

PBT Bewertung – Schließen von Datenlücken

Dr. Marc Brandt
Umweltbundesamt
Fachgebiet IV 2.3
Chemikalien



PBT Bewertung – Schließen von Datenlücken

Übersicht

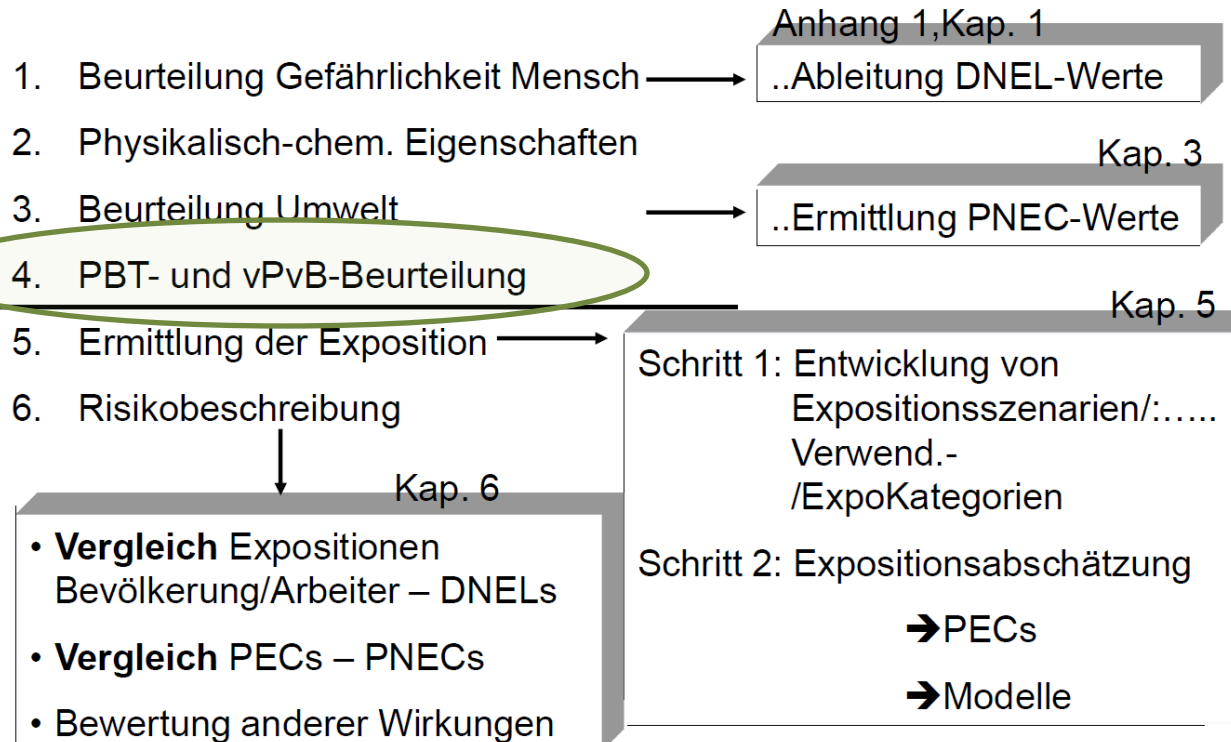
1. PBT-Bewertung bei der Sicherheitsbeurteilung
2. Wiederholung der Grundlagen aus WS 2
3. PBT-Kriterien und Vorgehen bei ihrer Bewertung
4. Read Across und QSAR an einem Beispiel
 - a. Read Across – OECD QSAR-Toolbox
 - b. QSAR (EPISuite, VEGA)
5. Anforderungen an die Dokumentation
6. Zusammenfasssung



PBT Bewertung – Schließen von Datenlücken

PBT-Bewertung bei der Sicherheitsbeurteilung

Stoffsicherheitsbeurteilung (CSA) (REACH, Anhang 1)



