New TTC Database Compilation to Support Thresholds of Toxicological Concern in the Risk Assessment of Antimicrobials Beyond Cramer Classes

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MOTIVATION

- Thresholds of Toxicological Concerns (TTC): (1) alternative method to reduce/replace animal testing for systemic endpoints related to human health; (2) In regulatory programs for food contact substances, fragrances and flavorings at low exposure; (3) Considered for cosmetics and other types of substances (SCCS, EFSA)
- Outstanding issues: (1) Cramer decision tree limitations (2) TTC databases - chemical space; (3) Toxicity data quality
- Route-to-route extrapolation: Oral, dermal, inhalation

AM TTC APPROACH

Database
- TTC database to enhance statistical power and chemical space
  - Munro 613 to over 1600 test substances
- Antimicrobial Inventory: 66 AMs (in Munro) expanded to 658 in AM TTC

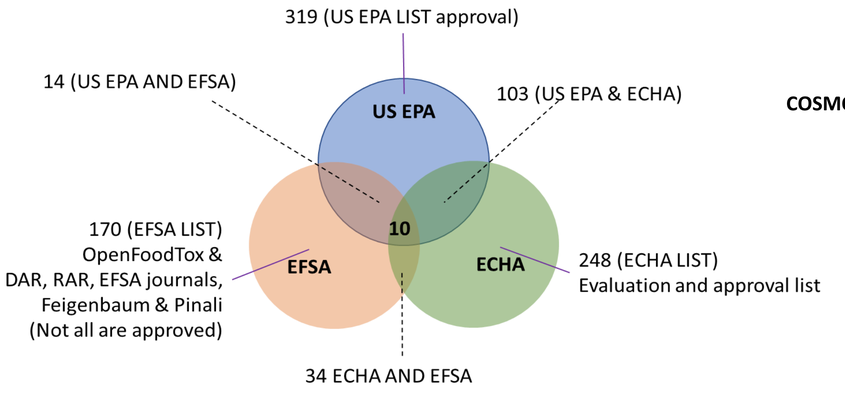
Structure & Tox Analysis
- Classify chemicals to reflect the AOP or MOA pathways rather than Cramer Classes
- Develop antimicrobial chemotypes (categories)

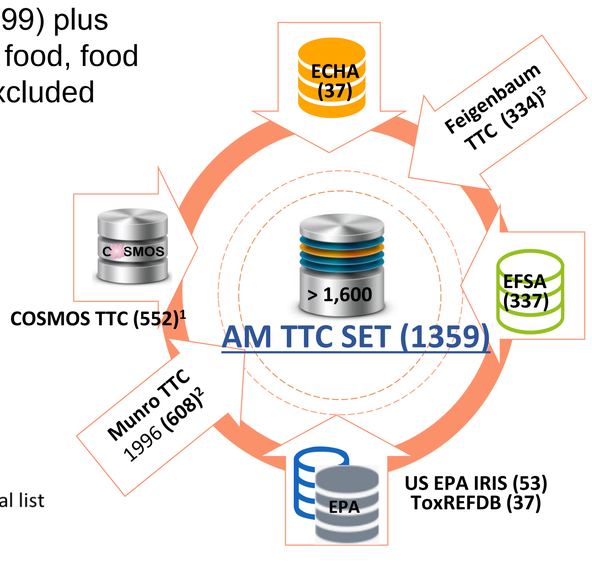
Regulatory Framework
- Regulatory thresholds
- Establish methods to leverage toxicity data

AM TTC DATASET

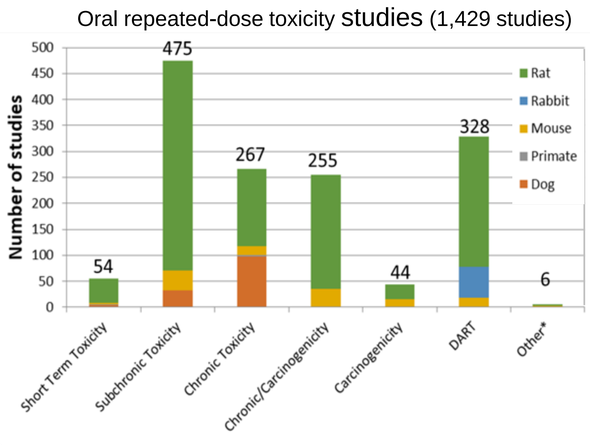
AM INVENTORY

- "Pesticidal AM inventory" (599): AM pesticidal and biocidal formulations; 86 % Cramer Class III
- "Global AM Inventory" (658): Pesticidal AM inventory (599) plus antimicrobials, preservatives, and disinfectants used in food, food contacts materials, and cosmetics formulations (94); Excluded antimicrobial pharmaceuticals; 82 % Cramer Class III
- Only ~60% with tox data (398 AMs, 302 organic)



