ADMIN

Read-Across Working Group

EXPERT PANEL MEETING
March 28-29, 2024

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Memorandum

Date: March 4th, 2024
From: Bart Heldreth, Ph.D., Executive Director, Cosmetic Ingredient Review
To: The Read-Across Working Group – Drs. Klaassen, Rettie, Ross, and Tilton
Re: 1st Meeting of the Read-Across Working-Group

The Expert Panel for Cosmetic Ingredient Review has been utilizing read-across strategies for a number of years. One early example can be found in the Alkyl PEG Ethers report, affording the safety assessment of 369 ingredients in one report, even though there were data gaps for numerous ingredients therein (if read-across was not used). With the trend away from new animal studies and toward new approach methodologies (NAMs), the necessity of utilizing read-across strategies is ever increasing. And the complexities of these strategies are often well beyond simple interpolations between various length, straight-chain hydrocarbons or various numbers of ethoxy repeat units.

This is the 1st meeting of the Read-Across Working-Group (RAWG). However, the Panel has discussed the topic of read-across, both basic and applied, many times over the years. The most recent basic discussion was at the September 2021 meeting wherein a draft Read-Across Resource Document was presented (*Draft_Read-Across_Resource_Document_082021.pdf*). At that meeting, the Panel reviewed a revised draft of the document. They agreed that it was a great start to outline a framework, which articulates the initial phase and step processes of measuring and layering chemical and toxicological similarities, to systematically identify potential read-across analog candidates for the Panel's consideration by utilizing currently available public databases enriched with cosmetics-related chemicals. Also included therein, were a variety of computational tools as well as expert judgement in chemical clustering, subcategorization, and property profiling. The Panel also discussed the cautionary issues of using read-across and its inherent risks corresponding to different safety evaluation scenarios. The Panel agreed that this document would be a living document that needs to change and harmonize with developing technologies to improve the feasibility of read-across approaches in the assessment of cosmetic ingredient safety (*Transcripts_082021.pdf*). The details of that draft document are provided here merely as historical background, and the RAWG is not being asked to fully review those meeting documents or transcripts included herein, or provide revisions on those documents (unless there is consensus in the RAWG that such would be useful to their work).

As a sub-group of the Expert Panel for Cosmetic Ingredient Safety, the RAWG does not make any final ingredient safety decisions or even vote (when acting as the sub-group). Instead, this sub-group

is expected to determine what parameters are needed, on a case-by-case (report-by-report or ingredient-by-ingredient) basis, and to propose a threshold of confidence (or lack thereof) to the full Panel, wherein a read-across strategy is utilized. Essentially, the RAWG is charged in each case with determining if the provided data and associations between read-across source(s) and target(s) are sufficient and valid, and that there is a consensus of confidence (or lack thereof) in the strategy for filling a specific data gap. ***Thus, in this 1st meeting of the RAWG, the sub-group is being asked to discuss general parameters they would require in submissions where a read-across strategy is proposed.*** For example, excerpted from the draft Read-Across Resource Document of 2021 is a conceptual approach to identify read-across analogues from public datasets enriched with cosmetics-related chemicals (e.g., COSMOS database):

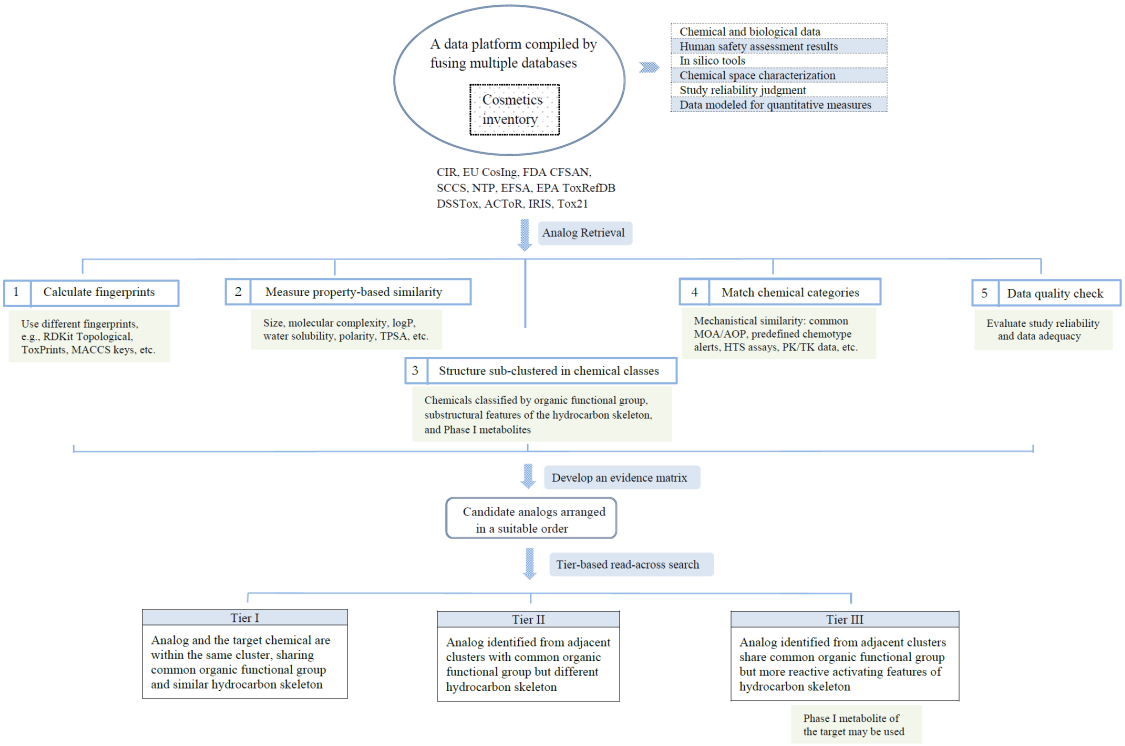


Figure 1. A conceptual approach to identify read-across analogs leveraging public data sources, computational methods, and expert judgment.

Additionally, how should the use of read-across strategies be presented in CIR reports? For example, a format was proposed previously for how to represent the Panel's thinking on the use of a particular source and target, and related endpoint(s). These are only historical examples; the RAWG may edit or start from scratch.

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. At each point wherein data are not available on an ingredient under review, a statement of such is to be made. When a source analog is proposed for read-across to substitute for the lack of data on a target ingredient, the source and target are to be identified in the heading of each Endpoint Summary in the Report. The Discussion is to reiterate the lack of specific data points, the proposed sources and targets, and rationale describing the utility therein. Finally, a justification table should further reiterate the

identities of the target ingredients and read-across source 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 source for PPG 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….

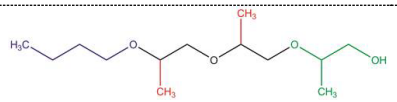
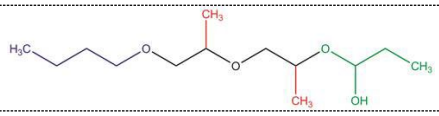
Example 2 (Endpoint Summary):

…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 source analogs 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 source analogs for read-across, and determined that data 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 are 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 Ingredient	Source Analogue
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(s)*		• 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 purposes. In pragmatic analysis, read-across endpoints are determined based on quality of existing data and similarity rationales.

Cosmetic Ingredient Review

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Memorandum

To: Expert Panel for Cosmetic Ingredient Safety Members and Liaisons
From: Jinqiu Zhu, PhD, DABT, ERT, CIR Toxicologist
Date: August 20, 2021
Subject: Draft Revised Read-Across Resource Document

Enclosed is a revised draft of the CIR Precedents – Read-Across Document (*readac092021rep*). The Panel first reviewed this document at the December 2019 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 in the previous meetings are identified as *readac092021min.*

The updated Document describes a systematic approach for identifying read-across analogs from well-structured databases enriched with cosmetics-related chemicals, involving a tiered system for chemical classification and a hierarchy of similarity measures for structure-, property-, and mechanism-based similarity. Expert judgment is required to select the appropriate in silico methods and tools, and test data to provide the critical information needed to strengthen a similarity rationale.

A high-level grouping via clustering of chemical inventories would facilitate identifying read-across analogs to address data gaps. The organization of the cosmetics inventory into clusters of structurally and toxicologically similar chemicals has been conducted to some extent by database platforms such as COMOS NG/ChemTunes™, supported by various computational tools and models to systematically access analogs with relevant experimental data. Methods for inventories clustering as well as chemical classification are further optimized in the Document to subclassify compounds into different clusters to allow tier-based read-across to predict toxicity in the context of specific endpoints.

While the workflow is designed to encompass the crucial scientific aspects 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 Panel should determine whether the read-across framework is scientifically sound and feasible in the scope and decision context of their safety assessments, and determine how, and to what extent, the attached draft Document should be revised further.***

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EXPERT PANEL FOR COSMETIC INGREDIENT SAFETY

Expert Panel Resource Document

Read-Across

09/2021 - DRAFT

The Expert Panel for Cosmetic Ingredient Safety members are: Chair, Wilma F. Bergfeld, M.D., F.A.C.P.; Donald V. Belsito, M.D.; David E. Cohen, M.D.; Curtis D. Klaassen, Ph.D.; Daniel C. Liebler, Ph.D.; Lisa A. Peterson, Ph.D.; Ronald C. Shank, Ph.D.; Thomas J. Slaga, Ph.D.; and Paul W. Snyder, D.V.M., Ph.D. The Cosmetic Ingredient Review (CIR) Executive Director is Bart Heldreth, Ph.D. This resource document was prepared by Jinqiu Zhu, Ph.D, D.A.B.T., E.R.T, CIR Toxicologist.

Introduction

Grouping, category formation, and read-across methods are broadly applicable in chemical safety assessment for data gap filling. A central premise of read-across approaches is that structurally similar molecules exhibit similar biological activities, and thus test data from one or more source chemicals can be used to predict the toxicity of a target substance for the same endpoint.[1,2] In order to facilitate a systematic approach to identify read-across analogs from well-structured databases enriched with cosmetics-related chemicals, a workflow is proposed on the basis of a hierarchy of similarity measures for structure-, property-, and mechanism-based similarity.[3,4] Candidate similar chemicals are profiled by employing techniques and tools to analyze fingerprints, calculate molecular descriptors, and assemble cosmetic materials into groups with common characteristics that are toxicologically relevant to a particular endpoint of interest.

The read-across workflow described in the Document enables characterizing and screening the chemical structures through a flatform leveraging large amounts of chemical and biological data from many diverse sources, inclusive of a tiered system for chemical classification to support read-across searching.[3,4] Prioritization of source chemicals within chemical categories should be conducted in terms of similarity in structural and substructural features, physicochemical properties, bioavailability, chemical reactivity, binding affinity, toxicity, and metabolism. After lining up all available information, analogue quality can be determined based on the overall weight-of-evidence outcomes associated with quantitative measures for each piece of evidence. The content of this document provides the scientific background for using separate chemical clusters and descriptors of molecular structures and properties to support the similarity rational and toxicological prediction.

Building and Analyzing Cosmetics Inventory

To improve the quality and efficiency for searching read-across analogues, a tier-based approach has been applied to cluster the compounds in the Research Institute for Fragrance Materials (RIFM) chemical inventory into chemical class-based groups, in which chemical similarities are evaluated and weighted according to their impact on the toxicity.[3] In the context of structural similarity measurement, chemicals are categorized based on organic functional group, substructural fragments, reactivity features of the hydrocarbon skeleton as well as the metabolic products of the target compound. Expert refinement is needed in identifying the association of physical-chemical properties with biological activities to further assign chemicals into appropriate clusters.

