acid
SM (CB)	Silicates	TR (WJ)	Vanilla
FR (MF)	MIPA	TR (PR)	Glycerin Ethoxylates
TR (MF)	Caprylhydroxamic Acid	RR (PR)	Methicones
RRsum (MF)	Isopropyl Lanolate	Admin (JZ)	Read-Across

The purpose of the Cosmetic Ingredient Review is to determine those cosmetic ingredients for which there is a reasonable certainty in the judgment of competent scientists that the ingredients are safe under intended conditions of use.

FR: Final Report // FAR: Final Amended Report // TR: Tentative Report // TAR: Tentative Amended Report // DR: Draft Report // DAR: Draft Amended Report // RR: Re-Review // RRsum: Re-Review Summary // SM: Strategy Memo // Admin: Administrative item

(CB): Christina Burnett || (BH) Bart Heldreth || (MF): Monice Fiume || (PC): Priya Cherian || (WJ): Wilbur Johnson || (PR) Preethi Raj || (JZ) Jinqiu Zhu

*Team moves to breakout room.

Tuesday, December 10th			
8:00 am	**CONTINENTAL BREAKFAST**		
8:30 am	**WELCOME TO THE 153rd FULL CIR EXPERT PANEL MEETING**		**Dr. Bergfeld**
8:45 am	Admin	**MINUTES OF THE SEPTEMBER 2019 EXPERT PANEL MEETING**	**Dr. Bergfeld**
9:00 am	**DIRECTOR'S REPORT**		**Dr. Heldreth**
9:10 am	**FINAL REPORTS, REPORTS ADVANCING TO THE NEXT LEVEL, OTHER ITEMS**		

Final Reports

FR (PC)	Mannitol – *Dr. Belsito Reports*
FR (MF)	MIPA – *Dr. Marks Reports*
FAR (WJ)	Capryloyl Salicylic Acid – *Dr. Belsito Reports*
FR (WJ)	Palm – *Dr. Marks Reports*
FAR (CB)	MCI/MI – *Dr. Belsito Reports*
FR (CB)	Pomegranate – *Dr. Marks Reports*

Reports Advancing

DR (CB)	Coconut – *Dr. Belsito Reports*
DR (CB)	Amino Acid Diacetates – *Dr. Marks Reports*
TR (PR)	Glycerin Ethoxylates – *Dr. Belsito Reports*
RR (PR)	Methicones – *Dr. Marks Reports*
TR (MF)	Caprylhydroxamic Acid – *Dr. Belsito Reports*
TR (PC)	Soy – *Dr. Marks Reports*
DR (PC)	Polysilicone-11 – *Dr. Belsito Reports*
DR (PC)	Honey – *Dr. Marks Reports*
TR (WJ)	Vanilla – *Dr. Belsito Reports*

Other Items

RRsum (MF)	Isopropyl Lanolate – *Dr. Marks Reports*
RRsum (CB)	Naphthalenesulfonate – *Dr. Belsito Reports*
SM (CB)	Silicates – *Dr. Marks Reports*
Admin (JZ)	Read-Across – *Dr. Belsito Reports*

ADJOURN - *Next meeting Monday and Tuesday, March 16-17, 2020, at The Carnegie Endowment for International Peace, 1799 Massachusetts Ave NW, Washington, District of Columbia, 20036*

On the basis of all data and information submitted, and after following all of the Procedures (https://www.cir-safety.org/supplementaldoc/cir-procedures), the Expert Panel shall determine whether each ingredient, under each relevant condition of use, is safe, safe with qualifications, unsafe, or there are insufficient data or information to make a determination of safety. Upon making such a determination, the Expert Panel shall issue a conclusion and/or announcement.

FR: Final Report // FAR: Final Amended Report // TR: Tentative Report // TAR: Tentative Amended Report // DR: Draft Report // DAR: Draft Amended Report // RR: Re-Review // RRsum: Re-Review Summary // SM: Strategy Memo // Admin: Administrative item

(CB): Christina Burnett || (BH) Bart Heldreth || (MF): Monice Fiume || (PC): Priya Cherian || (WJ): Wilbur Johnson || (PR) Preethi Raj || (JZ) Jinqiu Zhu

Cosmetic Ingredient Review

Commitment & Credibility since 1976

ONE HUNDRED FIFTY-SECOND MEETING

OF THE

EXPERT PANEL

September 16-17, 2019

The Westin Hotel

Washington, D.C.

Expert Panel Members

Wilma F. Bergfeld, M.D., Chair

Donald V. Belsito, M.D.

Ronald A. Hill, Ph.D.

Curtis D. Klaassen, Ph.D.

Daniel C. Liebler, Ph.D.

James G. Marks, Jr., M.D.

Ronald C. Shank, Ph.D.

Thomas J. Slaga, Ph.D.

Paul W. Snyder, D.V.M., Ph.D.

Liaison Representatives

Consumer

Thomas Gremillion, J.D.

Industry

Jay Ansell, Ph.D.

Government

Nakissa Sadrieh, Ph.D.

Adopted (Date)

Wilma F. Bergfeld, M.D.

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Others Present at the Meeting

Jay Ansell	PCPC
Don Bjerke	P & G
Christina Burnett	CIR
Priya Cherian	CIR
Carol Eisenmann	PCPC
Monice Fiume	CIR
Kevin Fries	CIR
Bart Heldreth	CIR
Carla Jackson	CIR
Wilbur Johnson, Jr.	CIR
Jon Lalko	Estee Lauder
Preethi Raj	CIR
Teresa Washington	FDA
Michael K.Wyatt	FDA

MINUTES FROM THE 152nd CIR EXPERT PANEL MEETING

CHAIRPERSON'S OPENING REMARKS

Dr. Bergfeld welcomed the attendees to the 152nd meeting of the CIR Expert Panel, and thanked the CIR Executive Director, Senior Director, and CIR staff for the excellent quality of the safety assessments that are included In today's meeting agenda. Additionally, the CIR Science and Support Committee and the industry, consumer, and FDA liaisons on the Panel were thanked for their input. Dr. Bergfeld noted that 16 ingredient reports had been reviewed in Teams on the preceding day, three of which will be issued as final reports. The reports reviewed also included 6 draft tentative reports, 2 of which are amended reports, 3 draft reports, 4 re-reviews, and 4 re-review summaries. Silicates, Parabens, and Brown Algae are among the safety assessments that were reviewed, and extensive discussions on these ingredient groups are anticipated at today's meeting. An inhalation resource document was also reviewed on the preceding day.

Dr. Bergfeld mentioned the Panel's consideration of the generally recognized as safe (GRAS) status, relating to use in foods, of some of the botanical ingredients reviewed. She noted that, given this GRAS classification for some of these ingredients, the Panel would not require systemic toxicity data as long as some other types of human or animal toxicity data are available for consideration.

Referring to the rather detailed Team discussions on Parabens, Dr. Bergfeld recalled Dr. Marks' suggestion relating to the need for a Parabens resource document. She stated that this document, like the CIR hair dye and inhalation resource documents, could be modified/updated as needed.

APPROVAL OF MINUTES

The minutes of the June 6-7, 2019 (151st) CIR Expert Panel meeting were approved.

DIRECTOR'S REPORT

Dr. Heldreth expressed gratitude for the Panel's and other stakeholders' continued support of the Cosmetic Ingredient Review program. He also reported on a vacancy on the CIR Expert Panel and the addition of a new member of the CIR Staff. Regarding the Panel vacancy, CIR is seeking nominations for an expert chemist to join the Marks team as a voting member. In addition to renowned expertise in chemistry and a lack of financial conflicts, nominees should also have expertise in one or more of the following: QSAR, grouping/clustering rationale, read-across, computational predictions, biochemistry (including chemical aspects of ADME), and naturally, synthetic methodology and natural products separations. Nominations may be submitted directly to Dr. Heldreth no later than the end of this month. Thereafter, the CIR Steering Committee will select the new Expert Panel member. [This vacancy has been filled.]

Regarding the new staff member at CIR, Dr. Heldreth welcomed Ms. Preethi Raj, CIR's newest Senior Scientific Analyst & Writer. Preethi comes to CIR with some great credentials, including a master's degree in public health from UMass and experience working as an epidemiologist at the National Cancer Institute. Expect to see CIR reports from her starting this December.

Additionally, Dr. Heldreth noted that the CIR Expert Panel, since its inception in 1976, has always comprised a group of world-renowned, independent experts of science and medicine. The CIR Steering Committee recently met to discuss potential steps forward to better highlight, publicly, this Panel's independence. Indeed, the Committee voted and approved a number of advancements, such as a publicly available conflict of interest statement. Dr. Heldreth is working to bring those advancements to bear, in one cohesive package, which will likely be presented sometime in early 2020.

Final Safety Assessments

Silica & Hydrated Silica

The Panel issued a final amended report with the conclusion that synthetically-manufactured amorphous Silica and Hydrated Silica are safe in the present practices of use and concentration described in the safety assessment when formulated to be non-irritating.

The Panel emphasized that this report applies to the safety of synthetically-manufactured amorphous Silica and Hydrated Silica only. Crystalline silica is not toxicologically similar to synthetically-manufactured amorphous silica and would need to be reviewed separately, if used in cosmetics.

The Panel reviewed the current safety test data on synthetically-manufactured amorphous Silica and Hydrated Silica and determined that these two ingredients do not pose an inhalation risk. The concentrations that were tested in inhalation studies were at much higher concentrations than those found in cosmetics and yet had very few adverse effects. The carcinogenicity study used such high concentrations of Silica that the noted effects on the lymph nodes were due to the load on the animal system; incidental inhalation of Silica in cosmetics is not a concern.

Additionally, the Panel moved 22 silicate ingredients from this report to be reviewed at a later date with other silicate ingredients that are determined to be naturally sourced (i.e. mined), including clay materials, zeolites, and any other similar ingredients that are mined. Currently, the data on those ingredients are insufficient to support the determination of safety. The additional data needed for those ingredients comprise at least:

- Chemical characterization (structure), composition (including degree and % of crystallinity), and impurities data
- Method of manufacturing and/or source data ○ Depending on the information provided, additional data on toxicological endpoints may be needed

Parabens

The Panel issued a final amended report with the conclusion that the following 20 alkyl parabens are safe in the present practices of use and concentration described in the safety assessment when the sum of paraben concentrations in the final formulation does not exceed 0.8%.

Butylparaben	Potassium Ethylparaben*	Sodium Isobutylparaben
Calcium Paraben*	Potassium Methylparaben*	Sodium Isopropylparaben*
Ethylparaben	Potassium Paraben*	Sodium Methylparaben
Isobutylparaben	Potassium Propylparaben*	Sodium Paraben
Isopropylparaben	Propylparaben	Sodium Propylparaben
Methylparaben	Sodium Butylparaben	4-Hydroxybenzoic Acid*
Potassium Butylparaben*	Sodium Ethylparaben	

**Not reported to be in current use. Were ingredients in this group not in current use to be used in the future, the expectation is that they would be used in product categories and at concentrations comparable to others in this group*.

However, the Panel concluded that the available data are insufficient to determine the safety of Benzylparaben. (This ingredient is not reported to be in use.) The data needed to determine the safety of this ingredient comprise a no-observed-adverse-effect-level (NOAEL) derived from developmental and reproductive toxicity (DART) studies.

Because of the extensive metabolism of parabens, the Panel determined that safety data for one of these alkyl parabens can be used to support the safety of the other alkyl parabens. Indeed, the Panel clarified that studies appearing to report high levels of paraben dermal penetration were instead demonstrating high levels of a metabolite (4-Hydroxybenzoic Acid (i.e. not an actual paraben)).

The Panel further noted that the constant influx of newly published associative studies seems to indicate that epidemiological research is ongoing, and may be for some time. Thus, the Panel proposed the continued tracking of this research and the formulation of a resource document in which these new studies can be considered periodically.

Brown Algae

The Panel issued a final report with the conclusion that 68 of the 82 brown algae-derived ingredients reviewed are safe in the present practices of use and concentration described in the safety assessment.

Agarum Cribrosum Extract
Alaria Esculenta Extract
Ascophyllum Nodosum Extract
Ascophyllum Nodosum Powder
Ascophyllum Nodosum*
Cladosiphon Okamuranus Extract
Cystoseira Amentacea/Caespitosa/Branchycarpa Extract*
Cystoseira Baccata Extract*
Cystoseira Compressa Extract*
Cystoseira Compressa Powder*
Cystoseira Tamariscifolia Extract*
Dictyopteris Polypodioides Extract
Ecklonia Cava Extract*
Ecklonia Cava Water*
Eisenia Arborea Extract*
Fucus Serratus Extract
Fucus Spiralis Extract*
Fucus Vesiculosus
Fucus Vesiculosus Extract
Fucus Vesiculosus Powder
Halidrys Siliquosa Extract
Halopteris Scoparia Extract*
Himanthalia Elongata Extract
Himanthalia Elongata Powder*
Hizikia Fusiforme Extract*
Hizikia Fusiformis Callus Culture Extract*
Hizikia Fusiformis Water*
Hydrolyzed Ecklonia Cava Extract*
Hydrolyzed Fucus Vesiculosus Extract*
Hydrolyzed Fucus Vesiculosus Protein*
Laminaria Cloustoni Extract
Laminaria Diabolica Extract*
Laminaria Digitata Extract
Laminaria Digitata Powder
Laminaria Japonica Extract
Laminaria Hyperborea Extract
Laminaria Japonica Powder*
Laminaria Longissima Extract*
Laminaria Ochroleuca Extract
Laminaria Saccharina Extract
Macrocystis Pyrifera (Kelp)
Macrocystis Pyrifera (Kelp) Blade/Pneumatocyst/Stipe Juice Extract*
Macrocystis Pyrifera (Kelp) Extract
Macrocystis Pyrifera (Kelp) Juice*
Macrocystis Pyrifera (Kelp) Protein
Nereocystis Luetkeana Extract
Pelvetia Canaliculata Extract
Phyllacantha Fibrosa Extract*
Saccharina Angustata Extract*
Saccharina Japonica Extract*
Saccharina Longicruris Extract
Sargassum Filipendula Extract
Sargassum Muticum Extract
Sargassum Fulvellum Extract
Sargassum Fusiforme Extract
Sargassum Glaucescens Extract*
Sargassum Horneri Extract*
Sargassum Pallidum Extract*
Sargassum Siliquastrum Extract*
Sargassum Thunbergii Extract*
Sargassum Vulgare Extract
Sphacelaria Scoparia Extract
Undaria Peterseniana Extra
Undaria Pinnatifida Cell Culture Extract*
Undaria Pinnatifida Extract
Undaria Pinnatifida Leaf/Stem Extract
Undaria Pinnatifida Powder
Undaria Pinnatifida Root Powder*

**Not reported to be in current use. Were ingredients in this group not in current use to be used in the future, the expectation is that they would be used in product categories and at concentrations comparable to others in this group.*

The Panel determined, based on a lack of adverse reactions in their clinical experience and in clinical reports, combined with the historically safe use in foods, that concern for dermal sensitization or irritation resulting from cosmetic exposure to these ingredients is confidently mitigated. In addition, the Panel explained that the compositions of these brown algae are consistent across the different genera, and no allergenic constituents of concern were found therein.

However, the Panel determined there were insufficient data to determine the safety of the remaining 14 ingredients. The insufficiencies include a lack of composition data, use in foods/GRAS status, or sensitization data for these ingredients:

Cladosiphon Novae-Caledoniae Extract**
Cystoseira Balearica Extract**
Cystoseira Caespitosa Extract**
Dictyota Coriacea Extract**
Durvillaea Antarctica Extract
Ecklonia Kurome Extract**
Ecklonia Kurome Powder**
Ecklonia Maxima Extract**
Ecklonia Maxima Powder**
Ecklonia Radiata Extract
Ecklonia/Laminaria Extract**
Lessonia Nigrescens Extract
Lessonia Nigrescens Powder*

**Not reported to be in current use.

Tentative Safety Assessments

Mannitol, Sorbitol, & Xylitol

The Panel issued a tentative report for public comment with the conclusion that Mannitol, Sorbitol, and Xylitol are safe in the present practices of use and concentration described in the safety assessment. Positive phototoxicity results were reported for a test material containing Xylitol; however, Xylitol is a chromophorically inert molecule that lacks a UV-visible light-absorbing structure and cannot directly trigger phototoxicity. The Panel noted that it was not clear whether other components of the cream or gel formulations may have contributed to the positive phototoxicity results. In addition, levels of irradiation used in this phototoxicity study were far greater than typical exposure. Two negative phototoxicity results with Mannitol support this interpretation (Mannitol is also void of a chromophore). Thus, the Panel felt that the available data do not indicate a risk of phototoxicity with these ingredients.

The Panel determined, based on a lack of adverse reactions in their clinical experience and in clinical reports, combined with the historically safe use in foods, that irritation data at use concentration were unnecessary to determine safety for this ingredient group. The addition of a negative guinea pig maximization test (GPMT) mitigated the need for sensitization data at maximum use concentrations (as this method of testing utilizes a combination of exposures, including intradermal injections which bypass the stratum corneum). Because the dermal barrier is eliminated in this method of testing, it may be surmised that sensitization studies at higher concentrations would also yield negative results.

