ADMIN

Tool List

EXPERT PANEL MEETING
December 4-5, 2023

Cosmetic Ingredient Review

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Memorandum

To: Expert Panel for Cosmetic Ingredient Safety Members and Liaisons
From: Jinqiu Zhu, PhD, DABT, ERT, DCST, CIR Toxicologist
Date: November 9, 2023
Subject: CIR SSC submission on Tools

In response to the Panel's inquiry, the CIR Science and Support Committee (SSC) of the Personal Care Products Council shared a list of tools for literature exploration and toxicity evaluation. The submission made to the CIR included relevant published papers and user manuals; however, due to copyrights, only the memo providing the list of tools is included with this submission (*CIRSSC_Tools_122023*). The CIR SSC also presented tools that the Research Institute for Fragrance Materials (RIFM) uses for safety assessments of fragrance ingredients (*RIFM_Tools_122023*). Gaining access to the RIFM database provides the opportunity to utilize various tools, including the Skin Absorption Model (SAM), the Toxicology Data Engine (TSDE), the 2-Box Air Dispersion Model, and the Multiple Path Particle Dosimetry (MPPD) Inhalation Exposure Model.

The features and functionality of each tool listed in the two documents are summarized in the Table below for the Panel's consideration. Furthermore, the CIR SSC provided several review papers on new approach methodologies (NAMs) to support the "Next Generation Risk Assessment" (NGRA) for cosmetics ingredients and materials, including the application of machine learning and artificial intelligence approaches in toxicology, such as physiologically-based pharmacokinetic (PBPK) modeling, quantitative structure activity relationship (QSAR) modeling for toxicity prediction, adverse outcome pathway (AOP) analysis, etc.

The submission features an article that introduces Vermeer Cosmolife, formerly known as SpheraCosmolife, which is a freely accessible software designed for the toxicological assessment of cosmetic ingredients. The software has been developed considering the regulatory framework for cosmetics. It may apply defined exposure scenarios, depending on product type, to derive risk for cosmetic consumers. This tool has already been used to calculate the margin of safety (MOS) for ingredients, such as Octoxynols, and will be discussed in the draft report being reviewed at the upcoming December Panel meeting.

In the submission, a review paper (Cronin et al. 2022) highlights prominent databases that may provide a broad selection of toxicological information and data for cosmetics-related materials. One example is the COSMOS NG (the public component of the ChemTunes·ToxGPS® web services). It has been proposed for use in read-across, as discussed at previous Panel meeting (See pdf pages 59-71 at https://www.cir-safety.org/sites/default/files/Admin_13.pdf). Of note, COSMOS Threshold of Toxicological Concern (TTC) datasets played a pivotal role in the development of TTC specifically for cosmetics ingredients. This COSMOS approach led to the SCCS's most recent decision on the thresholds of 2.3 and 46 µg/kg bw/d for Cramer classes III and I, respectively, for use in relation to cosmetics-related substances.

It is worth mentioning that some of the tools listed in the two documents are commercial. Their in silico predictions might be based on the provider's proprietary databases. Some companies have reservations about sharing complete analysis and prediction details. For instance, Lhasa Limited representatives assert that they cannot allow public access to Derek alerts and the full reports generated by Derek Nexus.

The Panel is being asked to review the information provided in the submission, and consider the potential applications of the highlighted tools. Specially, the Panel should determine when results predicted by in silico approaches might be employed for assessing the safety of cosmetic ingredients.

Table 1. Summary of tools presented in the CIR SSC submission

Tools	Function/Feature	Used by RIFM	Notes
Abstract Sifter	Microsoft Excel-based application for amplifying search capabilities of PubMed;: quicker and easier to find and rank relevant articles; the Landscape function is useful to quickly get an idea of how well certain topics have been covered in the literature.	—	Free
ICF Litstream®	Systematic literature review consulting and software: this tool suite covers literature search, prioritization, text screening, inventory, data extraction and analysis, risk-of-bias or study quality assessments, and visualization.	—	Counselling fee applied
ICF DoCTER	Web-based software application that helps explore and prioritize documents: it possesses a feature for topic extraction or clustering that aids in identifying the principal themes within a set of literature; after training its machine learning algorithm, it can further classify a set of documents and determine which articles are pertinent or not to a particular topic.	—	Free
SpheraCosmolife (now known as Vermeer Cosmolife)	Make predictions on ingredients when experimental data are absent. Users are requested to input information regarding the concentration use and the product type (as defined within SCCS NoG*). The software may verify if the ingredient is listed in the Annexes of Regulation (EC) No. 1223/2009, and perform a risk characterization of the given chemicals based on a battery of QSAR models (from the VEGA platform). The software can search for values present in its database useful for TTC, genotoxicity and skin sensitization; additionally, it can define an exposure scenario, predict figures for NOAEL and SED, and consequently derive the MOS.	—	Free
DEREK NEXUS	Predict toxicity for various endpoints based on chemical structures, such as mutagenicity, skin sensitization (may provide EC3 predictions to inform potency), carcinogenicity, etc. The comments accompanying the structure features will describe the alert mechanism of action. The predictions are supported by both public and proprietary member data sources.	Used in the Dermal Sensitization Threshold (DST) expansion project.	$6,127 per year
OASIS TIMES platform	TIMES (Tissue Metabolism Simulator) predicts toxicity of chemicals taking into account the metabolic activation of chemicals, e.g., skin sensitization, mutagenicity, chromosomal aberrations, micronucleus formation, and hormonal toxicity (ER/AR and AhR binding affinities) The systems are capable of assessing metabolic similarities between chemicals, considering different similarity criteria; grouping of chemicals; providing theoretical/experimental support to the adequacy of the simulated metabolic pathways, and so forth.	Utilized by RIFM for genotoxicity, repeat-dose evaluations and in support of read-across	$20,000 for purchase

