OECD QSAR Toolbox

Supporting Substance Hazard Assessment and REACH Registrations

Experiences and Needs

René Hunziker – The Dow Chemical Company

Workshop on Use of QSAR Toolbox – Feedback from Industry Users and Development Needs

24th November 2011, ECHA, Helsinki

Predictive Tox Program in Dow's

Toxicology, Environment Research and Consulting (TERC)

Two Pillars of Predictive Tox Program

1. New business service:
   Screening of new chemical candidates or formulations for internal decision making.
2. New paradigm
   Lead Dow's transition to 21st century safety assessment.

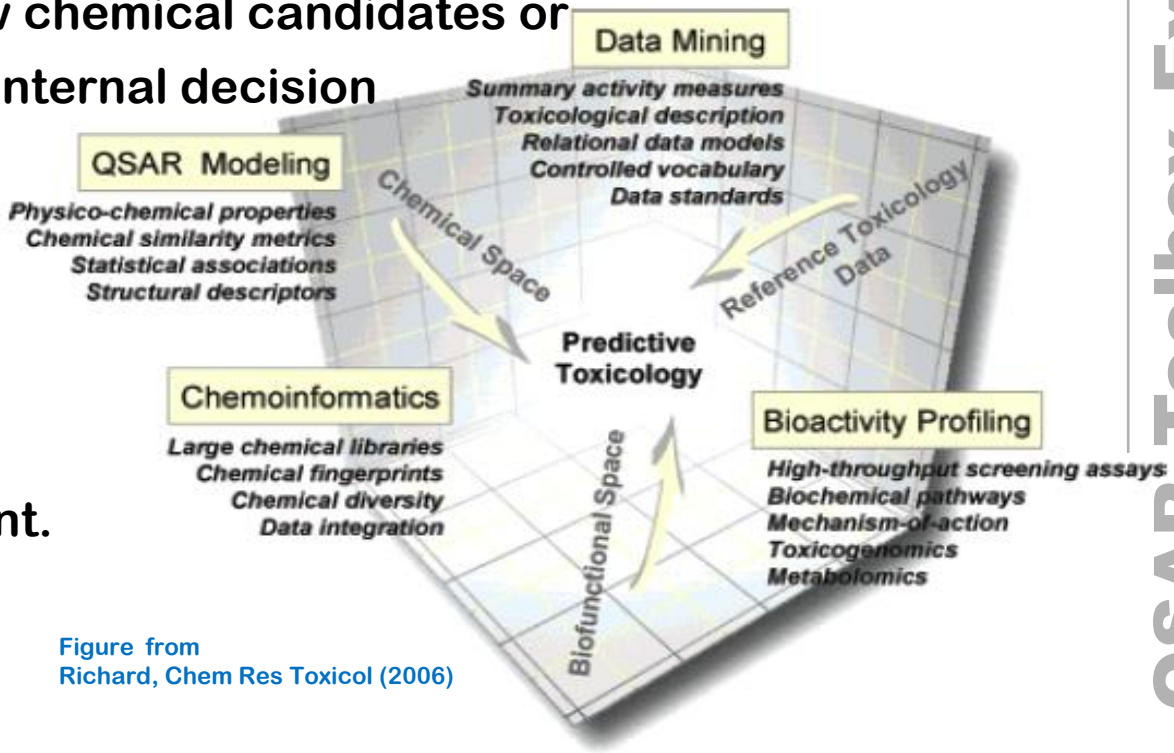


Figure from
Richard, Chem Res Toxicol (2006)

QSAR Toolbox Experience

External Program:
Research Collaborations & Partnerships

EPA
- Prototype toxicity pathway assessment
- NextGen Risk Assessment

P&G
- Use of human cell lines, microarray and informatics for screening and read across

Givaudan
- Rapid in vitro assays for skin sensitization

Unilever
- Sharing of best practices

Hamner Institutes
- $ 1MM/year x 5 years

OECD Toolbox Management Group.
- OECD QSAR Toolbox

LMC Laboratory Mathematical Chemistry.
- Improvement of predictive tools

Traditional Regulatory Toxicology (i)

- Risk Assessment (RA) estimates the risks for:
  - Short term and chronic effects.
  - Local and systemic effects.
  - Individuals with different sensitivities.
- Uses tiered sets of animal tests:
  - Identify the critical effects
  - Set a Point of Departure (POD)
  - Derive route-specific reference doses or can
- Account for remaining uncertainties using assess

Traditional Regulatory Toxicology (ii)

- Has served well and prevented adverse impacts to humans and the environment.
- Is time consuming, expensive, and requires large numbers of animals.
- Resulted in uneven decision making – the 'uncertainty paradox' (Schaafsma et al, 2009).
  - Detailed assessment for few substances
  - open-ended findings (each new study brings new uncertainties).