Methylchloroisothiazolinone/Methylisothiazolinone (MCI/MI)

The Panel issued a tentative amended report for public comment with the conclusion that the ingredient mixture MCI/MI is safe in cosmetics when formulated to be non-sensitizing, based on the results of a quantitative risk assessment (QRA) or similar methodology; however, at no point should concentrations exceed 7.5 ppm in leave-on products or 15 ppm in rinse-off products. However, the Panel concluded that the data are insufficient to support the safety of MCI/MI in products which may be incidentally inhaled. The Panel requested an inhalation study of at least 3 months in duration that is in accordance with the Organization for Economic Co-operation and Development (OECD) test guideline (TG) 413. This request is in response to reports of adverse events observed in infants following inhalation exposure to humidifier disinfectants that contained this preservative mixture.

The Panel noted the results of a QRA for skin sensitization performed by the CIR Science and Support Committee. The results indicated that some leave-on products comprising MCI/MI at the recommended safe concentration of 7.5 ppm may yet increase the risk of inducing dermal sensitization. In most rinse-off products, 15 ppm MCI/MI was not associated with a potential increased risk of skin sensitization induction. Individuals previously sensitized to MCI/MI should avoid products that contain this ingredient mixture.

Pomegranate

The Panel issued a tentative report for public comment with the conclusion that the data were insufficient to support a determination of safety for the following 18 ingredients:

Punica Granatum Extract
Punica Granatum Bark Extract
Punica Granatum Bark/Fruit Extract
Punica Granatum Callus Culture Extract
Punica Granatum Flower Extract
Punica Granatum Fruit Extract
Punica Granatum Fruit Juice
Punica Granatum Fruit/Root/Stem Powder
Punica Granatum Fruit/Sucrose Ferment Filtrate
Punica Granatum Fruit Water
Punica Granatum Juice Extract
Punica Granatum Leaf Cell Extract
Punica Granatum Peel Extract
Punica Granatum Pericarp Extract
Punica Granatum Seed
Punica Granatum Seed Cell Culture Lysate
Punica Granatum Seed Extract
Punica Granatum Seed Powder

The additional data needed for these cosmetic ingredients are:

- A no-observed-effect-level (NOEL) for skin lightening effects for all ingredients
- Method of manufacturing for the extracts with regard to solvent-type used
- For Punica Granatum Bark Extract, Punica Granatum Bark/Fruit Extract, Punica Granatum Callus Culture Extract, Punica Granatum Flower Extract, Punica Granatum Fruit/Root/Stem Powder, Punica Granatum Leaf Cell Extract, and Punica Granatum Peel Extract
    - Composition and impurities data
    - Systemic toxicity data
    - Dermal irritation and sensitization data

Alkyl Amide MIPA

The Panel issued a tentative report for public comment with the conclusion that the 14 alkyl amide MIPA ingredients named below are safe in cosmetics in the present practices of use and concentration described in the safety assessment when formulated to be non-irritating.

Cocamide MIPA
Coconut Oil MIPA Amides*
Hydroxyethyl Stearamide-MIPA*
Isostearamide MIPA*
Lauramide MIPA
Linoleamide MIPA*
MIPA- Myristate*
Myristamide MIPA*
Oleamide MIPA
Palmamide MIPA*
Palm Kernelamide MIPA*
Peanutamide MIPA*
Ricinoleamide MIPA*
Stearamide MIPA*

**Use not reported in the VCRP and/or concentration of use survey. The expectation is that if used in cosmetic formulations, these ingredients would be used in product categories and at concentrations comparable to those reported for others in this group.*

The ingredients in this group are fatty amides resulting from amidation with MIPA. Accordingly, the Panel specified that these ingredients should not be used in cosmetic products in which *N*-nitroso compounds can be formed.

The alkyl amide MIPA ingredients are primarily used in rinse-off formulations. However, leave-on uses are reported, with 0.4% Oleamide MIPA reported as the highest concentration of use in leave-on formulations. The Panel noted that delayed contact hypersensitivity was reported in a GPMT performed with high concentrations of Oleamide MIPA (75% for topical induction/50% at challenge), but not in GPMTs on Cocamide MIPA (25% at topical induction/5% at challenge) and Isostearamide MIPA (100% at topical induction/1% at challenge). The Panel stated that the sensitization observed with Oleamide MIPA was most likely a result of the high concentrations and a stressing of the system (as this method of testing utilizes a combination of exposures, including intradermal injections which bypass the stratum corneum). Because the Panel felt that it was appropriate to read-across from Cocamide MIPA and Isostearamide MIPA, concern that Oleamide MIPA would be a sensitizer in cosmetic

formulations was mitigated. However, the Panel was concerned that the potential exists for dermal or ocular irritation with the use of products formulated with the ingredients named in this assessment. Therefore, the Panel specified that products containing the ingredients listed above must be formulated to be non-irritating.

Published studies were not found, and unpublished data were not submitted, for certain toxicological endpoints on the alkyl amide MIPA ingredients. Nevertheless, because these ingredients are structurally similar to the diethanolamides, the Panel determined that information on diethanolamides of equivalent chain lengths (from a previous CIR report, as well as from European Chemical Agency (ECHA) dossiers) could be used for read-across for the missing data endpoints.

The acyl groups (i.e. fatty acid chain residues) in Peanutamide MIPA are derived from peanut oil. The Panel has previously reviewed the safety of Arachis Hypogaea (Peanut) Oil as used in cosmetics, and discussed therein the relationship between food allergies and exposure to refined oils. Individuals who have food allergies to a plant protein rarely exhibit allergic reactions when exposed to refined oils of the same plant; proteins do not partition into the oil. Additionally, the Panel noted that aflatoxins, which could be associated with peanuts, do not partition into the oil. However, the Panel does caution manufacturers to make certain that Peanutamide MIPA is free from proteins and aflatoxins.

Capryloyl Salicylic Acid

The Panel issued a tentative amended report for public comment with the conclusion that the data are insufficient to support a determination that Capryloyl Salicylic Acid is safe under the intended concentrations of use in cosmetic formulations. The data needs (unchanged from those requested in a June 2019 insufficient data announcement (IDA)) comprise:

- Phototoxicity
- Impurities

Impurities data were not provided; therefore, that data need remains outstanding. Additionally, although phototoxicity data were received, the Panel were not satisfied with the data. In response to the Panel's data requests, the results of an *in vitro* 3T3 neutral red uptake (NRU) phototoxicity test were submitted. The study was performed in accordance with the OECD Guideline for Testing of Chemicals Draft Proposal for a New Guideline (draft document, dated February 2000). According to the evaluation criteria that were used, a test article was considered to be phototoxic in this assay if a marked decrease in cell viability (as measured by OD540 in the NRU) was observed in the presence of UVA (by comparison with the viability seen in the absence of UVA) such that photo-irritation factors (PIF) values of ≥ 5 were obtained. Furthermore, a test article was considered to be non-phototoxic in this assay if there was no marked decrease in cell viability when cells were exposed to the test article in the absence and presence of UVA, or if similar toxic profiles were observed in the absence and presence of UVA (PIF < 5). The test yielded PIF's of 4 and 2.6 - 1.7 in separate experiments that were performed. Based on these PIF values, the author concluded that, according to the proposed OECD guideline evaluation criteria, Capryloyl Salicylic Acid was not phototoxic in the *in vitro* 3T3 NRU phototoxicity test. However, the Panel noted that, according to OECD Guideline 432 (adopted April 2004), the results of this test are to be interpreted based on the following criteria: a test substance with a PIF of < 2 predicts "no phototoxicity," a PIF of > 2 but < 5 predicts "probable phototoxicity," and a PIF of $>$ 5 predicts "phototoxicity." Thus, the Panel agreed that Capryloyl Salicylic Acid (PIF values of 4 and 2.6 - 1.7) should have been classified as probably phototoxic in the *in vitro* 3T3 NRU phototoxicity test. Furthermore, the Panel agreed that because this test is prone to false positives, additional data would be needed in order to evaluate the phototoxicity potential of Capryloyl Salicylic Acid. The reactive oxygen species test for phototoxicity was mentioned as one of the phototoxicity tests that could be performed to meet this data need.

Additionally, the Panel discussed the issue of skin sensitization potential for this ingredient. Capryloyl Salicylic Acid induced skin sensitization in GPMTs at challenge concentrations of 0.5%, 2%, and 5%, but not at 1%. However, in human repeated insult patch tests (HRIPTs), cosmetic products containing 0.5% or 2% Capryloyl Salicylic Acid were classified as non-sensitizing. After reviewing the HRIPT results, considering that the highest reported maximum use concentration of Capryloyl Salicylic Acid is 0.5% in leave-on cosmetic products, and noting the stressing of the system that occurs in the GPMTs, the Panel concluded that the sensitization potential of exposure to this ingredient via cosmetic use is not a risk.

Palm (açaí & juçara)

The Panel issued a tentative report for public comment with the conclusion that 3 palm tree (açaí)-derived ingredients, Euterpe Oleracea Fruit Extract, Euterpe Oleracea Juice, and Euterpe Oleracea Pulp Powder, are safe in the present practices of use and concentration described in the safety assessment when formulated to be non-sensitizing. The skin sensitization potential of a face and neck product containing 3% Euterpe Oleracea Pulp Powder (the highest maximum use concentration in leave-on products that is reported in this safety assessment) was evaluated in a study involving 214 subjects. Although definite erythema and damage to the epidermis (but no edema) were observed in 1 subject at the 5th induction evaluation, the results were classified as negative. However, because final product formulations may contain multiple botanicals, each possibly containing the same constituents of concern, formulators are advised to be aware of these constituents and to avoid reaching levels that may be hazardous to consumers. Therefore, when formulating products, manufacturers should avoid reaching levels of plant constituents that may cause sensitization or other adverse health effects.

Additionally, the Panel concluded that the available data are insufficient to support a determination that the following 5 palm tree (açaí and jaçara)-derived ingredients are safe under the intended conditions of use in cosmetic formulations:

Euterpe Edulis Fruit Extract
Euterpe Edulis Juice Extract
Euterpe Oleracea Palm Heart Extract
Euterpe Oleracea Seed Powder
Hydrolyzed Euterpe Oleracea Fruit

The data needs are as follows:

Euterpe Edulis Fruit Extract and Euterpe Edulis Juice Extract

- Method of manufacture
- Skin sensitization

Euterpe Oleracea Seed Powder and Hydrolyzed Euterpe Oleracea Fruit

- Method of Manufacture

Euterpe Oleracea Palm Heart Extract

- Skin irritation and sensitization

Insufficient Data Announcements

Adenosine

The Panel issued an IDA for Adenosine, Adenosine Phosphate, Adenosine Triphosphate, Disodium Adenosine Phosphate, and Disodium Adenosine Triphosphate. In order to conclude on safety, the Panel requested impurities data on all five ingredients. The Panel noted that these ingredients are naturally-occurring, ubiquitous chemicals, but, found impurities data to be necessary as methods of manufacture specific to these cosmetic ingredients are unknown. The Panel also noted the lack of sensitization/irritation data for these ingredients, but decided that the available sensitization/irritation data on Disodium Adenosine Phosphate and Adenosine can be read-across to those ingredients lacking these data.

Wheat

The Panel issued an IDA for the following ingredients:

Triticum Aestivum (Wheat) Flour Lipids
Triticum Aestivum (Wheat) Germ Extract
Triticum Aestivum (Wheat) Leaf Extract
Triticum Aestivum (Wheat) Peptide

Triticum Aestivum (Wheat) Seed Extract
Triticum Monococcum (Wheat) Seed Extract
Triticum Monococcum (Wheat) Stem Water
Triticum Spelta Seed Water
Triticum Turgidum Durum (Wheat) Seed Extract
Triticum Vulgare/Aestivum (Wheat) Grain Extract
Triticum Vulgare (Wheat) Bran
Triticum Vulgare (Wheat) Bran Extract
Triticum Vulgare (Wheat) Bran Lipids
Triticum Vulgare (Wheat) Flour Extract
Triticum Vulgare (Wheat) Flour Lipids
Triticum Vulgare (Wheat) Germ
Triticum Vulgare (Wheat) Germ Extract
Triticum Vulgare (Wheat) Germ Powder
Triticum Vulgare (Wheat) Germ Protein
Triticum Vulgare (Wheat) Gluten
Triticum Vulgare (Wheat) Gluten Extract
Triticum Vulgare (Wheat) Kernel Flour
Triticum Vulgare (Wheat) Protein
Triticum Vulgare (Wheat) Seed Extract
Triticum Vulgare (Wheat) Sprout Extract
Triticum Vulgare (Wheat) Straw Water
Wheat Germ Glycerides

The additional data needed for these cosmetic ingredients are:

- Method of manufacturing, composition, and impurities data for Triticum Aestivum (Wheat) Germ Extract, Triticum Aestivum (Wheat) Seed Extract, Triticum Monococcum (Wheat) Seed Extract, Triticum Turgidum Durum (Wheat) Seed Extract, Triticum Vulgare (Wheat) Germ Extract, Triticum Vulgare (Wheat) Seed Extract, and Triticum Vulgare (Wheat) Sprout Extract
- Dermal irritation and sensitization data at maximum leave-on use concentrations for Triticum Aestivum (Wheat) Germ Extract, Triticum Vulgare (Wheat) Germ Extract, Triticum Vulgare (Wheat) Sprout Extract, and Wheat Germ Glycerides

Scutellaria

The Panel reviewed the safety of the following 4 *Scutellaria baicalensis*-derived ingredients for the first time and issued an IDA.

Scutellaria Baicalensis Extract
Scutellaria Baicalensis Root Extract
Scutellaria Baicalensis Root Powder
Scutellaria Baicalensis Sprout Extract

The following data were requested:

- Genotoxicity (in vitro and mammalian); for ingredient extracts, methanol and aqueous extracts should be tested
- Phototoxicity

Scutellaria Baicalensis Root Extract and Scutellaria Baicalensis Root Powder

- An NOAEL for skin pigmentation and anti-inflammatory effects, including the suppression of delayed contact hypersensitivity, is needed

Scutellaria Baicalensis Extract

- Skin irritation and sensitization
- 28-day dermal toxicity; if dermal absorption occurs, additional data may be needed

Scutellaria Baicalensis Sprout Extract

- Method of Manufacture
- Composition
- Impurities
- Dermal absorption; if dermal absorption occurs, additional data may be needed
- Skin irritation and sensitization

The Panel expressed concern over the genotoxicity potential of Scutellaria Baicalensis Root Extract, and possibly other *Scutellaria baicalensis* plant part extracts. In the *Bacillus subtilis* rec-assay (strains H17 Rec+ and M45 Rec-) without metabolic activation, results for the methanol and aqueous extracts of a *Scutellaria baicalensis* root extract were positive and negative, respectively. In the Ames test (*Salmonella typhimurium* strains TA98 and TA100), results for the aqueous extract of a *Scutellaria baicalensis* root extract were positive in strain TA100 with, but not without, metabolic activation. However, results for the methanol extract were negative (with or without metabolic activation) in both bacterial strains in the Ames test. The Panel agreed that the conflicting results for the aqueous and methanol extracts in the 2 *in vitro* assays are inconclusive. Thus, the Panel noted that the *in vitro* assays should be repeated and that genotoxicity should also be evaluated using a mammalian system.

Re-Reviews

Quaternium-18 & Quaternium-18 Bentonite

In 1982, the final report on Quaternium-18 and Quaternium-18 Bentonite was published with the conclusion that these ingredients are safe as cosmetic ingredients in the present practices of use and concentration, as described in that report. In 2003, after considering new studies and updated use data on these ingredients, the Panel published a re-review summary in which it was stated that the Panel determined not to re-open the safety assessment. It should be noted that Quaternium-18 Hectorite, which was included in the 1982 and 2003 documents, was not included in the current re-review because it was recently part of a separate assessment (Safety Assessment of Ammonium Hectorites as used in Cosmetics). The Panel re-opened the safety assessment on Quaternium-18 and Quaternium-18 Bentonite due to a lack of inhalation toxicity data, and requested information on aerosolized Quaternium-18 Bentonite.

Sodium Naphthalenesulfonate and Sodium Polynaphthalenesulfonate

The Panel first reviewed the safety of Sodium Naphthalenesulfonate and Sodium Polynaphthalenesulfonate in a report published in 2003 with the conclusion that these ingredients were “safe as used in cosmetic formulations intended to be applied to the skin. The available data, however, are insufficient to support the safety for use in cosmetic products which may contact mucous membranes or be ingested.” Because it has been at least 15 years since the original review was published, in accord with CIR Procedures, the Panel considered whether the safety assessment of Sodium Naphthalenesulfonate and Sodium Polynaphthalenesulfonate should be re-opened.

The Panel reviewed data that have been published since the original safety assessment, as well as updated frequency and concentration of use data. The frequency of use for Sodium Polynaphthalenesulfonate has decreased since the original review was considered. Uses were neither reported for Sodium Naphthalenesulfonate in the 2003 report, nor in 2019. The Panel determined that there were no new relevant data that informed a new review of this ingredient. Therefore, the Panel reaffirmed the original conclusion, and did not re-open this safety assessment.

Isopropyl Lanolate

The Panel first reviewed the safety of Isopropyl Lanolate in 1980, concluding that “on the basis of the information available, which the Expert Panel believes to have been accumulated in a reasonable manner, it is concluded that Isopropyl Lanolate is safe as currently used in cosmetic products.” In 2003, after considering new studies and updated use data, the Panel determined to not re-open the safety assessment. Because it has been at least 15 years since the first re-review summary was published, in accord with CIR Procedures, the Panel again considered whether the safety assessment of Isopropyl Lanolate should be re-opened.