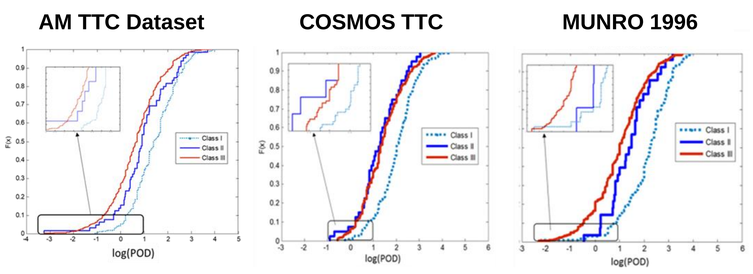


AM TTC DATASET – STUDY PROFILE



- COSMOS TTC methodology[1]:
- Repeated Dose, Target Organ Toxicity, Chronic / Carc, DART studies with non-neoplastic systemic effects; Duration ≥ 28 days; Oral; Rat, Mouse, Dog, Monkey/Primates, Rabbit (DART)
- QC Study Reviews: 5% of the lowest NOAELs; Conflicting studies between Munro and US EPA DER

AM TTC DATASET – DISTRIBUTION

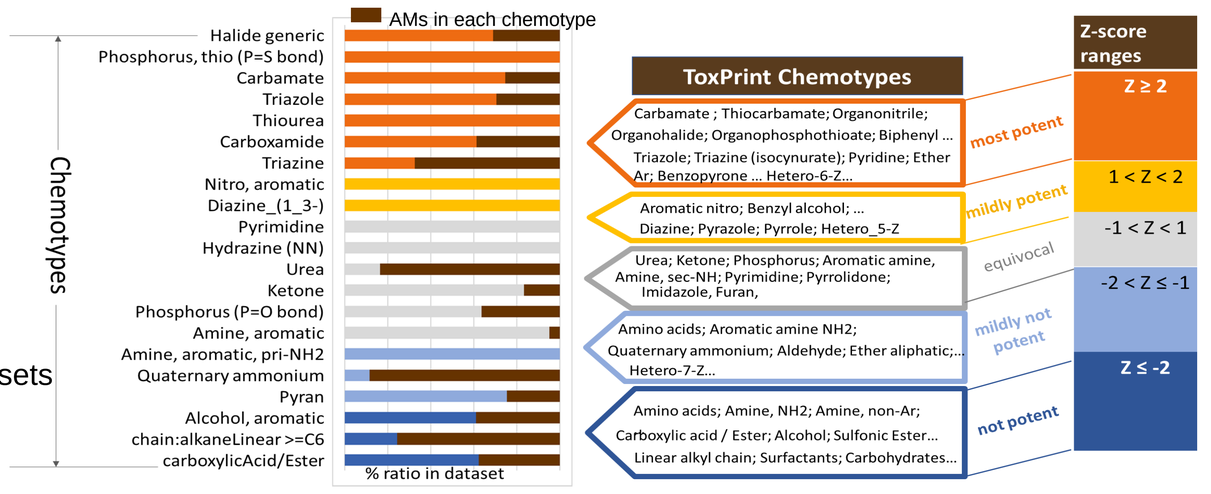


- Adjustment factors for POD: LOAEL to NOAEL extrapolation: 3X; Duration adjustment: 3X for 90 days to chronic, 6X for 28 days to chronic
- New dataset - 5th percentiles are similar to those of other TTC datasets

