Bridges and Barriers to Meeting your Information Requirements

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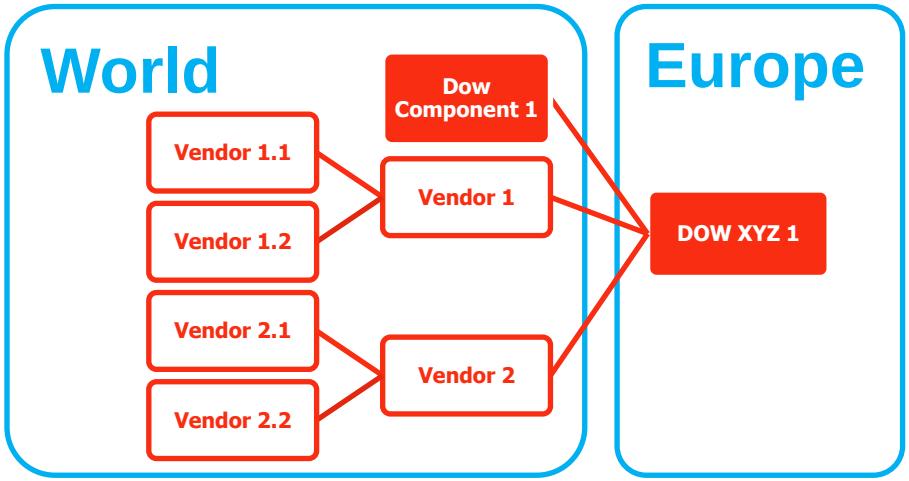
Table of Contents

- 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 ORT coverage for REACH?..."

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



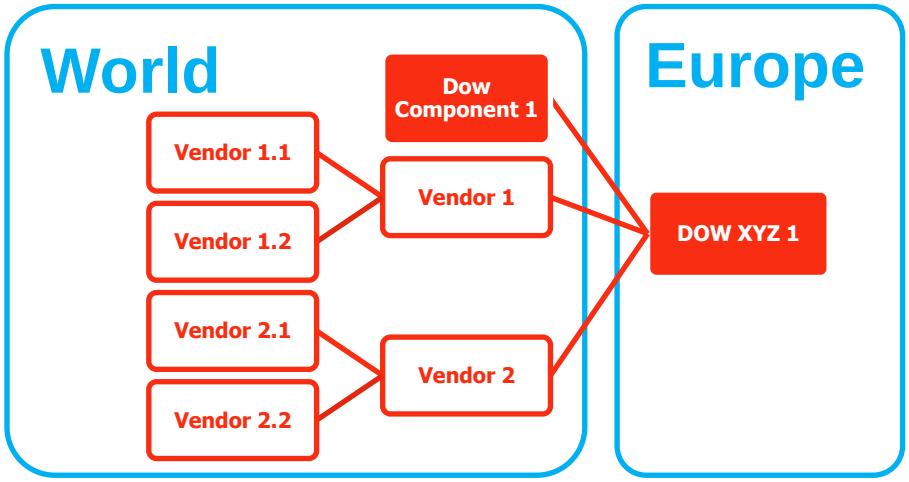
Dow REACH 2018 Materials

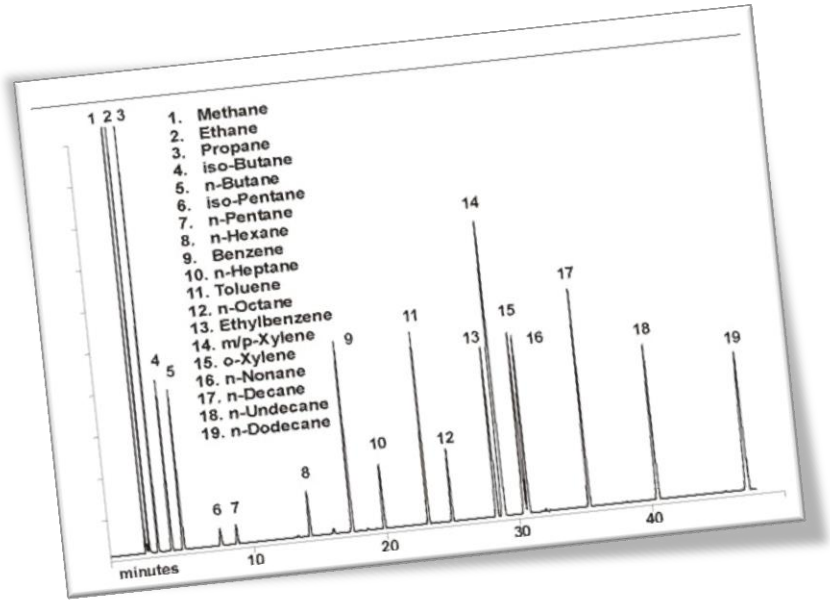
Annual Volume 2012-14 [mt]	Dow XYZ 1	Dow XYZ 2	Dow XYZ 3	Dow XYZ 4	in scope volume [mt]
	25 ± 50	75 ± 20	0	8 ± 6	
Dow Component 1	64 %	0 %	0 %	20 %	18 ± 33
Dow Component 2	0 %	22 %	0 %	0 %	16 ± 4
Dow Component 3	0 %	43 %	51 %	39 %	36 ± 11
Vendor 1.1	13 %	0 %	0 %	0 %	3 ± 6
Vendor 1.2	19 %	22 %	0 %	20 %	23 ± 15
Vendor 2.1	3 %	0 %	26 %	0 %	1 ± 2
Vendor 2.2	0 %	0 %	1 %	0 %	0 ± 0
Vendor 3.1	0 %	2 %	3 %	2 %	2 ± 1
Vendor 3.2	0 %	11 %	0 %	20 %	10 ± 3
Vendor 3.3	0 %	0 %	20 %	0 %	0 ± 0
	100 %	100 %	100 %	100 %	