An exhaustive search of the world’s literature was performed for studies dated 1995 forward, but no relevant new data were found. The Panel did review updated frequency and concentration of use data. The frequency and maximum concentrations of use have decreased significantly since the initial re-review was considered, and even more so when compared to the use data included in the 1980 assessment. Therefore, the Panel reaffirmed the original conclusion, and did not re-open this safety assessment.

Sulfites

The Panel first reviewed the safety of Sulfites in 2003. The Panel concluded that Ammonium Bisulfite, Ammonium Sulfite, Potassium Metabisulfite, Potassium Sulfite, Sodium Bisulfite, Sodium Metabisulfite, and Sodium Sulfite are safe as used in cosmetic formulations. Because it has been at least 15 years since this report was published, in accordance with CIR Procedures, the Panel considered whether the safety assessment of these 7 ingredients should be reopened. After considering new studies and updated use data on these ingredients, the Panel determined that the safety assessment should be reopened.

The Panel's decision to reopen the safety assessment is based mostly on the following types of toxicity data that have entered the published literature since the final report was issued: genotoxicity (*in vitro* and *in vivo*), dermal sensitization, reproductive toxicity, and enhancement of the allergic response to dust mites. Of particular interest are both the positive *in vivo* and *in vitro* genotoxicity data (mostly on Sodium and Potassium Metabisulfite) that were reviewed. The Panel noted that positive *in vitro*, but not *in vivo*, genotoxicity data are found in the published report.

Re-Review Summaries

Acetyl Trialkyl Citrates

The Panel approved the re-review summary of Acetyl Trialkyl Citrates, reaffirming that these ingredients are safe as cosmetic ingredients in the present practices of use and concentration. This conclusion was originally published by CIR in 2002. Limited new data that were identified in the published literature, as well as updated information regarding frequencies of use, provided by the FDA, and maximum use concentrations of use, provided by the Council, were reviewed by the Panel.

BHT

The Panel approved the re-review summary of BHT (Butylated Hydroxytoluene), reaffirming that BHT is safe as used in cosmetic ingredients in the present practices of use and concentration. This conclusion was originally published by CIR in 1999. Limited new data identified in the published literature that have become available since the 1999 report was published, as well as updated information regarding frequencies of use (provided by the FDA) and maximum use concentrations of use (provided by the Council), were reviewed by the Panel.

Imidazolidinyl Urea

The Panel approved the re-review summary of Imidazolidinyl Urea, reaffirming that Imidazolidinyl Urea is safe as used in cosmetic ingredients in the present practices of use and concentration. This conclusion was originally published by CIR in 1980, and reaffirmed in 2001. Limited new data identified in the published literature that have become available since the 2001 re-review, as well as updated information regarding frequencies of use (provided by the FDA) and maximum use concentrations of use (provided by the Council), were reviewed by the Panel.

EDTA

The Panel approved the re-review summary of EDTA and Salts, reaffirming that the following ingredients are safe as cosmetic ingredients in the present practices of use and concentration:

EDTA	TEA-EDTA	HEDTA
Calcium Disodium EDTA	Tetrasodium EDTA	Trisodium HEDTA
Diammonium EDTA	Tripotassium EDTA	
Dipotassium EDTA	Trisodium EDTA	

This conclusion was originally published by CIR in 1998. New data identified in the published literature that have become available since the 1998 report was published, as well as updated information regarding frequencies of use (provided by the FDA) and maximum concentrations of use (provided by the Council), were reviewed by the Panel.

Inhalation – Respiratory Exposure Resource Document

At the December 2018 meeting, the Panel suggested a number of changes to this resource document. At that meeting, the Panel concluded that, while particle/droplet size is an important parameter, the physicochemical properties of ingredients in a spray formulation, as well as the realistic exposure factors under in-use conditions, also play significant roles in evaluating inhalation safety of ingredients in spray formulations. When spray parameters are absent or provide an insufficient basis to support a robust inhalation exposure assessment, the Panel would request additional information from Industry and further evaluate the sufficiency of other exposure data that may be available on a case-by-case basis. All such changes were made to the document, and at this current meeting, the Panel voted to finalize this resource document and publish it to the CIR website. It may now be found under the CIR Findings & Resource Documents tab (https://www.cir-safety.org/cir-findings).

Cosmetic Ingredient Review

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Memorandum

To: CIR Expert Panel Members and Liaisons
From: Jinqiu Zhu, PhD, DABT, ERT, CIR Toxicologist
Date: November 15, 2019
Subject: Draft Revised Read-Across Resource Document

Enclosed is a revised draft of the CIR Precedents – Read-Across Document (*reacac122019rep*). The Panel first reviewed this document at the June 2017 meeting, and agreed that it would be a living document, constantly growing with the advancement of the related sciences and regulatory acceptance. The transcripts of the discussion at the June 2017 meeting are identified as *reacac122019min.*

The updated Document includes a read-across framework to provide a rationale for supporting the scientific justification of read-across in CIR safety assessments. While the framework is designed to encompass the approaches most frequently encountered during the evaluation of cosmetic ingredients under assessment, each read-across case is unique. Therefore, it is intended to be understood as a living framework for analysis, rather than a series of steps to be followed mechanically.

The framework focuses on the crucial scientific aspects of the examination of read-across approaches. Algorithms for read-across predictions of skin sensitization and mutagenicity are presented in a figure, as examples to demonstrate the application of OCED QSAR Toolbox workflow within the proposed framework. In addition, the format of read-across justification table in CIR reports was revised to promote scientific confidence associated with a read-across prediction, taking into consideration more aspects of the target chemical in terms of structural, physicochemical, and biological similarities as well as mechanisms of action across different toxicity endpoints.

The Panel should carefully review the strategy for structuring and reporting read-across, the proposed algorithms and the updated justification table in the Document. The Panel should determine whether the read-across framework is scientifically sound and feasible in the scope and decision context of CIR safety assessment, and determine how, and to what extent, the attached draft Document should be revised further.

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Day 1 of the June 12-13, 2017 CIR Expert Panel Meeting – Dr. Belsito's Team

DR. BELSITO: Do we know what page that is?

DR. HELDRETH: PDF page 46.

DR. BELSITO: Okay. So this is looking at just a general statement that I guess will appeal on our website, is that true? Or this try to get a consensus approach as to what the panel agrees about read across?

DR. HELDRETH: Yeah, essentially, this is at the moment we're trying to generate kind of a SOP for the analyst and the writers to go forward when they're trying to present read across in a report to the panel. Ultimately, if the panel would like to have a document that would be put on our website, we would be happy to work with you to create something like that.

DR. BELSITO: I mean, I think we definitely should state how we do this in some general terms. Just looking at the document just in terms of comments. So I'm not sure what you're trying to say in the last sentence of read across in general. I mean it was just very confusing to me.

DR. HELDRETH: So what I was trying to get across here, there are instances where SANTOS (phonetic) have been able to apply read across with well characterized mixtures to other well characterized mixtures. But that isn't really something that is amendable to the CIR process cause we typically either look at discrete molecules that we know very well. Or we look at mixtures such as botanicals where we don't know that mixture very well. And so, the read across for the kinds of mixtures we typically look at it it just isn't appropriate.

DR. BELSITO: But it is very appropriate for single ingredients. So I'm not sure why you have that in there. I mean -- it would seem -- what you're trying to get across is for botanicals those type of multi constituent's substances read across is very difficult.

DR. HELDRETH: Yes.

DR. BELSITO: So I think I would get rid of the single ingredient stuff and just say that, you know, read across for some mixtures such as botanicals with the which the panel feels can be very challenging or something like that.

DR. HELDRETH: Okay. Will do.

DR. BERGFELD: Sorry. Dan, do you have any comments on this read across information, or document?

DR. LIEBLER: Sure. I do. I was a little puzzled by that sentence also, because I get the idea that read across for mixtures is mostly not doable. But I didn't understand what you meant by that second clause in that sentence. "The evaluation of single ingredients that (inaudible) single chemicals. Does not -- or not fully characterize mixtures." I mean, discrete single chemicals are what you would use read across for. Maybe it's just a wording.

DR. HELDRETH: It's certainly a wording thing. My intention was that we typically only look at discrete chemicals for mixtures that are not well characterized.

DR. LIEBLER: Yes.

DR. HELDBRETH: Neither of which are multi constituent substances

that could be done with read across.

DR. LIEBLER: Yeah. And I appreciate the point about not being a useful -- read across not really being useful for inorganics. Or any -- for that matter any molecule for which the inorganic component drives the -- drives the function or properties. Even if it's a organo metallic, okay. Um, and then I don't know if you want to talk about this yet. I had no problem with your draft texts with the yellow highlights. I don't know if anybody else did.

The justification table I think that this is okay, it's a good start but it's probably incomplete. I think that read across now has gotten to the point where there is a quantitative aspect that's not fully developed but it's certainly developing. There are tool kits and prediction models and various software utilities that generate quantitative or at least as close as we can come right now to quantitative estimates. Which is where this really needs to go so it's not just, you know, Ron or I are looking at it and saying -- tasting it and saying it's Hershey's.

I think that this summary makes it more of a, you know, more of just a judgement call. It's very generic language. For example, you could wrap in some data from the analog in the target from some of the models that you cited on the top of page 47 of the second paragraph of page 47. OEC QR tool box, EPI suite those are ones we also utilize for the RIFM assessments.

We've recently decided to get away from the Caesar models because of some shortcomings with those. So those are kind of on the list for RIFM. Another parameter we calculated is the tanimoto score and we find that useful but not entirely restrictive. So we don't for the tanimoto score for example, we calculate that number. And it's a number perfectly identical as 1.0 and then lower numbers are less identity but those can be driven by quirks in the scoring algorithm. And they're not necessarily -- and any particular cut-off is not a hardline for us.

But we basically say similarity is reflected by the tanimoto score degree of similarity. And sometimes when the tanimoto score looks really out of whack with respect to what's obviously similar in the structure we briefly explained. But that's a useful parameter to list and I think that it would be good for us if we're going down this road to begin to incorporate material like that into this table.

Now, that would be, you know, when you're able to do that may depend and significantly to whether or now you have somebody who can actually have the band width and time to generate the data. And put that on the table and that might not be something CIR can do right now. But I think that's where this needs to go, because it's very important for the field for us not to simply rely on "experts" to say, yeah, this is similar, and that's similar enough. Because it's just too much arbitrary judgement. Even if it's informed arbitrary judgment. It still um, in my opinion not the right way to go.

So I like this it's a good start, we can do this but I think that it might be better if we hold our fire until you're able to actually implement this in a more thorough quantitative manner using some data from the models.

DR. HELDRETH: That's certainly something we're trying to go towards. I mean we're working on developing some in house understanding and knowledge of these tools that are already out there. We're also making new strides in our

internal chemistry and toxicology database. That ultimately molecular networks are putting together for us. So that's getting us closer to being able to do these sorts of similarity scores on our owns.

So what you're saying is for example in this justification table you would like to see something of a comparison with tanimoto scores and maybe see a comparison of, like, chemical and physical properties of the deanalog and the read across selection listed there what those predictions are so you can see how well they line up?

MR. LIEBLER: Yeah, um. You know, I'm not saying you need to copy the RIFM documents. The RIFM documents give you an idea of what has evolved. I and some of the RIFM chemist staff, couple of my colleagues Terry Schultz in Knoxville and Trevor Pennington at Penn. Have kind of collaborated on development use of this format. And I think um, yeah, the tanimoto scores obviously just one line in a table.

If you're going to have outputs from like OEC tool box, the outputs would be more along the lines of what structure alerts there are to consider. Now, sometimes those structure alerts border on the trivial and non-applicable, you know, anything with a carbonyl in it might be considered potentially DNA addict forming because of shift based chemistry. Even though it probably won't really happen to any breachable extent.

But, you know, data from a couple of models would be the most thorough thing you could do. I think It's worth -- it's worth including that even though it's not optimal right now. But it will get you positioned so that you can easily evolve as the model building and read across chemistry and computational features continue to evolve. Rather than waiting for it to be perfect.

DR. HELDRETH: So then we could -- as we develop the know-how and are able to perform these in house. We could essentially put a little bit too much there of the structural alerts and allow the panel to use their judgment (inaudible)

DR. LIEBLER: Right exactly. You can acknowledge that and you don't have to be completely driven by it.

DR. BERGFELD: So you're not suggesting that even go up for public comment?

DR. BELISTO: I can go for public comment.

DR. BERGFELD: Yeah.

DR. LIEBLER: Yeah. You could. This is a good first draft. If the questions is public comment and then using this format. My suggestion would be take this a little further before we actually use this.

DR. BERGFELD: Okay.

DR. LIEBLER: Because -- perhaps I'd like to hear from colleagues on this one and perhaps the other team as well. You want to get to adding the features I described. Whether you can do that in the timeframe you want to introduce something is another question. And strategically it might make more sense to advance something like this or some modified formative without going the full monte. It's going to be more of logistic personnel band width thing I suspect.

DR. HELDRETH: Some of this was a little bit of stepping back and seeing what we had done. We can see what I've copied and pasted in here is much of

what came out of Monice's recent report that had some of this read across in it. And so, we were just trying formalize that so that we can make it look at least that good and get better as we go forward.

DR. BELSITO: And just a couple of other points, and I'm not sure that it completely came across in this document. For different end points, she may use different materials for your read across. (Inaudible) contact sensitization, you know shift base Michael acceptor are very important. Whereas, they may not be as important for carcinogency. I think putting log KOW (phonetic) as some idea of how well these will penetrate molecular weight.

You know, little things about physical chemistry into a chart. I mean, Dan or I can send you a very typical set of -- and again not that this should be modeled after RIFM. But what RIFM does in terms of just straight down how they're justifying read across. And they do it for different end points. Sometimes because they have that end point for one chemical but not another that they're using for read across. But sometimes because of very important aspects of the way that particular material behaves for that end point.

DR. LIEBLER: Yeah, in fact if you have, you know, in the example here. You've got a read across material for something that looks like that you've got no data for. But in many cases, you may have -- you need read across for genotox or for repro or something like that. And if you have one analog we've got genotox data but that analog you don't have repro data, then you have another analog. So that becomes another column. So another feature of this is giving yourself additional columns for additional data types.

DR. HELDRETH: Great. Thank you.

DR. BELSITO: Paul.

DR. SNYDER: So I have quite a few edits on the read across in general. I think that the -- what you really want to do is you want to -- like the first time I think should be the rationale for read across. For the assessment of safety of ingredients used in cosmetics. That should be the opening -- where are strategy is going to be different than for other applications. I think that really sets the stage.

And then when you -- then we talk about strategies. In this context and how they're applicable to cosmetic ingredient use. Because I think it -- we have to make sure we stay honed in on and what our objective is. Not read across and the world of read across. Because I think it gets really cumbersome. And then once we define how we utilize or how we want to utilize read across. Then we go to everything being end point driven, everything being filling gaps or common needs for filling gaps and really focus on those.

And I look at this as a living document it's going to grow as we become more comfortable and more people come and give us presentations on these different models and things like that. And then we just rolled those into this document. So I think this is a good start. But I think we need to go a little cautiously like my colleagues are stating. And how much we put out there and how we're going to utilize it. Because I just don't want us to get tied here to anything right out of the gate so to speak.

DR. HELDRETH: And sure this doesn't need to be a dictating document

that tells us what we have to do. This is really -- really we're just trying to bring this forward to give the panel the option to tell us the staff what we need to do to help make your jobs easier. And for certain we can go through multiple iterations of this. (Inaudible) time to perfect it as much as possible as things change.

DR. BERGFELD: Has the CIR SSC Committee looked at this?

DR. HELDRETH: No, not yet.

DR. BERGFELD: Can that be another group to look.

DR. ANSELL: Yeah. We will be filing a more specific comments but, you know, let me emphasize that this is absolutely critical in terms of moving forward in the development of safety assessment. We are fully supportive of the use and integration of these methods like read across, like TTC as part of an integrated assessment. I think what I've hear and what we've heard and what we've tried to iterate in defining some principles for these types of things, is really transparency.

And that's the critical issue is to explain how these proximities or scores, analogs were derived. And we in fact met last week with a model developer and urged them to bring more transparency. Spitting out a number in the end is not going to make it. I'd also like to see some expansion, not only in terms of using read across to access an ingredient. But use read across form families. To determine whether materials are -- can be brought together. So I think there's a lot of things that we can do with this and really encourage CIR to make the developments into these methods a priority.

DR. LIEBLER: Actually with respect to Jay's last comment about forming families. So one of the first steps we have way in advance of the panel reviewing draft reports for RIFM. Is that the chemistry people actually review candidate clusters of molecules and make sure they can arrive at consensus? And the cluster of reviews are basically done from Excel spreadsheets that are sent around and the draft clusters are based on what molecules appear to be related. But also, what molecules have read across data potentially available to use.

So the read across data -- the read across decision about whether or not to use an analog is actually made in advance of the drafting of the final drafting of the reports. So before the panels sees it.

DR. HELDRETH: So then, I mean, there of course some types of groupings that have nothing to do with read across. For example, when we're looking at botanicals or the in organics that we talked about. But let's say for those examples where we do have discrete molecules and there is a good possibility of there being a read across analogs out there that would help the situation. Do you think it would be useful to make that part of our priority setting process in future?

DR. LIEBLER: Yes, I do.

