CADASTER

CAse studies on the Development and Application of in-Silico Techniques for Environmental hazard and Risk assessment

Grant agreement no.: 212668

Collaborative Project

Sub-Priority ENV2007 3.3.1.1: In-silico techniques for hazard-, safety-, and environmental risk assessment

Overview of (Q)SAR models and their specific features for assessing fate and effects
(Deliverable 2.2)

Due date of deliverable: December 31, 2009
Actual submission date: December 31, 2009

Start date of project: 1 January 2009 Duration: 4 years

Lead Contractor: National Institute of Public Health and the Environment (RIVM), Laboratory for Ecological Risk Assessment
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Deliverable no: 2.2 (Overview of (Q)SAR models and their specific features for assessing fate and effects)
Nature: Report restricted to consortium partners and EU services

Project co-funded by the EU Commission within the Seventh Framework Programme		
Dissemination Level		
PU	Public	
RE	Restricted to a group specified by the consortium (including the Commission Services)	
CO	Confidential, only for members of the consortium (including the Commission Services)	X

WP 2: Database on experimental parameters and (Q)SARs for chemical and biological endpoints

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Task 2.2- Collection of (Q)SAR models and non-testing approaches. Overview of (Q)SAR models and their specific features for assessing fate and effects (Deliverable 2.2)

Overview

A survey of the existing QSAR/QSPR models for the four classes of chemicals selected in this project (Brominated flame retardants, Fragrances, Perfluorinated chemicals, Triazoles and Benzotriazoles), stated in previous reports, has been completed. At the moment, just a few QSAR models specifically developed on the four chemical classes of compounds studied in CADASTER, have already been published. The analysis of these models according to the requirements of the 'OECD principles for QSAR validation' for regulatory applicability is the topic of Deliverable 3.2. (due per December 2009) Publicly available EPI Suite models were also taken into consideration. In this case, it has been assessed, which of these models are reliably applicable to the four classes of chemicals.

At this stage of knowledge, QSPR models are available only for some SIDS physico-chemical properties of BFRs (Henry's low constant, vapor pressure, water solubility, LogK_{OW}, photodegradation rate), while for the other three classes of chemicals EPI Suite models are the only tools available to predict SIDS physico-chemical properties.

The same applies for existing QSAR models, which are predominantly developed for non-SIDS endpoints, such as endocrine disruption (for BFRs and PFCs) or skin sensitization (for fragrances). There is only one QSAR model based on acute toxicity to fish which is developed for a large data set containing a few substituted triazoles. In the absence of *ad hoc* QSAR models for the four classes of chemicals selected in this project, the ECOSAR estimation program included in EPI Suite could be used to predict acute and chronic toxicity to fish, aquatic invertebrates and algae (SIDS endpoint for ecotoxicity). The problems linked to the applicability of ECOSAR models to BFRs, fragrances, PFCs, TAZs and BTAZs are better explained in the following paragraph.

Activities performed

Below are summarized the existing QSARs collected for individual classes. Tables containing all the useful information and details on the models are attached in Appendix 2.2. The same models have been verified for their application of the OECD Principles of QSAR in regulation (Deliverable 3.2).

BFRs

QSPRs models have been published for the following physico-chemical and degradation properties:

- Henry's Low Constant, H (SIDS) (Xu et al., 2007);
- Subcooled Liquid Vapor Pressure, PL (SIDS) (Xu et al., 2007; Wania and Dugani, 2003; Wang et al., 2008; Öberg, 2002);
- Water Solubility, WS (SIDS) (Wania and Dugani, 2003);
- Octanol-Air Partition Coefficient, $LogK_{OA}$ (Xu et al., 2007; Wania and Dugani, 2003 ; Wang et al., 2008; Chen et al., 2003 ; Zhao et al., 2005) ;
- Octanol-Water Partition Coefficient, $LogK_{OW}$ (SIDS) (Wania and Dugani, 2003; Braekevelt et al., 2003; Li et al., 2008);
- Photodegradation rate, Kp, measured in different solvents (methanol/water, methanol, hexane) (SIDS) (Niu et al.,2006; Chen et al., 2007 ; Fang et al., 2009);
- Quantum yield, Φp, measured in different solvents (methanol/water, methanol, hexane) (Niu et al.,2006; Chen et al., 2007 ; Fang et al., 2009).

