

Comprehensive Evaluation of Existing QSAR Models for Chronic Toxicity Endpoints



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Introduction and Aims

One of the tasks within the COSMOS project is the comprehensive evaluation of existing QSAR models and expert systems predicting the chronic toxicity endpoints that "drive" the TTC thresholds, e.g. repeated dose toxicity and selected target organ/tissue toxicities. Issues involved in oral-to-dermal extrapolations are also addressed as a part of strategies to extend the current TTC approaches to cosmetics ingredients and chemicals found as impurities in cosmetics formulations. As a first step this requires consideration of absorption/permeability via dermal or oral routes.

Here a comprehensive evaluation of existing QSAR models for chronic toxicity endpoints as well as dermal and oral absorption/permeability is presented.

Results (1) – QSARs for Chronic Toxicity

Chronic systemic toxicity^[1-2]



Traditional approaches to toxicological risk assessment focus primarily on **adverse health outcomes** as the end points for assessing the risk posed by environmental agents^[3].

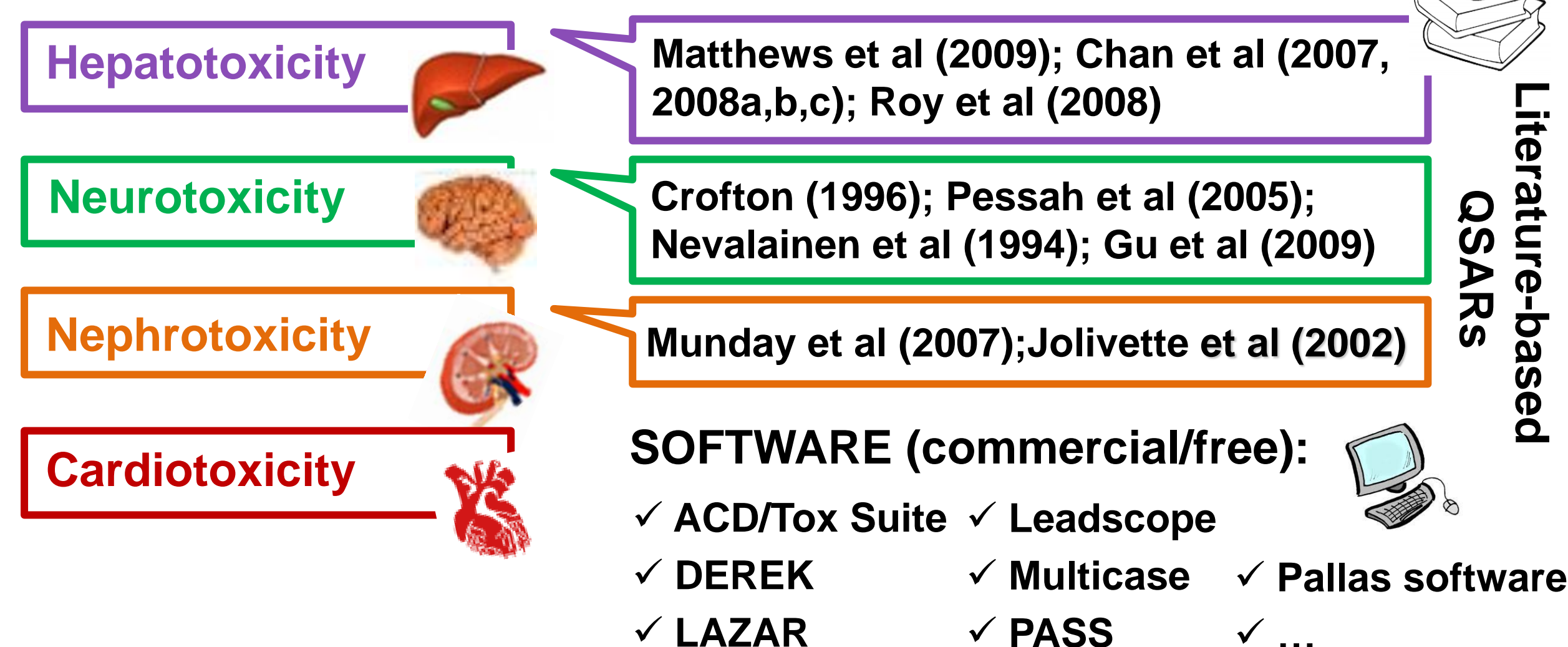
	Rat chronic LOAEL	MRTD
Software	• TOPKAT • MolCode Toolbox	• LAZAR (free) • ADMET Predictor
Literature QSARs	• Garcia-Domenech <i>et al</i> (2006) • Mazzatorta <i>et al</i> (2008)	Matthews <i>et al</i> (2004)

LOAEL (Lowest Observed Adverse Effect Level)
MRTD (Maximum Recommended Therapeutic Dose)

(Q)SARs based on general apical endpoints

Organ-specific and system-specific toxicity^[1-2]

The toxicological approach undertaken in the context of the above paradigm has evolved and expanded over the last decades to reflect increasing concern about a wider variety of toxic responses^[3].