Compared to fragrance inventory that contains chemicals with relatively uniform properties - volatile and low molecular weight, the cosmetics inventory comprises a great number of mixtures, extracts, polymeric compounds, and botanicals, which make the inventory relatively

diverse in chemical properties.[4-6] Chemical structures that qualify as good analogues for read-across should be identified from databases that provide adequate coverage of cosmetics- and food ingredients-related chemicals listed in public sources, in addition to allowing for comparisons to a more diverse set of industrial and environmental chemicals. Due to the necessary functions of cosmetics-related chemicals such as skin penetration, hydration/moisture retaining, and emollients, molecular and physicochemical properties of these structures can be quite unique.

As a core resource-communication base, the COSMOS Next Generation (NG) platform, sharing features from ChemTunes™ database for public access,[4,7] provides a centralized cosmetics inventory, covering cosmetics ingredients and other substances that have been reported to be present in cosmetics products in the European Union (EU) and the USA, e.g., merging the substance lists from the EU CosIng (Cosmetic Ingredients)[8] and the US Personal Care Products Council (PCPC)/Cosmetic Ingredient Review (CIR) Databases.[9,10] Chemical compounds are also compiled from other regulatory or reporting systems, including FDA CFSAN CERES project,[4,11] EPA inventories (ToxRefDB,[12] DSSTox,[13] ACToR,[14] IRIS,[15] and Tox21[16]), US NIEHS NTP,[17] and WHO IARC.[18] The COSMOS cosmetics inventory contains 15,904 unique the International Nomenclature for Cosmetics Ingredients (INCI) names and 9857 Chemical Abstract Services (CAS) registry numbers, varying greatly across 100 chemical function categories, e.g., antioxidant, antimicrobial, hair conditioning, plasticizer, emollient, skin conditioning, etc.[4] COSMOS NG features multiple fingerprints for organizing chemical class and analyzing structure similarity. It further provides computational tools to calculate molecular descriptors, create chemical categories, and access the quality of toxicity data.[4] In addition, a set of generic chemical functionalities called ToxPrint chemotypes that describe molecule substructure and reaction features, atom and bond properties have been used in toxicity modelling.[19] Chemicals are first fragmented by ToxPrint chemotype for structural classes analysis. Numerical quantities of molecular descriptors are then used to represent the molecules, to differentiate metabolites and parents across species between humans and mammals, and to calculate chemical properties, including colligative properties and surface activities, such as charge distributions, polarity, connectivity indices and topological complexity.[20,21]

Chemicals compiled from diverse toxicity datasets of cosmetics relevance and regulatory inventories are well classified by a set of features, including structural fragments and predefined chemotypes to represent chemical patterns and properties especially relevant to various toxicity concerns.[19] For instance, chemotype classes of aromatic amine, nitro, and azo groups are more prevalent in datasets enriched with repeated dose toxicity data for cosmetics relevant substances.[22] Chemical structures described by a total set of 729 chemotypes are organized into five top classes by atoms, bonds, chains (aliphatic, alicyclic, aromatic-aliphatic, oxy-aliphatic), ring systems (aromatic, polycyclic, heterocyclic, fused ring), and groups (carbohydrate,

nucleobase, ligands); predefined chemotypes further encode molecular properties important in capturing biological or toxicity information from matched chemical structures.[19] In this approach, chemicals can be fragmented to capture structural representatives for substances with different types of use or technical effects (e.g., skin conditioning, emulsifying, hair dying, antioxidant, preservative, etc.). Subclasses are further identified to differentiate cosmetics chemical space within a category. For example, a set of antimicrobial categories stratified across potency have been developed by the application of antimicrobial chemotypes, to subclassify antimicrobials beyond the capability of the conventional Cramer Tree approach.[23]

Measures of Chemical and Toxicological Similarity

As a single chemical substance amenable for read-across, it is essential the target structure is defined definitively, with recognized stereochemistry and tautomerism.[24] Chemical similarity can be assessed by a variety of means including comparing physicochemical properties, functional groups, connectivity and substructural features as well as using calculated measures of similarity.[4] A high-level grouping via clustering of chemical inventories into chemical class-based groups may facilitate efficient search of structurally similar chemicals.[3] In such circumstance, the searching of similar structures may simply be within a well-classified database.[24] The potential source structures, together with the target structure, then form the initial grouping. Once analog candidates are identified, different approaches to estimating similarity are applied.

A chemical category refers to a group of chemicals whose physicochemical and toxicological properties follow a regular pattern.[25] The chemical similarity for category formation is defined using mechanism-based structural alerts, distinguishing the key molecular features required to interact with a biological system and initiate a toxicity pathway at molecular and cellular levels. For instance, the formation of a covalent bond between an electrophilic chemical and a protein has been shown to play roles in a number of toxicological endpoints such as skin and respiratory sensitization.[26] Mode of action (MOA) or adverse outcome pathway (AOP) based approaches are also applied, generally including consideration of effects at higher levels of the tissue, organ and organism.[27] Within the category, toxicological data may exist for different chemicals for each of the endpoints of interest. On a practical level, different groups or categories can be formed for the same chemical.[2]

A strategy for analog retrieval requires data mining for similarity measures across three phases. The first phase (1) is the calculation of molecular similarity in a database containing a diverse set of experimental data for cosmetics-related chemicals, e.g., oRepeaTox DB,[22] a dataset compiled with oral, repeated-dose, non-cancer toxicity data for chemicals related to cosmetics from subchronic, chronic, and developmental and reproductive (DART) studies, using different types

of fingerprints (dynamic generation or predefined expert features) and molecular descriptors. Molecular fingerprints encode properties of small molecules (electron/atom/bond) and occurrence count of structure features, and assess similarities computationally through comparisons of bit representations for chemical structure, which may be based upon supervised machine learning approaches using large quantities of data and thus can distinguish subtle but important structural details.[28,29] Fingerprints can also be generated from predefined chemotypes to represent chemical substructures and patterns for categorization.[28] The structure and property space of chemicals can thus be captured by chemotype frequencies, allowing comparison of the similarities and differences between toxicological datasets. Molecular similarity is quantified by the Tanimoto coefficient calculated from molecular fingerprints such as RDKit and ToxPrint.[28,30,31] Pairwise similarities are further used to identify nearest neighbor substances that qualify as good analogues for read-across and to compare parent chemicals and their metabolites.

Generic fingerprint-derived similarities are more predictive in structurally homogeneous datasets for chemicals acting via a common mechanism.[32] Considering the limitations and weaknesses of various types of fingerprints, more than one fingerprint can be applied in comparing the similarity of structures.[4] Tanimoto scores, calculated from different fingerprints within large and diverse chemical datasets, may show less concordance and warrants further investigation to determine whether the similarity matrices clearly relate to biologically relevant structural variations after following sub-categorization to remove biologically irrelevant substructures.[28]

The second phase (2) is to filter similar structures by expert examination of the structure features within a mechanistically derived category for the specific toxicological endpoints. The direct method for chemical classification involves identifying functional groups and/or chemical substructural fragments in the initial grouping obtained from phase (1), which contains the target chemical and candidate read-across analogs identified through fingerprints screening from a database enriched with high-quality data from diverse experimental studies and interpretable in silico methodologies. Common organic functional groups are recognized by profiler available within the OECD QSAR toolbox.[33] When more than one organic functional group, the most reactive functional group in the structure is selected by applying toxicological profilers, such as protein or DNA binding to prioritize functional groups.[3] After classifying chemicals in the classes of discrete organic functional groups, at a second level, chemical subclusters under each class are formed based on structural features of the hydrocarbon skeleton attached to the functional group, especially saturated and unsaturated olefinic moieties due to their significant impact on the chemical reactivity. The subclustering approach within functional group classes has been described in detail elsewhere.[3] Briefly, three basic forms of alkyl groups are considered: straight, branched, or cyclic; chemicals are further divided into subclusters dependent on chain length (divide chemicals into subclusters C1 to C5, C6 to C13, C14 to C22 and C>22), substitution position, and patterns that may affect metabolism, binding affinity,

chemical reactivity and toxicity; chemicals are then sequenced in each subcluster according to $\log K_{ow}$; as for cyclic structures, chemicals are inserted into appropriate cluster of cyclic hydrocarbon skeleton via various ways of rings arrangement: monocyclic, fused, bridged, fused-bridged, spiro, multicyclic, or macrocyclic. On the next level, similarities in Phase I metabolic products of the clustered materials are considered for subclustering, e.g., measuring similarities of phase I metabolites of the candidate analogs and the target substance.

In the third phase (3), chemical categories are further refined based on physicochemical and toxicological properties, and the reliability of read-across is examined by executing weight-of-evidence combination. Consistency of properties within each cluster is scrutinized to assess the bioavailability toxicity of chemicals via appropriate exposure schemes (e.g., volatility, solubility, reactivity, etc.), which also plays an important role in making a clear read-across hypothesis and justification.[2]

Workflow for Identifying Read-Across Analogues from Public Knowledge Base

A workflow has been proposed for identifying potential read-across structures from public datasets enriched with cosmetics-related chemicals, relying both on computational approaches for similarity measures, supported by COSMOS NG/ChemTunes™ platform,[4] and expert judgment in selection of analogues based on hierarchical clustering of chemical structures.[3] In particular, the workflow involves key steps in the definition of appropriate measures of similarity by which to group the chemicals for read-across prediction: chemoinformatic measures of similarity, common organic functional groups, structural and reactivity features of the hydrocarbon skeletons, and mechanism-based similarity. A conceptual approach, as shown in Figure 1, would guide prioritization of candidate analogs to fill data gaps for the target substance.

Step 1: Initial grouping of source structures

Structural similarity-based grouping is facilitated by applying the Tanimoto coefficient for multiple fingerprints such as RDKit topological, ToxPrint chemotypes, and MACCS keys.[34] A recommended cutoff for the similarity threshold is 0.7, which suggests high similarity of core structure.[28] Molecule fingerprint methods allow for identifying additional compounds with a higher chance of displaying similar biological activities against the target chemical.[35] The potential analogs are compiled from COSMOS NG/ChemTunes™ database. The candidate similar structures, together with the target structure, then form the initial grouping. While Tanimoto structural similarity index may fail to reflect the substructural features that affect toxicity and reactivity of chemicals, further scrutiny on structure/property similarity is carried out to prioritize the read-across analogs in the context of different endpoints or effects.

Step 2: Analysis of structural classes by property space.

Source structures are further profiled by properties that govern chemical bioavailability, reactivity and binding affinity. Set of molecular and physicochemical properties can be quantitatively measured by in silico tools such as CORINA Symphony,[36] including size (molecular weight, molar volume, topological complexity), water solubility, octanol-water partition coefficient (logP), polarity, and topological polar surface area (TPSA), hydrogen bond acceptors and donors, dipole moment, and Lipinski rule-of-five violations.[4] Based on the selected properties, property-based similarity matrices can be derived from a Pearson Correlation Coefficient or Euclidean Distance.[4] Pearson similarity is preferred when similarity is based on the extent to which properties are corrected, while the Euclidean similarity is designated when similarity is based on a measure of property values. Candidate analogues and the target chemical can then be compared using structure- and property-based similarities for all pairs, according to the calculation results of selected fingerprints and properties, respectively.

