SAFETY ASSESSMENT OF COSMETICS AND THEIR INGREDIENTS IN THE EU

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CONTENTS

- ACTUAL EU COSMETIC LEGISLATION
- SAFETY ASSESSMENT OF COSMETIC INGREDIENTS
- AVAILABILITY OF VALIDATED ALTERNATIVE METHODS
- SAFETY ASSESSMENT OF FINISHED PRODUCTS
- CONCLUSIONS
COUNCIL DIRECTIVE
76/768/EEC

11/7/2013

COSMETICS REGULATION / RECAST
N° 1223/2009

SAME BASIC PRINCIPLES APPLY

TESTING & MARKETING BANS
ARTICLES & ANNEXES

RESPONSIBILITY OF COMPANY

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

AUTHORITIES
Notification (CPNP)
(art. 13)

CONSUMER
Safe use
(art. 19-21)
TWO CHANNELS ARE FUNCTIONAL IN THE SAFETY ASSESSMENT PROCESS

**COMMISSION**

- SUBSTANCES ON ANNEXES
  - II, III, IV, V, VI
  - SCCS
    - WRITTEN SAFETY EVALUATION *(opinion)*
    - DG SANCO
      - RISK MANAGEMENT
        - BY COMMISSION FOR CONSUMER PROTECTION

**INDUSTRY**

- ALL SUBSTANCES/MIXTURES IN FINISHED PRODUCT
  - PIF: COSMETIC SAFETY REPORT A & B
  - SAFETY ASSESSOR
    - RESPONSIBLE PERSON
    - RISK MANAGEMENT
      - INDUSTRIAL MEASURES FOR CONSUMER PROTECTION

*KimyaKongreleri.org*

AT THE COMMISSION LEVEL: SCCS

EVALUATION OF SUBSTANCES WITH CONCERN FOR HUMAN HEALTH

- ANNEX II: FORBIDDEN
- ANNEX III: RESTRICTED
+ ANNEX IV: COLORANTS
+ ANNEX V: PRESERVATIVES
+ ANNEX VI: UV-FILTERS

ACCORDING TO NOTES OF GUIDANCE (NoG) 8th REVISION (SCCS/1501/12) ON EU WEBSITE
http://ec.europa.eu/health/scientific_committees/consumer_safety/statements/index_en.htm

AT THE INDUSTRIAL LEVEL

EVALUATION OF ALL INGREDIENTS

BOTH APPLY THE SAME PRINCIPLES OF RISK ASSESSMENT.
1) HAZARD IDENTIFICATION
2) DOSE-RESPONSE
3) EXPOSURE ASSESSMENT

RISK CHARACTERISATION

RISK MANAGEMENT

RISK COMMUNICATION

BOTH CHANNELS USE SAME SAFETY EVALUATION STRATEGY
1) HAZARD IDENTIFICATION
2) DOSE-RESPONSE
3) EXPOSURE ASSESSMENT

RISK CHARACTERISATION

- CAN X CAUSE ADVERSE HEALTH EFFECT?
- BASED ON:
  - EPIDEMIOLOGICAL STUDIES
  - CLINICAL STUDIES
  - IN VIVO STUDIES
  - IN VITRO STUDIES
  - IN SILICO (QSAR)
  - IN CHEMICO (PHYSICOCHEMISTRY, STABILITY)
  - SCIENTIFIC LITERATURE

HAZARD:
INTRINSIC PROPERTIES
OF SUBSTANCES
Traditionally, hazard tests are based on use of animals.

In EU, clear wish of all stakeholders to implement 3Rs strategy, consisting of refinement, reduction and replacement.

Whenever possible results of in vitro replacement tests are given to guarantee safety of cosmetics in Europe. These must be validated.
HAZARD IDENTIFICATION TESTS MOSTLY AVAILABLE

- **PHYSICO-CHEMICAL CHARACTERISATION**: emphasis for ingredients on:
  - purity
  - solubility
  - partition coefficient (log Pow)
  - stability in solution

  \[(in \ chimico\ tests)\]

- **ACUTE TOXICITY**: oral rat \((in\ vivo)\) test; mostly for classification

- **LOCAL TOXICITY**:
  - Irritation and corrosivity
    - Skin irritation: non-irritative at maximal use concentration \((in\ vitro\ tests)\)
    - Eye/mucosa irritation: non-irritative at maximal use concentration \((in\ vitro \ screening\ tests; \ in\ vivo)\)
  - **Skin sensitisation**:
    - Sensitisation not excluded; preferably non-sensitising
    - LLNA: \(in\ vivo\) test
SAFETY ASSESSMENT OF COSMETIC INGREDIENTS