To our knowledge, no *ad hoc* QSAR models have already been published for ecotoxicity endpoints (acute toxicity to Algae, Daphnia and Fish), probably due to the lack of sufficient amounts of experimental data. However different QSARs have been found in literature for endpoints related to endocrine disrupting activity of BFR, that is:

- Aryl hydrocarbon Receptor Relative Binding Affnity, RBA (Wang et al, 2005; Wang et al., 2006; Zheng et al., 2007);
- *Luciferase* activity (Harju et al., 2002);
- Androgen Receptor Antagonism, AR_{ANT} (Harju et al., 2007; Yang et al., 2009).

In addition to the above mentioned *ad hoc* QSARs/QSPRs, different EPI Suite estimation programs can be used to predict SIDS physico-chemical properties, such as Henry's Law Constant, Melting Point (MP), Boiling Point (BP), Vapor Pressure (VP), Water Solubility (WS), $LogK_{OA}$ and $LogK_{OW}$.

For most of EPI Suite models no experimental data of brominated flame retardants, and in particular of PBDEs, are included in the training set used to build the models. Comparing available experimental physico-chemical data of BFRs with those estimated by the EPI Suite programs, the latter ones tend to either overestimate or underestimate the experimental values, especially for highly brominated compounds. This evidence suggests that BFRs are not included in the structural applicability domain of EPI Suite models. Reported below is a table containing comparisons between EPI Suite models and models recently published by the Univesrity of Insubria (UI) within the CADASTER Project (Papa *et al.,* QSAR & Comb.Sci, 2009), realized through the calculation of RMSE values (*Root Mean Square of Errors*).

Table 1. Comparison between EPI Suite models and *ad hoc* models by UI (Papa *et al.,* 2009).

Phys-Chem Property	Model	N_{obj}[a]	RMSE
LogH [Pa m^3/mol]	EPI Suite	7	0.79
	BEHe7		0.11
MP [°C]	EPI Suite	25	57.47
	X2A		18.92
LogVp [Pa]	EPI Suite	34	0.93
	T(O..Br)		0.16
LogWS [mol/L]	EPI Suite	12	1.88
	Mor23m		0.22
LogKoa	EPI Suite	30	0.81
	T(O..Br)		0.23
LogKow	EPI Suite	20	0.91
	T(O..Br)		0.19

[a] experimental data collected by UI

As it can be seen in Table 1, RMSE values of EPI Suite are always higher than those of the *ad hoc* models developed by UI.

Another important tool included in EPI Suite is the ECOSAR estimation program, which predicts toxicity to fish, aquatic invertebrates and algae using an extensive set of structure-activity relationship models (SARs). The majority of BFRs (PBDEs, CH_3O-BDE metabolites, hexabromocyclododecane, hexabromobenzene, 2,4,6-tribromophenol) are classified by ECOSAR as "Neutral Organics". For these chemicals baseline toxicity is estimated by logKow.

Since acute toxicity models (e.g. Fish LC50 96-h, Daphnid LC50 48-h, Green Algae EC50 96-h …) can be used only for compounds with LogKow values less than 5.0 (6.4 for Green Algae), these models are not applicable to BFRs, which are characterized by LogKow values higher than 5.

For chronic toxicity endpoints (i.e. Fish ChV 30-d, Daphnid ChV 16-d, Green Algae ChV) ECOSAR models can be used for compounds with LogKow values less than 8.0. Thus, these models could be applicable for most of BFR, with the exception of higher brominated PBDE.

In any case, ECOSAR highlights that, according to water solubilities estimated by the program WSKOWWIN, BFRs "may not be soluble enough to measure the predicted effects".

Fragrances

Till now, to our knowledge, no *ad hoc* QSAR/QSPR models have been developed for the prediction of physico-chemical properties and environmental toxicity of fragrances. Nevertheless different QSARs exist for skin sensitization, an endpoint related to human toxicity but not included in SIDS.

