

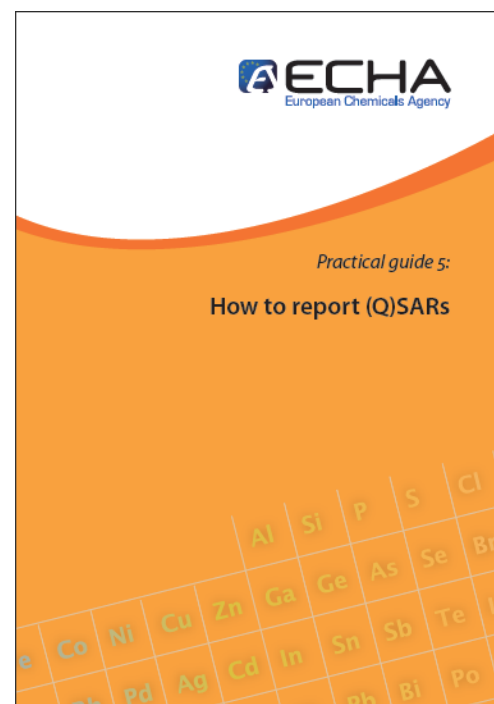
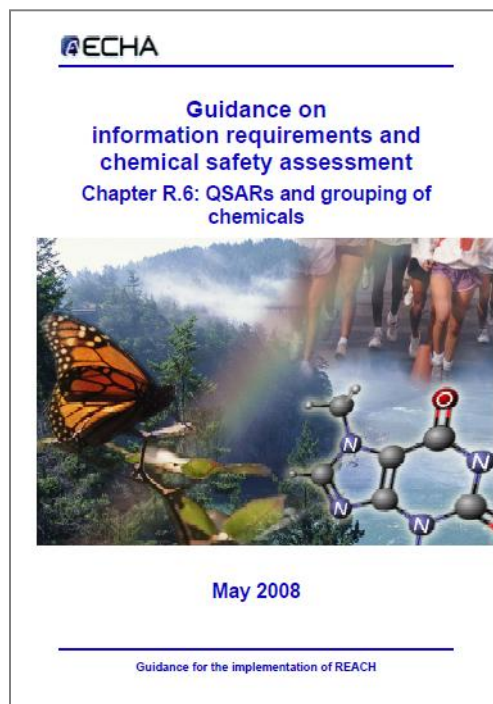
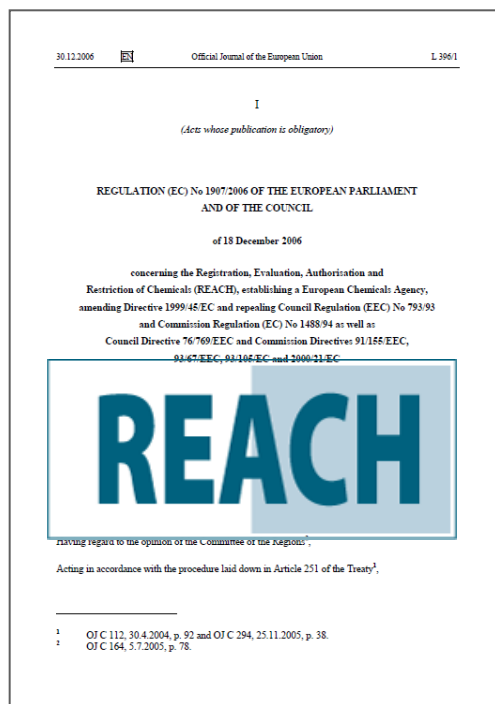
How QSAR has been used for the dossier preparation? Lessons from the registrations of substances so far done

*ORCHESTRA Workshop: REACH and
QSAR - What can we learn from case
studies?*

6 April 2011

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(Q)SARs and REACH



Aim of REACH Regulation

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.

Generation of information under REACH

Article 13

General requirements for generation of information on intrinsic properties of substances

1. Information on intrinsic properties of substances may be generated by means other than tests, provided that the conditions set out in Annex XI are met. In particular for human toxicity, information shall be generated whenever possible by means other than vertebrate animal tests, through the use of alternative methods, for example, in vitro methods or qualitative or quantitative structure-activity relationship models or from information from structurally related substances (grouping or read-across).

