Databases, Tools and TTC Approach Applied To Chemicals In Cosmetics Products

COSMOS

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- US FDA: Kirk Arvidson, Kristi Jacobs

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†now in EU Commission, JRC Institute for Transuranium Elements (ITU), Karlsruhe – Germany.
Overview

Data

Threshold of toxicological concern

Tools

Decisions

Next steps
Data availability for cosmetics-related chemicals

• **Regulatory requirements**
  – Few cosmetics ingredients are subject to EU regulation
    • e.g., coloring agents, preservatives and UV filters

• **Different levels of toxicity testing**
  – application, substance types
  – repeated dose toxicity data are often not available for minor components or impurities

• **Proprietary data**
Identified needs for data and tools

- Repeated dose toxicity data for cosmetics ingredients, minor components, and impurities
- Immediate availability for safety evaluation
Cosmetics Inventory

- A reference (look-up) list for defining substances used in cosmetics products
  - Cosmetics-related chemicals

FDA VCRP list is provided by US CIR (2013, 2014)
Compilation of Ingredients Used in Cosmetics in US, JE Bailey, Ed. 2010
Cosmetics Inventory

• COSING chem function
• VCRP (voluntary cosmetics registration program) product category

SKIN CONDITIONING, PROTECTING
EMULSIFYING, EMULSION STABILIZER, SURFACTANT
PERFUMING
HAIR DYEING, COSMETIC COLORANT
HAIR CONDITIONING
EMOLLIENT
ANTIOXIDANT
AM, PRESERVATIVE
UV FILTER, ABSORBER
PLASTICISER

% of all chem functions (log scale)
Cosmetics Inventory – Chemical Space

ToxPrint chemotypes

- alcohol
- alcohol, phenol
- alcohols, diols
- aldehyde
- amine
- amine, aromatic (NH2)
- azo
- halide
- ketone
- ketone, ACAC
- carboxylic ester
- organometal
- phosphorus
- pyran, generic
- silicon
- steroid
- sulfide
- sulfonyl group
- urea
- aliphatic chain >= C8
- non-ionic surfactant
- anionic surfactant
- cationic surfactant - QUAT

Cosmetics inventory v1.0

% in collections (in Log scale)

Hair dye
Perfume, Fragrance
Emulsifying agent, Emulsion stabilizer, Surfactant
US FDA CERES
(Chemical Evaluation and Risk Estimation System)

- CFSAN regulatory workflow
- CERES content (FDA in-house)
  - Over 82,000 substances
  - Over 55,000 unique structures
  - Over 7,200 food-related chemicals (PAFA+)*

System jointly designed and developed by Altamira, Molecular Networks, US FDA CFSAN

* PAFA is a CFSAN’s legacy (public) database for “priority-based assessment of food additive”. CERES contains also other regulatory data beyond PAFA (such as impurities).

* FDA chemical space by Kirk Arvidson (this session)
**COSMOS DB**

- **CERES public content**
  - ~81,600 substances
  - ~44,800 unique structures*
  - ~7,200 food-related substances (PAFA)

*Initial structures: FDA, DSSTox, P&G

- **Cosmetics Inventory in v1.0**
  - INCI names (17,101) from COSING and FDA VCRP
    - Curated ~5,500 structures
    - Over~2,200 structures in common with PAFA

- **Toxicity data**

[http://cosmosdb.cosmostox.eu/](http://cosmosdb.cosmostox.eu/)
INCI name

connect to COSING and SCCS opinion
COSMOS Inventory in COSMOS DB v1.0

* COSMOS DB: Expo Booth # 439; Poster #158 (Abstract #431)
### Compare Cosmetics and Food

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<th>ToxPrint chemotypes</th>
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<th>Total</th>
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<td>Amine(NH2) aromatic</td>
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<tr>
<td>CarboxylicEster_phthalate</td>
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</table>

Cosmetics overlap was removed from PAFA structures.

