

El apoyo desde la industria química a las alternativas a la experimentación animal.

Programa LRI

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Directora de Tutela de Producto e Internacionalización

feiQue



X Jornada



Trabajamos colaborando en red



Miembro fundador





Agenda

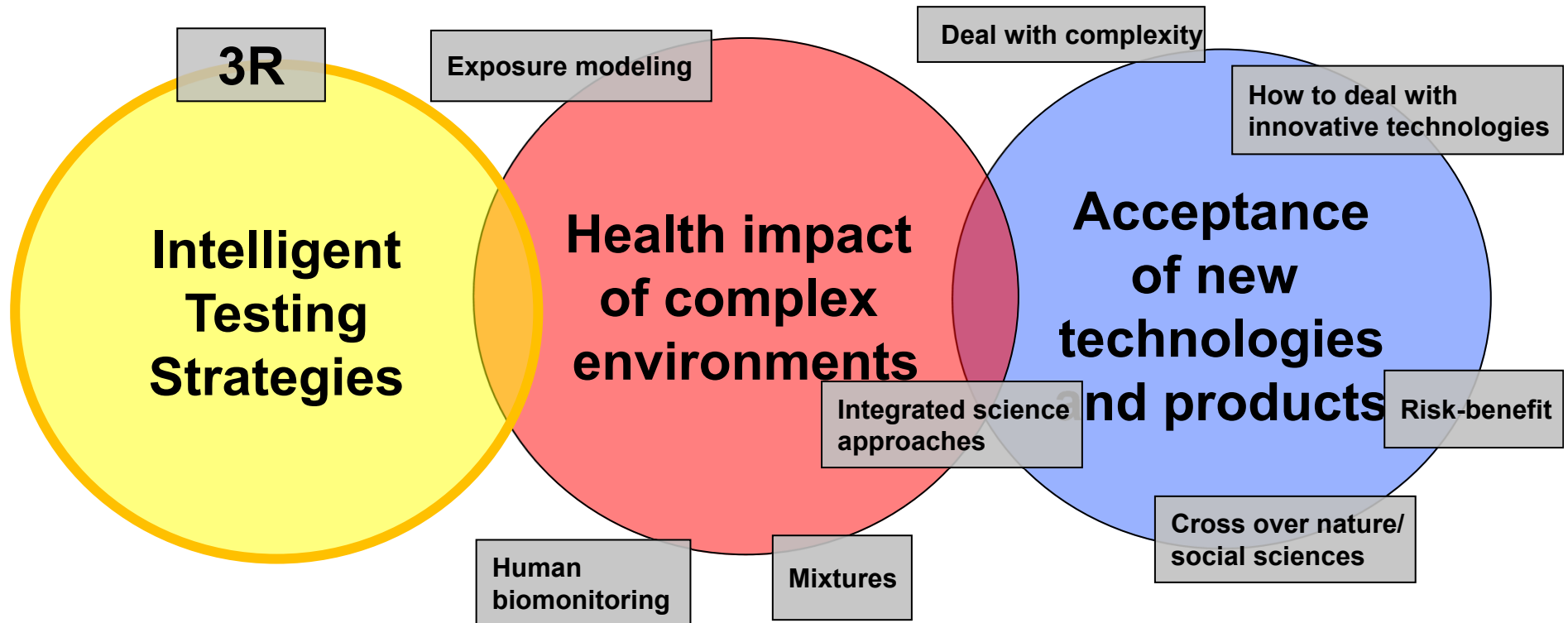
- **Program Intelligent Testing**
- LRI Awards
- QSAR ToolBox OCDE



¿Que es el LRI?

- Programa de caracter Global de ICCA (Europa, USA, Japón)
- Investigación de alta calidad para mejorar la gestión de productos químicos.
- Aumentar las capacidades científicas para hacer frente a problemas emergentes.
- Colaboración de expertos de la industria, academia y gobiernos.
- Aportaciones al debate político basadas en el conocimiento (P^o de precaución) y el impacto esperado consecuencia de las decisiones políticas o regulatorias.

Tres grandes áreas de trabajo



INNOVATING CHEMICAL TESTING

UNDERSTANDING EVERYDAY EXPOSURES

TRANSLATING RESEARCH OUTCOMES FOR PRODUCT SAFETY

CEFIC



- ▶ Link information at the molecular level to health and environmental impacts
- ▶ Support the 3Rs – replace, reduce, and refine – for animal testing

- ▶ Evaluate effects of cumulative and aggregate exposures in real life scenarios
- ▶ Develop predictive models that incorporate environmental stressors

- ▶ Apply new population-relevant concepts for ecosystems
- ▶ Reduce complexity and robustly predict health effects using pragmatic approaches

ACC



- ▶ Incorporate exposure and dose information to advance interpretation of data from high-throughput assays
- ▶ Advance application of cell-based testing systems for chemical safety assessments

- ▶ Develop predictive models for estimating consumer exposures
- ▶ Improve interpretation of biomonitoring data for environmentally-relevant exposures

- ▶ Advance new approaches to evaluate the scientific basis for epidemiological studies linking health effects to chemical exposures
- ▶ Develop an innovative framework that integrates multiple data streams and facilitates chemical safety assessment

JCIA



- ▶ Develop and evaluate new testing methods, such as those that use stem cells, to improve assessment of chemicals and products
- ▶ Innovate high-throughput methods to evaluate large numbers of chemicals

- ▶ Develop predictive and practical models for estimating worker exposures
- ▶ Research health impacts for groups with potential chemical sensitivities, such as the young and the elderly

- ▶ Evaluate the safety of new chemical substances, such as nanomaterials, for future technological developments
- ▶ Assess the effects of chemicals on ecosystems and the environment

CEFIC-LRI TOOLBOX

Online solutions to chemical risk assessment!