Generation of information under REACH

Article 25

Objectives and general rules

1. In order to avoid animal testing, testing on vertebrate animals for the purposes of this Regulation shall be undertaken only as a last resort. It is also necessary to take measures limiting duplication of other tests.



Annex XI of REACH - QSAR

General rules for adaptation of the standard testing regime

1.3. Qualitative or Quantitative structure-activity relationship ((Q)SAR)

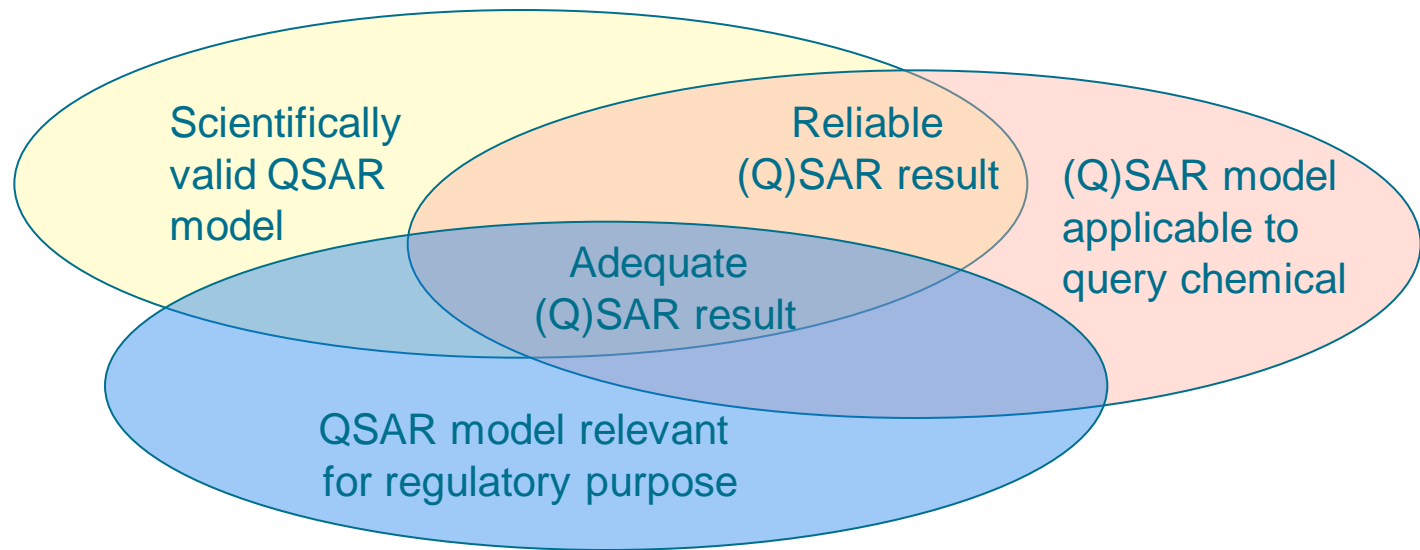
Results obtained from valid qualitative or quantitative structure-activity relationship models ((Q)SARs) may indicate the presence or absence of a certain dangerous property.

Results of (Q)SARs may be used instead of testing when the following conditions are met:

- results are derived from a (Q)SAR model whose scientific validity has been established,
- the substance falls within the applicability domain of the (Q)SAR model,
- results are adequate for the purpose of classification and labelling and/or risk assessment, and
- adequate and reliable documentation of the applied method is provided.

ECHA Guidance on use of (Q)SARs

The **adequacy** of a (Q)SAR prediction for regulatory purposes is related to the model **validity and applicability** to a given chemical, as well as to the model relevance for a regulatory purpose. The validity and applicability together determine the (Q)SAR **reliability**.




Practical guide: How to report (Q)SARs

3.5. How do I report a (Q)SAR prediction in IUCLID 5?

Block “Administrative data”

- the field “Purpose flag” to state whether the estimate is used as a key study, a weight-of-evidence approach, or as supporting information
- the field “Study result type” to state “(Q)SAR”

Administrative Data

 Purpose flag: key study robust study summary used for classification used for MSDS

Data waiving:

Justification for data waiving:

Study result type: (Q)SAR Study period:

Reliability:

Rationale for reliability:

Select a suitable reliability score but bear in mind that for (Q)SAR predictions it should normally be maximum 2.

