PRINCIPLES OF COSMETIC SAFETY ASSESSMENT

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OUTLINE

- ACTUAL COSMETIC LEGISLATIVE FRAMEWORK IN EU
- DIFFERENCE BETWEEN HAZARD AND RISK
- SAFETY EVALUATION OF COSMETICS
- ALTERNATIVE METHODS FOR HAZARD & RISK ASSESSMENT
- CONCLUSIONS
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ACTUAL COSMETIC LEGISLATIVE FRAMEWORK IN EU

ACCORDING TO:
COSMETICS REGULATION N° 1223/2009

- SAFE PRODUCT (art. 3)
- SAFETY IS BASED UPON SAFE INGREDIENTS (toxicological profile, chemical structure, exposure, art. 10)
- DEMONSTRATION OF SAFETY (art. 10 – 11)
- PROVIDING ADEQUATE INFORMATION

SAFETY EVALUATION IS MANDATORY FOR EVERY COSMETIC PRODUCT PLACED ON EU MARKET
IN THE EU TWO CHANNELS ARE FUNCTIONAL IN THE SAFETY EVALUATION PROCESS OF COSMETIC SUBSTANCES/MIXTURES

**COMMISSION**
- **SUBSTANCES ON ANNEXES**
  - II, III, IV, V, VI, ANNEXES
  - SCCS (under DG SANTE)
  - DG GROW
  - RISK MANAGEMENT
  - BY COMMISSION FOR CONSUMER PROTECTION

**INDUSTRY**
- **SUBSTANCES / MIXTURES IN FINISHED PRODUCT AND PRODUCT**
  - PIF: COSMETIC PRODUCT SAFETY REPORT A & B
  - SAFETY ASSESSOR
  - RESPONSIBLE PERSON
  - RISK MANAGEMENT
  - BY INDUSTRY FOR CONSUMER PROTECTION

**ACTUAL COSMETIC LEGISLATIVE FRAMEWORK IN EU**

**IN THE EU TWO CHANNELS ARE FUNCTIONAL IN THE SAFETY EVALUATION PROCESS OF COSMETIC SUBSTANCES/MIXTURES**

**COMMISSION**
- **SUBSTANCES ON ANNEXES**
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**ANNEXES**
- II: forbidden substances
- III: restricted substances
- IV: colorants
- V: preservatives
- VI: UV-filters

**SCCS**
- GROUP OF INDEPENDENT EXPERTS GIVING ADVICE
- COMPULSORY FOR ANNEX SUBSTANCES
- NOTES OF GUIDANCE
THE SCCSs NOTES OF GUIDANCE FOR THE TESTING OF COSMETIC INGREDIENTS FOR THEIR SAFETY EVALUATION
9th REVISION (SCCS/1564/15)

• Notes of Guidance available on website (NoG):
  http://ec.europa.eu/health/scientific_committees/consumer_safety/docs/sccs_o_190.pdf

• Opinions available on website:

ACTUAL COSMETIC LEGISLATIVE FRAMEWORK IN EU

IN THE EU TWO CHANNELS ARE FUNCTIONAL IN THE SAFETY EVALUATION PROCESS OF COSMETIC SUBSTANCES/MIXTURES

PIF = PRODUCT INFORMATION FILE

- UNIQUE DOSSIER PER PRODUCT WITH 2 PARTS: - SAFETY - EFFICACY
  - SAFETY PART IS CARRIED OUT BY SAFETY ASSESSOR (EU and non-EU)
  - DIPLOMA IN PHARMACY, TOXICOLOGY, DERMATOLOGY, MEDICINE OR SIMILAR
  - INDEPENDENCE & OBJECTIVITY
  - FINAL RESPONSIBILITY IS WITH RESPONSIBLE PERSON (EU)

SUBSTANCES/ MIXTURES IN FINISHED PRODUCT AND PRODUCT

PIF:

COSMETIC PRODUCT SAFETY REPORT A & B

SAFETY ASSESSOR

WRITTEN SAFETY EVALUATION (cosmetic product safety assessment)

RESPONSIBLE PERSON (EU)

RISK MANAGEMENT

BY INDUSTRY FOR CONSUMER PROTECTION

INDUSTRY
OUTLINE

ACTUAL COSMETIC LEGISLATIVE FRAMEWORK IN EU

DIFFERENCE BETWEEN HAZARD AND RISK

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DIFFERENCE BETWEEN HAZARD AND RISK

"Everything is a poison, nothing is without poison; Only the dose decides that something is not a poison."

