Evaluation of Genotoxicity and Carcinogenicity Profile for the TTC Database Used to Develop Safety Thresholds of Industrial Chemicals

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INTRODUCTION

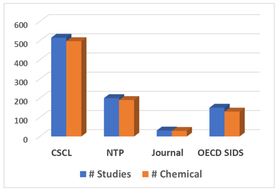
In the absence of or with limited chemical-specific toxicity data, the threshold of toxicological concern (TTC) approach has been applied for foods (flavorings and food contact materials) and fragrances to address whether the exposure is below the appreciable risk to human health. Recently the approach has been extended to cosmetics-related chemicals and metabolites of pesticides as well as impurities of pharmaceuticals. This study develops a TTC database of industrial chemicals based on Tolerable Daily Intake (TDI) derived from the Hazard Evaluation Support System (HESS) Integrated Platform. The results are compared with other existing TTC datasets (Munro and COSMOS) for thresholds and chemical space. Moreover, genotoxicity and carcinogenicity profile for the HESS TTC database was evaluated.

METHODS

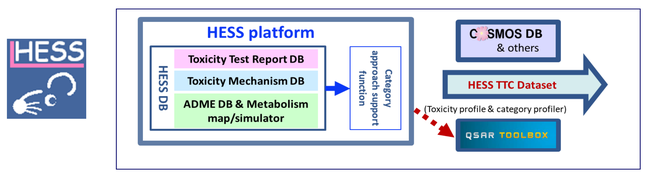
STEP 1: HESS TTC Database

- Database of subchronic toxicity studies mainly under Japanese Chemical Substances of Control Law (CSCL)
- Industrial chemicals
- Data sources

Data sources	# Studies	# Chemical
CSCL Japan	515	497
NTP	200	190
Journal	31	29
OECD SIDS	150	130



TTC Dataset from Hazard Evaluation Support System



STEP 2: HESS TTC Dataset

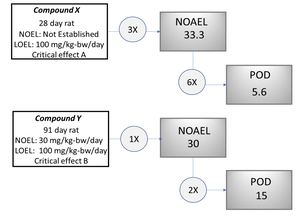
- A TTC dataset is extracted from this HESS database applying the study inclusion criteria defined in COSMOS project.

Study Inclusion Criteria for TTC Dataset

Study Parameters		Exceptions
Study type:	Short-term, Subchronic	None
Duration:	Treatment time ≥ 28 days	None
Species:	Rat	None
Route:	Oral – dietary, drinking water, gavage	None
Dose:	• No single dose studies; reasonable dose separation (LD, MD, HD) • Studies with clear mg/kg-bw/day	Dose information required. Animal studies whose dose is reported in mg/kg-bw/day were used for this study
Effects:	• Effects description at dose level • Non-neoplastic • Systemic effects	• None • None • For toxicity database, all effects are recorded at dose level; but for TTC, only studies with systemic affects are selected.
Study quality	• Klimisch scores in Japanese studies: 1(536); 2 (16); not reported (10) • Guidelines: OECD, NTP	• Klimisch scores for 149 NTP studies and other literature publications (22) were not assessed.

STEP 3: POD Preparation and Threshold Setting

- The POD preparations followed in general the method described by COSMOS project[2].
- In general NOAELs were determined by taking the lowest values based on the toxicologically meaningful systemic effects.
- All NOAELs are annotated with critical effects / sites at the accompanying LOAEL.
- Tolerable Daily Intake (TDI) was used to derive a human safe level.



The subchronic to chronic adjustment factors were:
- 6X for studies with 28-84 day
- 2X for studies ≥84 day

When NO(A)EL is not established, the LO(A)EL value was identified and applied a LOAEL-to-NOAEL conversion factor of 3.

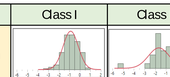
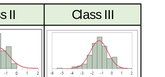
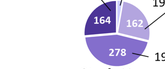
STEP 4: Chemistry / Biology Space Characterization

◆Chemistry profiles
- ToxPrint Chemotypes, https://toxprint.org/

◆Biology profiles
- Genotoxicity and Carcinogenicity
  - ◊ OECD QSAR Toolbox, http://www.oecd.org/chemicalsafety/risk-assessment/oecd-qsar-toolbox.htm
  - ◊ Japan Existing Chemical Database (JECDB), http://dra4.nihs.go.jp/mhlw_data/jsp/SearchPageENG.jsp
  - ◊ Ministry of Health, Labour and Welfare (MHLW), http://anzeninfo.mhlw.go.jp/anzen_pg/GHS_MSD_FND.aspx
- Receptor binding
  - ◊ Molecular Initiating Events from HESS toxicity mechanism DB
  - ◊ in vitro positive (hepatic nuclear receptor activation from PubChem); in vivo positive (hepatocyte hypertrophy from HESS toxicity test report DB)