HAZARD IDENTIFICATION TESTS MOSTLY AVAILABLE

SYSTEMIC TOXICITY

- **Dermal absorption**: *(in vitro test)*
  Dermatomed pig or human skin

- **Repeated dose toxicity**: *(in vivo test)*
  90- day oral study in rat

- **Mutagenicity/genotoxicity tests** *(in vitro tests)*
  3 endpoints of genotoxicity
  - gene mutation
  - structural aberrations (clastogens)
  - aneuploidy (aneugens)

  when ➕ → overruled by ￮ *in vivo* test

- **Carcinogenicity**: *(in vivo test)*

- **Reproductive toxicity**: *(in vivo test)*
  - maternal toxicity
  - mostly : teratogenicity
1) HAZARD IDENTIFICATION

2) DOSE-RESPONSE

3) EXPOSURE ASSESSMENT

RISK CHARACTERISATION

- WHAT IS RELATIONSHIP BETWEEN DOSE AND INCIDENCE / SEVERITY OF ADVERSE HEALTH EFFECT?

- NOAEL ! (= No Observable Adverse Effect Level = the highest dose or exposure level within a specific system where no adverse treatment-related findings are observed)

- NOAEL taken from:
  → 90-DAY ORAL REPEATED DOSE TOXICITY STUDY
  → REPRODUCTIVE TOXICITY STUDY
  (MATERNAL TOXICITY, MOSTLY TERATOGENICITY)

- Use existing in vivo data (also of analogues; read across)
- Use data generated for other legislative purposes (REACH !)
- New cosmetic ingredients 😞😞 → PROBLEM!
SAFETY ASSESSMENT OF COSMETIC INGREDIENTS

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

RISK CHARACTERISATION

WHAT IS AMOUNT AND TIME OF EXPOSURE?
- EXPOSURE DATA IN NoG SCCS/1501/12

EXPOSURE ASSESSMENT

- Type and size of exposed population
- Stage of development
- Route of exposure
- Body surface location
- Frequency of use
- Interferences within product
- Percutaneous absorption
- Duration of contact
- Excessive use pattern
- Quantity applied
- Concentration in product
- Rinse-off - leave-on
- Type of product
- Frequency of use
- Body surface location
- Route of exposure
- Stage of development
- Type and size of exposed population
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SAFETY ASSESSMENT OF COSMETIC INGREDIENTS
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1) HAZARD IDENTIFICATION
2) DOSE-RESPONSE
3) EXPOSURE ASSESSMENT

RISK CHARACTERISATION

What is the probability that harm will be produced? Nature? Uncertainty?

MoS = NOAEL / SED ≥ 100

MoS: Margin of Safety
SED: Systemic Exposure Dosage
NOAEL: No Observable Adverse Effect Level

Inter-species kinetics 4.0
Inter-species dynamics 2.5
Variability human kinetics 3.2
Variability human dynamics 3.2

10 10
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WHAT IS A VALIDATED METHOD?

METHOD MUST BE

- RELEVANT
- REPRODUCTIBLE
  (intra-, inter-laboratory, transferability)
- PREDICTION MODEL MUST BE AVAILABLE

EURL-ECVAM

WITH EURL-NETVAL, ICATM, ESTAF, PARERE and ITS SCIENTIFIC COMMITTEE

ESAC

IN EU REGULATION 440/2008/EC

EC number

OECD

OECD GUIDELINES
WHAT VALIDATED 3R-ALTERNATIVES DO WE ACTUALLY HAVE?

