



Bridges and Barriers to Meeting your Information Requirements

René Hunziker

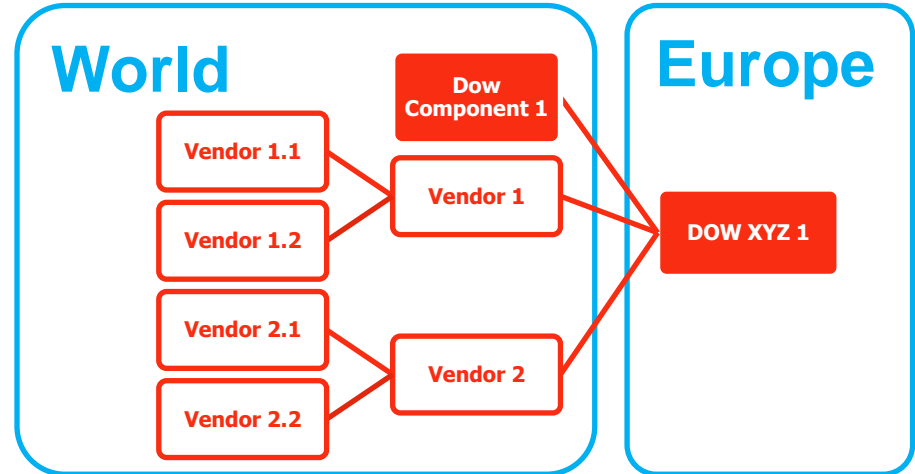
Global Sustainability Leader DCP

- The Dow Chemical Company

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- REACH for complex value chains.
- The opportunity with the available data from 2010/13.
- The advancement of the science for non-testing information.
- Classification and Labelling – from an interpretation scheme to a barrier for opportunities of the future.
- Sneak Peek on opportunities of the future.
- Wrap up and conclusions.

Barriers: In-Scope Materials from a Complex Value Chain



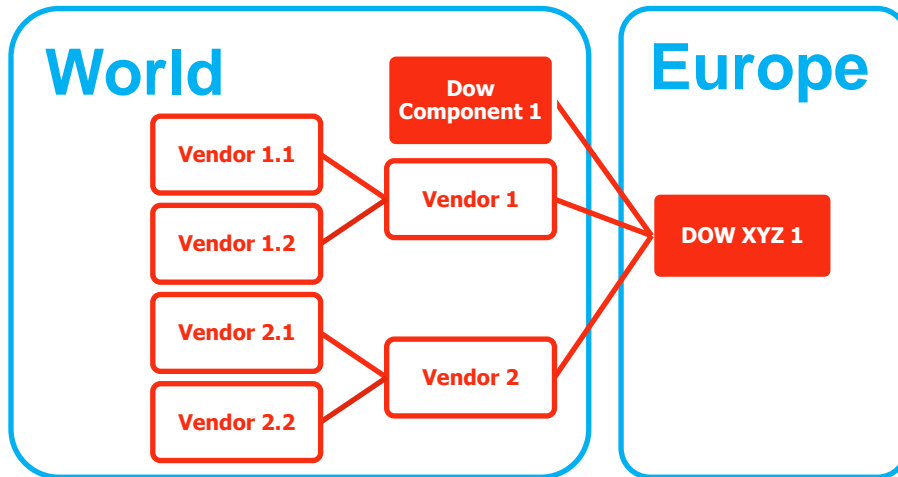
"... would you be willing to provide DRT coverage for REACH? ..."

*"... committed to customer service (...)
where is REACH? ..."*

	A	B	C	D	E	F
1	Dow REACH 2018 Materials					
2		Dow XYZ 1	Dow XYZ 2	Dow XYZ 3	Dow XYZ 4	
3	Annual Volume 2012-14 [mt]	25 ± 50	75 ± 20	0	8 ± 6	in scope volume [mt]
4	Dow Component 1	64 %	0 %	0 %	0 %	18 ± 33
5	Dow Component 2	0 %	22 %	51 %	39 %	16 ± 4
6	Dow Component 3	0 %	43 %	0 %	0 %	36 ± 11
7	Vendor 1.1	13 %	0 %	0 %	20 %	3 ± 6
8	Vendor 1.2	19 %	22 %	0 %	0 %	1 ± 2
9	Vendor 2.1	3 %	0 %	26 %	0 %	0 ± 0
10	Vendor 2.2	0 %	0 %	1 %	0 %	2 ± 1
11	Vendor 3.1	0 %	2 %	3 %	2 %	10 ± 3
12	Vendor 3.2	0 %	11 %	0 %	0 %	0 ± 0
13	Vendor 3.3	0 %	0 %	20 %	100 %	0 ± 0
14		100 %	100 %	100 %	100 %	
15						
16						