DR. HELDRETH: So that when we start at the beginning of the year the groupings that would present. Would already have those types of clustering.

DR. LIEBLER: You can get an idea at least an idea where the data gaps are. And you can get some input on what the panels likely be receptive to in terms of clusters or for groupings in read across. One other point, I think you do make a good point at the bottom of page 46. About whenever possible experimental data always preferred read across is not considered when there are no gaps in the available data.

And I certainly agree with that. That's a point I made in a couple recent meetings. However, there are times you when you actually do technically have data, but the data set may be pretty minimal. And then it might make sense to have data from an analogous ingredient or analogous chemical. But it's not really read across. We often --we use a term a weight of evidence. So we distinguish that on our tables and we have actually -- we have used the same table but have a slightly different column heading for the weight of evidence material. And that's just to shore up something where the date -- the primary data are suggestive but a little edgy about clearing it just on that if we have additional weight of evidence for related molecules that increases our confidence level.

DR. HELDRETH: All right. Thank you.

DR. BELISTO: Curt.

DR. KLASSEN: Yes. I had the same comment that the last two speakers mentioned. And that is I think we need to put more in here about what belongs to a family. I think that could be a major use of read across to see what may be belongs and does not belong. I guess, you know, I do feel that we need to do this and we need to understand what we're doing. And what is our read across -- I think needs to be quite different for various effects.

And we got to make sure that we're not just looking at cancer or what have you. And that there may be need to be divided up into somehow into various toxicity. Is this likely to be a neurotoxicant, in comparison to cancer etcetera. I guess my major concern about the philosophy of read across, is what toxicology is most important is to find the exceptions in toxicology.

And in fact, in pharmacology it's all the exceptions. And so, if we would have done this when you started this committee, we would have concluded because ethane, methane, propane, butane etcetera. Either smaller or larger than hexane are safe, hexane should be safe. And if you would have done that shortly before I started this committee you would have said it was safe but that's the exception.

And read across does not give you the exceptions. And that's what we need to remember, that if it's the average chemical this is okay. Well, it doesn't tell you the exceptions. And you know, toxicology is becoming closer to pharmacology. And to make a drug you have to make the exception. And as we're learning more about toxicology and how a lot of toxicity is being actually produced by binding two the receptors. Transcription factors and other receptors, those chemicals therefor are the exceptions and not the rule.

So we just have to remember all the time, that when you're doing your read across, that you're assuming this chemical works just like all the other chemicals in this class. But that isn't always true. And we have dozens of examples if not hundreds of where that's true. So... but without having the data this is best that you can do.

DR. HELDRETH: Thank you.

DR. BELSITO: Anything else, Paul?

DR. SNYDER: No, I absolutely agree. I just kind of react. It isn't making assessment without data. It's making assessments with different data than we're used to. And so, I think some of these models are enormously complex. I think that the

last one we looked at had 70,000 candidate molecules. So I think when I bring transparency and start looking at them with that in mind as well. I think we're going to find these are very powerful tools.

DR. KLAASSEN: I agree they're powerful tools but as this one sentence in here says, "it doesn't replace data."

DR. LIEBLER: I think Curtis's absolutely right. I would have been disappointed if he didn't make that point. And I would have been particularly disappointed if he didn't use hexane to make that point. Because it's the classic case that illustrates the risk. I would simply say that that scenario has I think brings to this process the greatest hazard when we're trying to reason from small amounts of data.

My sort of dream, I suppose, I don't know if it's our chemist children, or chemist grandchildren will be able to do this. Or maybe even us one of these days. Is that there are very rich data sets out there on chemical safety. Now, and they're underutilized simply because much of the data is beyond the ability of individual. Even experienced individual toxicologist to keep straight and compare and manipulate. But just like with genenomics and other high dimensional data. The richness of the data becomes more powerful as you evolve tools to make quantitative estimates.

And it's my hope, but I can't prove it that those kinds of resources will eventually help us identify the characteristics of the odd -- or the unusual exceptional chemicals that produce the pharmacologic and toxicologic responses. So I think moving in this direction is important for that reason. I think we should be guided by the cautions that Curt mentioned. But ultimately, I think taking a quantitative approach to high dimensional data sets are going to be good for us in the long run. It'll make the process make safer.

DR. KLAASSEN: Well, I just like to say that, I agree with doing this and this is the method or technique that's going to get better and better with time. As we get more and more, you know, data to extrapolate from. But there is that danger and I just want everybody to realize that the interesting part of toxicology is really the exceptions. And as we don't understand the mechanism of more and more of those exceptions. We will do better and better and better by just looking at the molecule. But we're not there a 100 percent and we are going to miss some toxicity (inaudible).

DR. BELISTO: Other comments Jay, Paul, Dan. Bart, you need anything more from us on this?

DR. HELDRETH: No. This is great. Thank you very much.

Day 1 of the June 12-13, 2017 CIR Expert Panel Meeting – Dr. Mark's Team

DR. MARKS: So, now, I have -- the next is read-across report usage, and then page, what?

DR. SHANK: PDF 26.

DR. MARKS: Yep; in admin.

DR. MARKS: So, read across in general. Read across in practice. And then you give some examples here. And some chemical structures and like that. So, Bart, maybe have you to (inaudible) and lead this, because you have, I mean, we can either start by just commenting on the -- what you've proposed here. Or we could go straight to the end and the -- beyond the questions. Team, how do you want to move? Do you want to just go section by section? And then answer those questions at the end? Or do you want to start with the questions, the end and then go?

DR. SHANK: Let's go to the questions at the end.

DR. MARKS: Okay. Bart, do you want to lead it?

DR. HELDRETH: I mean, I just -- I could, you know, maybe intro it a little bit.

DR. MARKS: Yeah.

DR. HELDRETH: The idea here was to create, essentially a document for our analysts and our writers to use when they're trying to incorporate read across into a report and have it come through the way that the panel would find it most acceptable. So, this is just a first draft of the guidance for our internal use. Ultimately, you know, it may be worthwhile to develop this further down the road, and make it a public document that we can post on our website, and say, this is how we approach these sorts of things. But at this level, at this point, we're just trying to lay out some guidance for our staff --

DR. MARKS: Okay.

DR. HELDRETH: -- so that we know how to present the potential read across for the panel to decide, did they agree with it, did they not, is this sitting? So any input, any and all input on how we could do that best.

DR. MARKS: So I, it's interesting, I would say now it's already a public document, because this goes in part of the minutes, so.

DR. HELDRETH: Sure.

DR. MARKS: And then the second thing is, I actually thought it was going to come out like we do with the boiler plates. This is our reasoning behind this is how we do read across, because it's been, I would say relatively vague. And I commend you on trying to put some meat on our read across. So, I kind of look at it, and team, I would like your input, that this would eventually become --

DR. SLAGA: Boiler plate.

DR. MARKS: -- boiler plate. And this would be our guidance. And then in, you know, five years from now, if there's something new in terms of a way to approach read across. Because you have good references in here. So, that was my take. I would -- I would want it, not just to be an internal document for the writers to use by going in. The general public could see and get a glimpse on to how we do this.

DR. HELDRETH: Okay.

DR. MARKS: Team? What's your feeling?

DR. SLAGA: Oh, I agree with you. I think it would be good to put out in say, a document.

DR. MARKS: Mm-hmm.

DR. HILL: So pertinent to that issue, I have -- the only reason I jumped in instead of letting him talk, is because he's paging through. I think the most important thing here is this needs to be a living document. Something we would review annually, routinely. And with respect to any particular point, when something comes up in the context of applying it in a particular ingredient group where we find that maybe we need to add something or qualify something more.

DR. SLAGA: You can even leave samples to change the time to keep it updated.

DR. MARKS: Mm-hmm.

DR. HELDRETH: Yeah. We had this recent example of -- from one of Bernice's reports.

DR. MARKS: Fortuitously.

DR. HELDRETH: And it just felt like, well, you know, here we've done something that all the input we got back. Like the way that we laid out read across there. So, maybe we should jump on this.

DR. HILL: Mm-hmm. Yeah.

DR. HELDRETH: And take it forward and make it something we can use. So across the board.

DR. SLAGA: So the big question that was brought up before. How would you relate PHMB to PHMG as a read across?

DR. HELDRETH: Sure. Sure.

DR. EISENMAN: That was a thought to be appointed here, that not only do you need to support safety, but you also have to look for bad things too.

DR. HELDRETH: Right. The exceptions.

DR. EISENMAN: That I'm up that point. Right. And right.

DR. MARKS: And that -- and that actually happens, because --

DR. EISENMAN: Right.

DR. MARKS: -- I'd see when they go down to these ingredients, and the comments come out that well, this has a toxic effect on customer (inaudible) so. And that's, I think, sometimes done as a read across. So, okay. Ron, did you have any comments before Bart starts on -- starts on the questions?

DR. SHANK: Well.

DR. MARKS: You probably have a number of editorial --

DR. SHANK: This is a --.

DR. MARKS: -- things in the text, which is good.

DR. SHANK: Rapidly developing area in toxicology. Pardon me. And, our own Carol, just published a paper.

DR. EISENMAN: I did?

DR. SHANK: You're the senior author. I'm trying to find it.

DR. EISENMAN: Oh, the pedcopamine paper?

DR. SHANK: Yes.

DR. EISENMAN: That's been a little while. But --.

DR. SHANK: Well, that was all on read across.

DR. EISENMAN: Yes.

DR. SHANK: And very well written.

DR. EISENMAN: Well, thanks. Thanks it was a (inaudible).

DR. SHANKS: There are lots of, well not thoughts, but several computer programs based on quantitative structure activity relationships, physiologically based pharmacokinetic -- pharmacokinetic data. APA has developed one or two. I think FDA has one. And with a parallel to this is the whole field of computational toxicology. Which has a very similar goal. If you know the structure of the chemical, can you say what the toxicity is? Based on that chemical structure, determines biological activity. Biological activity determines toxicity. So what do you need to fill that in? A very, very active field. And I think it's a good idea for us to put together your statement of -- to put it on the website. When we say we're doing read across, what do we mean by that? It means a lot of different things to other people. Different fields. So, pardon me, you know, this is a good start. We can build on it a lot. And we'll probably have 100 references next time instead of what we have here.

DR. MARKS: Should we go to the questions then? Or did - - were --?

DR. SHANK: Yeah. Let's -- it's probably more productive.

DR. MARKS: I actually want -- you probably. Well, you probably have editorial comments on all this. Have you already?

DR. SHANK: No I didn't edit it at all.

DR. MARKS: Yeah. Okay. So. So, we'll start with this. Did -- let's go to the questions then.

DR. SHANK: Sure.

DR. MARKS: Bart.

DR. HELDRETH: So, the first questions was, you know, is this going in the right direction for what the panel wants? Or, would you like to see, you know, a different goal for this type of document? Would you rather see this be the basis for how we select groups?

DR. SHANK: Yes.

DR. HELDRETH: You know, when read across is possible? Or, is that a separate document? We'd rather keep this just for how we present read across in a report.

DR. MARKS: Hmm.

DR. SHANK: I think, how do we do it, is what's important. Here we have a document with 240 compounds. Data on three of them. And we end up saying, yeah, they're safe. Or it's efficient. How did we do that read across? And is this strictly on the basis of chemistry? Or -- or what?

DR. HELDRETH: Right.

DR. SHANK: So, I think that would be most helpful in this to say, this is how the panel does read across.

DR. MARKS: Okay.

DR. HELDRETH: Well, I had highlighted some instances where read cross might be appropriate, or might be inappropriate.

DR. SHANK: Okay.

DR. HELDRETH: Are there other specifics that the panel would like to elaborate on, where they think read across should absolutely be used, or it absolutely should not be attempted?

DR. HILL: I cheated on answering that question and said, I can think of some possibilities here where greater care is needed.

DR. HELDRETH: Okay.

DR. HILL: But I would worry listing any of these would seem to suggest a complete list. And I don't think the complete list will materialize until it's used for some years, honestly.

DR. HELDRETH: I think with any writing, we can start with what we have, and worry about the completeness down the road.

DR. SHANK: I agree.

DR. HELDRETH: We'll take anything that can go our way.

DR. HILL: But part of that is, and I don't know, I used a couple of words in my notes that might not exist yet. I used the word toxicophores by analogy to pharmacophores, but I've never seen that in writing, so I don't know if there is such a thing yet. But I know exactly what I mean when I say pharmacophore. I make sure that, well, anyway. And that applies to something like sensitization. So, on one the hand, certain kinds of sensitization, the worst thing will happen is somebody gets a rash and maybe misses a day of work. And then, there are other things. So for Type 1 -- for Type 1 reactions where the potential endpoint is death, the one we just discussed, for example, that would certainly be one where any potential read across would --

DR. HELDRETH: (inaudible)

DR. HILL: -- would have to be done with --. Yeah. Because we're looking at binding proteins. The immune systems. Antibodies and specific immune synapses and so forth. And, so those are very specific based on the biological macromolecules involved. We have enzymes that are highly selective in most cases. You have binding proteins. If you have immune recognition by antibodies, those are highly, highly selective than trying to do read across from we know there's explicit structural sensitivity as problematic. And the, I mentioned this before, the one that got my attention was the strange way by which, in certain genetically susceptible individuals, a bacovere , which is an anti-viral sensitizes. And the molecular details of that are known. And in my wildest dreams, I wouldn't have dreamed that up. But it's very clear. So, you can't always predict. But, again, usually you get an incident, or two incidents before --. Like, if my wife ever has another sulfur antibiotic, she will surely die. Because the last time I carried her into an emergency room in anaphylactic shock. So. But that's, you know, those are the kinds of things versus contact hypersensitivity, where, again, I'm going to get hives. But I'm not going to die.

DR. HELDRETH: So, the severity of the potential response --

DR. HILL: Yeah.

DR. HELDRETH: -- if it's high, decreases our dependence, our confidence in using read across in place of raw data.

DR. HILL: Yeah. And then you know, we were, if you read the feedback on -- that came out of that senate hearing. One of the documents, I don't remember whose document it was. And we were criticized for being overly focused on acute, and not enough focused on long term chronic type things. And one of the long term product type things is the cancer endpoints. So, the -- again, I think their computational and cellular systems are going to get us rapidly to a place where we'll have a better idea of how to make good solid confident predictions in the future. We're kind of in between now. But then there's this whole big Wild, Wild West that's rapidly evolving. So right now, there are 240, when I counted them a few weeks ago, 240 black box warnings based on pharmacogenetics among drugs. It's not 240 drugs. It's fewer than 200. But there are a lot. And clinically, right now, how many of those are actually taken into account? And on the whole flip side, we've got the precision medicine initiative. And I know this seems like a long rabbit trail, but right now, on the consumer base, what percentage of them could actually take their genetic data that they got? You don't get a complete set with something like 23andMe, but it keeps being a moving target. But I keep saying, and I've been saying for five years from -- five years -- five years from now, we'll have everybody's genome. At some point, the insurance companies are going to demand that as part of, I'm not going to insure you, unless I have your genome. And it's coming. And then, then the question is, what do you do about that, with cosmetic and personal care products right now. I think we got there just briefly on one ingredient today with the breast cancer cells that were pulled from people. And the cellular experiments that were done to see what happened in those cells versus less susceptible or less high risk breast cancer cells. So anyway. Yeah, so the endpoint matters. But, I would hate to list them. Or at least not -- try to make sure that nobody thinks that's a complete list. So that's all I wrote. I can think of some possibilities where greater care is needed, but I would worry about listing any of these if they would seem to suggest a complete list.

DR. HELDRETH: And then I had, unless there's other things to that question. You know, I had mentioned in this document about, you know, we only look at read across when there's an absence of valid experimental data. Should we write out a more detailed use of read across in other strategy systems? For example, if we have some data, but we don't think it's all that great, supplementing in an aggregate approach or weight of evidence approach, use read across to support that, maybe weak data. Or data that we don't have complete trust in. That may be beyond my expertise. I'm sure it is. So input from the panel members here, who have more expertise in that, would be really helpful.

DR. SLAGA: I personally think we have to keep it pretty general. But we don't want to make it where we have to come back and kick ourselves for making some kind of more specific analysis of something based upon read out. We have to keep it general.

DR. HELDRETH: Okay.

DR. HILL: And, I mean, I think we had a couple of good presentations

over the past several years. Or papers that we've received that talk about the value of having multiple data points on multiple chemicals, even if for that one chemical, it seems like you have a complete set that you actually get more information, provided you use it right. So, I think what you said is valid. And, I think we're already doing that in some cases. But it falls in the general category of, are we interpolating? Are we extrapolating? And the meaning of interpolate or extrapolate is very clear, if I had a linear aggression of set data points. It's a lot fuzzier, when we're talking about relationships of chemical structures to, once again, the endpoint. And so, right now, I mentioned earlier, if we're just talking about predicting (inaudible) and even my extension of that dermal penetrability of the intact substance and not worrying about what happens to it on the way in. I believe we will make great predictions at this point. But again, then there are other cases where something much more specific has happened biologically, where we have an enzyme. And that, how that enzyme functions is very exquisitely sensitive to the structure of that substrate. Or a binding protein or a transporter or any neurological synapse.

DR. SHANK: There's a recent publication, a new publication where the doctors scare on the scary.

DR. EISENMAN: Mm-hmm.

DR. SHANK: On the (inaudible). And you actually had an algorithm decision --

DR. HILL: Mm-hmm.