Cramer Class	Fifth Percentile (mg/kg-bw/day) [a]			
	AM TTC Master (1359)	COSMOS + Munro 2016 Federated[b] (963)	Munro 1996 publication (613)	COSMOS[b] 2017 publication (552)
Class I	2.67* (N=277)	3.54 (N=243)	3.0 (N=137)	4.2 (N=219)
Class II	0.43 (N=54)	0.74 (N=49)	0.91 (N=28)	0.58 (N=40)
Class III	0.12 (N=1028)	0.22 (N=671)	0.15 (N=448)	0.78 (N=293)

[a] Thresholds were determined by parametric estimation of lognormal distribution of NOAEL values
[b] Yang et al. Food and Chemical Toxicology 109 (2017) 170-193
* When NOAELs were adjusted from subchronic to chronic by 2X, the Fifth percentiles were 3.2, 0.58, 0.13 mkd for Cramer Class I, II, III, respectively.

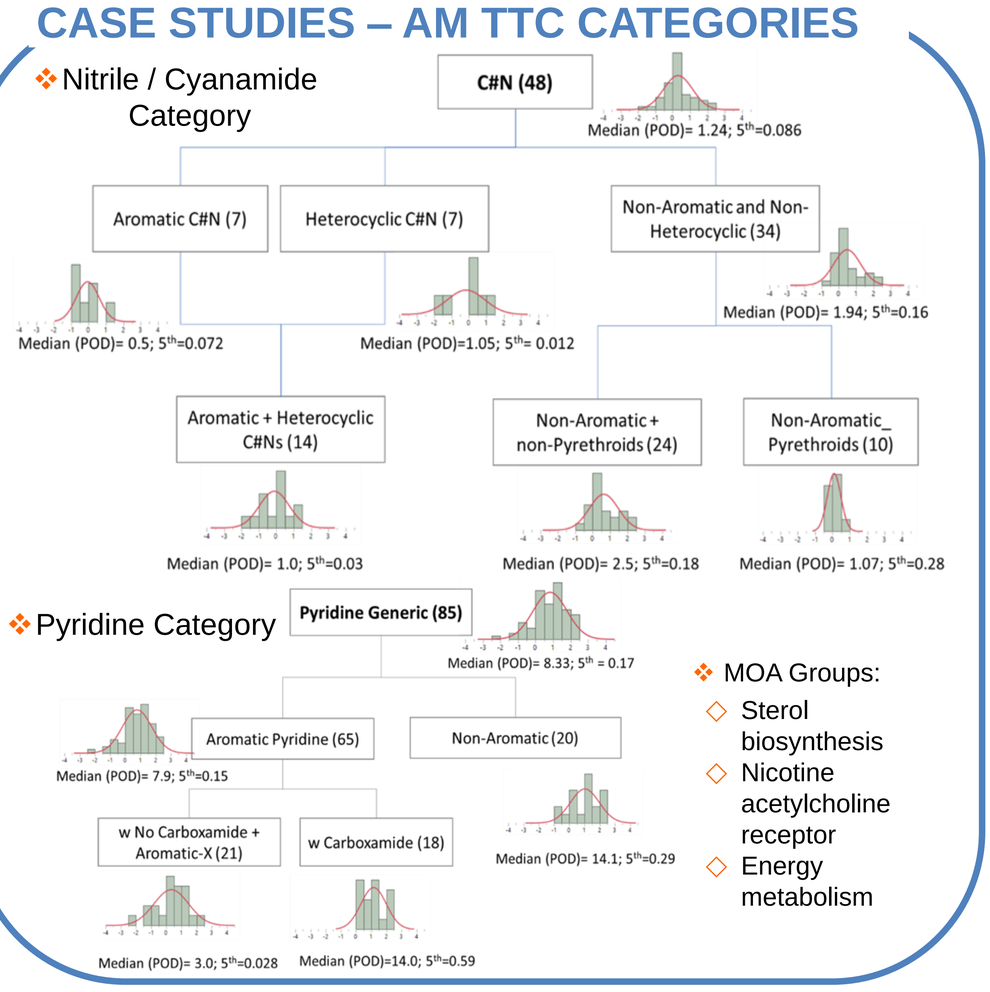
AM TTC DATASET – POTENCY AWARE CHEMOTYPES



- Roughly assigned to 5 potency groups; For each potency group, chemotype categories are designed around known biological MOAs; Potency-aware chemotypes are developed by analyzing NOAEL distributions

