The CONCERT Gateway

EU LIFE CONCERT REACH final workshop Milan, 19 June 2023

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ISTITUTO DI RICERCHE FARMACOLOGICHE MARIO NEGRI · IRCCS



THE PROJECT Sept 2018 - June 2023

Evaluate the **potential impact** of CS in the EU by exp + *in silico* **A big network** of systems offering nontesting methods (NTM) useful both for authorities and industries.







PROJECT ACTIVITIES











112 (Q)SAR freely available models for regulatory purposes.

VEGA



-Human toxicity
-Eco-toxicity
-Environmental
-Physico-chemical
-Toxicokinetics



Reproducible **read-across evaluation** for 23 endpoints showing **similar compounds** and **SAs** in common between chemicals.

TOXREAD







DQ DATABASE

Estimates for more than 650,000 substances obtained with more than 200 (Q)SARs from free and commercial platforms.

DQ MODELS

New portal to access some of the models of the database directly, also for new substances.

Downloadable QPRF report is generated.



Home + Database + Models +

Welcome to OCHEM! Your possible actions

Explore OCHEM data Search chemical and biological data: experimentally measured, published and exposed to public access by our users. You can also upload your data.

Create QSAR models

Build QSAR models for predictions of chemical properties. The models can be based on the experimental data published in our database.

Run predictions Apply one of the available models to predict property you are interested in for your set of compounds.

Screen compounds with ToxAlerts

Screen your compound libraries against structural alerts for such endpoints as mutagenicity, skin sensitization, aqueous toxicity, etc.

Optimise your molecules

Optimise different properties for your molecules (e.g., reduce their toxicity or improve their ADME properties) using the state-of-the at MolOptimiser utility based on matched molecular pairs

Tutorials Check our video tutorials to know more about the OCHEM features.

Our acknowledgements

Check out the properties available on OCHEM

OCHEM contains 3345610 records for 689 properties (with at least 50 records) collected from 15083 sources

Online chemical database

search chemical and biological data supervisedatly manufed, published and exposed to public access by satisfies. You can also proved over calco Cliefs and the properties analytic on CORDI CORDIV andress 154100 records to 100 properties (and at land 50 records) collected than 15420 record Motification Control Log Corporation (Log Control Log Control Lo

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CYP450 modulation

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Koo BCF CHEL

 Melting Point
 logPow
 logBB
 LogL(water)
 LogD
 logP(+)

 Water solubility
 LogL(blood)
 LogL(oil)
 ER
 Cbrain/Cplasma
 IC50
 Papp(Caco-2)

 Papp(MDCK)
 Oral absorption
 LIC 50
 Papp ratlo(Caco-2)

 Plasma protein binding
 Papp ratlo(MDCK-mdr1)
 pIC50
 %Human FA
 Human IA

 Human FA
 fraction unbound (fu)
 fraction ionized (fi)
 pKa
 VDss
 LogIC50
 LogPI

 BBB permeability (qualitative)
 LogKoa
 LogRBA
 CYP450
 modulation

 CYP450 reaction
 Vapor Pressure
 EC50 aquatic
 NOEC aquatic

 LOEC aquatic
 IC50 aquatic
 LC50 aquatic
 log(IGC50-1)
 LEL

 Henry's law constant
 EC50 EROD induction
 LC 50
 Boiling Point
 LD50 dermal

 LD50 oral
 LC50 terrestrial
 AMES
 LD50
 Biodistribution

Water solubility Kinetic Papp(PAMPA) IC50 CYP450 Inhibition Ki CYP450 logK' hsa Dissipation half-life DT50 Freundlich coefficient Kr BMF

 Atmospheric OH Rate Constant
 Ki
 TDLo
 LDLo
 Cancerogen
 Anti-inflammatory activity

 Methanol solubility
 LogLD50
 MIC
 Retention Time
 Surface tension
 Cblood/Cair(Human)

 Cfati/Cair(Rat)
 Chrain/Cair(Rat)
 Cliver/Cair(Rat)
 Cmusole/Cair(Rat)
 IC50
 PDE4
 % inhibition PDE4

IC50 inhibition Density pKa (smiles as ob. cond.) DMSO Solubility Iog Kb IogK0 IogLOAEL hERG K+ Channel Blocking (IC50) 5-HT28 (Ki) LogKoc BCF CHSEL % inhibition hERG, K+ Channel Blocking hERG K+ Channel Blocking (Ki) IogP Chloroform Water 5-HT2C (Ki) 5-HT26 (Kb) PgP substrate 5-HT2A (Ki) D2R (Ki) of adrenergic receptor (Ki)



The OCHEM package offers a database of molecules and their ADMET properties.