Paracelsus
1493-1541

Still the most important principle in toxicology and safety assessment!
JUST A QUESTION OF TERMINOLOGY?

HAZARD:
- POTENTIAL TO CAUSE INJURY
- INTRINSIC PROPERTIES OF COMPOUND
- NO RELATION WITH DOSE OR EXPOSURE
  - Physicochemistry
  - Stability
  - Analytical data
  - (Q)SAR
  - Set of toxicological tests
DIFFERENCE BETWEEN HAZARD AND RISK

HAZARD: • POTENTIAL TO CAUSE INJURY
• INTRINSIC PROPERTIES OF COMPOUND
• NO RELATION WITH DOSE OR EXPOSURE

RISK: • CALCULATED PROBABILITY OF HARM
• RELATED TO EXPOSURE IN A SPECIFIC SITUATION
• IT CONCERNS YOU!

→ HAZARD ≠ RISK

OFTEN MISUNDERSTOOD BY CONSUMERS & MEDIA

A LION IS A DANGEROUS ANIMAL ...
DIFFERENCE BETWEEN HAZARD AND RISK

THE LION IS STILL A DANGEROUS ANIMAL … … BUT BEHIND BARS HE PRESENTS A LOW RISK

DIFFERENCE BETWEEN HAZARD AND RISK

POTENTIAL RISK OF A HAZARDOUS SUBSTANCE (CYANIDE)

- Cyanide locked away labelled
- Cyanide accessible labelled
- Cyanide in kitchen cupboard unlabelled
- Cyanide in your tea

THE RISK CHANGES ACCORDING TO THE SPECIFIC SITUATION
Potential Risk of a Non-Hazardous Substance (Water)

The risk changes according to the specific situation.

Hazard ≠ Risk
DIFFERENCE BETWEEN HAZARD AND RISK

OFTEN CONFUSION EXISTS BETWEEN
HAZARD AND RISK

→ CAN EVEN INFLUENCE LEGISLATIVE DEBATES!

EXAMPLE IN EUROPE

- TRACES OF ACRYLAMIDE MONOMER WERE FOUND IN COSMETICS
- ACRYLAMIDE MONOMER IS GENOTOXIC
  → HAZARD
- EMOTIONAL REACTION WAS: BAN ALL ACRYLAMIDE POLYMERS!
- IS THIS CORRECT? NO!

→ SCIENTIFIC QUESTIONS SHOULD BE:

- HOW MUCH MONOMER IS PRESENT IN COSMETICS?
- IS DERMAL ABSORPTION OCCURRING?
- WHAT IS THE SYSTEMIC EXPOSURE?
- WHAT IS THE CALCULATED RISK?
- IS THIS RISK ACCEPTABLE OR NEGLIGIBLE?

OUTLINE

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SAFETY EVALUATION OF COSMETICS

RISK ASSESSMENT PROCESS

1) HAZARD IDENTIFICATION → 2) DOSE-RESPONSE → 3) EXPOSURE ASSESSMENT

RISK CHARACTERISATION → RISK MANAGEMENT → RISK COMMUNICATION

→ SAFETY EVALUATION = RISK ASSESSMENT

→ FOR ALL TYPES OF SUBSTANCES THE SAME PRINCIPLES APPLY

- CAN X CAUSE ADVERSE HEALTH EFFECT?

- BASED ON:
  1) PHYSICO-CHEMICAL DATA
  2) QSAR (in silico studies)
  3) IN VITRO STUDIES
  4) IN VIVO STUDIES
  5) CLINICAL STUDIES
  6) EPIDEMIOLOGICAL STUDIES

INTRINSIC PROPERTIES
DETERMINATION OF INTRINSIC PROPERTIES OF COMPOUNDS:
- NOAEL values
- target organs
- nature of toxic effects

Derived from a set of hazard tests:
- Acute toxicity
  - Local toxicity
    ✓ Skin irritation
    ✓ Eye irritation
    ✓ Skin sensitization
    ✓ Phototoxicity
- Systemic toxicity
  ✓ Repeated dose toxicity
    ▪ Subacute (28d)
    ▪ Subchronic (90d)
    ▪ Chronic (85% of life)
  ✓ Reproductive toxicity
  ✓ Toxicokinetics
  ✓ Mutagenicity / genotoxicity
  ✓ Carcinogenicity

SAFETY EVALUATION OF COSMETICS

WHAT IS HAZARD IDENTIFICATION?