Barriers:
Substance ID for Materials from a Complex Value Chain

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

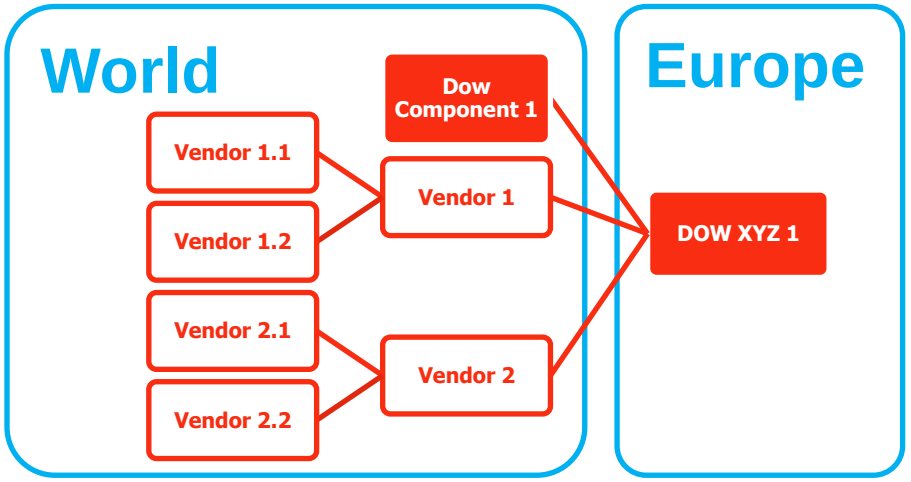
"... committed to customer service (...) where is REACH?..."

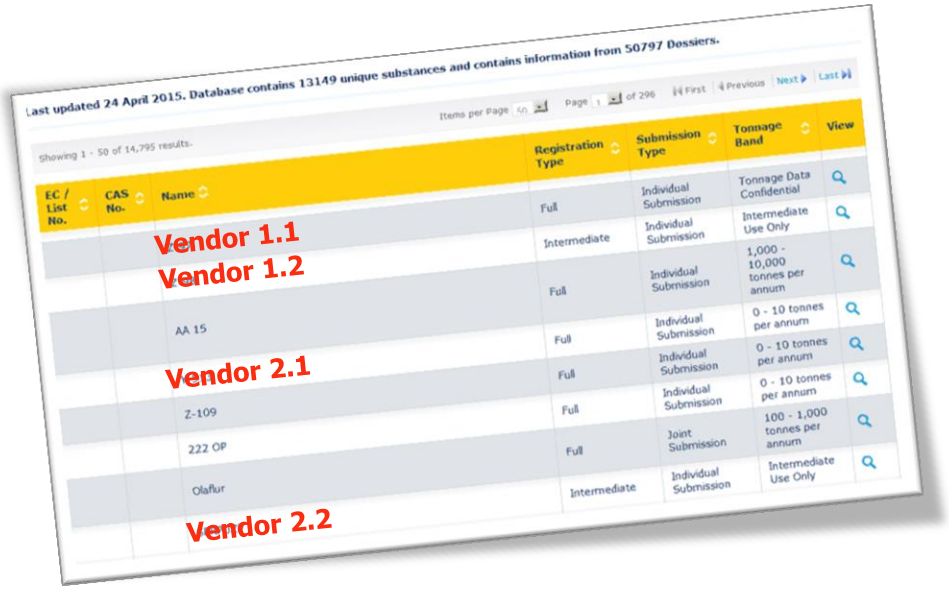




Bridges:
Substantial Number of Substances already Registered

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





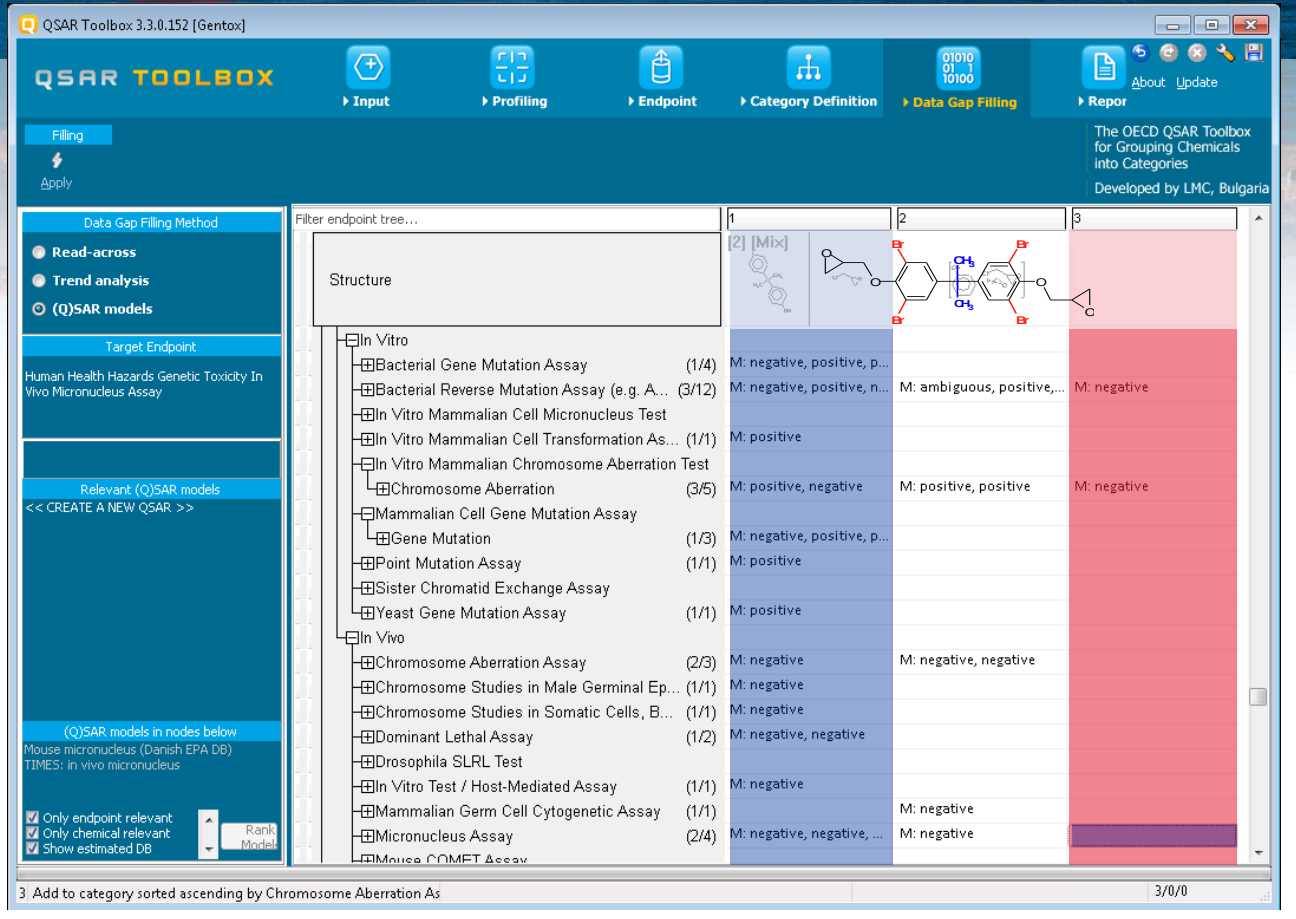
Read across and other Non-testing Approaches

