

## Safety Assessment of Cosmetics in Europe

# **Current Problems in Dermatology**

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# Safety Assessment of Cosmetics in Europe

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## Current Problems in Dermatology



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## List of Abbreviations

3R	Refinement, reduction, replacement
3T3 NRU PT	3T3 Neutral Red Uptake Phototoxicity Test
A	Amount
ADI	Acceptable daily intake
AICS	Australian Inventory of Chemical Substances
Art.	Article
ASHP	American Society of Health-System Pharmacists
BCOP	Bovine corneal opacity and permeability
BMD	Benchmark dose
BMDL	BMD lower limit
bw	Body weight
C	Concentration
CAS nr	Chemical Abstracts Service registry number
CCRIS	Chemical Carcinogenesis Research Information System
CHRIS	Chemical Hazard Response Information System
CI	Colour index
CICAD	Concise International Chemical Assessment Document
CIR	Cosmetic ingredient review
CMR	Carcinogenic, mutagenic, toxic to reproduction
Colipa	European Cosmetic Toiletry and Perfumery Association
CoNTC	Concentration of no toxicological concern
CSNB	Chemical Safety NewsBase
CSTEE	Scientific Committee on Toxicity, Ecotoxicity and the Environment
CTFA	Cosmetic, Toiletry and Fragrance Association
CV	Curriculum vitae
DA	Dermal absorption

DA <sub>a</sub>	Dermal Absorption reported as amount/cm <sup>2</sup>
DA <sub>p</sub>	Dermal Absorption expressed as a percentage
DART	Developmental and Reproductive Toxicology Database
DG ENTR	Directorate-General Enterprise
DG ENV	Directorate-General Environment
DG SANCO	Directorate-General Health and Consumer Protection
Dir.	Directive
DNA	Deoxyribonucleic acid
Doc.	Document
DSL	Domestic Substances List (Canada)
EC	European Community
ECB	European Chemicals Bureau
ECETOC	European Centre for Ecotoxicology and Toxicology of Chemicals
EChA	European Chemicals Agency
ECL	Existing Chemicals List (Korea)
<i>ecopa</i>	European Consensus Platform on 3R Alternatives
ECVAM	European Centre for the Validation of Alternative Methods
EDETOX	Evaluations and predictions of dermal absorption of toxic chemicals
EEC	European Economic Community
EEMCO	European expert group for Efficacy Measurements of Cosmetics and Other topical products
EFSA	European Food Safety Authority
EHC	Environmental Health Criteria
EINECS	European Inventory of Existing Commercial Chemical Substances
ELINCS	European List of Notified Chemical Substances
EMBASE	Excerpta Medica database
EMEA	European Agency for the Evaluation of Medicinal Products
ENCS	Existing and New Chemical Substances (Japan)
EPA	Environmental Protection Agency (USA)
<i>epaa</i>	European Partnership for Alternative Approaches
ESAC	ECVAM Scientific Advisory Committee
EST	Embryotoxic Stem Cell Test
EU	European Union
F	Frequency of application
FDA	Food and Drug Administration
FDIS	Final Draft International Standard (ISO)
GLP	Good Laboratory Practice
GMP	Good Manufacturing Practice
GPSD	General Product Safety Directive
HERA	Human and Environmental Risk Assessment
HET-CAM	Hen's Egg Test-Chorio Allantoic Membrane