Uncertainty Non-Testing

Schaafsma, G., E. D. Kroese, et al. (2009). "REACH, non-testing approaches and the urgent need for a change in mind set." Regulatory Toxicology and Pharmacology 53(1): 70-80.

http://echa.europa.eu/doc/press/events/non_test_methods_workshop_20100923/qsarws_hunzike.pdf

The REACH approach ... (bold print)

- Address a large set of substances in short time
- Start assessment from a minimal dataset ('base-set').
- Only generate information required for the assessment (e.g. external exposure based waiving).
- Allow for alternative methods and non-testing options to generate hazard information.
- Resolve the 'uncertainty paradox'

Small print

- Risk assessment approaches (reference dose) have been moved to the hazard assessment. – How to deal with uncertainty in the Hazard assessment?

Uncertainty Non-Testing

http://echa.europa.eu/doc/press/events/non_test_methods_workshop_20100923/qsarws_hunzike.pdf

Point of Departure

- Setubal Workshop – OECD QSAR validation criteria.
- Ad-hoc QSAR group later on Toolbox Management Grp.
- CEFIC LRI sponsor projects:
  - Secretary of OECD Toolbox Management Group.
  - Building blocks for (Q)SAR decision support system – AMBIT.
  - Metabolism prediction of industrial chemicals (OLIMPIC).
  - Reference Database for bioconcentration factors, BCF.
  - RepDose database and identification SAR alerts for substances with low NOELs.
  - Mechanism-based characterisation of systemic toxicity for substances employing in vitro toxicogenomics.

Use of QSAR under REACH 2010 – Dow

- Used for less complex endpoints where confidence in the result is high and
- By and large in a qualitative way to support choice of the (experimental) point of departure.
- QSAR is preferred for environmental endpoints; read across from analogue for mammalian endpoints. Very few categories.
- For complex endpoints, testing *or waiving* is preferred.
- When the endpoint is not considered relevant (e.g. absence of chronic exposure), the known unknown is preferred to the uncertain 'known'.

Use of QSAR under REACH 2010 – Dow

- Used for less complex endpoints where confidence in the result is high and
- By and large in a qualitative way to support choice of
(experimental) point of
- QSAR is prefe
across from a
few categories
- For complex en
- When the endpo
absence of chro
preferred to the