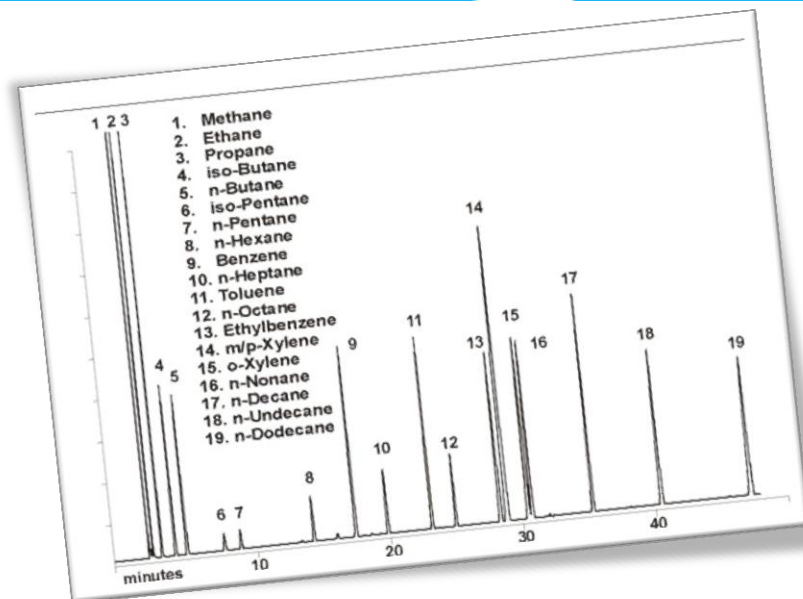


Barriers: Substance ID for Materials from a Complex Value Chain

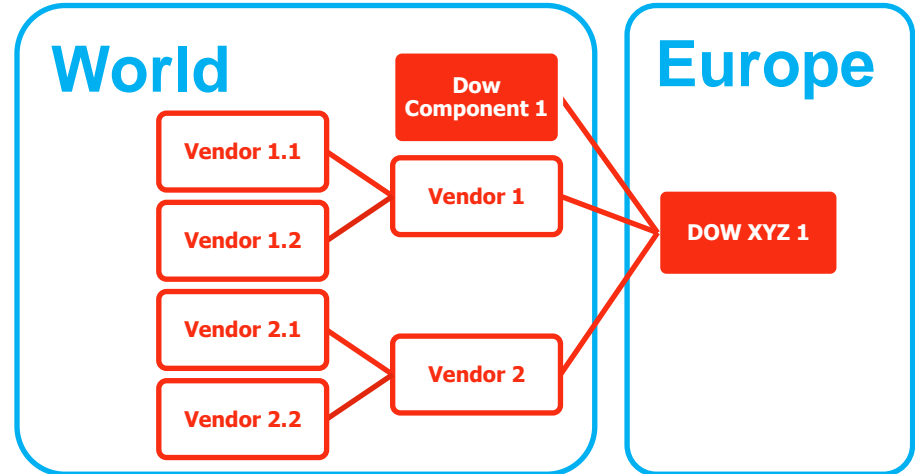


"... would you be willing to provide analytical Data for REACH? ..."

*"... committed to customer service (...)
where is REACH? ..."*



Bridges: Substantial Number of Substances already Registered



"... would you be willing to provide Hazard Data for REACH? ..."



Last updated 24 April 2015. Database contains 13149 unique substances and contains information from 50797 Dossiers.

Showing 1 - 50 of 14,795 results. Items per Page: 10 Page: 1 of 296 First Previous Next Last

EC / List No.	CAS No.	Name	Registration Type	Submission Type	Tonnage Band	View
		Vendor 1.1	Full	Individual Submission	Tonnage Data Confidential	Q
		Vendor 1.2	Intermediate	Individual Submission	Intermediate Use Only	Q
		Vendor 2.1	Full	Individual Submission	1,000 - 10,000 tonnes per annum	Q
	AA 15		Full	Individual Submission	0 - 10 tonnes per annum	Q
	Z-109		Full	Individual Submission	0 - 10 tonnes per annum	Q
	222 OP		Full	Individual Submission	0 - 10 tonnes per annum	Q
	Olafur		Full	Joint Submission	100 - 1,000 tonnes per annum	Q
		Vendor 2.2	Intermediate	Individual Submission	Intermediate Use Only	Q



A wide-angle photograph of the Golden Gate Bridge in San Francisco, California. The bridge's iconic red-orange towers and suspension cables are prominent against a clear blue sky with a few wispy clouds. The bridge spans across the water, with rolling hills visible in the background.

Read across and other Non-testing Approaches

“I have not failed.
I have just found
10'000 ways that
don't work”

Thomas Edison

Infrastructure

- Substantial data is available from 2010/13.
- Data can support 2018 requirements.
- 2018 registrations can expand to Annex IX and X endpoints.
- LoA Prices have been agreed in 2010 and are not up for negotiation.

QSAR Toolbox 3.3.0.152 [Gentox]

QSAR TOOLBOX

Input Profiling Endpoint Category Definition Data Gap Filling Report

Filling Apply

Data Gap Filling Method

- Read-across
- Trend analysis
- (Q)SAR models

Target Endpoint

Human Health Hazards Genetic Toxicity In Vivo Micronucleus Assay

Relevant (Q)SAR models

<< CREATE A NEW QSAR >>

(Q)SAR models in nodes below

Mouse micronucleus (Danish EPA DB) TIMES: in vivo micronucleus

Only endpoint relevant

Only chemical relevant

Show estimated DB

Rank Model

Filter endpoint tree...