PEC: vorhergesagte Umweltkonzentration

07. Oct. 2011

UBA Conference Sustainable Chemistry

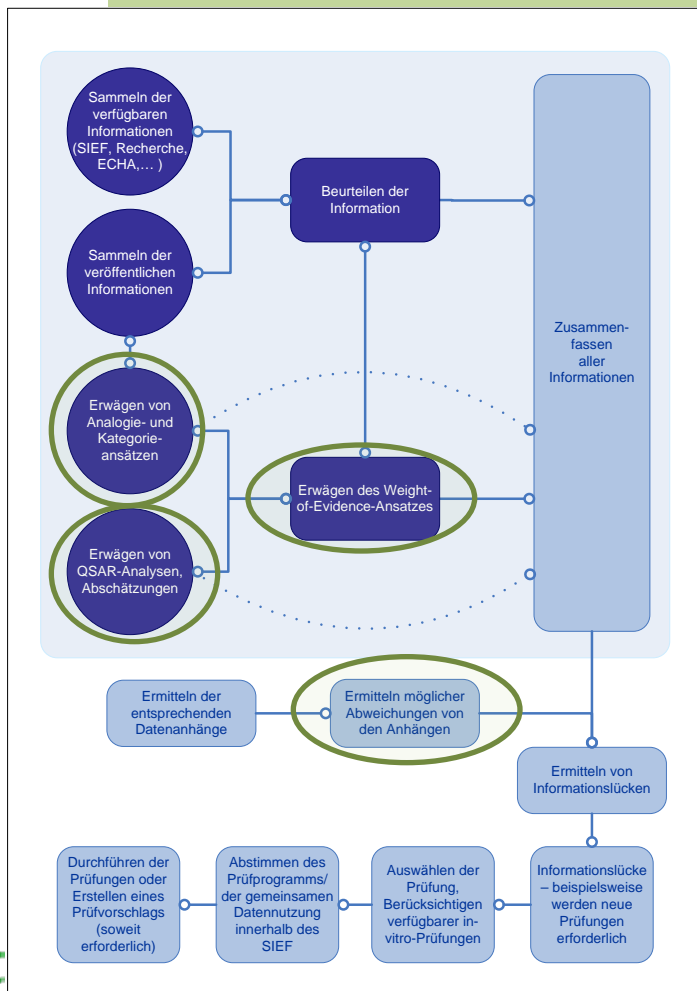


5
5



PBT Bewertung – Schließen von Datenlücken

Wiederholung WS2: Adaptation, Read Across, QSAR, ...





PBT Bewertung – Schließen von Datenlücken

Wiederholung WS2: Begriffe

Begriff	Erklärung
Intelligent Testing Strategy (ITS)	Intelligente Teststrategie: Flexible und schrittweise Generierung von neuen Daten durch Tests
Adaptation:	Abweichung von Standarddatenanforderungen (Anhang XI, Abschnitt 1.1 – 1.5)
Waiving:	Verzicht auf die Erfüllung von Datenanforderungen (Spalte 2 der Anhänge VII-X)
Read Across:	Übertragen von Informationen zu Stoff B auf Stoff A
Grouping oder Category Approach:	Zusammenfassen von verwandten Stoffen zu einer Gruppe in der Informationen übertragen werden können
(Q)SAR:	(Quantitative) Struktur-Wirkungs-Beziehungen, mathematische Modelle zur Vorhersage von Endpunkten aufgrund von Strukturmerkmalen oder anderen Endpunkten
Weight-of-Evidence (WoE)-Betrachtung:	Gesamtschau aller Daten zum Schließen von Datenlücken



PBT Bewertung – Schließen von Datenlücken

Kriterien des Annex XIII zu PBT/vPvB

		PBT	vPvB
Persistenz	<i>Screening-Kriterium</i>	<i>nicht leicht biologisch abbaubar</i>	
	Halbwertszeit in:		
	Meerwasser,	> 60 d	> 60 d
	Süßwasser	> 40 d	> 180 d
	Meersediment	> 180 d	-
Bioakkumulation	Süßwassersediment	> 120 d	-
	Boden	> 120 d	> 180 d
Toxizität	<i>Screening-Kriterium</i>	<i>LC50/EC50 < 0.1 mg/l</i>	-
	NOEC	< 0.01 mg/l CMR	

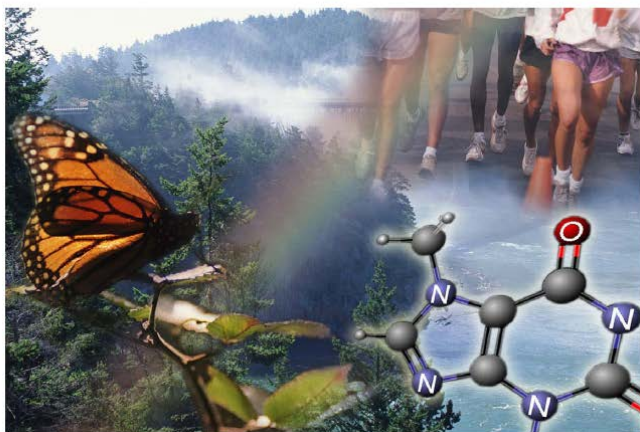


PBT Bewertung – Schließen von Datenlücken

Vorgehen entsprechend ECHA-Leitfaden R.11



Guidance on information requirements and chemical safety assessment Chapter R.11: PBT Assessment



May 2008

Guidance for the implementation of REACH

Screeningkriterien:

PART R11 – PBT ASSESSMENT

Table R. 11-2 : Screening criteria for P, vP, B, vB and T

Type of data	Criterion	Screening assignment	See section
Persistence			
Ready biodegradability test	readily biodegradable	Not P and not vP	
Enhanced ready biodegradability test	readily biodegradable	Not P and not vP	
Specified tests on inherent biodegradability			
Zahn-Wellens (OECD 302B)	≥70 % mineralisation (DOC removal) within 7 d; log phase no longer than 3d; removal before degradation occurs below 15%; no pre-adapted inoculum	Not P	R.11.1.3.1
MITI II test (OECD 302C)	≥70% mineralisation (O ₂ uptake) within 14 days; log phase no longer than 3d; no pre-adapted inoculum	Not P	
Biowin 2 (non-linear model prediction) and Biowin 3 (ultimate biodegradation time) or Biowin 6 (MITI non-linear model prediction) and Biowin 3 (ultimate biodegradation time)	Does not biodegrade fast (probability < 0.5) ³ and ultimate biodegradation timeframe prediction: ≥ months (value < 2.2) or Does not biodegrade fast (probability < 0.5) and ultimate biodegradation timeframe prediction: ≥ months (value < 2.2)	P	
Bioaccumulation			
Convincing evidence that a substance can biomagnify in the food chain (e.g. field data ⁴)	e.g. BMF > 1	B or vB, definitive assignment possible	R.11.1.3.2
Octanol-water partitioning coefficient (experimentally determined or estimated by valid QSAR)	Log Kow ≤ 4.5	Not B and not vB	
Toxicity			
Short-term aquatic toxicity (algae, daphnia, fish)	EC50 or LC50 < 0.01 mg/L	T, criterion considered to be definitely fulfilled	R.11.1.3.3
Short-term aquatic toxicity (algae, daphnia, fish)	EC50 or LC50 < 0.1 mg/L	T	
Avian toxicity (subchronic or chronic toxicity or toxic for reproduction)	NOEC < 30 mg/kg food	T	