OASIS CATALOGIC	A sister platform to TIMES. It covers environmental fate properties notably abiotic and biotic biodegradation. Models also exist for bioconcentration and half-life in fish. Catalogic models incorporate a microbial metabolism simulator.	Utilized by RIFM to support read-across	$20,000 for purchase
ToxTree	A QSAR tool that can be used to determine the Cramer class of a chemical substance and estimate its relative toxic hazard, such as predictions of skin/eye irritation, identification of DNA and protein binding alerts, and structural alerts of Michael acceptors.	Utilized by RIFM to support read-across	Free
OECD QSAR Toolbox	It may identify structural characteristics and potential mechanism or mode of action of a target chemical; it may further identify other chemicals that share similar structural features and/or mode of action; data gaps can be filled using read-across, trend analysis or external QSAR tools. It is useful to fill data gaps through the development of endpoint-specific groupings, as well as to profile substances on the basis of their similar attributes and evaluate the context of similarity with respect to specific endpoints and across endpoints.	Utilized by RIFM for genotoxicity, repeat-dose, skin sensitization, and phototoxicity evaluations	Free
EPA Analog Identification Methodology (AIM) Tool	Facilitates analog analysis in support of read-across: it can identify potential analogs from a library of more than 86,000 chemicals; it can conduct structural analysis by leveraging a predefined database with over 700 individual atoms, groups, and super fragments.	Utilized by RIFM to support read-across	Free
EPISuite™	EPI (Estimation Programs Interface) Suite estimates a range of physiochemical properties (e.g., Kow, MW, vapor pressure), environmental fate parameters	Utilized by RIFM to support read-across	Free
VEGA	Predict toxicity and physiochemical properties based on an independent algorithm (Applicability Domain Index); the QSAR prediction models derive from CAESAR, T.E.S.T., EPISuite, Toxtree, and other tools.	Utilized by RIFM to support read-across	Free
MultiCASE platform	It implements CASE (Computer Automated Structure Evaluation) approach; automatically generates predictive models from datasets provided by the user. It also consists of two additional programs: METAUltra - predict human metabolites and identify reactive metabolites; QSAR Flex - assess complex toxicological endpoints with limited experimental data.	Utilized by RIFM for genotoxicity and repeat-dose evaluations	$ 50,000/year, covering 3 models (Carci, Skin Sensitization, and DART)
TOPKAT	It makes predictions for a wide range of endpoints, such as carcinogenicity, mutagenicity, developmental toxicity, maximum tolerated dose in rats, skin sensitization/irritation, eye irritation, etc.; currently with integration as a component in BIOVIA Discovery Studio Suite, users can integrate their own data and information and refine the scope of the modelled endpoints.	Utilized by RIFM for genotoxicity and repeat-dose evaluations	Free

ToxCast	EPA's Toxicity Forecaster generates data and predictive models on 1800 chemicals; it screens chemicals in more than 700 high-throughput assay endpoints that cover a range of high-level cell responses.	Utilized by RIFM for repeat-dose evaluations	Free
2-Box Air Dispersion Model	It is a computational, indoor environment, air exposure model that characterizes the movement of a single chemical inside two connected, enclosed zones. It takes into account the dilution of the substance over time. It is a hybrid of the Dutch National Institute for Public Health and the Environment, RIVM Consumer Exposure (ConsExpo) model and the U.S. Environmental Protection Agency (EPA) Multi-Chamber Chemical Exposure Model (MCCEM).	Utilized by RIFM in exposure assessment	Available to RIFM members ($12,500 for subscription)
RIFM MPPD model	The Multiple Path Particle Deposition (MPPD) model is to study the uptake of vapors and deposition of aerosol particulate/droplet components using a computational model of the nasal and lung airways. It allows the direct extrapolation of laboratory animal data to human exposure and is capable of estimating specific doses deposited at various sites of the respiratory tract.	Utilized by RIFM in exposure assessment	Available to RIFM members ($12,500 for subscription)
Creme-RIFM Chronic Aggregate Exposure Model	It provides a detailed aggregate systemic and dermal exposure assessment system for fragrance compounds. It has data to assess realistic exposure on many products such as body lotions, deodorants, toothpaste, lipstick, perfumes, shower gels, etc. Product usage data are based on real habits and practice information (including detailed usage data for over 36,000 consumers representing the EU and US populations).	Utilized by RIFM in exposure assessment	Available to RIFM members ($12,500 for subscription)