1) HAZARD IDENTIFICATION
2) DOSE-RESPONSE
3) EXPOSURE ASSESSMENT

NOAEL = No Observable Adverse Effect Level =
highest dose or exposure level where no adverse effect occurs
SAFETY EVALUATION OF COSMETICS

1) HAZARD IDENTIFICATION  2) DOSE-RESPONSE  3) EXPOSURE ASSESSMENT

RISK CHARACTERISATION

- WHAT IS AMOUNT, FREQUENCY AND TIME OF EXPOSURE?

SCCS: Scientific Committee on Consumer Safety

SAFETY EVALUATION OF COSMETICS

1) HAZARD IDENTIFICATION  2) DOSE-RESPONSE  3) EXPOSURE ASSESSMENT

RISK CHARACTERISATION

RISK MANAGEMENT

RISK COMMUNICATION

- WHAT IS THE PROBABILITY THAT HARM WILL BE PRODUCED?
- WHAT IS THE NATURE OF IT?
- IMPORTANCE OF VARIABILITY, UNCERTAINTY

LOOKING FOR A "SAFE DOSE" WITH NEGLIGIBLE OR ACCEPTABLE RISK
What is the probability that harm will be produced? Nature? Uncertainty?

MoS = NO(No Observable Adverse Effect Level)_{sys} \geq 100

When MoS ≥ 100, substance is considered to be safe.

SAFETY EVALUATION OF COSMETICS

1) HAZARD IDENTIFICATION
2) DOSE-RESPONSE
3) EXPOSURE ASSESSMENT

RISK CHARACTERISATION

RISK MANAGEMENT

RISK COMMUNICATION

Once a risk is known and characterised, actions are taken:
- on a voluntary basis
- prescribed by law

REDUCTION OF RISK TO ACCEPTABLE LEVEL
SAFETY EVALUATION OF COSMETICS

1) HAZARD IDENTIFICATION  2) DOSE-RESPONSE  3) EXPOSURE ASSESSMENT

Risk Characterisation

Risk Management

Risk Communication

Providing relevant information to consumer

Use of product by consumer in a safe way

SAFETY EVALUATION OF COSMETICS

Safety evaluation of cosmetics determines whether the products, under normal conditions of use, are safe for the general population

Safety evaluation is carried out prior to marketing, on the basis of all available safety information. It is a predictive exercise

It is also a “living” exercise when new relevant data becomes available, safety evaluation needs updating

Real life experience from the market is an important feed-back loop into safety evaluation cosmetovigilance!
WHAT TYPES OF RISKS WOULD A SAFETY ASSESSOR BE WORRIED ABOUT?

→ Immediate, acute damage at the site of application (local toxicity):
  skin irritation,
  eye irritation,
  skin sensitisation,
  phototoxicity (sunscreens)

→ Microbiological contamination:
  bacteria,
  moulds,
  fungi

→ Damage from long term exposure / damage that goes beyond the site of application (systemic toxicity):
  systemic effects, organ toxicity
  mutagenicity / genotoxicity/carcinogenicity
  reproductive toxicity

SOURCES OF RISK IN COSMETIC PRODUCTS

→ Use of unsuitable ingredients
  e.g. use of an unsafe substance, use of a safe substance under unsafe conditions
  Example: mercury as skin whitener; preservative at 10x of approved concentration
  → Risk can be high

→ Inadequate microbial quality management
  e.g. contamination with pathological germs such as Staphylococcus aureus, Pseudomonas aeruginosa, ...
  → Risk can be high
SAFETY EVALUATION OF COSMETICS

**SOURCES OF RISK IN COSMETIC PRODUCTS**

→ Presence of traces of banned substances
  e.g. traces of lead in lipstick; formaldehyde in shampoo
  → Actual risk is limited (low exposure !)

