

Mario Negri Institute of Pharmacological Research - IRCCS

17/05/2023, LIFE CONCERT REACH Web-Seminars
QSAR models under REACH: Practical Examples
Nelly Giuseppa Raitano



THE PROJECT



September

June

2018

2019

2020

2021

2022

2023



Istituto di Ricerche Farmacologiche Mario Negri, Italy
Research institute, **Coordinator**

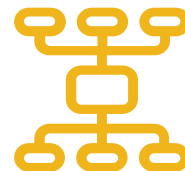
Associated Beneficiaries



External supporting

Evaluate the **potential impact** of CS in the
EU by *exp + in silico*

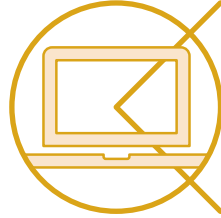
A big network of systems offering non-
testing methods (NTM) useful both for
authorities and industries.



Results


VIRTUAL EXTENSIVE READ-ACROSS

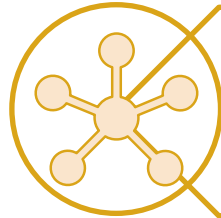
SWAN



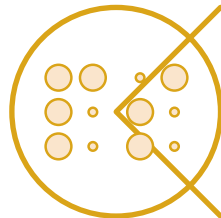
The network offers **more than 450 *in silico* tools**