Hence, the only existing models for the prediction of SIDS endpoints for fragrances are EPI Suite models. EPI Suite programs can be used to estimate physico-chemical properties such as Melting Point, Boiling Point, Vapor Pressure, Water Solubility, $LogK_{OA}$ and $LogK_{OW}$.

In general, EPI Suite estimations are quite in agreement with experimental data, although they are less accurate than those obtained using *ad hoc* models recently developed by UI within the CADASTER

Project. In Table 2 a comparison between EPI Suite models and *ad hoc* models developed by UI is reported (Papa et al., SAR & QSAR Environ. Res., in press, 2009).

Table 2. Comparison between EPI Suite models and *ad hoc* models by UI.

Phys-Chem Property	**Model**	**N_{obj}[a]**	**RMSE**
LogVp [Pa]	EPI Suite	37	1.91
	piPC01 nHDon		0.2
LogWS [mg/L]	EPI Suite	37	0.3
	BEHm3 JGI3 nCconj		0.45
LogKow	EPI Suite	52	0.64
	X2v RDCHI		0.47

[a] experimental data collected by UI

In relation to the ECOSAR models, they classify the fragrances based on the different fragments of the chemicals and, in many cases, give different toxicity results for a single compound, depending on the class to which the compound is assigned. As an example, for the fragrance Cinnamyl acetate (CAS: 103-54-8) ECOSAR identifies two classes, “Esters” and “Vinyl/Allyl Esters”; in addition, the program gives also baseline toxicity predictions based on the Neutral Organic SAR. The predicted toxicity values are highly different depending on the assigned class (Table 3).

Table 3. ECOSAR predictions (mg/L) for the fragrance 103-54-8.

Endpoint	**Ester SAR**	**Vinyl/Allyl Esters SAR**	**Neutral Organic SAR**
Fish LC50 - 96 hr	7.845	0.932	26.007
Fish (SW) LC50 – 96 hr	10.791		
Fish LC50 - 14 day	316.753 *		
Daphnid LC50 – 48 hr	14.454	5.896	16.627
Green Algae EC50 – 96 hr	5.623	1.475	10.152
Mysid Shrimp LC50 – 96 hr	7.241		
Earthworm LC50 – 14 day	1224.109 *		
Fish ChV	0.575	0.016 !	2.423
Fish (SW) ChV	1.846 !		
Daphnid ChV	7.331	0.175 !	1.784
Green Algae ChV	1.868	0.315	4.289
Mysid Shrimp (SW) ChV	92.035		

* Chemical may not be soluble enough to measure this predicted effect.
! The toxicity value was determined from a predicted SAR using established acute-to-chronic ratios and ECOSAR regression techniques which are documented in the supporting Technical Reference Manual. When possible, this toxicity value should be considered in a weight of evidence approach.

In addition, most of the models used by the ECOSAR program to estimate ecotoxicity for fragrances are not validated QSARs, and based on very few experimental data.

Perfluorinated chemicals (PFCs):

For QSPRs on SIDS physico-chemical properties, data on boiling point, Fluorophilicity - Fluorous partition coefficient are modeled (Rucker et al., 2005; Kiss et al., 2001). In addition, commercial softwares were used to derive "polyparameter linear free energy relationships" for various end points.

EPI Suite models have been also considered. Their performances have been compared with those of some preliminary models developed by UI on MP, BP and VP (presented in Conferentia Chemometrica 2009, Siofok, Hungary).

Table 4. Comparison between EPI Suite models and *ad hoc* models by UI.

Phys-Chem Property	**Model**	**N_{obj}[a]**	**RMSE**
MP [°C]	EPI Suite	111	46.68
	AAC F02[C-F] C-013		40.36
BP [°C]	EPI Suite	130	43.05
	Ms ATS1m nROH		27.57
LogVp [Pa]	EPI Suite	35	1.12
	CIC0 MATS1v TPSA(Tot)		0.83

[a] experimental data collected by UI

QSAR models on T4-TTR binding are published using the PLS approach (Weiss et al., 2009). In addition, ECOSAR predictions can be considered as toxicity models for PFCs but as in above cases (eg. Fragrances) they are derived from a fragment based approach, with either few or with predicted data, and the baseline toxicity value which is used belongs to different chemical classes and not specifically for the PFCs. In some cases, the differences between the predictions from different chemical classes (eg. CAS 360-58-7) are 10 fold (Table 5).