REACH Registration deadlines

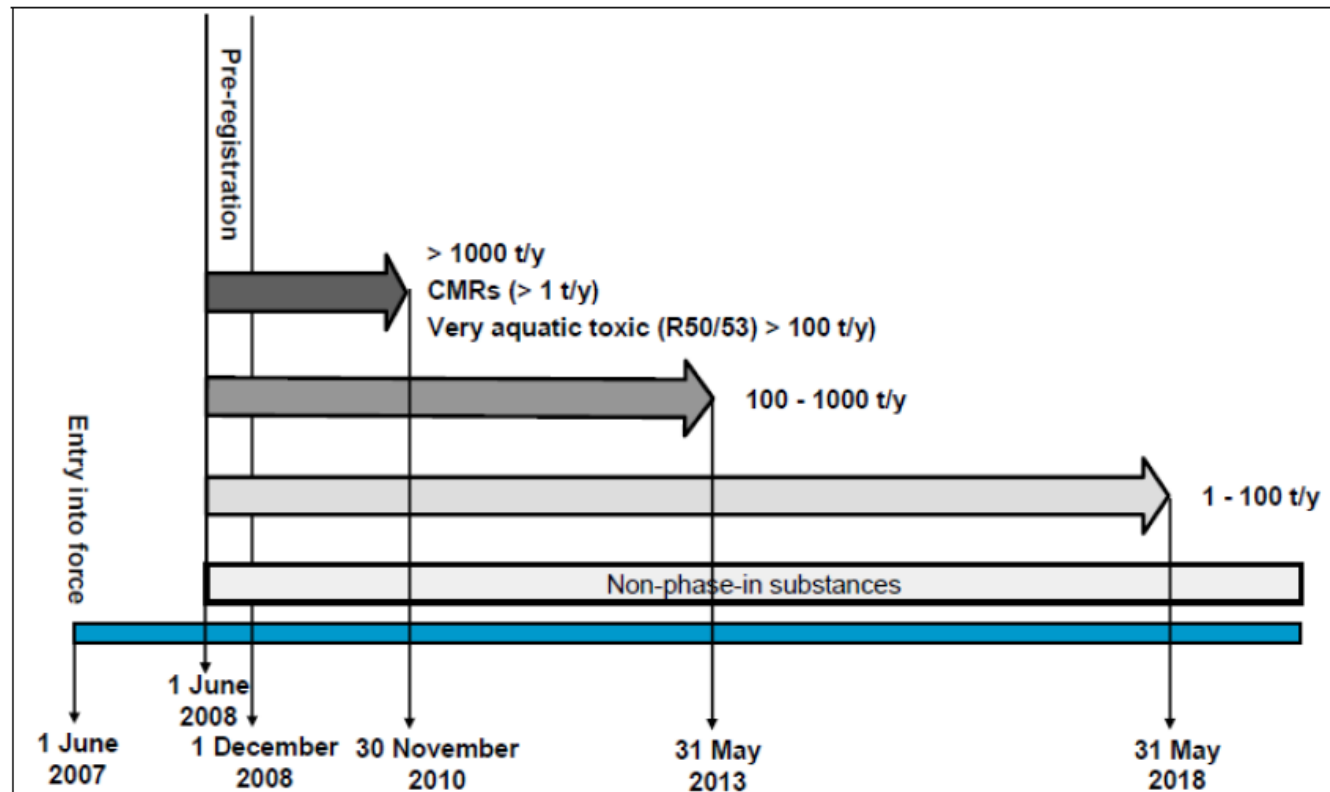


Figure 2: Registration deadlines under REACH

How many dossiers?