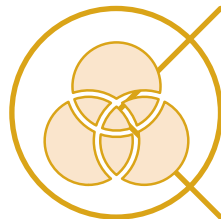
42 new *in silico* models



A new tool for grouping

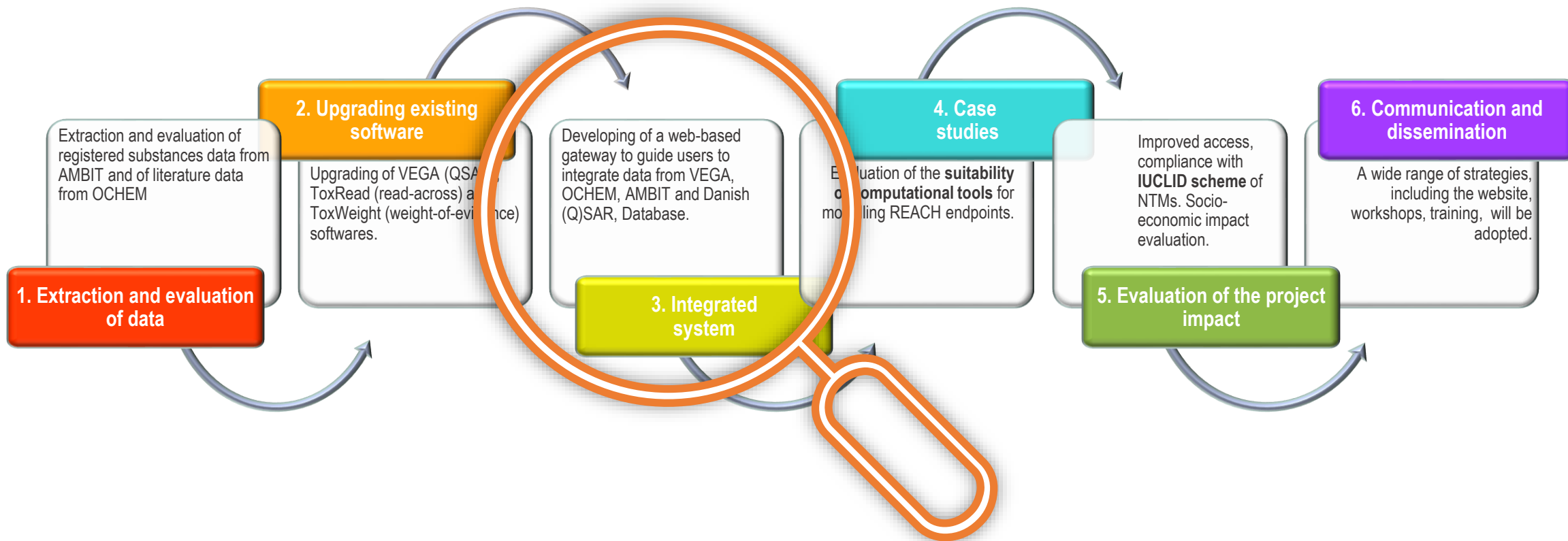


Updated version of **read-across tools**, freely available and user-friendly

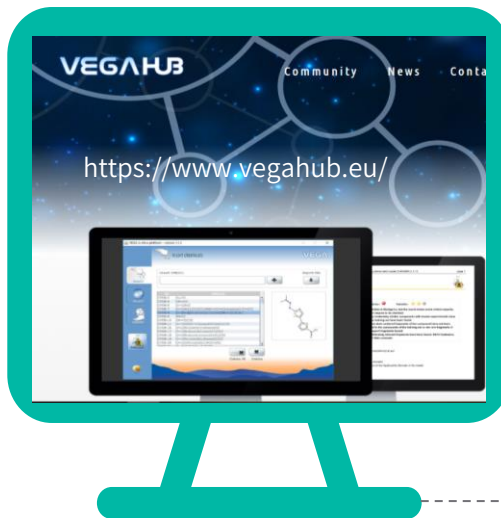


New strategy integrating the results of read-across and *in silico* models (**weight-of-evidence**).

