Institution: Liverpool John Moores University (LJMU)		
Unit of Assessment: UoA3		
Title of case study: Computational Models for Safe Cosmetics		
Period when the underpinning research was undertaken: 2000-2020		
Details of staff conducting the underpinning research from the submitting unit:		
Name(s):	**Role(s) (e.g. job title):**	**Period(s) employed by submitting HEI:**
Prof Mark Cronin	Professor of Predictive Toxicology	1994 - present
Prof. Judith Madden	Professor in *In Silico* Chemical Assessment	1998 - present
Dr Steve Enoch	Reader in Computational Toxicology	2011 - present
Period when the claimed impact occurred: January 2011- December 2020		
Is this case study continued from a case study submitted in 2014? N		

1. Summary of the impact

The cosmetics industry has a highly significant economic impact in the UK and globally. In order to assist with the safety evaluation of ingredients in cosmetic products we have developed a variety of computational approaches linking chemical structure to potential harmful effects. In addition, the COSMOS Database has provided a rich source of repeated dose toxicity data that has been utilised to update the Threshold of Toxicological Concern (TTC) concept. The computational models and TTC have been recognised by international regulatory authorities for their impact on the risk assessment of cosmetics ingredients.

2. Underpinning research

Since the implementation of the 2013 ban on animal testing of cosmetics ingredients in the European Union, many other countries and regions have followed suit (Brazil, California etc.). As a result, safety assessment of cosmetics ingredients requires non-animal methods, which are acceptable to both regulatory and industrial bodies. LJMU has been at the forefront of developing computational methods that assist in the evaluation of cosmetic ingredients.

For over 25 years, LJMU has been a world leader and innovator in the application of knowledge from chemical structure and the implementation of computational methods (e.g. QSAR and read-across) to predict the effects of chemicals on human health. More recently, LJMU led the COSMOS Project (2011-2015) as part of the SEURAT-1 cluster, which developed alternatives to assess the safety of cosmetics ingredients [R1]. A key focus the COSMOS Project was the development of a database of safety data (such as No Observable Effect Levels (NOELs)) for cosmetics ingredients. LJMU led activities in data collection and evaluation in COSMOS. The resultant database, COSMOS DB, is freely available and maintained as a significant output from the Project. COSMOS has more than 80,000 chemical records with more than 40,000 unique structures. Importantly, there are data from in excess of 12,000 toxicity studies, across 27 endpoints for more than 1,600 compounds. The database has become a fundamental source of information on the safety of cosmetics ingredients, as well as the basis for further analysis and modelling [R2].

Data from the COSMOS project have underpinned the derivation and update of Thresholds of Toxicological Concern (TTC) values for cosmetics ingredients. LJMU co-ordinated careful curation of the data through collaboration with scientists from industry and regulatory agencies. For the Repeated Dose Toxicity data included in COSMOS DB, thorough analysis was made to create the dataset of NOEL values from which the TTC value was derived [R3]. LMJU performed analysis of the dataset, enriched with cosmetics ingredients and materials, and confirmed it as being suitable

to make a risk assessment of ingredients in low concentration, negating the need for any further assessment (and hence animal or other tests). This approach was extended to make it relevant for the dermal route of exposure, as is common with most cosmetics [R4].

Further analysis of the COSMOS database was undertaken and these repeated dose toxicity data and informatics structure enabled a detailed assessment of the chemistry that underpins organ level toxicity. This has been organised in accordance with the respective Adverse Outcome Pathways (AOPs), the AOP paradigm having been endorsed by the Organisation of Economic Cooperation and Development (OECD). Structural alerts focussing on mechanisms of action for liver toxicity have been developed which allow for the identification and grouping (hence a precursor for read-across) of compounds with the potential to act as mitochondrial toxicants [R5]. Work arising from the COSMOS Project and LJMU has enabled improved reporting of use of read-across and computational models [R6].

3. References to the research

All journal articles have been through a rigorous peer-review process.

[R1] Gocht T, Berggren E, Ahr H, Cotgreave I, **Cronin M**, Daston G, Hardy B, Heinzle E, Hescheler J, Knight D, Mahony C, Peschanski M, Schwarz M, Thomas R, Verfaillie C, White A, Whelan M. (2015) The SEURAT-1 approach towards animal free human safety assessment. *ALTEX-Alternatives to Animal Experimentation* 32: 9-24. 10.14573/altex.1408041 [Cited 28 times: Web of Science, 30 November 2020]

[R2] COSMOS DB - https://cosmosdb.eu/cosmosdb.v2/

[R3] Yang C, Barlow SM, Muldoon Jacobs KL, Vitcheva V, Boobis AR, Felter SP, Arvidson KB , Keller D, **Cronin MTD**, **Enoch S**, Worth A, Hollnagel HM. (2017) Thresholds of Toxicological Concern for cosmetics-related substances: New database, thresholds, and enrichment of chemical space. *Food and Chemical Toxicology* 109: 170-193. 10.1016/j.fct.2017.08.043 [Cited 24 times: Web of Science, 30 November 2020]

