Food and Chemical Toxicology 109 (2017) 170–193

Contents lists available at ScienceDirect

Food and Chemical Toxicology

journal homepage: www.elsevier.com/locate/foodchemtox

Thresholds of Toxicological Concern for cosmetics-related substances: New database, thresholds, and enrichment of chemical space

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ARTICLE INFO

Article history:
Received 15 May 2017
Received in revised form
23 August 2017
Accepted 28 August 2017
Available online 1 September 2017

Keywords:
Threshold of Toxicological Concern
TTC
Cosmetics
Cheminformatics
Cramer classification

ABSTRACT

A new dataset of cosmetics-related chemicals for the Threshold of Toxicological Concern (TTC) approach has been compiled, comprising 552 chemicals with 219, 40, and 293 chemicals in Cramer Classes I, II, and III, respectively. Data were integrated and curated to create a database of No-/Lowest-Observed-Adverse-Effect Level (NOAEL/LOAEL) values, from which the final COSMOS TTC dataset was developed. Criteria for study inclusion and NOAEL decisions were defined, and rigorous quality control was performed for study details and assignment of Cramer classes. From the final COSMOS TTC dataset, human exposure thresholds of 42 and 7.9 μg/kg-bw/day were derived for Cramer Classes I and III, respectively. The size of Cramer Class II was insufficient for derivation of a TTC value. The COSMOS TTC dataset was then federated with the dataset of Munro and colleagues, previously published in 1996, after updating the latter using the quality control processes for this project. This federated dataset expands the chemical space and provides more robust thresholds. The 966 substances in the federated database comprise 245, 49 and 672 chemicals in Cramer Classes I, II and III, respectively. The corresponding TTC values of 46, 6.2 and 2.3 μg/kg-bw/day are broadly similar to those of the original Munro dataset.

1. Introduction

The Threshold of Toxicological Concern (TTC) is a risk assessment approach that can be used to screen substances with few or no toxicological data for which human exposures are likely to be low. The TTC approach utilizes generic human exposure threshold values (TTC values) that have been derived from oral experimental data on cancer and non-cancer toxicity endpoints. If human exposure to a substance is below the relevant TTC value, it can be judged "with reasonable confidence, to present a low probability of a risk" (Munro et al., 1996). The work presented here was undertaken in order to underpin and facilitate the use of the TTC approach for substances found in cosmetics.

The TTC approach was inspired by, and can be considered an extension of, the Threshold Of Regulation (TOR) that was adopted by the US Food and Drug Administration (FDA) for substances used in food-contact articles (US FDA, 1993; 1995). The original TOR concept used a single threshold for all chemicals, based on the

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http://dx.doi.org/10.1016/j.fct.2017.08.043

Abbreviations

ADI	Acceptable Daily Intake
BMD	Benchmark Dose
BMDL	Benchmark Dose Lower 95% confidence limit
bw	body weight
CAS RN	Chemical Abstract Services Registry Number
CFSAN	Center for Food Safety and Nutrition
DB	Database
DFG	Deutsche Forschungsgemeinschaft
ECHA	European Chemicals Agency
EDTA	Ethylenediaminetetraacetate
EFSA	European Food Safety Authority
EINECS	European INventory of Existing Commercial Substances
EMA	European Medicines Agency
EMEA	European Agency for the Evaluation of Medicinal Products
EPA	Environmental Protection Agency
EU	European Union
FCN	Food Contact Notification
FDA	Food and Drug Administration
HNEL	Highest No-Effect Levels
INCI	International Nomenclature for Cosmetics Ingredients
IRIS	Integrated Risk Information System
JECFA	Joint FAO/WHO Expert Committee on Food Additives
LEL	Lowest Effect Level
LOAEL	Lowest-Observed-Adverse-Effect Level
LOEL	Lowest-Observed-Effect Level
MINIS	MINImum Study
MoS	Margin of Safety
NEL	No-Effect Levels
NOAEL	No-Observed-Adverse-Effect Level
NOEL	No-Observed-Effect Level
NTP	National Toxicology Program
oRepeaTox DB	Oral repeated-dose toxicity database
PAFA	Priority-based Assessment of Food Additives
POD	Point of departure
REACH	Registration, Evaluation, Authorisation and Restriction of Chemicals
RfD	Reference Dose
SCCS	Scientific Committee on Consumer Safety
SCENIHR	Scientific Committee on Emerging and Newly Identified Health Risks
SCHER	Scientific Committee on Health and Environmental Risks
SEURAT	Safety Evaluation Ultimately Replacing Animal Testing
TOR	Threshold Of Regulation
TTC	Threshold of Toxicological Concern
USA	United States of America
UVCB	substance of Unknown or Variable composition, Complex reaction products or Biological materials
WHO	World Health Organisation