PROJECT ACTIVITIES

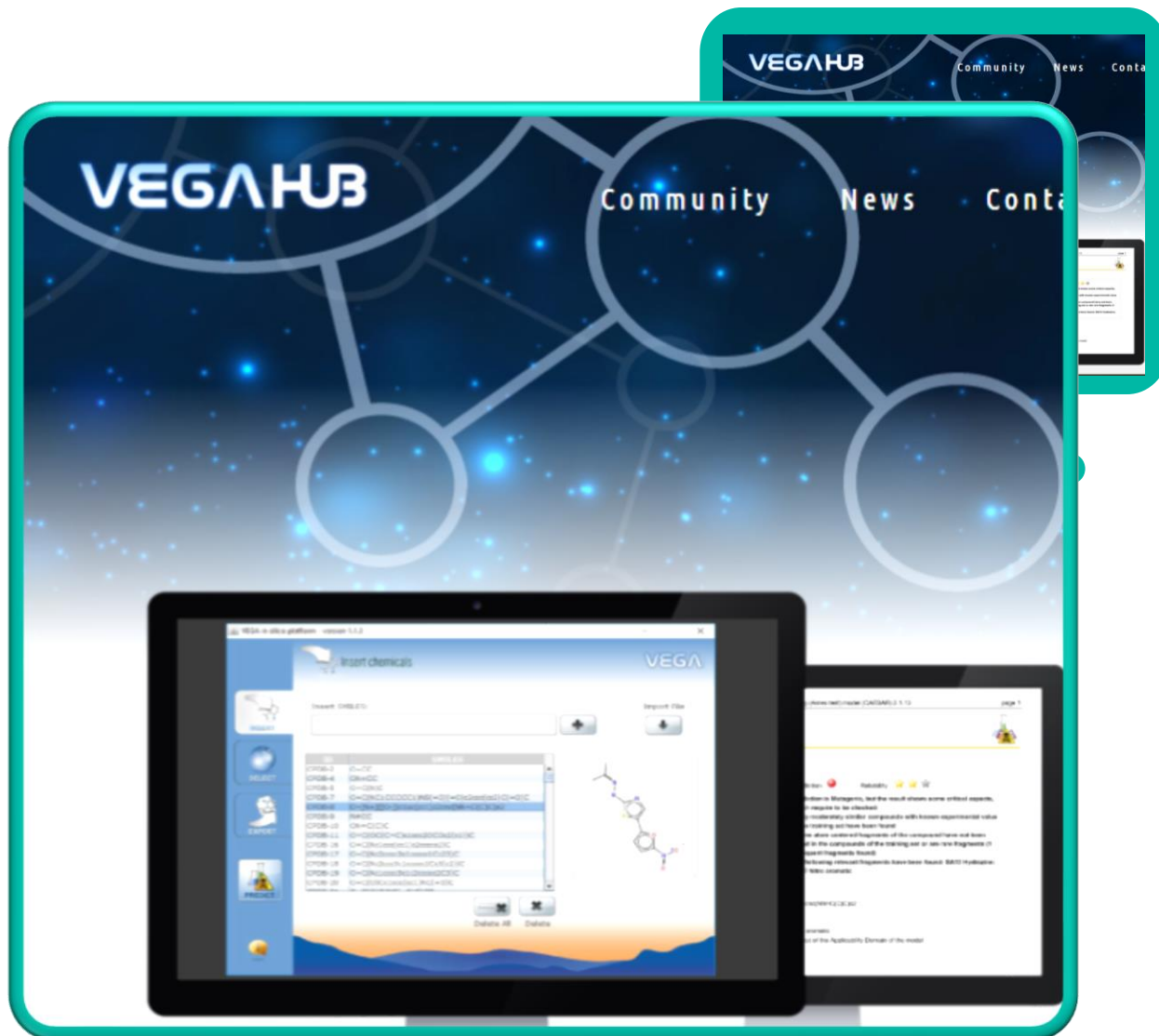


THE TOOLS



The network is composed by **VEGA**, the **Danish (Q)SAR Database**, **OCHEM** for the *in-silico models*, and for the read across workflow and data from the registered substances by **ToxRead** and **AMBIT**.

THE TOOLS



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

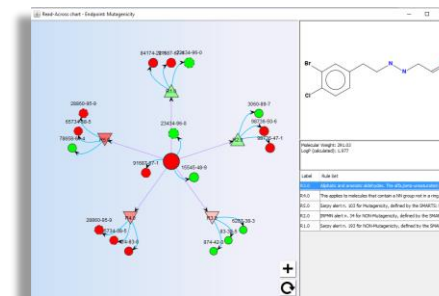
Different areas:

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



Reproducible read-across evaluation for 25 endpoints showing similar compounds and SAs in common between chemicals.

TOXREAD



THE TOOLS



ECHA
EUROPEAN CHEMICALS AGENCY

Ministry of Environment and Food of Denmark
Environmental Protection Agency

Danish (Q)SAR Database

650,000 Substances

Enter Danish (Q)SAR Models

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.

THE TOOLS



LIFE17 GIE/IT/000461

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

Online chemical database
with modeling environment

Home Database Models

Welcome to OCHEM! Your possible actions

Check out the properties available on OCHEM

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

Melting Point logPow logBB LogL(water) LogD logPI(+)
Water solubility LogL(blood) LogL(oil) ER Cbrain/Cplasma IC50 Papp(Caco-2)
Papp(MDCK) Oral absorption LIC 50 Papp ratio(Caco-2)

Plasma protein binding Papp ratio(MDCK-mdr1) pIC50 %Human FA Human IA
Human FA fraction unbound (fu) fraction ionized (f) 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 KT BMF

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

Methanol solubility LogLD50 MIC Retention Time Surface tension Cblood/Cair(Human)
Cfat/Cair(Rat) Cbrain/Cair(Rat) Cliver/Cair(Rat) Cmuscle/Cair(Rat) IC50 PDE4 % inhibition PDE4