DR. SHANK: -- on the algorithm. Which I thought was very helpful. We could develop something like that. Which would be a general thing, not specific for one category or another. But, if we had this information, we go this way. If we don't, we go this way.

DR. HELDRETH: Okay.

DR. SHANK: I had the paper here. But --.

DR. HILL: I'm wondering if you couldn't just reference it with a few brief statements.

DR. HELDRETH: Sure. Sure.

DR. MARKS: Well, I like -- actually I'd like to get an idea of how many in the boiler plate, the algorithm. And it's rather than going to a reference, here it is. This is our thought process and how we go through it. I like that idea (inaudible) very much.

DR. HILL: Isn't that what we're really already doing with the discussion? I mean, when we have to use read across to support safety.

DR. HELDRETH: Right.

DR. HILL: Or support that we have a problem with safety.

DR. MARKS: Yeah.

DR. HILL: I think we're already including those as discussion points.

DR. MARKS: Yeah. Like, now Carol, you've read this document that Bart proposed.

DR. EISENMAN: Yes.

DR. MARKS: Did you have suggestions? Because it's interesting. Ron Shank has already wrote, referred to you twice in peer review publications. So, it's

interesting. I'm sure you've got ideas in terms of perhaps changing the wording. Technique, we're in one endpoint where data -- set of data from at least one chemical is used to predict or suggest the same or a quite similar endpoint for a set of data for at least one other chemical. And then you made the point that this has got to be all chemical structure based. That's your base.

DR. SHANK: Well, that's how it starts I think.

DR. MARKS: Yeah. Yeah. Well, I think and then you referenced, so I'm not sure. That's quite as clear in there, that really it's the chemical structure is the starting point. And then from there, we start making a read across.

DR. SHANK: Right.

DR. MARKS: And depending on either what we know from studies of that chemical. Or from what we know of predictions, which say computerized, quantitative assessments.

DR. HILL: We're going to come to the computerized part in a minute. I have a few comments.

DR. MARKS: I like the decision algorithm. And then Carol, I didn't -- I was talking. I didn't give you a chance to pipe in.

DR. EISENMAN: Well, I was going to -- at some point, we'd like CRSSE to look at it.

DR. MARKS: Oh yeah.

DR. EISENMAN: I don't know, what -- let us know when you're ready to have them look at it.

DR. HELDRETH: Of course.

DR. EISENMAN: We haven't sent it to them yet.

DR. HELDRETH: Of course.

DR. EISENMAN: But, I wasn't going to provide specific elements until we had a discussion with CRSSE. DR.

MARKS: Oh yeah. I would think, just like we do with the boiler plates, we would expect to have the -- DR. EISENMAN: Mm-hmm.

DR. MARKS: -- Science and Support Committee give input. I think this is potentially one of the most important boiler plates we have. Because, as you said earlier, you know, Ron and the example we have three chemicals. And then we read across to 50 others. Okay. So, any --?

DR. SLAGA: It would have to be a no brainer of chemistry.

DR. MARKS: Yeah.

DR. SLAGA: Right? With all these (inaudible).

DR. SHANK: It should be, but it ain't.

DR. SLAGA: It ain't. You're right.

DR. HILL: Well, I have more comments about the computational end of this. When you want --

DR. MARKS: Yeah.

DR. HILL: -- to move to that other question.

DR. MARKS: Okay.

DR. HILL: Because it relates to the starting point is the chemical. And

this word I want to invent that probably already exists, or maybe it doesn't. Toxicophores, which is for the specific endpoint of interest. How much do we know? And how very specific is or isn't the biology? So, when you wrote which tools, I wrote, not yet applicable. Except for generating information, such as (inaudible), which has become relatively reliable. Then I put, in vitro tests under circumstances as pertains to particular known toxicophores. I don't know if that's a word, but it should be, such as the DRPA test for protein reactivity. They're informative, but they have to use these with great caution, because of the specificities of enzymes, transporters, binding proteins, DNA motifs, membrane micro domains, which are lipid raft structures, etcetera. And it's important to recognize the protective mechanisms in the degree to which these may be overcome and a certain threshold is crossed. Or of just as great importance as the deleterious pathways. So, we have a pathway that's a problem, but it may not be a problem, because we can protect ourselves. If that weren't the case, we would not live past age six months.

DR. HELDRETH: So, would then, a general comment such as, you know, these read across approaches are not one with the one replacement? You know, the experimental data. But, in practically every case, will have to be part of a greater aggregate approach.

DR. HILLS: I think that's the thing is, what I -- when I teach about the use of computational tools, which I do a lot at the graduate level, is that, you always have to have validation at some level, in some place, with reasonable comparator, well, with bi- actual experimental biology, I guess is the best way to put it. To just make a computer based prediction, you've got a black box. Without knowing what the boundary conditions or the boundary parameters are, that control how good that predictions going to be, is always problematic. In fact, that -- that came to the fore when we had our (inaudible) meltdown in the fall of 2008, because the mathematics got overused. Anyway, and that's a general problem, because the more sophisticated the computational tools gets, the more and more they tend to become black boxes, with only a small number of people who actually know the inner workings of that. And so, then you get a prediction out, if you don't have a basis for knowing whether that's complete hogwash. Or it's very valid because it's well within the boundary parameters. And here's what -- here's the compound set that you're using to make the predictions with. That -- that controls whether that computational tool is highly valid. You can use it for read across. Or it's complete hogwash. But everybody will love it, because we're saying it's safe.

DR. HELDRETH: And that's what I was trying to get to in that question, was, you know, which types of tools that are available now, do we feel are useful and for what? So, do we feel the most recent version of EPI Suite comfortably predicts (inaudible)? You know, if we feel that can be a tool, so that when we populate a table, say like, the Example Justification Table, if we could put the predicted (inaudible) for both of those analogs in there, are we comfortable using EPI Suite for that? Not so much just flat out predicting tox or dart or any part of it.

DR. HELDRETH: I stumped for doing exactly that. Which - - which ingredients that was. And it the glycol esters, where we -- I looked and said, why don't

we have at least predicted (inaudible) in there, if you don't like that suite. Or if somebody has a problem with using just one, we could have a couple that are known to be very reliable. Generate the data and put them in there. Similar to with molecular weight. We seem to have been operating under these rules where, if the molecular weight's not given in the literature somewhere, you know, why? If we've got an exact structure and we know it's an exact structure, then you calculate it and put it there. And you can notate that this is what we calculated, assuming this structure. But, yeah, so there --. But, then you get to the more questionable things, where you have to ask the question, this is dependent on biology, how much do we really know? So that the one that's easy, because we've been using it already quite a bit as drug metabolism. Yeah, but the reality is, knowing that that route of metabolism is possible, versus it actually happens to any significant extent with that molecule, is important. And there's a yin and yang there, because it -- that's why we invent something called a soft drug, is to get it to go that way in metabolism, and not go that way, where we're making something toxic. Or we -- we make a third generation drug, because we've learned that this route of metabolism is problematic for this guy.

DR. MARKS: Ron Shank, what did you refer to this field now, where we're -- the read across? The attempt to do that. You said -- was there a specific name you called that?

DR. SHANK: I just said (inaudible) one called computational toxicology. Which is a little different.

DR. HILL: Well, the whole cosmos program is, I think is designed to articulate the use of computational tools with cellular tools, to get around. Because animals aren't humans anyway. It's to ultimately bring that all back together. But the point there is, if you have experimental tools that are used, cellular models or tissue models or, you know, heart on a stick model or liver in a box model or whatever. I mean, those are coming along very fast and very robustly. And to put all that back together with the computational tools, validated based on this is what we've seen in humans with this kind of compound. And -- and come up with a good big picture from which you could get a valid read across. So, I don't know, is that toxico informatics? I hadn't hear that word yet either. But it's, toxicologically applied. Bio informatics. There should be a toxico informatics word now. I think we're there. If it hasn't been coined.

DR. HELDRETH: Toxico-amatics. (Laughter)

DR. MARKS: Okay. Any other comments? Specifics? Because we're going to -- to more --?

DR. SHANK: Something specific. There's a good series of programs now where you were giving a compound to a -- a rat. And then you made sure it changes in gene expression. And we feel

(inaudible) of interest. And if you compare compounds that have similar changes in gene expression --

DR. MARKS: Mm-hmm.

DR. SHANK: -- versus this alert, and come up with some very, very interesting things. It's a tool. Just a tool.

DR. HILL: But not strictly computational. Right? You're

proving -- you're putting it in a rat and getting gene expression?

DR. SHANK: Well, you've got to have -- you have to have the gene expression data.

DR. HILL: Right. And we already looked at that once today in the parabens report and said -- and showed the parabens had something unique compared to estrogens.

DR. SHANK: This goes more detailed than that. But still, it's the general idea.

DR. HILL: So any more --?

DR. SHANK: Mm-hmm. The goal is now to take the chemical structures to see, can you predict any chain change? Any chain expression, changed based just on the chemical structure. It's a big step and --.

DR. HELDRETH: Structural alert, type of -- type of --?

DR. SHANK: Yes. Type of (inaudible).

DR. MARKS: Okay. Any other comments about this, in terms of --? The -- the only --.

DR. HELDRETH: The answer is no.

DR. MARKS: I mean, I hear us talk all the time about read across. I don't hear us talk about inferences. And you included inference in that last part of this. So, I -- I kind of wanted the team's feedback on --.

DR. EISENMAN: In the read across class I went to at SOT, they said inference is for --. So you have small to large compounds in your category. So it's from the outer compounds in. Or it's extrapolated from -- from --.

DR. HELDRETH: Yeah. But that's interpolation not inference, right?

DR. EISENMAN: Oh right, right, right.

DR. HELDRETH: Okay.

DR. EISENMAN: Correct.

DR. MARKS: So I don't know. I -- again, I -- we're at the beginning of this. And Bart, thanks for --.

DR. SLAGA: This was a very good start.

DR. MARKS: Yeah. No. That's what I -- I felt.

DR. SHANK: I did too.

DR. MARKS: And, what I want to do is be sure tomorrow, since I'm going to do the first one commenting, I -- I have feeling we'll have a fair, pretty robust discussion. We'll see. But I want to --. So, I think the points, at least I got, to begin with, a really good start Bart. But, a final document that it's like a boiler plate, that it would be searchable by the public. We always start with a chemical structure than we use a computational toxicology. Included molecular biology gene expression, you know, and that. So there are a number of things we have a decision algorithm in the boiler plate. I really like that, because it's -- it's some -- visually -- if you're visually oriented, it's really nice to use an algorithm and go down decision points. And you should be able to take what's in the text and -- and synthesize that into a decision algorithm and then the other thing, was having the Science and Support Committee evaluate, obviously.

DR. SHANK: I think another --

DR. MARKS: Any other --?

DR. SHANK: -- another (inaudible).

DR. MARKS: Please do.

DR. SHANKS: Last month, in Chemical and Engineering News, had a cover story on macro-bio's in cosmetics. And, discussed things like the flora existing on human skin. It was extremely important in governing penetration metabolism, and all kinds of things. And, it varies, depending on what part of skin you consider. So, not only do you consider absorption through hair follicle tissue, hair follicle populated skin versus none. You should also consider which bacteria or fungus is there as well. Because, that will chem change the chemistry. So that's -- that's coming down (inaudible). But, I just filled that in as, read across is going to be very, very complicated.

DR. HELDRETH: Tenuous.

DR. MARKS: Mm-hmm. Okay. Any other comments? Bart? Anything else you'd like to --?

DR. HELDRETH: No. This is a good (inaudible) a good start.

DR. MARKS: Okay. And then, and it -- the last item we - -.

DR. HILL: I -- I do have one more general thing.

DR. MARKS: Okay.

DR. HILL: And this is actually operationally important. So, you wrote about computational tools described. And I'm just going to read my comments, so I don't babble. I vote for any and all such tools. We will need much more detail concerning the way that these work inside the black box, to establish a degree of confidence and application. And the extent to which something would need to be regarded as interpolation versus extrapolation, giving these workings and boundary parameters. I already said something about that. Those don't have to be conveyed via CIR group seminars necessarily. But, we can be, at least, kept apprise of symposia. For example, national meetings or forums or maybe webinars. Or can keep on top of developments in these areas. When I was very active and most active in computational chemistry in my life, there was involvement in working groups. Online discussion groups and so forth, to try to keep up on really what was being learned about the use of such tools. And, so I don't -- I don't know what the best way, but if we're an expert panel, for the panel to maintain expertise in this area, I mean, that's going to be -- that's a fundamental part of your job already. But, just to be sure that, somehow, we -- we keep that. Or, in the extreme that members or whatever, is necessary to be sure. I mean, I pride myself in being a generalist. But that doesn't mean on any given tour, I'm going to be in an online discussion group pertaining to its use. So, I -- I don't know that this is really a rhetorical question or issue or something for future consideration.

DR. HELDRETH: No. I think that's good to look at, you know, different ways to provide, you know, continuing education on these, continuing to develop tools

DR. HILL: This what I'm saying.

DR. HELDRETH: Okay. Thank you.

DR. BELSITO: Okay. Then moving on to the next item, which is the read-across that Bart so nicely did for us, which I believe will become a living document, and Dr. Marks is going to be presenting on this.

DR. MARKS: So that's page 46 in the admin book. And our team commended Bart for having a very good start in this subject, which is very important. Our team felt the document should end up being a final boilerplate, and that it should be searchable or researchable by the public. There was some discussion whether this was going to be an internal document. We felt it should be, even though the minutes are public, we felt it should end up being a boilerplate and very easily accessed by the public.

We would start -- always start with this read-across with the chemical structure and include computational toxicology, which is a rapidly expanding field. It included Molecular biology and gene expression. We would include a decision algorithm, so it would be very clear in the paper what our decision thought process would be and it would be visually evident. And then Ron Shank, I'm going to ask you to make more comments. And then lastly, the SSC should evaluate this, obviously, as the document progresses.

Ron Shank, did you want to make any more comments?

DR. SHANK: No, you covered it. If anybody wants to question anything, I'll be happy to respond.

DR. BELSITO: Dan had some comments. I'll let him --

DR. LIEBLER: So I think we also agreed that this was a great start. So we actually like the boilerplate text sections, and some of our thoughts were actually that Don and I, based on our experience on the RIFM panel, where the read- across justification has really been very extensively developed. The table format is a good idea. We suggested a column for each end point, or each end point did a particular ingredient -- or read-across material is used for read-across to a particular endpoint. So you don't put genotox and dermal irritation and all these other things under a particular chemical unless that chemical is used for those specific things. So it might be more columns.

The other thing is to, in some cases, we can use a chemical substance as a read-across material for which we have data. There might be cases where we don't really have -- well, we might have some data but we have additional data, for example, for metabolites that would reasonably be predicted to be formed, for example, in an oral endpoint. You know, chronic tox, for example, or repro, where metabolism is likely to occur and be reasonably extensive. Then we can also consider the metabolite if we have data for the metabolites as weight of evidence. So make the distinction between read- across, per se, and weight of evidence. And weight of evidence doesn't really substitute for read-across, but if our only have a little read-across but a lot of WOE, you're probably okay. So that's something that can be developed and used in a kind of flexible manner.

The other thing that we felt was very helpful is to have the tables also include some lines for chemical properties to show document similarities between the read- across ingredient and the target ingredient. For example, log KOW molecular weights and things like that. We also recommended that the Tanimoto score could be calculated for these. It's essentially a measure of chemical similarity. It's imperfect, but it is another documentation piece to document something more than a purely subjective assessment that this chemical looks like the target. And we, in RIFM, we don't use the Tanimoto score in a cutoff threshold mode but we --

(Interruption)

DR. LIEBLER: No, we don't. But we do use it -- I know, they're all over the place -- we do use it -- say similarity as indicated by the Tanimoto score of X. There are some other computational outputs that predict potential structure alerts. Those could be listed. One of the tools that was listed was CESAR, I think. I just note that on the RIFM panel we're kind of edging away from that, but some of the others, the EPI suite and the OECD QSAR toolbox are very useful. So we think that these tables could be a little bit more -- this table could be a little more extensive and incorporate more useful information so you could literally look down the columns and better assess the quantitative or computational justification for the read-across.

DR. BERGFELD: Ron Shank?

DR. SHANK: That's a very good approach. I wonder if we could try to develop in addition an algorithm that we follow in doing read-across, starting with the chemical structure of the ingredient and then doing structure activity relationships similar or not similar. And then is there a physiological base, pharmacokinetic study or not? This kind of tier system where there are decision points as an algorithm, which is might be easier to follow for some of us than a whole series of tables both.

DR. BELSITO: Actually, it's not. I mean, I can, or Dan can send you the RIFM tables. It's not a whole series of tables, and what it is is under each endpoint. It may be that you need a different read-across molecule for that endpoint or it may be that there's data for that endpoint on this molecule but not data for another endpoint on that molecule. So you use a different one. But it has all of that information. This log KOW, log P and its molecular weight. It has chemical structure. You know, in the case of sensitizers, it has whether it's a Michel acceptor or why it could potentially be a sensitizer. So it just lists all the way down and then a brief sentence as to why it was the, you know, expert opinion of the panel that these could be used as adequate read- acrosses. And that's done -- it's done as Dan said, sometimes because the amount of data that we have is limited. You know, say that you have data that there's some quirky genotoxicity data and you don't have enough carcinogenicity data but you can get carcinogenicity data on a good read-across. Then there will be a little note, you know, data limited read- across for weight of evidence support.