Step 3: Subclustering chemicals within the initial grouping

Further structural class analysis is conducted to identify subclasses and differentiate structural similarities through a tiered approach based on i) organic functional group, ii) structural fragments and substructural features of the hydrocarbon skeletons, and iii) Phase I metabolites. In a preferred grouping scheme, substructural diversity within sets of chemical structures should be assigned a weight corresponding to its impact on the toxicity in subclustering of a class.[3] Read-across between chemicals within a same cluster, or from adjacent clusters is defined as Tier I or Tier II read-across, respectively, whereas Tier III read-across is termed if a Phase I metabolite of the target substance needs to be used.[3] To qualify as read-across analogs, the direct metabolites via Phase I metabolism should be more reactive and toxic than the parents. For instance, to search a read-across analog in a target cluster for carboxylic acids or alcohols, Tier I read-across commonly bases on differences in chain lengths in the same cluster; Tier II read-across considers diversity in branching, substitution or unsaturation that yield more reactive structures in the adjacent cluster; while Tier III read-across can be employed in a target cluster for esters, in which esters are further subclustered based on the substructural features of alcohol and acid moiety separately. However, in cases when analogs are searching from clusters with α,β-unsaturated aldehydes and ketones, Tier III read-across usually is not applied due to the fact that alcohol or carboxylic acid metabolites are capable of undergoing biotransformation to the carbonyl target molecule efficiently.[3]

When prioritizing source chemicals in adjacent clusters, the reactivity and toxic potential of the candidate analogs should be equal to or greater than for the target chemical. For example, α-methyl substitution of α,β-unsaturated compounds decrease reactivity toward nucleophiles significantly, thus, an α,β-unsaturated carbonyl compound may be used as a source analog for a saturated or α-methyl substituted compound.

Step 4: Chemical profiling by toxicity hazard categories

To form a group or category of similar chemicals, suitable criteria for assessing similarity are required, ranging from molecular fingerprint similarity to toxicological similarity involving comparability in mechanisms of action, toxicokinetics, and metabolism. COSMOS NG /ChemTunes™ database provides the ability to profile and sub-group source chemicals by categories and pathways. The design of a new category can be used to perform toxicity predictions for new compounds entering these structural domains. The subclassification often requires experience and knowledge of chemical reactivity, structure-activity relationships and potential toxicity pathways.[2,37] Structural determinants for the MOA can be captured by predefined features, e.g., Toxprint chemotype.[19] If the structure matches any of the categories defined by chemotype fragment, the structure will fit into particular categories or rules to characterize alerts against certain toxicity endpoints. This step confirms that the source structures and the target structure belong to the similar related toxicity hazard categories. Criteria such as common functional group, biochemical processes and MOA, mechanistic plausibility in the form of AOP come into play for judging the suitability of candidate chemicals.[2,20] Broad high-throughput screen (HTS) data can be used to identify potential key molecular initiating event (MIE) in the MOA that may cause adverse effects in humans, e.g., pharmacokinetics or toxicokinetics as well as toxicogenomics or transcriptomics data are utilized as parameters for similarity profiling method.[38] Sets of these parameters for similarity profiling are adopted as new approach methodologies (NAM) in the next generation risk assessment (NFRA).[39]

Well-known grouping categories are available for searching the matched structures, including hepatotoxicity, skin sensitization/irritation, DART, phototoxicity, carcinogenicity, genotoxicity/mutagenicity, metabolic reaction pathways as well as DNA and protein binding.[7,21,22] The extent to which structures match the chemotype rules and alerts can then be transformed to a quantitative measure, from which the final read-across reliability can be derived.[4] Additional chemical categories generated by external QSAR profilers, such as VEGA,[40] OECD QSAR toolbox, and physiologically based kinetic (PBK) models,[41] are also expected to be integrated for structural alerts analysis and for providing insights into mode of mechanism, taking into account the absorption, distribution, metabolism, and excretion (ADME) characteristics of the chemical to reduce the uncertainties in the biokinetics and biotransformation process. When appropriate categories are identified for the query, a matrix of data availability is then constructed for the target endpoint and all other relevant endpoints.

Within the category, on a practical level, toxicological data will exist for some, but not all of the chemicals for the endpoints of interest. When the target substance has insufficient data for multiple human health toxicity endpoints, several candidate analogs with sufficient data for at least one endpoint can be identified. In the context of specific human health endpoints, read-across analogs are prioritized based on substantial differences in bioavailability, systemic

absorption and metabolism.[3]

Step 5: Evaluation of read-across reliability

Sources of uncertainty include a variety of elements associated with the similarity justification and reliability of supporting toxicity data. Different weights-of-evidence may apply to making predictions for different endpoints.[42] Cosmetics-related chemicals vary broadly in physicochemical characteristics, and hence, in their bioavailability and systemic absorption through dermal penetration and inhalation exposure. Given some endpoints are less well understood while other such as skin sensitization have been characterized based on MOA/AOP concept that facilitates building toxicologically meaningful categories, which raises the uncertainty in filling data gaps, there is a potential risk in over- or under-characterizing the hazards of a specific chemical under consideration.[20] Special attention is devoted to access toxicity data quality and reliability in determining analogue quality. Data from several existing databases are consolidated following inclusion criteria such as Minimum Inclusion (MINIS) Grade and then are scored to quantify the reliability of studies.[4,22] Quantitative measures for each piece of evidence (i.e., the calculation of structural fingerprints, molecular properties and chemotype categories) are combined with expert opinions to determine if an analogue is qualified and supported by reliable experimental data.

Conclusion

The organization of the cosmetics inventory into clusters of structurally and toxicologically similar chemicals provides an opportunity for efficient read-across analog identification. The workflow proposed in the document describes a systematic approach for prioritization of source chemicals based on a hierarchy of similarity measurement that requires expert opinions on chemical subclustering and category profiling, and selection of appropriate in silico methods and tools as well as curated toxicity data to provide the critical information needed to strengthen a similarity rationale and to determine analogue quality. Predictions for mixtures are more complex, but still achievable if the individual components are considered.[20] The iterative refinement of data generation, structural classification, property and toxicity profiling is critical to improving the quality of read-across predictions in chemical safety assessment.

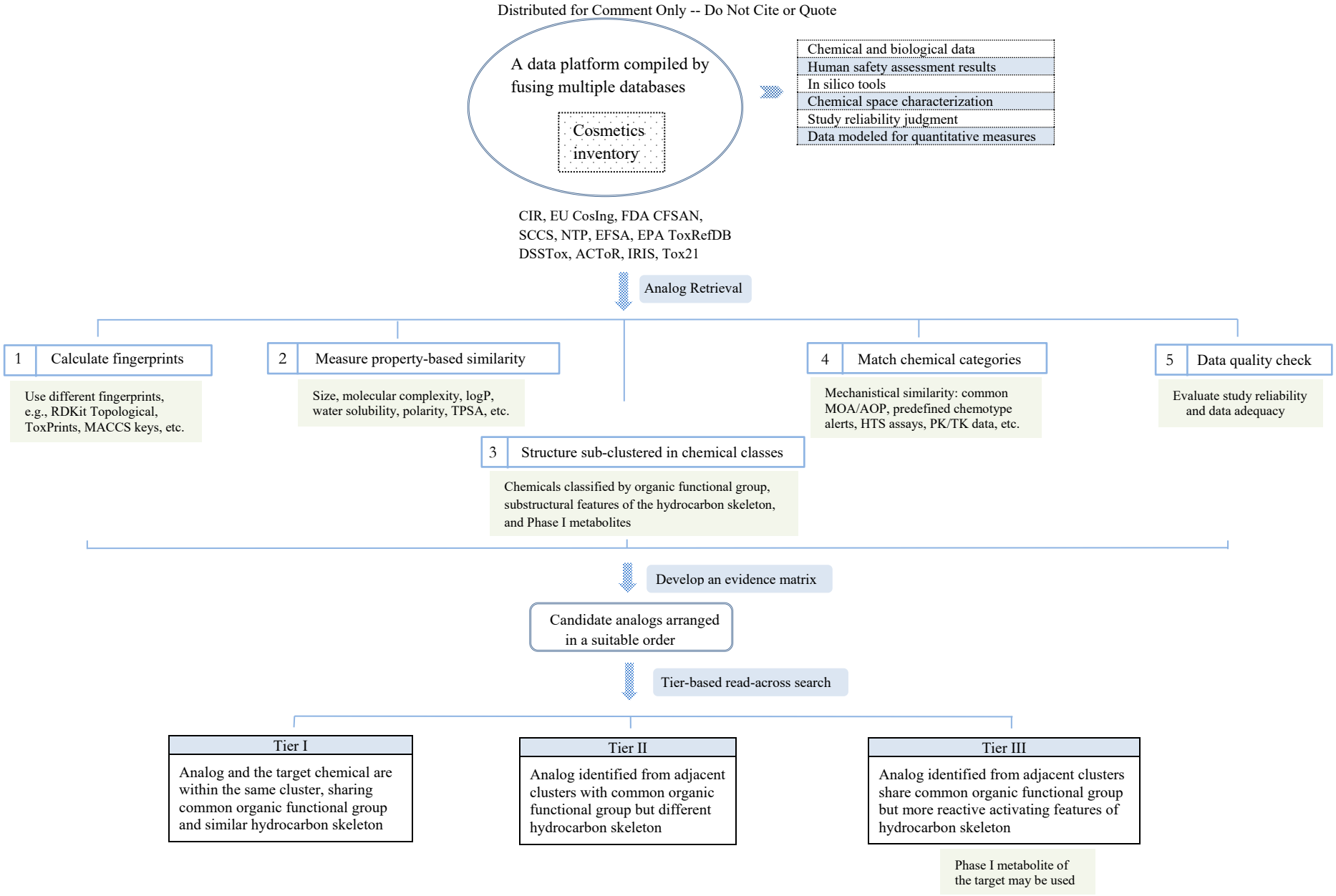

Figure 1. A conceptual approach to identify read-across analogs leveraging public data sources, computational methods, and expert judgment.

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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.

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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 l 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.

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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.

Day 1 of the December 09-10, 2019 CIR Expert Panel Meeting – Dr. Mark's Team

DR. MARKS: Okay. And I'll welcome you, Lisa. Thank you. So our first bit of work here is the read across in the administration tab. And this is a revised read across resource document from discussions we had at the June 2017 meeting. So, Lisa, as you can see, we sometimes don't move like the roadrunner. Sometimes it's a little slower.

DR. PETERSON: That's the way science goes.

DR. MARKS: So ,a few things, hard data is always the best with bottom line. Start with the chemical structures, Ron Shank. Each read across is unique. The framework is not mechanical steps for analysis, is some of the highlights I took from the document.

Lisa, Ron, Tom, your comments about the document? How did you like it, particularly the -- what Jinqiu or James wrote? He's doing this remotely, Lisa. He's doing this from China actually, I believe, correct?

DR. HELDRETH: That's correct.

DR. MARKS: So, one of the mentions in his memo is the algorithms versus the tables, how you like those. But I'm going to throw it open, Ron or Tom, if you want to start; and then, Lisa, any comments you have to add obviously.

DR. SHANK: I thought it was a good document. It serves the purpose for in house guidance. And we can make it available to the public. And as we have more experience with it, we'll probably tweak it. But I like it the way it is.