- **ACUTE ORAL (INHALATION) TOXICITY**
  - Fixed dose
    - Acute toxic class
    - Up-and-down
  - dermal in progress

- **SKIN CORROSIVITY**
  - TER, EPISKIN™, EpiDerm™, Skin Ethic™, EST-1000™

- **SKIN IRRITATION**
  - EPISKIN™, modified EpiDerm™, Skin Ethic™ RHE

- **SKIN SENSITISATION**
  - LLNA also reduced and non-radioactive LLNA
  - KERATINOSENS, DPRA, hCLAT, (MUSST)

- **EYE IRRITATION**
  - Screening tests for strong irritants (BCOP, ICE)

- **PHOTOTOXICITY**
  - 3T3 NRU PT

- **DERMAL ABSORPTION**
  - *In vitro* (human / pig)

- **MUTAGENICITY/GENOTOXICITY**
  - Ames
    - *In vitro* mammalian cell mutation
    - *In vitro* micronucleus
    - *In vitro* mammalian chromosome aberration

- **CARCINOGENICITY**
  - CTA

- **EMBRYOTOXICITY**
  - WEC, MM, EST

⇒ ADDRESSING HAZARD IDENTIFICATION IN PARTICULAR FOR ACUTE AND LOCAL TOXICITY
### What Validated Replacement Alternatives Do We Actually Have?

<table>
<thead>
<tr>
<th>Category</th>
<th>Methods</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Acute Oral (Inhalation) Toxicity</strong></td>
<td>Fixed dose, Acute toxic class, Up-and-down, dermal in progress</td>
</tr>
<tr>
<td><strong>Skin Corrosivity</strong></td>
<td>TER, EPISKIN™, EpiDerm™, Skin Ethic™, EST-1000™</td>
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<td><strong>Skin Irritation</strong></td>
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<td><strong>Skin Sensitisation</strong></td>
<td>KERATINOSENS, DPRA: protein activation, hCLAT, (MUSST): dendritic cell activation</td>
</tr>
<tr>
<td><strong>Eye Irritation</strong></td>
<td>Screening tests for strong irritants (BCOP, ICE)</td>
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<tr>
<td><strong>Phototoxicity</strong></td>
<td>3T3 NRU PT</td>
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<tr>
<td><strong>Dermal Absorption</strong></td>
<td><em>In vitro</em> (human / pig)</td>
</tr>
<tr>
<td><strong>Carcinogenicity</strong></td>
<td>CTA: LIMITED</td>
</tr>
<tr>
<td><strong>Embryotoxicity</strong></td>
<td>WEC, MM, EST: LIMITED</td>
</tr>
</tbody>
</table>

**Addressing Hazard Identification in particular for Acute and Local Toxicity**
WHICH REPLACEMENT VALIDATED ALTERNATIVES ARE LACKING (⊙) ?

⊙ Acute toxicity
⊙ Eye irritation (partly)
⊙ Subacute and subchronic toxicity
⊙ Chronic toxicity
⊙ Reproduction toxicity
⊙ Target organ and systemic toxicity
⊙ (Non-genotoxic) carcinogenicity
⊙ Biokinetics

⇒ LACK OF ALTERNATIVES FOR SYSTEMIC AND LONG-TERM TOXICITY TESTING !!

⇒ PROBLEM FOR QUANTITATIVE RISK CHARACTERISATION, IN PARTICULAR FOR COSMETICS CONTAINING NEW INGREDIENTS (testing & marketing ban) !!
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SAFETY ASSESSMENT OF FINISHED PRODUCTS

**ALL INGREDIENTS**
- Evaluation of local toxicity
- MOS calculation for systemic toxicity whenever possible (at least for active ingredients)

**FINISHED PRODUCT**
- Evaluation of local toxicity of finished product
- *In chimico, in silico and in vitro* tests (validated or not) compared to benchmarks
- When SAFE, *in vivo* skin compatibility testing on human volunteers using non-invasive bioengineering methods ..........ETHICS !
- Incorporation, if necessary, of extra safety factor(s)

WoE APPROACH
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CONCLUSIONS

★ COSMETICS IN THE EU ARE SAFE !!!
UNTIL NOW EVALUATION STILL MOSTLY BASED ON EXISTING IN VIVO DATA

★ ALTERNATIVES ARE BEING DEVELOPED AND VALIDATED AND TAKEN UP IN COSMETIC SAFETY EVALUATIONS AS THEY BECOME AVAILABLE

★ EXISTING VALIDATED ALTERNATIVES ADDRESS IN PARTICULAR ACUTE AND LOCAL TOXICITY, NOT SYSTEMIC AND LONG-TERM TOXICITY TESTING

DATA GENERATED FOR OTHER LEGISLATIONS NEED TO BE USED: REACH!
COMMISSION PROVIDED PRACTICAL INTERPRETATION OF ART 18 (13/SANCO/COS/COSCOM/19)
Thank you for your attention!

Questions?