(H)PV	(High) production volume
HPVIS	High Production Volume Information System (USA)
HSDB	Hazardous Substances Data Bank
IARC	International Agency for Research on Cancer
ICCG	Inter-Committee Coordination Group
ICCVAM	Interagency Coordinating Committee on the Validation of Alternative Methods
ICE	Isolated chicken eye
IFRA	International Fragrance Research Association
IFSCC	International Federation of the Societies of Cosmetic Chemists
ILSI	International Life Sciences Institute
INCI	International Nomenclature of Cosmetic Ingredients
INCOS	Intergovernmental Information Network for Cosmetic Products
INN	International Non-Proprietary Name
IPA	International Pharmaceutical Abstracts
IPCS	International Programme on Chemical Safety
IRE	Isolated rabbit eye
IRIS	Integrated Risk Information System
ISO	International Organization for Standardization
IUCLID	International Uniform Chemical Information Database
IUPAC	International Union of Pure and Applied Chemistry
JaCVAM	Japanese Center for the Validation of Alternative Methods
JRC	Joint research centre
LD <sub>50</sub>	Lethal dose 50%
LED <sub>10</sub>	Lower limit on effective dose-10
LLNA	Local lymph node assay
LO(A)EL	Lowest observed (adverse) effect level
LVET	Low Volume Eye Test
MD	Medical doctor
MEST	Mouse Ear Swelling Test
(MK)GPMT	(Magnusson Kligman) Guinea Pig Maximisation Test
MM	Micromass
MoS	Margin of safety
MR	Mitotic recombination
MSDS	Material Safety Data Sheet
MSN	Microsoft Network
MTT	3-(4,5)-dimethyl-2-thiazolyl-2,5-dimethyl-2H-tetrazolium bromide
NDSL	Non-Domestic Substances List (Canada)
NICNAS	National Industrial Chemicals Notification and Assessment Scheme (Australia)
NIOSH	National Institute for Occupational Safety and Health (USA)
NLM	National Library of Medicine

NLP	No longer polymer
NO(A)EL	No observed (adverse) effect level
NRU	Neutral red uptake
NTP	National Toxicology Program (USA)
OECD	Organisation for Economic Co-operation and Development
OHMTADS	Oil and Hazardous Material, Technical Assistance Data Systems
OHS	Occupational health and safety
OSHA	Occupational Safety and Health Administration (USA)
PBT	Persistent, bioaccumulative and toxic
Ph. Eur.	European Pharmacopoeia
PI(R)(F)	Product information (requirement)(file)
P <sub>ow</sub>	n-Octanol/water partition coefficient
QSAR	Quantitative Structure-Activity Relationship
R	Retention factor
RAPEX	Rapid exchange of information
RBC	Red blood cell
REACH	Registration, Evaluation, Authorisation and Restriction of Chemicals
RIVM	RijksInstituut voor Volksgezondheid en Milieu
rLLNA	Reduced local lymph node assay
RTECS	Registry of Toxic Effects of Chemical Substances
SCCNFP	Scientific Committee on Cosmetic Products and Non-Food Products intended for consumers
SCCP	Scientific Committee on Consumer Products
SCE	Sister Chromatid Exchange
SCENIHR	Scientific Committee on Emerging and Newly Identified Health Risks
SCHER	Scientific Committee on Health and Environmental Risks
SD	Standard deviation
SED	Systemic exposure dosage
SHE	Syrian hamster embryo
SME	Small and medium-sized enterprise
SOP	Standard operating procedure
SPF	Sun protection factor
SSA	Skin surface area
STN	Scientific and Technical Network
TD <sub>50</sub>	Tolerated dose 50%
TER	Transcutaneous electrical resistance
TIF	Technical Information File
TOXLINE	Toxicology Literature Online
TSCA	Toxic Substances Control Act (USA)
TTC	Threshold of toxicological concern
UDS	Unscheduled DNA synthesis
UV	Ultraviolet

VIS	Visible light
vPvB	Very persistent and very bioaccumulative
WoE	Weight of evidence
WEC	Whole embryo culture
WHO	World Health Organisation



## Foreword

Many European citizens consider the European Commission in Brussels as very bureaucratic, making their lives with directives more complicated and putting national diversity in danger. They often do not realize that important initiatives for the consumer, safety and health have resulted from the work of European institutions. A paramount example is the field of cosmetics that is regulated by the Cosmetic Products Directive (76/768/EEC). This Directive defines what a cosmetic product is and what safety requirements have to be fulfilled to bring it onto the European market. The safety assessment of cosmetics as demanded by the Directive strives to protect the consumer on one side, while avoiding animal experiments on the other side. In this respect, stringent deadlines for animal testing have been implemented which will seriously affect the safety assessment process.