I had one question. On page 52, it mentions ecotoxicology or ecotoxicity. And I wondered why we, of all things, we would pick out ecotoxicity? That's not our main concern. It's mammalian toxicity. So, I would change that word. Other than that, very minor things. I think it's a good document as is.

DR. MARKS: Who's taking notes for Jinqiu? The eco? Do I need to mention that tomorrow, or is that just editorial?

DR. HELDRETH: I think that that's probably pretty much editorial.

DR. MARKS: Yeah. Okay. That's what I figured, but I wanted to be sure. I agree with you, Ron.

DR. SHANK: Okay.

DR. MARKS: Tom, anything?

DR. SLAGA: No, I agree with Ron. Obviously as you said it, I'd prefer to see hard data, but we don't have to use the read across. But this is a good document, and I think it brings out most of the important points. But it's one of these continuations that we'll modify it with time.

DR. MARKS: That's been used multiple times. It's a living document. How about the -- and Lisa, did you have any comments? This is the first time you've seen it.

DR. PETERSON: Yeah. It's the first time and read across is a bit new to me. As such, I was able to follow it. I thought I, sort of, could be the outsider reading it without any preconceived notions; and I thought it read quite well. And it was a good starting point with the understanding that it would be modified over time.

DR. MARKS: Did you -- algorithms versus table, both of them? I thought both were good.

DR. SHANK: They're both there.

DR. MARKS: It was interesting. I kind of -- in the skin sensitization Jinqiu picked protein binding alert, which is futuristic, I think. I don't recall the last time we used protein binding alert as a read across. Usually, it's more what do the actual facts show and what's the chemical similarity with the other chemicals.

That was just -- I'm not sure why that was picked. I think it's kind of cool.

DR. HELDRETH: I think Jinqiu, and the source that he got it from, called that out because some of the alternative approaches still looking at sensitization, you know, they take a weight of evidence approach of a number of different things like the QSAR and maybe an LLNA test. And one of them that's become quite popular is the direct peptide reactivity assay.

DR. MARKS: Yes.

DR. HELDRETH: So, that's a really simple in-chemical test that can be done without any animals or any people or anything. Maybe that's a stream of data that's easy to get our hands on; and therefore, maybe it's something that can be incorporated in the process.

DR. MARKS: Yeah. Good. Yeah.

DR. ANSELL: It's a very expansive interpretation of what read across is. And we only briefly looked at it, we'll be filing more specific comments. But it's more an amalgam of alternative methods all meshed together, as opposed to a precise read across. So, we certainly agree with these computational methods, these in silico methods, read across TTC. And they're all kind of in here.

So, I don't know where our comments will be, whether it'll be to try to precise what read across means, or to talk about alternative assessments. But yeah. There's a lot of stuff in here.

DR. MARKS: Yeah. Okay. Well, let me see. I think tomorrow the Belsito team will be -- let me see, 25. They'll be the one that is making the first comments. Our comments are all very positive, and I won't even mention the eco tomorrow unless it comes up.

DR. SHANK: Right.

DR. MARKS: Okay.

MS. LORETZ: Is there going to be a public comment period, or an official comment period so CIR SSC can weigh in?

DR. HELDRETH: I see no problem with that, that's the prerogative of the panel, if the panel would like to see this go out for a public comment period before we stamp final on it. That's up to the panel. I don't see a problem with that, but it's the panel's choice.

DR. SHANK: Well, it's an inhouse document, isn't it?

DR. HELDRETH: Well, it'll be used inhouse, certainly, for the staff when we're trying to put together pieces of information that might inform read across for the panel. But it is also meant to be something that we'll post on the CIR findings page; so that the public, or anybody interested in how the panel looks at read across, will have a document to look at. So, it is meant to be a publicly-available document as well.

DR. MARKS: I would think one being open, which we have been, so the public -- their input is important. And as we've done in the past, we will consider input from the public and adjust the document as appropriate. So, my feeling would be, Linda, yes, we'd welcomed.

MS. LORETZ: Okay.

DR. HELDRETH: So, we could certainly do something similar to a report and put it out there for a 60-day comment period, at the very least. And once that's elapsed, whatever we get in we'll bring back to the panel and decide on.

DR. MARKS: Obviously, it's no urgency in this since this has been around for two years now.

DR. HELDRETH: That's right.

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DR. BELSITO: This is in the admin book.

DR. KLAASSEN: We've been doing that all day. Now we're going to discuss it.

DR. BELSITO: I mean, I thought overall it was good, I just had some question and I had some wordsmithing.

You didn't like it, Dan?

DR. LIEBLER: No. I think -- I mean, I heard Wilma's positive comments this morning and your mention right now, I think we're off on the wrong foot here.

So, first of all, I appreciate a lot of work that's gone into this since the last time we talked about this. But I think this is a dense, hard to read, nine-page, meandering, unfocused first run at this concept. We may think we've been doing read-across in CIR, but we have barely scratched the surface. We don't really do it.

Now, I can say that because on the RIFM committee we live and die by read-across. Now, we have some advantages in the RIRM inventory. It's a much more constrained chemical universe.

All of the ingredients are volatile to be fragrances, and therefore the structural space is much more limited. There are more data, about more molecules, and read-across can be more easily organized and rationalized.

We also have evolved the process within the RIFM expert panel, the expert panel for fragrance safety, principally myself, Terry Schultz, and Trevor Penning, from the panel working with RIFM staff on read-across.

And the process has evolved over several years. And we are just now getting ready to submit the first, sort of, big paper description of how we cluster and prioritize read-across analogs in the RIFM inventory to fill gaps for safety assessments.

So, we did that because -- we're able to write the paper now, because we've sort of taught ourselves how to do this, learned a little bit from things in the field, gotten a feel for the process of where it's useful and where it's not, as opposed to just having it being a theoretical exercise. We could have written that paper five years ago.

And I've just -- literally, just last night, I finished the edits on the final version that will be submitted for review. So you know, it took a long time to get to this point.

So, I was doing that at the same time I'm reading this. And I realized -- I started editing and wordsmithing thinking, well, we have sort of a CIR document. It might not be submitted for publication yet, but it will -- and I thought, wait a minute. In CIR there are some similarities.

First of all, we haven't done read-across because on the panel we haven't been able to sort of even agree on the concept. That is now possible, I think.

And I think that once, you know, Lisa Peterson has sort of gotten in the groove, I think we need to evolve a little different way in which we consider read-across and utilize read-across analogs to fill data gaps, and how we work on that.

But I think this report, or this document, is really premature until we've figured out how we're going to do this, practically, within the CIR operational framework. And it'll require us to change some things.

Now, the general thing that I think will need to change, is something that we learned from the RIFM experience. Instead of getting reports with possible read-across analogs already in the reports, and then we have to react to those, and say we like this, or we don't like it, or bad choice of analog or good.

Before the reports are written and reach the panel members, Terry and Trevor and I and two or three of the RIFM staff have weekly -- or not, month conference calls for about an hour a month. Where we go across a list of candidates and possible analogs with data.

So, we have a target that has no genotox and we need to consider what other possible read-across analogs with genotox data we could use. And then that's already been teed up for us.

So on the calls, Terry and Trevor and I essentially pass judgement on these and talk about them. And we kind of have a rule, if we can all three agree, done. If we can't agree for whatever reason, then it's not good enough. We either have to get test data or look for another analog.

But that has required the RIFM staff to developing a clustering framework on which to organize the entire inventory. Now, the CIR chemical space is much larger, and the framework probably will take a while to organize, but it will actually be a really interesting exercise to do.

And I think this is something where we could work very productively with, you know, the science and support committee perhaps and with CIR staff, to kind of come up with a first-generation version of this.

And I think I could probably get permission to share the manuscript with you guys, you know, just to see, kind of get an idea of how we do this. I could share it probably confidentially, although I need to ask Anne Marie and people at RIFM.

But then I think what we could do is when we have -- you go from the priority list to a report, as we go from -- in that transition, we should probably look at the ingredients that would go from the priority list to the report.

So when we do a priority list we don't necessarily think too long and hard about the ingredients. I mean, we had that with the, you know, amino acid derivatives earlier today, you know, what should be in, what shouldn't be in.

They went through our consideration as priorities, but we didn't really spend a lot of time thinking about the pros and cons. We should decide what ingredients should be in the report, between the chemists and CIR staff, and maybe somehow some input from the Science and Support Committee.

And then we should identify what the data are going to be -- what we've got. So this is before the draft report is done, but it's at the point where you're searching for the data. You've kind of got a list of what data you got and what you don't have.

Then we need to look at endpoints and molecules that we could bring in for candidate read-across and this is where we're just going to learn by doing for a while.

And we'll -- I'm confident that we will evolve an organized system to do it. But initially it'll be just more of a question of talking about it, making some data requests, bringing in the data, and at least satisfying perhaps the chemists and the council, that the data that we would bring in could plausibly -- from candidate analogs -- could plausibly support the data need for the targets that we have.

And I think that's going to take like a year of doing this, and maybe longer. But once we have a system that works and we've kind of learned by doing, and we get to the point where we have these meetings.

What I'd like to do is within a year, get to the point where when the panel sees the first draft tentative report, that they can feel confident that there's a consensus of what should be in there, and what read-across candidate analogs have been identified, and that those will already be weaved into the report.

And it won't be a question of arguing about which ingredients should or shouldn't be kept in the report in our first meeting. And plus, we definitely don't want to have this thing where we, you know, sort of have this face to face faceoff between the chemists like we used to, to decide what ingredients should be in a report or not. That's just really counterproductive.

So anyway, I think that this document should just be put on the table for the time being. It's premature. We're sort of describing sort of what we think we might end up doing. But until we actually have to deal with it and figure out how the read-across process works for CIR, and for this expert panel, it's premature to try and issue any document at all.

DR. HELDRETH: So, you and I have discussed this a little bit before. And so, I've given it some thought and looked at our procedures for how this year-long type of process would work for CIR.

And within the procedures, there is an option for Dr. Bergfeld to essentially commission a working group. Basically, you know, a handful of panel members can work on a subject like this. And so I think this could be a twofold working group.

First, you and Lisa could evaluate, you know, here's the priority groups, do they make sense, go through those.

And then you also mentioned another stage where once our analysts have looked to see what's available in the literature, doing analysis there to -- could we do some data gap filling there with different analogs. So, that point is between what we call our scientific literature review and that draft report.

DR. LIEBLER: Right.

DR. HELDRETH: So, we could have a situation where scientific literature reviews go to this working group, you and Lisa, to make those sorts of analysis before we start drafting our draft report. That seemed to kind of fit in what you were thinking?

DR. LIEBLER: Yeah, that's seems really good. I think we could work with that.

DR. HELDRETH: Okay.

DR. BERGFELD: Well, there's several things. I agree with you, Dan, that this is living document. It has to be changed with experience and if this is the experience that you've had that far outreaches what the CIR panel has been doing, I think we should go with that.

I think, though, that we've been doing read-across and for someone who is less knowledgeable about the chemistry, I found that the overall construction of what we might be looking at as to what we could coordinate with other ingredients, its similarities, either biological or chemical or tox points or whatever, was just a starting point and very interesting for me when I read it.

As far as dealing with a sea of words, it's very difficult. Algorithms are a little bit better. And I agree with it totally. But if it's my duty to say this work group shall be formed, I so do that at this moment.

DR. HELDRETH: Thank you.