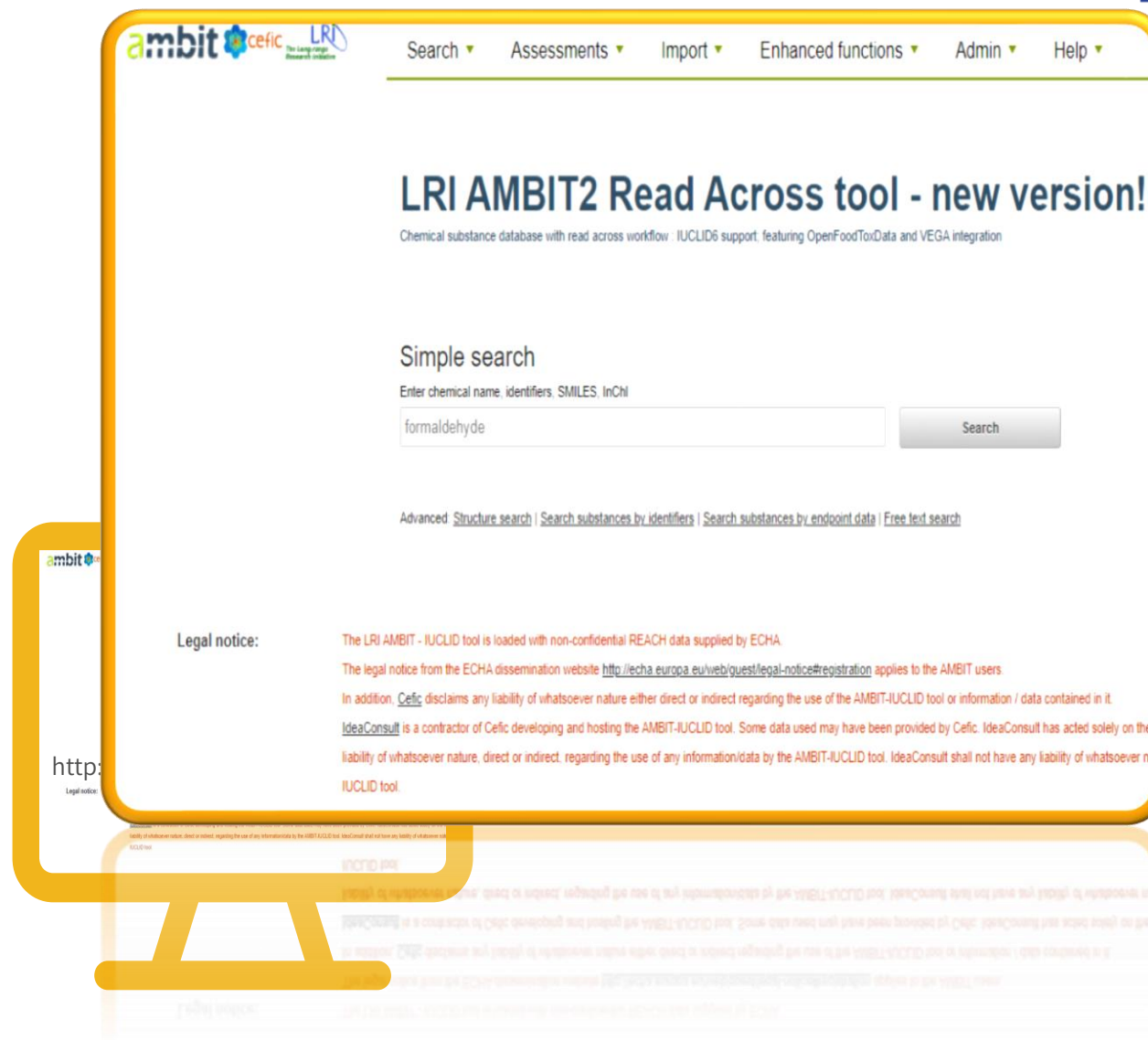
IC50 inhibition Density pKa (smiles as ob. cond.) DMSO Solubility
log Kb logk'0 logLOAEL hERG K+ Channel Blocking (IC50) 5-HT2B (Ki) LogKoc

BCF CHSEL % inhibition hERG, K+ Channel Blocking hERG K+ Channel Blocking (Ki)
logP Chloroform/Water 5-HT2C (Ki) 5-HT2b (Kb) Pgp substrate 5-HT2A (Ki) D2R (Ki) o1 adrenergic receptor (Ki)

