(Q)SAR in Regulatory Praxis

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Introduction and objectives

According to REACH Annex XI, 1.3, “Results obtained from valid qualitative or quantitative structure-activity relationship models ((Q)SARs) may indicate the presence or absence of a certain dangerous property”. These results can be used instead of testing if certain relevant conditions are met [1].

In the regulatory praxis of REACH Phase I and II, (Q)SAR techniques were often used and incorporated in registration strategies. Results obtained from (Q)SAR models were submitted and accepted as key values, supporting information, or contributions to the weight of evidence approach. The endpoints addressed included mainly physico-chemical and environmental fate related properties and furthermore to less extent ecotoxicological and human toxicity information.

We present a summary of (Q)SAR use by our company throughout the REACH registration Phases I and II. The statistics covers the purpose of (Q)SAR studies (key study, supporting study, weight of evidence), substance types (mono-constituent, multi-constituent, UVCB), endpoints where (Q)SARs were applied, as well as models and software used and other related information. .

Applicability of (Q)SARs for various endpoints

Figures 1 and 2 show the contribution of various QSAR models in REACH phase I (Fig. 1) and type of endpoints for which QSARs were used (Fig. 2). For 142 lead dossiers QSARs were applied in REACH Phase I resulting in 777 QSAR applications per endpoint per substance.

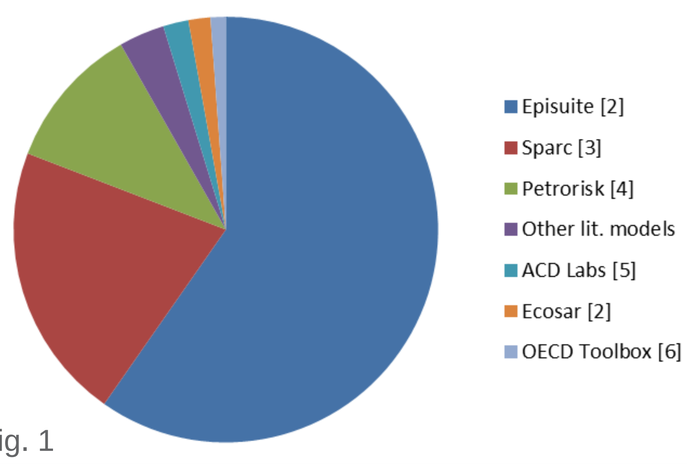

Fig. 1

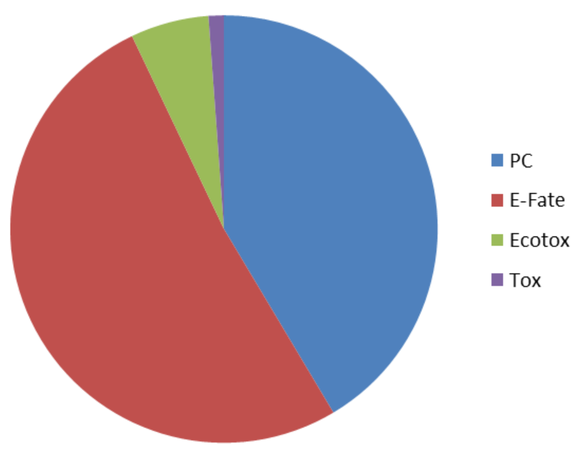

Fig. 2

Percentage of substances where (Q)SAR calculations were applied related to single endpoints:	
Photodegradation in air	79.4
Adsorption	75.7
Vapour pressure	71.3
Partition coefficient (log Pow)	63.2
Dissociation constant	54.4
Bioaccumulation	48.5
Density	29.4
Hydrolysis	27.9
Distribution modeling	23.5
Henry´s Law constant	22.1
Aquatic ecotoxicological endpoints	12.5
Water solubility	11.0
Biodegradation	11.0
Toxicological endpoints (human health)	5.9
other PC-endpoints	2.9

Other practical applications of (Q)SAR – our experience

- Searching for read-across candidates
- Substance profiling and comparison of analogues (OECD Toolbox)
- Estimation of physico-chemical properties (trend analysis in chemical categories)
- Analogue approach and category justification
- Generation and profiling of metabolites
- Structure-based data waiving

(Q)SAR strategy for data gaps in a large-scale project

Figures show used purpose flags (i.e. key, supporting, weight of evidence), taking into account substance type mono-constituent (Fig.3) vs UVCB/multi-constituent (Fig.4) of one large project in Phase I and II. In this project QSARs were applied for 66 mono-constituent substances and 156 multi-constituent substances/UVCBs.

