



Bridging and Read-across

Ilse Schoeters, Rio Tinto

Classification of substances - Background (1)

- Classification of all substances produced and/or imported into Europe by December 2010
 - Physical properties (explosive, oxidising, flammable,...)
 - Health hazards (acute toxicity, skin corrosion/irritancy, eye irritation/damage, sensitisation, mutagenicity, carcinogenicity, reproductive toxicity, STOT, aspiration hazard)
 - Environmental hazards (acute toxicity, chronic toxicity)
- Testing under CLP (Art 8): the manufacturer, importer or downstream user
 - shall perform the tests required for all physical hazards unless there is adequate and reliable information
 - may perform the tests for all health and environmental hazards, ...
 - Note: for REACH registration → Testing for tox and ecotox endpoints required

Classification of substances - Background (2)

- Accepted test guidelines

- by EC and Agency ((EC) No 440/2008) or
- Internationally recognized

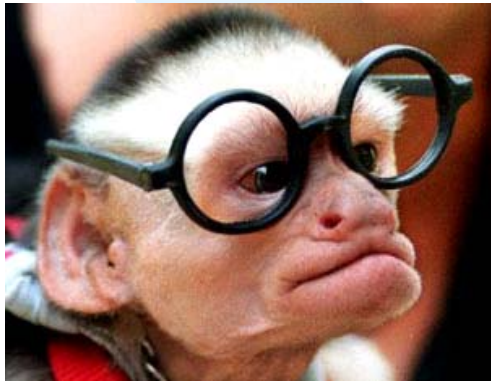
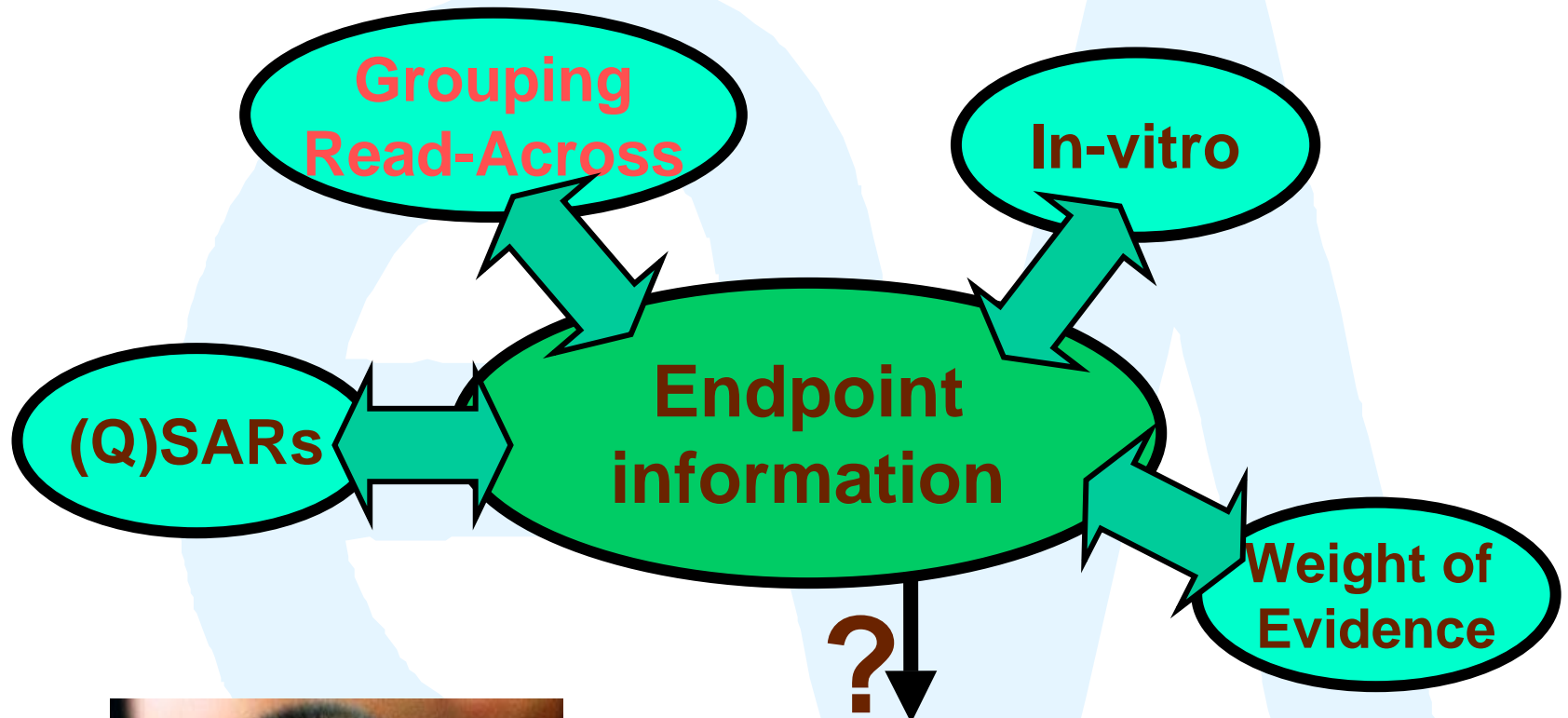
- Test results should be of acceptable quality and relevant

- Performing the tests to fill the datagaps of all endpoints

- can be costly (42 000 to > 2 000 000 euro)
- will require a lot of animal testing
- Article 8(1): obligation to carry out vertebrate testing only as a last resort

“provided that he has exhausted all other means of generating information including by applying the rules provided for in section 1 of Annex XI to REACH Regulation”

Alternative methods: REACH Annex XI



TESTING

Grouping of Substances and Read-across approach

- REACH - Annex XI 1.5:

“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.

