**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**

Traditional approaches to toxicological risk assessment focus primarily on adverse health outcomes as the end points for assessing the risk posed by environmental agents.[2]

**Organ-specific and system-specific toxicity**

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]

**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

**Results (2) – QSARs for Oral and Dermal Absorption/Permeability**

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 assay:** Parallel artificial membrane permeability assay
- **MLR or bilinear QSAR models.**

**QSAR Models for dermal absorption**

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

**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 absorption/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).**

**References**


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