RESULTS – Dataset Characterization

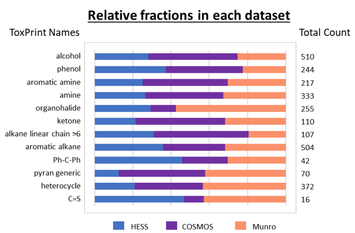
Cumulative Distribution Function

	Class I	Class II	Class III
HESS histogram			
HESS TDI (μg/person/day)	800 (N=190)	348 (N=23)	166 (N=520)
Munro TDI (μg/person/day)	1800 (N=137)	546 (N=28)	90 (N=448)
COSMOS TDI (μg/person/day)	2500 (N=219)	350 (N=40)	470 (N=293)

All counts on the HESS TTC dataset are preliminary.

Cramer Classes (Toxtree v2.6.13)

Chemical Space Comparison of TTC Datasets



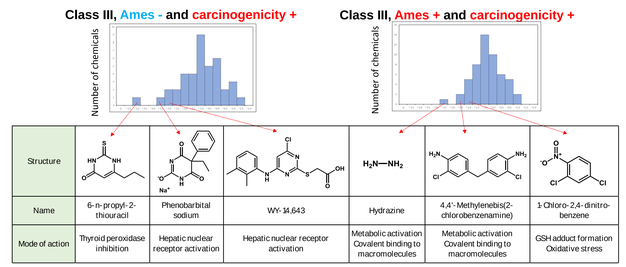
- HESS dataset has more structures of alkyl substituted aromatic rings (aromatic alkane, Ph-C-Ph)
- HESS has more phenols and C=S bonds.
- HESS has less heterocycles or ketones than Munro or COSMOS.
- HESS has less organohalides than Munro.
- HESS chemical space is sufficiently different from that of Munro or COSMOS TTC.

RESULTS – Dataset Characterization

Genotoxicity and Carcinogenicity Profile for HESS TTC Dataset

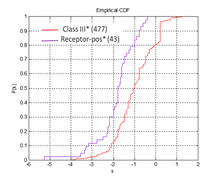
Class	Ames	Carcinogen	TDI (NOAEL/UF)	N	Observations
III	Negative	All	0.00167	266	For all Class III, no significant differences due to Ames mutagenicity.
		Non-carcinogen	0.00168	23	
		Carcinogen	0.00012	40	Ames-negative carcinogens may be more potent (for non-neoplastic lesions) than Ames-positive carcinogens.
III	Positive	All	0.00304	131	For all Class III, no significant differences due to Ames mutagenicity.
		Non-carcinogen	0.00833	11	
		Carcinogen	0.00232	53	Ames-positive carcinogens may be less potent (for non-neoplastic lesions) than the Ames-negative carcinogens
I	Negative	All	0.0167	140	No difference on potency due to Ames mutagenicity (size is too small)
		Non-carcinogen	0.0757	12	Size is too small to make observation.
		Carcinogen	0.248	9	Size is too small to make observation.
1	Positive	All	0.0183	15	No difference on potency due to Ames mutagenic (the size too small)
		Non-carcinogen	NA	1	Size is too small to make observation.
		Carcinogen	0.0183	7	Size is too small to make observation.

Class III, Ames - and carcinogenicity + **Class III, Ames + and carcinogenicity +**



Effect of Receptor Binding Ability to Cumulative Distribution Function

- The receptor-positive chemicals are more potent than the rest of Class III.*
- Similar to pharmacological actions in drugs, biologically active chemicals are not classified sufficiently by Cramer Classes.



SUMMARY AND FUTURE

- ◆The Cramer Class III threshold derived from HESS DB is similar to that of Munro.
- ◆Genotoxic and/or carcinogenic compounds affect the fifth percentiles. Before the derivation of thresholds they will be identified and treated accordingly.
- ◆ Receptor-binding chemicals tend to result in lower thresholds. They will be further identified and treated separately.
- ◆The potent NOAEL values will be confirmed by strategic study QC as defined in COSMOS TTC dataset development[2].
- ◆Cramer Classifications by Toxtree needs to be reviewed.
- ◆The TTC Dataset will be distributed within COSMOS DB.

REFERENCES

1. HESS DB. Sakuratani et al., SAR QSAR Environ. Res., 24 (2013) 35-46.
2. COSMOS TTC Dataset. C. Yang et. al. Food & Chemical Toxicology.
3. Munro TTC Database. Munro et. al. Food & chemical Toxicology 34 (1996) 829-867.

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