READ MORE



Who we are, what we do

LRI's mission is to identify and fill gaps in our understanding of the hazards posed by chemicals and to improve the methods available for assessing the associated risks.

CEFIC-LRI TO INVEST
€100,000 INTO
BETTER TESTING
METHODS FOR
PERSISTENT
CHEMICALS

LEARN MORE



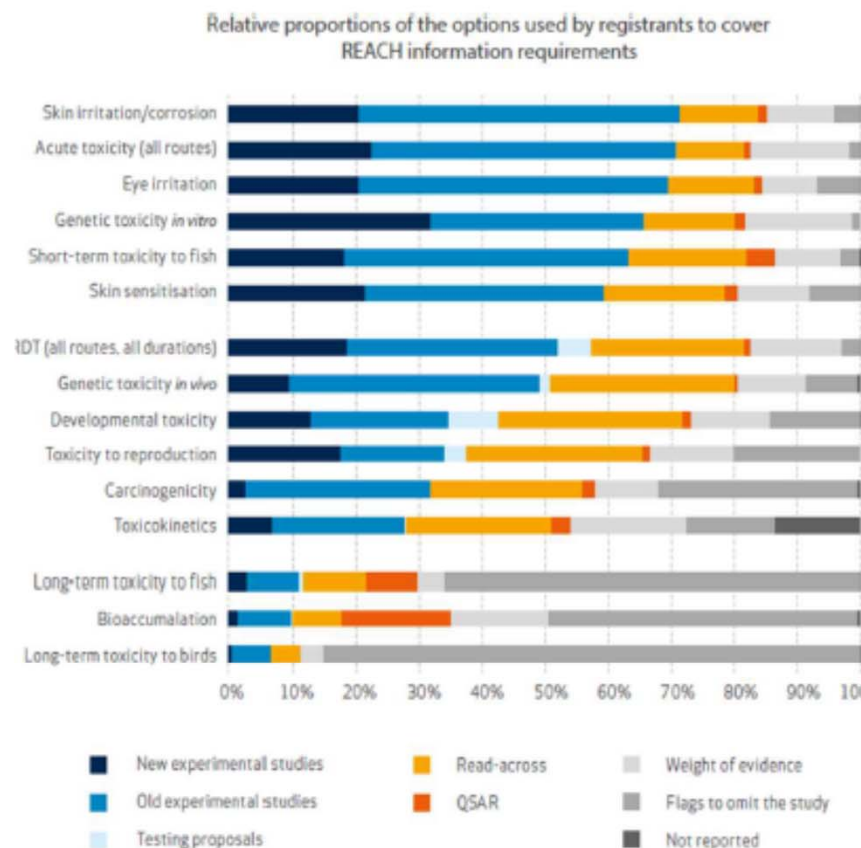
Register for updates

Sign up to receive updates on LRI Projects, News and Events.