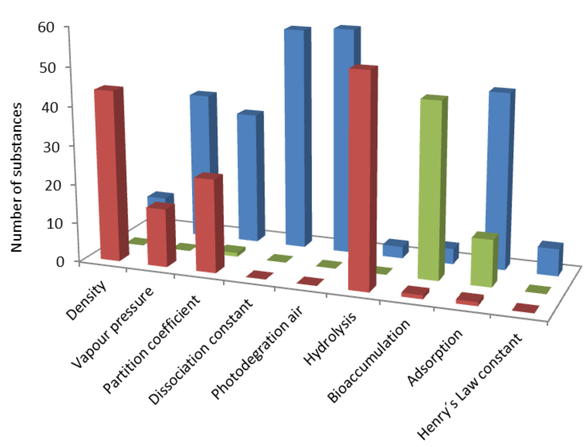

Fig. 3

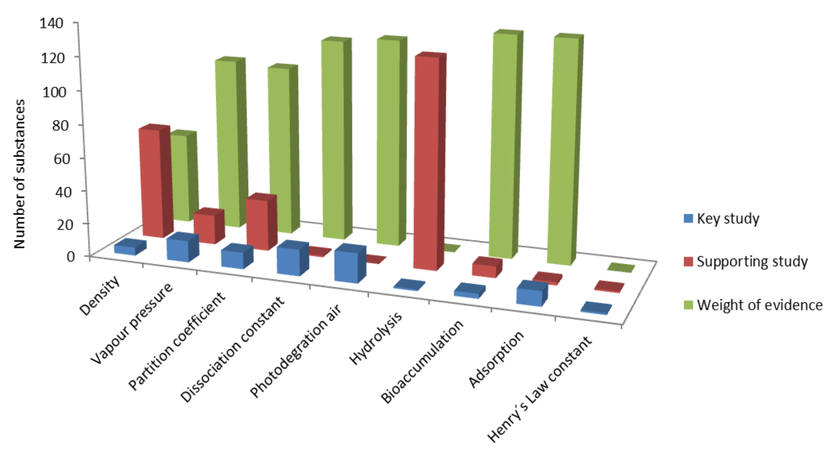

Fig. 4

In Phase I and II the following programs were used for covering respective endpoints indicated in Fig. 3 and 4.	
Density	Sparc v4.5/4.6
Vapour pressure	Sparc v4.5/4.6
Partition coefficient	Kowwin v1.68
Dissociation constant	Sparc v4.5/4.6
Photodegradation in air	Aopwin v1.92
Hydrolysis	Hydrowin v2.0
Bioaccumulation	BCFBAF v3.01
Adsorption	Kocwin v2.0
Henry´s Law constant	Henrywin v3.1/3.2

Outlook – REACh Phase III

- Continuation and development of registration strategies involving (Q)SAR applications
- Use of further tools and software packages, e.g. VEGA Platform, US EPA T.E.S.T., ChemProp
- Advanced toxicological profiling (OECD Toolbox, Toxtree, and others)
- Collaboration and contact with software developers

References

[1] REGULATION (EC) No 1907/2006

[2] US EPA. (2010-2013) Estimation Programs Interface Suite v 4.10/4.11.

[3] Carreira, et al. (1994) SPARC v4.5/4.6

[4] Petrorisk v5.3, CONCAWE, 2010

[5] Advanced Chemistry Development, Inc., Toronto, Canada

[6] The OECD QSAR Toolbox for grouping chemicals into categories, v3.2 and earlier

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