Non-ionic surfactant

Quat cationic surfactant
Toxicity data from PAFA – Pros and Cons

- Assessed by FDA toxicologists
  - Study completeness and endpoints (effects level)

- Great reference for finding test substances with available toxicity data
  - Over 900 substances with > 6000 oral repeated dose studies
  - Nearly 70% of PAFA chemicals with oral repeated-dose toxicity data are found in Cosmetics Inventory.
  - Nearly 800 substances (> 7000 studies) with genetic toxicity data (in vivo and in vitro)

- Hazard identification approach, not safety assessment

- Limited granularity of toxicity data due to limited database technology in 1980’s
  - Not a toxicity database describing at dose-level effects
COSMOS oRepeatTox DB - Oral repeated-dose toxicity database

- Manually harvested (2011-2013)
  - Original publication/documents were harvested whenever available.
  - ToxRefDB entry tool adopted for COSMOS

- 228 chemicals
  - 186 Cosmetics-related chemicals
  - 42 impurities (CERES originated)

- 340 oral toxicity studies
  - chronic, repro-dev, subacute with ≥ 28 days, subchronic studies

*ECHA: REACH Substance Registration Database
† SCCS: Published opinions from EC Scientific Committee of Consumer Safety

Black dotted line: manual harvesting
COSMOS addition – oRepeatTox DB

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<th>Dose</th>
<th>Finding Category</th>
<th>Assay</th>
<th>Site</th>
<th>Effect</th>
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<th>Treatment Related</th>
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<td>BODY WEIGHT</td>
<td>BODY WEIGHT GAIN</td>
<td>No Change</td>
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<td>CLINICAL SIGNS</td>
<td>STOOL/URINE</td>
<td>STOOL &gt; FECES &gt; SOFT STOOL</td>
<td>Increase</td>
<td>Treatment-related</td>
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<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>ORGAN WEIGHT</td>
<td>KIDNEY</td>
<td>ABSOLUTE WEIGHT</td>
<td>No Change</td>
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<tr>
<td></td>
<td>ORGAN WEIGHT</td>
<td>KIDNEY</td>
<td>RELATIVE TO BODY WEIGHT</td>
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<tr>
<td>1000.0 mg/kg/day</td>
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<td>Increase</td>
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<td>Treatment-related</td>
<td>Significant</td>
<td></td>
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</table>
Data quality assessment

Data Governance Concept

- Data Concept
- Data and Metadata Management
- Data Quality
- Pieces of Data
- Data Authorization
- Data Availability

Data record reliability
- PAFA - study completeness score
- ToxREFDB – data usability
- COSMOS MINIS grade
  - MINIS: MINI mum Study inclusion criteria
  - Apply at the time of data harvesting and data record QC

Data acceptability
Klimish scores assigned by toxicologists during study reviews or data content QC

COSMOS Deliverable D1.10; Hall et. al. ACM Comput. Surv., 1980
COSMOS oRepeatTox DB and *minimum study (MINIS) inclusion criteria*

**Must meet:** Subacute, subchronic, chronic, reproductive-developmental, carcinogenicity (no neoplastic lesions)

- **Species:** Must meet: rat, mouse, dog, monkey, rabbit (only for DART studies)
- **Study type:** Must meet: subacute, subchronic, chronic, reproductive-developmental, carcinogenicity (no neoplastic lesions)
- **Dose and regimen:** Must meet COSMOS MINIS criteria: dose groups, # of animals, days/week treatment...
- **Oral exposure:** Must meet: ≥ 28 days (except DART studies)
- **Reference Data sources:** Must meet: All original documents when ever available (except regulatory study reports)
- **Effects findings at dose-group:** Must meet COSMOS MINIS criteria: All effects are recorded (neoplastic lesions are not included)
Power of ontology-driven database: oRepeatTox DB profiles

- Most sensitive species
  - rat

- Most common organs:
  - liver, kidney, stomach, forestomach, spleen, lung, thyroid, heart...

