

Toxicity Data Curation Process for the COSMOS Non-Cancer TTC Dataset



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Introduction and Aims

The Threshold of Toxicological Concern (TTC) approach is being considered as one of the alternatives for the safety assessment of cosmetics ingredients. In 2012, European Scientific Committees (SCs) published the opinion that the TTC approach in itself is scientifically acceptable for human health risk assessment of systemic toxic effects caused by chemicals present at very low levels [1]. Both SCCS/SCHER/SCENIHR and EFSA reports [2] noted the activities of COSMOS partners in the efforts related to develop a new non-cancer TTC dataset enriched with cosmetics ingredients and to address the oral-to-dermal extrapolation. This poster illustrates the construction process of the TTC dataset including data sources, toxicity data curation process, and the NOAEL/LOAEL decisions through quality control sessions.

Methods

STEP 1: Establish a COSMOS Oral Toxicity Database

1-A. oRepeatDose ToxDB

- A subset of COSMOS DB
- Oral repeat-dose toxicity data were compiled either from the existing sources or harvested according to the following inclusion criteria. (See Figure 1)

1-B. Substance inclusion criteria

- Cosmetics ingredients and chemicals used in cosmetics products
 - Chemicals in Cosmetics Inventory (EU CosIng and US PCPC)
 - > 60% of US FDA PAFA substances are found in Cosmetics Inventory.

1-C. Study inclusion criteria

Study Parameters	Exceptions
Study type: Chronic, Carcinogenicity, Subacute, Subchronic, Reproductive-developmental, Neurotoxicity, Immunology	Repro-dev, Neuro, and Immunology endpoints are only considered if effects are considered critical.
Duration: Treatment time ≥ 28 days	For reproductive developmental or multigen. studies, simple duration days are not applied..
Species: Rat/mouse/dog/monkey	Rabbit is considered for reproductive-developmental studies
Route: Oral – dietary, drinking water, gavage	None
Dose: No single dose studies; reasonable dose separation (LD, MD, HD)	Dose information required.
Effects: <ul style="list-style-type: none">- Effects description at dose level- Non-neoplastic- Systemic effects	<ul style="list-style-type: none">- None- None- For toxicity database, all effects are recorded at dose level. For TTC, only studies with systemic effects are selected.