Table 5. Examples of ECOSAR predictions (mg/L) for some PFCs compounds.

Compound	**Fragments**	**Fish LC50 96-hr**	**Daphnid LC50 48-hr**	**Green Algae EC50 96-hr**
376-89-6	Halo Nitriles	No current SARS		
	Nitriles, Polyaliphatic	628.510	332.588	106.871
360-58-7	Vinyl/Allyl Ethers	0.270	9.711	12.056
	Halo Ethers	20.597	5.583	No data

Triazoles and Benzotriazoles (TAZs and BTAZs)

QSPR models specifically on TAZs and BTAZs have been not found in the literature. Only logP data are modeled where few TAZs are part of the larger dataset. Regarding EPI Suite models, their predictions for MP, VP, $LogK_{OW}$ and WS do not show lare deviations from available experimental data. However, preliminary *ad hoc* QSPRs developed by UI for triazoles and benzotriazoles have RMSE values always

lower than those calculated for EPI Suite models, the main exception being the LogKow model (Table 6).

Table 6. Comparison between EPI Suite models and *ad hoc* preliminary models developed by UI .

Phys-Chem Property	Model	N_{obj} [a]	RMSE
LogVp [mmHg]	EPI Suite	31	1.725
	RBN MATS4e EEig15x	31	0.785
LogWS [mg/L]	EPI Suite	49	1.247
	AMW CICO MATS7e	49	0.537
MP [°C]	EPI Suite	56	71.728
	X1A GGI4 R2e F03[N-N]	56	26.634
LogKow	EPI Suite	62	0.604
	T(0..0) GATS1m W3D	62	0.685

[a] experimental data collected by UI

QSAR models on the following end-points are found for TAZs/BTAZs (Trohalaki et al., 2002; Klink, 2003; Wei et al., 2006):

1. EC_{25}MTT (mM)
2. LSCROS (mM)
3. EC_{25}LDH (mM)
4. EC_{50}GSH (mM)
5. Sensitization and/or irritancy potential
6. Fungicide (wheat head blight) (FA) (50 ug/ml)

Although these models are not specifically for SIDS endpoints, they are related to human and to plant toxicity. In addition, models based on "LC_{50}-96h acute toxicity of rainbow trout" are developed for large datasets which contain only few TAZs (Benfenati, 2006; Benfenati, 2008).

ECOSAR models on TAZs and BTAZs have the same problems as described above. In Table 7 ECOSAR predictions for the compounds 8-Azaxanthine (CAS 1468-26-4) and Acetamide, N-(3-(5-nitro-2-furyl)-s-triazol-5-yl) (CAS 1704-66-1) are reported as an example.

Table7. ECOSAR predictions (mg/L) for the compounds 1468-26-4 and 1704-66-1.

Compound	Classes/Fragments	Fish LC50 96-hr	Daphnid LC50 48-hr	Green Algae EC50 96-hr
1468-26-4	Imides	14909.459	12330.157	35.158
	Amides	6905.285	1280.314	2.649
	Triazoles (Non-Fused)	3062.8	14933.703	125.656
1704-66-1	Amides	463.87	155.959	1.359
	Triazoles (Non-Fused)	407.283	1329.625	34.103

In general, most of ECOSAR models available are based on very few data and thus they are of limited utility for the specific classes of compounds studied under the project CADASTER. From this analysis

the need of the development of specific QSAR models in CADASTER Project (WP3) is highly evident. The main problem in this respect is the lack of SIDS data in sufficient amounts to develop new QSARs. For this reason, all the available data that have been collected will be modeled.

Activities foreseen

In line with the Description of Work of CADASTER, the collection and evaluation of available QSAR models will continue during the whole Project.

Appendix to Deliverable 2.2

The Appendix to Deliverable 2.2 contains tables containing all the useful information and details on the QSAR models highlighted above.