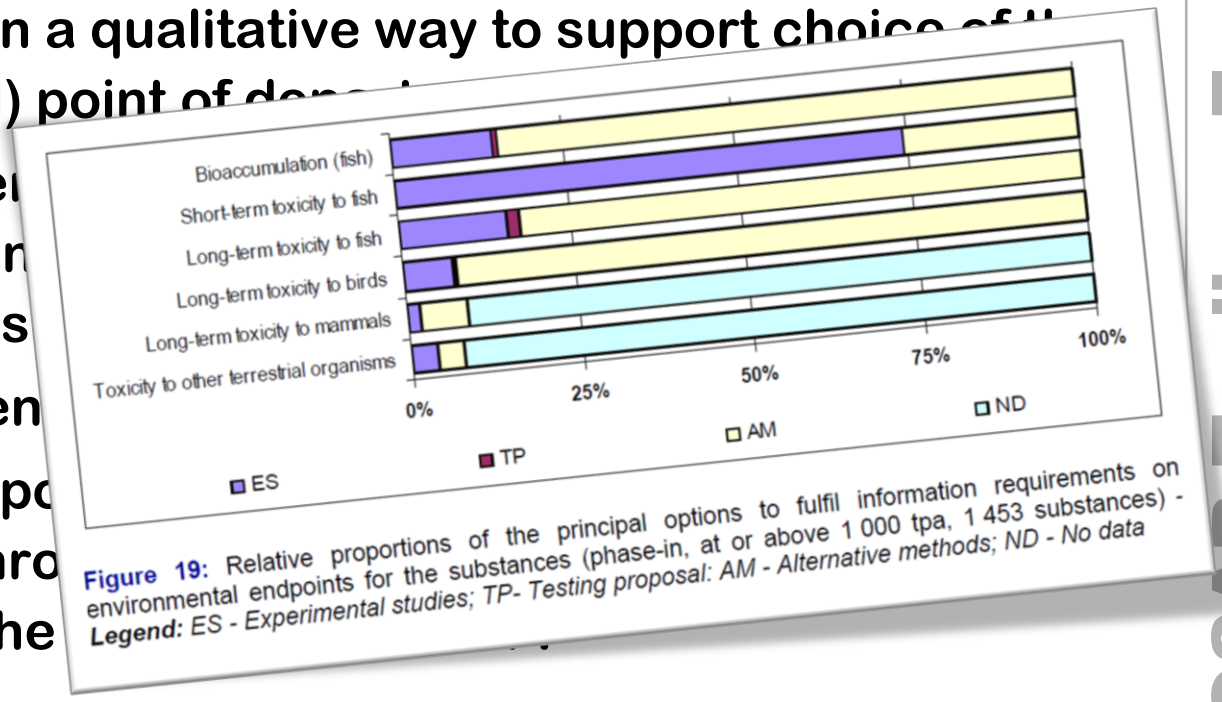


Figure 19: Relative proportions of the principal options to fulfil information requirements on environmental endpoints for the substances (phase-in, at or above 1 000 tpa, 1 453 substances) - ***Legend:*** *ES - Experimental studies; TP- Testing proposal: AM - Alternative methods; ND - No data*

The Use of Alternatives to Testing on Animals for the REACH Regulation – 2011:
http://echa.europa.eu/doc/117reports/summary/alternatives_test_animals_2011_summary_en.pdf

QSAR Toolbox Experience

Challenges under REACH today:

i. ‘Guidance barriers’ to apply Dow’s preferred process.
ii. ‘Off-the-shelf’ solutions for relevant endpoints.
iii. Lack of data and/or Art. 10/17 “legitimate possession or have permission to refer to *the full study report”*
iv. Absence of toxicological findings to support hypothesis.
v. ‘Guidance barriers’ for the use of categories
vi. Cost impact of misclassification of potency vs. cost of testing.

Challenge i)
Dow Process vs. REACH Guidance

- Dow process (defined list of endpoints):
  1. Define analogues by OECD QSAR Toolbox or SME.
  2. Process unknown and analogue through 2–3 'off-the-shelf' tools.
  3. Assess for domain and for performance of the analogues.
  4. Assess relevance of unknown domain **using Toolbox**.
     Perform assessment for 'unknown' using the best performing tool under 3) or use analogues within Toolbox.
- REACH Guidance would imply:
  1. Verify QMRF for 2–3 tools.
  2. Fill in QPRF for 2–3 results and write 2–3 RS on QPRF to meet Technical Completeness Check.
  3. Write 'WOE' summarising 2–3 results.

Challenge ii)
'off-the-shelf' Solutions vs. Toolbox

Currently Supported endpoints for regulatory use:

1. Env. fate and tox:
   Log Kow, log Koc, pKa, solubility, acute aquatic tox, BCF, (ready) biodegradability.
2. Human Health Hazards:
   Metabolism (!), ADME, Skin and eye irritation, Skin Sensitisation, in vitro genotoxicity.

Read Across:

1. 'Worst Case': (reactive) starting material to reaction mass (e.g. monomer to NLP). Sufficient for risk management, not sufficient for C&L of 'REACH substance'
2. 'Realistic' based on 'immediate' metabolism to common systemic exposure.

Challenge iii)
Lack of data and study access requirement

Challenge iv)
Absence of toxicological findings to support hypothesis

Molecule/ Effect	28d oral NOEL/NOAEL [mg/kg/d]			
	A-EO_3-PO_2	B-EO_5	C-EO_2-PO_2	D-PO_5
Liver weight ↑ <10%	1000		1000	1000
Blood	≥ 1000		≥ 1000	≥ 1000
Urine	≥ 1000		≥ 1000	≥ 1000
Body weight	≥ 1000		≥ 1000	≥ 1000

Challenges: v) Analogue vs. category

Registration and completeness check for each member of category has resulted in preference for analogue approach.