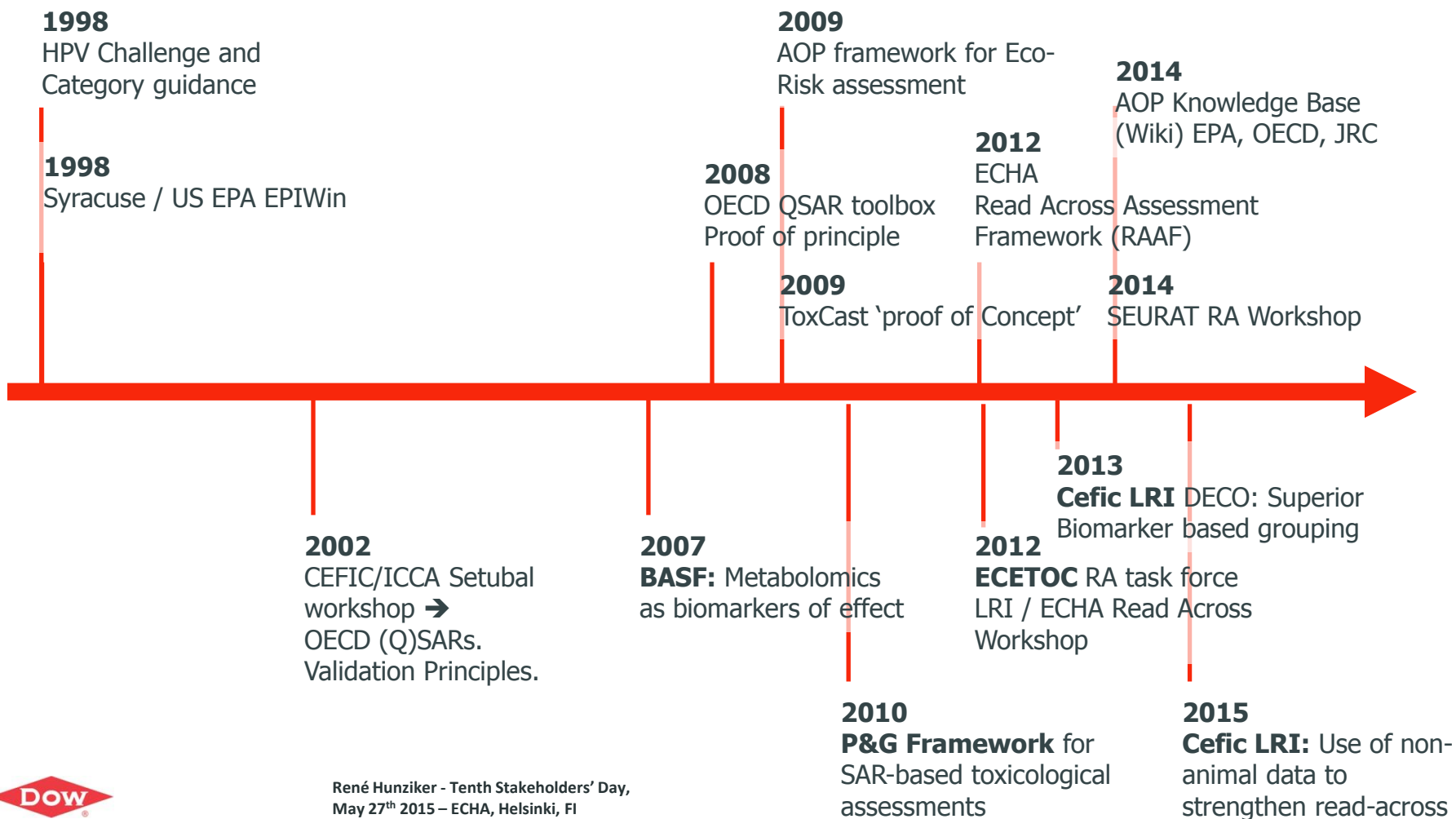
Structure

	1	2	3
[2] [Mix]			
Bacterial Gene Mutation Assay (1/4)	M: negative, positive, p...		
Bacterial Reverse Mutation Assay (e.g. A... (3/12)	M: negative, positive, n...	M: ambiguous, positive, ...	M: negative
In Vitro Mammalian Cell Micronucleus Test			
In Vitro Mammalian Cell Transformation As... (1/1)	M: positive		
In Vitro Mammalian Chromosome Aberration Test			
Chromosome Aberration (3/5)	M: positive, negative	M: positive, positive	M: negative
Mammalian Cell Gene Mutation Assay			
Gene Mutation (1/3)	M: negative, positive, p...		
Point Mutation Assay (1/1)	M: positive		
Sister Chromatid Exchange Assay			
Yeast Gene Mutation Assay (1/1)	M: positive		
In Vivo			
Chromosome Aberration Assay (2/3)	M: negative	M: negative, negative	
Chromosome Studies in Male Germinal Ep... (1/1)	M: negative		
Chromosome Studies in Somatic Cells, B... (1/1)	M: negative		
Dominant Lethal Assay (1/2)	M: negative, negative		
Drosophila SLRL Test			
In Vitro Test / Host-Mediated Assay (1/1)	M: negative		
Mammalian Germ Cell Cytogenetic Assay (1/1)		M: negative	
Micronucleus Assay (2/4)	M: negative, negative, ...	M: negative	
Mouse COMET Assay			

