Exploring Toxic Structural Features and Properties of Extractables and Leachables

Suman Chakravarti, email: chakravarti@multicase.com
MultiCASE Inc., Beachwood, OH, USA, *www.multicase.com*

MultiCASE

Background

- E&Ls are compounds that migrate from materials to products and pose safety risks to human, animal health and the environment.
- A system of QSAR models, databases, and toxicity alerts has been developed to aid in the safety assessment of more than 400 E&Ls.
- The system covers 14 endpoints, such as LogP, water solubility, and various toxicity, and provides predictions and experimental data.
- Knowledge-based and statistically mined structural alerts enable expert evaluation and analysis of potential toxic properties.
- Useful queries can be answered, such as the number of E&Ls with positive Ames data, functional groups helpful in biodegradation, and those that may cause skin sensitization.

Objectives

- To help build a modular in silico risk assessment workflow for E&Ls.
- To investigate the causal factors behind E&L toxicity.
- To enable confident expert evaluation and analysis.

Methods

- *FlexFilters* methodology in *QSAR Flex* was used for building models, databases and alert systems.
- Both regression and classification QSAR models were built.
- Statistical and expert alerts can be used outside of the models.

Data, Models and Alerts

| Description	Purpose*	Database Size	Number of Alerts
Extractables and Leachables[1]	db	412	-
Estrogen receptor (ER) binding	model, alert, db	97266	852
Androgen receptor (AR) binding	model, alert, db	10231	595
Hepatotoxicity	model, alert, db	1767	522
Ames mutagenicity	model, alert, db	17647	1731
Carcinogenicity	model, alert, db	2194	300
Skin sensitization	model, alert, db	1238	147
LD50 (very toxic)	model, alert, db	8458	473
BBB	model, alert, db	921	85
Ready biodegradability	model, alert, db	1603	297
Bio-concentration factor	model, alert, db	625	100
Daphnia acute toxicity	model, alert, db	2394	338
LogP	model, db	14050	-
Water solubility	model, db	4222	-
Vapor pressure	model, db	2032	-
Mutagenicity Expert Alerts	alert	-	240
Skin Sensitization Expert Alerts	alert	-	85
Aquatic Toxicity Expert Alerts	alert	-	71

*model, alert, db – model building, alert identification, database building
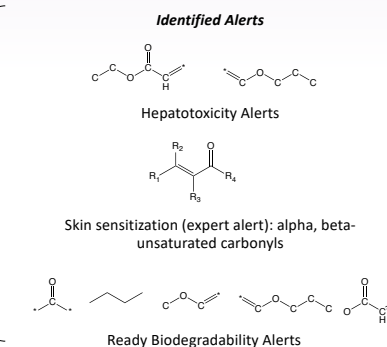
DATABASES experimental tox data, read-across

(Q)SAR MODELS toxicity predictions

ALERTS mechanistic explanations, read across

Example

Dibutyl maleate
CAS RN: 105-76-0
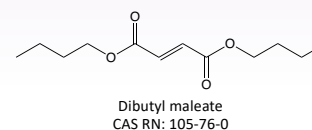
Property/Toxicity	Prediction	Experimental Data
LogP	3.17	
VP		-3.206
Water Solubility		0.500
BCF	1.206	
Ready biodegradability	biodegradable	
Daphnia acute toxicity	4.589	
ER Binding		non-binder
AR Binding		non-binder
Skin sensitization		sensitizer
LD50 (very toxic)		non-toxic
Ames mutagenicity		Ames negative
Carcinogenicity	non carcinogenic	
Hepatotoxicity	hepatotoxic	
BBB	permeable	

Identified Alerts

Hepatotoxicity Alerts

Skin sensitization (expert alert): alpha, beta-unsaturated carbonyls

Ready Biodegradability Alerts

Conclusions

- The software platform provides a combination of databases, models, expert and statistically mined alerts for E&L evaluation at different levels.
- A variety of toxicity and physicochemical property end points are supported which can easily be extended.
- Potentially useful in expert evaluation of E&Ls.

References
1. ELSIE database: https://comptox.epa.gov/dashboard/chemical-lists/ELSIE.