Science in the regulatory process (REACH)

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Norbert BORNATOWICZ

Senior Scientific Officer, Toxicology Evaluation
European Chemicals Agency

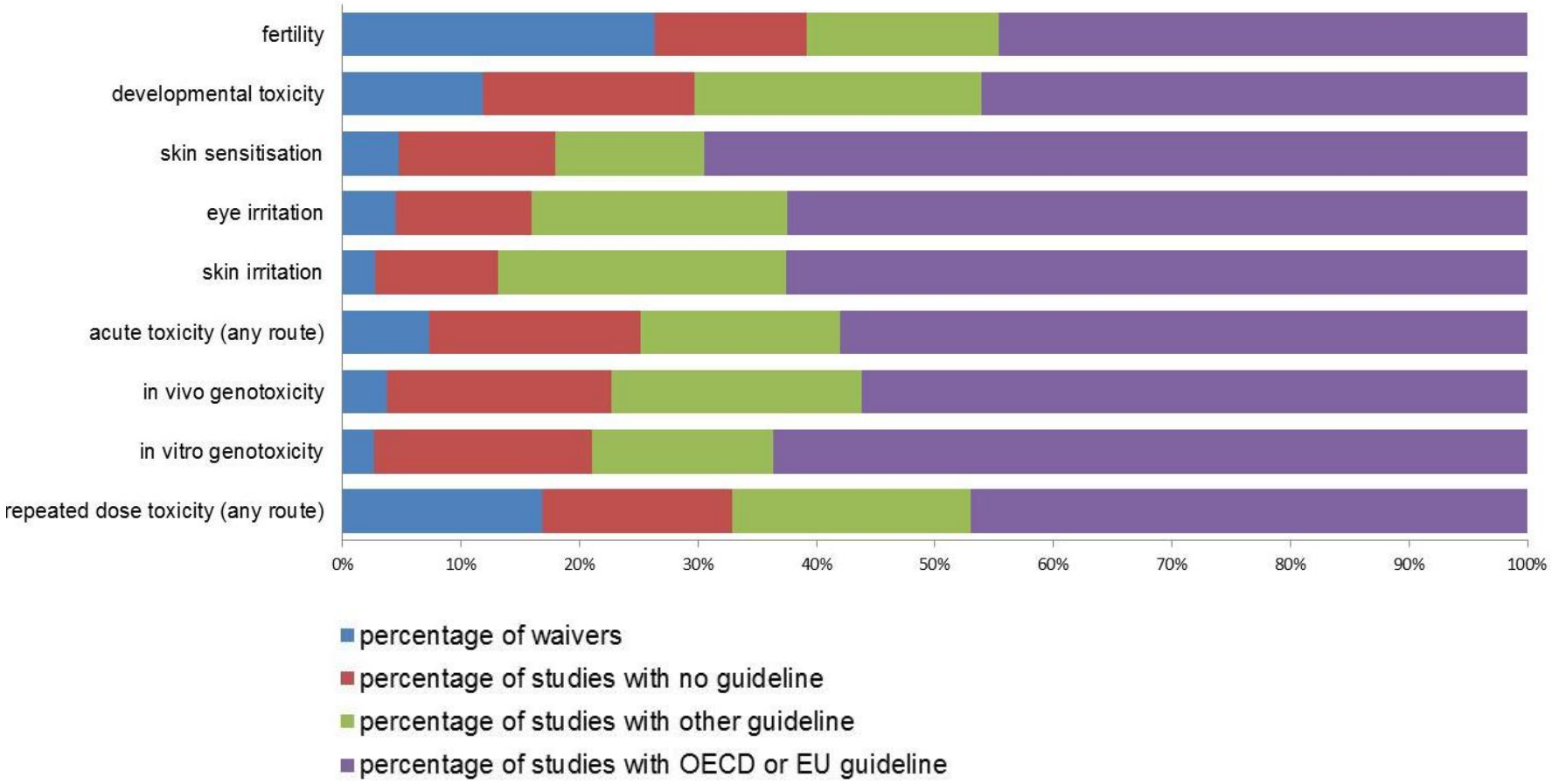
Disclaimer: This presentation represents exclusively the opinion of the author and is not an official position of the European Chemicals Agency.