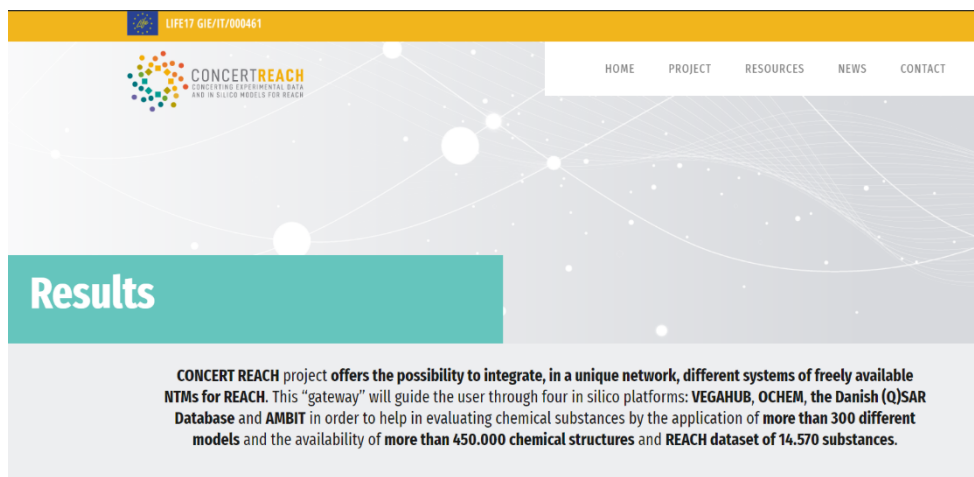
OCHEM contains more than 1 million experimental records for about 499 properties collected from 12428 sources