→ Unwanted interactions between ingredients
  e.g. pH change, precipitation of substances, ...
  → Unwanted interactions are usually detected through change of product properties
    (smell, texture, colour, ...)
  → Not a frequently occurring risk

SAFETY EVALUATION OF COSMETICS

**SOME IMPORTANT CONSIDERATIONS**

→ A COSMETIC PRODUCT IS A MIXTURE OF CHEMICALS (= ingredients)

→ ITS SAFETY IS LARGELY BASED ON THE SAFETY OF THE INGREDIENTS

→ BUT IT NEEDS TO BE COMPLEMENTED BY CONFIRMATORY INFORMATION ON THE FINISHED FORMULATION (TYPICALLY WITH REGARD TO ACUTE AND LOCAL EFFECTS)

→ THERE IS NO DIFFERENCE IN SAFETY EVALUATION BETWEEN SYNTHETIC AND NATURAL SUBSTANCES

SAFETY EVALUATION OF COSMETICS

WHAT IS CONTENT OF A COSMETIC SAFETY EVALUATION?

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ALTERNATIVE METHODS FOR HAZARD & RISK ASSESSMENT

DIRECTIVE 2010/63/EU ON THE PROTECTION OF ANIMALS USED FOR SCIENTIFIC PURPOSES

3R PRINCIPLE

Replacement

Reduction

COSMETIC REGULATION N° 1223/2009 CONTAINS TESTING AND MARKETING BANS

FOR COSMETICS ONLY VALIDATED REPLACEMENT METHODS MAY BE USED

ALTERNATIVE METHODS FOR HAZARD & RISK ASSESSMENT

What are validated methods ?

✓ VALIDATED

- RELEVANCE
- REPRODUCIBILITY
- PREDICTION MODEL
- APPLICATION DOMAIN

✓ OECD GUIDELINES

✓ EU LEGISLATION REGULATION 440/2008/EC

✓ IATA = Integrated Approach on Testing and Assessment

⇒ Alternative methods endorsed by EU RL ECVAM, ICCVAM and OECD

VALIDATION PROCESS AND ENTIRE LIFE CYCLE OF ALTERNATIVE METHODS IS FOLLOWED UP BY EU RL ECVAM*

* European Union Reference Laboratory for Alternatives to animal testing
VALIDATED REPLACEMENT TESTS EXIST IN PARTICULAR FOR HAZARD ASSESSMENT OF LOCAL TOXICITY NOT YET FOR SYSTEMIC TOXICITY AND QUANTITATIVE RISK ASSESSMENT

REPLACEMENT METHODS FOR LOCAL TOXICITY

SKIN CORROSIVITY:
- Transcutaneous Electrical Resistance (TER) test
- Corrositex®
- EpiSkin SM™
- EpiDerm SIT™
- SkinEthic RHE™
- epiCS®

Reconstructed human epidermis (RHE) tests

SKIN IRRITATION:
- EpiSkin SM™
- EpiDerm SIT™
- SkinEthic™ RHE

Reconstructed human epidermis (RHE) tests

* Corrositex not taken up in EU list, used in USA
REPLACEMENT METHODS FOR LOCAL TOXICITY

**EYE IRRITATION:**
- Bovine Cornea Opacity Permeability (BCOP) test*
- Isolated Chicken Eye (ICE) test*
- Isolated Rabbit Eye (IRE) test
- Hen’s Egg Test-Chorio-Allantoic Membrane (HET-CAM) test
- Fluorescein Leakage Test (FLT)*
- Cytosensor Microphysiometer (CM)
- Short Time Exposure (STE) test method*
- EpiOcular™ test (EIT: human reconstructed tissue model)*

**PHOTOTOXICITY:**
- Neutral Red Uptake Toxicity (3T3NRUPT) test*

SERIOUS DAMAGE/EYE IRRITATION

**SKIN SENSITISATION:**
- Direct Peptide Reactivity Assay (DPRA)*
- KeratinoSens*
- Human Cell line Activation Test (hCLAT)*