... A new vision: focus on **key toxicity pathways**, i.e. cellular response pathways that, when sufficiently perturbed, are expected to result in adverse health effects^[3].

Adverse Outcome Pathways (AOP)

- hERG channel inhibition
- binding to Nuclear Hormone Receptors (e.g., LXR, PXR, AhR)
- ...

Examples of existing *in-silico* tools:

- ✓ VirtualToxLab ✓ ACD/ToxSuite
- ✓ DEREK ✓ ADMET predictor

QSAR modelling of **biologically significant perturbations** known to trigger adverse effects in a defined AOP

References

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- [5] Avdeef A (2003) Absorption and Drug Development, Wiley-Interscience.
- [6] Akamatsu *et al* (2009) In silico Prediction of Human Oral Absorption Based on QSAR Analyses of PAMPA Permeability. *Chemistry & Biodiversity* – Vol. 6.
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Results (2) – QSARs for Oral and Dermal Absorption/Permeability

Strategies for oral-to-dermal extrapolation^[4]

	ORAL high	ORAL low
DERMAL high	SCENARIO 1 Oral > Dermal 1 st pass sig - use dermal NOAEL or apply (class specific) safety factors 1 st pass not sig - use oral NOAEL use dermal NOAEL or apply a dermal absorption derived safety factor	SCENARIO 3 Oral NOAEL not protective dermally activating worst possible scenario categorize compounds by their metabolic structural rules and reactivities dermally deactivating apply a safety factor based on skin absorption to oral NOAEL Kp, Jmax modeling
DERMAL low	SCENARIO 2 oral NOAEL over-protective - Dermal NOAEL desired - Use liver metabolism to adjust the safety factor	SCENARIO 4 This is in general not a problem since oral and dermal NOAELs will both be high.

Bioavailability differences between oral and dermal exposures:

- 1) Absorption/permeability via dermal or oral routes
- 2) Metabolism differences between skin and liver

In order to evaluate the degree of oral and dermal absorption/permeability, available experimental data are being collected and, in parallel, development of QSAR models for skin penetration and oral absorption is currently ongoing. Here a **review of existing QSAR models** is presented.

QSAR Models for oral absorption: PAMPA permeability^[5-6]

PAMPA assay	Parallel Artificial Membrane Permeability Assay: experimental model to predict human intestinal absorption for passively diffusing compounds .
QSAR algorithm	MLR or bilinear QSAR models.
Significant parameters	lipophilicity; H-bond capacity; molecular size; polar surface area (PSA); pKa

QSAR Models for dermal absorption^[7-8]

- ✓ *Endpoint*: permeability coefficient **Kp** (few QSARs predict Jmax)
- ✓ *Statistical methods*: MLR, PLS, PCR, ANN, Gaussian process models, etc...
- ✓ *Basic model*: $\log k_p = a + b \cdot \log P - c \cdot MW$ (Further developments include additional descriptors, e.g. H-bond properties, polarisability, topological and electrotopological indices, quantum-chemical desc., and non-linear modelling)
- ✓ *Main problems*: few models calculate finite dose permeability^[9]; complete statistics not always available; using large pools of theoretical molecular descriptors often cannot be justified.

QSARs	Dataset	Comments
Flynn (1990)	N=97 (Flynn dataset)	- human skin - 94 <i>in vitro</i> + 3 <i>in vivo</i> data
Wilschut <i>et al</i> (1995) Patel <i>et al</i> (2002) Vecchia & Bunge (2003)	N=99 N=158 N=127	- human skin - extended datasets including Flynn dataset
	EDETOX database (N=320)	- <i>in vivo</i> and <i>in vitro</i> data
Brian <i>et al</i> (2009)	N=169 (Oklahoma database)	- human or porcine skin
Lee <i>et al</i> (2010) Buist <i>et al</i> (2010), ...	Isolated datasets	

Conclusions

(1) Review of QSARs for predicting repeated dose toxicity

- ✓ The availability of (Q)SAR models for chronic toxicity endpoints is currently limited, or related to specific chemical classes.
- ✓ Toxicity testing systems and *in silico* strategies, traditionally based on general apical endpoints (toxicological effects), are moving toward a new paradigm of toxicology, which focuses on specific biological mechanisms known to trigger adverse effects in key toxicity pathways (AOP approach).
- ✓ Within the AOP approach, *in silico* methods, such as (Q)SAR and read-across, represent key support tools to other non testing strategies (e.g. *in vitro* testing).

(2) Review of QSARs for oral and dermal adsorption/permeability

- ✓ PAMPA permeability increases with hydrophobicity and the higher ratio of neutral molecules, and decreases with the surface area occupied by hydrogen bond acceptor/donor atoms.
- ✓ QSAR models for skin absorption outline the importance of parameters related to lipophilicity, size/shape and polarity.
- ✓ High quality data are needed for modelling of skin absorption; prediction models for realistic exposure data are needed (low dose, repeated exposure, mixtures).