- Most common lesions for liver
  - inflammation, fatty change, cellular infiltration, cytoplasmic vacuolation

COSMOS poster: Data mining for liver steatosis/steatohepatitis/fibrosis

Poster #434 (Abstract #2254)
Power of ontology-driven database: oRepeatTox DB profiles

- Most sensitive species: rat
- Most common organs:
  - liver, kidney, forestomach, spleen, lung, thyroid, heart...
- Most common lesions for liver:
  - inflammation, fatty change, cellular infiltration, cytoplasmic vacuolation

COSMOS poster: Data mining for liver steatosis/steatohepatitis/fibrosis

Poster #434 (Abstract #2254)
Overview

1. Data
2. Threshold of toxicological concern
3. Tools
4. Decisions
5. Next steps
Threshold dose below which no relevant effects are expected, regardless of the substance.

**Cancer endpoints:**
- TD50 cancer potency
- Selected from CPDB

**Non-cancer endpoints:**
- Repeated dose NOAEL
- Munro 613 substances

Threshold at mean virtual safe dose (one in million cancer risk)

3 Cramer structure classes, 5\textsuperscript{th} percentile threshold for each class

Cheeseman et. al. 1999

Munro et. al. 1996
Requirements of non-cancer TTC approach

Food Cosmetics Toxicol 16, p255-276, 1978

Structure categories
Class I, II, III

Pragmatic TTC approach

Tox data – NOEL/NOAEL LOEL/LOAEL

NOEL/NOAEL database

Example a decision tree approach

FDA CFSAN TOR (Threshold of Regulation)

Munro, Kroes, Renwick, Cheeseman... (1996, 1999, 2004...)

0.5 ppb
(1.5 μg)

a low probability of a risk to humans

Kroes, et. al. 2004
Issues when applying TTC Concept to Cosmetics

• Chemical space
  – TTC Concept developed from oral exposure studies primarily for food assessment
    • does Munro cover typical cosmetic ingredients and impurities?

• Oral-to-dermal extrapolation
  – Current TTC approach is based on oral toxicity database. However, primary exposure route of cosmetics products is dermal.

K. Blackburn et al. 2005
A feasibility study based on a small personal care products
A. Worth et. al. 2012
Analysis of a preliminary COSMOS TTC dataset
Reg. Tox, Pharm. 43 (2005) 249–259
EUR 25162 EN, 2012

Kroes et. al 2007
Feasibility study of oral-to-dermal extrapolation including bioavailability based on Munro dataset
COSMOS Project and TTC Expert Groups

**ILSI Europe Expert Group 1:**
- Extend oral TTC dataset with cosmetics-related chemicals
- Review reliability and relevance of selected NOAELs

**Toxicity assessment (ILSI EWG1/FDA)**

**Bioavailability assessment (ILSI EWG2/COSMOS)**

**ILSI Europe Expert Group 2:**
- Estimate exposure differences between dermal and oral delivery
- Address metabolism differences between skin and liver
Curation strategy of COSMOS TTC database

1. Toxicity database
   - Study inclusion criteria

2. NOAEL database
   - Study inclusion criteria
   - NOAEL selection criteria

3. TTC dataset
   - Study relevance
   - NOAEL decision

All compounds in COSMOS TTC dataset have toxicity data either in oRepeatTox DB v1.0 or data in FDA PAFA, or EPA ToxRefDB unless the compounds are in either Munro or EPA IRIS.

7 iterations of dataset evaluation and 2 QC sessions of study reviews.

V1.7 current interim version
Data filters in the curation of COSMOS TTC dataset

1. Toxicity database

2. NOAEL database

3. TTC dataset

Study inclusion criteria of oRepeatTox DB are applied to all studies from other data sources (FDA PAFA or ToxRefDB).