DR. BELSITO: Okay. Anything else? Curt.

DR. KLAASSEN: I would agree with this new way of doing this. And I guess, you know, some of the real

-- there are some real simple things to help all of us thinking in this regard. Could be -- well, first of all, this only is probably going to work on pure chemicals. It's not going to work on these plant materials and snake poisons and what have you.

So I think, you know -- and half of our chemicals that we look at are plant products, et cetera. And I don't know if we're getting close to the end of those or not. So we'll make a lot better progress on this if we can have a real singular chemical or at least a group of chemicals.

But I thought that, you know, at least, maybe we should add on this sheet where we always have, you know, the reported use, GRAS, and all of that. Is that we make sure that for each chemical that we at least have the molecular weight, the octanol water partition, and you know, if there is a PKA.

It will at least get us started to looking at some of the more simplistic things and we can go from there.

DR. HELDRETH: Certainly, for those discrete chemicals that, you know, we can put a structure in like epi-suite or something like that for -- we can certainly, at the very least, predict -- I mean, the molecular weight is calculated but --

DR. KLAASSEN: That's fine.

DR. HELDRETH: -- the other two properties, you know, are estimated because very often there's no experimental literature that we can get our hands on for it.

DR. KLAASSEN: Well, the estimated octanol water is good enough for me. I believe in those calculations, and I definitely believe in the molecular weight. And so those things should be right there.

DR. LIEBLER: Yeah, I mean, I think that read-across is best initially practiced, at least, on individual molecules and their analogs. And then we can gradually extend it to those families of ingredients where we might have a core individual piece with various polyethoxy chains or fatty acyl chains, or so on. So, the systematic variation on the larger family is still easy enough to handle. And then it sort of breaks down after that.

When we -- on RIFM, we actually, you know, save the hardest to last. And we are doing what they call the natural complex substances, which is what we call botanicals on this panel. And we actually are building a framework to do read-across within those.

But it's based on, again, a smaller universe of much more data-rich -- richly data annotated mixtures. And I think it will be a useful principle that might be applicable for us, but it's -- very

DR. BELSITO: Yeah, but that's usually, Dan, when there's an overwhelming fragrance material that composes that botanical.

DR. LIEBLER: Correct. So, I think we're a ways away from doing it with any of our botanicals. That should not be an objective for us. And for the inorganics, for the most part, I don't think you can read-across.

So, we'll have enough examples of where we -- you know, like we had the earlier with the -- oh, shoot. Which one was it?

Was it the MIPA where we had other analogs, other chemically similar structures that we had lots of data in, and we are able to read across from those? We didn't have a formal procedure for doing it. We just said, look, all these things are very similar. This is weight of evidence.

So we -- that's a start. But that's what we've used as read-across, quote-unquote, on this panel and that's -- it's not quite the same thing. But we can make real use of the real thing. Real use of the real thing.

DR. BERGFELD: I am dismayed in the fact that if this be the way the panel is going to go, that in the documents as they've been developing in the last few months, in the discussion, the read-across is stated, read across for this, and the data gap. We have to look carefully --

DR. BELSITO: But that's usually been --

DR. BERGFELD: -- carefully at that and make a description of what that is.

DR. BELSITO: But that's usually, Wilma, been like we're looking at pegs. And we have data on peg 2, peg 7, peg 29, da-da-da. And we're using that to read across against the pegs.

DR. BERGFELD: We had several this time.

DR. BELSITO: No, I understand, but they weren't different --

DR. BERGFELD: They were botanicals.

DR. BELSITO: They weren't different distinct chemicals. They weren't -- they were pegs.

DR. LIEBLER: One thing that will come out of this, when we start sort of formally implementing this, it's not that we can't say the words read-across until we've got a procedure. But we can make more use of it, more effectively, once we have a procedure.

When we do that, one of the things we'll have is going to be a new section in the reports. It doesn't need to be lengthy but needs to just summarize the rationale for the choice of read-across analogs, and the endpoints for which they're used.

And that, for the RIFM reports, is a little appendix at the end, and we can come up with something that is

similar for the CIR reports, that I think will be very important touchstone for using read-across.

DR. BELSITO: But you know, and it may not be that we need the type of read-across that we need for RIFM for a couple of reasons. One, for political reasons, the fragrance industry is now not allowing grouping; so we have to look at one material at a time.

And sometimes you have X, Y, Z and there's absolutely no data on X, Y, Z. It's a low volume of use. We're never going to get the data, and we have to clear it somehow. So we need to go out and find something that is very similar to X, Y, Z in many different criteria across. So, there may be one for sensitization, one for genotox.

I don't think we have that type of issue with fragrances. You know, the low volume of use materials usually are getting grouped into a peg group, or no volume of use, you know.

They're getting -- you know, so I think our needs for read-across on this panel and what we call read-across are much different than what we call read-across on the expert panel for fragrance safety.

Where the two materials we're comparing -- if you look at them sometimes structurally, I have to go -- we colloquially call them T, T and D. Trevor and --

DR. LIEBLER: TDT. Trevor, Terry, and Dan.

DR. BELSITO: Yeah, TDT and Dan -- to go, whoa guys, how the hell are these the same? And they'll walk us through it. You know, they're metabolized or whatever. I don't think we're going to be doing that here.

So I think that level of read-across that we do for the expert panel, Dan, is very different from the level of read-across we're going to be doing here, just personally.

DR. LIEBLER: Sure. I just I think there's much to be gained for us in CIR to make more effective use of this approach.

DR. BELSITO: Right.

DR. LIEBLER: But in order to do it, we just need to have more of a framework.

DR. KLAASSEN: I agree. I would like to say I wish we could come up with a better scientific description for this methodology rather than read-across.

DR. BELSITO: But that's what it's called.

DR. KLAASSEN: I know, but I said, I would like to have a better scientific terminology. When you talk to people in other areas and you say, oh, we read across. That sounds like Kindergarten.

DR. BELSITO: Talk about the threshold of toxicologic concern.

DR. KLAASSEN: If that's what it is.

DR. BELSITO: Okay. We are done.

Day 2 of the December 09-10, 2019 CIR Expert Panel Meeting – Full Panel

DR. BELSITO: Well, I'll let Dan address it. He thought the document was rather dense and difficult to read, and that's why he suggested that a working group be formed with the chemist to look at how to do this. So, Dan, if you want to further comment?

DR. LIEBLER: Sure, I'll be brief since we're at the end of our meeting here. I mean, I thought the document needed work. I realized that a lot of work had already gone into the document. I think though that as I thought about this, you know, I take with me the experience that we've had recently with RIFM and much more extensive and systematic implementation of read across.

And, I've just been editing a manuscript that's about to be submitted that describes how we use read across and how we cluster ingredients and identify and fill data gaps. And, I realized that we weren't able to produce that document, that manuscript, until we've been doing this for a few years.

And I thought that having a document, and then saying we're going to use this as our guide to read across was exactly backwards. The document's sort of theoretically and hypothetical in its way of doing things. And I thought that maybe with addition of Dr. Peterson to the panel, we have an opportunity to kind of reset ourselves with respect to how we approach read across for CIR. It is a different chemical universe than RIFM, and there are some other bigger challenges.

But, nevertheless, I think what we could do is, I think we could try doing something a little different. And, Wilma, refers to this working group, I guess that's a good way to put it initially.

But, I think this is that in the interval, in going from a priority list to a draft report, when the data are being assembled and the ingredients are being assembled in the first report, that's a critical juncture at which I think the chemist could have input. And assist with the question, first of all, do these things all belong together? If we could come to agreement before the report goes to the panel, then we don't have to argue about that later on and have some uncertainty and then have this sort of confusion on the Tuesday morning when one team thought these chemical belong, the other didn't. I mean, that doesn't need to be an issue of suspense, it needs to be agreed on up

front. Because then that allows the report writers to gather the right data.

And the other thing we could do is using information that could be suggested from the report writers and from the Council, we could identify potential read across analogs to fill our data gap.

And the part that I think we need to sort of figure out, learn by doing, is the part where we figure out what will be sort of the most systematic process that we use to identify read across analogs. Because we sort of done that in a haphazard way.

The more that we can learn to systematize that, the more of this process will work well for us and will be consistent, you know, from one report to another.

So, my suggestion was we just put the document -- leave the document in a folder for now. And see if we can pick a report or two, have a couple of calls. And, you know, on the RIFM panel it's not an extra onerous duty, we end up talking -- we have about a one-hour conference call once a month. But we don't even need to do it necessarily that often.

But, maybe before the March meeting, you know, if that's the right timing for the stage, we could identify -- just look at the list of reports that we think might be coming out, what might be going in there. And then kind of have a quick look at the ingredients and start to talk about which ones we're going to be able to use read across for.

I think we won't be doing it for the clays, the silicates, inorganics. We're not going to be doing it, at this point, for the botanicals. But I think if we have a family of defined, pure substances or systematic, you know, mixtures of series of analogs, that's ideal for us to start working with this on. So, that's probably going to be one or two reports coming up in March that might fit that description.

So, that's my suggestion. I think it's going to take us a couple of years to get this really working, but we need to start a process now.

DR. BERGFELD: I think this has been a concern of the panel for years now, the term read across, and the interpretation of read across. What concerns me most recently is, 1) the incorporation of the term read across in a botanical.

DR. LIEBLER: Right, I think we have to be careful how we use that.

DR. BELSITO: Well, I mean, I think read across in a botanical is saying that this part of the plant, coconut, has the same composition, expected impurities, et cetera, as this other part of the plant and, therefore, we can use sensitization and irritation, or genotox, or whatever data to cover plant parts where we don't have it. I don't think we're going to go from coconut to pomegranate; we're not going to do that kind of read across.

DR. BERGFELD: No, but it has been sneaking into our reports.

DR. BELSITO: Oh, I understand.

DR. BERGFELD: We need to define what we're actually doing.

DR. BELSITO: But I think we do define it in the discussion on a case-by-case basis. That, you know, we're reading across because the composition is the same, we feel, the sensitization data. I think for us read across is going to be very different and it will be unique for different materials.

You know, as Dan was mentioning about RIFM. The issue with RIFM is we do one material at a time. And sometimes we get very low-volume materials where we have absolutely no data. We'll get no data because they are low-volume. And we're forced to do read across and identify, sometimes, a material that to me looks structurally very different, but meets -- ticks all the boxes in terms of metabolism, whatever.

For us, that may be an issue, sometimes, where we have a discreet material that we're being asked to analyze, and we're missing certain data points. You know, and Dan and Lisa can come up with a material that meets the criteria for read across -- or different materials. Because one may be for sensitization. There may be a different one for genotox, and there may be a different one for DART endpoints. And we can use that to read across to this discreet.

That'll be a very different read across than reading across against coconut leaf to flower.

DR. BERGFELD: True.

DR. BELSITO: So, you know, I agree with Dan. Trying to create a document at this point until we see how we're using read across, as long as we define what we meant by read across in that specific document. So, for coconut it will be because the composition is essentially the same. You know, so for other materials, non-botanical, it may be different.

So, but I think you're right, we need to define what we mean when we're saying read across and that can be done right now in the discussion rather than having this boilerplate that's very dense and very hard for people to understand, okay what portion of this boilerplate did you use to read across.