How to meet the standard information requirements (REACH, Annexes VII-X)

- Standard (testing) methodologies (OECD guidelines, EU methods)
- Adaptations according to column 2 of Annexes VII-X:
  - Adaptation possibility depends on the specific requirement
  - Adaptation may be related to another standard information requirement from a lower Annex
- Adaptations according to Annex XI
  - Testing does not appear scientifically necessary
  - Testing is technically not possible
  - Substance-tailored exposure-driven testing

Guideline vs non-Guideline studies

Endpoint study records (IUCLID) from all submissions until 5 September 2013



Use of non-standard methodologies: Annex XI

1.1 Use of existing data

- Experiments not carried according to GLP or the test methods referred to in Article 13(3)(REACH)
- Adequacy for the purpose of classification and labelling and/or risk assessment
- Adequate and reliable coverage of key parameters (as identified in test methods)
- Exposure duration comparable or longer than test methods
- **Adequate and reliable documentation**

Noted shortcomings:

Not well justified, not well reported, common places ("substance is known to be non toxic")

Use of non-standard methodologies: Annex XI

1.2 Weight of evidence

- From several independent sources of information:
  There may be sufficient weight of evidence from several independent sources of information leading to the assumption/conclusion that a substance has or has not a particular dangerous property, while the information from each single source alone is regarded insufficient to support this notion
- Newly developed test methods recognised as equivalent by COM or ECHA:
  There may be sufficient **weight of evidence from the use of newly developed test methods, not yet included in the test methods referred to in Article 13(3) or from an international test method recognised by the Commission or the Agency as being equivalent**, leading to the conclusion that a substance has or has not a particular dangerous property
- **Adequate and reliable information**

Noted shortcomings:

Not well justified, not well reported, key endpoints not addressed

Use of non-standard methodologies: Annex XI

1.3 QSARs

- Scientific validity of the QSAR model
- Substance falls within the applicability domain
- Results adequate for classification and labelling and/or risk assessment
- **Adequate and reliable documentation**

Noted shortcomings:

Rarely used, not well reported/documented, training datasets not included, cannot replace higher tier studies

Use of non-standard methodologies: Annex XI

1.4 In vitro methods

- Scientific validity established according to internationally agreed principles
- Results adequate for classification and labelling and/or risk assessment
- **Adequate and reliable documentation**

- Results obtained from suitable *in vitro* methods may indicate the presence of a certain dangerous property or may be important in relation to a mechanistic understanding, which may be important for the assessment
- If the results obtained from the use of such *in vitro* method do not indicate a certain dangerous property, the relevant test shall nevertheless be carried out at the appropriate tonnage level to confirm the negative result, unless testing is not required in accordance with Annexes VII to X or the other rules in this Annex.
- Confirmation (of the negative results) can be waived based on scientific validity (see above), adequacy for C&L and adequate and reliable documentation

Noted shortcomings:

Rarely used for supporting read-across (but well used when required), cannot replace higher tier studies

Use of non-standard methodologies: Annex XI

1.5 Grouping and read-across approach

- Adequate for classification and labelling and/or risk assessment
- Adequate and reliable coverage of key parameters (as identified in test methods)
- Exposure duration comparable or longer than test methods
- **Adequate and reliable documentation**

Noted shortcomings:

In many cases reporting unclear or not sufficient,
supporting information (studies, QSARs, WoE) missing,
read-across to read-across substances,
read-across based only on chemical similarity

Other options: Integrated testing strategies (ITS)

http://echa.europa.eu/documents/10162/13632/information_requirements_r7a_en.pdf:
Any approach to the evaluation of the hazard which **serves to reduce, refine or replace an existing animal procedure**, and which is based on the use of two or more of the following: physicochemical data, in vitro data, human data (for example, epidemiological, clinical case reports), animal data (where unavoidable), computational methods (such as quantitative structure activity relationships (QSARs) and biokinetic models.

http://alttox.org/ttrc/emerging-technologies/its/**:**
Approaches that integrate different types of data and information into the decision-making process. In addition to the information from individual assays, test batteries, and/or tiered test schemes, integrated testing strategies **may incorporate approaches such as weight-of-evidence and exposure/population data into the final risk assessment** for a substance.

Types of data and information for ITS

- Physicochemical data
- In vitro data
- Human data (for example, epidemiological, clinical case reports)
- Animal data (where unavoidable)
- Computational methods (such as QSARs)
- -omics data
- Biokinetic models

All data and information listed above can also be used in a weight-of-evidence approach – is there a difference?

Several strategies within an ITS

- Tiered testing: sequence of tests (see skin irritation)
- Test batteries: several tests together lead to a conclusion (see genotox battery for pharmaceuticals), tests complement each other
- Read across, category building
- Weight-of evidence (WoE)
- Modes of action (MoAs)
- Adverse outcome pathways (AoPs)

All these strategies can be part of an ITS –

But still: what is the difference between WoE and ITS?