DR. SHANK: So is that a single decision point at the bottom of the table?

DR. BELSITO: It's a combination of all the elements you want. It's not, you know, if this has a molecular weight of this, then we go there. It's not an algorithm. It's actually these are all the individual physicochemical, you know, structural activity

relationships, et cetera, that we want to justify this as a read-across.

DR. MARKS: What I would suggest is that neither are exclusionary. Why don't we have both the table and the algorithm? You start working on that, Bart. That'll keep you busy. And then if we decide to not have one or the other or expand, we can. And then I think, Ron, didn't you reference yesterday a couple papers from Carol, and one of your papers had an algorithm, did it not, Carol?

DR. SHANK: It did. It was a paper on read-across for PEGs. It was written by Dr. Skare and Carol and others. I think it was published --

DR. HILL: I have it with me, actually.

DR. SHANK: I had it but I lost it someplace.

DR. HILL: I thought I had it with me.

DR. SHANK: the tables sound to me much more specific to every ingredient reviewed. And I was thinking something much more generic is some kind of an algorithm that the panel follows, independent of any one ingredient.

DR. LIEBLER: So I want to respond to that, but Jay is ahead of me. So go ahead.

DR. ANSELL: No, no, go ahead.

DR. LIEBLER: All right.

DR. SHANK: Go ahead.

DR. LIEBLER: I think one distinction to make is is the algorithm the process that you use to get to identify the read-across ingredient? Or is the algorithm the process you use to evaluate the read-across data or justify the read- across? So before we assign anybody to come up with an algorithm, we need to decide what the algorithm is specifically for. In other words, is it to get to the read- across compound or is it to justify using the data from the read-across compound. That's one question. What did you have in mind?

DR. SHANK: Well, the early part of the algorithm would be to identify the read-across and then to evaluate that. So the answer is yes.

DR. LIEBLER: Okay. All right.

DR. BERGFELD: Yes. Yes.

DR. LIEBLER: So I suspect the idea of an algorithm is appealing and the closest thing we had in the RIFM framework to an algorithm like this is the series of steps that is used to assign compounds to Cramer classifications for the threshold of toxicologic concern. And in fact, that whole process has just blown up to include a much more extensive and detailed algorithm. But that's just to classify into these bins of, you know, one, two, three, or whatever the new classifications will be. So we could, and that might be instructive to some extent. It's a little hard for me to see how you would, to get down to the specifics of an algorithm for the first part, let's say. You know, I can also add -- this is captured in our discussion yesterday, so upstream of all this, again, on the RIFM side, the process of selecting molecules to consider as read-across is actually done upstream of the development of the initial report so that three chemists -- Terry Schultz, and I and Trevor Penning work with the RIFM staff to evaluate spreadsheets full of ingredients, what we have data for, and then we circulate and evaluate these and decide which groups of compounds we could cluster and plausibly have good read-across, you

know, kind of right there that we could reach to for the individual reports when those get written. So that's actually done upstream. And that's a process that isn't truly algorithmized, but it's the process that we use to get to the point where we can reach into the box and pull out this one for genotox and this one for repro and so on. I think it would be hard to turn it in to something that's very substantive, but I haven't given it a whole lot of thought. So, you know, I would suggest, perhaps, if you wanted to see an algorithm, that you might at least sketch out your thoughts on it to share with Bart or the rest of the team. Because I'm open to doing it but I think it's going to be harder to come up with something that's really useful than it sounds.

DR. SHANK: When you do this preliminary review, the chemists, you feel that could not be expressed? Your process cannot be expressed in an algorithm?

DR. LIEBLER: I wouldn't say that. We don't formally use an algorithm.

DR. SHANK: Okay.

DR. LIEBLER: But anything could be algorithmized, I suppose. The question is would it be a useful tool for us?

DR. SHANK: Right.

DR. LIEBLER: And that I'm not sure.

DR. SHANK: Okay.

DR. BERGFELD: Jay?

DR. SHANK: It was just a suggestion.

DR. BERGFELD: Jay?

DR. ANSELL: So we just want to throw out that we consider this project to be critically important in terms of 21st century toxicology and how integrated assessments are actually conducted today, particularly in an industry which is facing prohibitions on the use of animal data. I think we are working in an area to bring a great deal of -- to understand the principles underlining these integrated assessments. And one of the critical ones is transparency. So I'm not sure we're ready to look at a table and decide what columns there should be there, but we do believe that you need to be able to see where these decisions arose. And we will be filing more detailed comments going forward. But let me emphasize Dan's areas, because of the areas that we consider this to be most critical is actually in the formation of the families before the assessments are actually even started, to understand what data can be aggregated to assess the entire family and used reliably in the safety assessments.

DR. BERGFELD: Could I ask a question? Is the SCCIR Committee working on a read-across format? Or are you waiting to comment on ours?

DR. ANSELL: We will, of course, be commenting on yours, but we are also as an industry, working on understanding basic principles on what these integrated assessments look like. And it's not just read-across. It's how to use in vivo data from the literature. The importance of conducting thorough systematic reviews of the literature. How to integrate in vivo, ex vivo, in silico methods, along with methodologies like read-across and TTC into a comprehensive safety assessment package. And that presumably will be -- one of the first papers presumably will be available soon as well as some of the work you've already cited that we've done in support of ingredients going through the Cosmetic Ingredient Review.

DR. BERGFELD: Curt, did you want to say something? Then, Jim.

DR. KLAASSEN: Yes. I'd like to say that I think this is fantastic what we're trying to do here. And I think, you know, it's most appropriate for cosmetics and chemicals on the skin. However, I want us all to remember that what we're doing is looking at what the average toxicity might be for a bunch of chemicals, and we're not looking for the exceptions. And there are many, many exceptions. In fact, every compound that we teach students about are basically the exceptions in toxicology. You're never going to pick out hexane, for example, and there are many, many, many examples like that. Now that we, you know, the point is that you don't pick up the exceptions. And pharmacology is basically 100 percent exceptions, and toxicology, as we're learning more and more about, are working through receptors, just like pharmacology works through receptors. Those turn out to be the exceptions. So we don't -- I still think we need to do this but we don't want to get so confident. I mean, in one of the sentences in this document says, you know, hard data is still the best.

DR. HILL: Absolutely.

DR. KLAASSEN: And it's tremendously the best. You know, this is, with all of these, I mean, probably in another

years, as we learn about all of these receptors and how marked chemicals work, we will be able to become more, and maybe determine these exceptions. But, you know, they haven't been able to do it in pharmacology very well yet. And we've got to be careful that we don't get overly confident about it. But, now, the reason that we're doing this is, we have to remember, it's largely political, not scientific. But there is science to it. And we can learn a lot of science by doing this. So I really am for it. I just don't want us to get so confident with it that we're not going to miss chemicals this way, because we will. There's no question.

DR. HILL: Yeah. When I go back on Thursday, I'm going to be talking to the graduate students about why the presence or the absence of a methyl can make a thousand or tenfold -- or ten thousandfold difference in pharmacological activity. It's because you're interfacing with biology, which has very specific targets in many cases. And I used the word -- I think I invented the word yesterday, toxicophores, but maybe that's already out there. And so, and toxico- informatics, which to me is just another flavor. So I said a lot yesterday, and I don't want to repeat any of it today. I wasn't sure if we'd see the transcripts so I could read what these guys said yesterday or not, but I was rather hoping that I was at some point, even if we do that internally since this is right now an internal process.

DR. MARKS: Oh, you'll see it. It's public. Our meeting --

DR. HILL: Our meetings are public so we should -- yeah.

DR. MARKS: Yeah. So we'll see it the next time we see this document.

DR. HILL: Okay, great.

DR. BERGFELD: All right. Jim?

DR. MARKS: I wanted to ask two questions. One, Jay, would you like the subject be changed to integrated assessments? That's really -- I like that term rather than read-across and inference descriptions guidance. So I would just throw that out. Is this a better way to refer to what we're doing, calling them integrated assessments?

That's really broad but also it has a ring to it that I like. But we don't have to decide that now.

DR. ANSELL: The classic tox term we use now is read-across.

DR. MARKS: Read-across. Okay.

DR. ANSELL: The assessment is best described as an integrated assessment. Within that there's a variety of different methodologies and approaches, and read-across is a recognized approach under that umbrella of methods. But specifically what I was talking about was, in fact, an integrated assessment, and read-across will be addressed within it, as will TTC, as will in silico computational methods, as will other approaches on how they're all brought together.

DR. MARKS: Okay. So -- go ahead.

DR. BERGFELD: Bart?

DR. HELDRETH: Could I just respond to that quickly?

DR. MARKS: Go ahead.

DR. HELDRETH: So as Dr. Bergfeld had mentioned, this document is intended to be a living document and in many directions, not the least of which is the changes and the advancements in in silico techniques and the way we view read- across. But also in the scope of this document. The initial scope of this document is simply to give us guidance as to how to report potential read-across items to the panel so that you have the tools in front of you to make the kinds of decisions and go through whatever, whether it be formal or nonformal algorithms, to get to a read-across decision. But I certainly see this as being something that we'll expand upon and maybe at some point in the future this will become an aggregate approach document instead of simply just read-across.

DR. MARKS: And then the other comment, Carol, did you want to mention about your algorithm and your paper? I mean, you put it in there so you thought it was worthwhile, and I assume it was peer reviewed and the editors thought it was worthwhile.

DR. EISENMANN: I mean, we have a copy of it we can share with you.

DR. MARKS: No, I'd like your perspective as the author.

DR. EISENMANN: Well, I wasn't the main author.

DR. MARKS: I know that.

DR. EISENMANN: And it's been a long time since I've looked at it. So I don't really have any input to give you at this point.

DR. MARKS: That's okay.

DR. BERGFELD: Okay. I think that we've beaten this one up a little bit. And everyone's opinions have been put on the table, and certainly recorded in the minutes. And we'll keep looking at this read-across tool. So we're going to move on to the priorities list for 2018.

COSMETIC INGREDIENT REVIEW

CIR Resource Document

Read-Across

DRAFT **- 12/2019**

This document is a compilation of issues discussed by the CIR Expert Panel along with precedent language used in CIR Reports to articulate the Panel's views. Standard formats used in Panel Reports are also addressed. This is intended to provide background on issues and serve as a reference explaining the reasoning behind previous Panel decisions.

BACKGROUND

Read-Across in General

Read-across is an alternative technique used within analogue or category approaches for data gap filling, in which information for one or more source chemicals is used to make a prediction for a target chemical considered to be similar in some way, usually on the basis of structural similarity.[1,2]

The application of read-across is based on the hypothesis that similar compounds should have similar biological activities.[3] A category approach is employed between several substances whose physico-chemical properties and toxicity effects are similar.[4] These source substances are grouped together based on defined structural similarity and for one or more (toxicological or other) properties, e.g., predicting mutagenicity on the basis of a chemical containing a nitro-aromatic moiety.[5] The predictions are made within the group for the target substance based on the observed regular pattern of some members of a category.[6] It is assumed that the known value of a property for one member can be used to estimate the unknown value of the same property for another member.

The category read-across can be performed qualitatively or quantitatively.[6] It involves the application of structure-activity-relationship (SAR) by using data that are internal to the chemical category, or the identification of a chemical substructure that is common to two or more members of the category. By contrast, an analogue approach typically involves using data on one chemical structure and making some assessment about the relevance of toxicological endpoints for a second chemical structure.[1] The outcome of a study conducted with the source substance is read-across for all investigated parameters to the target substance.[7] In addition, the prediction constitutes a worst-case scenario that the strength of effects in the target substance is actually expected to be lower than the strength of effects observed for the source substance.[1] It is recognized that the robustness of a category approach would be expected to be considerably greater than that of an analogue approach, as there is more measured data available in such a wider approach.

Read-across is typically applied for discrete, well defined, organic molecules and their simple salts. It may be appropriate for well-defined mixtures (e.g., between two or more plant-based triglyceride ingredients, that only vary by small, characterized differences in fatty acid chain lengths) through trend analysis. Extrapolating from one botanical active substance to another with respect to the same or similar component(s) of toxicological concern can only be considered when accompanied by evidence of their composition regarding the particular substance of concern.[8] Meanwhile, categories can sometimes apply to series of chemical reaction products or chemical mixtures that are related in some regular fashion.[6] In this respect, read-across may be applicable for complex substances when the properties of the single components of a complex mixture are similar. In addition, properties of a complex mixture can be read-across to another complex mixture if the composition of the two are similar. However, read-across is not typically useful for purely inorganic chemicals (e.g., metal compounds) due to a number of assumptions underlying grouping of such compounds for estimating their biological properties.

The Cosmetic Ingredient Review (CIR) Expert Panel (Panel) has adopted read-across data from structurally similar ingredients, on numerous occasions, to fill safety data gaps for cosmetic ingredients. In addition to meeting needs where toxicity data is unavailable, read-across strategies can contribute to the effort for phasing out reliance on animal testing to address information needs for hazard and risk assessment. While each read-across case is unique, the living framework is designed to present the rationale according to which the human health properties of the target substance may be predicted from data for reference substance(s) by interpolation as well as to encompass the approaches most frequently encountered during the evaluation of cosmetic ingredients under assessment. The intent of this document is to suggest draft guidance for how potential read-across may be presented, so that the members of the Panel, may apply these rationale and strategies, and use such as part of aggregate approaches to assessing safety of cosmetic ingredients. However, there are a number of steps which are followed on a case-by-case basis. This document does not cover all scientific aspects or issues, and expert judgement remains largely important when applying this framework, as non-animal approaches to address information needs for hazard and risk assessment.

Read-Across in Practice

In practice, formal use of read-across strategies should be specific and, where possible, quantitative. The experimental data for one or more specific endpoints, from a single or limited number of chemicals, should be used to read-across to gaps in the data profile for another chemical, for those same endpoints, as supported by properties shared between the two chemicals. It is the appropriate data-gap filling method for “qualitative” endpoints like eye

irritation for which a limited number of results are possible (e.g., positive, negative, strong irritating, weak irritating). Interpolating a rating of "weak irritating" from multiple analogs to an ingredient can be very useful. However, such determinations can be even more useful if there is some numerical score (e.g., a NOAEL = 3.9mg/kg; or 4 out of 5), and degree of certainty (e.g., a Klimish[9] score), versus an endpoint such as, "weak irritating." On the other hand, use of all of the endpoints from one chemical to read-across to all of the endpoint gaps of a large group of other chemicals is not specific. In reality, read-across uses relatively small datasets compared to other approaches such as Quantitative SAR (QSAR) because there are usually only a few analogs for a given chemical. While (Q)SARs require a large number of chemicals in model development to achieve statistical significance, statistical similarity measures do not provide biological insight of toxicity.[10] For mammalian endpoints, (Q)SAR have been applied less frequently with the exception of endpoints such as Ames mutagenicity and, to a lesser extent, skin irritation/sensitization where the mechanisms of action are relatively well understood and where the underlying data are more readily available. For more complex endpoints, e.g., reproductive/ developmental effects, (Q)SAR plays a role as supporting information to highlight potential chemical mode of actions (MOA)s or to offer indications for similarity in effect. However, read-across is not encouraged for basic physico-chemical properties (e.g., water solubility, log K_{ow}) as these types of parameters often drive the ecotoxicity response, and experimental data or valid QSAR predictions should be reasonably obtainable.[8]

In the read-across context, the source substance is a substance with available in vivo data, and the target substance is a similar substance without sufficient data.[3] Whenever possible, experimental data is always preferred, and read-across is not considered when there are no gaps in the available, valid, experimental data. However, when such relevant, valid experimental data is not available, the Panel members, CIR staff, members of industry, or any other stakeholders may identify and propose potential read-across analogs. Indeed, proposal of read-across analogs may be found in the published literature or unpublished resources, and incorporated into CIR safety assessments. The read-across accuracy depends on a variety of parameters, including the number and choice of analogs, similarity metrics, strength in chemicals' similarity, chemical properties, and category boundaries.[10] These factors are very subjective, mutually dependent, endpoint-specific, and may require expert opinions. Therefore, the validity of each use of read-across in a safety assessment must be confirmed by the judgement of the Panel.

While a read-across could conceivably start from a structural alert (SA) as a means of identifying structurally related analogues, the Panel considers the overall process of substantiating the similarity both structurally and biologically involves weight of evidence (WoE) approaches of many different pieces of information, both directly and indirectly related to the endpoint data gap under consideration. This is because SAs use only qualitative endpoints (e.g., carcinogenic or non-carcinogenic), and do not provide insights into the biological pathways of toxicity and may not be sufficient for predicting toxicity.[10] Further scientific justification is normally required to justify the chemical grouping, typically including considerations of bioavailability, metabolism and biological/mechanistic plausibility. In analysis of complex endpoints such as repeated dose toxicity, knowledge of the mechanism of action is not always available.[7] Thus, large datasets derived from experimental studies, as well as toxicokinetic information and absorption, distribution, metabolism, and excretion (ADME) information, will be used to achieve statistical significance contribute to justify the prediction.

The proposal of structural analogues may be supported, qualitatively or quantitatively, by estimations performed using one or more of the numerous accepted in silico tools, including (though not exhaustively) databases for storing data about their physiochemical properties and toxicity (e.g., US EPA's EPI Suite™), software for generating molecular descriptors and generating prediction models (e.g., the Organization for Economic Co-operation and Development's (OECD) QSAR Toolbox, ToxTree, AmbitDiscovery, Deductive Estimation of Risk from Existing Knowledge (DEREK), etc.), and simulation tools for systems biology and molecular dynamics (e.g., the Istituto di Ricerche Farmacologiche Mario Negri Milano's CAESAR models (VEGA)). However, as this is a quickly evolving area of understanding, many new tools may be used in the very near future, including the predictive ToxGPS estimation unit of the CIR Chemistry and Toxicology database, which is currently under development.