Appendix to Deliverable 2.2

Existing QSPR models on Brominated Flame Retardants (BFRs)

Reference	Method / Tool	Endpoint	Train obj.	Test obj.	n°Var	n° PLS comp	R^2%	Q^2_{cum}/ R^2_{CV}%	Experimental Data set
Xu *et al.* (2007)	MLR	Log H	7	-	2		99.74	99.79	Cetin and Odabasi (2005)
		Log P_L	22	-	2		98.13	97.59	Wong et al. (2001)
		Log K_{OA}	22	-	2		97.61	97.25	Wania et al. (2002)
		-Log RBA	18		4		64.73	28.94	Chen et al. (2001)
Wania and Dungani (2003)	LR	Log P_L	6	-	1		99.62	-	Wania and Dugani (2003)
		Log S	6	-	1		99.19	-	
		Log K_{OW}	6	-	1		97.54	-	
		Log K_{OA}	6	-	1		99.41	-	
Braekevelt et al. (2003)	LR	Log K_{OW}	9	-	1		97	-	Braekevelt et al. (2003)
Wang *et al.* (2008)	MLR	Log P_L	23	7	3		99.71	99.58	Wong et al (2001), Tittlemier et al. (2002)
		Log K_{OA}	22	6	3		99.73	99.64	Wania et al (2002), Harner and Shoeib (2002)
Öberg (2002)	PLS	Log P_L	23	9	?	1	99.2		Wong et al (2001), Tittlemier et al. (2002)
Chen *et al.* (2003)	PLS	Log K_{OA}	9 (?)	-	10		97.9	97.5	Harner and Shoeib (2002)
Zhao *et al.* (2005)	MLR	Log K_{OA}	13	-	2		92.74	-	Harner and Shoeib (2002)
Li et al. (2008)	PLS	Log K_{OW}	9	-	3		98.93	96.1	Braekevelt et al. (2003)
US-EPA	EPI SUITE	H, MP, VP, S, Log K_{OW}, Log K_{OA}	RMSE of UI models are lower than that of EPI suite models						SRC- PhysProp
Niu *et al.* (2006)	PLS	Log $K_{p\ MET/H2O}$	15	-	6	1	95.8	95.7	Eriksson et al. (2004)
		Log $K_{p\ MET}$	9	-	6	3	97,81	98,4	Eriksson et al. (2004)
		Log $\Phi_{p\ MET/H2O}$	11	-	8	3	98.2	91.4	Eriksson et al. (2004)

Reference	Method / Tool	Endpoint	Train obj.	Test obj.	n°Var	n° PLS comp	R^2%	Q^2_{cum}/ R^2_{CV} %	Experimental Data set
Chen *et al.* (2007)	PLS	Log $K_{p\ MET/H2O}$	15	-	8	3	98.2	97.3	Eriksson et al. (2004)
		Log $K_{p\ MET}$	9	-	9	2	95.8	95.8	Eriksson et al. (2004)
		Log $\Phi_{p\ MET/H2O}$	11	-	4	2	86.1	70.2	Eriksson et al. (2004)
Fang *et al.* (2009)	PLS	Log $K_{p\ HEX}$	18	-	7	1	91.97	90.7	Fang et al. (2009)
		Log $K_{p\ MET}$	18	-	9	1	89.87	88.3	Fang et al. (2009)
		Log $\Phi_{p\ HEX}$	18	-	5	1	78.85	75.4	Fang et al. (2009)
		Log $\Phi_{p\ MET}$	18	-	5	2	86.49	93.0	Fang et al. (2009)

Existing QSAR models on Brominated Flame Retardants (BFRs)

Reference	Method / Tool	Endpoint	Train obj.	Test obj.	n°Var	n° PLS comp	R^2%	Q^2_{cum}/ R^2_{CV} %	Experimental Data set
Wang *et al.* (2005)	CoMFA	-Log RBA	18	-		6	99.5	58	Chen et al. (2001)
	CoMSIA	-Log RBA	18	-		6	98.2	68	Chen et al. (2001)
Wang *et al.* (2006)	Heuristic Met.	-Log RBA	18	-	4		90.3	84.4	Chen et al. (2001)
Zheng *et al.* (2007)	SVM_{3f}	-Log RBA	15	3	7		-	88.9	Chen et al. (2001)
Harju *et al.* (2002)	PLS	*Luciferase* activity	17	-		1	61.8	48.6	Meerts et al. (1998)
Harju *et al.* (2007)	PLS	-Log IC_{50} ARant	20	-	?		90	77	Hamers et al. (2006)
Yang *et al.* (2009)	CoMSIA	-Log IC_{50} ARant	15	4		3	97.6	54.6	Hamers et al. (2006)
US-EPA	ECOSAR	ecotoxicity endpoints (acute and chronic)	ECOSAR models are not applicable to BFR both for their high LogKow values and for their very low water solubility.						