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

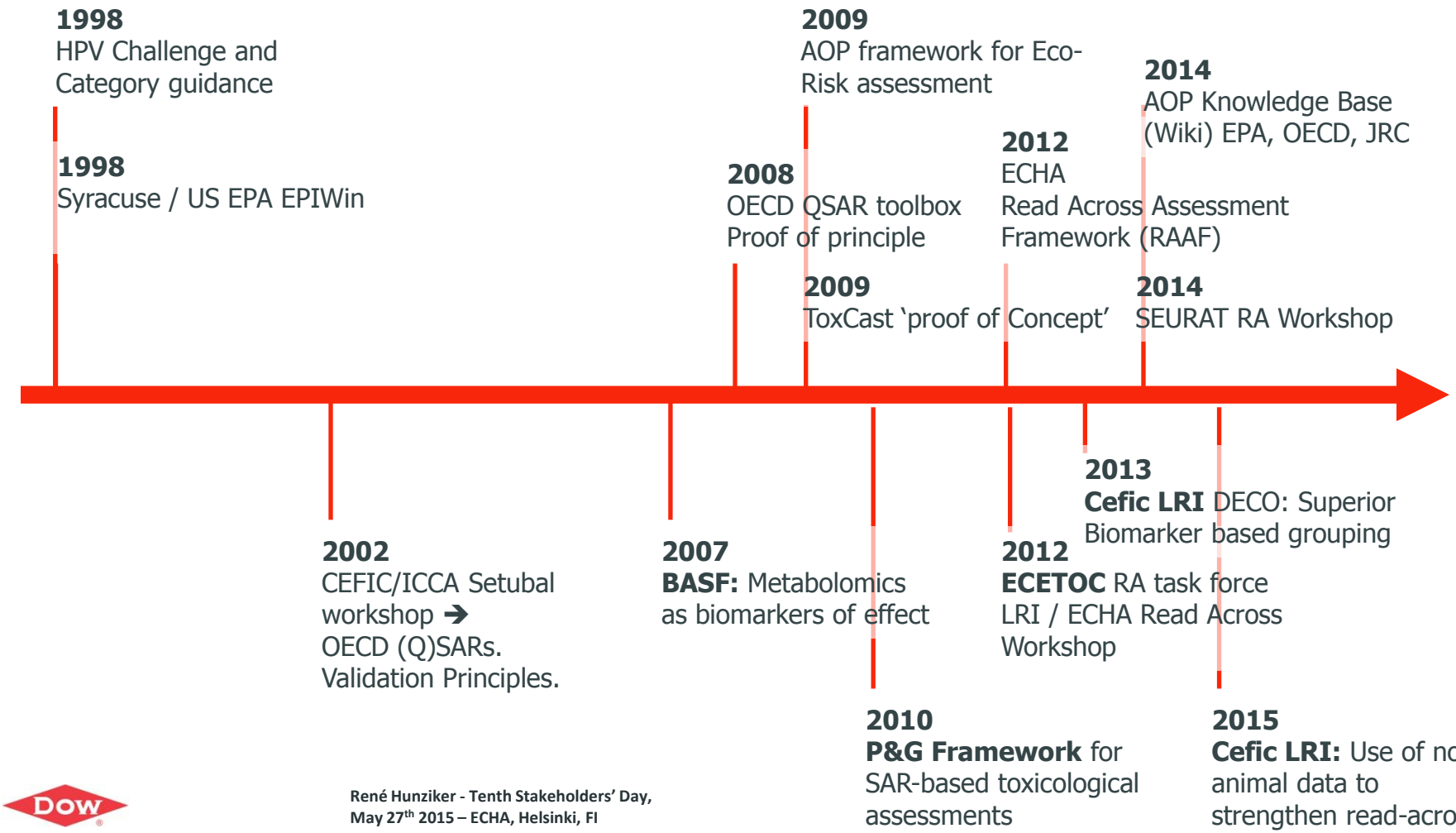
Thomas Edison

Infrastructure

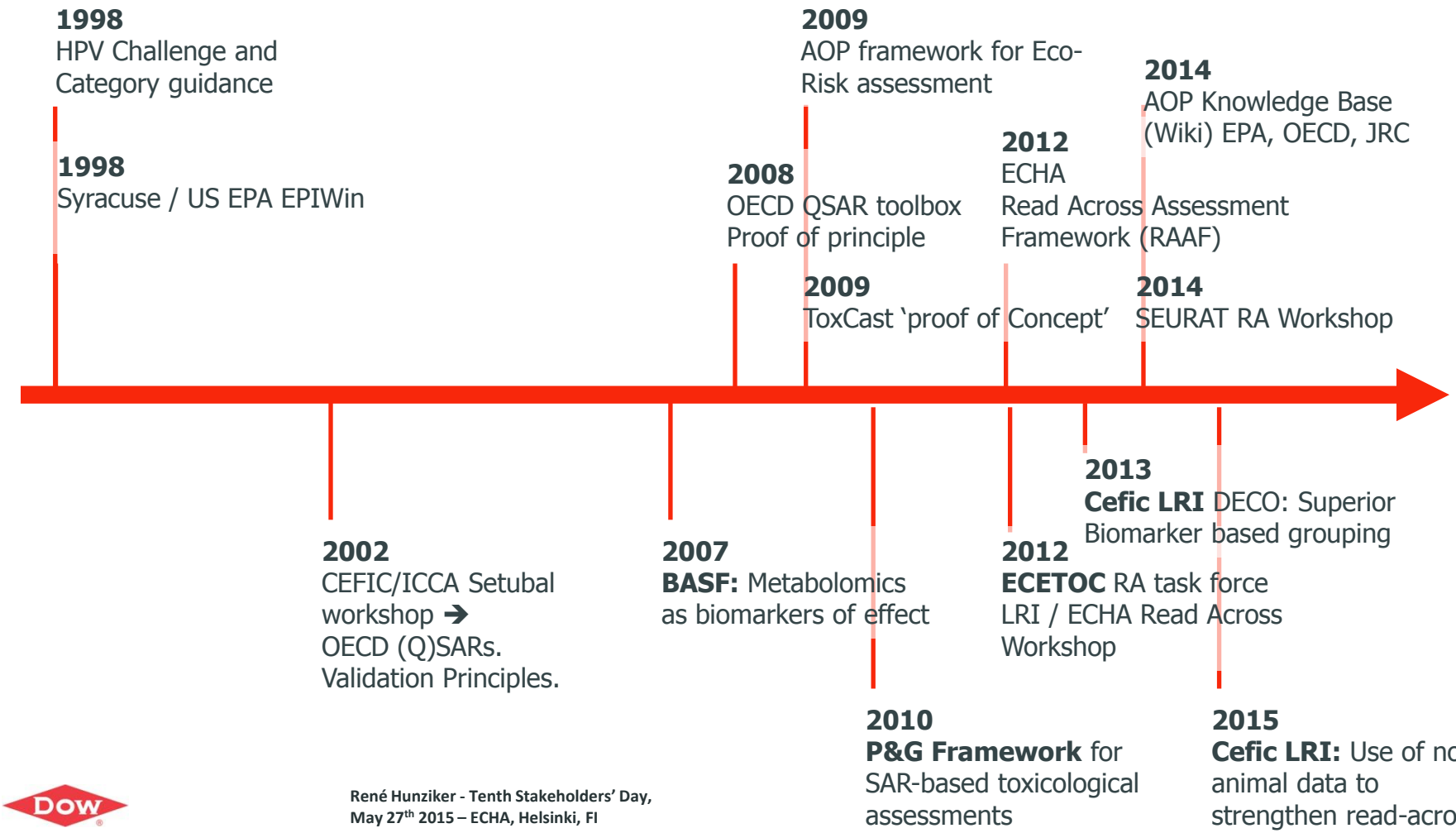
- Substantial data is available from 2010/13.
- Data can support 2018 requirements.
- 2018 registrations can expand to Annex IX and X endpoints.
- LoA Prices have been agreed in 2010 and are not up for negotiation.



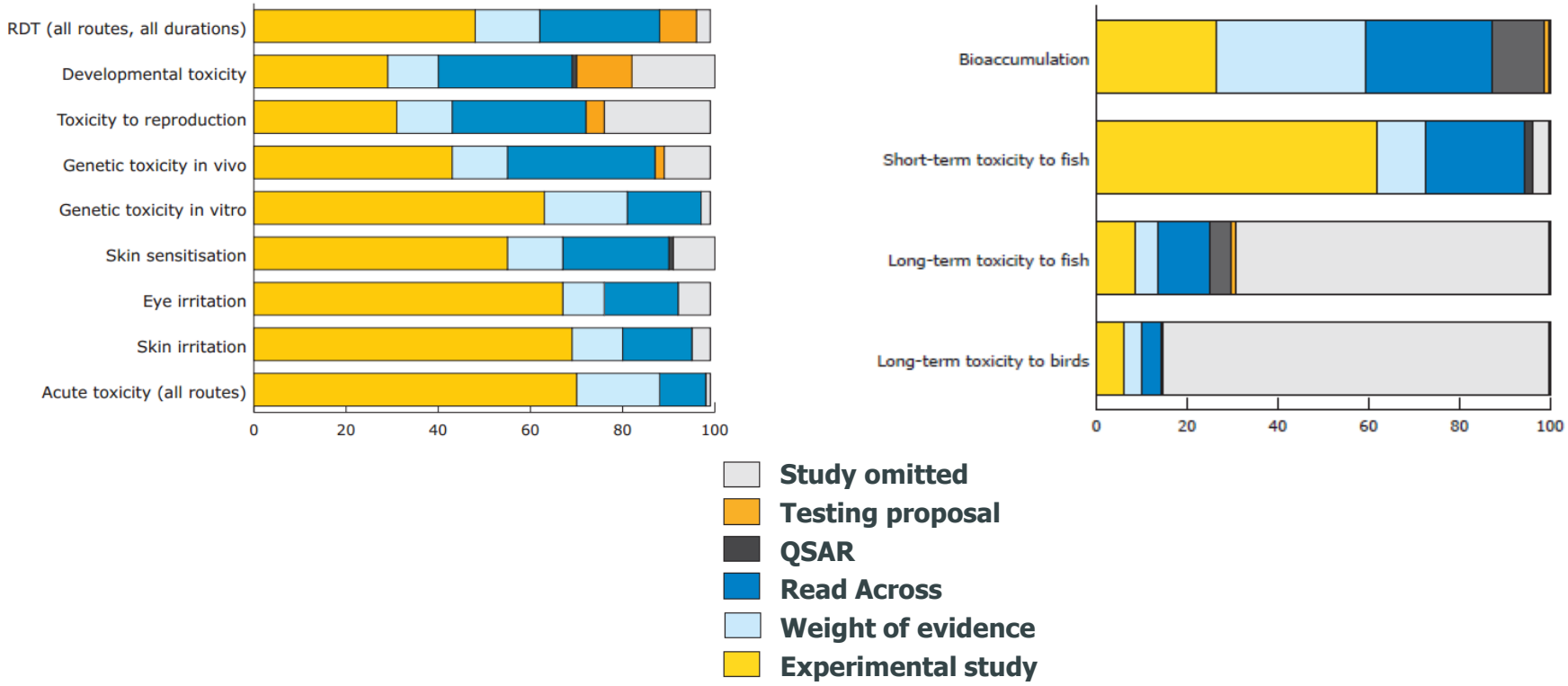
Bridges: Science of Non-testing is Growing – From 'Similar Structure' to 'Similar Biology'



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



Bridges: Testing vs. Non-Testing for REACH Registrations

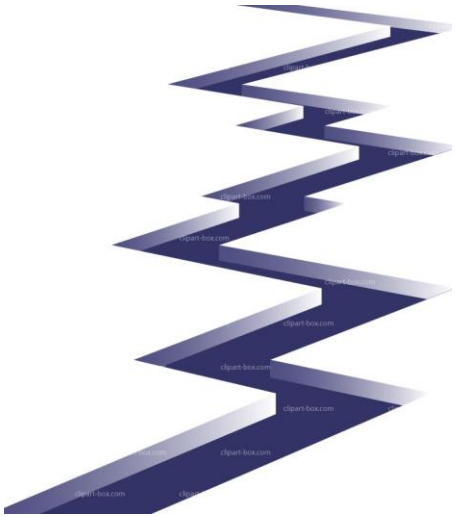


From "ECHA's second report on the use of alternatives to testing on animals"; http://echa.europa.eu/documents/10162/13639/alternatives_test_animals_2014_en.pdf

Uncertainty

Hazard characterisation („*adequate for risk assessment*“):
➔ Quantify the lowest adverse effect level/concentration.