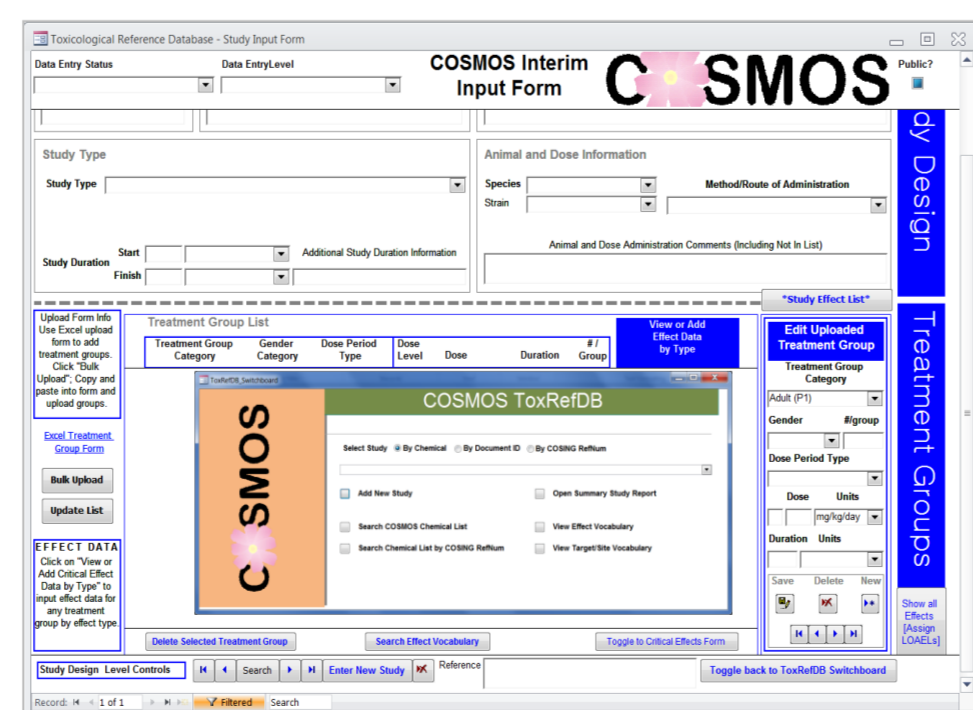
1-D. Data record reliability criteria

Categories	EPA ToxRefDB [3]	FDA PAFA [4]	Example: FDA Redbook [5] vs. Core minimum
Meet the guideline and acceptable studies	Meet OPPTS or OCSPS guidelines	Meet the current standard of FDA Redbook	# animal 20/dose/sex, 3 dose levels, all full scale tests including histopathology required
Not meet the guideline, but meet the database minimum standard	Not meet the guidelines, but acceptable literature publications	Not meet the current FDA Redbook, but meet the core minimum standard	# animal 5/dose/sex (10/dose/sex for chronic), min 2 dose levels, clinical signs/ food-water consumption/ ophthalmology/ clinical chemistry not required, hematology with RBC and WBC only, 7 minimum organs for histopath.
Not meet the minimum/ core standard	Deficient studies (data not used)	Unacceptable studies (data not used)	

1-E. Reference traceability criteria – citations must be traceable.

1-F. Curation Method

- Existing data** from FDA PAFA/CERES and ToxRefDB were automatically imported. Some data from NTP, ECHA substance registration database, and SCCS opinions were manually entered.
- New studies** as well as corrections were added to the database by (re)harvesting data. (~ 30 % of the PAFA data in the TTC dataset has been revisited.)
- Data entry tool – ToxRefDB modified for COSMOS use
- Data harvesting – Harvesting organised with a full-time COSMOS toxicologist
- Data record quality control (QC) – scheduled reviews and discussions within COSMOS



Methods

STEP 2: COSMOS TTC Database

oRepeatDose ToxDB was queried to select studies that meet the rules:

- For PAFA studies, minimum NO(A)EL with accompanying LOAEL was selected.
- When NO(A)EL is not established, the study with minimum LO(A)EL value was identified.
- NO(A)EL values from other sources (ToxRefDB, SCCS, Munro, IRIS, etc.) were used as provided.
- All NO(A)ELs are annotated with source, critical effects and sites, or other rationale.

STEP 3: COSMOS TTC Dataset

- A TTC dataset is extracted from this COSMOS TTC database.
- The subchronic NOAEL values were adjusted by a factor of 3.
- The minimum NOAEL value is selected from several data sources.
- When NOAEL values are not available for a given compound, a minimum LOAEL value was taken for the test substance and adjusted by a factor of 3.

ILSI Europe QC of NO(A)EL Decisions

- Studies in lowest 10th percentile were reviewed by ILSI Europe Expert Group.
- This QC process was modelled into COSMOS data curation steps to continue to improve the results interpretation/acceptance issues, which are rated currently by Klimisch score [6].