OCHEM contains more than **1 million** experimental records for about 499 properties collected from 12428 sources

Our acknowledgeme

Union xus
 Check our video futorials to know more about 1
 OCHEM features.

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ICSD Initialition Density pKa (smilles as ob. cond.) DMSO Solubility reg rea regro logLOAEL hERG K+ Channel Blocking (IC50) 54/T2B (%) LogKoc BCF CHSEL % initibition hERG, K+ Channel Blocking hERG K+ Channel Blocking (%) set 5 constraints \$44720 (%) 54/T28 (%) DPP Substrate \$44724 (%) 028 (%) of service (%)

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CONCERTING EXPERIMENTAL DATA CONCERTING EXPERIMENTAL DATA AND IN SILICO MODELS FOR REACH LIFE17 GIE/IT/000461 Admin Help •

The AMBIT system consists of a database including more than **450.000 chemical** structures and REACH data on **14.570** substances

mbit @cefic LRO Enhanced functions * Search • Assessments * Import • LRI AMBIT2 Read Across tool - new version! Chemical substance database with read across workflow . IUCLID6 support, featuring OpenFoodToxData and VEGA integration Simple search Enter chemical name, identifiers, SMILES, InChI formaldehyde Search Advanced: Structure search | Search substances by identifiers | Search substances by endpoint data | Free text search ambit 🕸 Legal notice: The LRI AMBIT - IUCLID tool is loaded with non-confidential REACH data supplied by ECHA. The legal notice from the ECHA dissemination website http://echa.europa.eu/web/guest/legal-notice#registration applies to the AMBIT users In addition, Cefic disclaims any liability of whatsoever nature either direct or indirect regarding the use of the AMBIT-IUCLID tool or information / data contained in it. IdeaConsult is a contractor of Cefic developing and hosting the AMBIT-IUCLID tool. Some data used may have been provided by Cefic. IdeaConsult has acted solely on the liability of whatsoever nature, direct or indirect, regarding the use of any information/data by the AMBIT-IUCLID tool. IdeaConsult shall not have any liability of whatsoever n http: IUCLID tool



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The GATEWAY



CONCERT REACH project offers the possibility to integrate, in a unique network, different systems of freely available NTMs for REACH. This "gateway" will guide the user through four in silico platforms: VEGARUB, OCHEM, the Danish (Q)SAR Database and AMBIT in order to help in evaluating chemical substances by the application of more than 300 different models and the availability of more than 450.000 chemical structures and REACH dataset of 14.570 substances.



The "gateway" reports all the predictive software available in the four platforms relative to REACH endpoints.

However, please consider that we cannot guarantee that they are correct and usable for the REACH legislation. Additionally, if industry wants to use the result from a certain model, it has to verify if this is legally legitimate. For certain very specific endpoints we have reported models that may have been developed using more general data. These models may not perfectly adhere to the endpoint.

The GATEWAY





The GATEWAY

	CONCERTREACH HEADING THE AND AND HEADING THE AND	HOME	PROJECT	RESULTS	RESOURCES	NEWS	CONTACT
	REACH ENDPOINTS	_					
	^O 7 PHYSICOCHEMICAL PROPERTIES			1) REACH According	I ENDPOIN	NTS eds, the	e user can filter the models by the
	+ 7.2. Melting/freezing point			endpoints	list, as in th	ne REA	CH regulation.
	+ 7.3. Boiling point			The main	categories	are:	
	+ 7.5. Vapour pressure			8. TOXIC	OLOGICAL	INFOF	RMATION
CD	+ 7.8. Partition coefficient n-oc anol/water			9. ECOTO	DXICOLOG	ICAL IN	IFORMATION