Register now

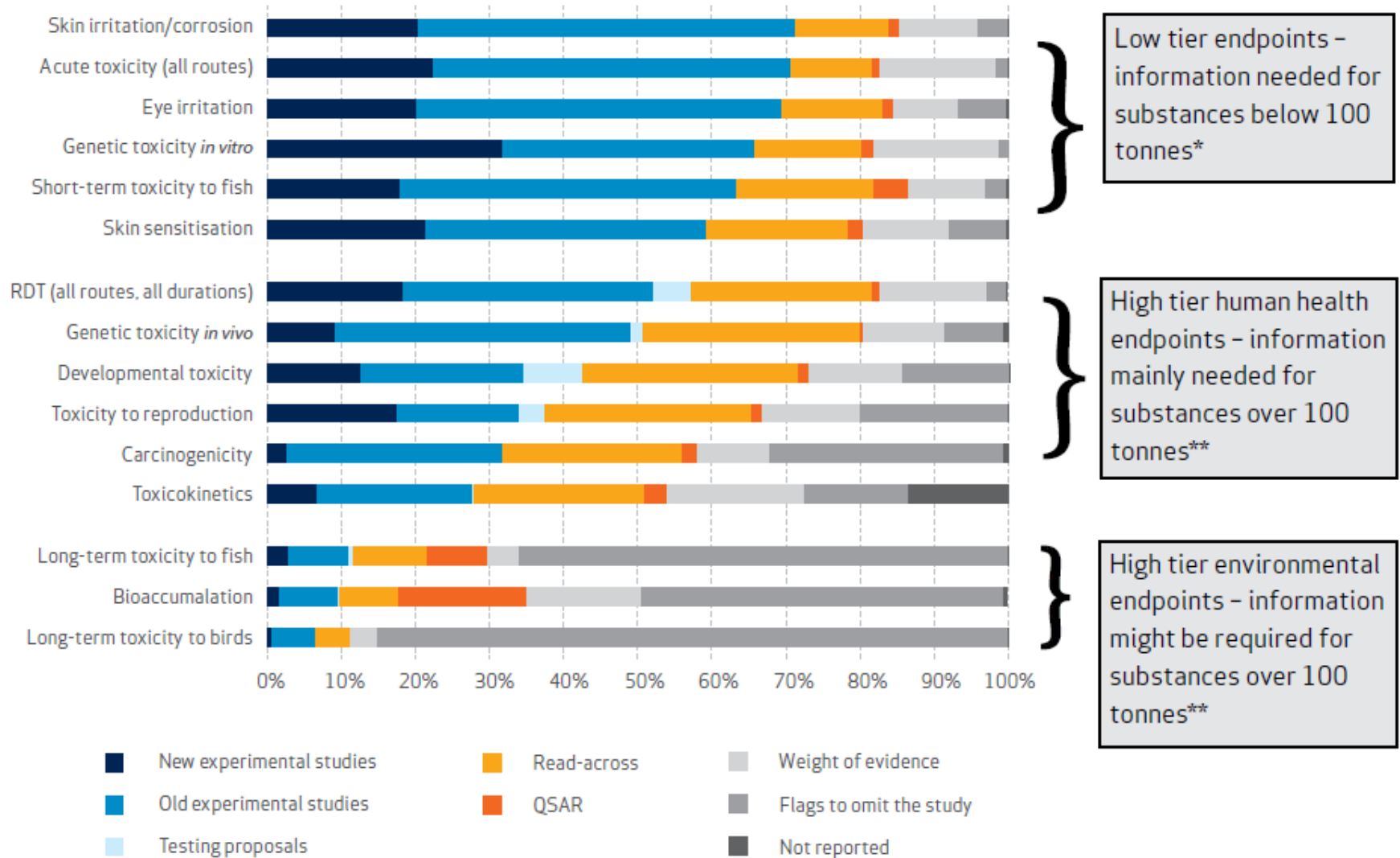
Issue overview

- Read-across is a well-established concept in regulatory science & a powerful tool for minimizing new animal testing (an Article 1 priority under REACH), particularly for complex endpoints
 - *Also an important tool to allow cosmetic manufacturers to innovate in an era of sectoral animal testing restrictions*
- According to ECHA*, among adaptations to information requirements for endpoints involving vertebrate animal testing:
 - *89% contain at least one endpoint in the dossiers where an adaptation or other argument was provided instead of a study result*
 - *63% contain at least one read-across adaptation*
 - *43% contain at least one weight-of-evidence argument*
 - *34% contain at least one QSAR prediction*



* The use of alternatives to testing on animals for the REACH Regulation - Third report under Article 117(3) of the REACH Regulation, ECHA 2017

General aspects on non-testing approaches



Options that registrants use to cover REACH information requirements for different data endpoints

Extract from "The use of alternatives to testing on animals for the REACH Regulation" Third Report, under Article 117(3) of the REACH Regulation **(2015)**

Overview, cont'd

- Despite the wealth of existing guidance, support tools & related work over many years, read-across proposals often face resistance from regulators
- Reported quality deficiencies*:
 - Poor documentation
 - Insufficient substance identification
 - Significant deficiencies in the quality of the source studies
 - Lack of or low quality of supporting data,
 - Lack of qualitative and quantitative data to support predictions based on toxicokinetics
 - Shortcomings in the toxicological hypothesis

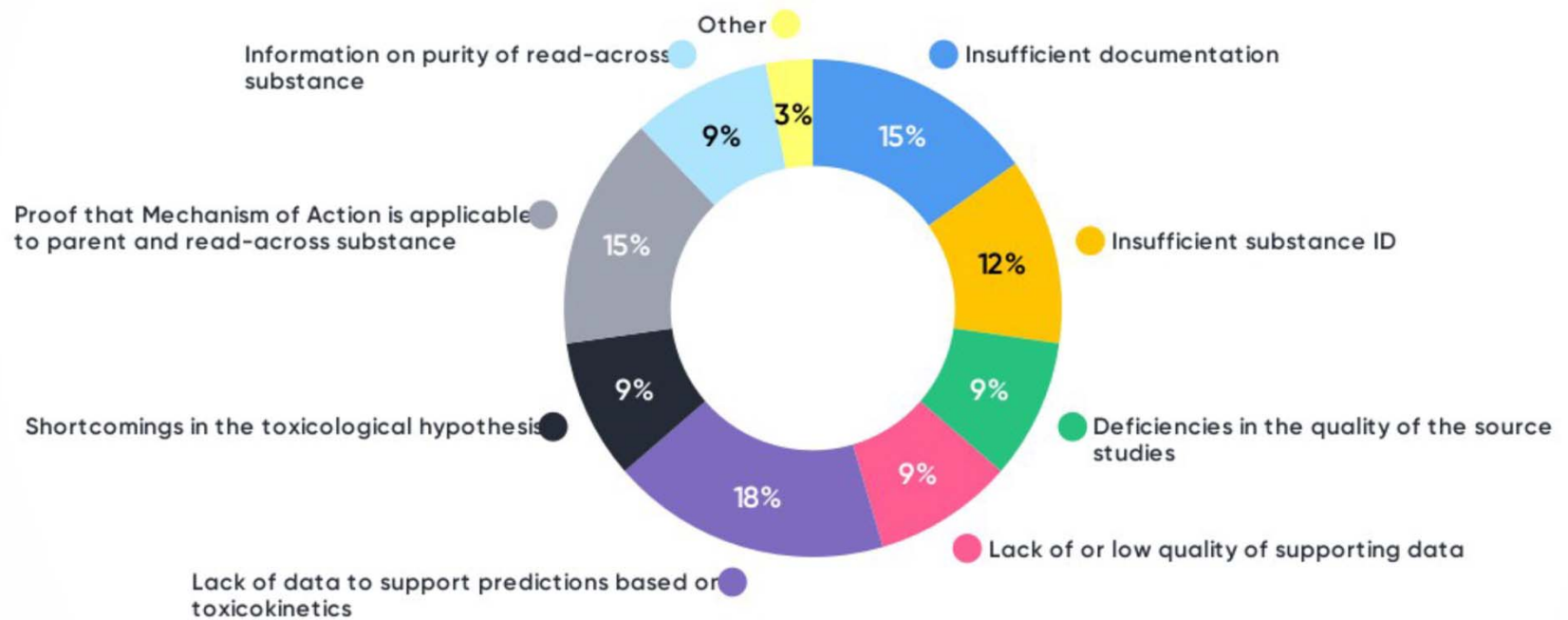
*The use of alternatives to testing on animals for the REACH Regulation - Third report under Article 117(3) of the REACH Regulation, ECHA 2017