Table 1: Number of complete registration dossiers by the end of 2010

Tonnage per year	Registrations (non-intermediates)		Transported intermediates		TOTAL
	Phase-in ⁶	Non-phase-in ⁷	Phase-in	Non-phase-in	
1 - 10	765	528	775	460	4 844
10 - 100	751	137			
100 - 1000	1 351	77			
> 1000	14 592	55	2 158	13	16 818
TOTAL by status (phase-in/ non phase-in)	17 459	797	2 933	473	21 662

http://echa.europa.eu/doc/evaluation_under_reach_progress_report_2010.pdf

What is evaluated?

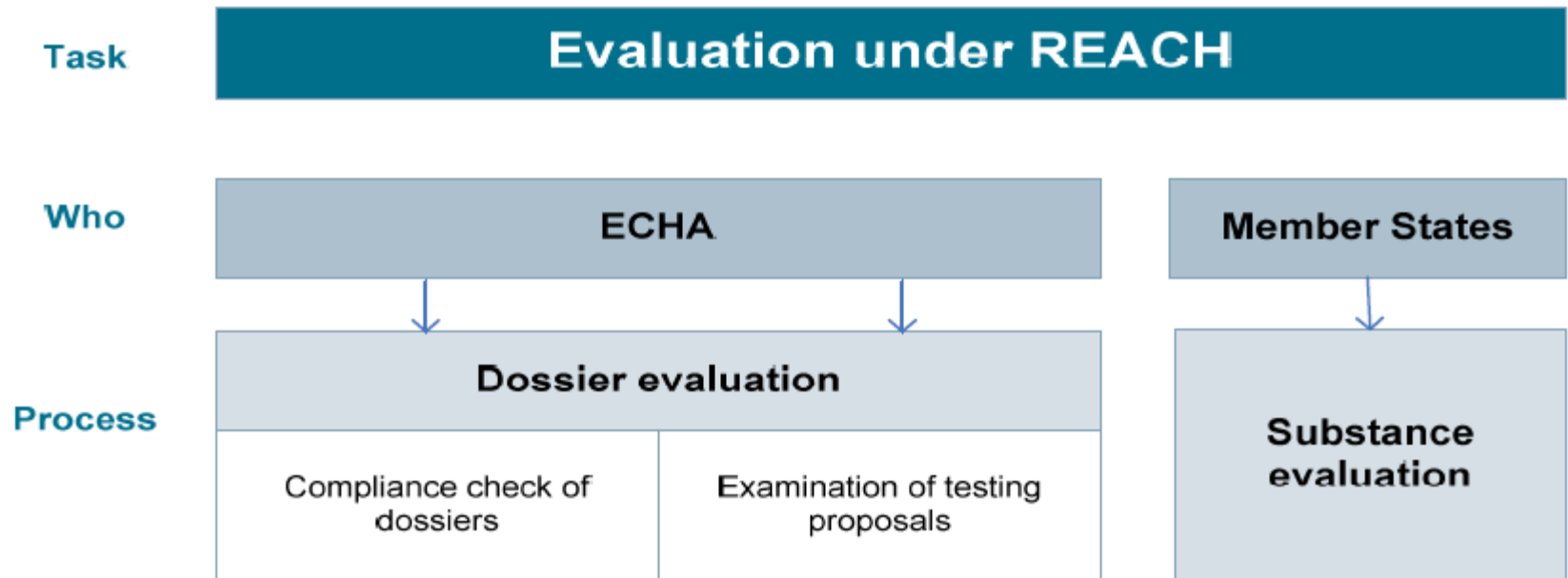


Figure 1: Evaluation processes under the REACH Regulation

Dossiers checked for compliance

Table 2: Compliance checks undertaken in 2010

	Phase-in	Non phase-in
No of compliance checks initiated in 2010	39	96
No of compliance checks carried over from 2009	16	
Total number of dossiers examined under compliance check in 2010	151	