DR. LIEBLER: I think one other thing; this might help to address your concern, Wilma. Is when we do read across, particularly in the context I've described with discreet substances or systematic families of isomeric substances or different chain lengths, or whatever, is that we should have a new section at the end of the report

describing the rationale for the selection and use of read across materials and what endpoints they are for, etcetera. That will just have to become a standard part of our report formats whenever we do read across.

DR. BERGFELD: I think that's a great idea. I'd like to make that recommendation. Any other discussion before we end our wonderful pre-Christmas, pre-holiday meeting?

DR. MARKS: This won't be long, Dan. Obviously, I think, having this working group is an excellent idea that Wilma's going to form. The urgency has already been demonstrated, the first rendition was in 2017; so we're two years later. So it's obviously not an urgent item.

I think as the group it'd be helpful to really, and you brought it out, Don, in some of the comments, that we had some bullet points. And, Curt, you made this, I think, the last meeting, is hard data is always the best. That's where we want to come from.

DR. SLAGA: Yup.

DR. MARKS: And when we don't have the hard data then we do read across. We start with a chemical structure when we have it, or in the case of botanicals it'll be the composition of the various botanicals.

And then, Don, you said this actually, each read across is unique. And I think that's going to be important to stress that we're to look in this -- and then the framework -- again, this was just abstracted from what Jinqiu said. The framework for the steps are not mechanical, it's an analysis. Although perhaps when you refine it it'll become more straightforward.

Yeah, and then, Don, just -- I wanted Don's input in terms of when Jinqiu put in the algorithm versus the table; we like both the algorithm and the table.

But it's interesting that the sensitization algorithm was on protein binding alert and we rarely have that, it seem like, when we discuss sensitization read across, at least at this point. Now, maybe in two years, if it takes another two years to get the resource document, maybe we'll have that as data we get most of the time.

DR. BELSITO: So, I think what he was saying is that you don't want to -- so, you can do this in silico, you can predict protein binding. Or you can do it, you know, in chemical using DPRA.

You certainly don't want to use a read across that is protein binding when your ingredient is not protein binding. You want that same, you know, sort of fit across. That's what I gather he was trying to say.

DR. MARKS: Yeah, I just kind of, if this is our example.

DR. BELSITO: Yeah, I mean, if you read across is adequate and, you know, the DPRA is negative, you know, then -- you still need sensitization data in some way. Because then if you're going to do it all, you know, in vitro you're going to want a KeratinoSens or an h-CLAT or U-SENS assay to go along with it and verify that it's negative in two of the three components of the AOP, so.

DR. BERGFELD: Well, we're very lucky we're getting more in vitro studies regarding sensitization as well as other things.

DR. BELSITO: Yeah. Yeah.

DR. BERGFELD: Any other comments to make? Lisa, I hope you've enjoyed your first meeting, and thank you and welcome again. Merry Christmas to everybody, happy New Year, happy holidays.

DR. BELSITO: Happy Holidays.

DR. BERGFELD: We are adjourned, see you next March.

158th Cosmetic Ingredient Review Expert Panel Meeting

Read-Across Discussions

Virtual Meeting

September 13-14, 2021

READ ACROSS – BELSITO BREAKOUT

DR. BELSITO: So we're looking at the read across in the Admin doc first. Okay, it looks like this is going to be on page 34 of the Admin.

DR. LIEBLER: PDF 59.

DR. BELSITO: Oh, 59, sorry.

DR. LIEBLER: Yep.

DR. BELSITO: Why do I have 34?

MS. FIUME: The minutes start on page 34.

DR. BELSITO: Ah, I see. Okay, here we go. Thanks, Dan.

DR. LIEBLER: Sure.

DR. BELSITO: Okay, so there were questions posed to us, as I have them, first question is about a deletion of chemicals from the 2022 Priority Groupings is proposed. Is that the first one? Is that correct?

DR. ANSELL: I have read across.

DR. LIEBLER: I thought we were talking about read across.

DR. BELSITO: Oh, I guess I keep going back to the

wrong part. So we're on 59. Okay.

DR. LIEBLER: Yeah.

DR. BELSITO: I don’t know why this is doing this. Okay. Yeah, I had excellent, a few minor comments is what I said. Dan, you're probably better equipped to comment on this.

DR. LIEBLER: Sure, I'd like to start out by complementing Jinqiu on this really terrific draft. I mean, I think you made a tremendous amount of progress with this, so it's very nice work. I have a lot of comments for you in the text. Jinqiu, you can review those when you get my file.

But I'd like to make just a few high-level comments. First of all, I just want to state, you know, what I feel are the sort of the key rules in read across here. You only use read across when there are inadequate data to support a chemical. You use clustering and selection to get to the candidate read-across molecules. And then the read-across molecules are only useful if they have good data that clears the endpoint. And even if read across have data weak spots, then weight of evidence

chemicals can be used to cover those data gaps created by the read across.

So, with that having been said, most of this document outlines the strategy to do that second item, which is getting to a systematized way of selecting candidate read-across molecules. So the general approach is very familiar to me based on my role in the RIFM panel where we make very extensive use of read across.

And this is really very nicely developed. It's essentially a very similar framework for clustering based on chemical properties. And sort of a systematic consideration of structural features and rules for grouping. This also makes use of some tools that I actually was not familiar with and looking at the -- I'm talking about the ChemTunes database and the COSMOS Next Generation platform.

I talked to my colleague Terry Schulz on the RIFM panel who is, as far as I know, you know, one of the best authorities on all of these tools for computational chemistry as applied in the area of read across. And he says that essentially this resource that Jinqiu describes

in the report is equivalent to the collection of tools that RIFM uses, and it includes the content of, like, the RIFM compounds database, but also others. That's, of course, the challenge for us in CIR for read across, we actually have a broader chemical universe because we're not simply limited to volatile chemicals.

So, although I don't anticipate myself being, you know, hands-on with any of these resources, it sounds like the right collection of tools will be available to do evaluation, not only for clustering, but also for in-silico simulations of metabolism identification of features that could drive potential toxicity mechanisms and so forth.

I think that this is really, you know, a great start. I should say that I think the report is very well-written and clear. I think it represents the first half of read across as we would see it as members of the expert panel, which is to say that the first part is, you know, once you identify that you have a data gap that you'd like to fill to try and clear an endpoint in a safety assessment, you need to identify read-across candidate molecules that have data. And that's what this document is

all about. It essentially puts the framework together to organize all of the relevant chemicals that we might consider as read-across analogs in our reviews.

The second part of read across is, once you're presented with some options, then you have to review those, evaluate those, and decide whether they're going to really work in the specific context of the report that you're doing. And this is the part that is actually not systemized and automatic. This is still the part that is completely manual or at least at the present time.

So, again, based on my experience with RIFM, we are presented -- we actually have a meeting every Tuesday morning with three of us: Terry Schulz, Trevor Penning, and I, and RIFM staff; where they present read-across candidate molecules that they have identified using a framework similar to what's described in this report and then target molecules. And then we have to decide whether or not, you know, which of the options is the best fit for read across, what's the best totality of the supporting data, what are the potential complications or ambiguities in the chemistry for the read across, because there always are.

And this is something that we've gradually developed a set of procedures and rules and preferences for accepting or not accepting read-across molecules. And this is something where I think it's going to be a challenge to put that into a report framework, and I think that maybe we shouldn't rush that, but this first part is a great start.

The only other thing I'll say is that this process, the conversations every Tuesday morning, I've gone ahead and arranged to have Lisa Peterson invited to sit in and listen to our discussions for a couple of meetings, and we had one last week where Lisa dialed in and listened and we're going to do, hopefully a couple more that she can sit in on. So she's going to be invited to our meetings starting in late September. And I think that will help Lisa get an idea of how it's currently working in RIFM. And then we can have some further discussion of how we will go from candidate read-across molecules, you know, to their application in our safety assessments.

And I forgot, one last thing I want to mention is that in RIFM most of our read-across problems are we've got a chemical, we don't have data for a particular endpoint,

we identify read-across molecules, and so it's a one-to-one chemical to chemical read across to clear the endpoint.

In the CIR situation, I think we also have something that's somewhat different, but it can be served, I think, by the read-across mechanism. And that's a situation where we have a big family of chemicals that differ, they all have a sort of a common chemical structure or theme, but then they differ considerably in chain lengths or varieties of substituents or things like that. And we might only have data on one or two of them, and the question for us often is, can the data for the one or two that we have clear the family? And that's one where I think we're going to have to kind of strike out on our own.

It's a little bit of a different problem, and I think that's the next thing we need to think about once we've got this report in the bag because I think this report will at least help cluster the elements of the family and then help us think in a more systematic way about how we use relatively few read across, or relatively few members of the family to systematically clear the others and how we can develop again a set of rules that

allow us to do it systematically and consistently. So those are my main comments, and I'll be happy to answer any other questions if people have, but again, Jinqiu, this is a really nice job and I've got a lot of comments for you in the document.

DR. ZHU: Thank you, Dr. Liebler.

DR. BELSITO: Paul, any comments?

DR. SNYDER: Yeah, actually, I read this entire document, I agree that it was very well written, and my only comment was exactly what Dan just went over. I really think that we need like almost a preamble or something to discuss exactly what Dan just, very eloquently, stated. We need the cosmetic context, and so I really like that the key rules -- you know, upfront some rules of how you use the data and then how we use those rules in the cosmetic context. I think we just -- we need to -- you know, like Dan alluded to there right at the very end, there's some cosmetic nuances with regards to the families and the groupings and how we look at things, and how the groupings actually drive us -- or how some of the chemical structures and things actually drive us to come up with those

groupings and what the title of the document's going to be and everything.

So, I think, this will be polished really nicely if we could add a preamble or something and then maybe some more details in our cosmetic approach to, not only the read across, but how we group them such that we can use read across to support safety. So I thought that was really nicely done, Dan, so thank you. I didn't really know how to do that, I just had a sticky note that says we need the cosmetic context, but you pretty much hit the nail on the head there for it.

DR. LIEBLER: Sure. And I would be happy to have some offline discussion with Jinqiu, perhaps after the meeting once Lisa has had a chance to weigh in, we could have a little discussion with you outside of our regular, you know, meeting where we can talk a little bit about what, you know, what the introduction to this report might look like. I think it can be done in a page or less, but I think we ought to sort of step a little further back and state exactly what we're doing here in the context of CIR because it almost goes very quickly -- your introduction,

goes quickly to the grouping problem. And that's what this report is really about, but we should have a broader context that we can present to say this is a part of where we're going.

DR. ZHU: Sure. Thank you.

DR. SNYDER: Well, I think it gives us too, it gives us the out when we think we have adequate read-across data, then it also gives us the out when we don't have adequate and why we say we don't have adequate, despite the fact that somebody might provide us with data and we don't think it's adequate, so --

MS. FIUME: I see Jay has his hand raised.

DR. ANSELL: Yeah, I certainly agree with everything that Dan and Paul have said. But I don't think it really goes to the latter point; I think it goes more to the CIR process than a change to read across. I think some of our reports contain multiple families. I don't think that what we do really changes the principles of read across. So sometimes we end up having multiple families in a single report, as opposed to trying to merge a number of those families into a single read-across process.

DR. LIEBLER: Yeah, I agree with you, Jay, we're not talking about the changing the principles at all. As I see it, it's a question of how the principles apply in the context in which we will commonly encounter a need to do read across on CIR.

DR. ANSELL: Yeah.