The collage includes the following elements:

- ECHA** logo (European Chemicals Agency)
- Read-Across Assessment Framework (RAAF)** title
- QSAR TOOLBOX** logo
- VEGAHUB** logo
- EUTOXRISK** logo with text "Biological read-across"
- ECHA** logo
- Guidance on information requirements and chemical safety assessment** title
- Chapter R.6: QSARs and grouping of chemicals** title
- ENV/JM/MONO(2014)4** reference number
- 14-Apr-2014** date
- English - Or: English** language
- ENVIRONMENT DIRECTORATE** and **JOINT MEETING OF THE CHEMICALS COMMITTEE AND THE WORKING PARTY ON CHEMICALS, PESTICIDES AND BIOTECHNOLOGY** text
- GUIDANCE ON GROUPING OF CHEMICALS, SECOND EDITION** text
- Series on Testing & Assessment No. 194** text
- Cat-App** logo
- AFSA** logo

➤ **Accepted by most Regulatory Bodies if the approach taken is sufficiently justified and documented (RAAF-ECHA)**

If your company has submitted read-across proposals for regulatory purposes, have you ever had any of the following issues pointed out?





Global trends

US EPA moves to end animal testing by 2035



UNITED STATES ENVIRONMENTAL PROTECTION AGENCY
WASHINGTON, D.C. 20460

September 10, 2019

THE ADMINISTRATOR

MEMORANDUM

SUBJECT: Directive to Prioritize Efforts to Reduce Animal Testing

FROM: Andrew R. Wheeler
Administrator

I am pleased today to establish the following commitments that will ensure our work in this area makes a real and significant difference. The EPA will reduce its requests for, and our funding of, mammal studies¹ by 30 percent by 2025 and eliminate all mammal study requests and funding by 2035. Any mammal studies requested or funded by the EPA after 2035 will require Administrator approval on a case-by-case basis. The EPA also will come as close as possible to excluding from its approval processes any reliance on mammal studies conducted after January 1, 2035, including those performed by third parties, subject to applicable legal requirements, including the *Administrative Procedure Act*.

Dutch government plans to stop animal testing by 2025



National Committee on animal testing policy > Documents >

NCad opinion Transition to non-animal research

World leader in innovations without laboratory animals by 2025. That is the aim of the Dutch Minister of Agriculture, Martijn van Dam. In March 2016, the Minister asked the Netherlands National Committee for the protection of animals used for scientific purposes (NCad) to draw up a schedule for phasing out animal procedures.

EU REACH promotes the use of alternative methods

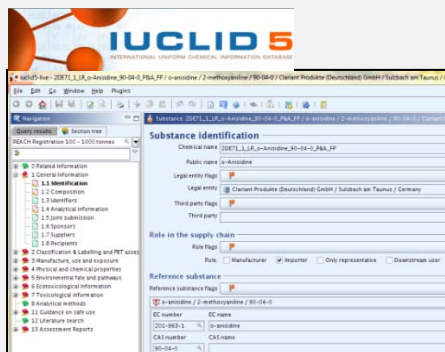
Article 1

Aim and scope

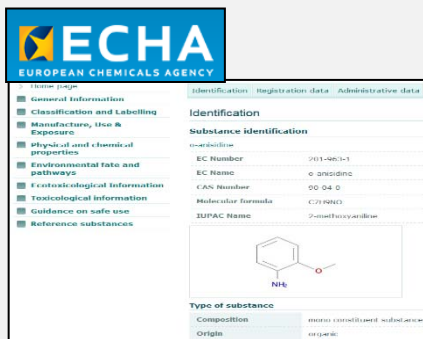
1. The purpose of this Regulation is to ensure a high level of protection of human health and the environment, including the promotion of alternative methods for assessment of hazards of substances, as well as the free circulation of substances on the internal market while enhancing competitiveness and innovation.



LRI AMBIT2 Chemoinformatics System (Substances)



**Company IUCLID DB
& ECHA IUCLID DB
as
Major Data Sources**



**Transfer
of 14570
Dossiers**

ambit



**LRI AMBIT
Supporting
Read across &
Category formation**

*Data
transfer*



*Data
transfer*



*Data
transfer*



Key advantage of AMBIT: large and structured database



Formación

Videos, demos, y mas...