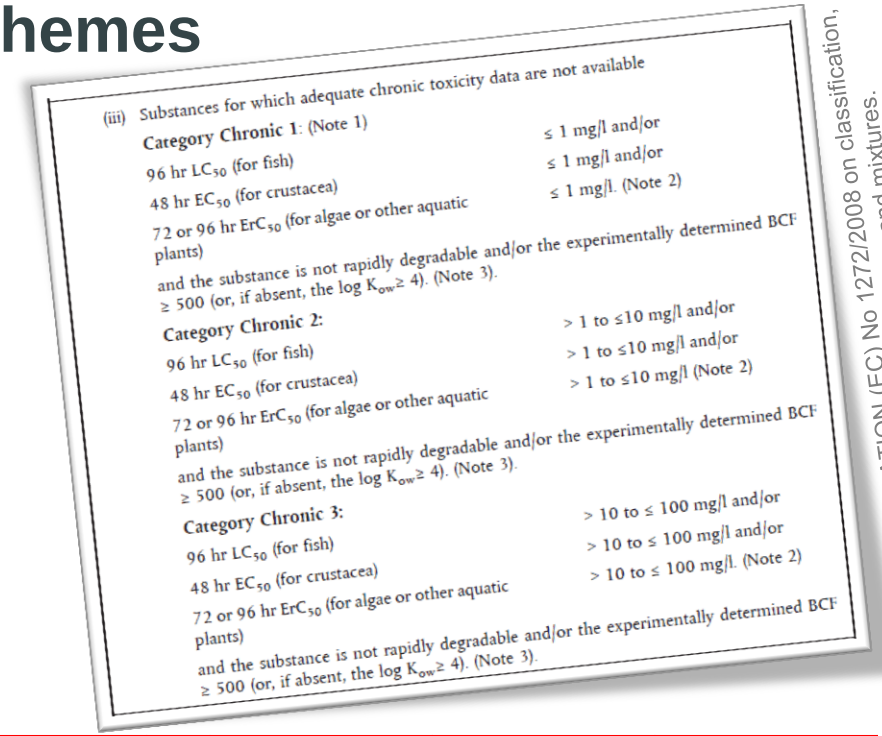
Hazard identification („*adequate for Classification and Labelling*“)**:**
➔ Recognise the full *detailed* spectrum of hazards.



Exemplary Classification Schemes

Environment:

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



(iii) Substances for which adequate chronic toxicity data are not available

Category Chronic 1: (Note 1)

96 hr LC_{50} (for fish) ≤ 1 mg/l and/or

48 hr EC_{50} (for crustacea) ≤ 1 mg/l and/or

72 or 96 hr ErC_{50} (for algae or other aquatic plants) ≤ 1 mg/l. (Note 2)

and the substance is not rapidly degradable and/or the experimentally determined BCF ≥ 500 (or, if absent, the log K_{ow} ≥ 4). (Note 3).

Category Chronic 2:

96 hr LC_{50} (for fish) > 1 to ≤10 mg/l and/or

48 hr EC_{50} (for crustacea) > 1 to ≤10 mg/l and/or

72 or 96 hr ErC_{50} (for algae or other aquatic plants) > 1 to ≤10 mg/l (Note 2)

and the substance is not rapidly degradable and/or the experimentally determined BCF ≥ 500 (or, if absent, the log K_{ow} ≥ 4). (Note 3).

Category Chronic 3:

96 hr LC_{50} (for fish) > 10 to ≤ 100 mg/l and/or

48 hr EC_{50} (for crustacea) > 10 to ≤ 100 mg/l and/or

72 or 96 hr ErC_{50} (for algae or other aquatic plants) > 10 to ≤ 100 mg/l. (Note 2)

and the substance is not rapidly degradable and/or the experimentally determined BCF ≥ 500 (or, if absent, the log K_{ow} ≥ 4). (Note 3).

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

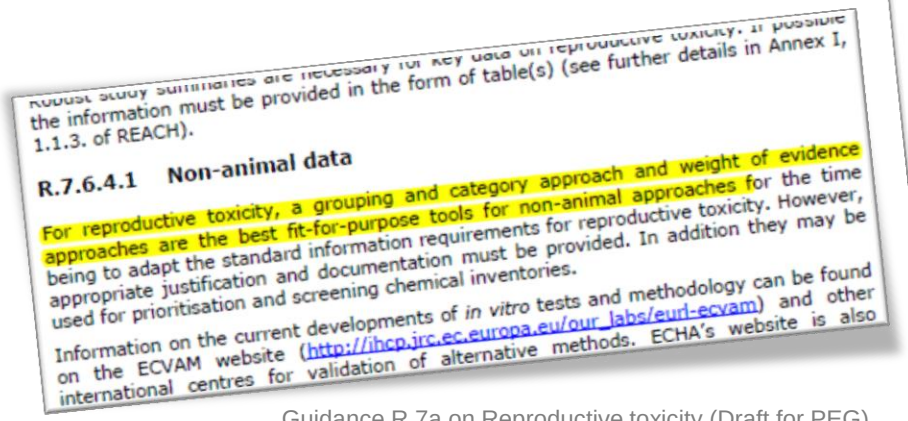
Dow REACH 2018 Materials

Annual Volume 2012-14 [mt]	Dow XYZ 1 25 ± 50	Dow XYZ 2 75 ± 20	Dow XYZ 3 0	Dow XYZ 4 8 ± 6		ac. Fish ECOSAR	ac. Daphnia ECOSAR	Biodegradation 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?