2) SELECTION OF THE SUITABLE MODEL



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HOME PROJECT RESOURCES

NEWS

CONTACT

REACH ENDPOINTS

7. PHYSICOCHEMICAL PROPERTIES

+ 7.2. Melting/freezing point	
+ 7.3. Boiling point	
+ 7.5. Vapour pressure	
+ 7.7. Water solubility	
+ 7.8. Partition coefficient n-octanol/water	
+ 7.16. Dissociation constant	







3) **PREDICTING**

Once selected the model of interest, click on the link present in the "model" column; you will be redirected to the access page of the models.



https://www.life-concertreach.eu/results/

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Once selected the model of interest, click on the link present in the "model" column; you will be redirected to the access page of the models.





https://www.life-concertreach.eu/results/

4) INTERPRETATION OF THE RESULTS

The user can consult all the available documentation of the *in silico* tools in the dedicated section.



Environment International Volume 131, October 2019, 105060



Review article

Integrating *in silico* models and readacross methods for predicting toxicity of chemicals: A step-wise strategy

Emilio Benfenati ^a 은 쩓, Qasim Chaudhry ^b, Giuseppina Gini ^c, Jean Lou Dorne ^d

Show more

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Target molecule Tools Assessment







All VEGA AND	ToxRead DANISH QS/	AR DATABASE	AMBIT	OCHEM	4				GATEWAY
End Point	Model	Туре	Dataset size	Training set size	Test set size	Cross- validation procedure	Platform	Remarks	VEGA
TOX 7.6.1. Genetic toxicity in vitro	Mutagenicity	reproducible read-across	6060				VEGA	=	4 individual models + 1 consensus
1OX 7.6.1. Genetic toxicity in vitro. Ames test (OECD 471)	Mutagenicity (Ames test) CONSENSUS model	classification	٥	D	0		VEGA		 CAESAR - Hybrid model (statistical +
TOX 7.6.1. Genetic toxicity in vitro. Ames test (OECD 471)	Mutagenicity (Ames test) model (CAESAR)	classification	4204	3367	837		VEGA	—]	 knowledge-based) KNN-Read-Across - read-across
TOX 7.6.1. Genetic toxicity in vitro. Ames test (OECD 471)	Mutagenicity (Ames test) model (KNN-Read-Across)	classification	5770	5770	0		VEGA	=	model
TOX 7.6.1. Genetic toxicity in vitro. Ames test (OECD 471)	Mutagenicity (Ames test) model (ISS)	classification	670	670	0		VEGA		alerts (Benigni-Bossa rule-base)
TOX 7.6.1. Genetic toxicity in vitro. Ames test (OECD 471)	Mutagenicity (Ames test) model (SarPy-IRFMN) (version 1.0.8)	classification	4204	3367	837		VEGA	=	alerts

1. In vitro gene mutatio	a study in bacteria					HU	ME	PROJECT	GATEWAY LISER GUIDE
All VEGA AND	ToxRead DANISH QS	AR DATABASE	ambit	OCHE	M				GATEWAY
End Point	Model	Туре	Dataset size	Training set size	Test set size	Cross- validation procedure	Platform	Remarks	ToxPood 1 modulo
TOX 7.6.1. Genetic toxicity in vitro	Mutagenicity	reproducible read-across	6060				VEGA		Detect = 6060 substances and their
TOX 7.6.1. Genetic toxicity in vitro. Ames test (OECD 471)	Mutagenicity (Ames test) CONSENSUS model	classification	0	٥	٥		VEGA	_	public data
TOX 7.6.1. Genetic toxicity in vitro. Ames test (OECD 471}	Mutagenicity (Ames test) model (CAESAR)	classification	4204	3367	837		VEGA		 4 different rulesets: ISS (knowledge-based structural
TOX 7.6.1. Genetic toxicity in vitro. Ames test (OECD 471)	Mutagenicity (Ames test) model (KNN-Read-Across)	classification	5770	5770	D		VEGA	—	 alerts) SARpy (statistical structural alerts)
TOX 7.6.1. Genetic toxicity in vitro. Ames test (OECD 471)	Mutagenicity (Ames test) model (ISS)	classification	670	670	D		VEGA		 CSR4 (statistical structural alerts) IRFMN (knowledge-based structur)
TOX 7.6.1. Genetic toxicity in vitro. Ames test (OECD 471)	Mutagenicity (Ames test) model (SarPy-IRFMN) (version 1.0.8)	classification	4204	3367	837		VEGA	=	alerts)