In putting the Directive into practice, the independent Scientific Committee on Consumer Products (SCCP) provides scientific advice to the Directorate-General of Health and Consumer Protection. This advice helps the Commission when preparing policy and proposals related to consumer safety and public health especially regarding cosmetics. In particular, the safety of cosmetic ingredients including UV filters, colorants, preservatives, and hair dyes are scientifically evaluated by the SCCP. This is a monumental review work of toxicological data performed by a group of scientists covering a wide field of experience and expertise and coming from several European countries. The work of the SCCP is documented in opinions that are freely accessible through the Internet. For many academics, regulatory bodies dealing with cosmetics and scientists from the cosmetics industry the EU regulatory framework and the process of the safety assessment of cosmetics are a great puzzle, difficult to put together. Therefore, a monograph explaining the ‘mechanics’ of the EU regulations in the field of cosmetics and their practical application was badly needed. The present book, written by Prof. Vera Rogiers and Dr. Marleen Pauwels from the Department of

Toxicology of the Vrije Universiteit Brussel fills this gap. Prof. Vera Rogiers has been an active member of the SCCP (previously called SCCNFP) for many years and is also leading a renowned research group on in vitro experimental toxicology intensively involved in the development of 3R-alternative methods. As such, she knows the EU activities on cosmetics and their ingredients from a close perspective. Together with Dr. Pauwels, she has been organizing in Brussels the course Safety Assessment of Cosmetics in the EU for more than a decade teaching cosmetic safety assessors from all over the world. Their extensive experience and knowledge are laid down in this book. It will be most useful to everyone interested in cosmetics and the protection of consumer health in Europe. Especially safety assessors will find the new information important for their daily work. I hope this excellent book will spread the message that high-quality work for consumer safety is done in Brussels from which so many people in Europe can benefit.

*Peter Elsner, Jena*

## Preface

The cosmetic world is often perceived as the land of luxury, in which science fails to play any part. This is, however, not justified since several aspects of the development of cosmetic products require significant scientific input. Multiple research groups are involved in the formulation of innovative cosmetic products in the quest for new galenic forms on the macro- or nano-scale and/or in the objective assessment of the efficacy of cosmetic products. In addition and most importantly, cosmetic products are not allowed to be placed on the market unless their safety for the consumer has been scientifically proven. Whereas the safety standards for cosmetic products vary between different parts of the globe, it is generally agreed upon that Europe has put in place a relatively stringent regulatory framework to ensure cosmetic safety, in which the development of validated alternative methods plays a key role. It is a real challenge for industry, academia and regulatory bodies to maintain, under these conditions, the standards for cosmetic safety high. This book, therefore, solely focuses on the challenging subject of safety assessment of cosmetics in the current European regulatory framework and does not cover the interesting topics of cosmetic product development and claim substantiation.

Cosmetic safety evaluation appears to be a complex process, which in first instance requires knowledge of the extensive web of Directives, Regulations and Recommendations intended to ensure the free movement and safe use of these products. Of most relevance is the Cosmetic Products Directive (76/768/EEC), laying down the principal rules for marketing and labelling cosmetic products in the EU. One of its major provisions is that every cosmetic product on the EU market is considered to be safe for use. In order to substantiate this, a specific set of technical data must be assembled and made readily accessible to the competent authorities of the EU Member States. This data set is more commonly referred to as a cosmetic product's technical information file or TIF. Within the context of this TIF (sometimes called PIR or product information requirement), a document needs to be provided in which

a qualified safety assessor declares the cosmetic product safe for use. The guidance on how to perform such a safety assessment is usually summarised as *'the manufacturer should take into consideration the general toxicological profile of the ingredients, their chemical structure and their level of exposure'*. As a positive answer to the need expressed by small and medium-sized enterprises for guidance on the compilation of cosmetic TIFs, a practical proposal for a structured standard format was developed in the year 2000 and refined over the years. The currently presented chapter on the subject is based upon 8 years of personal experience with constituting TIFs for cosmetic companies and upon interactions with competent authorities and industrial senior regulatory persons, expressing their views. To that respect, the yearly postgraduate courses of 'Safety Assessment of Cosmetics in the EU – Training Course', organised at the Vrije Universiteit Brussel by our Department under the wings of the Instituut voor Post-Academische vorming, were of high value.

The second and most debated feature of the EU cosmetic legislation is that since 1993, the European authorities have expressed their disapproval to the performance of animal experiments with cosmetic products and their ingredients. This resulted in the enforcement of a European animal testing ban on cosmetic ingredients from March 2009 on, accompanied by a gradual marketing ban for cosmetic ingredients tested on animals. As such, cosmetics are still considered to be inherently safe, but the tools that have enabled the scientific exercise of hazard and safety assessment of cosmetic ingredients to date, will be significantly restricted in the near future.