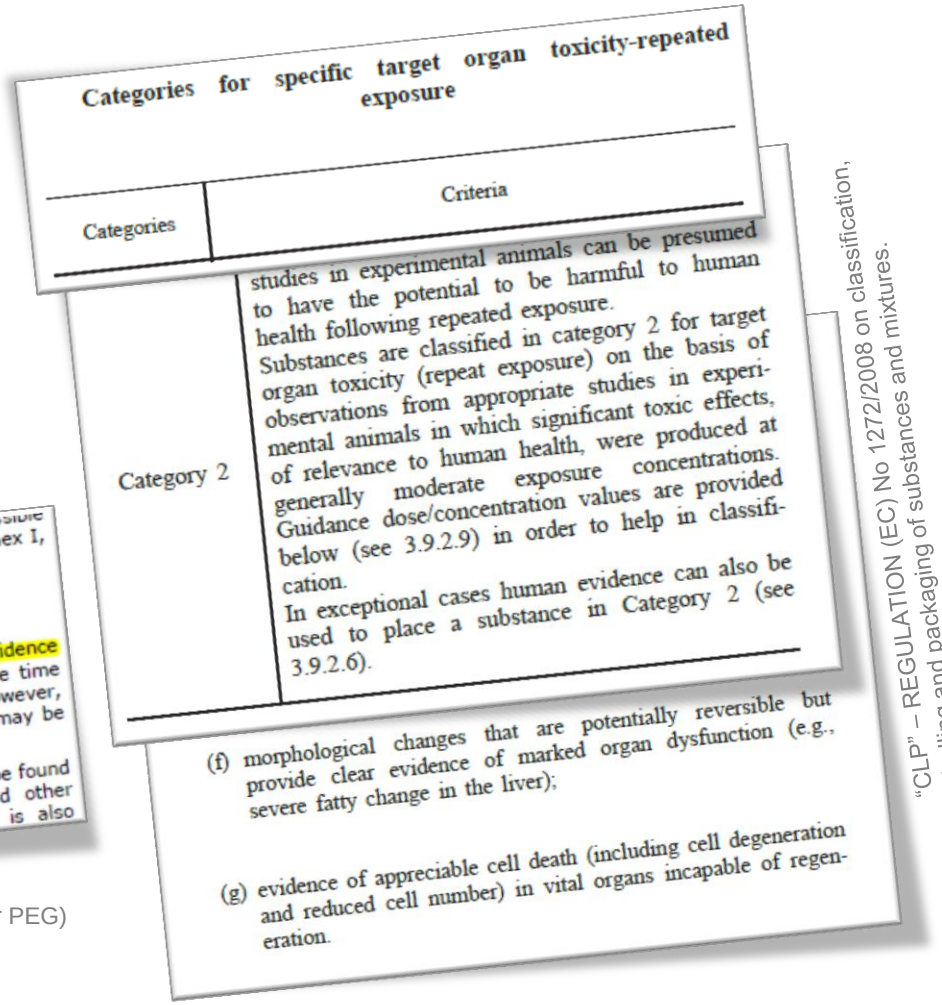
the information must be provided in the form of table(s) (see further details in Annex I, 1.1.3. of REACH).

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/eurl-ecvam) and other international centres for validation of alternative methods. ECHA's website is also

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



Categories for specific target organ toxicity-repeated exposure

Categories	Criteria
Category 2	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. In exceptional cases human evidence can also be used to place a substance in Category 2 (see 3.9.2.6).

(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.

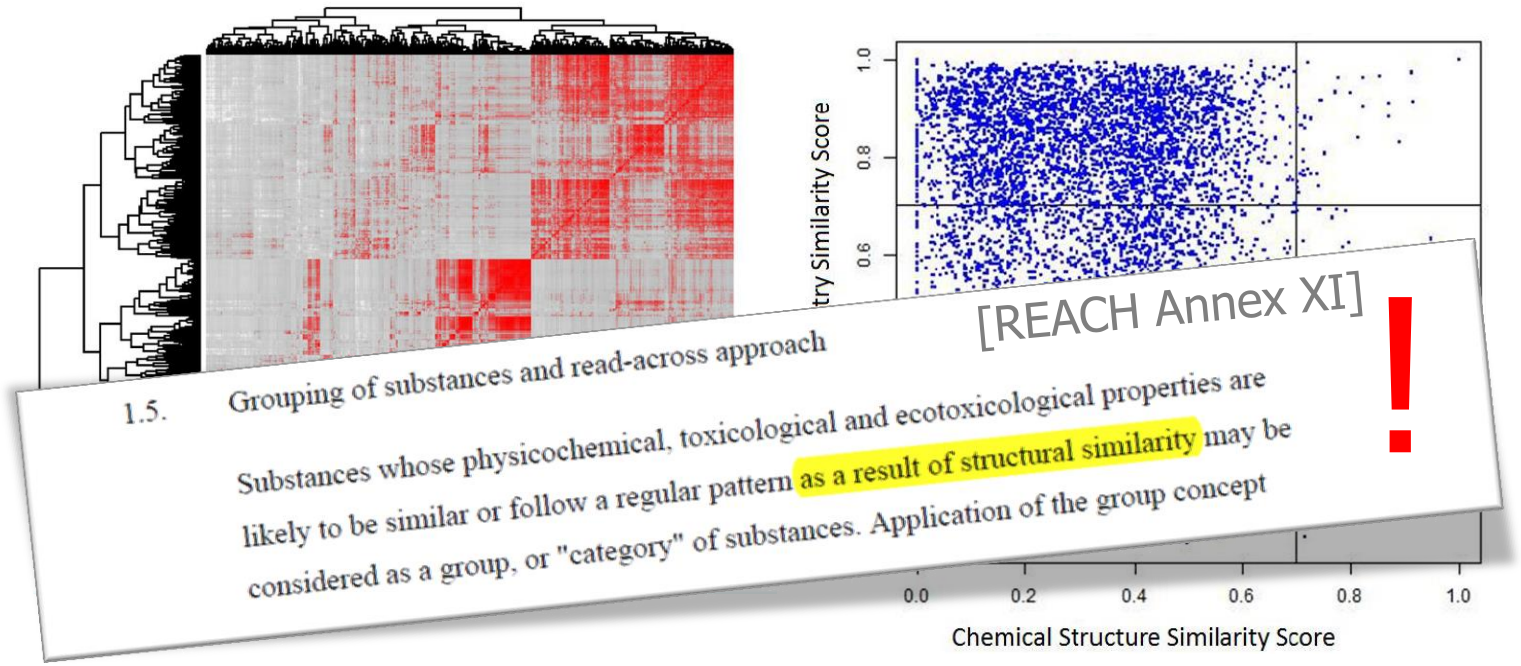
"CLP" – REGULATION (EC) No 1272/2008 on classification, labelling and packaging of substances and mixtures.