http://echa.europa.eu/doc/evaluation_under_reach_progress_report_2010.pdf

Dossiers checked for compliance

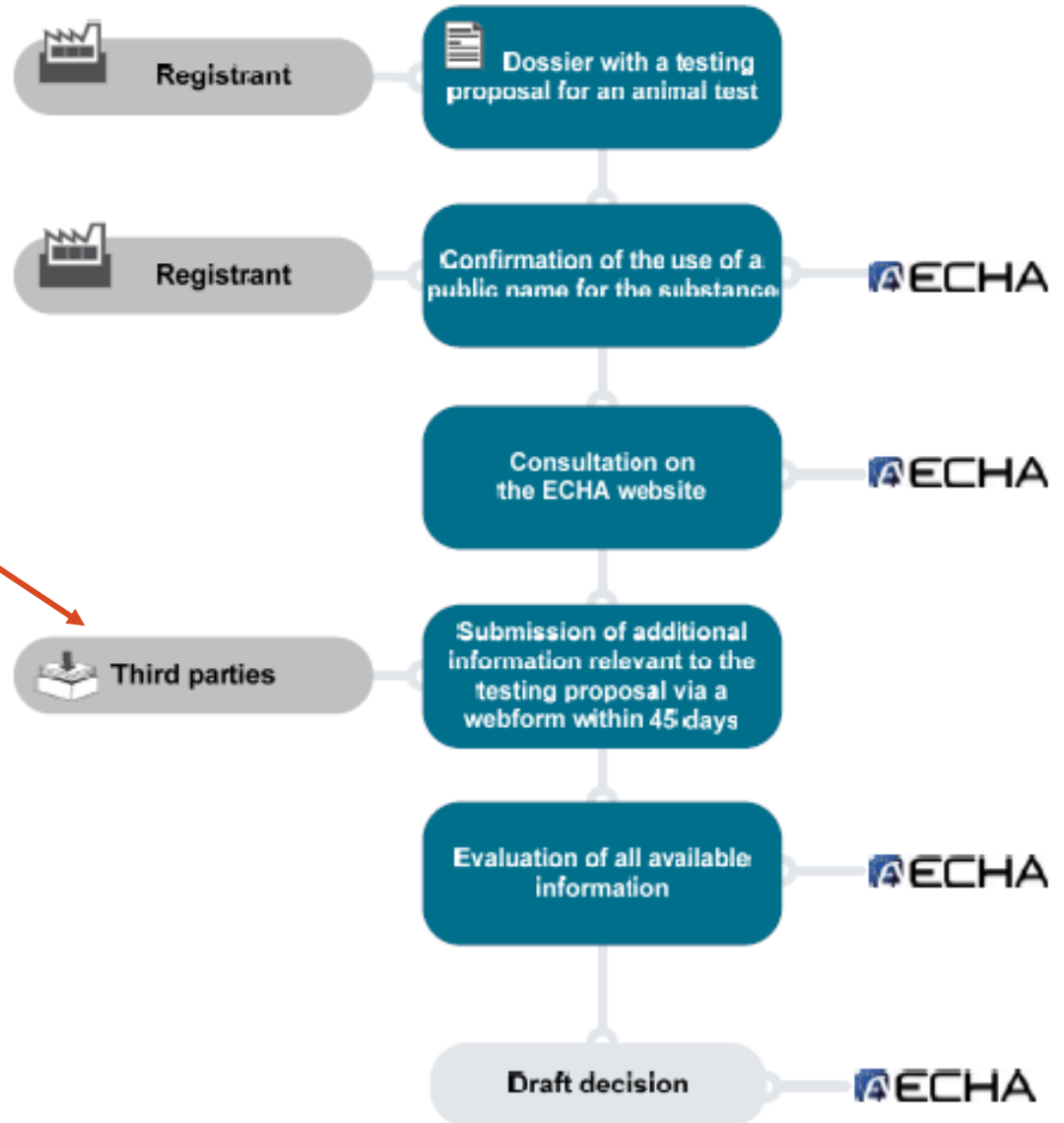
- The REACH Regulation is relatively new and there is a learning phase in its implementation.
- Most of the substances registered in 2010 are manufactured or imported in high volumes (>1000 tpa). Higher use of non-test methods is expected for 2013 and 2018.
- Only a small number of dossiers evaluated so far.