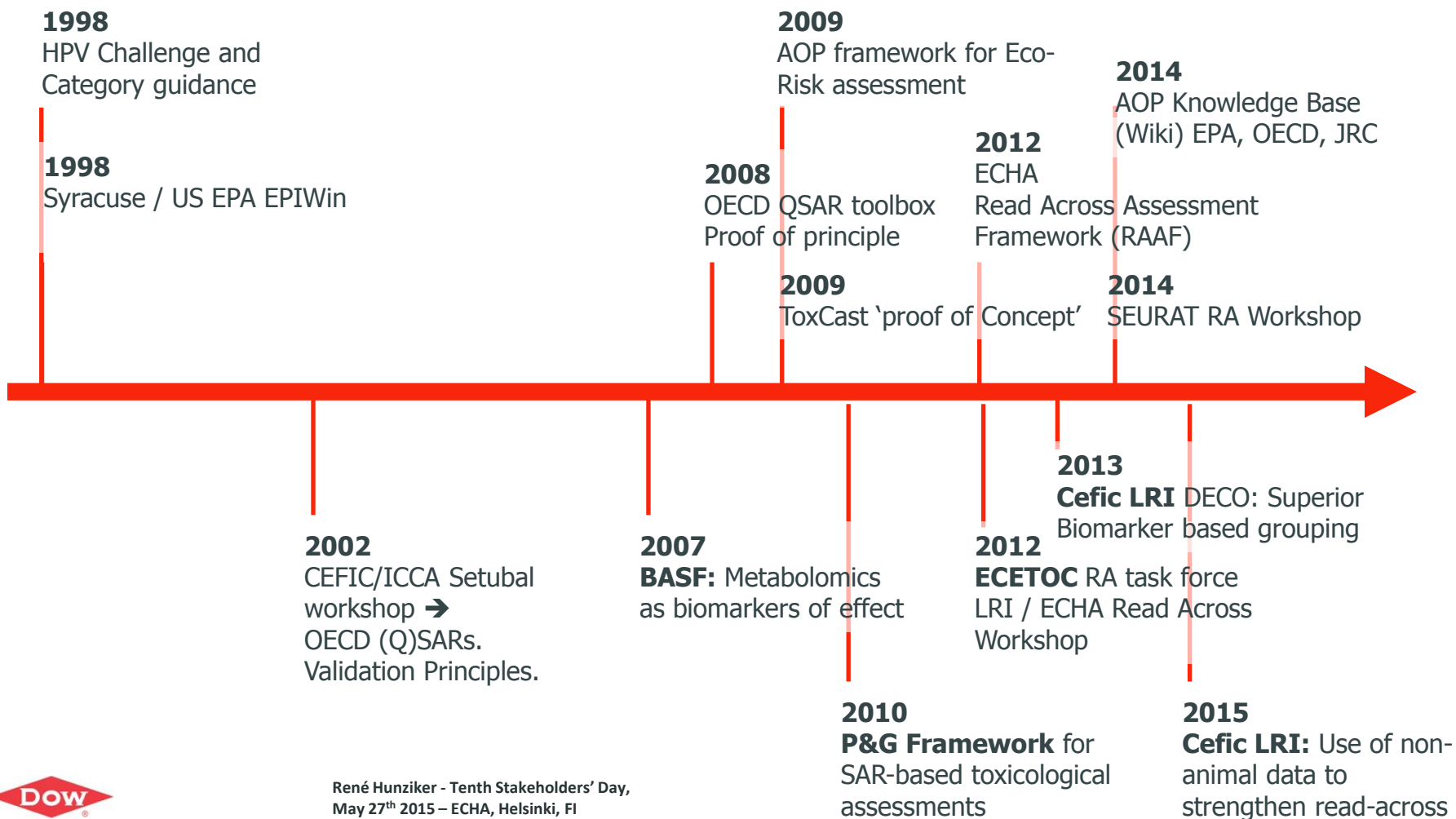
3 Add to category sorted ascending by Chromosome Aberration As

3/0/0

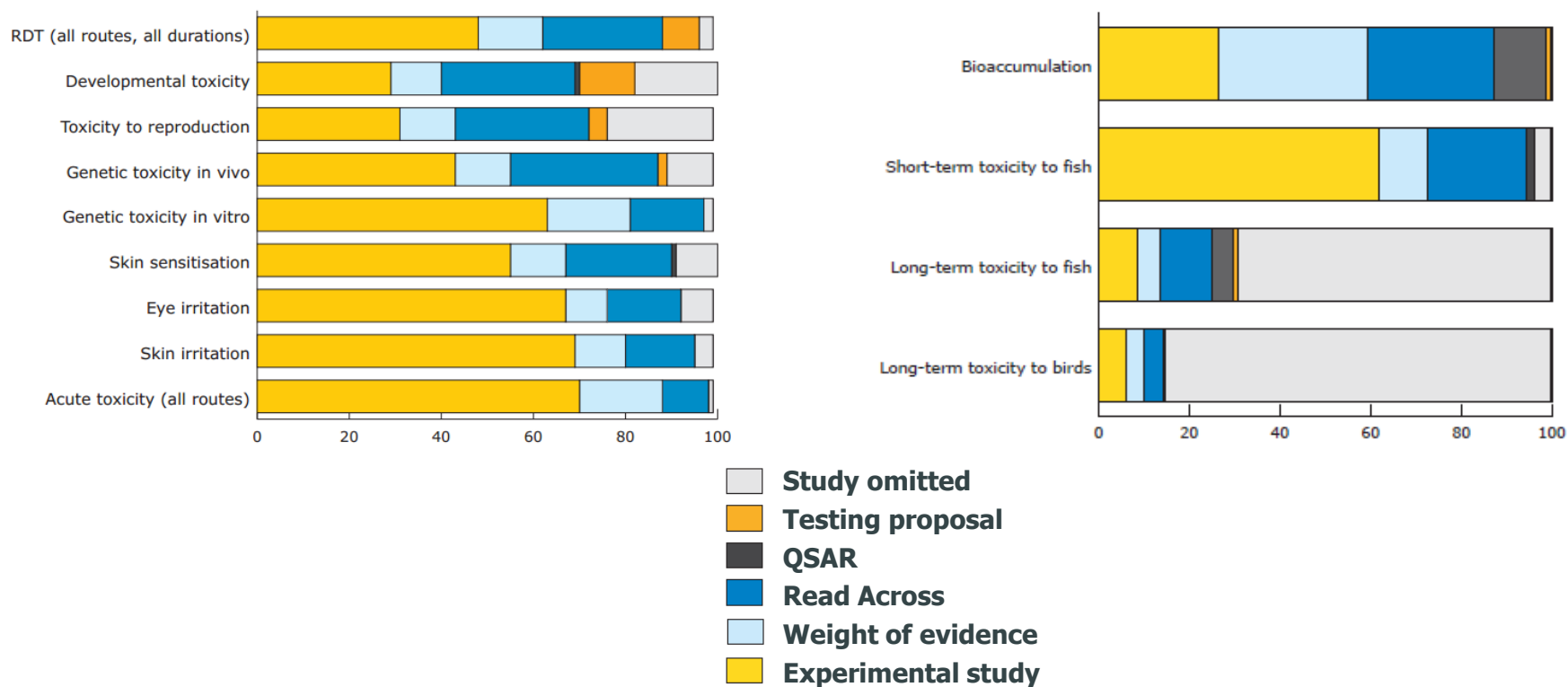
Bridges: Science of Non-testing is Growing – From ‘Similar Structure’ to ‘Similar Biology’



Bridges: Science of Non-testing is Growing – From ‘Similar Structure’ to ‘Similar Biology’