conservative assumption that an untested chemical could pose a cancer risk, even though it was not intended to be used for chemicals with structural alerts or other reason for concern for genotoxicity. Tetra sodium ethylenediaminetetraacetate (EDTA) (Chemical Abstract Services Registry Number [CAS RN]: 64-02-8) was the first chemical to which TOR was applied in 1996 at US FDA Center for Food Safety and Nutrition (CFSAN).[2] It was subsequently expanded into the TTC concept to include non-cancer endpoints by Munro et al. (1996) and further elaborated by Kroes et al. (2004), who proposed the addition of another tier intended to be protective for DNA-reactive carcinogens.

The TTC approach was originally developed for substances present at low levels in the diet and consumed orally (Barlow, 2005) and was used by JECFA for evaluating flavouring substances. It was subsequently evaluated in detail for use in food safety by the European Food Safety Authority (EFSA) (EFSA, 2012). Improvement and expansion of the TTC approach were also discussed in an Expert Workshop convened by EFSA and the World Health Organisation (WHO) in 2014 (EFSA/WHO, 2016). Application of the TTC approach has also been proposed for, or extended to, the risk assessment of other types of substances. These include substances present in consumer products (Antignac et al., 2011; Blackburn et al., 2005; SCCS, SCHER and SCENIHR, 2012; SCCS NfG, 2016): micropollutants, drug residues, pesticide metabolites and other impurities in drinking water (Brüschweiler, 2010; EFSA, 2016; Houeto et al., 2012; Laabs et al., 2015; Melching-Kollmuß et al., 2010; Mons et al., 2013); genotoxic impurities in human pharmaceuticals (EMEA, 2006); herbal preparations (EMEA, 2008); homeopathic medicines (Buchholzer et al., 2014); and human pharmaceutical substances carried over in multiproduct manufacturing facilities (Bercu and Dolan, 2013; Stanard et al., 2015). It has also been used as a first-level screening tool to prioritize for review a large number of substances identified as needing an assessment under the Canadian Environmental Protection Act (Health Canada, 2016). Consideration has also been given to whether the TTC approach could be applied to human biomonitoring data (Becker et al., 2012) and to human exposures by non-oral routes (Carthew et al., 2009; Escher et al., 2010; Hennes, 2012; Kroes et al., 2007; Partosch et al., 2015).

The original reference dataset (Munro et al., 1996) consisted of 613 organic substances representing a “range of industrial chemicals, pharmaceuticals, food substances and environmental, agricultural and consumer chemicals likely to be encountered in commerce”. Although the intent was to cover a broad chemical domain, the dataset is now over 20 years old, and questions have been raised as to whether it is adequately representative of chemicals and structures used in contexts other than its original application in food (Dewhurst and Renwick, 2013). This issue was first raised in relation to cosmetics by Blackburn et al. (2005) and was an important consideration for the use of TTC for chemicals in cosmetics and consumer products in the opinion of the European Commission's non-food Scientific Committees (SCCS, SCHER and SCENIHR, 2012). The Scientific Committees stated that the TTC approach is scientifically acceptable, whilst noting some concerns, including that all risk assessment approaches have some degree of uncertainty, that many complex chemical structures are not adequately represented in currently available databases, and that there is limited knowledge of effects due to dermal and inhalational exposure routes that are more common for consumer products (SCCS, SCHER and SCENIHR, 2012).

Better understanding of the applicability of the TTC concept to substances present in cosmetic products would be particularly

[2] Information provided by Kirk Arvidson at the Office of Food Additive Safety of US FDA CFSAN https://www.accessdata.fda.gov/scripts/fdcc/index.cfm?set=TOR&id=1996-001.