³ The probability is low that it biodegrades: fast

⁴ See Guidance on information requirements



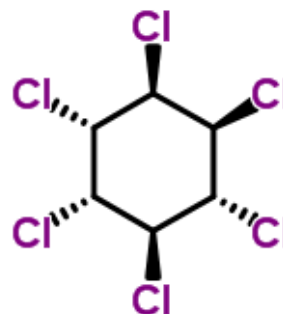
PBT Bewertung – Schließen von Datenlücken

Anwendung Read Across und QSAR am Beispiel

Ausgangssituation:

- Registrant eines Stoffs
- Hat schon viele Daten, will aber verantwortlich handeln und prüfen, was noch vorliegt

Beispielstoff:



- α -Hexachlorocyclohexan
- CAS: 319-84-6
- EINECS: 206-270-8
- SMILES: Cl[C@@H]1[C@H](Cl)[C@@H](Cl)[C@@H](Cl)[C@H]1Cl

Beispielanwendungen:

Read Across: OECD QSAR Toolbox

QSAR: EPISuite 4.1, VEGA NIC 1.0.6



PBT Bewertung – Schließen von Datenlücken

Vorstellung OECD QSAR Toolbox

Typical actions performed by the Toolbox

- Describes the structure of a chemical.
- Indicates if a chemical is included in national/regional regulatory inventories or existing chemical categories.
- Searches for available experimental results for the chemical of interest.
- Explores a chemical list for possible similar chemicals.
- Groups chemicals based on mechanism of action and/or structural similarity.
- Groups chemicals based on a common metabolite.
- Enables exclusion of different chemicals from the group.
- Extracts experimental data for similar chemicals.
- Fills data gaps for chemicals using read-across, trend analysis or QSAR models, where applicable.
- Designs a data matrix of a chemical category for printing/exporting results.
- Connects to IUCLID software for direct data exchange.
- Generates reports.

The QSAR Toolbox

- Facilitates the practical application of grouping of chemicals and read-across approaches for data gap filling.
- Serves as a platform that incorporates various modules and databases from other sources.
- Is applicable to discrete organic chemicals.
- Is available free of charge. Download instructions and free training material are available online at: www.qsartoolbox.org

In cooperation:



© European Chemicals Agency, 2011
Reproduction is authorized provided the source is acknowledged.
ECHA-11-L-08-EN

QSAR TOOLBOX

The OECD QSAR Toolbox
for Grouping Chemicals
into Categories



<http://www.qsartoolbox.org>

Quelle: OECD

Neue Version 3.0 wird ab Ende Oktober frei verfügbar sein



PBT Bewertung – Schließen von Datenlücken

QSAR Toolbox: Schritt 1 - Stoff finden

QSAR Toolbox 2.3.0.1132 (Document_2)

QSAR TOOLBOX

Input Profiling Endpoint Category Definition Data Gap Filling Report

Document New Open Close Save CAS# Name Structure Select Database Inventory List

Documents






Document_1

Document_2

Filter endpoint tree...

Structure

☒ Substance Identity
☐ Physical Chemical Properties
☐ Environmental Fate and Transport
☐ Ecotoxicological Information
☐ Human Health Hazards

1	2	3	4	5
				

Document_2

2/0/0

The OECD QSAR Toolbox for Grouping Chemicals into Categories
Developed by IMC, Bulgaria

QSAR Toolbox: Schritt 2 – Daten finden

Filter endpoint tree...

- Structure
- Substance Identity
- Physical Chemical Properties
- Environmental Fate and Transport
 - Bioaccumulation: Aquatic
 - BAF
 - BCF
 - Animalia
 - Polychlorinated biphenyls (1/1) M: 2.76E3
 - Polychlorinated biphenyls (1/1) M: 60.60-200.90...
 - Polychlorinated biphenyls (1/1) M: 140.140.250.4...
 - Polychlorinated biphenyls (1/1) M: 105.161
 - Polychlorinated biphenyls (1/1) M: 0.31-3
 - Polychlorinated biphenyls (1/1) M: 200(153-267). 2...
 - Polychlorinated biphenyls (1/1) M: 342.2.26E3
 - Polychlorinated biphenyls (1/1) M: 1.45E3 L/kg wet
 - Polychlorinated biphenyls (1/1) M: 1.5E3
 - Polychlorinated biphenyls (1/1) M: 0.112 kg organi
 - Polychlorinated biphenyls (1/1) M: 0.0323 1/Days, ...
 - Polychlorinated biphenyls (1/1) M: 1.23 log(Days)

Table Data:

Endpoint	1	2	3	4	5
Polychlorinated biphenyls	(1/1) M: 2.76E3				
Polychlorinated biphenyls (EC50)	(1/1) M: 0.37 mg/L, 0.48				
Polychlorinated biphenyls (EC50)	(1/1) M: 0.5 mg/L				
Polychlorinated biphenyls (EC50)	(1/3) M: 1.1 mg/L, 1.1 m...				



