How Chemicals are Determined to be “Safe”

The “Safe” Beauty E-Summit
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Why Care About Cosmetic Ingredient Safety?

- Formulators ask: “Why does Product Safety want so much information?”

- Brand Management asks: “Why are we spending so much time and money on reformulations?”

Why Care About Cosmetic Ingredient Safety?

- We all want our cosmetic products to be safe – few adverse reaction complaints, high consumer preference.
- In most cosmetic products (except permanent hair dyes) the ingredients ***do not*** chemically react with each other.
- Therefore, the Safety Profile of Product is based on Safety Profiles of ***all*** the chemicals (ingredients) that you add.

$$\frac{100}{\text{ATEmix}} = \sum_{n} \frac{C_i}{\text{ATE}_i}$$

- Many laws relate to chemical safety

Presentation Overview:

- Regulatory Background
- Hazard vs. Risk
- Risk Assessment
  - What's in the Bottle? What are the Ingredients' characteristics?
  - How Will the Product be Used?
  - Where to Find Information?
- Summary

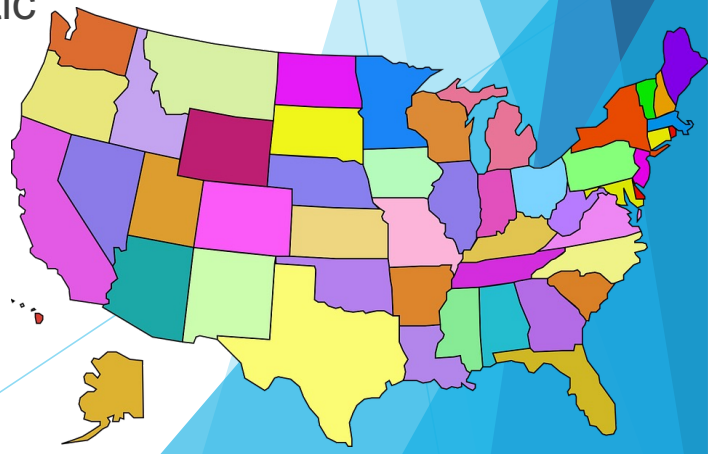
- Focus on the USA
  - Additionally on EU and Canada
  - Will not discuss environmental or packaging safety

Regulatory Background

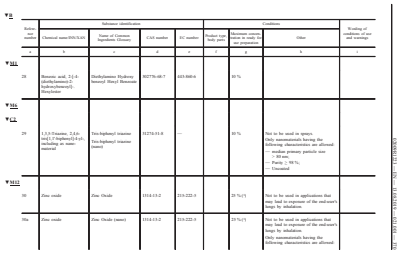
Cosmetic products: Brand owners have responsibility for the safety of their products in normal and expected use (US, Canada &EU).

Laws that Affect Ingredients (USA)

- Federal:
  - FD&C Act (1938) No adulterated products
    - Few specifically banned or restricted chemicals
    - Regulations on BSE / TSE, Color Additives, Microbeads
  - TSCA / Frank Lautenberg Act – Do not apply to cosmetic ingredients
- State / Local:
  - California Proposition 65
  - NY State – 1,4 Dioxane limits
  - Children's products safety: examples: MN and WA



Regulatory Background - II



Over 370 pages

EU

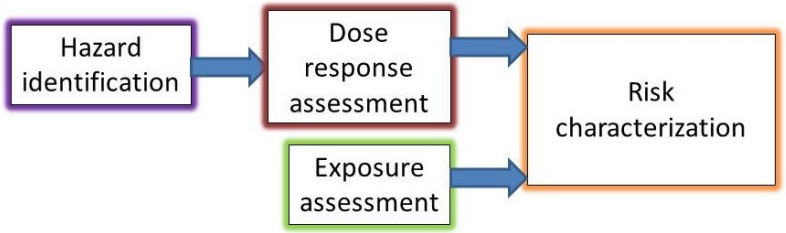
- Chemical Law: REACH
  - Environmental and human safety
    - Cyclomethicones, Microplastics, Fragrance ingredients
- Cosmetic Regulations (EC 1223 / 2009)
  - Annex II: Prohibited, Annex III: Restricted, IV, V-----Annex VI: Sunscreens

Canada

- Food and Drugs Act (revised 1985) and regulations .
  - Similar definition of “Adulterated” as USA.
  - Cosmetic Ingredients: Hot List - ingredients that are banned or restricted

Two Approaches to Cosmetic Ingredient Safety

	Hazard Avoidance	• Risk Assessment
What is it?	If a chemical is toxic, then it should not be used	Chemical's adverse effects are dependent on: • Concentration (Dose / Response) • How it is used • On whom it is used
Ease of Communication	Easy to Explain	More difficult to explain, especially to a large audience
Impact on Ingredient Palette	Many useful chemicals are excluded.	More functional chemicals can be used at lower levels and with appropriate safeguards.



