The Science of Risk Assessment as it Applies to Cosmetic Products

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MASOT Webinar "Safety Assessment of Consumer Products"

OUTLINE

- Definition of Risk Assessment and Margin of Safety
- General process of conducting a safety evaluation for cosmetics
- Hazard identification
- Exposure Assessment
- Risk Characterization and Finished Product Assessment
- Examples

Risk Assessment

- The systematic scientific characterization of potential adverse health effects resulting from human exposure to hazardous agents

- Hazard identification: Determination of whether exposure to a chemical or ingredient is likely to cause a specific adverse health effect in humans (e.g. eye irritant; liver toxin)

- Dose-response assessment: Association between dose and the incidence of a defined biological effect in an exposed population (e.g. No-Observable-Adverse-Effect-Level or NOAEL)

- Exposure assessment: determine source, type, magnitude, duration of contact

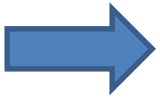
- Risk characterization: integrates Hazard identification, Dose-Response Assessment, and Exposure Assessment to determine…
    - the probability of an adverse effect to a human population by a toxic substance
    - permissible exposure levels from which standards of exposure are set
    - Margin of Safety

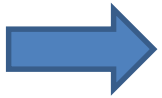
Margin of Safety (MoS)

- Ratio of the NOAEL to the estimated systemic exposure dose (SED)

$$MoS = \frac{NO(A)EL}{SED}$$

- Safety factors are considered
  - Species differences
  - Human variability
  - Differences between adults and children/babies





Safety Evaluation of Cosmetics

- Safety evaluation of cosmetic ingredients is based upon the principles of the risk assessment process typically applied for chemical substances

Federal Food, Drug, and Cosmetic Act (FD&C Act): The FD&C Act prohibits the marketing of adulterated or misbranded cosmetics in interstate commerce

EU Regulation 1223/2009 aims to protect human health, **reduce and regulate animal testing** and make information more available to consumers (introduced concept of product ingredient file)

Directive 76/768/EC (2013) is the primary European Union law on the safety of cosmetics; includes amendment concerning the **prohibition of animal testing for cosmetic products**

Safety Evaluation of Cosmetics

- In accordance with European regulations a product information file (PIF) must be created for each cosmetic product and made accessible to the competent authorities on demand

  - PIF must contain a safety assessment (Cosmetic Product Safety Report)

  - A safety assessment for a finished product considers
    - Toxicological profile of each substance in the finished product (includes Hazard Identification)
    - Chemical and physical specifications of the substances
    - Exposure level for each substance
    - The risk characterization for each substance obtained via the risk assessment process

Hazard Identification of Cosmetic Ingredients

- First step in overall safety evaluation of cosmetic products

- Traditionally published toxicological data considers same route of exposure intended for humans (e.g. oral ingestion, inhalation, dermal application)





- Minimum toxicological data required for assessing the safety of cosmetic ingredients
  - Acute toxicity: allows for estimation of severe acute toxic effects
  - Local toxicity: adverse effects on skin and eyes (irritation and/or sensitization)
  - Repeat dose toxicity: daily administration for a prolonged period of time (28-, 90- days, or longer) allowing for determination of NO(A)EL and target organs for toxicity
  - Genotoxicity: evaluates potential for gene mutations

Hazard Identification of Cosmetic Ingredients

- Additional toxicological data (if available) for assessing the safety of cosmetic ingredients
  - Dermal/percutaneous absorption: amount of substance expected to penetrate through skin into the body
  - Carcinogenicity data
  - Reproductive toxicity data
  - Toxicokinetics: time-dependent fate of a substance within the body (absorption, distribution, metabolism, excretion)
  - Photo-induced toxicity: toxicity induced from exposure to UV light

Alternative Approach to Hazard Identification of Cosmetic Ingredients

- If minimal, or no toxicological data is available for a cosmetic substance alternative methods of obtaining missing data may be available

  - Validated alternative non-animal methods: mainly for genotoxicity and local toxicity (including skin sensitization and phototoxicity)

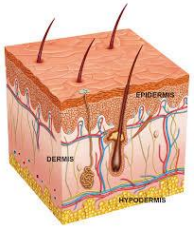


  - Read-across methodology: uses structure activity relationship technology to find structurally similar chemical substances from which available toxicity data may be applied