PBT Bewertung – Schließen von Datenlücken

QSAR Toolbox: Schritt 3 – Verwandte Stoffe finden

QSAR Toolbox 2.3.0.1132 (Document: 1)

QSAR TOOLBOX

Input Profiling **Endpoint** Category Definition Data Gap Filling Report

Database: Select All Unselected All Invert About

Filter endpoint tree...

Structure: ClC1(Cl)CC(Cl)CC1

Substance Identity: (52/98)

Physical Chemical Properties: M: 323 °C, 7.85, 3...

Environmental Fate and Transport: M: 1.6 log(Days), 1...

Bioaccumulation: Aquatic: M: 0.314 log(Days)

Biodegradation: M: 1.41E3 Days

Stability in Water: M: 1.90E-13 cm³/...

Transport and Distribution Between Environment: M: 0.521 Pa-m³/m...

Ecotoxicological Information: M: 1.01 mg/L, 1.18...

Human Health Hazards: M: 0.136 mg/kg/day...

Profile: M: 140 mg/kg/day...

Database Affiliation: Biota-Sediment Ac... kMDatabase

Inventory Affiliation: Aquatic US-EPA E...

OECD HPV Chemical Categories: Discrete chemical

Substance Type: (N/A)

US-EPA New Chemical Categories: No alert found

DNA binding by OASIS: 1,2-Dihaloalkanes

DNA binding by OECD: MA: Episulfonium I...

Estrogen Receptor Binding: Mechanistic Domai...

Protein binding by OASIS: Non binder, without

Protein binding by OECD: No alert found

Protein Binding Potency: 1,2-Dihaloalkane

Superfragments: Alkyl halides

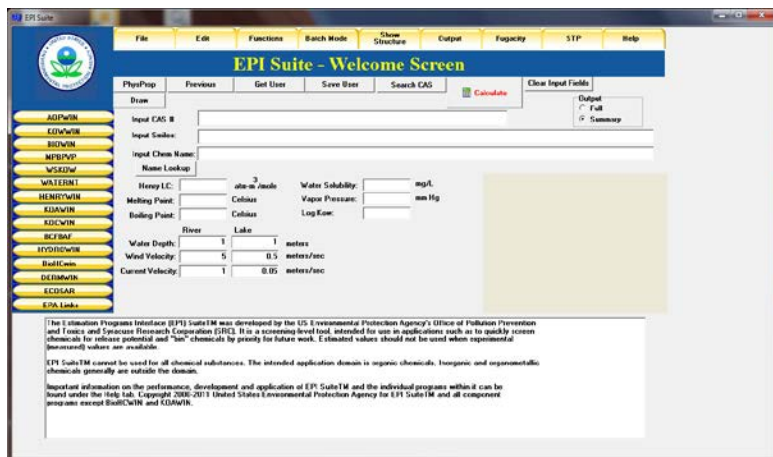
Toxic hazard classification by Cramer (original): MA: Episulfonium I...

Toxic hazard classification by Cramer (with extension): MA: SN2 reaction a...



PBT Bewertung – Schließen von Datenlücken

Vorstellung Beispiel-QSAR-Programme für PBT-Bewertung



EPI Suite for Windows
= Estimation Programs Interface Suite

Entwickelt von U.S. EPA

Aktuelle Version: 4.10

<http://www.epa.gov/oppt/exposure/pubs/episuite.htm>

offline verwendbar
kostenlos



VEGA
= Virtual models for property Evaluation
of chemicals within a Global Architecture

Entwickelt u.a. von Istituto Mario Negri
und Politecnico di Milano

Aktuelle Version: VEGA NIC1.06

<http://www.vega-qsar.eu/index.php>

offline und online verwendbar
kostenlos



PBT Bewertung – Schließen von Datenlücken

QSAR: EPISuite - Stoffeingabe

EPI Suite

File Edit Functions Batch Mode Show Structure Output Fugacity STP Help

Results

All Results | KOWWIN | MPBPVP | Water Solubility | ECOSAR | HENRYWIN | KOWWIN | BIOWIN | BioHCwin | AEROWIN | AOPWIN | KOCWIN | HYDROWIN | BCFBAF | Volatilization | STP

CAS Number: 319-84-6
SMILES : C(C(C(C(C1CL)CL)CL)CL)CL (C1CL)CL
CHEM : alpha-Hexachlorocyclohexane
MOL FOR: C6 H6 CL6
MOL WT : 290.83

----- EPI SUMMARY (v4.10) -----

Physical Property Inputs:

Log Kow (octanol-water): -----
Boiling Point (deg C) : -----
Melting Point (deg C) : -----
Vapor Pressure (mm Hg) : -----
Water Solubility (mg/L): -----
Henry LC (atm-m3/mole) : -----

Log Octanol-Water Partition Coef (SRC):

Log Kow (KOWWIN v1.68 estimate) = 4.26
Log Kow (Exper. database match) = 3.72
Exper. Ref: HANSCH,C ET AL. (1995)
Log Kow (Exper. database match) = 3.80
Exper. Ref: HANSCH,C ET AL. (1995)
Log Kow (Exper. database match) = 3.78
Exper. Ref: HANSCH,C ET AL. (1995)

Create MS Word File Print Results Print Results - No Structure Create a Text file ISIS Base/Upload TBL File View Main Screen

☐ Append Data to End of Selected Files

A Note about Creating MS Word files

C1 !