FRAMEWORK

This draft guidance document proposes a stepwise approach, on the basis of consensus algorithms of different assessment frameworks, for analogue or category read-across in the decision context of CIR.[11-14] Different decision contexts will dictate the level of uncertainty that can be tolerated.[4] The predicted toxicity is derived from a review of the relevant scientific literature using CIR methods, sources of data and guidance for value derivation. The strategy is consistent with the guidance provided by OECD within Integrated Approaches for Testing and

Assessment (IATA)[15] and the European Chemical Agency (ECHA) read-across assessment framework.[1] Application of this framework represents an effort to facilitate a consistent, transparent and structured read across review process in CIR safety assessments. The workflow outlined below, however, only considers a discrete organic chemical as the target, which may well vary when applying to mixtures or polymers.

The chemical structure of substances usually provides the initial rationale and impetus for developing an analogue or category approach. In the preparatory assessment, chemical composition, including structural information should be well defined. Then the purity profile is assessed as it has a significant impact on the hazard of a substance. On a case-by-case basis, variation in manufacturing processes may result in differences in chemical composition, thus the chemical structure(s) need to be described in sufficient detail to convey an understanding of the elements within a category that will affect the properties of the category members and set boundaries for the category. Exposure to impurities has to be considered in the category justification.

Step 1 Data gap analysis

Determine the number and type of data gaps for the target chemical in accordance to the exclusive scope and risk-decision context of CIR safety evaluation process. Environmental fate parameters such as biodegradation and ecotoxicity endpoints such as acute aquatic toxicity in the species of fish, daphnia, or algae are generally not considered. This step identifies what is known about the hazard profile of the target chemical by gathering biological data that contain associations between chemicals and toxicity endpoints.

Read-across starts with a specific target substance and uses models and analogues to fill data gaps for specific endpoints either for single or multiple chemicals that share similarities in structure, reactivity, and/or metabolism. The analogue approach typically makes a prediction for a single target using one source substance, whereas the category approach makes a prediction for a target chemical considering data points from multiple source chemicals. The type of data gaps will drive the practical gap filling strategy. Toxicokinetic information is generally required as such information is viewed as key to help rationalize certain read-across approaches, particularly for endpoints like reproductive/developmental effects where QSAR analysis is applicable. While read-across is anchored with conventional in vivo and in vitro data, additional evidence from new approach data, e.g., high throughput/high content (HT/HC) screening data, "-omics" assays (e.g., metabolomics), and computational models, as a means of substantiating biological similarity, can be integrated into a prediction model.[3,16,17] When special concerns about the quality of the read-across case are raised (e.g., to meet the Panel members' specific concerns or the regulatory standard of substance registration under the Registration, Evaluation, Authorization and Restriction of Chemicals (REACH)), it would be to necessary to read across the full findings of longer term effects such as 90-day repeated dose toxicity studies or reproductive/developmental effects, with a high degree of confidence in the predicted set of toxicological properties for the target substance.

Step 2 Overarching similarity rationales

The fundamental underlying premise underpinning the analogue and the category approach is upon the expectation that structurally similar chemicals will have similar physical attributes and biological effects. The similarities typically elaborate with a couple of features: a common functional group, a common mode or mechanism of action or adverse outcome pathways (AOPs), the likelihood of common precursors and/or breakdown products; and an incremental and constant change across the category (e.g., a chain-length category). The physicochemical properties are compared since properties such log P_{ow}, aqueous solubility may provide insights to the likely absorption characteristics of a chemical. The likely toxicokinetics are evaluated to consider how stable the chemical is and whether it will metabolize, decompose, or hydrolyze in some manner. A broad criteria of similarity (chemistry, transformation, and toxicology) has been discussed by OECD/REACH category definition.[5,6] Overarching possible similarity rationales within the scope of the endpoints being addressed, and help form the basis for how analogues should be identified to develop analogue/category approaches.

It is important to know which aspect of similarity between two chemicals is governing their similar hazardous properties. Perform an initial profiling of the target chemical to examine the data applicability and data adequacy: check whether the chemical is a member of an existing category, whether anything is known about the mechanisms of action or toxicokinetics, whether effects are probably to be driven by the target or its abiotic or metabolic transformation product, whether empirical data are available for some endpoints, what effects can be predicted using QSAR analysis? Use of QSARs can retrieve background information of the target substance based on its structure: numerous categorizing tools help identify the affiliation to previously defined categories (e.g., the categories defined by the US-EPA for the assessment of new chemicals), observed or simulated metabolites as well as mechanisms or toxicological MOAs.[18] For instance, the OECD QSAR toolbox provides several sets of profilers

which are the tool to group chemicals into adequate analogues (users can also build their own profilers. The outcome of the profiling determines the most appropriate way to develop a category and search for analogues. Within a category, different members may be selected for the endpoint desired. If the available test results show that the chemicals in a category behave in a similar or predictable manner, then interpolation and/or extrapolation may be used to assess the chemicals instead of conducting additional testing. A category approach with several data points for one specific property should increase the confidence in the prediction of this property.

In practice, when specific mechanisms or modes of action are identified for a target chemical, which are relevant for the investigated endpoint, then chemicals can be grouped into specific category, with the help of computational tools, to search for chemicals which have the same mechanisms or modes of action. In contrast, if no specific mechanisms or modes of action are identified for a target chemical, then it is recommended to search for chemicals which are structurally similar to the target chemical. Categorization can also be performed with accounting for abiotic (e.g., autoxidation) or biotic (e.g., skin metabolism) transformation of the analogues. The search results in identification of the most appropriate analogues that are both similar in terms of structure and mechanism of action with the target chemical and that have been tested for the assessed hazard endpoints. The robustness of a chemical category could be evaluated in a similar way to that of QSARs. The features that relate the category members is assessed together with an assessment of the scope of the category. In principle, a representative set of chemicals within the scope could be identified and tested in the same way as would be done for an external validation of a QSAR.

Step 3 Analogue identification

The identification of analogues aims to search for analogues similar to the target chemical by defining an endpoint specific category to predict.[7,19] Directed by the outcomes of the data gap analysis and overarching rationale steps, one or more chemicals are grouped into a toxicologically meaningful category that includes the target molecule, so that within a category data gaps can be filled by read-across. Within the applicability domain of a chemical category, specific endpoint assessments can be achieved by performing read-across in the following four ways to fill data gaps:[20] 1) one-to-one (one analog used to make an estimation for a single chemical), 2) many-to-one (two or more analogs used to make an estimation for a single chemical), 3) one to many (one analog used to make estimations for two or more chemicals), or 4) many-to-many (two or more analogs used to make estimations for two or more chemicals). The way 3 and 4 may be considered as being multiple simultaneous applications of ways 1 and 2, respectively. Generally, more confidence can be achieved when data from more than one source chemical are evaluated.

Analogous sets of chemicals are often selected based on the hypothesis that the toxicological effects of each member of the category will show a common behavior. For example, skin sensitization is a toxicological endpoint as a result of protein binding; starting from a target chemical for which a sensitization binding mechanism is identified, analogues can be identified within a group of chemicals which can bind to the proteins by the same mechanism and for which experimental results are available. Thus, specific category definition allows to group target and source substances into one chemical category with respect to skin sensitization which is driven by protein binding mechanism can be dissimilar with respect to effects such as endocrine disruption which are often driven by non-covalent receptor-mediated interactions, so that within a category data gaps can be filled by read-across. Ideally, suitable analogs have the same functional groups and core structure compared to the target chemical, as well as similar potential for bio/chemical reactivity, metabolic pathways and physicochemical properties.[12,19] In some cases, analogs can also be categorized as suitable with interpretation (have bio/chemical reactivity and toxicological activity in common but with different physicochemical properties) or suitable with preconditions (involves bio/chemical transformation). Read-across based on mechanistic similarity (e.g., common chemical interaction with a receptor) is generally considered a better similarity hypothesis than an informatics-based similarity metric.

Structural similarity is being used as the initial criterion for identifying potential analogue(s). If the target is not a member or could be a member of an existing category, consider the use of analogue search tools to identify and evaluate structural analogue(s) with experimental data, such as the OECD QSAR Toolbox, ChemID plus, DEREK, AIM tool and Distributed Structure-Searchable Toxicity (DSSTox) Database, etc. The initial evaluation of search results based upon structural similarity relies on a chemoinformatic index of molecular similarity to filter the number of analogues. Statistical similarity of two chemicals can be calculated using different types of distances, such as Hamming, Euclidean, Cosine, Mahalanobis, Tanimoto distance, or linear or nonlinear relationships of the features. Web-based tools that permit structure searching typically include an algorithm to search for structurally similar chemicals with a Tanimoto similarity cut off (e.g., Scifinder, Leadscope, and Chemspider). Structural characteristics are weighted alongside physicochemical characteristics. It could also consider other similarity

contexts SAs or bioactivity profiles from high throughput screening data sequentially.[17] The similarity justification is also based on a rationale that the differences in chemical structure do not affect the properties relevant to the specific endpoint under consideration. The identified read across analogs were confirmed by using expert judgement. In the case of complex endpoints, analogues are often identified by WoE, looking at consistency in empirical data across a number of mechanistically relevant endpoints. For instance, read across for skin sensitization may require a WoE when uncertainty is gauged regarding skin metabolism or chemical reactivity that leads to dendritic cell activation.[7]

Step 4 Analogue evaluation

Evaluation entails gathering associated properties or parameters pertinent to a specific endpoint. General factors in evaluating the validity and relevance of source analogues comprise in considerations beyond structural similarity.[11] A systematic expert-driven process for evaluating analogues for use in QSAR assessments has been described in detail in the published literature.[12,19,21,22] Source analogues with limited data, and particularly for the endpoint(s) of interest required for the target chemical, are not viable candidates for further consideration. In principle, the categorization of potential analogs is based upon their degree of structural, reactivity, metabolic and physicochemical as well as biological and toxicological similarity to the target chemical. Major considerations to evaluate the suitability of a source analogue include:

- The similarity of structural features (e.g., SAs of nitrosamines, alkylhalides and aromatic amines etc. associated with specific toxic effects), key functional groups (e.g. esters, aldehydes, amides, amines, etc.), and core substructures
- The similarity of the physicochemical properties (e.g., Molecular weight, log K_{ow}, pKa, vapour pressure, water solubility); how the existing differences are expected to impact likely bioavailability by the oral/dermal or inhalation route?
- The similarity of toxicokinetics/metabolic pathway; consider available metabolism database and predictive software that simulate metabolism, as well as the utility of in vitro hepatocyte studies to provide information of metabolic linkage
- The similarity of toxicological MOAs or chemical reactivity; are there differences in the alert functional groups of the analogues that could impact the toxicological profiles?

No single tool addresses all aspects of the workflow. A preliminary indication of the relative similarity can also be made by reference to existing QSAR tools. There are several types of algorithms to generate QSAR models for toxicity prediction. Endpoints prediction would be accomplished by implementing a tiered methodology:

- Describe the target and source chemical(s) with CAS numbers, names and chemical structures
- The physical–chemical properties of the target substance and the read-across analogs are calculated using EPI Suite (US EPA)
- Evaluate structural similarity based upon a chemoinformatic index of molecular similarity (e.g., Tanimoto score);[18] a similarity value greater than 0.75 is commonly used
- Analogues are searched by OECD QSAR Toolbox, the Analog Identification Methodology (AIM, US EPA), Toxmatch, Toxread, AMBIT, or Derek Nexus; such tools can identify structural alerts and thus help to judge whether the toxicity profile of the source analogues relative to the target chemical are likely to be similar
- DNA binding, mutagenicity, genotoxicity alerts, and oncologic classification predictions were generated using OECD QSAR Toolbox
- The developmental and reproductive toxicity (DART) scheme implemented in the OECD QSAR Toolbox or CAESAR was employed to profile chemicals for their expected DART potential[19]
- Estrogen receptor binding and repeat dose categorization are generated using OECD QSAR Toolbox
- Most organic chemicals must react covalently with skin proteins in order to behave as skin sensitizers; Protein binding alerts for skin sensitization can be predicted by Toxtree, CAESAR or OECD QSAR Toolbox
- The major observed or simulated metabolites for the target and read-across analogs are determined and evaluated using OECD QSAR Toolbox

The evaluation process requires ascertaining the data quality and quantity the data variability when multiple studies from the same endpoint are available.[9] Also evaluate consistency and concordance of experimental data (both effects and potency) of the source analogues across the endpoint or between endpoints. The greatest weight is given to the available experimental results in the data matrix that support the justification of the read-across.

Step 5 Data gap filling

Data gap filling is the process of estimating the property of target chemical using the test results available for other member(s) within the same category. A data gap for some "qualitative" endpoints, such as eye irritation, skin sensitization or mutagenicity, could be readily addressed using a combination of (Q)SAR models and/or in vitro techniques. However, in the case of complex endpoints (e.g., repeated dose toxicity, that would merit higher tier testing in animals, e.g., a 90-day study), predictions are made via the WoE across different source analogues, which rely on several lines of corroborating evidence whether it be consistent metabolic profiles, similarity in effects at shorter exposures, (Q)SAR estimates or other supporting analogies with experimental data that are not necessarily part of the main category/analogue approach.[23,24] If a high number of analogues with experimental results are identified, consider trend analysis to fill data gap for "quantitative endpoints". When sufficient data allow, taking the most conservative value among the source chemicals within the whole category. Some computational tools also provide (Q)SAR models for filling a data gap if no adequate analogues are found for a target chemical.[25] Specify any known caveats in the endpoints where the approach is not expected to be applicable.

While the acceptance of read-across predictions is often made according to a framework, ultimate judgement must be convinced of the scientific credibility of the read-across and the supporting data provided. Final acceptance of the read across prediction is contingent on reducing the level of uncertainty associated with the justification of similarity as well as the overall approach.[26] Sources of uncertainty include a variety of elements: the number of analogues), completeness of the data matrix (e.g., number of data gaps), data quality for the underlying analogues for the target and source analogues, consistency of data across the data matrix-concordance of effects and potency across analogues, etc.

Read-across algorithms for the endpoints of skin sensitization and mutagenicity, presented by OCED QSAR Toolbox workflow, are shown in Figure 1.

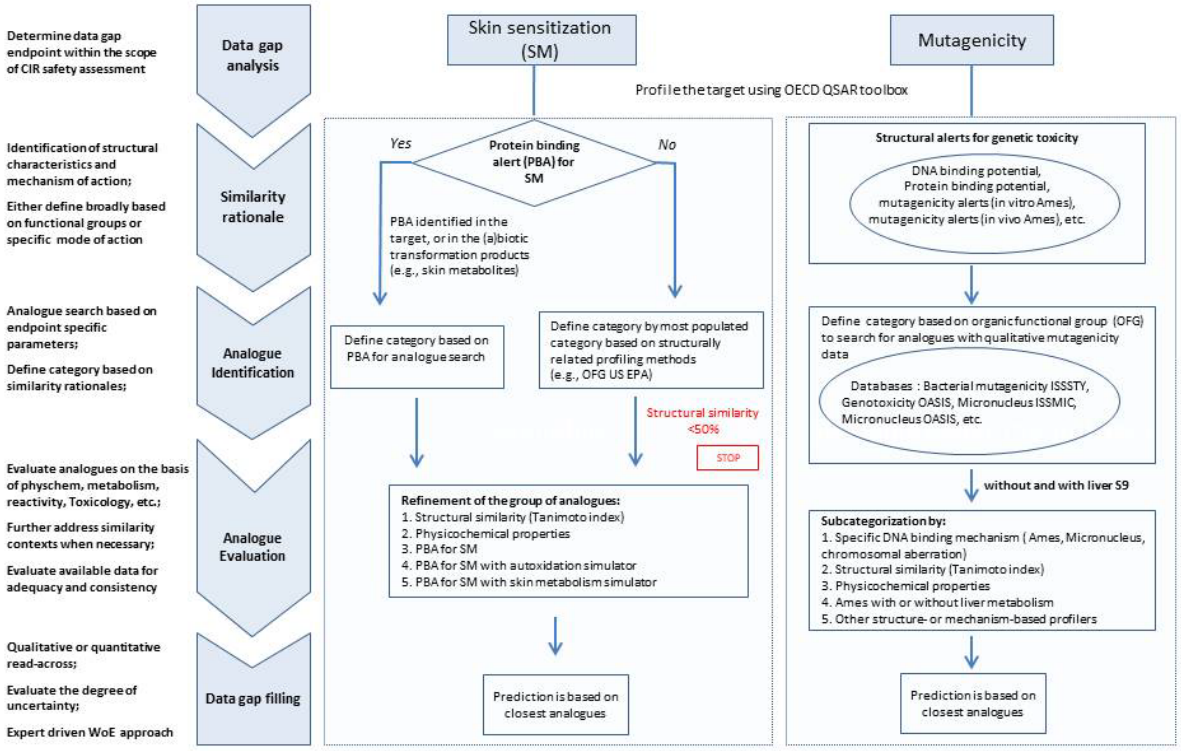


Figure 1. Algorithms of skin sensitization and mutagenicity workflow presented by OECD QSAR toolbox

EXAMPLE

Literal examples of how read-across may be incorporated into CIR safety assessment reports are illustrated below, with highlighting of the general points of rationale.[8] At each point wherein data are not available on an ingredient under review, a statement of such is to be made. When an analog is proposed for read-across to substitute for the lack of data on an ingredient, the analog and ingredient are to be identified in the heading of each Endpoint Summary. The Discussion is to reiterate the lack of specific data points, the proposed read-across analogs, and rationale describing the utility therein. Finally, a justification table should further reiterate the identities of the ingredients and read-across analogs; the end-point(s) under consideration; and the justification for using read-across in such instances.