THE TOOLS

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



The GATEWAY

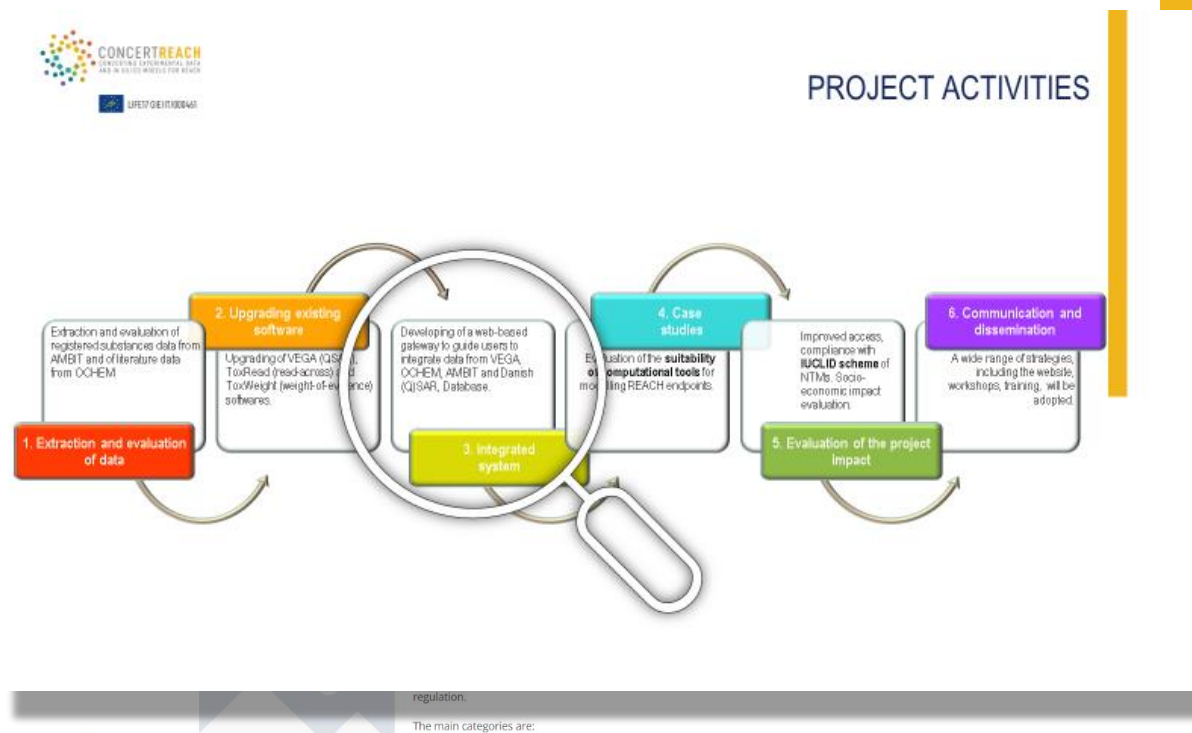


Results

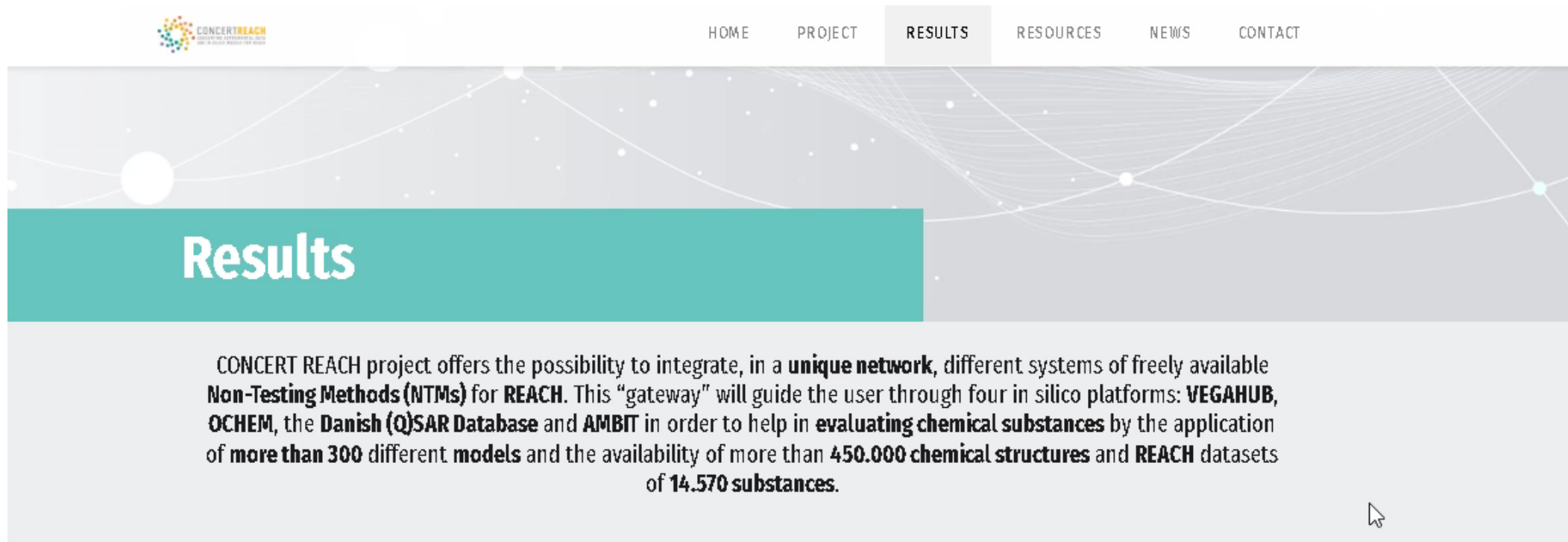
CONCERT REACH project offers the possibility to integrate, in a unique network, different systems of freely available NTMs for REACH. This "gateway" will guide the user through four in silico platforms: VEGA HUB, OCHEM, the Danish (Q)SAR Database and AMBIT in order to help in evaluating chemical substances 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.