WoE and ITS

WoE

jigsaw pieces are put together

you have them on the table (or beneath) and look which ones could fit

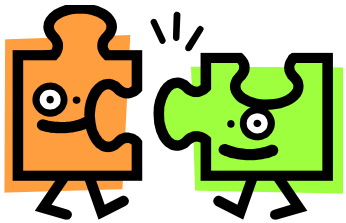
the pieces can also be other WoEs, MoAs, test batteries etc.

ITS

jigsaw pieces are put together

you either **design** them all from scratch or you find some and design the missing ones

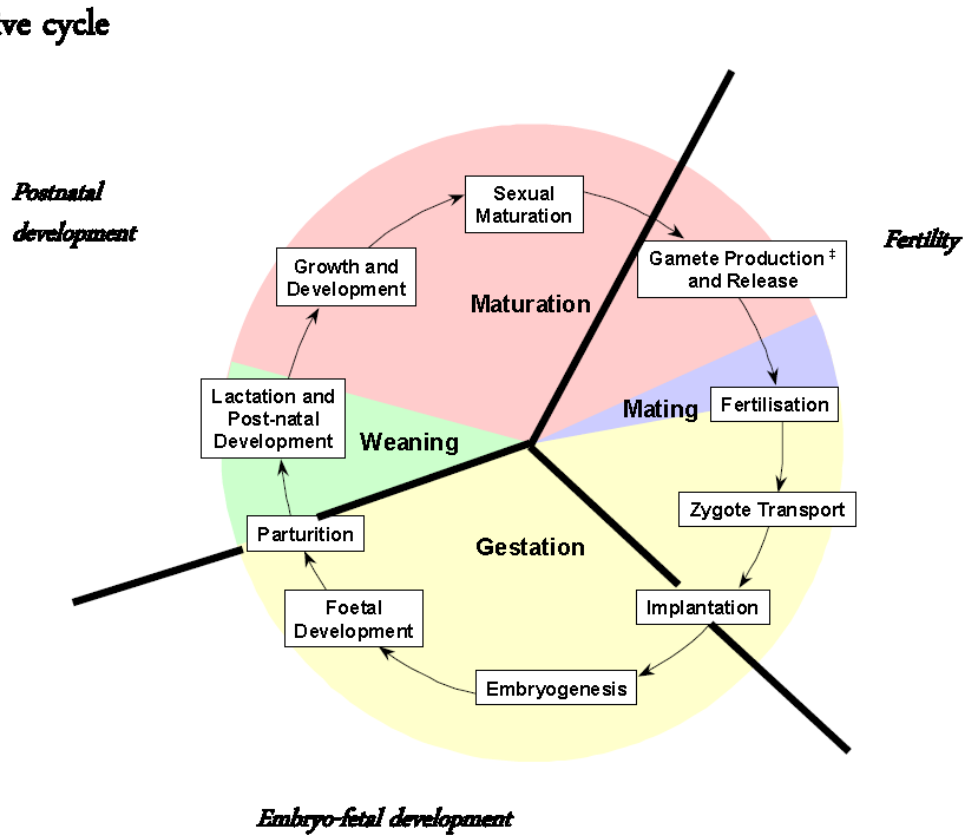
the pieces can also be WoEs, MoAs, test batteries etc.



➔ ITS is kind of WoE plus **strategy**

➔ the strategy will be different for each case

Some super-endpoints in toxicity to reproduction



In vitro and in vivo models in reproductive toxicology
Nicole Clemann, PhD, F. Hoffmann-La Roche AG, Basel
Master Course in Toxicology, Section: Reproductive Toxicology

ITS would aim to cover each of these super-endpoints with at least one study/test/WoE/…

This would produce tons of data.

These data would have to be evaluated.

Uncertainty

- Each test result has some uncertainty
- New scientific knowledge usually includes greater uncertainty
- Combining several test results which complement each other for one endpoint multiplies uncertainty
- How much uncertainty is acceptable from a regulatory point of view?
- What is the “gold standard”?

Ensuring the regulatory use of data:

Standard studies:

- If relevant, use the standardised guideline
- If adaptation is needed, ensure that all relevant endpoints are covered and explain clearly the deviations
- For "new protocols", describe test conditions in comparison with relevant tests
- Submit a Robust Study Summary

"Non-standard" studies

- Prepare a detailed protocol and indicate deviations/adaptations to it
- Consider related standard guidelines
- Indicate clearly the relevance and coverage of the measured endpoints
- Submit a Robust Study Summary

Top tips

- Indicate clearly, which adaptation you had in mind (select proper justification, make reference to the respective Annex/paragraph)
- Give as much information in the robust study summaries as possible
- If you refer to articles, scientific papers, compilations etc: attach them to the dossier
- If you build categories or groups:
  submit a data matrix, make clear why you think that the substances belong to a category/group

Thank You.

Norbert.Bornatowicz@echa.europa.eu