Challenges: vi)
Cost of misclassification vs. cost of testing.

- Requirements from hazard classification based regulation
  - Transport and storage
  - End of life treatment
  - Emergency preparedness

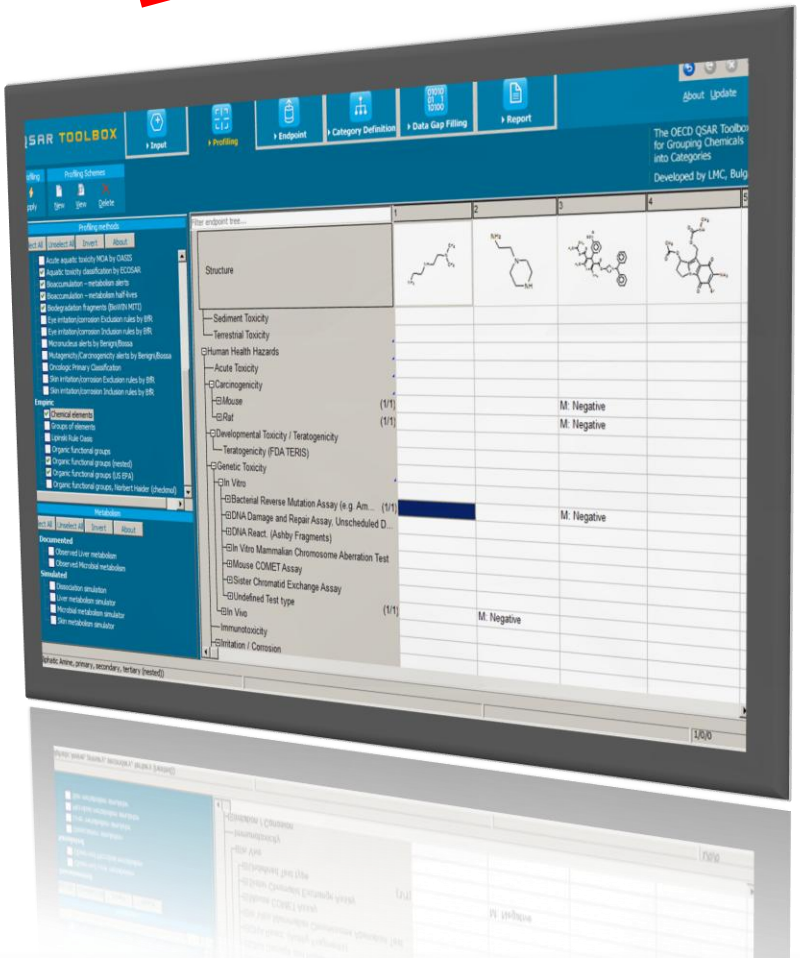
  have significant cost impact.
- Cost of testing are compared against those expenses.

Opportunities today and in the future

READY NOW!

Applications:

- Impurities
  - PBT
  - Food migrants
  - Pesticides
- Candidate Chemicals screening
  - R&D molecules
  - Supplier materials