CASE STUDIES – AM TTC CATEGORIES

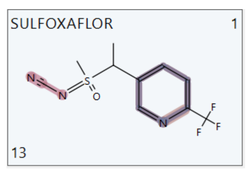
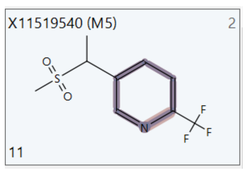
- Nitrile / Cyanamide Category
- Pyridine Category

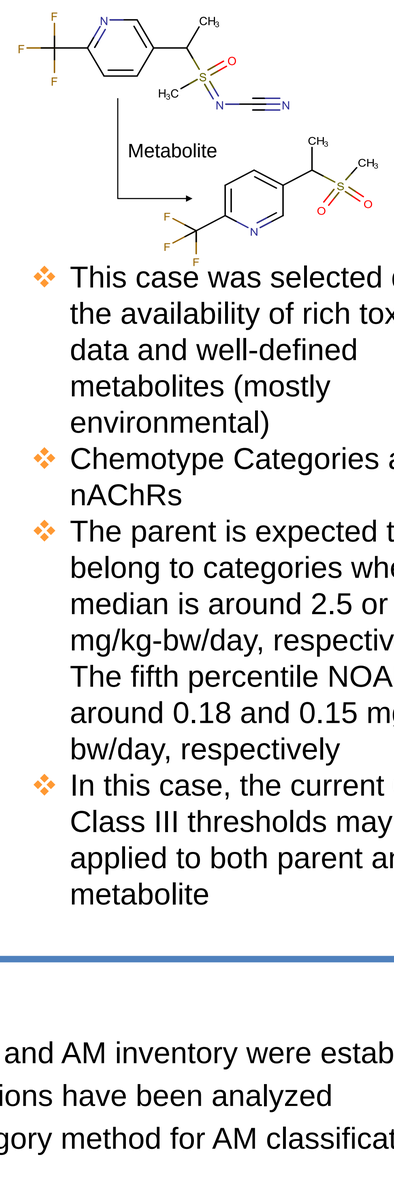


- MOA Groups:
  - Sterol biosynthesis
  - Nicotine acetylcholine receptor
  - Energy metabolism

CASE STUDIES – SULFOXAFLOR

Properties	Description
CAS RN	946578-00-3
Cramer Class	Class III
Possible MOAs	Binding to nAChRs
Potency category	Cyano-cyanamide (C#N) & N_Pyridine

Chemical Species[4]	Studies	NOAEL | LOAEL (mkd)	Critical Effects
	Rat, 28-D, Dietary	24 | 79	Liver
	Rat, 90-D	6.4 | 47	Liver
	Dog, 90-D	6 | 10	Food consumption decrease
	Rat, 2-Y, Dietary	4.2 | 21	BW Gain; Clin Chem-cholesterol; Liver (non-neopl)
	Mouse, 18-M, Dietary	10.4 | 79.6	Liver (non-neopl)
	Rat, 28-D, Dietary	Not reported	Liver OW; hypertrophy, eosinophilia. Very slightly increased number of mitotic figures (# only, 100 ppm)
	Rat, 90-D, Dietary	5 | 25	Liver OW increase; Histopath



- This case was selected due to the availability of rich toxicity data and well-defined metabolites (mostly environmental)
- Chemotype Categories are nAChRs
- The parent is expected to belong to categories where median is around 2.5 or 7.9 mg/kg-bw/day, respectively. The fifth percentile NOAEL is around 0.18 and 0.15 mg/kg-bw/day, respectively
- In this case, the current Cramer Class III thresholds may be applied to both parent and metabolite

CONCLUSIONS

- Larger TTC dataset enriched with antimicrobial (AM) chemicals and AM inventory were established
- Over 20 AM chemotypes are defined and their potency distributions have been analyzed
- NEXT STEP: set up a framework to apply the MOA-driven category method for AM classification when applying TTC to AM and their metabolites

REF

[1]Yang et al. Food and Chemical Toxicology 109 (2017) 170-193; [2]Munro et al. Food and Chemical Toxicology 34 (1996) 829-867; [3]Feigenbaum et al. Food and Chemical Toxicology 75 (2015) 24-38; [4]Terry et al. Regulatory Toxicology and Pharmacology 71 (2015) 301-317