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

LRI
The Long-range Research initiative

Hypothesis

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

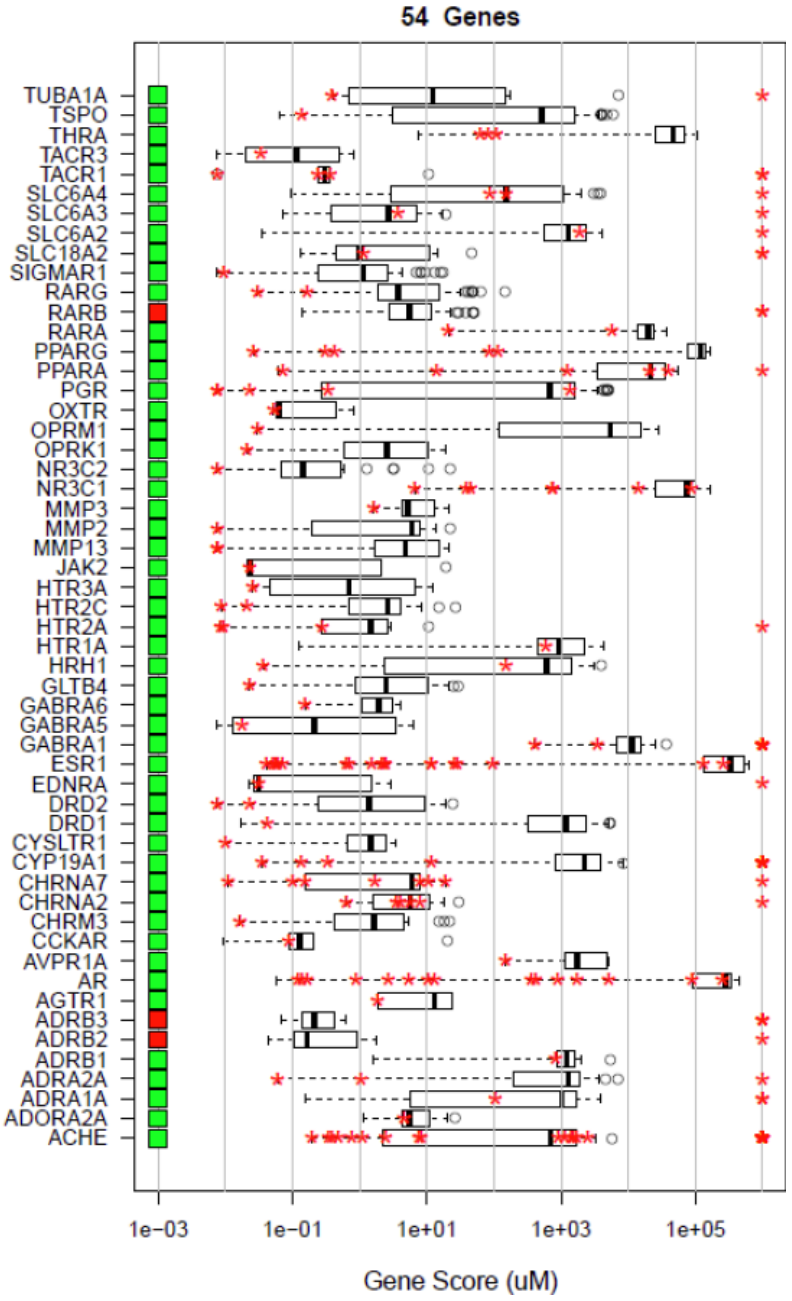


van Delft, J; Polman, J.; et al. (2014): DECO: Data-integration for Endpoints, Chemoinformatics and Omics; Cefic-LRI annual meeting, Brussels, Belgium. http://cefic-lri.org/wp-content/uploads/uploads/Project%20publications/AIMT3%20poster%20DECO%20November%202012.pdf

Barrier or Bridge? Specificity vs. 'Burst'

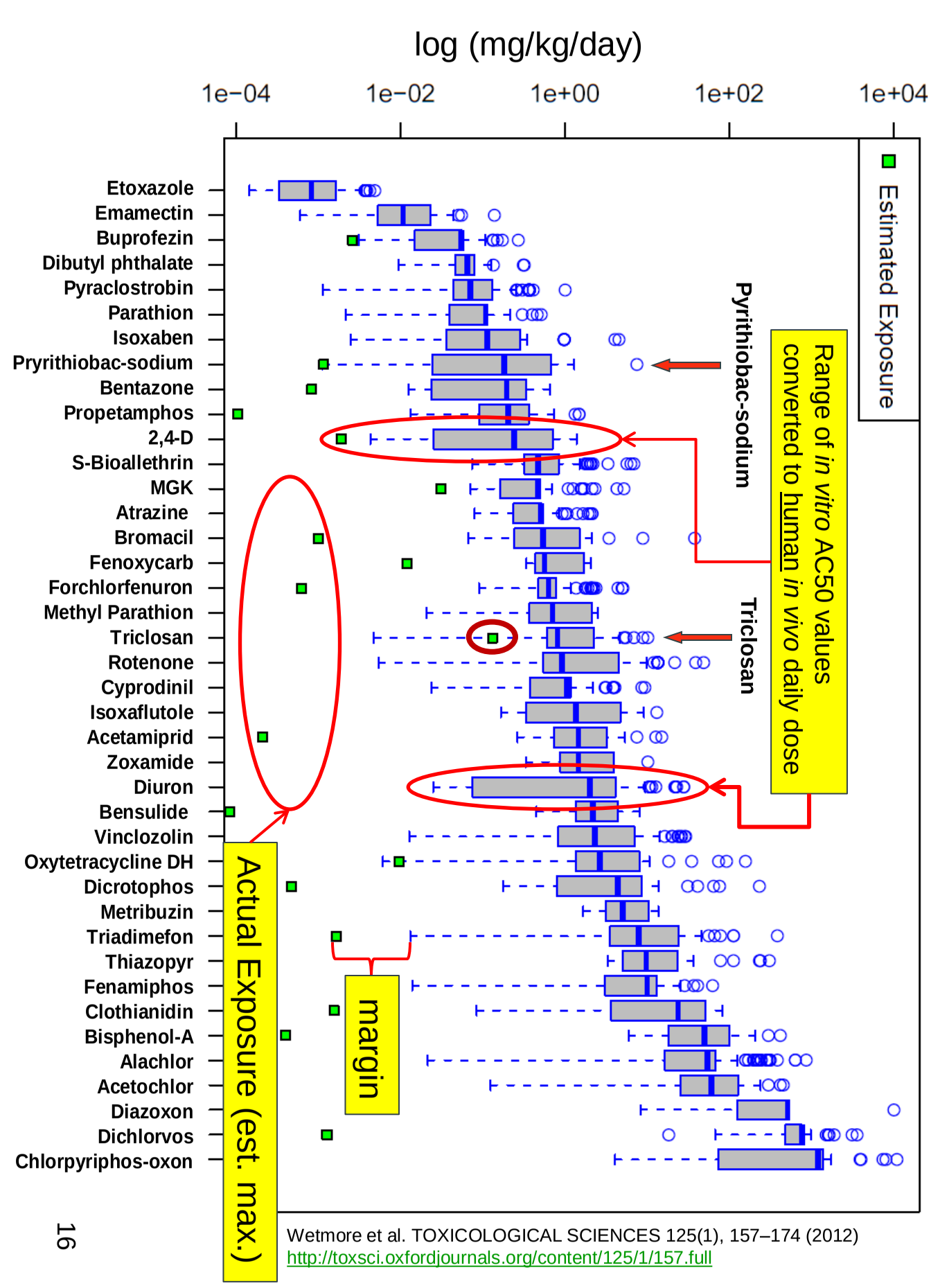
* Reference Chemicals with pronounced MoA are identified by high Gene score (right boundary). Judson, 2014.