PBT Bewertung – Schließen von Datenlücken

QSAR: EPISuite – P-Screening

Biowin V 4.10

Rapid Probability Models

Biowin1 (Linear Model): -0.0593

Biowin2 (Non-Linear Model): 0.0000

Expert Survey Biodegradation Results

Biowin3 (Ultimate Survey Model): 1.5174 (calcitrant)

Biowin4 (Primary Survey Model): 2.8245 (weeks)

Anaerobic Probability Model

Biowin7 (Anaerobic Linear Model): 0.9848

MITI Probability Models

Biowin5 (MITI Linear Model): -0.0719

Biowin6 (MITI Non-Linear Model): 0.0000

Ready Biodegradability Prediction: NO

Buttons: Create MS Word File, Print Results, Print Results - No Structure, Create a Text file, ISIS Base/Upload

A Note about Creating MS Word files

☐ Append Data to End of Selected Files

P-Verdacht nach R11:

BIOWIN2 < 0.5 UND BIOWIN3 < 2.2

ODER

BIOWIN6 < 0.5 UND BIOWIN 3 < 2.2

→ Hier P-Verdacht bestätigt



PBT Bewertung – Schließen von Datenlücken

QSAR: EPISuite – B-Screening

Results

All Results | KOWWIN | MPBPVP | Water Solubility | ECOSAR | HENRYWIN | KOWWIN | BIOWIN | BioHCwin | AEROWIN | AOPWIN | KOCWIN | HYDROWIN | BCFBAF | Volatilization | STP

Log BCF from regression-based method: 2.399 (BCF = 250.4 L/kg wet-wt)

Log Biotransformation Half-Life (HL): 1.2297 (HL = 16.97 days)

Log BCF Arnot-Gobas method (upper trophic): 3.121 (BCF = 1322)

Log BAF Arnot-Gobas method (upper trophic): 3.287 (BAF = 1935)

Log Kow used: 4.14 (expkow database)

Create MS Word File | Print Results | Print Results - No Structure | Create a Text file | ISIS Base/Upload TBL File | View Main Screen

A Note about Creating MS Word files

Append Data to End of Selected Files

R11:

Kein B-Screening-Kriterium nach R.11, aber für WoE-Betrachtung möglicherweise hilfreich

>2000



PBT Bewertung – Schließen von Datenlücken

QSAR: EPISuite – T-Screening

Ecolin Results

Print Save Results Copy Remove Window Help

SMILES : C(C(C(C(C1CL)CL)CL)CL)(C1CL)CL
 CHEM :
 CAS Num:
 ChemID1:
 ChemID2:
 ChemID3:
 MOL FOR: C6 H6 CL6
 MOL WT : 290.83
 Log Kow: 4.26 (KowWin estimate)
 Melt Pt:
 Wat Sol: 8 mg/L (experimental database)

ECOSAR v1.00 Class(es) Found

Neutral Organics

ECOSAR Class	Organism	Duration	End Pt	Predicted mg/L (ppm)
Neutral Organics	: Fish	96-hr	LC50	2.308
Neutral Organics	: Fish	14-day	LC50	2.420
Neutral Organics	: Daphnid	48-hr	LC50	1.817
Neutral Organics	: Green Algae	96-hr	EC50	2.300
Neutral Organics	: Fish	30-day	ChV	0.280
Neutral Organics	: Daphnid		ChV	0.301
Neutral Organics	: Green Algae		ChV	1.281
Neutral Organics	: Fish (SW)	96-hr	LC50	2.703
Neutral Organics	: Mysid Shrimp	96-hr	LC50	0.460
Neutral Organics	: Fish (SW)		ChV	1.231
Neutral Organics	: Mysid Shrimp (SW)		ChV	0.020
Neutral Organics	: Earthworm	14-day	LC50	294.867 *

Note: * = asterisk designates: Chemical may not be soluble enough to measure this predicted effect.

Neutral Organics:

For Fish LC50 (96-h), Daphnid LC50, Mysid: If the log Kow is greater than 5.0, or if the compound is solid and the LC50 exceeds the water solubility by 10X, no effects at saturation are predicted.

For Fish LC50 (14-day) and Earthworm LC50: If the log Kow is greater than 6.0, or if the compound is solid and the LC50 exceeds the water solubility by 10X, no effects at saturation are predicted.