The screenshot shows a web browser window displaying the Cefic-LRI website. The address bar shows the URL <http://cefic-lri.org/toolbox/ambit/>. The page features a navigation menu with options like HOME, ABOUT, RESEARCH PROGRAMME, FUNDING OPPORTUNITIES, PROJECTS, TOOLBOX, and NEWS & EVENTS. Below the navigation, there are social media sharing buttons for Facebook, Twitter, LinkedIn, and Google+. The main content area is titled "AMBIT" and includes a search bar, a "TOOLBOX" sidebar, and a main text block describing the tool. A "Publications" section highlights a "Mini guide to LRI funding" with a thumbnail image. An "Events calendar" for June 2018 is also visible.

CEPIC-LRI PROGRAMME | European Chemical Industry Council

CONTACT | WWW.CEFIC.ORG | MEMBERS PORTAL

Search ... ADVANCED SEARCH

HOME | ABOUT | RESEARCH PROGRAMME | FUNDING OPPORTUNITIES | PROJECTS | TOOLBOX | NEWS & EVENTS

All Tools | Human Health Database | Human Health Models | Environmental Models | External Useful Links

Home | Tools | AMBIT

Share 0 | Tweet | Share | Share

Search ...

AMBIT

AMBIT is an open chemoinformatic system designed to **support companies by facilitating chemical safety assessment**. Developed by Cefic-LRI, the software has the contribution of the European Chemicals Agency (ECHA) through sharing non-confidential REACH data to industry.

The AMBIT system consists of a **database including more than 450.000 chemical structures and REACH dataset of 14.570 substances**, which access was given to Cefic-LRI. AMBIT contributes to the safer use of chemicals and a reduction in testing and innovation cost by making it easier for companies to comply with regulations governing chemicals.

Users can search and access a wide range of existing information and prediction about a chemical. This process makes the tool both unique and powerful, particularly for data-poor small and medium sized enterprises (SMEs).

Several in-silico prediction models (e.g. Toxtree) are integrated in AMBIT. Molecular descriptors and structure alerts can be generated in the tool. The import and export function is enhanced in AMBIT which allows communication with a variety of additional prediction models such as

Publications

Mini guide to LRI funding

Events calendar

June 2018

SU	MO	TU	WE	TH	FR	SA
					1	2
3	4	5	6	7	8	9
10	11	12	13	14	15	16

AMBIT 3: A READ-ACROSS FREE TOOL TO FACILITATE CHEMICAL SAFETY ASSESSMENT

—

- **Purpose:** make it easier for companies to comply with regulations governing chemicals
- Contains information on more than **450 000 chemical structures** from:
 - **ECHA database** (20.000 REACH dossiers)
 - **EFSA OpenFoodTox** database
 - **US EPA CompTox Dashboard (700.000 chemicals)**
- Accessed in more than **60 countries** around the world



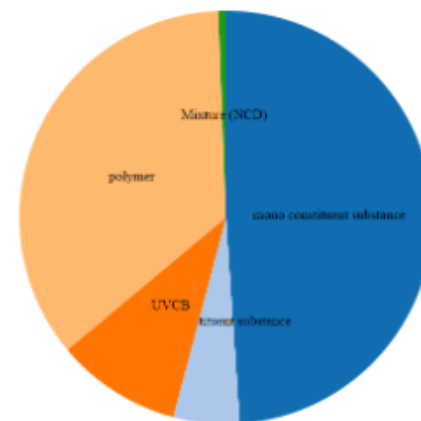
- Integration and compatibility with **prediction models**
- **Read-across** and **category** formation
- Superior **substance search requests** formatted for all data export formats (including REACH IUCLID format)



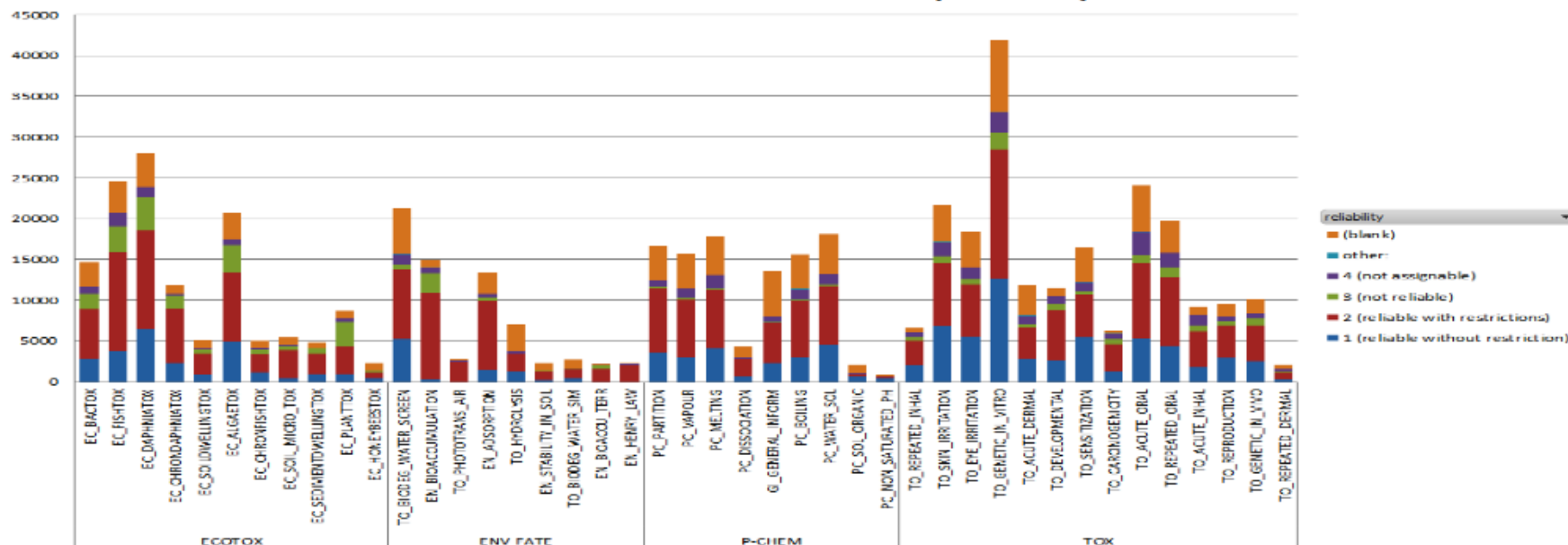
The LRI AMBIT- IUCLID tool is loaded with non-confidential REACH data supplied by ECHA http://echa.europa.eu/view-article/-/journal_content/title/echa-gives-out-registration-data-to-support-development-of-non-test-methods