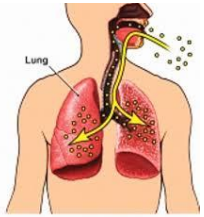
  - Threshold of Toxicological Concern (TTC): risk assessment tool intended to identify exposure levels below which no toxicity is expected to occur
    - Applicable for specific types of chemical classes
    - Applied only in situations of very low exposure

Chemical and Physical Specifications

- Physical and chemical properties of a substance can be used to predict certain toxicological properties
  - Certificate of analysis: provides full characterization of chemical
  - A small molecular weight (MW) hydrophobic molecule can more easily penetrate skin than a high MW hydrophilic compound

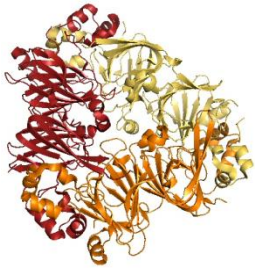


  - Highly volatile compounds can cause inhalation exposure when present in products applied to skin
  - Nano: consider inhalation exposure



  - Physical form (size, shape)

  - Characterization of Impurities or accompanying contaminants



  - Homogeneity and stability

Exposure Assessment

- The safety evaluation of a cosmetic product is also based on the way the cosmetic product will be used

- Many product types = many exposure scenarios
  - soaps, shampoos, conditioners
  - Mascara, eye liner, eye shadow
  - Lipstick, lip balm
  - Body lotions, creams
  - Sunscreens
  - Hair dyes













Exposure Assessment

- Every exposure scenario is linked to a certain amount of substance exposure
  - Ingestion
  - Inhalation
  - Absorption through skin or mucous membranes

- Many factors influence human systemic exposure
  - **Method** of application (rubbed on, spray, washed off)
  - **Concentration** of substance
  - **Quantity** of product applied
  - **Frequency** of application
  - **Duration** of contact
  - **Total area** of skin contact
  - **Site** of contact (mucous membrane, sunburned skin, is the skin intact?)
  - **Consumer target** group (children, people with sensitive skin)

Exposure Data

- Exposure can be translated into daily amount exposed per kg body weight from which a SED can be calculated
  - used in calculating the MoS through the process of conducting risk characterization

$$MoS = \frac{NO(A)EL}{SED\ (mg/kg\ bw)}$$

- Most human systemic exposure calculations rely on oral exposure toxicity data
  - Consider skin surface area
  - Retention factor (e.g. 10% retained on skin after use)
  - Skin penetration data

Exposure to Preservatives

- Global daily exposure value for a preservative can be estimated
- Worst-case scenario is assumed: consumer would use a set of cosmetics containing the same preservative
- Aggregate value of cosmetic use in adults is estimated to be **17.4 g/d or 269 mg/kg bw/day***

Type of Exposure	Product	g/d	mg/kg bw/d
Rinse-off skin & hair cleansing products	shower gel	0.190	2.79
	Hand wash soap	0.200	3.33
	Shampoo	0.110	1.51
	Hair conditioner	0.040	0.67
Leave-on skin &hair care products	Body lotion	7.820	123.2
	Face cream	1.540	24.14
	Hand cream	2.160	32.7
	Deo non-spray	1.500	22.08
	Hair styling	0.400	5.74
Make-up products	Liquid foundation	0.510	7.9
	Make-up remover	0.500	8.33
	Eye make-up	0.020	0.33
	Mascara	0.025	0.42
	Lipstick	0.060	0.9
	Eyeliner	0.005	0.08
Oral care cosmetics	Toothpaste	0.140	2.16
	Mouthwash	2.160	32.54
TOTAL		**17.4**	**269**

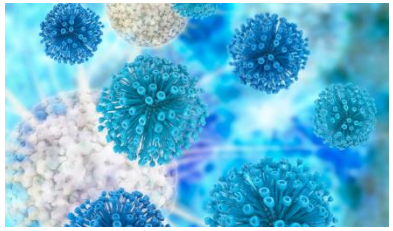
***SCCS/1564/15: The SCCS's Notes of Guidance for the testing of cosmetic ingredients and their safety evaluation - 9th Revision, adopted by the SCCS during the 11th plenary meeting of 29 September 2015**

Risk Characterization

- SED in humans is calculated taking into consideration the following factors
  - Toxicology data from Hazard Identification
  - NO(A)EL derived from published dose-response toxicity data (mg/kg/day)
  - Exposure data specific to the product being evaluated
  - Skin penetration data of the substance
  - Body Weight of average female adult (60 kg)
  - Calculation of MoS