Example 1 (Endpoint Summary):

> **Animal**
> **Oral**
> 1-(2-Butoxy-1-methylethoxy)-propan-2-ol (read-across for PPG-n Butyl Ethers)
>
> ADME data were not available for the PPG Butyl Ethers. But an appropriate read across material was identified; an ADME study was conducted in accord with….

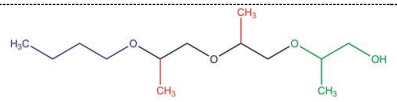
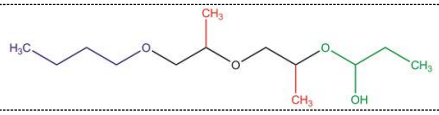
Example 2 (Endpoint Summary):

> …the short-term and subchronic toxicity studies summarized below are described in Table 10. No repeated-dose dermal, oral, or inhalation toxicity data were available for PPG-3 Butyl Ether or PPG Butyl Ethers in general. Appropriate read-across materials were identified for dermal subchronic toxicity, oral short-term and subchronic toxicity, and short-term inhalation toxicity testing, and those data are included in this table….

Example 3 (Discussion):

> The Panel addressed the use of chemicals for read-across, and determined that information reported for [(butoxymethylethoxy)methylethoxy]propan-1-ol, poly[oxy (methyl-1,2-ethanediyl)], α-butyl-ω-hydroxy-, and 1-(2-butoxy-1-methylethoxy)-propan-2-ol is appropriate for read-across. [(Butoxymethylethoxy)methylethoxy] propan-1-ol and PPG-3 Butyl Ether are positional isomers. The Panel stated that, because the chemical and physical properties and metabolism of these two compounds should be essentially identical, the information on [(butoxymethylethoxy)methylethoxy] propan-1-ol is useful for evaluating the safety of ingredients included in this assessment. Poly[oxy(methyl-1,2-ethanediyl)] α-butyl-ω-hydroxy contains the common core structure of the butyl polyoxyalkylene ethers; therefore, the information on this chemical supports the safety of the butyl PPG ethers named in this report. 1-(2-Butoxy-1-methylethoxy)-propan-2-ol is a potential metabolite of the butyl PPG ethers; accordingly, data on this ingredient are included to strengthen the toxicity profile.

Example 4 (Justification Table):

	Target Material	Read-Across Material
Name	***PPG-3 Butyl Ether***	***[(Butoxymethylethoxy)methylethoxy]propan-1-ol***
CAS No.	55934-93-5	55934-93-5
Structure		
Similarity (Tanimoto score)		
Read-across endpoint*		• metabolism • repeated dose toxicity • genotoxicity • reproductive and developmental toxicity • skin sensitization • ocular irritation
Molecular Formula	$C_{13}H_{28}O_4$	$C_{13}H_{28}O_4$
Molecular Weight	248.3	248.3
Melting Point (°C, EPI Suite)	65.87	54.57
Boiling Point (°C, EPI Suite)	316.47	303.46
Vapor Pressure (Pa @ 25°C, EPI Suite)	0.00258	0.00768
Log Kow (KOWWIN v1.68 in EPI Suite)	1.34	1.77
Water Solubility (mg/L, @ 25°C, WSKOW v1.42 in EPI Suite)	5561	2387
Henry's Law (Pa·m3/mol, Bond Method, EPI Suite)	5.61E-006	2.81E-005
Repeated dose toxicity		
Repeat dose	Not categorized	Not categorized
Skin Sensitization	No alert found	No alert found
Protein Binding (OASIS v1.1)	No alert found	No alert found
Protein Binding (OECD)	No alert found	No alert found
Protein Binding Potency	No alert found	No alert found
Protein Binding Alerts for Skin Sensitization (OASIS v1.1)	No alert found	No alert found
Skin Sensitization prediction (OECD Toolbox v4.2)	Non sensitizer	Non sensitizer
Genotoxicity		
DNA binding by OECD QSAR Toolbox (v4.2)	No alert found	No alert found
Carcinogenicity (genotoxicity and non-genotoxicity) alerts	Not alert found	Not alert found
DNA alerts for Ames, MN, CA by OASIS	No alert found	No alert found
In vitro Mutagenicity (Ames test) alerts by ISS	No alert found	No alert found
In vivo mutagenicity (Micronucleus) alerts by ISS	No alert found	No alert found
Oncologic Classification	Not classified	Not classified
Reproductive and developmental toxicity		
ER Binding by OECD QSAR Tool Box (3.4)	Non-binder, no cyclic structure	Non-binder, no cyclic structure
Developmental Toxicity Model by CAESAR v2.1.6		
Metabolism		
OECD QSAR Toolbox (v4.2)	Not tested	Not tested
Rat liver S9 metabolism simulator and Structural Alerts for Metabolites	Not tested	Not tested

Justification	Chemical properties, physical properties and metabolism are expected to be essentially identical for these two positional isomers

*Read-across endpoints covered herein are for demonstration purpose. In pragmatic analysis, read-across endpoints are determined based on quality of existing data and similarity rationales.

INFERENCE

The use of inference can be a solid tool in the assessment of safety when, for one reason or another, neither experimental data acquisition nor read-across are feasible. Inference can be broadly defined as a combination of data analysis and expert judgement to confidently estimate the general level of concern with regard to certain endpoints.

The utilization of inference in a group of ingredients is an important strategy in the evaluation of chemicals that may be considered difficult to test experimentally. For instance, ADME (absorption, distribution, metabolism, and excretion) analyses of non-fully characterized mixtures (e.g., some botanical ingredients) are essentially impossible. In such an instance, all of the chemicals in a botanical ingredient family may be derived from the same generally recognized as safe (GRAS for use in foods) fruit, and the maximum exposure from cosmetic use for each ingredient (which are typically very small concentrations compared to a whole fruit, even if absorption of the cosmetic is 100%) may be significantly lower than that resulting from dietary consumption (and first pass metabolism is not expected to be a confounding factor). Therein, it can be inferred that, in the absence of data, and a historical lack of adverse event reports to the contrary, the risk of systemic toxicity from cosmetic use is exceedingly low. Accordingly, the ingredients therein share this conclusion in common and the safety assessment on such a botanical ingredient family can focus primarily on local effects, such as irritation and sensitization. The analysis can be further supported by the Threshold of Toxicological Concern (TTC) approach. Derivation of TTC values from a cosmetics toxicity dataset (e.g., COSMOS TTC dataset/ Munro 1996) would provide higher confidence in the use of the TTC approach. If human exposure to a substance is below the relevant TTC value, it can be judged "with reasonable confidence, to present a low probability of a risk."[27]

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Memorandum

To: CIR Expert Panel Members and Liaisons
From: Christina L. Burnett, Senior Scientific Writer/Analyst
Date: November 15, 2019
Subject: Strategy Memo on Silicates, Clays, and Zeolites

In June 2018, the Panel considered the re-review of the CIR Final Report on the Safety Assessment of Aluminum Silicate, Calcium Silicate, Magnesium Aluminum Silicate, Magnesium Silicate, Magnesium Trisilicate, Sodium Magnesium Silicate, Zirconium Silicate, Attapulgite, Bentonite, Fuller's Earth, Hectorite, Kaolin, Lithium Magnesium Silicate, Lithium Magnesium Sodium Silicate, Montmorillonite, Pyrophyllite, and Zeolite, which was published in 2003. This re-review proposed the addition of 14 possible "add-on" ingredients that had not yet been looked at by CIR; Potassium Silicate, Sodium Metasilicate, and Sodium Silicate from the safety assessment published in 2005; and 6 ingredients from the Safety Assessment of Silica and Related Cosmetic Ingredients that was finalized in 2009. The Panel voted to re-open the 2003 review of the 17 ingredients and include 23 additional ingredients.

In subsequent meetings (April 2019 and September 2019), the Panel decided to split off Silica and Hydrated Silica into a report separate from the remaining 38 ingredients due to concerns over ingredient sourcing and potential constituents/ impurities from the sourcing. The Panel tentatively determined that the data were insufficient to support safety of the outstanding 38 ingredients, although the conclusions of safety for the re-reviewed ingredients still stand officially (safe as used). The Panel charged CIR staff to propose sensible grouping of the remaining ingredients into reports for new re-reviews. Such proposed groupings are below. CIR staff have proposed deleting some of the "add-on" ingredients as they are no longer considered to be "no brainers" for addition. The proposed deletions are noted with ~~red strikethrough~~. CIR staff suggest that the remining ingredients be presented in 3 separate reports.

Silicates

Aluminum Silicate
Aluminum Calcium Sodium Silicate
Aluminum Iron Silicates
~~Aluminum Iron Calcium Magnesium Germanium Silicates~~
~~Aluminum Iron Calcium Magnesium Zirconium Silicates~~
~~Ammonium Silver Zinc Aluminum Silicate~~
Calcium Silicate
~~Calcium Magnesium Silicate~~
Lithium Magnesium Silicate
Lithium Magnesium Sodium Silicate
Magnesium Aluminometasilicate
Magnesium Aluminum Silicate
Magnesium Silicate
Magnesium Trisilicate
Potassium Silicate
Pyrophyllite
Sodium Magnesium Silicate
Sodium Metasilicate
~~Sodium Magnesium Aluminum Silicate~~
Sodium Potassium Aluminum Silicate
~~Sodium Silver Aluminum Silicate~~
Sodium Silicate
~~Tromethamine Magnesium Aluminum Silicate~~
~~Zinc Silicate~~
Zirconium Silicate

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Clays

~~Activated Clay~~	Hectorite
Attapulgite	Kaolin
Bentonite	Montmorillonite
Fuller's Earth	

Zeolite

~~Ammonium Silver Zeolite~~	~~Titanium Zeolite~~
~~Gold Zeolite~~	Zeolite
~~Silver Copper Zeolite~~	~~Zinc Zeolite~~

Accordingly, does the Panel agree with this proposal of 3 separate safety assessments?

Isopropyl Lanolate

The CIR Expert Panel first published the safety assessment of Isopropyl Lanolate in 1980. The Panel concluded that "on the basis of the information available, which the Expert Panel believes to have been accumulated in a reasonable manner, it is concluded that Isopropyl Lanolate is safe as currently used in cosmetic products."[1] In 2001, after considering new studies and updated use data, the Panel determined to not re-open the safety assessment.[2] No new data were discovered in the published literature in a search for information that would have become available since the last rereview. The Panel did consider updated information regarding product types and ingredient use frequencies as reported in the US Food and Drug Administration (FDA) Voluntary Cosmetic Registration Program (VCRP) database,[3] and the maximum use concentrations provided by the Personal Care Products Council.[4] The Panel again determined to not re-open this safety assessment, reaffirming the original conclusion that Isopropyl Lanolate is safe as a cosmetic ingredient in the present practices of use and concentration, as given in Table 1.

The frequency and maximum concentrations of use have decreased significantly since the initial re-review of Isopropyl Lanolate was considered. According to VCRP data, Isopropyl Lanolate was reported to be used in 415 formulations in 2001,[2] but is only reported to be used in 122 formulation in 2019.[3] The maximum reported concentration of use decreased from 26% in 2001[2] to 14.5% in 2019.[4] Additionally, the maximum concentration of use in products that could result in incidental ingestion (lipsticks) has remained basically the same (~14%), but for products that result in dermal contact, that concentration has decreased from 26% (in foundations; 2001) to 6% (in eyeliners; 2019). It should also be noted that when compared to the use data included in the 1980 assessment, the decreases are even more significant; at that time, Isopropyl Lanolate was reported to be used in 1194 formulations at concentrations up to 50%.[1]

Table 1. Current (2019) and historical (2001) frequency and maximum concentration of use of Isopropyl Lanolate according to duration and exposure

	# of Uses		*Max Conc of Use (%)*	
	2019[3]	**2001[2]**	**2019[4]**	**2001[2]**
Totals*	**122**	**415**	**0.005 – 14.5**	**0.4 – 26**
Leave-On	*118*	*393*	*0.05 – 14.5*	*1 – 26*
Rinse-Off	*4*	*21*	*NR*	*0.4 – 6*
Diluted for (Bath) Use	*NR*	*1*	*NR*	*NR*
Eye Area	35	41	6	2 – 10
Incidental Ingestion	19	183	2.7 – 14.5	2 – 14
Incidental Inhalation-Spray	3; 4[a]; 13[b]	27[a]; 25[b]	4[a]	10; 1-15[a]; 1-5[b]
Incidental Inhalation-Powder	11; 13[b]	13; 25[b]; 1[c]	1.5[c]	3-6; 1-5[b]
Dermal Contact	100	226	0.5 – 6	1 – 26
Deodorant (underarm)	1[a]	NR	NR	NR
Hair - Non-Coloring	1	4	4	2
Hair-Coloring	NR	NR	NR	0.4
Nail	1	2	NR	1 – 9
Mucous Membrane	19	188	2.7 – 14.5	2 – 14
Baby Products	NR	1	NR	NR

*Because this ingredient may be used in cosmetics with multiple exposure types, the sum of all exposure types may not equal the sum of total uses.

[a] It is possible these products are sprays, but it is not specified whether the reported uses are sprays.

[b] Not specified whether a spray or a powder, but it is possible the use can be as a spray or a powder, therefore the information is captured in both categories

[c] It is possible these products are powders, but it is not specified whether the reported uses are powders.

NR – no reported use

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Sodium Naphthalene and Sodium Polynaphthalene

The Cosmetic Ingredient Review (CIR) Expert Panel (Panel) first published the Final Report on the Safety Assessment of Sodium Naphthalenesulfonate and Sodium Polynaphthalenesulfonate in 2003.[1] The Panel concluded that these ingredients were "safe as used in cosmetic formulations intended to be applied to the skin. The available data, however, are insufficient to support the safety for use in cosmetic products which may contact mucous membranes or be ingested." Data identified in the published literature[2-5] that have become available since the publication of the 2003 report, support the conclusion reached by the Panel in the original review. The Panel also reviewed updated information regarding product types and ingredient use frequencies as reported in the US Food and Drug Administration (FDA) Voluntary Cosmetic Registration Program (VCRP) database,[6] and the maximum use concentrations provided by the Personal Care Products Council (Council).[7] The Panel determined to not reopen this safety assessment and reaffirmed the original conclusion that Sodium Naphthatlenesulfonate and Sodium Polynaphthalenesulfonate safe as cosmetic ingredients in cosmetic formulations intended to be applied to the skin. The Panel also determined that the available data are still insufficient to support the safety for use in cosmetic products which may contact mucous membranes or be ingested.

The frequency of use for Sodium Polynaphthalenesulfonate has decreased since the original review was considered, as seen in Table 1. According to VCRP data, Sodium Polynaphthalenesulfonate was reported to be used in 50 formulations in 1998.[1] In 2019, VCRP data indicate that Sodium Polynaphthalenesulfonate is used in 12 formulations.[6] The current maximum concentration of use in leave-on products (0.1%) is slightly lower than that reported in 1999 (0.3%).[1,7] While no uses were reported by the VCRP in products that may be used on mucous membranes or may be incidentally ingested, a concentration of use was reported in products that may come into contact with mucous membranes (bath soaps and detergents at 0.0074%).[6,7] Uses were neither reported for Sodium Naphthalenesulfonate in the 2003 report, nor are there uses reported in 2019.[1,6,7] The Panel determined that there were no new relevant data that necessitated a new review of these ingredients.

Table 1. Current and historical frequency and concentration of use for Sodium Polynaphthalenesulfonate according to duration and exposure.

	# of Uses		*Max Conc of Use (%)*	
	2019[6]	**1998[1]**	**2019[7]**	**1999[1]**
Totals*	**12**	**50**	**0.000051-0.19**	**0.1-0.3**
Duration of Use				
Leave-On	11	50	0.036-0.1	0.1-0.3
Rinse-Off	1	NR	0.000051-0.19	NR
Diluted for (Bath) Use	NR	NR	NR	NR
Exposure Type				
Eye Area	2	12	NR	0.1-0.3
Incidental Ingestion	NR	1	NR	NR
Incidental Inhalation-Spray	NR	1[a]	0.036; 0.1[a]	NR
Incidental Inhalation-Powder	NR	NR	NR	NR
Dermal Contact	9	41	0.0074-0.027	0.1-0.3
Deodorant (underarm)	NR	NR	NR	NR
Hair - Non-Coloring	2	NR	0.008-0.1	NR
Hair-Coloring	NR	NR	0.000051-0.19	NR
Nail	NR	NR	NR	NR
Mucous Membrane	NR	1	0.0074	NR
Baby Products	NR	NR	NR	NR

*Because this ingredient may be used in cosmetics with multiple exposure types, the sum of all exposure types may not equal the sum of total uses.
[a] It is possible these products are sprays, but it is not specified whether the reported uses are sprays.
NR – not reported

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