<https://www.life-concertreach.eu/>



CONCERTREACH
CONCERTING EXPERIMENTAL DATA
AND IN SILICO MODELS FOR REACH

HOME PROJECT RESULTS RESOURCES NEWS CONTACT

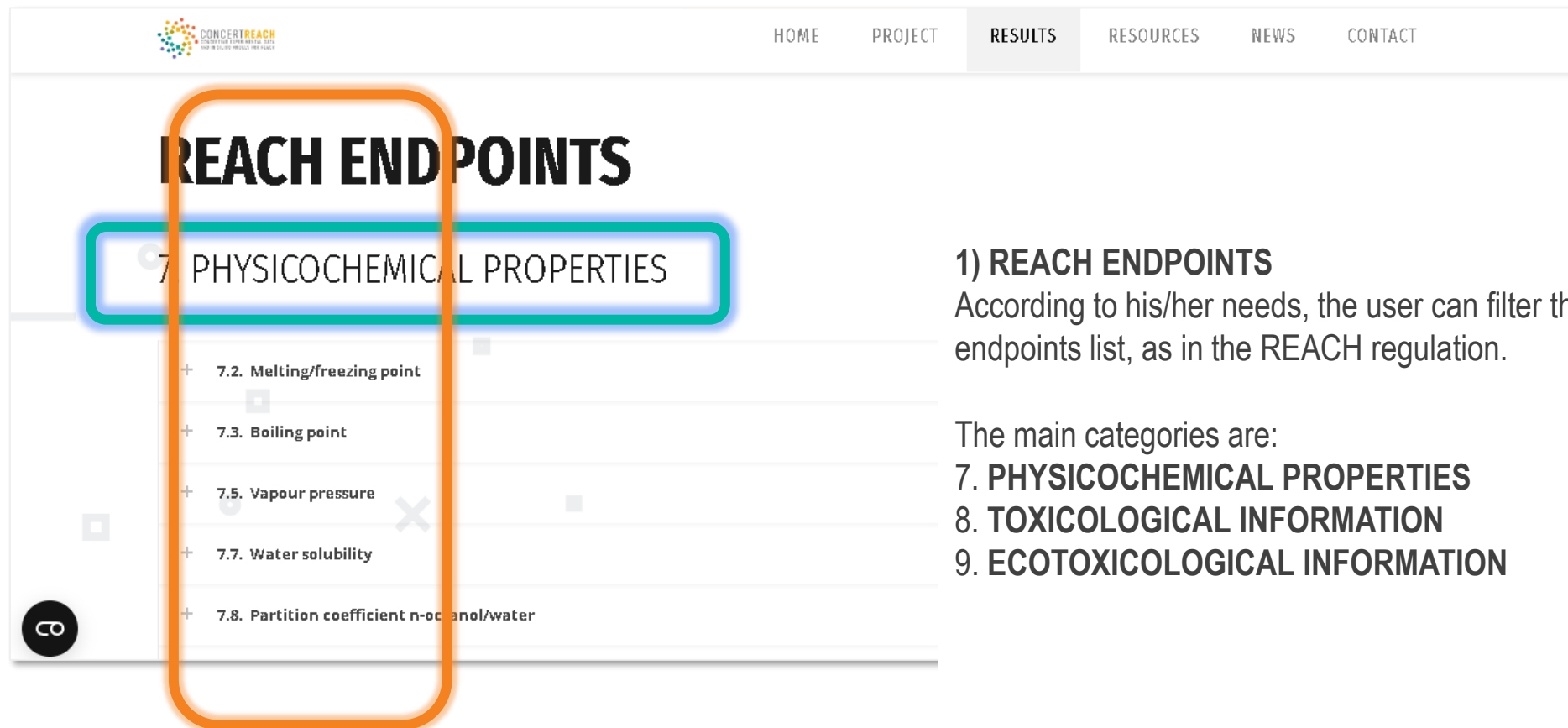
Results

CONCERT REACH project offers the possibility to integrate, in a **unique network**, different systems of freely available **Non-Testing Methods (NTMs)** for **REACH**. This “gateway” will guide the user through four in silico platforms: **VEGAHUB**, **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** datasets of **14.570 substances**.

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

<https://www.life-concertreach.eu/>





HOME PROJECT **RESULTS** 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

1) REACH ENDPOINTS

According to his/her needs, the user can filter the models by the endpoints list, as in the REACH regulation.