The screenshot shows the AMBIT web interface with a search results table. The table columns are Substance Name, Substance UUID, Substance Type, Public name, and Reference substance UUID. The table lists several substances, including n-butyl acetate, 9-Octadecenoic acid (Z)-, reaction products with 2-[[2-(aminoethyl)amino]ethanol], 3,9-dicyclohex-2-enyl-2,4,8,10-tetraoxaspiro[5.5]undecane, 4-tert-butylcyclohexanone, and Reaktiv-Scharlach F01-0467.

Substance Name	Substance UUID	Substance Type	Public name	Reference substance UUID
n-butyl acetate	ECHA-d7a6b67c...	mono constituent substance	n-butyl acetate	ECHA-f2f7fab9-1...
9-Octadecenoic acid (Z)-, reaction products with 2-[[2-(aminoethyl)amino]ethanol	ECHA-Dac5eff1...	UVCB	9-Octadecenoic acid (Z)-, reaction products with 2-[[2-(aminoethyl)amino]ethanol	ECHA-147fd272--
3,9-dicyclohex-2-enyl-2,4,8,10-tetraoxaspiro[5.5]undecane	ECHA-d8b46732...	mono constituent substance	Vulkazon AFS	ECHA-b39227aa...
4-tert-butylcyclohexanone	ECHA-52f236af...	mono constituent substance	4-(1,1-dimethylethyl)-cyclohexanone	ECHA-bc771dd8...
Reaktiv-Scharlach F01-0467	ECHA-ab52b348...	mono constituent substance	Reaktiv-Scharlach F01-0467	ECHA-04265692...
tert-butyl g.p.	ECHA-e1be68f5...	mono		ECHA-3a0a5968...



Number of substances in ECHA Disseminated endpoint study records



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



Agenda

- Programa Intelligent Testing
- **LRI Awards**
- QSAR ToolBox OCDE



Desde 2004 apoyando a los jovenes investigadores en este campo

-



- 100.000 €
- Estimulando investigaciones “out of the box”:
 - Nuevos enfoques en el desarrollo y aplicación de la evaluación del riesgo de los productos quimicos.



PREMIADOS HASTA 2018

-



Roger Godschalk



Paul van den Brink



Ellen Fritsche



Roman Ashauer



Emma Taylor



Hector Keun



Maria Saborit



Thomas Preuss



Andreas Bender



Sabine Langie



Alexandra Antunes



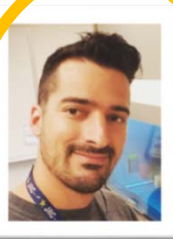
Alice Limonciel



Wibke Busch



Spyros Karakitsios



David Pamies

2018 CEFIC-LRI INNOVATIVE SCIENCE AWARDEE:
Dr DAVID PAMIES



- MSc in Bioengineering, Miguel Hernandez University, Spain
- PhD in Bioengineering, Miguel Hernandez University, Spain
- JRC-IHCP Trainee, Ispra, Italy
- Research Associate, Center for Alternatives to Animal Testing
- PDF in the Department of Physiology, Lausanne University, Switzerland



Agenda

- Programa Intelligent Testing
- LRI Awards
- **QSAR ToolBox OCDE**



The OECD QSAR Toolbox

To increase the regulatory acceptance of (Q)SAR methods, the OECD is developing a QSAR Toolbox to make (Q)SAR technology readily accessible, transparent, and less demanding in terms of infrastructure costs.

[Download the Toolbox](#) [Guidance Documents and Training Materials](#) [Webinar](#) [Help Desk](#) [Public Discussion Forum](#)

WHAT'S NEW?

18 February – OECD launches QSAR Toolbox version 4.3, along with an updated website: <https://qsartoolbox.org/>.

New features of the QSAR Toolbox version 4.3 include:

- > 2 new Databases (pKa OASIS and ADME database)
- > 5 New Profilers (Acute Oral Toxicity, Blood brain barrier (beta), Oral absorption (beta), Skin permeability (beta), Uncouplers (MITOTOX))
- > 2D parameters: 5 new methods for assessing pKa
- > 159 new (Q)SAR models including pre-calculated online Danish QSAR DB models and new pKa models
- > Toolbox Application Program Interface (API) is now publicly available allowing for:
 - Enrichment of the Toolbox tools library with additional parameter calculators, profilers, (Q)SAR models and metabolism simulators
 - Use of the new (Q)SAR Editor – create custom (Q)SAR models using equations or by dynamic linking to external online QSAR computational platforms
 - Connection between Effectopedia and the Toolbox via the new Effectopedia Wizard

For the complete list of new features please see the [release notes](#).