[R4] Williams FM, Rothe H, Barrett G, Chiodini A, Whyte J, **Cronin MTD**, Monteiro-Riviere NA, Plautz J, Roper C, Westerhout J, Yang C, Guy RH. (2016) Assessing the safety of cosmetic chemicals: Consideration of a flux decision tree to predict dermally delivered systemic dose for comparison with oral TTC (Threshold of Toxicological Concern). *Regulatory Toxicology and Pharmacology* 76: 174-186. 10.1016/j.yrtph.2016.01.005 [Cited 22 times: Web of Science, 30 November 2020]

[R5] Nelms MD, Mellor CL, **Cronin MTD**, **Madden JC**, **Enoch SJ**. (2015) Development of an *in silico* profiler for mitochondrial toxicity. *Chemical Research in Toxicology* 28: 1891-1902. 10.1021/acs.chemrestox.5b00275 [Cited 15 times: Web of Science, 30 November 2020]

[R6] Schultz TW, Amcoff P, Berggren E, Gautier F, Klaric M, Knight DJ, Mahony C, Schwarz M, White A, **Cronin MTD** (2015) A strategy for structuring and reporting a read-across prediction of toxicity. *Regulatory Toxicology and Pharmacology* 72: 586-601. 10.1016/j.yrtph.2015.05.016 [Cited 116 times: Web of Science, 30 November 2020]

4. Details of the impact

The European cosmetics and personal care market is the largest in the world with €78.6 billion retail sales in 2018, supporting over 2 million jobs directly and indirectly. The safety of cosmetics products must be assured; however, legislation has banned the traditional means of obtaining information through animal testing. Thus, there is a requirement for new methods in the safety assessment of cosmetics. The COSMOS Project supported this requirement by providing access to existing data and computational models through the development of the COSMOS DB, the creation of cosmetics materials enriched TTC values, and models for the screening of compounds for liver toxicity. These initiatives have built on several decades of work by Cronin, Madden, Enoch in the area of data compilation and curation and *in silico* model development.

COSMOS DB is a publicly available resource for toxicological information with a focus on data for cosmetics ingredients. Since the end of the COSMOS Project in 2015 it has been maintained by Molecular Networks GmbH (Nürnberg, Germany) and has over 2,800 registered and regular users [Corroborating Source 1, (CS1)] including manufacturers of cosmetics products. It is used by regulatory agencies, for instance the data from COSMOS DB has been included in the US EPA's Chemistry Dashboard and Japan NITE's HESS databases [CS2]. Due to the quality of the information and curation, the COSMOS DB has been recognised by the European Union's Scientific Committee on Consumer Safety (SCCS), the expert group that provides opinions on the health and safety risks of non-food consumer products including cosmetics [CS3].

The COSMOS DB is continually being extended through the COSMOS DataShare Point which is led by Cronin [https://www.mn-am.com/projects/cosmosdatasharepoint]. This initiative has led to a significant increase in the number and type of data, as well as inventories, held within COSMOS DB since the end of the COSMOS project, with significant donations from NITE (Japan), Cosmetics Ingredient Review (US) and KCII (Korea). Biannual meetings are held for users in Europe and the US respectively (with further outreach to South Korea and Japan). COSMOS DB is also being sustained through major investment from Cosmetics Europe's Long Range Science Strategy. The approaches formulated in COSMOS (e.g. the database, TTC, read-across) have been a major influence in Cosmetics Europe's strategy for systemic toxicity assessment based on non-animal approaches [CS4, CS5].

COSMOS DB itself had a major revamp in 2020 to allow for a more flexible software architecture and, more significantly, the inclusion of models for toxicity prediction. The models included those from the LJMU group for the identification of potential toxicants. These models have been documented and disseminated by EURL-ECVAM DB-ALM ensuring widespread uptake [CS6]. Taken as a whole, these models, or compilations of structural alerts termed profilers, are able to identify potentially toxic molecules directly or through category formation and read-across. Cronin et al undertook a number of case studies applying techniques, such as read-across, to groups of compounds relevant to the cosmetics industry. These studies were reviewed by the OECD with recommendations that the profilers will assist in the reduction of uncertainties associated with the models and their use as New Approach Methodologies [CS7].

The outputs of the COSMOS Project in terms of TTC are noted by the SCCS through their opinions [CS3] and recognised as a viable method in Next-Generation Risk Assessment [CS8]. In addition they form the basis (or lowest Tier) of strategies employed by the cosmetics industry to assess the safety of ingredients, e.g. International Cooperation on Cosmetics Regulation (ICCR) utilises

this approach in its Next-Generation Risk Assessment strategy allowing it to be more firmly based on exposure to an ingredient [CS9]. In addition, a further major output of the SEURAT-1 Project, an *ab initio* workflow for chemical safety assessment, makes use of COSMOS DB, the updated TTC and the models from COSMOS. The *ab initio* strategy, or chemical safety assessment workflow based on exposure considerations and non-animal methods, has been reviewed by OECD which highlighted the possibilities for using multiple data streams for safety assessment decisions [CS10]

Overall, the outputs from the COSMOS Project have been recognised by SCCS and ICCR for their role in the safety assessment of cosmetics across Europe and beyond without the use of animals. In addition, they have allowed for a dialogue and interchange to be achieved with government agencies.