Existing QSPR models on Perfluorinated chemicals (PFCs)

Reference	Method / Tool	Endpoint	Train obj.	Test obj.	n°Var	R^2%	Q^2_{cum}/ R^2_{CV} %	Experimental Data set
Rucker *et al.* (2005)	MLR / MOLGEN -QSPR	BP	82	-	7	0.99	0.98	
Kiss et al. (2001)	NN / 3D-NET	Fluorophilicity - Fluorous partition coef.	59	-	8		0.97	Kiss (1998) Szlavik (1999)
Arp et al. (2006)		Log P_L[a]	11	5				Shoeib et al. (2004),
	ClogP				Prediction from commercial softwares			Krusic et al. (2005), Kaiser et al. (2005)
	Sparc	Log K_{AW}[a]	4	12				Goss (2006)
	EPI Suite	Log K_{OW}	4	12	[a] ClogP calculation was			Goss (2006)
	COSMOtherm	Log Ki[a] (hexanedecane/air)	8	12	not available for these endpoints			Goss (2006)
		Log K_{OA}[a]	7	9				Shoeib et al. (2004)
Goss (2008)	Sparc COSMO-RS	pKa	33	-	Prediction from commercial softwares			Henne and Fox (1951)
US-EPA	EPI SUITE	MP, BP, VP	RMSE of UI models are lower than that of EPI suite models					SRC- PhysProp

Reported as Polyparameter linear free ebergy relationships (pp-LFER) in article

Existing QSAR models on Perfluorinated chemicals (PFCs) - continued

Reference	Method / Tool	Endpoint	Train obj.	Test obj.	n°Var	n° PLS comp	R^2%	Q^2_{cum}/ R^2_{CV} %	Experimental Data set
Weiss *et al.* (2009)	PLS	T4-TTR binding	23	-	56	2	-	0.41	Weiss *et al.* (2009)
US-EPA	ECOSAR	ecotoxicity endpoints (acute and chronic)	Prediction of the toxicity based on the baseline toxicity value of different fragments of chemicals but not specifically for PFCs						

Existing QSPR models on Triazoles and Benzotriazoles (TAZs and BTAZs)

References	Method /Tool	Endpoint	n	Model parameters	Experimental Data set
Devillers (1999)	Neural Network	Log P	593	Few triazoles commonly used as Pesticides are studied in a bigger training set	
US- EPA	EPI Suite	MP, VP, WS, LogP		RMSE of UI models (according to OECD principles) are lower than that of EPI suite models	SRC- PhysProp

Existing QSAR models on Triazoles and Benzotriazoles (TAZs and BTAZs)

References	Method / Tool	Endpoint	n	n of TAZ	Test obj.	n°Var	A	R^2%	R^2_{CV}% /Q^2_{LOO}
Benfenati (2006)	fragment-based QSAR	LC_{50}-96 h acute toxicity of rainbow trout	282	Few triazoles commonly used as Pesticides are studied in the bigger set					
Benfenati (2008)		LC_{50}-96 h acute toxicity of rainbow trout	125						
Benfenati (2006)		Daphnia toxicity	220 (42 test)						
Trohalaki (2002)	Heuristic and Best MLR / CODESSA Quantum-Chemical descriptor	EC_{25}MTT (mM) LSCROS (mM) EC_{25}LDH (mM) EC_{50}GSH (mM)	13	2	-	Not applicable			
Klink (2003)	TOPKAT 6.0	Sensitization and/or irritancy potential	2	2	-	use of commercial software to predict the response			
Wei Q-L et al. (2006)	MLR/SPSS	Fungicide (wheat head blight) (FA) (50 ug/ml)	18	18	-	2	-	96.9	-

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