* SCCS NoG: The SCCS Notes of Guidance for the Testing of Cosmetic Ingredients and Their Safety (10th revision)

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TO: Bart Heldreth Ph.D., Executive Director – Cosmetic Ingredient Review
Expert Panel for Cosmetic Ingredient Safety

FROM: CIR Science and Support Committee (CIR SSC) of the Personal Care Products Council

DATE: August 18, 2023

SUBJECT: Tools

During the June 2023 CIR meeting, there was a request to the CIR Science and Support Committee to suggest tools that may be used by CIR to identify and prioritize literature, and for a list of *in silico* tools. Attached is some information about tools that may be helpful.

Baker N, Knudsen T, Williams AJ. 2023. Abstract Sifter: a comprehensive front-end system to PubMed. [version 1; peer review: 2 approved] F1000Research 2017, 6(Chem Inf Sci):2164 https://doi.org/10.12688/f1000researcg,12865.1.

Abstract Sifter User Guide 5.0. 2020.

ICF. 2021. Livestream™.

ICF. 2021. Doctor: ICF's Document Classification and Topic Extraction Resource.

Lin Z, Chou W-C. 2022. Machine Learning and Artificial Intelligence in Toxicological Sciences. 189(1): 7-19.

Selvestrel G, Robino F, Baderna D, et al. 2021. SpheraCosmolife: A new tool for the risk assessment of cosmetic products. ALTEX 38(4), 565-579. doi:10.14573/altex.2010221.

Cronin MTD, Enoch SJ, Madden JC. 2022. A review of in silico toxicology approaches to support the safety assessment of cosmetics-related materials. Computation Toxicology 21 https://doi.org/10.1016/j.comtox.2022.100213 .

Lhasa has tools such as DEREK that may be helpful: https://www.lhasalimited.org/solutions/

The TIMES platform can be used to predict skin sensitization, mutagenicity, chromosomal aberrations and micronucleus formation: http://oasis-lmc.org/products/software/times.aspx#:~:text=Presently%2C%20the%20TIMES%20platform%20is,also%20available%20in%20the%20TIMES .

Free prediction programs include ToxTree (https://toxtree.sourceforge.net/) and the OECD Toolbox: (https://www.oecd.org/chemicalsafety/risk-assessment/oecd-qsar-toolbox.htm).

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TO: Bart Heldreth Ph.D., Executive Director – Cosmetic Ingredient Review
Expert Panel for Cosmetic Ingredient Safety

FROM: CIR Science and Support Committee (CIR SSC) of the Personal Care Products Council

DATE: October 18, 2023

SUBJECT: Tools used by the Research Institute for Fragrance Materials (RIFM)

October 2023

Tools Used by The Research Institute for Fragrance Materials (RIFM)
(based on 2015 Safety Evaluation Process paper* – plus updates provide by RIFM in red)

Exposure

2-Box Air Dispersion Model (Perry et al., 2013)

RIFM MPPD model (Asgharian et al., 2012)

Creme-RIFM Chronic Aggregate Exposure Model

TTC

Kroes et al. 2004; Munro et al. 1996 modified using default skin penetration values (Blackburn et al. 2005; Kroes et al., 2007)

Dermal sensitization threshold (Safford 2008; Safford et al. 2011)

For inhalation local effects (Carthew et al. 2009)

Read-across

Finding structural analogs – expert review with OECD QSAR Toolbox; EPA Analog Identification Method (or other appropriate computational models), Episuite, OASIS TIMES, OASIS CATALOGIC, Toxtree, Vega

Genotoxicity

Structural alerts identified by the methods of Ashby and Tennant (1991) and Benigni and Bossa (2008)

In silico tools include DEREK, MultiCASE, Oncologic, TOPKAT, TIMES, OECD toolbox (some based on more extensive list of structural alerts)

Repeat-dose

“RIFM will continue to investigate the potential of SARs”, e.g., OECD QSAR Toolbox, DEREK, MultiCASE, ToxCast, TOPKAT, TIMES, etc.

Skin Sensitization

SAR models such as those found in the OECD Toolbox used to classify substances as either reactive or non-reactive.

OECD Toolbox, Toxtree, and TIME-SS for structural reactivity alerts

EPISUITE for phys-chem properties like Kow, MW, vapor pressure

DEREK NEXUS was used in the DST expansion project but it is not used regularly for safety assessments.

Phototoxicity

OECD QSAR toolbox

*Api AM, Belsito D, Bruze M, et al. 2015. Criteria for the Research Institute for Fragrance Materials, Inc. (RIFM) safety evaluation process for fragrance ingredients. Food and Chemical Toxicology 82: S1-S19. https://fragrancematerialsafetyresource.elsevier.com/sites/default/files/Criteria_Document_Final_0.pdf