							HOME	PROJECT	RE	SULTS	RESOURCES	NEWS	CONTACT
1. In vitro g	gene mutation study in bacteria								GA	TEWAY USER	GUIDE		
All	VEGA AND ToxRead	ANISH QSAR DA	IABASE	AMBIT	(XCHEM			GA	TEWAY			
End Point	Model	Туре	Dataset size	Training set size	Test set size	Cross-validation procedure	Platform	Remarks		[15 stat	Danish (Q)S	AR Datal	base
Ames test (OECD 471)	Bacterial reverse mutation test (Amesitest in S. typhimurium in vitro) (CASE Ultra)	classification		4102		5 times 2-fold external crossvalidation	DanishQSARDatabase	=			based ale	rt profiler	S
Ames test (OECD 471)	Bacterial reverse mutation test (Ames test in S. typhimurium in vitro) (Leadscope)	classification		4102		5 times 2-fold external crossvalidation	DanishQSARDatabase	=		Bacteria typhimu	I reverse mutation rium in vitro)	on test (Am	es test in S.
Ames test (OECD 471)	Bacterial reverse mutation test (Ames test in S. typhimurium in vitro) (SciQSAR)	classification		4102		5 times 2-fold external crossvalidation	DanishQSARDatabase	=		Direct a Base pa	cting Ames muta ir Ames mutage	igens (witho ns	out S9)
(Mesitest (OECD 471)	Direct acting Ames mutagens (without S9) – ONLY use for Ames POS_IN (CASE Ultra)	classification		388		5 times 2-fold external crossvalidation	DanishQSARDatabase	=		Potent A controls	Ames mutagens,	reversions	≥ 10 times
Amesitest (OECD 471)	Direct acting Ames mutagens (without S9) – ONLY use for Ames POS_IN (Leadscope)	classification		388		5 times 2-fold external crossvalidation	DanishQSARDatabase			Pro DNA al	filers (OECD Q	SAR Toolb	ox V.4.2)
Ames test (OECD 471)	Direct acting Ames mutagens (without S9) – ONLY use for Ames POS_IN (SciQSAR)	classification		388		5 times 2-fold external crossvalidation	DanishQSARDatabase	=		only In vitro	mutagenicity (Ar	mes test) al	lerts by ISS,
Ames test	Base pair Ames mutagens -					5 times 2-fold				alerts ir	n parent only		

		J						HOME	PROJECT	RESULTS	RESOURCES	NEWS	CONTACT	
.1. In vitro gene mutal All VEGA AN	tion stud ID ToxRe	y in bacteria ad I	DANISH (QSAR DATAE	BASE AM	IBIT OCI	HEM			GATEWAY USER	GUIDE			
End Point	Model	Туре	D)ataset size	Training set size	Test set size	Cross-validation procedure	Platform	Remarks		00	HEM		
Ames test (OECD 471}	ASNN	Classificati	on		4361	2181		OCHEM		1 sta	1 statistical model & ToxAlert match			
All VEGA AN	D ToxRea	d Di	ANISH QS	SAR DATABA	lse amb	ПОСНЕ	:M			1				
End Point		Model	Туре	Dataset size	Training set size	Test set size	Cross-validation procedure	Platform	Remarks					
TOX 7.6.1. Genetic to vitro	xicity in	Dataset		50366				AMBIT	=		I Ua	alasel		



Tuesday 20/06, morning **Training sessions**





2-day workshop

Monday 19/06, full day Workshop presentations

Tuesday 20/06, morning **Training sessions**

Istitute di Nicerska Parmanchega ha Marin bagi registered participants:

ROLL

Administration of charge, the set of a pair type, provide advance, since Many is maximum round at of participants, We will workly proportions of the

THANKS

Does anyone have any questions? https://www.life-concertreach.eu/

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