

The use of the models for risk assessment and classification

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- Non-testing under REACH
- Quantitative and qualitative risk assessment
- Uncertainties
- Responsibilities

REACH

Aim

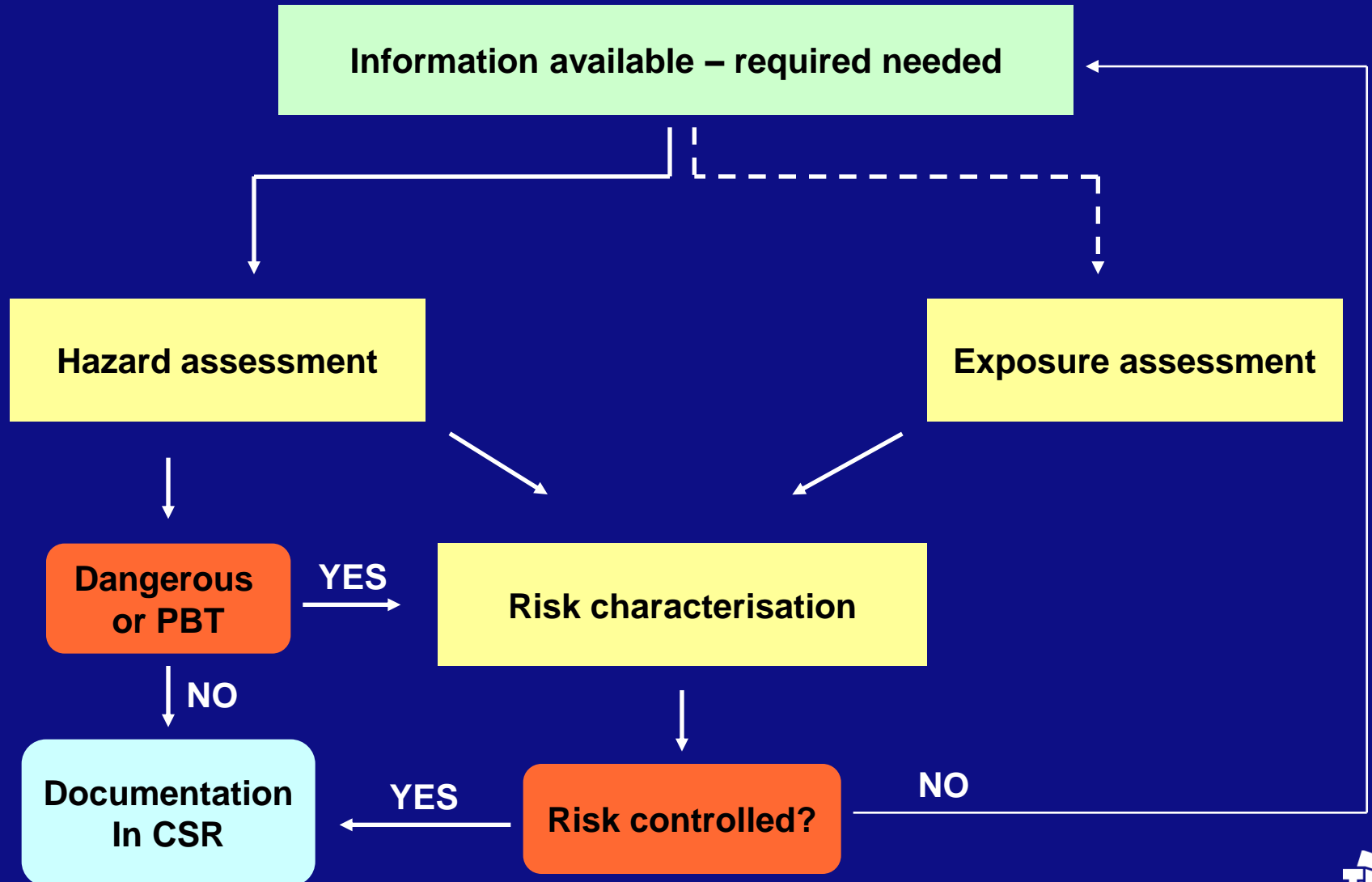
“To ensure a high level of protection of human health and the environment.....”