Bridges: Testing vs. Non-Testing for REACH Registrations



From "ECHA's second report on the use of alternatives to testing on animals"; http://echa.europa.eu/documents/10162/13639/alternatives_test_animals_2014_en.pdf

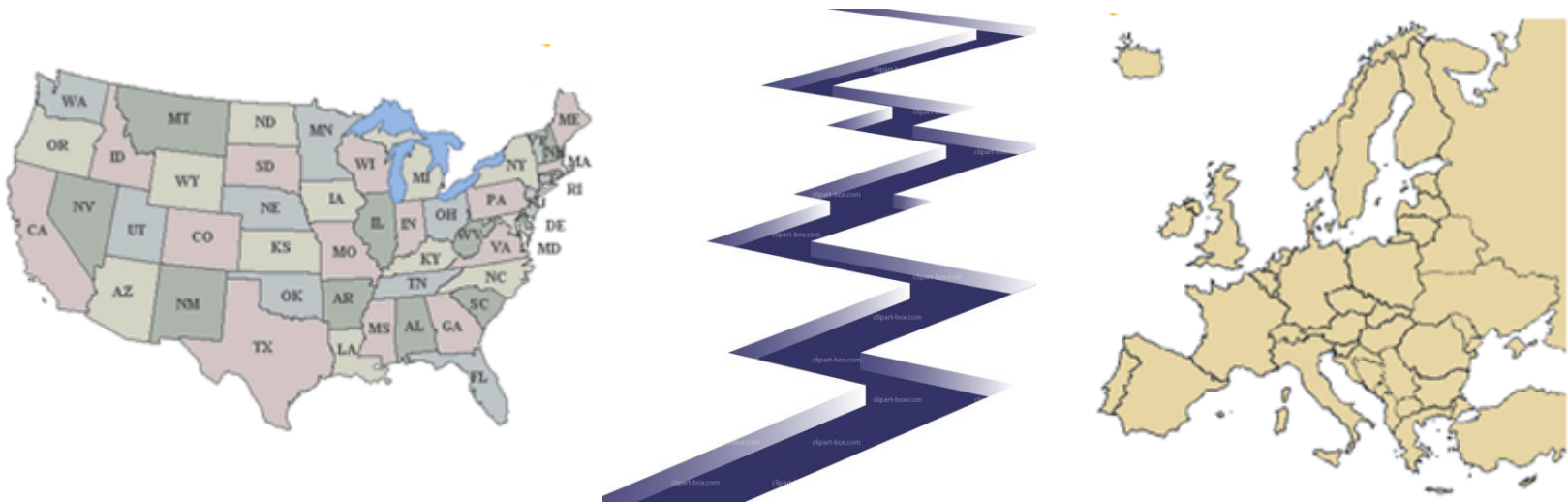
Uncertainty

Hazard characterisation („adequate for risk assessment“):

→ Quantify the lowest adverse effect level/concentration.

Hazard identification („adequate for Classification and Labelling“):

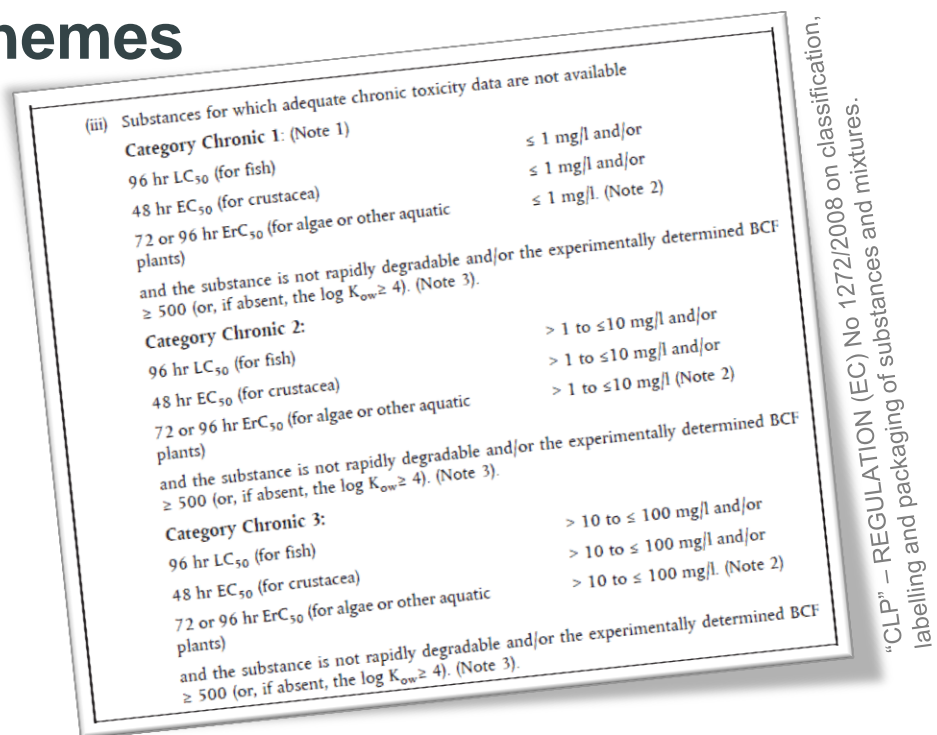
→ Recognise the full *detailed* spectrum of hazards.



Exemplary Classification Schemes

Environment:

- Effect concentration in the most sensitive species.
- Similar as for risk assessment and can be predicted well with QSAR.