Indeed, animal tests have been used for more than 4 decades and most toxicologists have gained a certain level of confidence. However, urgent replacement by non-animal alternative methods is now legally required.

The positive side of this legislative evolution is that not only the efforts in scientific research and ethics, but also financial resources in the field of in vitro toxicology have significantly increased over the past couple of years. The inclusion of the development of alternatives in EU funding (5th, 6th and 7th Framework Programmes), the creation of the European Consensus Platform on 3R-Alternatives and the foundation of the European Partnership for Alternative Approaches, are only a couple of examples of collaboration between all parties involved.

A negative outcome of the cosmetic animal testing ban, however, is the initiation of a political movement which introduced drastic measures such as a complete abolition of animal testing, without taking into account the scientific feasibility of the timely development of alternatives to prove human safety.

Experience in the field of safety assessment of cosmetic ingredients has been built up, especially by safety assessors of finished cosmetic products all over Europe, and by the scientific experts of the Scientific Committee on Consumer Products or SCCP (formerly called Scientific Committee on Cosmetic products and Non-Food Products intended for consumers or SCCNFP). This European scientific committee assesses on a regular basis colourants, preservatives, UV filters, hair dyes and other specific ingredients for which suspicion of potential toxicity exists. Over time, the SCC(NF)P

has studied dossiers for more than 250 substances and the detailed opinions can be freely downloaded from the European Commission's web pages.

With the existing uncertainty around the future safety assessment of cosmetics, the idea emerged to translate the multitude of knowledge on cosmetic ingredients gathered through the discussions of the SCC(NF)P, into a carefully tailored searchable database. With the help of this database, in first instance, the typical content of a toxicological data set considered complete by the SCC(NF)P, is determined. Subsequently, the quality of the individual types of tests is assessed and the mostly encountered hurdles in the safety assessment of cosmetic ingredients at EU level are identified. Finally, the database enables further in-depth analysis of these newly identified problem areas, resulting in some findings useful for the safety assessor.

It must be emphasised, however, that the data availability for a cosmetic ingredient discussed by the SCC(NF)P does not apply for all cosmetic ingredients as they appear on the EU market in finished cosmetic products. For ingredients not studied by the SCC(NF)P, the available toxicological data packages usually are much more restricted and, unless additional tests are performed on a voluntary basis or through extra-EU requirements, their data availability largely depends on the requirements of other EU Directives. Therefore, a separate section is dedicated to the question which toxicological data sets are expected to be available for those cosmetic ingredients not studied by the SCC(NF)P. Relevant data-generating EU legislations are summarised and personal practical experience on how to perform effective quality searches on toxicity data for cosmetic ingredients, is shared. Subsequently the process to come to a proposal for risk assessments of finished products is briefly discussed.

The database with the information on 185 substances studied by the SCC(NF)P between 2000 and 2006 is used to illustrate the specific problems related to the foreseen abolition of animal testing for cosmetic ingredients in the field of cosmetic safety assessment.

For each toxicological endpoint, the current status of the development of validated alternatives is discussed, together with figures and side information out of the database illustrating how safety assessment of cosmetic ingredients was performed over the past years. It allows evaluation of the number of animals involved, of the rate at which alternatives are currently being used and it helps to identify or confirm earlier identified problem areas.

In summary, the goal of this issue is to provide guidance and scientific background to the manifold challenges industrial/governmental/academic cosmetic safety assessors are faced with today and in the near future.

A practical proposal and guidance for constituting a European TIF is made, including the indication of relevant pieces of EU legislation and a procedure to effectively find toxicological data on cosmetic ingredients in public and commercial databases. Also the process of finished cosmetic product safety assessment is discussed.

Above all, this book aims at demonstrating the usefulness of a newly created database on SCC(NF)P-studied cosmetic ingredients. Therefore the database's content and search

possibilities are used to identify and further analyze problem points in the safety assessment of cosmetic ingredients, and to estimate animal numbers and the extent to which 3R-alternative methods have found their way into European cosmetic ingredient dossiers.

Without having the ambition to overcome the deadlock of the concurrent animal testing ban and the 'safe for use' requirement in the cosmetic field, the results obtained through this database enable the formulation of a number of important conclusions with regard to the present and future safety assessment of cosmetic products and their ingredients in the EU.

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