Industry is responsible for control of risk

“.....The Regulation is based on the principle that industry should manufacture, import or use substances or place them on the market with such responsibility and care as may be required to ensure that, under reasonably foreseeable conditions, human health and the environment are not adversely affected.”

(Regulation (EC) No 1907/2006)

Safety evaluation under REACH



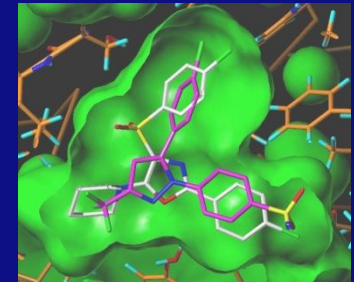
Testing and Non-testing



Animal tests



Human data



(Q)SAR

Information requirements



In vitro



Exposure



Grouping & read across

Non-testing under REACH

“New tests on vertebrates shall only be conducted or proposed as last resort when all other data sources have been exhausted...”

“Before new tests are carried out, all available in vitro data, in vivo data, historical human data, data from valid **(Q)SARs** and data from **structurally related substances (read-across)** shall be assessed first...”

→ **Non-testing has a high priority under REACH**

Risk assessment by non-testing

HAZARD Qualitative risk assessment	RISK Quantitative risk assessment
Discrete endpoints Mutagenicity Sensitisation Carcinogenicity Reprotoxicity	Continuous endpoints - EC3 TD50 NOAEL
Methods SARs / alerts Read-across (qualitative)	Methods QSARs Read-across (quantitative)

Qualitative risk assessment by non-testing

In case of negative prediction:

- Authority may not accept because of false negatives
- Industry is responsible for safety and liable in case of problems

In case of positive prediction:

- Classification and Labeling
 - Undesirable for industry → further testing?
 - Risk characterization needed

Quantitative risk assessment by non-testing

1) Statistically derived, global models

- May include very diverse mechanisms
- Difficult to derive high predictivity for complex endpoints

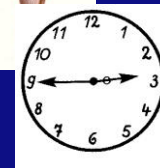
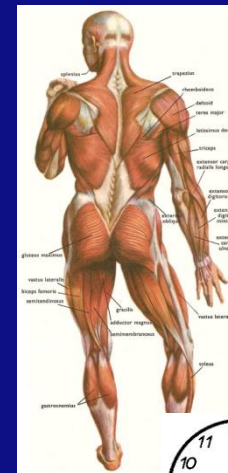
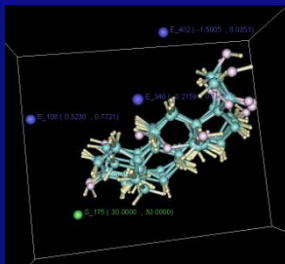
2) Mechanism based models, local models

- A single model describes one mechanism
- Various models describe the endpoint
- Do the models cover the whole endpoint?

Uncertainties

Models are inherently associated with uncertainties

Risk assessment inherently deals with uncertainties



Acceptability of (Q)SARs

In environmental risk assessment QSARs used for:

- Persistence (a.o. BIOWIN)
- Bioconcentration (BCF-WIN)
- Toxicity (ECOSAR)

These models are suggested in the guidance

No models for human endpoints are suggested

ECHA Guidance R.6:

“There will be no formal adoption process for (Q)SARs”

“There is no unique measure of model reliability and no criteria for (Q)SAR reliability are offered in this guidance”

“the process of (Q)SAR acceptance under REACH will involve **initial acceptance by industry** and **subsequent evaluation by authorities**, on a case-by-case basis”

Summary

At the moment (Q)SARs can be used for:

- Identification of alerts additional to the information requirements
- Prioritization of substances for evaluation
- Substantiation of chemical categories in view of read-across

Discussion

- **A discussion is needed on the acceptable uncertainty level. The discussion has to involve scientists, regulators, and industry (as industry is responsible)**
- **Further discussion on the procedure and acceptance of alternative methods is necessary**
- **Examples should be further discussed in which the use of alternative methods has been agreed upon by scientists, regulators, and industry**
- **A sufficient level of information has to be achieved also including non-Golden Standard data**