Result

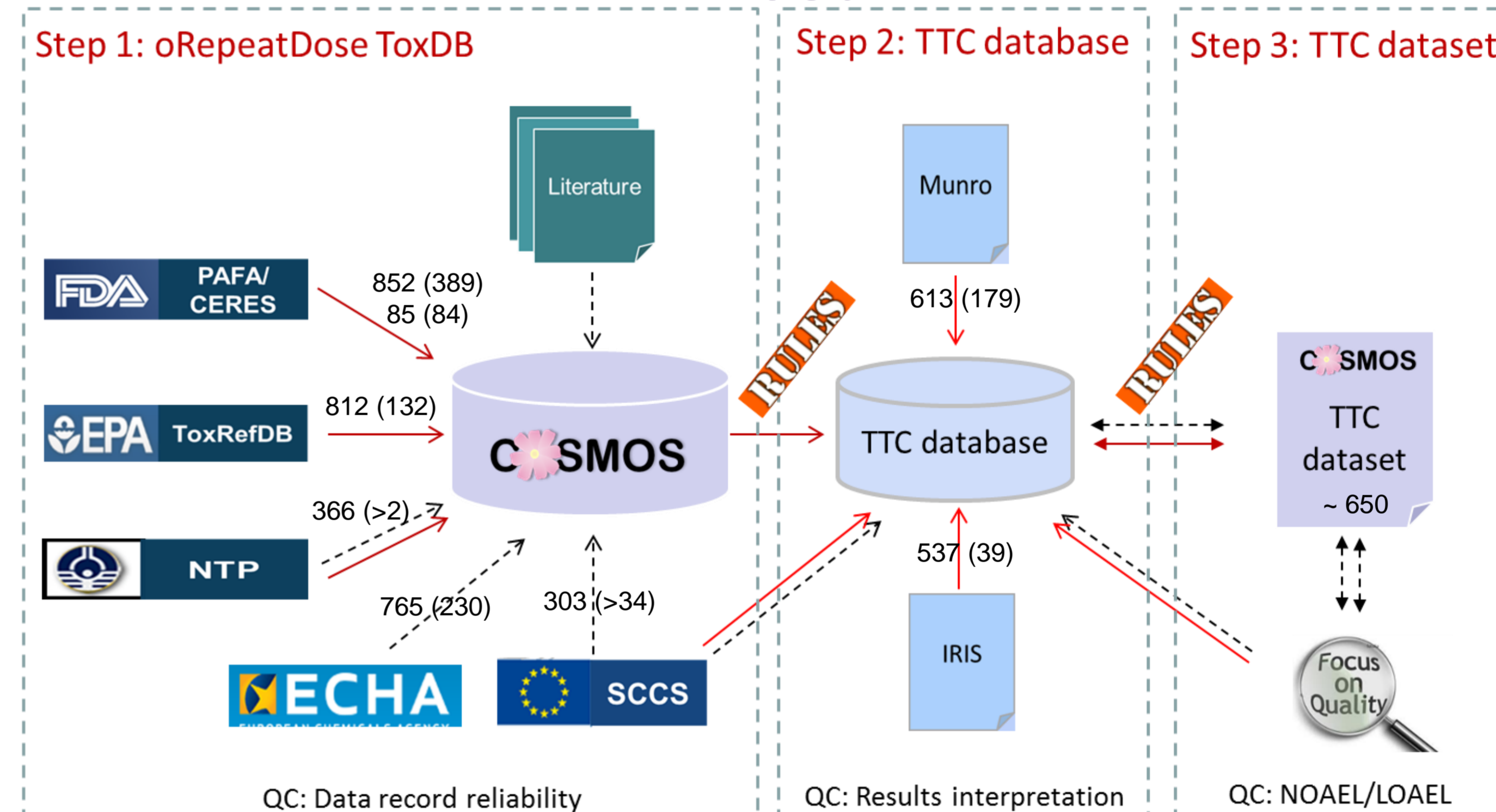
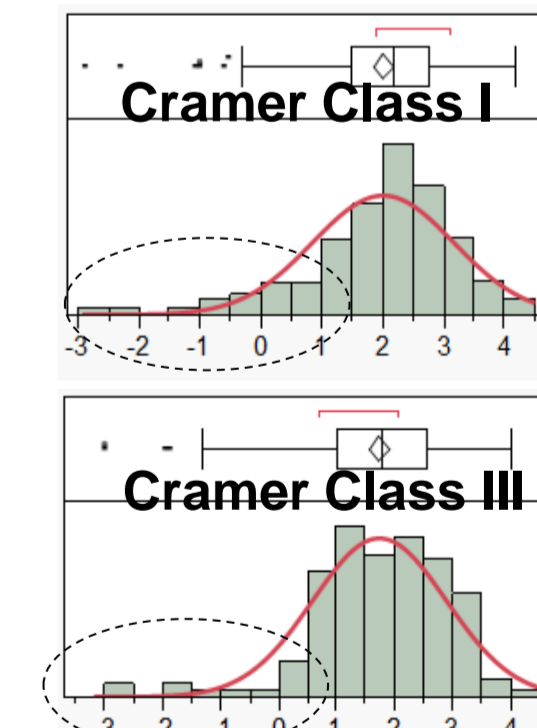


Figure 1. Summary of COSMOS Toxicity Data Curation Process
Black dotted arrow: manual; Red solid arrow: automatic process.
Numbers represent chemical counts from the source (or in the COSMOS DB/dataset).

Next Steps

- oRepeatDose Toxicity Database was implemented within COSMOS DB to be used as a basis for development of a new TTC dataset.
- Second ILSI QC of NOAEL decisions:
 - Studies in lowest 10th % for each Cramer Class will be reviewed once more regulatory data (e.g., SCCS opinions) are added into the database.
- The new TTC dataset will be used to apply the threshold analysis suitable for cosmetics ingredients. COSMOS will help build a decision tree framework.
- COSMOS plans to develop more objective methods for data reliability issues.

Example from current database



References

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