5. Sources to corroborate the impact

[CS1] Letter of evidence from MN-AM

[CS2] National Institute of Technology and Evaluation. Update history of Hazard Evaluation Support System Integrated Platform (HESS). March 2020. Available from: https://www.nite.go.jp/en/chem/qsar/hess_update-e.html

[CS3] SCCS (Scientific Committee on Consumer Safety), SCCS Notes of Guidance for the Testing of Cosmetic Ingredients and their Safety Evaluation 10th revision, 24-25 October 2018, SCCS/1602/18. Available from: https://ec.europa.eu/health/sites/health/files/scientific_committees/consumer_safety/docs/sccs_o_224.pdf [page 66] [Cites ref [3] in Section 3]

[CS4] Desprez B, Dent M, Keller D, Klaric M, Ouédraogo G, Cubberley R, Duplan H, Eilstein J, Ellison C, Grégoire S, Hewitt NJ, Jacques-Jamin C, Lange D, Roe A, Rothe H, Blaauboer BJ, Schepky A, Catherine Mahony C. (2018) A strategy for systemic toxicity assessment based on non-animal approaches: The Cosmetics Europe Long Range Science Strategy programme. *Toxicology in Vitro* 50: 137-146. 10.1016/j.tiv.2018.02.017 .

[CS5] Ellison CA, Blackburn KL, Carmichael PL, Clewell HJ, Cronin MTD, Desprez B, Escher SE, Ferguson SS, Grégoire S, Hewitt NJ, Hollnagel HM, Klaric M, Patel A, Salhi S, Schepky A, Schmitt BG, Wambaugh JF, Worth A. (2019) Challenges in working towards an internal threshold of toxicological concern (iTTC) for use in the safety assessment of cosmetics: Discussions from the Cosmetics Europe iTTC Working Group workshop. *Regulatory Toxicology and Pharmacology* 103: 63-72. 10.1016/j.yrtph.2019.01.016.

[CS6] European Commission Joint Research Centre, European Union Research Laboratory ECVAM DataBase service on Alternative Methods to animal experimentation (DB-ALM). Available from: http://cidportal.jrc.ec.europa.eu/ftp/jrc-opendata/EURL-ECVAM/datasets/DBALM/LATEST/online/dbalm.html Methods numbers: 177-182.

[CS7] Organisation for Economic Cooperation and Development (OECD) (2017) Report on Considerations from Case Studies on Integrated Approaches for Testing and Assessment (IATA). ENV/JM/MONO(2017)22. Series on Testing & Assessment, No. 270, OECD, Paris,

France. Available from: http://www.oecd.org/officialdocuments/publicdisplaydocumentpdf/?cote=env/jm/mono(2017)22&doclanguage=en [pages 16-18, 33, 34] [Cites ref [6] in Section 3]

[CS8] Rogiers V, Benfenati E, Bernauer U, Bodin L, Carmichael P, Chaudhry Q, Coenraads PJ, Cronin MTD, Dent M, Dusinska M, Ellison C, Ezendam J, Gaffet E, Galli CL, Goebel C, Granum C, Hollnagel HM, Kern PS, Kosemund-Meynen K, Ouédraogo G, Panteri E, Rousselle C, Stepnik M, Vanhaecke T, von Goetz N, Worth A (2020) The way forward for assessing the human health safety of cosmetics in the EU - Workshop proceedings. *Toxicology* 436: 152421. 10.1016/j.tox.2020.152421.

[CS9] Dent M, Teixeira Amaral R, Amores Da Silva P, Ansell J, Boisleve F, Hatao M, Hirose A, Kasai Y, Kern P, Kreiling R, Milstein S, Montemayor B, Oliveira J, Richarz A, Taalman R, Vaillancourt E, Verma R, Vieira O'Reilly Cabral Posada N, Weiss C, Kojima H. (2018) Principles underpinning the use of new methodologies in the risk assessment of cosmetic ingredients. *Computational Toxicology* 7: 20-26. 10.1016/j.comtox.2018.06.001.

[CS10] Organisation for Economic Cooperation and Development (OECD) (2017) Chemical Safety Assessment Workflow Based on Exposure Considerations and Non-Animal Methods. ENV/JM/MONO(2017)27. Series on Testing & Assessment, No. 275, OECD, Paris, France. Available from: http://www.oecd.org/officialdocuments/publicdisplaydocumentpdf/?cote=env/jm/mono(2017)27&doclanguage=en [pages 12, 16-17] [Cites refs [1, 4, 5, 6] in Section 3]