For Green Algae Acute Toxicity Values: If the log Kow of the chemical is

T-Verdacht nach R11:

EC50 oder LC50 < 0.1 mg/L (QSAR dabei nur im Rahmen einer WoE-Betrachtung verwenden)

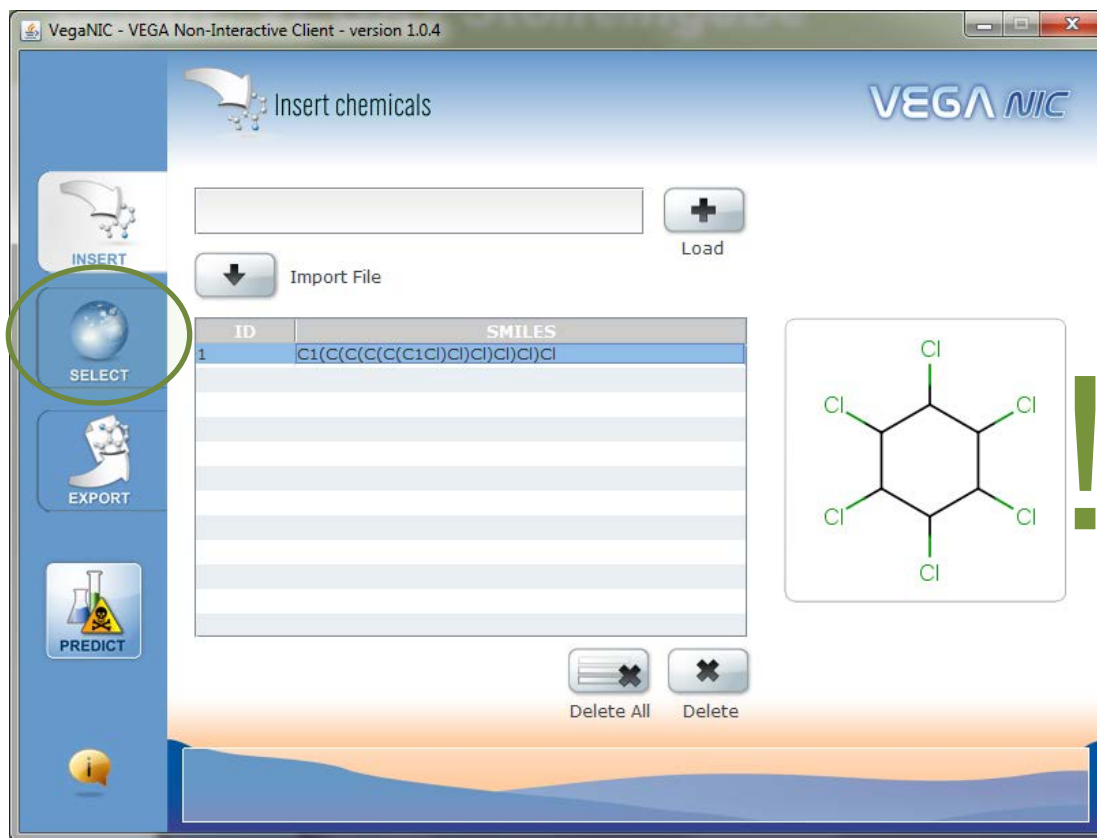
→ Hier kein T-Verdacht durch QSAR

Anmerkung: QSAR-Toolbox enthält T-Werte <0.01 mg/L



PBT Bewertung – Schließen von Datenlücken

QSAR: VEGA - Stoffeingabe



Beispiel am Offline-Tool VEGA NIC (weil aktueller)



PBT Bewertung – Schließen von Datenlücken

QSAR: VEGA - Endpunktauswahl

The image displays three overlapping screenshots of the VEGA NIC - VEGA Non-Interactive Client - version 1.0.4 software interface, illustrating the selection of models for different screening types.

- T-Screening:** The 'Ecotox' tab is selected. The list of models includes:
 - ☒ Fathead Minnow LC50 96h (EPA) - v. 1.0.4
 - ☒ Daphnia Magna LC50 48h (EPA) - v. 1.0.4
 - ☒ Daphnia Magna LC50 48h (DEMETRA) - v. 1.0.1-BETA
 - ☒ All models
- P-Screening:** The 'Environ' tab is selected. The list of models includes:
 - ☒ BCF model (CAESAR) - v. 2.1.11
 - ☒ BCF Read-Across - v. 1.0.0
 - ☒ Ready Biodegradability model - v. 1.0.6-DEV
 - ☒ All models
- B-Screening:** The 'Phys-Chem' tab is selected. The list of models includes:
 - ☒ LogP prediction - v. 1.0.4
 - ☐ All models

Additional annotations include a green oval around the 'P-Screening' models and the text 'zusätzlich zu B-Screening' (in addition to B-Screening). The 'B-Screening' screenshot also has a green oval around the 'LogP prediction' model and the 'EXPORT' and 'PREDICT' buttons.



PBT Bewertung – Schließen von Datenlücken

QSAR: VEGA – Ausgabe des Reports

1. Prediction Summary

Prediction for compound 1 (Molecule 1)

Chemical structure: ClC1C(Cl)C(Cl)C(Cl)C(Cl)C1Cl

Prediction: \odot Reliability: $\star\star\star$

Model assessment: Prediction is $\log P = 4.13$, but the result leaves some critical aspects, which require to be checked.

Similar molecules with known experimental values have experimental values that strongly disagree with the target compound predicted value.