Finished Product Safety Assessment

- Summarized in the PIF
  - The risk characterization data for each substance contained in the finished product
  - Any available human clinical data supporting the safety of the finished product
  - Stability
  - Microbiology



  - Safety attestation and a signed Cosmetic Product Safety Report

Example of Risk Assessment for Parabens

- **Proposed concentration of use in finished products: 0.4% (NOT APPROVED)**
- NOEL (subcutaneous, rat, 17 days): 2.0 mg/kg bw/day (propyl- and butyl parabens)
  - No clear NOAEL could be determined
- Assumptions:
  - Dermal absorption: 3.7% (butylparaben tested *in vitro* human skin; lipophilic)
  - Typical body weight: 60 kg (average adult female)
  - Cumulative exposure to preservatives: 17.4 g/day

$$\text{SED} = \frac{17400\ \text{mg/day} * 0.4\% * 3.7\%}{60\ \text{kg}} = 0.043\ \text{mg/kg bw/ day}$$

$$\text{MoS} = \frac{2.0\ \text{mg/kg bw/day}}{0.043\ \text{mg/kg bw/day}} = 46.5 < 100$$

- **APPROVED maximum concentration is 0.19%**

- Does not apply to isopropyl-, isobutyl-, phenyl-, benzylparaben, and pentylparaben as no, or only limited information is available for their safety evaluation

Example of Risk Assessment for Polymers

- **Proposed concentration of use for Polybutene in lip product: 15%**
- 10% monomers < 1000Da Molecular Weight (as per supplier specification)
- NOAEL (oral, dog, 2-year): 750 mg/kg bw/day (referenced: PCPC CIR)
- Assumptions:
  - 100% oral ingestion; Typical body weight: 60 kg (average adult female)
  - Monomers = butenes ($NOAEL_{isobutenes}$ = 148 mg/kg bw/day)

$$SED = \frac{57\text{mg/day (lips)} * 15\%\text{ polymer} * 100\%}{60\text{ kg}} = 0.1425\text{ mg/kg bw/day}$$

$$MoS = \frac{750\text{ mg/kg bw/day}}{0.1425\text{ mg/kg bw/day}} = 5263 > 100$$

$$SED = \frac{57\text{mg/day (lips)} * 15\%\text{ polymer} * 10\%\text{ monomers} * 100\%}{60\text{ kg}} = 0.01425\text{ mg/kg bw/day}$$

$$MoS = \frac{148\text{ mg/kg bw/day}}{0.01425\text{ mg/kg bw/day}} = 10385 > 100$$

- **APPROVED 15% in a lip product**

Example of Risk Assessment for Surfactant

- **Proposed concentration of use for Oleth-3 in hair wax product: 3.5%**
- 10ppm residual 1,4-dioxane (as per supplier specification)
- 1ppm residual ethylene oxide (as per supplier specification)
- NOAEL read across from Oleth-5 (oral, rat, 2-year): 50 mg/kg bw/day (referenced: Human and Environmental Risk Assessment database (HERA))
- Assumptions:

  10% retention factor; 10% dermal absorption; Typical body weight: 60 kg (average adult female)

$$\text{SED} = \frac{10000 \text{ mg/day (hairstyling)} * 3.5\% \text{ surfactant} * 10\% * 10\%}{60 \text{ kg}} = 0.0583 \text{ mg/kg bw/day}$$

$$\text{MoS} = \frac{50 \text{ mg/kg bw/day}}{0.0583 \text{ mg/kg bw/day}} = 857 > 100$$

$$\text{CEL}_{1,4\text{-dioxane}} = 10000 \text{ mg/day (hairstyling)} * 3.5\% \text{ surfactant} * 10\% * 10\text{ppm} = 0.35 \text{ ug/day}$$

0.35 ug/day < 30 ug/day (OEHHA Proposition 65 NSRL**)

$$\text{CEL}_{\text{ethylene oxide}} = 10000 \text{ mg/day (hairstyling)} * 3.5\% \text{ surfactant} * 10\% * 1\text{ppm} = 0.035 \text{ ug/day}$$

0.035 ug/day < 2 ug/day (OEHHA Proposition 65 NSRL**)

APPROVED 3.5% in a hairstyling product

**Office of Environmental Health Hazard Assessment (OEHHA) Proposition 65 Safe harbor levels, which include No Significant Risk Levels (NSRLs) for cancer-causing chemicals

Thank you!

Questions?