DR. BELSITO: Yeah, I mean, I think you hit the nail on the head, Dan, you know, because we're dealing in RIFM with very similar types of molecules, all small and most reactive, and I think it's going to be interesting to see how we apply this to the universe of cosmetic ingredients. Any other comments? Okay, if not, we're onto polyquaternium-6.

READ ACROSS – COHEN BREAKOUT

DR. COHEN: So it's an interesting document to review. Lisa, I'm going to ask you to comment on it. It seems to me that our read across protocols are to fill in data gaps, and then the teams are asked to assess the likelihood of similarity in biologic activity and perhaps toxicity. And this ambiguity in that penetration metabolism, method of manufacturing, impurities like monomerzole (phonetic) matter.

And one other comment for the group. I think we've purloined or sort of hijacked the read across when we're looking at plant and animal species like sea life. I don’t think that's the typical way we're using the read across, and it's more like a drag or yank across when we're taking, you know, 60 items, you know, and trying to pull them across or 8 items from a single plant. So, Lisa, would you walk us through this a little bit?

DR. PETERSON: Well, I am not a hundred percent sure that I can walk you through because read across is sort of a relatively new concept for me. I mean, I

understand the desire to do it. I have, actually personally, a lot of problems with it. I mean, some examples would be, you know, what happened with the amino acid diacetates, for example. That, you know, a very small change makes it -- it could be safe, it could make it similar to a dangerous compound, and where do you place it?

You know what, I thought overall this document was a good starting point. I didn't see, though, any real expression of what the caveats of this kind of approach are.

Dan graciously invited me to participate in these -- they have weekly meetings in RIFM to discuss these read across issues with the chemicals that they are dealing with, which is a lot of meetings actually.

I did sit in on the one last week, and, you know, there might be some value in using this approach for mixtures because they're working with a program, and please forgive me for not remember the name of the program, that actually can look at the composition of different -- that's been measured on different, for example, extracts coming

from a botanical. Then being able to group those based on a five or ten percent similarity in terms of composition.

You know, I think there's some value in that in terms of wanting to say, you know, this species versus this species, you know, can we read across in that sort of way? But one knows that, if you change this, you know, field that the plant was harvested in, you can change the composition very easily due to the fact that there's different nutrients and different other factors that contribute to the way this plant biosynthesizes the different constituents.

So I think that -- you know, I thought this document was reasonable, but I really think that you have to use the read across with extreme caution. And I think in the document we were shared with from the past discussions, there's been a lot of discussion about the exceptions.

So I thought this document should contain -- and if I missed it, I read it twice, and I didn’t see sort of a list of the potential caveats. I think it needs to be underlined that this is all a starting point for a

conversation. That, you know, in the end, you have to trust -- you know, there are some non-definable factor that has to be incorporated from, you know, a human, not just a software figuring stuff out.

I think, you know, there -- and the fact that there can be exceptions, and you just hate to put out a report that uses a read across that says something's safe and then have it be unsafe and cause harm. I think the other thing would be, you know, there's an economic harm if something gets labeled as unsafe as a result of a read across and is actually safe. So, nothing replace data, but I understand the cost of getting data.

So, I am long-winded, I think this is a good starting, but I think there needs to be a much more strong highlighting of the short -- that highlights the strengths in the approach, but I think, I wasn't sure that there was a strong statement about how, in the end, we have to be careful.

DR. COHEN: In the description of the phases of activity, Phase II is expert examination of the structure's

features. So that does include what you were mentioning, and it did go through this multi-step process of using it.

DR. PETERSON: Okay. Yeah.

DR. COHEN: No, no, no.

DR. PETERSON: I'm just saying that my initial reaction was there were a couple of things I think could be -- you know, a few sentences, maybe some statement of this is -- I just felt it wasn't underscored enough the issue of using the read across. But I agree that there's steps in there that are consistent with that.

DR. COHEN: Tom?

DR. SLAGA: Yeah. Like Lisa said, it's a starting point, but I just, when I read it, I just come up with all kind of exceptions to rules. It's very difficult when you're -- she was talking about plants. Plants, you know, there's too many variables. You know, where it's grown, what the temperature, everything, you know, changes things. I just think we have been doing a fairly good job of working this out when we get a series of compounds and try to make a decision if they really belong or not. I think

that's the point where we find exceptions and then we can work with the -- we do need a document.

(Inaudible) Don or Dan said, you need something on file, at least the process. You know, the process they use for fragrance is, obviously having several people get together, like Dan, very often. That is time-consuming, but then, when you do that and you come to the meeting, the other people have concerns, and I don't know if it solves that much, having the pre-meetings like that. I'm just being honest. It seems to me when we get together, that's when we finally make a decision what should be there and what should not.

DR. COHEN: Ron?

DR. SHANK: I'm going to be the wet blanket. When we first started this, the quest to create a document for a read across, I thought it was to explain how the Panel approaches read across. The current document bears no resemblance to what we do. It looks very much influenced by the European approach where they cannot use animals to test, so they have to rely on a variety of models to

predict, to use for read across. We don't have that limitation.

And I'm wondering what is the purpose of this document? Is this going to be a standard operating procedure, which was mentioned several times before a couple years ago, that that's what this is going to be? If it is, if this is what Panels are going to use, who's going to do it?

I have done these kinds of things. It requires an enormous amount of getting data for physiologically based pharmacokinetics for analysis of chemical structures for reactive groups. all kinds of databases that you have to integrate and use computer models. I don't think anybody on the Panel wants to do that routinely.

If you remember when we first started to use quantitative risk assessments, we don't do those. We have other people do them and give the analysis to the Panel. Is that what's going to be done here? Is if we adopt this approach that it will be farmed out to someone else to do it for the Panel? I really wonder what is the purpose of this because this is not what we do, but are we going to

change what we do and do this very complex analytical process?

Then, for specifics, I don't see how this is ever going to apply to biological mixtures for reasons which you already have stated, but there's another problem. When you're doing a read across you have a subject molecule and then you compare that to target molecules to see if you can read across from the subject molecule to the target molecule, what if you have a chemical group where you have at least two subject molecules where there are two -- a good database for two of the molecules in the group, but the toxicological profiles are different, then what do you do? That's not considered yet in this document.

As an example, if you look at the aliphatic alcohols, and you're going to do read across from alcohols where we don't have a database, or not a good one, are you going to use methanol or ethanol as the subject because you have very different profiles depending on which one you use. That has not been addressed.

Another example would be the alkanes, methane versus hexane. Very, very different toxicity profiles.

That's not treated yet in the document. But I would really like to know what is the Panel going to do with this document? Every time we want to do read across, are we going to ask to do all of these processes? That's my position. Sorry.

DR. COHEN: No, I guess the question will be is how this gets presented tomorrow. I think in the --

DR. SHANK: Who presents this?

DR. COHEN: Huh?

DR. SHANK: Who presents this tomorrow?

DR. COHEN: Don.

DR. SHANK: Don?

DR. COHEN: Yeah.

DR. SHANK: Okay. Do we know, is this what RIFM does? Is this a RIFM approach?

DR. PETERSON: You know, Dan and I had a brief email exchange, and overall, I know that he feels like the document's a good start. I think this approach is what they're doing as part of RIFM.

The group that meets every week is a group that has the chemists, so it's Dan, Trevor Penning, and another

person who meet with, I'm assuming, RIFM staff people who have been working on laying out sort of the read across. Then they discuss whether they agree with it or not. I think that's sort of how it works. I mean, mostly what sticks out in my mind from the meeting on last Tuesday, was how they were proposing to start to look at mixtures where the composition was known and how to compare across mixtures, and they had discussing their rules and how good they were or not good they were.

So, you know, I think, Ron, you bring up a lot of really good points.

DR. SHANK: Okay. I don't want to discourage this. It's just I would like to, before we go any farther, make sure we know how are we going to use this document? Is this going to be a standard operating procedure for the CIR Panel?

DR. PETERSON: I think that's, I just want to add a little bit, I mean, I haven't seen this actually applied yet to try to do any kind of safety. So I do think some clarification about the whole purpose of this would be good, knowing that.

DR. SHANK: Okay. I've done one on a statin, and it is very complex, and you need a lot of data from various fields of science to do it. And I just don't see how the Panel is going to do it within the Panel itself. Therefore, are we going to set up this as a procedure for somebody else to follow for our benefit?

DR. BERGFELD: I'd like to comment. You know, we started out with X number of thousands of ingredients, and we've covered, I don't know, five thousand of them, and they still continue to grow. But low toxicity, high volume types of things, where we took care of most of those biologically active ones at least 10-15 years ago. Having said that, the PCPC came back to the CIR and said we weren't reviewing enough documents, so they began to add all these, supposed, chemical similar chemicals to our reports.

Now we heard today that they don't desire that anymore and our priority lists are going to remove those. It comes to my mind that perhaps we ought to go for the simple form that we began with and that was the lead ingredient and simple salts. If they desire to do more

than the PCPC, we'll need to decide how much investment they're going to give this.

DR. SHANK: Okay, thank you.

DR. COHEN: Any other thoughts on this? Bart, Jinqiu?

DR. HELDRETH: Yeah, I would like to kind of give my thoughts on this a little bit. No, I completely concur with Ron. We're not looking to replace the Panel process, or expert judgment, or any of the things that we've come to expect from how the Panel works.

I think the primary, at least initially, the primary focus of using a read across document or framework, or whatever terminology you want to use to describe it, is more for curating types of information that come to the Panel. If someone wanted to provide a read across assessment to the Panel, are these pathways and steps towards it, are they valid? Does the Panel going to accept these types of things coming in?

If, for example, Jinqiu and I sat down together and we're looking at chemicals to include in the 2023 priority list and we used these tools to decide which

ingredients should be grouped therein, would these steps be considered valid and useful by the Panel? So, I think it's not so much a, here Panel, take all of this information and make sure you run through it all for every report where read across can be done, but I think it's more of a making it clear what types of information the Panel would find useful if provided either by CIR staff or by industry or any third party.

DR. SHANK: Okay. I feel better hearing that, because then this can be a very useful document that, if people want to do read across and present the read across analysis to the Panel, this is what we would like to see. But this is not necessarily what we're going to do with every report that comes up.

DR. SLAGA: Right.

DR. SHANK: Thank you.

DR. HELDRETH: Sure.

DR. COHEN: One thing is that when we're presented with a draft report and there's a table that is ostensibly a read across table, we don’t know how the sausage was made before that table was put together, right? So, we're

presented with a table, and we're assuming there's some of this phased activity has occurred before the table was presented to us. Then, Lisa, you'll look at it and the team will look at it and say, well, I'm not so sure this one makes the cut, and that's sort of a reiteration of the Phase II Expert Panel Review. But should we assume that some of this is going on before we even see that table?

DR. PETERSON: Are you talking about the table that's put in for every report? I mean, is there a --

DR. COHEN: Yes.

DR. PETERSON: --formal read across process happening for the generation of that table? I thought it was just somebody looking at the chemical ingredients and sort of eyeballing them and saying, do they fit together or not fit together, but I could be wrong about that.

DR. COHEN: I don’t know.

DR. HELDRETH: Yeah, concurrently, it's one of two things. Either some other risk assessment or safety assessment team globally has already decided that these are good read across source and target -- let's say the SECS said, hey, this ingredient is great for read across to this

other ingredient -- then that can be included. But, yeah, then there are other cases where we're left to wonder, would this chemical be useful for a read across? We don't have anybody else telling us, so, hey, Panel, do you think this is a valid read across?