Compound: 1
Compound SMILES: C1C(Cl)C(Cl)C(Cl)C(Cl)C1Cl
Explanation:
Prediction: 4.13 [log units]
AlogP: 4.16 [log units]
MLogP: 4.09 [log units]
Reliability: Compound could be out of model Applicability Domain
Requests for the prediction:
none

3.1 Applicability Domain: Similar Compounds, with Predicted and Experimental Values

Chemical Structure	CAS	Dataset id	Dataset size	SMILES	Similarity	Experimental value	Predicted value
<chem>ClC1CCCCC1Cl</chem>	1121-21-7	2044	(training set)	<chem>ClC1CCCCC1Cl</chem>	0.915	3.18 [log units]	2.92 [log units]
<chem>BrC1CCCCC1</chem>	108-85-0	1028	(training set)	<chem>ClC1CCCCC1Br</chem>	0.855	3.2 [log units]	2.79 [log units]
<chem>CCCCCCCC</chem>	111-25-1	1828	(training set)	<chem>CCCCCCCCBr</chem>	0.818	3.8 [log units]	3.18 [log units]
<chem>CCCCCCCC</chem>	111-83-1	954	(training set)	<chem>CCCCCCCCBr</chem>	0.807	4.89 [log units]	4.41 [log units]
<chem>CCCCCCCC</chem>	629-04-6	637	(training set)	<chem>CCCCCCCCBr</chem>	0.8	4.36 [log units]	3.57 [log units]
<chem>CCCCCCCC</chem>	110-53-2	696	(training set)	<chem>CCCCCCCCBr</chem>	0.772	3.37 [log units]	2.78 [log units]

3.2 Applicability Domain: Measured Applicability Domain Scores

Global AD Index
AD Index = 0.7
Explanation: predicted substance could be out of the Applicability Domain of the model.

Similar molecules with known experimental value
Similarity index = 0.882
Explanation: strongly similar compounds with known experimental value in the training set have been found.

Accuracy (average error) of prediction for similar molecules
Accuracy index = 0.305
Explanation: accuracy of prediction for similar molecules found in the training set is good.

Concordance with similar molecules (average difference between target compound prediction and experimental values of similar molecules)
Concordance index = 0.938
Explanation: similar molecules found in the training set have experimental values that strongly disagree with the target compound predicted value.

Maximum error (difference between target compound prediction and experimental values of similar molecules)
Max error index = 0.41
Explanation: the maximum error in prediction of similar molecules found in the training set has a low value, considering the experimental variability.

Model prediction reliability
AlogP/MLogP difference = 0.071
Explanation: both values of calculated logP agree.

Symbols explanation:
 \odot The feature has a good assessment, model is reliable regarding this aspect.
 \star The feature has a non optimal assessment, this aspect should be reviewed by an expert.
 \times The feature has a bad assessment, model is not reliable regarding this aspect.



PBT Bewertung – Schließen von Datenlücken

QSAR: Vergleich Ergebnisse und Beobachtungen

	EPISuite	VEGA
Persistenz	P-Verdacht	P-Verdacht
Bioakkumulation	Kein B-Verdacht	Kein B-Verdacht
Toxizität	Kein T-Verdacht	Kein T-Verdacht

Beobachtungen und Probleme:

- Konformation wird nicht berücksichtigt.
- Für Beispielchemikalie existieren teilweise Daten für sensitivere Spezies, aber von Modellen nicht berücksichtigt
- Bei EPISuite wird aus Modellen ohne weiteres nicht klar, ob Beispielmolekül in der Anwendungsdomäne ist.
- Ergebnisse sind nur für Screening und/oder WoE-Betrachtungen verwendbar.



PBT Bewertung – Schließen von Datenlücken

QSAR: Anforderungen an die Dokumentation des Modells

Im QSAR Model Reporting Format (QMRF):

- Strukturiert nach OECD-Prinzipien:
 1. Definierter Endpunkt
 2. Eindeutiger Algorithmus
 3. Definierte Anwendungsdomäne
 4. Angemessener Grad an Datenfit, Robustheit und Vorhersagekraft
 5. möglichst: Mechanistische Interpretation
- Detaillierte Beschreibung des Modells eigentlich durch Modellentwickler
- Aber: Liegt für nur sehr wenige Modelle vor



EUROPEAN COMMISSION
DIRECTORATE GENERAL
JOINT RESEARCH CENTRE
Institute for Health and Consumer Protection
Toxicology and Chemical Substances Unit

Ispira, 26/05/2008

QSAR Model Reporting Format (Version 1.2)

Please, try to fill in the fields of the QMRF for the model of interest. If the field is not pertinent with the model you are describing, or if you cannot provide the requested information, please answer "no information available". **The set of information that you provide will be used to facilitate regulatory considerations of (Q)SARs.** For this purpose, the structure of the QMRF is devised to reflect as much as possible the OECD principles for the validation, for regulatory purposes, of (Q)SAR models. You are invited to consult the OECD "Guidance Document on the Validation of (Quantitative) Structure-Activity Relationship Models" that can aid you in filling in a number of fields of the QMRF.