Adapted from National Academy of Sciences, 1983

Hazard Avoidance versus Risk Assessment

Hazard Avoidance

Assessing and Managing Risk

Risk Assessment:

Safety of a product is dependent on:

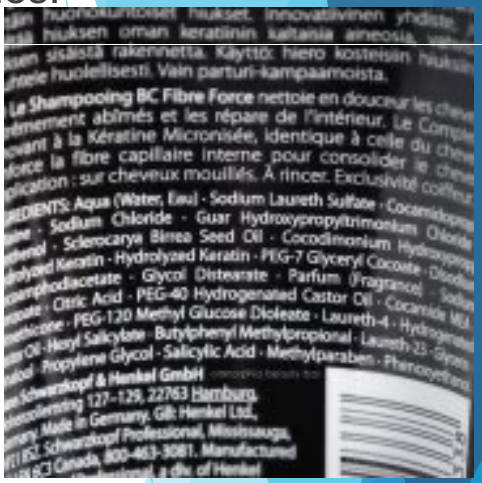
- What is in the bottle? *(All chemicals: main and minor)*
- How the product / ingredients are used?
- Who uses it?

How much is used?
Data is published for US and EU

What is in the Bottle?

Many Raw Materials (RMs) consist of several chemicals (ingredients). Includes:

- Primary ingredient(s)
- Minor functional ingredients e.g., preservatives, fragrances, anti-oxidants
- Non-functional ingredients e.g., contaminants



Can depend on manufacturer.

- Example: Cocamidopropyl Betaine (CAP Betaine)

Primary Ingredient(s)	CAP Betaine (30 – 46%), Water (qs)
Minor Functional Ingredients	Preservatives: Sodium benzoate, DMDM Hydantoin, None
Non-functional Ingredients	Sodium Chloride (≤6%), Glycerin (0? – 3%) *Amidoamine (up to 1%), DMAPA* *Dichloroaceteic acid (DCA), Formaldehyde, Methanol*

Potential Sensitizers

California Proposition 65

Human Toxicity End-Points

Multiple endpoints that vary in their seriousness!

- Acute toxicity (Oral / dermal)
- Sensory Irritation
- Skin Irritation (and Photo-irritation)
- Skin Sensitization (and Photosensitization)
- Percutaneous penetration
- Eye irritation
- Genotoxicity / Mutagenicity
- Carcinogenicity
- Reproductive and Developmental toxicity
- Systemic toxicity
- Does not include environmental toxicity / packaging

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NO Animal Testing

Cruelty Free INTERNATIONAL™

Human Toxicity End-Points

NO Animal Testing

- So, what do we do?
- Where do we get safety data on ingredients?

Work with an Experienced Toxicologist

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So Where Do We Find Ingredient Safety Data?

Sources of Safety Data – *Pre-Existing data*

Your data – both for prelaunch and in-market surveillance.

Can use animal data obtained *BEFORE* ban's cut- off date

- *Ingredient supplier* ex. SDS, TDS
  - Especially important for minor components
- Regulators
  - EU REACH data base, EU Cosmetic Regulations, Canadian Hot List, Australian NICNAS, California OEHHA *(for some Proposition 65 listed chemicals).*
- Expert panels
  - US CIR, RIFM for fragrances, EU SCCS
- Scientific literature

Threshold methods

New Data

- In silico, in chemico, in vitro and human data can be used.

Minor Components are Very Important!

- Minor components such as preservatives, anti-oxidants and contaminants can have a significant impact on Ingredient Safety.
  - There can also be legal implications (e.g., California Prop 65)
- The minor components present can be very dependent on manufacturer / supplier
- Some contaminants / components are characteristic of a type of Ingredient

Major Ingredient Group	Characteristic Contaminant
Ethoxylated Surfactants	Ethylene Oxide, 1,4 Dioxane
Plant Extracts	Pesticides, Heavy Metals
Cocamidopropyl Betaine	DCA, Amidoamine, DMAPA
Alpha Olefin Sulfonate	Sultones
Diethanolamines	Nitrosamines
Polymers *(e.g., polyacrylamide)*	Monomers *(e.g., acrylamide)*

Most Raw Materials with more that 70% water will contain a preservative

When There is Not Sufficient Safety Data Available and You Still Want to Use that Ingredient!