Dow REACH 2018 Materials

Annual Volume 2012-14 [mt]	Dow XYZ 1	Dow XYZ 2	Dow XYZ 3	Dow XYZ 4	ac. Fish	ac. Daphnia	Biodegradation
	25 ± 50	75 ± 20	0	8 ± 6	ECOSAR	ECOSAR	Biowin
Dow Component 1	64 %	0 %	0 %	20 %	out of domain	out of domain	in domain
Dow Component 2	0 %	22 %	0 %	0 %	in domain	in domain	in domain
Dow Component 3	0 %	43 %	51 %	39 %	out of domain	out of domain	out of domain
Vendor 1.1	13 %	0 %	0 %	0 %	in domain	out of domain	in domain
Vendor 1.2	19 %	22 %	0 %	20 %	out of domain	in domain	in domain
Vendor 2.1	3 %	0 %	26 %	0 %	out of domain	in domain	in domain
Vendor 2.2	0 %	0 %	1 %	0 %	in domain	out of domain	out of domain
Vendor 3.1	0 %	2 %	3 %	2 %	out of domain	out of domain	out of domain
Vendor 3.2	0 %	11 %	0 %	20 %	in domain	in domain	out of domain
Vendor 3.3	0 %	0 %	20 %	0 %	in domain	out of domain	out of domain
	100 %	100 %	100 %	100 %			

Exemplary Classification Schemes

Human Health:

- Approach almost entirely based on animal studies.
- Can it be predicted from methods other than the standard animal study?

Categories for specific target organ toxicity-repeated exposure	
Categories	Criteria
Category 2	<p>studies in experimental animals can be presumed to have the potential to be harmful to human health following repeated exposure. Substances are classified in category 2 for target organ toxicity (repeat exposure) on the basis of observations from appropriate studies in experimental animals in which significant toxic effects, of relevance to human health, were produced at generally moderate exposure concentrations. Guidance dose/concentration values are provided below (see 3.9.2.9) in order to help in classification.</p> <p>In exceptional cases human evidence can also be used to place a substance in Category 2 (see 3.9.2.6).</p>

Robust study summaries are necessary for key data on reproductive toxicity. If possible the information must be provided in the form of table(s) (see further details in Annex I, 1.1.3. of REACH).

R.7.6.4.1 Non-animal data

For reproductive toxicity, a grouping and category approach and weight of evidence approaches are the best fit-for-purpose tools for non-animal approaches for the time being to adapt the standard information requirements for reproductive toxicity. However, appropriate justification and documentation must be provided. In addition they may be used for prioritisation and screening chemical inventories.

Information on the current developments of *in vitro* tests and methodology can be found on the ECVAM website (http://ihcp.jrc.ec.europa.eu/our_labs/eur-ecvam) and other international centres for validation of alternative methods. ECHA's website is also

Guidance R.7a on Reproductive toxicity (Draft for PEG)

(f) morphological changes that are potentially reversible but provide clear evidence of marked organ dysfunction (e.g., severe fatty change in the liver);

(g) evidence of appreciable cell death (including cell degeneration and reduced cell number) in vital organs incapable of regeneration.

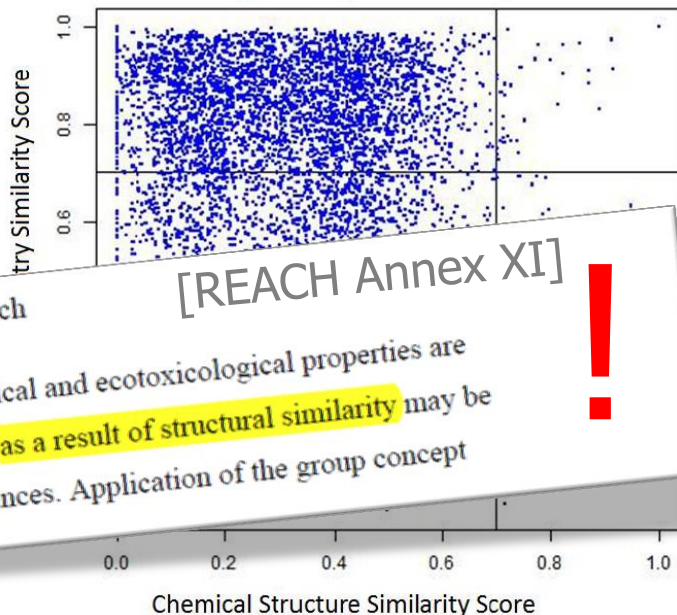
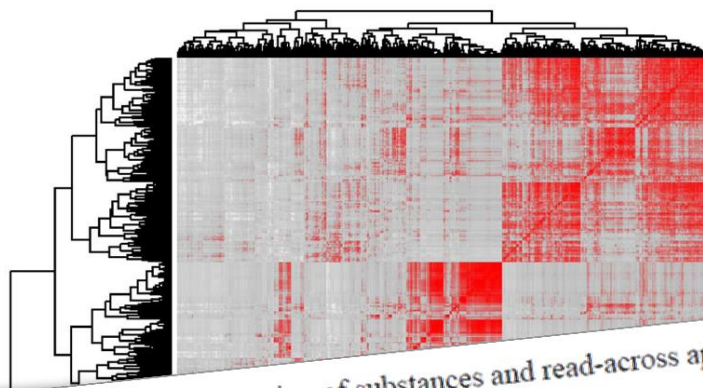
“CLP” – REGULATION (EC) No 1272/2008 on classification, labelling and packaging of substances and mixtures.

Bridges: DECO: Data-integration for Endpoints, Cheminformatics and Omics



Hypothesis

Integrating cheminformatics approaches with mechanistic data from 'omics' and HTS technologies, strengthens confidence that compounds within a category have similar toxicological profile.