These build on the new features of version 4.0 ([release notes](#)) and 4.1 ([release notes](#)) and 4.2 ([release notes](#)) that was launched in April 2017, in August 2017 and in February 2018.

Download the QSAR Toolbox and find more information at <https://qsartoolbox.org/>.

WHAT IS THE QSAR TOOLBOX ?

The Toolbox is a software application intended to the use of governments, chemical industry and other stakeholders in filling gaps in (eco)toxicity data needed for assessing the hazards of chemicals. The Toolbox incorporates information and tools from various sources into a logical workflow. Crucial to this workflow is [grouping chemicals into chemical categories](#). Download our brochure ([PDF](#)).

The seminal features of the Toolbox are:

1. Identification of relevant structural characteristics and potential mechanism or mode of action of a target chemical.
2. Identification of other chemicals that have the same structural characteristics and/or mechanism or mode of action.
3. Use of existing experimental data to fill the data gap(s).

The interface

Toolbox modules

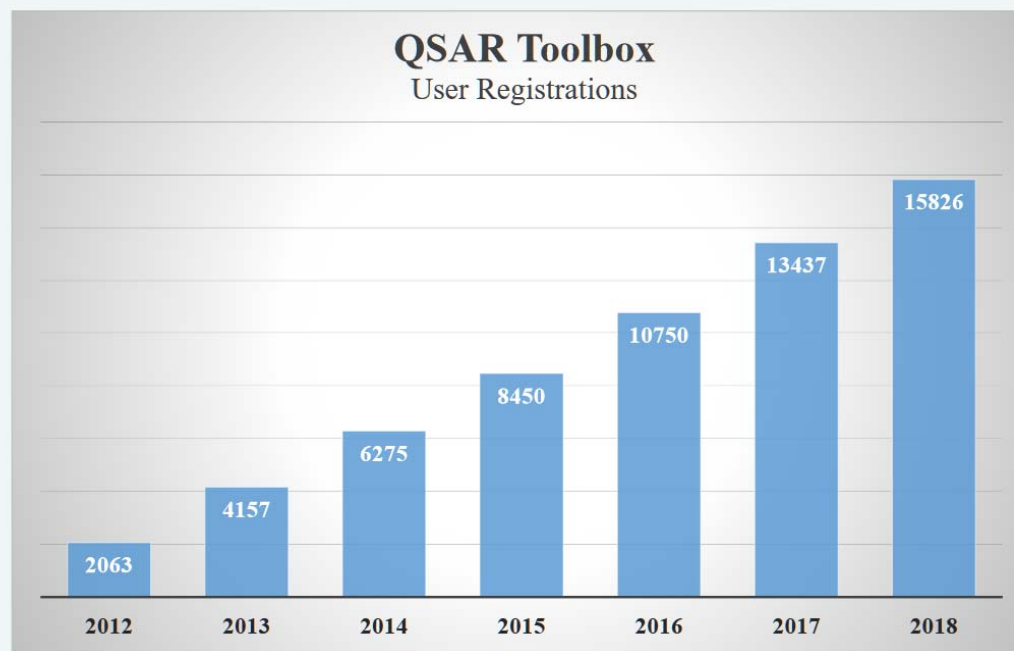
The screenshot shows the QSAR Toolbox interface. A red box highlights the top navigation bar with six numbered icons: 1. Input (hexagon with plus), 2. Profiling (crosshair), 3. Data (beaker), 4. Category definition (tree), 5. Data Gap Filling (matrix), and 6. Report (document). Below the navigation bar, the interface is divided into several panels. On the left, there are panels for 'Documents' (showing a project tree), 'Profiling methods' (with 'Suitable' and 'Plausible' categories), and 'Metabolism/Transformations' (with 'Suitable', 'Plausible', and 'Unclassified' categories). The main central area is a 'Filter endpoint tree...' table. The table has columns for 'Structure', '1 [target]', '2', '3', and '4'. The 'Structure' column shows chemical structures. The table lists various hazard endpoints like 'Acute Toxicity', 'Bioaccumulation', 'Carcinogenicity', etc., with associated counts and metrics. A blue box on the right contains a numbered list: 1. Input, 2. Profiling, 3. Data, 4. Category definition, 5. Data gap filling, 6. Report.

Structure	1 [target]	2	3	4		
Human Health Hazards						
Acute Toxicity						
Bioaccumulation						
Carcinogenicity						
Developmental Toxicity / Teratogenicity						
Genetic Toxicity						
Immunotoxicity						
Irritation / Corrosion						
Neurotoxicity						
Photoinduced toxicity						
Repeated Dose Toxicity						
Sensitisation						
Skin						
in Vivo						
GPMT	14/17	M: Category 1B	M: Positive	M: Negative	M: Negative	M: Category 1A
LLNA						
EC3	13/26	M: 0.882 %		M: 1.68 %	M: Positive	M:
Miscellaneous	6/31	M: Category C	M: Category B			
ToxCast						
Toxicity to Reproduction						
Toxicokinetics, Metabolism and Distributi...						