These test fit in an AOP (Adverse Outcome Pathway) approach

**TYPICAL EXAMPLE:** ELUCIDATION OF SENSITISATION AND TEST DEVELOPMENT FOR EVERY STEP

- electrophilic reactivity
- covalent interaction with proteins
- expression of cell surface markers and cytokines
- proliferation of memory T-cells in lymph nodes
- dermal inflammation after challenge

**BUILDING BLOCKS → IDEALLY: SPECIFIC IN VITRO TEST FOR EACH BUILDING BLOCK**

SEVERAL OTHER TESTS FOR AOP SENSITISATION AVAILABLE (OECD WEBSITE)

* Adopted OECD test guidelines
ALTERNATIVE METHODS FOR HAZARD & RISK ASSESSMENT

REPLACEMENT METHODS FOR SYSTEMIC TOXICITY

✓ **DERMAL ABSORPTION:**
  - Franz-cell with human/pig split-thickness skin

✓ **MUTAGENICITY/GENOTOXICITY:**
  - Bacterial reverse mutation test
  - *In vitro* micronucleus test

✓ **CARCINOGENICITY:**
  - Cell transformation Assay (CTA) Limited application!!

✓ **EMBRYOTOXICITY:**
  - Whole Embryo Culture (WEC)
  - Micromass test (MM)
  - Embryotoxic Stem Cell Test (EST)

✓ **ENDOCRINE DISRUPTION:**
  - Estrogenic receptor-α, agonist & antagonist protocols
  - Androgen receptor agonist & antagonist protocols
  - BG1Luc Estrogen Receptor Transactivation Assay (BG1LucERTA)
  - Human Recombinant Estrogen Receptor (hrER) *in vitro* assay

LIMITED!!

CURRENTLY LACKING VALIDATED REPLACEMENT TESTS

★ **ACUTE TOXICITY** (oral, dermal, inhalation)

★ **SUBACUTE TOXICITY**

★ **SUBCHRONIC TOXICITY**

★ **CHRONIC TOXICITY**

★ **REPRODUCTION TOXICITY**

★ **CARCINOGENICITY** (non-genotoxic compounds)

★ **BIOKINETICS (ADME)**

NEEDED FOR RETRIEVING NOAEL-VALUES
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CONCLUSIONS

1) RISK IS THE PRODUCT OF HAZARD AND EXPOSURE
2) RISK ASSESSMENT = SAFETY EVALUATION IS A SCIENCE-BASED PROCESS
3) SAFETY EVALUATION OF COSMETICS IS FOCUSED ON EXPOSURE TO SAFE INGREDIENTS
4) THE OBJECTIVE IS TO DETERMINE WHETHER THE PRODUCT IS SAFE UNDER NORMAL USE CONDITIONS
5) TYPICAL RISKS ARE LOCAL EFFECTS AND MICROBIOLOGICAL CONTAMINATION. SYSTEMIC EFFECTS ARE RARE, BUT NEED TO BE CONSIDERED IN THE EVALUATION
CONCLUSIONS

6) A COSMETIC SAFETY EVALUATION IS A LIVING DOCUMENT THAT NEEDS TO BE UPDATED BASED ON REAL-LIFE EXPERIENCE AND NEW DATA

7) A STRUCTURED APPROACH SHOULD BE FOLLOWED TO ENSURE A COMPLETE AND JUSTIFIED SAFETY EVALUATION

8) VALIDATED ALTERNATIVE METHODS ARE AN IMPORTANT SOURCE OF SAFETY INFORMATION

✓ LOCAL TOXICITY:
- Hazard assessment covered for skin and eye irritation, phototoxicity and skin sensitisation

✓ SYSTEMIC TOXICITY:
- In vivo tests still needed to retrieve NOAEL-values

CONCLUSIONS

AN OVERVIEW OF ALL VALIDATED 3R-ALTERNATIVES IS PRESENT IN:

- SCCS Notes of guidance for the testing of cosmetic ingredients for their safety evaluation, 9th revision, SCCS/1564/15

- EURLECVAM status report on the development, validation and regulatory acceptance of alternative methods and approaches (2016), on EURLECVAM website
  http://publications.jrc.ec.europa.eu/repository/handle/JRC103522
REGISTRATIONS ARE OPEN

Safety Assessment of Cosmetics in the EU
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Thank you for your attention!

Questions?