1. QSAR identifier

- 1.1 **QSAR identifier (title):** Provide a short and indicative title for the model including relevant keyword. Some possible keywords are: endpoint modelled (as specified in field 3.2, recommended), name of the model, name of the modeller, and name of the software coding the model. Examples: "BIOWIN 1 for Biodegradation"; "TOPKAT Skin Irritation Acyclics (No Acids, Amines, Esters) MOD v SEV Model".
- 1.2 **Other related models:** If appropriate, identify any model that is related to the model described in the present QMRF. Example: "TOPKAT Skin Irritation Acyclics (Acids, Amines, Esters) NEG/MLD v MOD/SEV Model" is related to the model mentioned in 1.1: "TOPKAT Skin Irritation Acyclics (Acids, Amines, Esters) MOD v SEV Model".
- 1.3 **Software coding the model:** If appropriate, specify the name and the version of the software that implements the model. Examples: "BIOWIN v. 4.2 (EPI Suite)"; "TOPKAT v. 6.2".

2. General information

- 2.1 **Date of QMRF:** Report the date of QMRF drafting (day/month/year). Example: "5 November 2006".
- 2.2 **QMRF author(s) and contact details:** Indicate the name and the contact details of the author(s) of the QMRF (first version of the QMRF).
- 2.3 **Date of QMRF update(s):** Indicate the date (day/month/year) of any update of the QMRF. The QMRF can be updated for a number of reasons such as additions of new information (e.g. addition of new validation studies in section 7) and corrections of information.
- 2.4 **QMRF update(s):** Indicate the name and the contact details of the author(s) of the updates QMRF (see field 2.3) and list which sections and fields have been modified.
- 2.5 **Model developer(s) and contact details:** Indicate the name of model developer(s)/author(s), and the corresponding contact details; possibly report the contact details of the corresponding author.
- 2.6 **Date of model development and/or publication:** Report the year of release/publication of the model described in the current QMRF.




PBT Bewertung – Schließen von Datenlücken

QSAR: Anforderungen an die Dokumentation der Ergebnisse

Im QSAR prediction reporting format (QPRF):

- Detaillierte Beschreibung der Vorhersage bezüglich
 1. Endpunkt
 2. Algorithmus
 3. Anwendungsdomäne
 4. Unsicherheiten
- Möglichst auch Bewertung der Eignung für Vorgang (hier PBT-Bewertung)
- Muss durch den Anwender erfolgen

EUROPEAN COMMISSION
DIRECTORATE GENERAL
JOINT RESEARCH CENTRE
Institute for Health and Consumer Protection
Toxicology and Chemical Substances Unit

Ispira, 26/05/2008

QSAR Prediction Reporting Format (QPRF)
(version 1.1, May 2008)

Please fill in the fields of the QPRF with information about the prediction and the substance for which the prediction is made. The information that you provide will be used to facilitate considerations on the adequacy of the prediction (model result) in relation to a defined regulatory purpose.

The adequacy of a prediction depends on the following conditions: a) **the (Q)SAR model is scientifically valid**: the scientific validity is established according to the OECD principles for (Q)SAR validation; b) **the (Q)SAR model is applicable to the query chemical**: a (Q)SAR is applicable if the query chemical falls within the defined applicability domain of the model; c) **the (Q)SAR result is reliable**: a valid (Q)SAR that is applied to a chemical falling within its applicability domain provides a reliable result; d) **the (Q)SAR model is relevant for the regulatory purpose**: the predicted endpoint can be used directly or following an extrapolation, possibly in combination with other information, for a particular regulatory purpose.

A (Q)SAR prediction (model result) may be considered adequate if it is reliable and relevant, and depending on the totality of information available in a weight-of-evidence assessment (see Section 4 of the QPRF).

1. Substance
This section is aimed at defining the substance for which the (Q)SAR prediction is made.

1.1 CAS number: Report the CAS number.
1.2 EC number: Report the EC number.
1.3 Chemical name: Report the chemical names (IUPAC and CAS names).
1.4 Structural formula: Report the structural formula.
1.5 Structure codes: Report available structural information for the substance, including the structure code used to run the model. If you used a SMILES or InChI code, report the code in the corresponding field below. If you have used any another format (e.g. mol file), please include the corresponding structural representation as supporting information.

a. SMILES: Report the SMILES of the substance (indicate if this is the one used for the model prediction).



PBT Bewertung – Schließen von Datenlücken

Zusammenfassung

- Methoden wie Read Across und QSAR können und sollen bei der PBT-Bewertung eingesetzt werden (Anhang XI REACH-Verordnung, Leitfaden R.11).
- Anwendung (bzgl. PBT-Bewertung) beschränkt sich im Wesentlichen auf
 - Darstellung der gesamten bekannten Datenlage
 - Screening von PBT-Eigenschaften
 - Weight-of-Evidence-Betrachtungen.
- Zur detaillierten Auswertung der Vorhersagen und ihrer REACH-konformen Dokumentation ist Expertise notwendig.
- Im Rahmen des Vortrags wurden einige Beispiele gezeigt (OECD QSAR-Toolbox, EPISuite, VEGA)
- Eine Empfehlung bestimmter Programme ist nur fallspezifisch möglich



PBT Bewertung – Schließen von Datenlücken



Source: vellex@sx.hu

Vielen Dank für Ihre Aufmerksamkeit!

Gibt es noch Fragen?

Dr. Marc Brandt
Umweltbundesamt
IV 2.3 Chemikalien
Wörlitzer Platz 1
06844 Dessau-Roßlau
Tel: +49 340 / 2103-2404
E-Mail: marc.brandt@uba.de