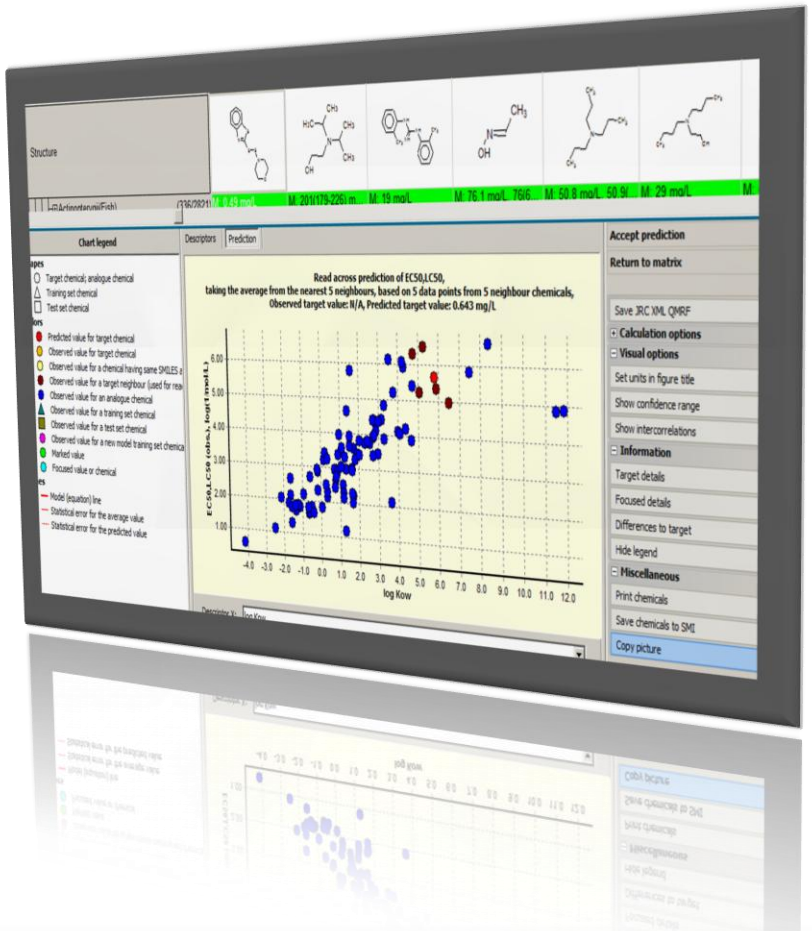
QSAR Toolbox Experience

Opportunities today and in the future

READY NOW!

Strengths of the Toolbox:

- Extremely versatile:
  From very specific, user lead, single molecule to batch processing.
- Transparency:
  Training data, model assumptions, model, outliers, …
- Importing, exporting, reporting.



QSAR Toolbox Experience

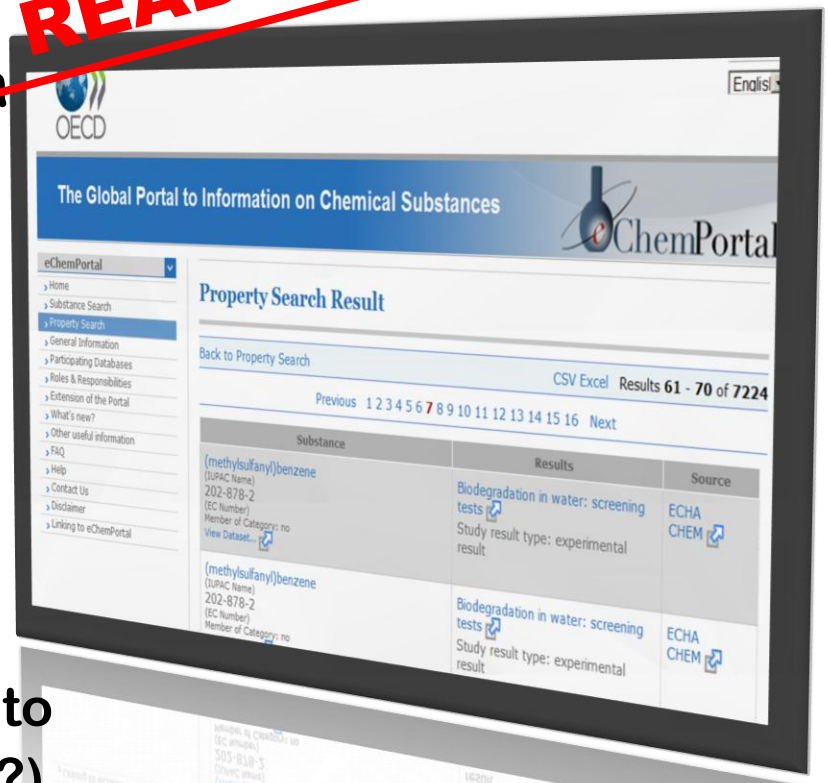
MUST HAVE!

Opportunities today and ~~in the future~~

READY NOW!

REACH Registration Data

- Published on e-chem portal (and ECHA chem)
- Approx. 4000 substances
- Dissemination by Toolbox in line with ICCA GPS and welcomed by BIAC and CEFIC for non commercial uses.
- Identification of data holder to be resolved (3rd party trusty?).



http://www.echemportal.org/

QSAR Toolbox Experience

MUST HAVE!