- 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.



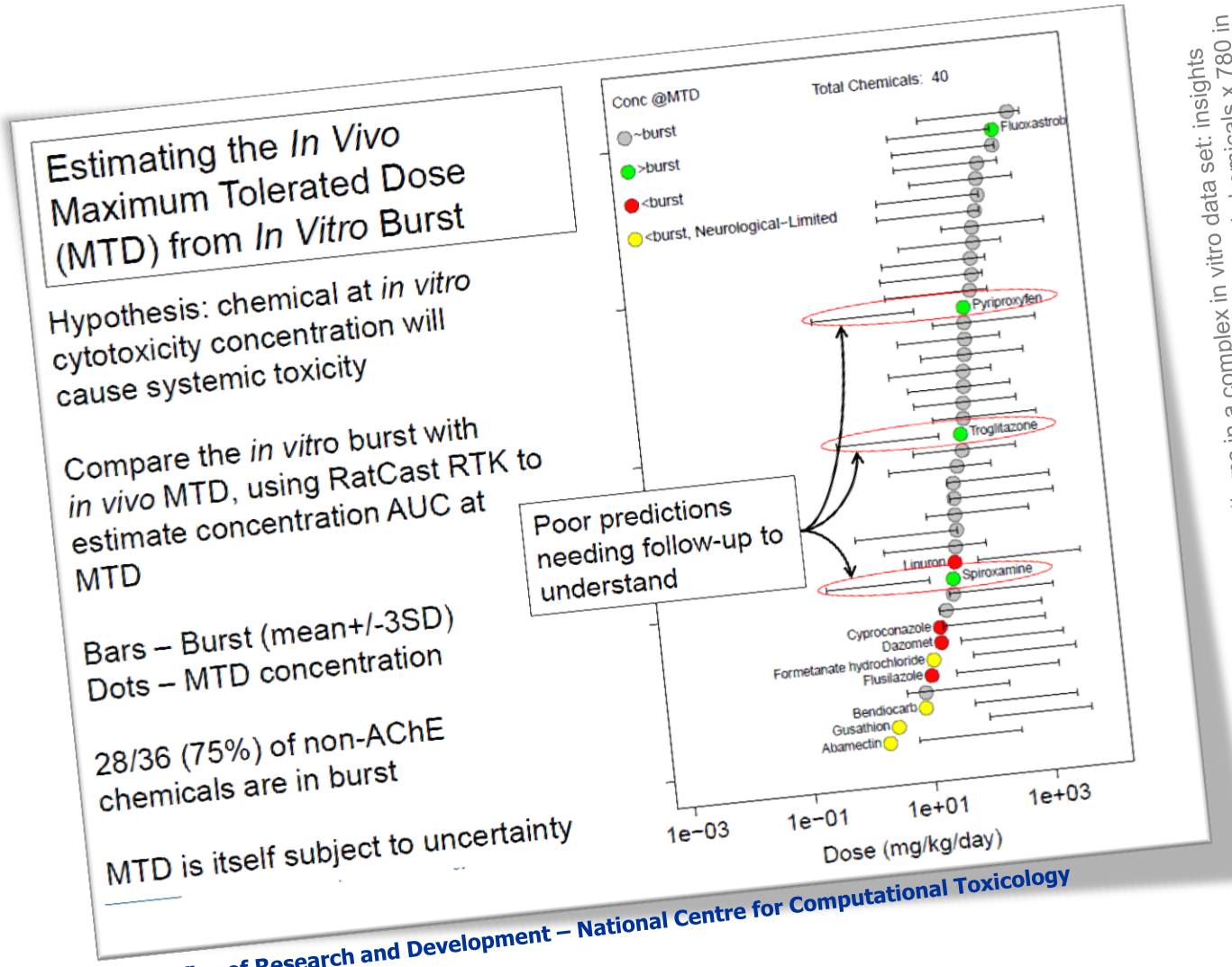
US Office of Research and Development – National Centre for Computational Toxicology

Judson , R. (2014): "Using Tox21 Data for Risk Assessment and Alternatives Assessment". U.S. Mid-Atlantic SOT, May 2014.
http://www.toxicology.org/isot/RC/midatlantic/Talk%203_MASOT%20Judson%20May%202014_FINAL.pdf



Wetmore et al. TOXICOLOGICAL SCIENCES 125(1), 157–174 (2012)
http://toxsci.oxfordjournals.org/content/125/1/157.full

Breakthrough for *Safety Assessment*:



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

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

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

- Build on the categorisation based on transcriptonomics 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!