[REACH Annex XI]

1.5. Grouping of substances and read-across approach

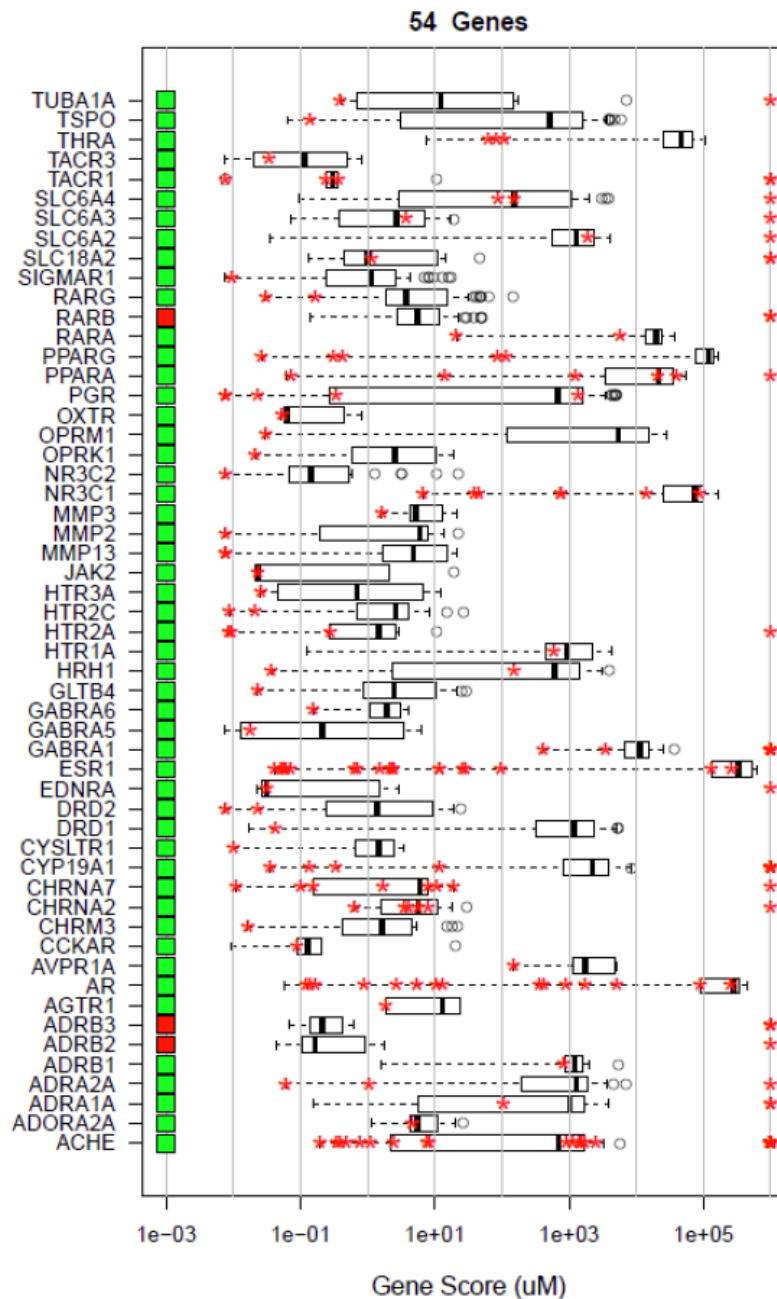
Substances whose physicochemical, toxicological and ecotoxicological properties are likely to be similar or follow a regular pattern as a result of structural similarity may be considered as a group, or "category" of substances. Application of the group concept

van Delft, J.; Polman, J.; et al. (2014): DECO: Data-integration for Endpoints, Cheminformatics and Omics; Cefic-LRI annual meeting, Brussels, Belgium.
<http://cefic-lri.org/wp-content/uploads/uploads/Project%20publications/AIMT3%20poster%20DECO%20November%202012.pdf>

Barrier or Bridge? Specificity vs. 'Burst'

* Reference Chemicals with pronounced MoA are identified by high Gene score (right boundary).
Judson, 2014.

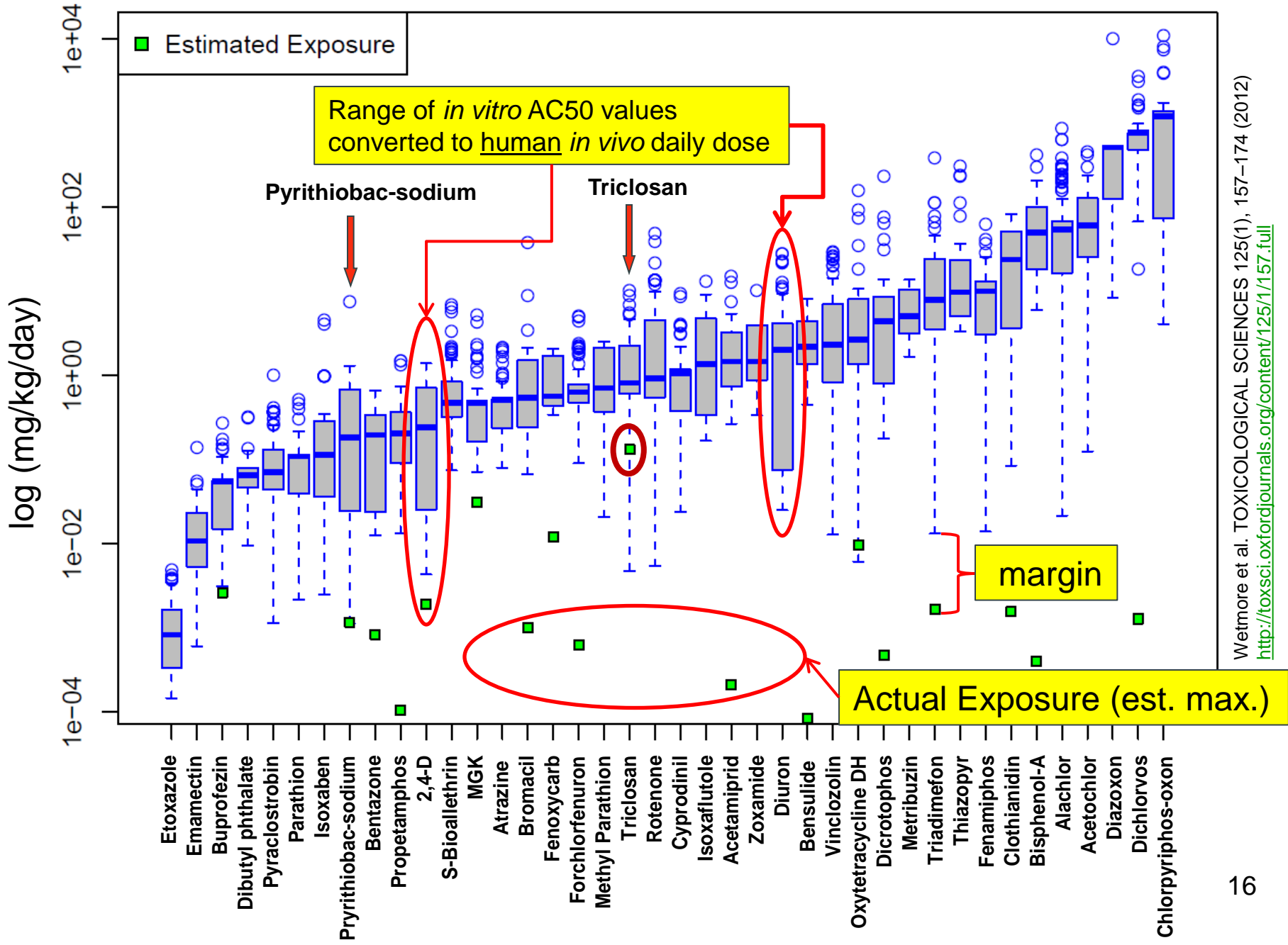
- ToxCast I comprises pharmaceuticals and Pesticides.
- ToxCast II comprises 'industrial chemicals.
- The *vast majority* of chemicals activates assays only at the cytotoxic concentration, **'Burst'**
- Both, Metabolomics and Deco concept are validated on the **'red asterix'** type chemicals.