Opportunities today and in the future

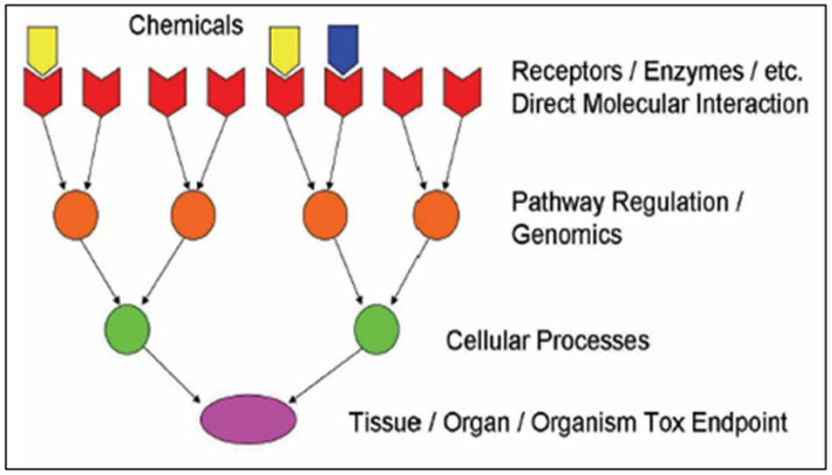
READY 5YRS!

The promise of the Adverse Outcome Pathway approach:

Truly *novel* combination of

- Categorisation by initiating event.
- Mechanistic database (receptor binding, genomics, …).
- Customisable hierarchical structure.
- Apical effect concentration database.
- Immediate feedback on the 'working hypothesis' for the family under consideration.

Figure 1. Toxicity pathways across multiple scales of biological organization.



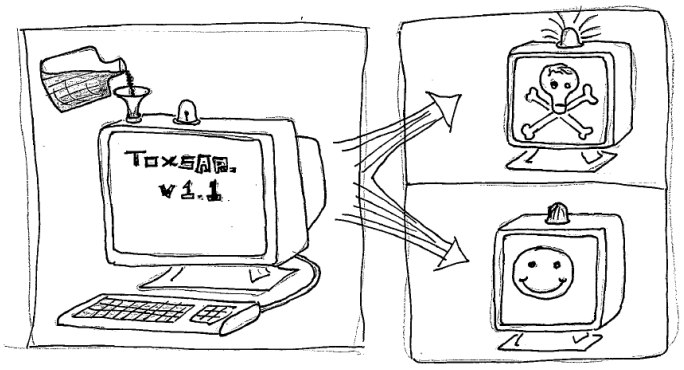
U.S. EPA, National Center for Environmental Research
Computational Toxicology: Biologically-Based Multi-Scale Modeling

QSAR Toolbox Experience

Opportunities today and in the future

CONTINUOUS

- Anker points: Proof of category across endpoints, (including the unknown).
- Data processing/aggregating
  - # positives / # negatives per sub-category
  - Category / subcategory statistics
- In IUCLID: Updated 'study summary' to report predictive results (multiple summary templates to choose from).
- More data …
- More and relevant profilers



QSAR Toolbox Experience

Use of Toolbox in Candidate Screening

Family of Amine hydrophobes:

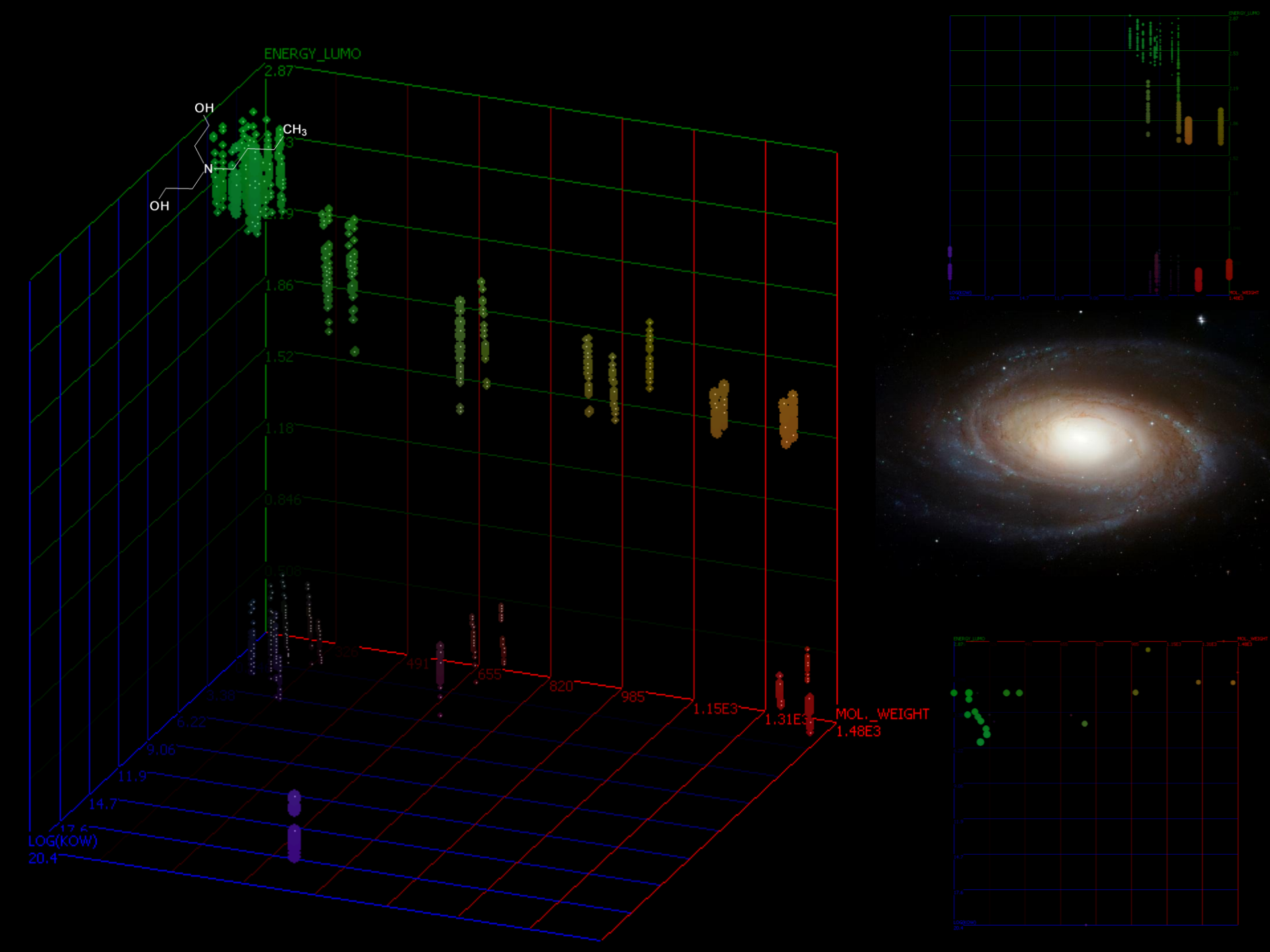
R1-N (-R2)-R3-OH

Endpoints of interest:

- aquatic toxicity,
- Ready biodegradation
- Generic toxicity.

Approach chosen:

- Domain assessment and candidate selection (Domain manager LMC).
- QSAR assessment using 'off-the-shelf' tools, e.g, ECOSAR. CATABOL
- Investigate opportunities for sub-categorisation and test hypothesis in multiple species
- Zebrafish embryo test (ZET).


ENERGY_LUMO
2.87
1.86
1.52
1.18
0.846
OH
CH3
N
OH
491
655
820
985
1.15E3
1.31E3
MOL._WEIGHT
1.48E3
3.38
6.22
9.06
11.9
14.7
LOG(KOW)
20.4

Conclusion

- Toolbox has emerged and has surpassed its initial vision.
- The increase in available data makes it to one of the preferred tools for experienced users for non-regulatory assessments.
- IP of data, acceptability of results, and complexity of apical endpoints are barriers for the use of the toolbox under REACH.
- Customisable integration of AOP concepts and HTP data will boost the use of HTP data and hopefully crack the door to reading across for complex apical endpoints.

Thank you

for your

attention