NOAEL selection criteria*

- Lowest NOAEL with clear LOAEL
- Free Standing NOAELS were excluded when ever possible
- Chronic studies were preferred when available
- Guideline studies were preferred

NOAEL QC (2 QCs by expert review sessions)

- Lowest 10% of each Cramer Class or the compounds whose NOAEL values greatly differ across various data sources

  - *Toxicologically meaningful* and *human relevant* when mechanism is known.
### Description of COSMOS TTC v1.7 (on-going)

- **Cosmetics Inventory:**
  - COSMOS TTC v1.7: 503
  - Munro*: 180

- **Cramer Class I: Class II: Class III:**
  - COSMOS TTC v1.7: 239: 36: 281
  - Munro*: 136: 28: 443

- **Nutrients:**
  - Lipid soluble vitamins
  - Essential amino acids
  - A, D, E, K removed
  - retinol phenylalanine

- **Compound classes:**
  - Hair dyes: 110
  - Parabens: 10
  - Phthalates: 7

---

* Munro* refers to the reference data set used in the COSMOS TTC v1.7 assessment.
COSMOS TTC v1.7 vs. Munro TTC dataset

<table>
<thead>
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<th>Munro: Munro-cos</th>
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</table>

*Cosmetics in Munro are not likely hair dyes, but many are anionic surface agents.*

COSMOS has more diverse physchem properties profile.
**Outstanding issues**

- **Parabens and phthalates:** Munro in general less conservative than COSMOS. These substances may affect the 5\(^{th}\) percentile of the Cramer Class I. EG1 is currently evaluating.*

- **Hair dyes:** Most of the 110 hair dyes are Class III compounds. However they do not affect the 5\(^{th}\) percentile.

- **Cramer Class II:** not a viable group. Combine either with Class III?

- **Unreliable data within 5\(^{th}\) percentile:** Isopropyl alcohol...

- **Cramer Class assignment** – discrepancy between Munro and ToxTree

*More details will be presented by ILSI Europe Expert Group: Poster #268 (Wed)*
Oral-to-dermal extrapolation

- Inclusion of bioavailability aspects to TTC decision workflow
  - Developed the decision tree in consideration of bioavailability and exposure cases

- Skin permeability database*
  - More than 50% are cosmetics-related chemicals (total of ~450).

- Metabolism knowledge development for skin

Faith Williams, ILSI Europe EG2 Poster #529 (Mon 1 pm)
ChemoTyper to differentiate liver and skin metabolism

COSMOS TTC dataset matching liver metabolic rules

COSMOS TTC dataset matching skin metabolic rules

Poster #457 (Abstract #2273-D); Poster #453 (Abstract #2273)
### Empowered by data

#### COSMOS Data map

- Skin permeability
- Oral toxicity
- COSMOS TTC v1.7
- ToxCast Phase I&II

#### Contributors

- Elena - bioavailability
- Mark – AOP/MoA
- Kirk - FDA
- Ann – EPA
- 6 COSMOS posters
- 2 ILSI Europe posters
- Kristi Jacobs - ILSI Europe EG1
- Faith Williams - ILSI Europe EG2
**Decision and next steps**

- **COSMOS DB (public)**
  - Further development and management (Booth # 439)
  - Exchange data content
    - Update with HESS data, NITE Japan (Booth # 1639)

- **Cosmetics Inventory**
  - Plan to update annually via collaboration with US CIR.

- **COSMOS non-cancer TTC dataset**
  - Plan to release when issues are resolved

- **COSMOS tools**
  - TTC tools in COSMOS DB
  - Selected metabolic rules and toxic alerts in ChemoTyper and KNIME nodes (COSMOS SPACE and COSMOS DB)
  - PBPK tools

* Other talks this session; Poster #446 (Abstract #2266); Poster #479 (Abstract #2273X)
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  – A Boobis, S Felter, H Hollnagel, K Jacobs, A Worth, C Yang
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  – QC2: K Blackburn, E Rufer

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  – G Barrett, M Cronin, R Guy, J Plautz, A Perry, N Monteiro-Riviere, C Roper, H Rothe, D Rua, F Williams, J Westerhout, C Yang

• Sue Barlow

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  – M Checheva, M Gajewska, D Hristozov, Yang Lan, J Madden, A Mostrag-Szlichtyng, Dan Neagu, M Nelms, F Steinmetz

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• US CIR
  – I Boyer, B Heldreth

• NITE Japan
  – Y Sakuratani

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