US Office of Research and Development – National Centre for Computational Toxicology

Judson, R. (2014). "Using ToxC21 Data for Risk Assessment and Alternatives Assessment". U.S. Mid-Atlantic SOT, May 2014.

http://www.toxicology.org/isot/RC/midatlantic/Talk%20Judson%20May%202014_FINAL.pdf



Breakthrough for Safety Assessment:

Estimating the *In Vivo* Maximum Tolerated Dose (MTD) from *In Vitro* Burst

Hypothesis: chemical at *in vitro* cytotoxicity concentration will cause systemic toxicity

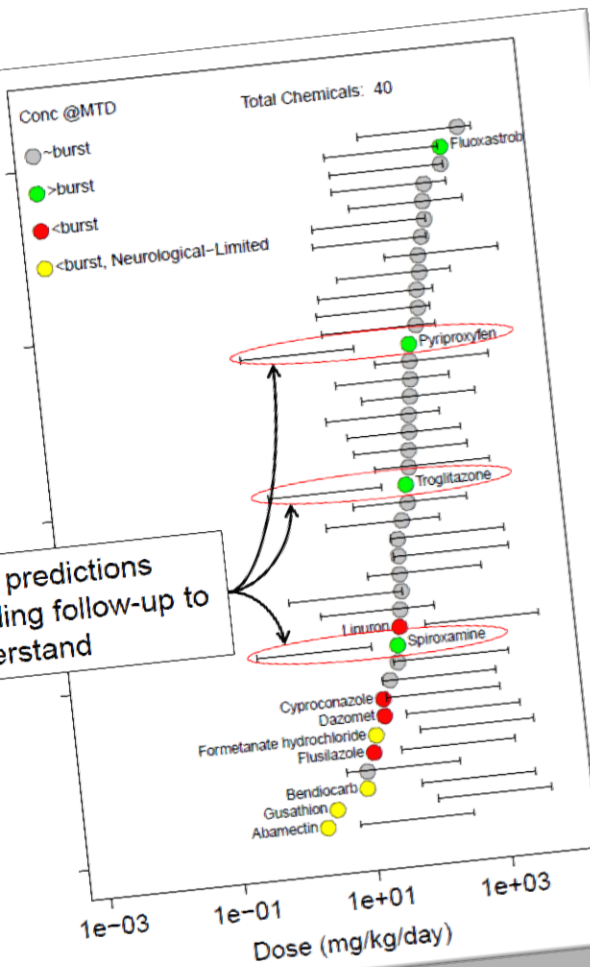
Compare the *in vitro* burst with *in vivo* MTD, using RatCast RTK to estimate concentration AUC at MTD

Bars – Burst (mean \pm 3SD)
Dots – MTD concentration

28/36 (75%) of non-AChE chemicals are in burst

MTD is itself subject to uncertainty

Poor predictions needing follow-up to understand



Judson, R. (2014): Finding patterns in a complex in vitro data set: insights from the ToxCast Project, a screen of 1000 environmental chemicals x 780 in vitro assays. SLAS, San Diego CA January 2014.
http://cfpub.epa.gov/si/si_public_file_download.cfm?p_download_id=519884

US Office of Research and Development – National Centre for Computational Toxicology



DECO 2: Moving from Data-integration for Endpoints, Cheminformatics and Omics towards OECD



- Build on the categorisation based on transcriptomics and clinical chemistry (DECO 1).
- Expand to additional endpoints (liver + kidney, carcinogenicity and developmental toxicity).
- Include non-selective (and non-genotoxic) substances.
- Develop a framework to characterise confidence in the read-across.
- Apply to case-studies.

Conclusions and Recommendations [for First Time Registrants]

- Get active despite remaining uncertainties (e.g. definitive volume).
- If you don't have the expertise in the company, partner with 3rd party consultants and laboratories.
- Significant amount of animal data is available to help meeting information requirements.
- Expert tools and guidance help with applying the data.
- Embrace new approaches *but*
 - Recognise the risk of investment for anything else than the standard information.
 - Allow time for failure.
- REACH *and* CLP build almost exclusively on animal data (directly or via read across).

The Future looks different!