Use of non-test methods

General observations:

- (Q)SAR predictions are used both as **key studies and as supporting evidence** in registration dossiers
- Based on dossier evaluation work it appears that read-across is used more frequently

Use of non-test methods



(Q)SAR models proposed by third parties

registrant is informed, but is not obliged to buy services

Shortcomings observed in dossiers

- Limited information about (Q)SAR model (e.g. version unclear, no QMRF, data model not transparent/available)
- Scientific validity of models not always demonstrated
- Applicability domain of the models often not analysed (or only partially analysed)
- Not relevant for regulatory purpose (e.g. the endpoint predicted is not suitable to meet the information requirements of REACH)

Shortcomings observed in dossiers

- Documentation limited: copy – paste from software without presenting further considerations



Lacking or limited documentation of (Q)SAR predictions and models used can lead to additional uncertainties for authorities

ECHA Progress report 2010

For a significant number of the evaluated dossiers the rules for adaptation of standard information requirements are known and well used by the registrants





For a number of cases, the adaptation of standard information requirements were either poorly justified or not justified at all.



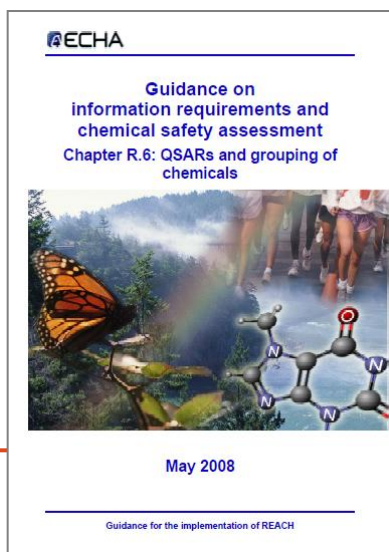
http://echa.europa.eu/doc/evaluation_under_reach_progress_report_2010.pdf

Use of (Q)SAR models

- In certain cases, (Q)SAR models fulfilled the conditions outlined in REACH Annex XI, either as stand alone for the prediction of certain properties or as part of supporting evidence in hazard assessment. 
- In other cases, data generated by (Q)SAR were considered inadequate as they did not provide sufficient information for predicting the presence or absence of certain properties, e.g. long term toxicity. 

Recommendations

“The set of information on the (Q)SAR model shall be provided in the (Q)SAR Model Reporting Format (QMRF), or in the corresponding IUCLID field; a QMRF is necessary for assessing the validity of the model.”



- (Q)SAR Model Reporting Format (QMRF)
- (Q)SAR Prediction Reporting Format (QPRF)

JRC (Q)SAR Model Database (QMDB) for (Q)SAR models submitted to JRC for peer review
(http://qsar.db.jrc.it/qmrf/search_catalogs.jsp).

Recommendations

“The use of (Q)SAR models as supportive evidence in hazard assessment is recommended. Information generated by expert systems on the presence or absence of alerts may provide valuable information in the overall of test data.”



Recommendations

“QSAR model predictions may be used in a weight-of-evidence approach, in correlation to test data, in order to develop and support justification for read-across and grouping approaches.”



Recommendations

“QSAR model predictions can often help in deciding on integrated testing strategy (ITS) when examining chemical categories.”



Support of regulatory use of (Q)SAR methodology

QSAR TOOLBOX

- The QSAR Toolbox is a software to help registrants and authorities
 - to use (Q)SAR methodologies to group chemicals into categories and
 - to fill data gaps by read-across, trend analysis and (Q)SARs for assessing (eco)toxicity hazards of chemicals under REACH,
 - and thus to help saving costs and the need for testing on animals.
- Project co-managed by ECHA and OECD (contractor LMC); version 2.1 released in Feb 2011