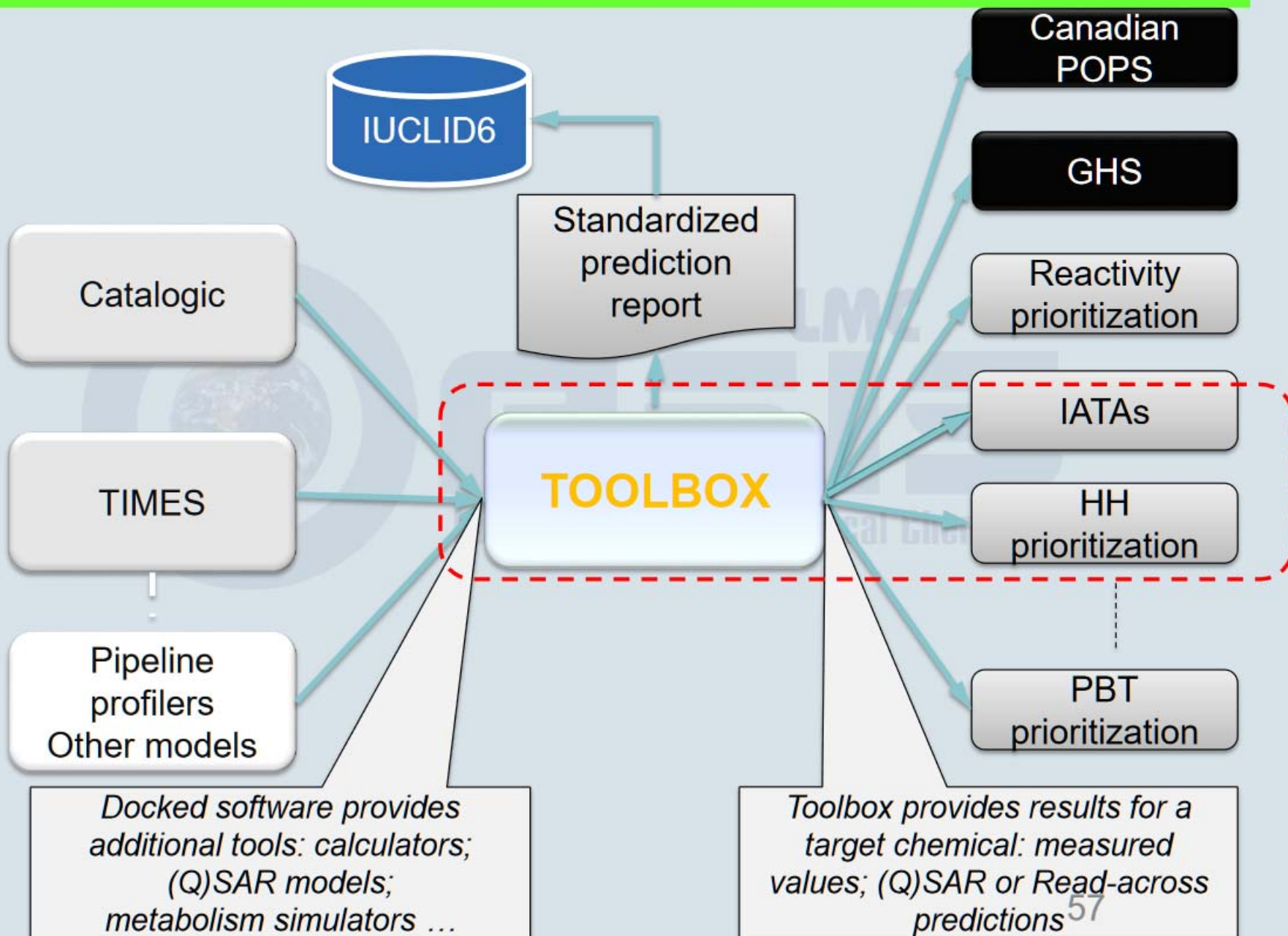
Main Toolbox Supporters

- ✓ OECD
- ✓ European Chemicals Agency
- ✓ US EPA, OPP
- ✓ US EPA, OPPTs
- ✓ US EPA, NHEERL
- ✓ Environment Canada
- ✓ Health Canada
- ✓ NITE Japan
- ✓ NIES Japan
- ✓ Danish EPA
- ✓ UBA Germany
- ✓ NICNAS Australia
- ✓ DEWNA Australia
- ✓ ISS Italy
- ✓ Fraunhofer Germany
- ✓ BfR Germany
- ✓ Cefic
- ✓ Oasis
- ✓ L'Oreal
- ✓ DuPont
- ✓ Givaudan
- ✓ Dow chemicals
- ✓ BASF
- ✓ ExxonMobil
- ✓ 3M
- ✓ Firmenich SV
- ✓ SRC, Syracuse
- ✓ Unilever
- ✓ Multicase
- ✓ ChemAxon
- ✓ International QSAR Foundation

Users registrations



Toolbox interactions



What can we do with Toolbox?

Predictions and much more...

- **Searching** for available experimental data
- **Profiling** chemicals
- **Grouping** analogues
- **Simulating** metabolites
- **Filling data gaps** with prediction workflows for (eco)toxicological endpoints

https://qsartoolbox.org/wp-content/uploads/2019/06/QSARToolbox_General_Workflow_TB43-1.pdf



INTERNATIONAL
COUNCIL OF
CHEMICAL
ASSOCIATIONS

Mas información: reach@feique.org

www.icca-chem.org/Home/ICCA-initiatives/Long-range-research-initiative-LRI


anchemistry.com


www.cefic-lri.org


www.j-lri.org/


Agradecimientos AMBIT


- CEFIC LRI EEM9.3-IC
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Nina Jeliaskova, Nikolay Kochev
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