The main categories are:

- 7. PHYSICOCHEMICAL PROPERTIES
- 8. TOXICOLOGICAL INFORMATION
- 9. ECOTOXICOLOGICAL INFORMATION

2) SELECTION OF THE SUITABLE MODEL

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

+ 7.5. Vapour pressure

- 7.7. Water solubility

All VEGA AND ToxRead DANISH QSAR DATABASE AMBIT OCHEM


End Point	Model	Type	Dataset size	Training set size	Test set size	Platform	Remarks
P-CHEM 4.8. Water solubility	Dataset		18126			AMBIT	
P-CHEM, 4.8 water solubility, OECD 105	Water solubility model (IRFMN)	continuous	5018	4014	1004	VEGA	
P-CHEM, 4.8 water solubility, OECD 105	Water solubility from Kow (mg/L) (EPI)	continuous				DanishQSARDatabase	
P-CHEM, 4.8 water solubility, OECD 105	Water solubility from Fragments (mg/L) (EPI)	continuous				DanishQSARDatabase	
Water solubility	ASNN	continuous		1311		OCHEM	 

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.

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.



The collage displays three web interfaces related to QSAR modeling. On the left is the VEGA Qsar interface, featuring a dark blue header with 'VEGA HUB' and 'Qsar' navigation, and a central section titled 'Try out VEGA Qsar and its features'. The middle section shows the 'Danish (Q)SAR Database' with a large 'QSAR' graphic and a list of model categories including Environmental Fate, Aquatic Toxicity, Genotoxicity, Biodegradation, Carcinogenicity, Phys-Chem, Human Health, and Prediction Profile. On the right is the AMBIT system login page, titled 'Please, login', with fields for 'Login ID' and 'Password', and a 'REGISTER A NEW USER' button. The AMBIT page also includes a search bar and a 'Publications' section.

2-day workshop

Monday 19/06, full day

Workshop presentations

Tuesday 20/06, morning

Training sessions




The screenshot shows the top of the ConcertReach website. At the top left is the European Union flag and the text 'LIFE17 GIE/IT/000461'. Next to it is the ConcertReach logo, which consists of a colorful circular pattern of dots and the text 'CONCERTREACH CONCERTING EXPERIMENTAL DATA AND IN SILICO MODELS FOR REACH'. To the right of the logo is a navigation menu with links for 'HOME', 'PROJECT', 'RESULTS', 'RESOURCES', 'NEWS', and 'CONTACT'. Below the navigation menu is a large banner with the text 'Final Workshop' in white on a dark background. Below the banner is a section with an illustration of two people (a man and a woman) and a computer monitor displaying code. To the right of the illustration is the text: 'The EU LIFE CONCERT REACH project opens a web-based "gateway" for the exploitation of (Q)SAR models in the (eco)toxicological evaluation of new compounds'. Below this text are the details: '2 days Workshop Hybrid Event', 'Organized by: Coordinating Beneficiary.', and a paragraph stating 'It can be attended in person at the Mario Negri Institute, in Milan, Italy and virtually.' Below this is another paragraph: 'Admission is free of charge. Please make your registration in advance, since there is maximum number of participants. We will notify acceptance of the registered participants.' Below the illustration and text are three sections: 'Date' with the text '19 - 20 June 2023.', 'Venue' with the text 'Istituto di Ricerche Farmacologiche Mario Negri IRCCS.', and 'Admission is free of charge. Please make your registration in advance, since there is maximum number of participants. We will notify acceptance of the registered participants.'

<https://www.life-concertreach.eu/final-workshop-19-and-20-june-2023/>

THANKS

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



CASE STUDY: using and integrating two QSAR models for assessing *in vitro* mutagenicity in bacteria

17/05/2023, LIFE CONCERT REACH Web-Seminars - (Q)SAR Models under REACH: Practical Examples

Rodolfo Gonella Diaz, Ph.D.
In silico expert
knoell Germany GmbH
qsar@knoell.com

www.knoell.com



giuseppa.raitano@marionegri.it