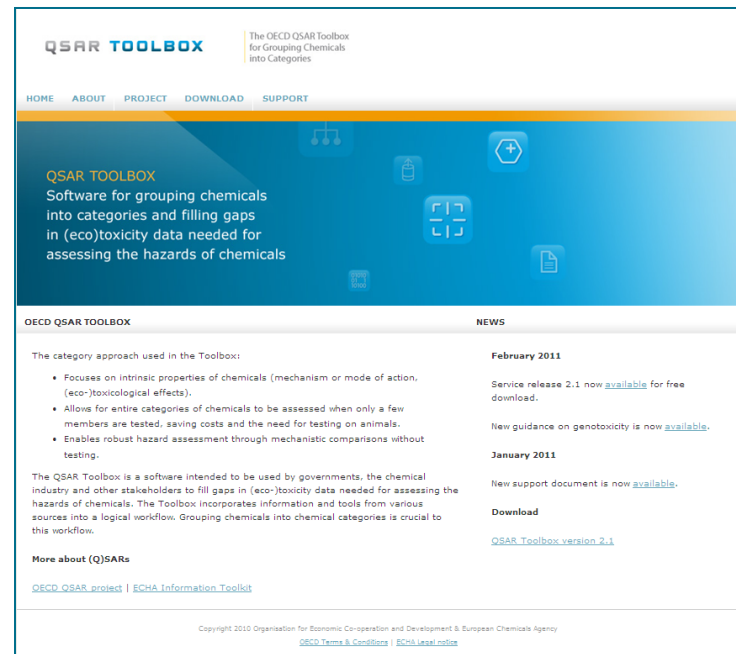
QSAR Toolbox webpages

- Information about the project, download of guidance documents and manuals, free software download:

www.qsartoolbox.org

- OECD QSAR project:

www.oecd.org/env/existingchemicals/qsar



General reflections on evaluation

- The main objective of REACH is to ensure safe handling of chemicals while enhancing competitiveness and innovation in the European market.
- Aim of compliance check: to check whether or not information submitted is in compliance with REACH (at least 5 % of the dossiers per tonnage band).
- The registrant is responsible for the safe use of chemicals and has to demonstrate this in the registration dossier.
- Appropriate documentation is needed for authorities in order to be able to verify compliance with REACH.

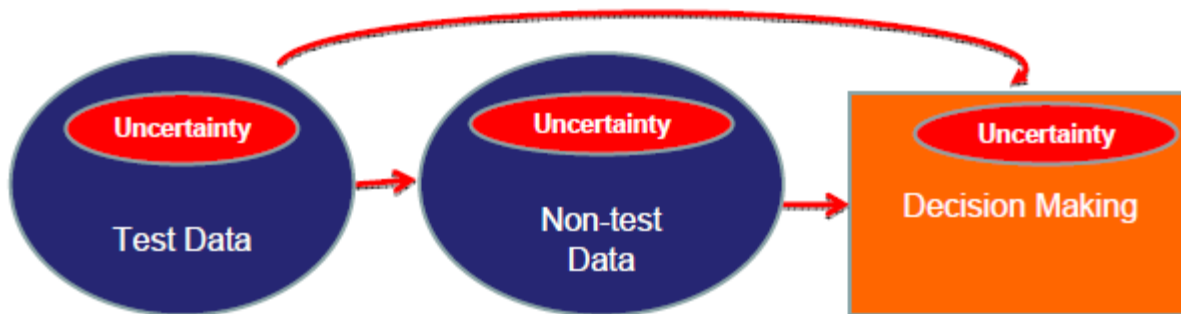
Major question: Uncertainty & Risk

- Information shall be adequate for C&L and/or risk assessment
- Uncertainty is associated with all types of data
- **Risk and uncertainty are interlinked**

Major question: Uncertainty & Risk

Non-test data contain uncertainty due to:

- i) uncertainty in the test data they are based upon, and
- ii) the expert judgment that is used to decide if they are adequate for decision making



Major question: Uncertainty & Risk

Non-test methods workshop (23-24 September 2010)

Workshop on dealing with uncertainty related to the application of non-test methods under REACH

The workshop was attended by experts in the field of non-test methods from Member States, the European Commission, industry bodies and non-governmental organisations as well as experts from other EU institutions or other international organisations.

More information can be found at

http://echa.europa.eu/news/events/non_test_methods_workshop_2010_en.asp

Useful Links

- REACH Regulation:
http://echa.europa.eu/reach_en.asp
- Guidance on information requirements and chemical safety assessment:
http://guidance.echa.europa.eu/guidance_en.htm
 - Guidance on substance and dossier evaluation
 - R.6 QSARs and grouping of chemicals
 - R.7 (a-c): Endpoint specific guidance
- Practical Guides on how to report (Q)SARs, read-across and chemical categories:
http://echa.europa.eu/publications_en.asp