But going forward, if we had a document like this, we would have ways that we could try to help validate, make that read across proposal to the Panel more quantitative and less of a just, okay, these look a little bit alike, but let's include these for potential read across.

It gives us a, hopefully, a way for the CIR staff and anybody that wants to submit information to the Panel a list of things to go through that maybe provide a more quality proposal to the Panel.

DR. SLAGA: Keep in mind, nothing replaces good data. If you have good data, this job is very easy.

DR. PETERSON: Yeah.

DR. HELDRETH: Agreed.

DR. PETERSON: Can I suggest once this conversation is done that we take a short break?

DR. COHEN: Sure.

DR. PETERSON: Thanks.

DR. COHEN: Jinqiu, do you have any comments on this and maybe how it's going to be presented tomorrow, and any thoughts that we could -- you've heard what we've said, what key points you think have high value for tomorrow and in our discussions going forward?

DR. ZHU: So, basically, this proposed workflow introduces a data source platform, called the COSMOS Next Generation. So it provides a data platform, essentially to cosmetic inventory and it covers chemicals from multiple regulatory inventories. So I think that is useful.

We can follow that guiding step to gather all necessary information regarding the molecular fingerprint derived similarity and in the protein-based similarity, and also, the mechanics-based similarity. Each piece of this evidence is actually based on the platform, and the computational tools provided by the platform, each piece of this narrative (inaudible) can be transformed to quantitative values. So that can be combined together and presented in a little evidence table to submit to the Panel

for the Panel's review to judge each mechanism, the similarity measures supported by the experimental data.

Also, for all the chemicals included in the database, they are always associated with experimental data. Also, the quality of the experimental data can be judged by expert opinions. All this information can be put together and presented to the Panel for that decision.

DR. BERGFELD: So, Jinqiu, what you're saying is that you will be participating with Bart in regard to developing these options of additions of these chemicals to our reports based on this technical review you just explained?

DR. ZHU: Yeah. I can get involved in this process, yes. By using that kind of -- or these tools, yeah. And, again, all this information. Yeah.

DR. COHEN: Thank you, I think I'll be able to put something together based on this conversation. Those are the hard parts on Monday night, trying to articulate these conversations. Don will be presenting this, and it will be the additive to his comments.

Lisa, I think you're right. You want to take -- it's 8:09 Eastern Time. You want to take, like, a six-minute bio break and then come back? Then we can go through a few more and then take lunch.

DR. BERGFELD: You mean 11:09?

DR. COHEN: What did I say?

DR. BERGFELD: 8:09 you said.

DR. COHEN: No, no, it's 11:09, sorry, 11:09 Eastern Time.

DR. BERGFELD: Okay.

DR. COHEN: So we'll break for a few minutes.

DR. PETERSON: Great. Thank you.

READ-ACROSS – FULL PANEL

DR. BELSITO: Okay, so, just to help you quickly it's going to be the Admin PDF 59. And, I'm just going to turn this over to Dan, since he's our read-across man.

DR. LIEBLER: So, I want to compliment Jinqiu for a really marvelous job on this document. It does a very nice job of capturing what I would call the first half of read-across, which is the organization of chemicals in our databases and other relevant databases into a way that we can systematically identify chemical analogues that could be used to fill data gaps in our evaluations.

The process of organization, clustering, et cetera, described in the document is very similar to the one that the RIFM staff employs for RIFM evaluations. The databases, the ChemTunes and the other data resource that's described here I wasn't familiar with, but I consulted with my RIFM colleague, Terry Schultz, who's a real officiator of computational chemistry tools for predicting metabolism and potential toxicity mechanisms. And he indicated that these resources encompass all the RIFM content as well as

some other content that could be useful to us. And this report very nicely enumerates the approach to clustering the chemicals and accessing databases for a content that would identify chemicals for us.

So, that's the first half. The second half of read-across is once you're presented with some read-across analogue options to help cover an endpoint, then there's usually more than one option, or even if there's only one option, you need to decide is that option really good enough, does it suffice. And that's a matter of expert judgement. Now, on the RIFM side, we have a group of three of us; myself, Terry Shultz, and Trevor Penning, who have Tuesday morning meetings every week for an hour with RIFM staff to evaluate these options, read-across analogue options that are presented for different endpoints.

And that's a process that is not automated. It's not algorithmised [sic] at this point. It's simply expert judgement and discussion. We have a sort of a set of rules that has evolved from our discussions. Those are not really published at this point, but they are perhaps something that could be assessed and shared.

Because we are just beginning to get into read across on the CIR panel, I thought that these weekly discussions it might be good to invite Lisa to join just to be able to log in and listen to some of the discussion. So, Lisa did listen into our chat last Tuesday, and Lisa has either been issued invitations or will be issued invitations for some upcoming discussions to get a sense of how we do this. And then Lisa and I and CIR staff can talk about how we might employ that approach or modify that approach to being read across practically speaking into CIR in a systematic way.

So, that's it in a nutshell. I had a lot of edits and comments to the document that I will share with Jinqiu, but those are my thoughts on it. So, if you have any questions I can answer, or hear from Lisa.

DR. BERGFELD: What you're presenting is an update of where we stand as we develop the documents and the procedures for read-across.

DR. LIEBLER: Um-hmm.

DR. BERGFELD: Okay. And, we're going to hear more about this later. Is that correct?

DR. LIEBLER: Correct. I mean, this will continue to evolve. I don't know, Lisa, if you had any thoughts or comments on all of this?

DR. PETERSON: Yeah, so I'm just going to say that I'm not an expert in read across, so this is a relatively new area for me. I thought the document was a good starting point for providing a process by which the community uses or the group uses to apply read-across under certain circumstances. You know, I again continue to have concerns about the read across (audio skip), but I think it can be helpful. And I think we should use it. And, you know, the caveat is always there're exceptions. And, that's what I guess the expertise of the panel is to help figure out what those exceptions might be. So, I thought the document read well. You know, it's hard for me to judge it critically because I just don't have enough experience.

DR. BERGFELD: Anyone else wishes to comment, or ask --

DR. COHEN: You know, I was trying to catalog all the comments that were made; this was a pretty long

discussion. And, I think one of the issues that we covered was the cautionary issues of using read-across, and its inherent risks. And how we sort of awkwardly used that process with plants and animals, right, we're awkwardly trying to do that when we look at that data. But I think the group was impressed with the document, particularly as it articulated the phases and processes of measuring and layering chemical and toxicological similarities between chemicals through a variety of domains.

It seem like our current process provides some risk assessment but relies heavily on the chemist to opine on the relativeness and potential toxicities with their hazard assessment looking at the structures and functional groups amongst other parameters.

So, we thought the resource document was an aspirational framework that sort of codified quantitative processes with qualitative filters from the chemists that we work with. And there was -- as for the question at hand in the document, I think we thought it was scientifically rigorous but collectively doubted the feasibility of fully rolling that out in all the reports that we see.

So I think Don and Bart have said this has been a living document that we'll need to change and harmonize with developing technologies, but that we liked it and hoped that we can incorporate some of it. But we just didn't think that our next set of draft reports were going to go through this entire exercise.

DR. LIEBLER: Oh, not at all. You know, let me just clari- -- let me repeat one thing that I think is very important. This document really only deals with how to organize the existing information so that we could have the opportunity to systematically identify analogues that might be used for read across. It doesn't really provide any pathway to taking those candidate read-across analogues and deciding whether they are sufficient. That is still a very manual process, as I described these Tuesday's meetings at RIFM for example. But, the part that you need to start with is just being able to organize the world of structures and data so that you can begin a read-across process.

So, yeah, this is not intended to be, well, here it is boys and girls, take it and use it. We're not at that stage. But I think the first step is represented by

the document and by the availability of these database resources. It's going to take a while to bring this into our process.

And I would further say that one point I made yesterday that I forgot to make this morning is I think probably the initial big read-across application for us is when we have a family of molecules that we have data for one or two of them, but the rest of them differ by various chain links or other substituents, but there's a common theme. Can we use the data from a couple of those to clear the family, and what would the limits be? That's our kind of the read-across problem I see presenting itself in CIR. More commonly than one pure chemical without sensitization, we have another analogue, and the question is can we use the sensitization data for the analogue? We do get that in RIFM. We seldom get it in CIR. And then, for naturals to naturals, timeout on that, that's not going to be until a lot later.

DR. BERGFELD: Well, thank you very much, lot of work, lot of innovative work. Bart, you want to make a comment?

DR. HELDRETH: No, I appreciate all that work and I agree what Jinqiu has done here is fantastic. But to David's point about this being an aspirational document, I agree. And we would like to know, you know, where you see this document going next. Of course we're going to take your edits and comments and incorporate them into the document, but should it remain an in-house document at this point until we've had a chance to use it, and Jinqiu's had an opportunity to work with Dr. Peterson, Dr. Liebler about these topics? Or do you think this is something that's ready for primetime and posting on the findings page of the CIR website?

DR. BERGFELD: I think this is in development, and not post it yet.

DR. SLAGA: Agreed.

DR. LIEBLER: I agree.

DR. COHEN: Right.

DR. HELDRETH: Wonderful, thanks.

DR. BERGFELD: Okay. I think that maybe we could add this to our agenda at least a couple times a year, for us to relook at it and see how we're coming. And, perhaps

utilize our experience with trying to use parts of it. And, Lisa, and, Dan, you are the key people, so we'll be counting on you.

Well, we've come to the end of the agenda as I see it. And, I want to thank everyone. Everybody very well prepared and lots of great discussion. Our next meeting will be virtual on December 6th and 7th. I'm going to look forward to seeing you and you all have a great Thanksgiving. Anyone else have a comment?

DR. BELSITO: Yeah, Wilma, can I just make a few comments?

DR. BERGFELD: Sure.

DR. BELSITO: First, and foremost, is it my understanding from yesterday that this is Wilbur's last meeting, Bart?

DR. HELDRETH: No, the December meeting will be his last.

DR. BELSITO: Oh, okay. I guess I was so shocked yesterday I misunderstood that.

MR. JOHNSON: Not so fast, Dr. Belsito.

DR. BELSITO: Okay, Wilbur, I'm fine with that. So, quite a few of us missed the document from Women's Voices for the Earth because it came through as an annotated agenda, and we would request any new materials come through as a Wave 2 and not annotated. Because at least myself and Dan and perhaps other people don't really look at that annotated agenda, we assume that it's just an update of what we may have gotten in Wave 2.

I also always struggle with the Admin Book trying to get to where I'm supposed to be for Zeolite or Read-Across. Is there a reason why we group those in Admin? Why don't we just create separate documents and make Admin's just the minutes and the program?

DR. HELDRETH: We can certainly do that. I think they've just been grouped together because that's how it's always been done, but that's not a reason (audio skip).

DR. BELSITO: I mean, and I struggle with it every time trying to get to the right page, because you're going through minutes. If you search zeolite, you see a million zeolites. If you're going through read across, you see nine million before you get to the right page.

DR. HELDRETH: We can do that.

DR. COHEN: Don, I would second that because when you print out -- I like to print out the agenda -- and you wind up printing 95 pages out instead of 12.

DR. BERGFELD: Okay, I think that's a done did. We did it.

DR. BELSITO: Right. This is the longest we've ever gone on a day two.

DR. BERGFELD: I know, and on a second day. All right everyone have a good holiday.

[THE MEETING WAS ADJOURNED]