Threshold Approaches:

There so little of Ingredients / contaminants that they don't have an effect. They can be used below the Threshold without further testing.

- Threshold of Toxicological Concern
  - Relates to systemic effects

  Originally used for indirect food additives, flavors and drug CMCs.

Thresholds for dermal sensitization and botanicals are being developed.

Cramer Class	Threshold	
	ug / person / day	ug / kg bw / day
Class I	1800	30
Class II	540	9
Class III	90	1.5

Kroes et al Food and Chemical Toxicol. v45 pp 2333-62 (2007)

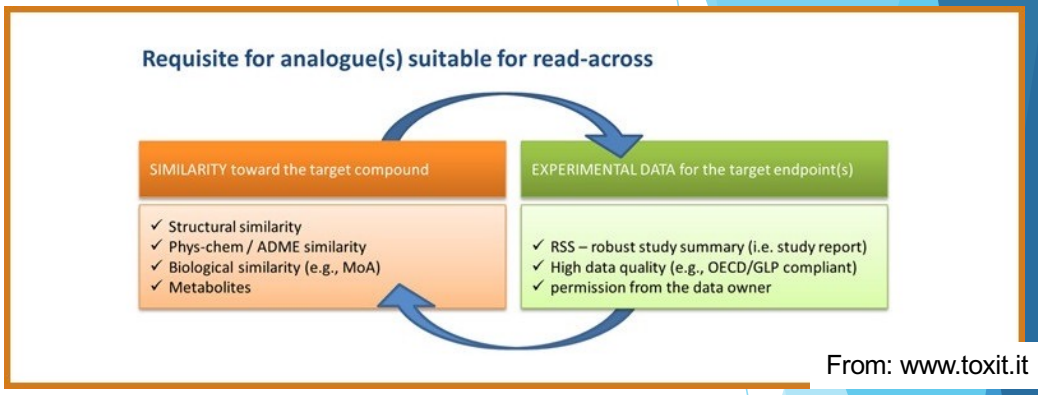
Polymers

- If Molecular Weight >> 1,000 Daltons then polymer does not penetrate skin. (but don't forget monomers!)

When There is Not Sufficient Safety Data Available and You Still Want to Use that Ingredient!

Read Across

- Using data from similar chemicals



From: www.toxit.it

In Silico

- OECD Toolbox, Derek

Running additional tests

- Can be expensive and time consuming
- These tests do not cover all end-points e.g., systemic toxicity and carcinogenicity
- Human tests for confirmation only

End Point	In Vitro, In Chemico (Examples)	Human
Skin Irritation	EpiDerm and other RHS models	Closed Patch Test. 14-Day Cumulative Irritation
Skin Sensitization	Combination of: DPRA, KeratinoSens, h-Clat	HRIPT
Eye Irritation	HET-CAM, BCOP, Epiocular	---------
Genotoxicity	Ames, In vitro micronucleus, and chromosomal aberration assays, Comet assay	---------

Summary:

- Manufacturer / Brand Owner/ Responsible Person is responsible for a cosmetic product's safety.
- Safety profile of a cosmetic product is dependent on safety profile of its ingredients.
- Ingredients should be used at "safe" level.
- In some jurisdictions, maximum level for an ingredient's use is specified in regulations.
- Ingredient's minor components e.g., preservatives, contaminants will impact profile. Dependent on supplier.
- Most cosmetic laws require Risk Assessment to assess ingredient / product safety.

Summary - II:

- There are many end-points for the different effects that an ingredient can have on the human body.
- Animal testing bans mean that data generated from animal tests after a critical date **cannot** be used in safety assessments.
- Information on the toxicology for many end-points are available from multiple sources on-line: regulators, expert panels, scientific literature.
- Additional non-animal methods include:
  - Use of Thresholds
  - Read Across
  - In vitro testing, human testing and in silico modeling.

Work with an Experienced Toxicologist

Thank You

- Eco Well – for inviting me
- You - for your attention

- Questions?

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