Eg: Metal ion

Application of the group concept requires that physicochemical properties, human health effects and environmental effects or environmental fate may be predicted from data for reference substance(s) within the group by interpolation to other substances in the group (read-across approach). This avoids the need to test every substance for every endpoint.”

Read-across approach

- A technique used to predict endpoint information for one chemical by using data from the same endpoint from another chemical which is considered to be 'similar'.
- Can only be applied for health and environmental endpoints, not for physical hazard endpoints!
- Example:
 - Cu salts: -perform environmental toxicity test with CuSO_4
 - predict environmental toxicity of CuCl_2 , CuNO_3 , CuO , Cu_2O ... from CuSO_4

How does it work? (1)

- Guidance on Information Requirements and Chemical Safety Assessment - Chapter R6
 - Chapter 6.2.5.6 Metals, metal compounds and other inorganic compounds
 - Includes also guidance for minerals!
- Principles for metals & inorganic substances:
 - **Metal ion** causes the effects
 - **Bioavailability** of the metal ion (or a redox form of this ion) at **target sites** determines the occurrence and severity of the effects to be assessed.
 - Trend in effect

ECHA

Guidance on
information requirements and
chemical safety assessment
Chapter R.6: QSARs and grouping of
chemicals



May 2008

Guidance for the implementation of REACH

How does it work? (2)

- Supporting information to assess the bioavailability of the metal ion at the target site
 - in vivo data on systemic effects
 - toxicokinetics
 - in vitro solubility
 - water solubility
 - particle size and structure

ECHA

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May 2008

Guidance for the implementation of REACH

Analogue approach

Read-across to predict the missing data for 1 substance

- Step 1: Check whether the chemical is a member of a suitable category that has already been defined
- Step 2: A) In case a category exists, go to step 5
B) In case no category exists, identify potential analogue substances
- Step 3: Gather data of analogue substances
- Step 4: Evaluate data for adequacy
- Step 5: Construct a matrix of data availability
- Step 6: Assess the adequacy of read-across criteria and fill data gaps
- Step 7: A) If not adequate, consider other analogue substances or perform test
B) If adequate, document well the read-across

Category approach

Read-across to build a Category of many substances

- Step 1: Identification of structure-based category and its members
- Step 2: Gather published and unpublished data for each category member
- Step 3: Evaluate data for accuracy
- Step 4: Construct a matrix of data availability
- Step 5: Perform an internal assessment of the category
- Step 6: Prepare category test plan
- Step 7: Conduct necessary testing
- Step 8: Perform an external assessment of the category
- Step 9: Fill data gaps by read-across, extrapolation, interpolation, etc.


Data availability matrix - Analogue approach (1)

Example for oral endpoints

	Metal	Metal oxide	Metal sulfide	Metal sulfate	Metal chloride	Metal nitrate
Water solubility	x	x	x	x	x	x
Bio-elution in gastro-intestinal fluids						
Toxicokinetics - oral				x		
Acute oral toxicity		x		x	x	
Repeated dose toxicity - oral		?		x		
Reproductive toxicity - oral		?		x		

Data availability matrix - Analogue approach (2)

Example for oral endpoints



	Metal	Metal oxide	Metal sulfide	Metal sulfate	Metal chloride	Metal nitrate
Water solubility	x	x	x	x	x	x
Bio-elution in gastro-intestinal fluids		Test		Test		
Toxicokinetics - oral		(Test)		x		
Acute oral toxicity		x		x	x	
Repeated dose toxicity - oral		Read-across		x		
Reproductive toxicity - oral		Read-across		x		

Data availability matrix - Category approach (1)

Example for oral endpoints

	Metal	Metal oxide	Metal sulfide	Metal sulfate	Metal chloride	Metal nitrate
Water solubility	x	x	x	x	x	x
Bio-elution in gastro-intestinal fluids						
Toxicokinetics - oral				x		
Acute oral toxicity	?	x	?	x	x	?
Repeated dose toxicity - oral	?	?	?	x	?	?
Reproductive toxicity-oral	?	?	?	x	?	?

Data availability matrix - Category approach (2)

Example for oral endpoints

	Metal	Metal oxide	Metal sulfide	Metal sulfate	Metal chloride	Metal nitrate
Water solubility	x	x	x	x	x	x
Bio-elution in gastrointestinal fluids	Test	Test	Test	Test	Test	Test
Toxicokinetics - oral		Test		x		
Acute oral toxicity		x		x	x	
Repeated dose toxicity - oral		Test		x		
Reproductive toxicity-oral		Test		x		

Data availability matrix - Category approach (3)

Example for oral endpoints

	Metal	Metal oxide	Metal sulfide	Metal sulfate	Metal chloride	Metal nitrate
Water solubility	x	x	x	x	x	x
Bio-elution in gastro-intestinal fluids	Test	Test	Test	Test	Test	Test
Toxicokinetics - oral	Read-across	Test	Read-across	x	Read-across	Read-across
Acute oral toxicity	Read-across	x	Read-across	x	x	Read-across
Repeated dose toxicity - oral	Read-across	Test	Read-across	x	Read-across	Read-across
Reproductive toxicity-oral	Read-across	Test	Read-across	x	Read-across	Read-across

Category, Read-across

- But watch for

- Speciation and valency (e.g. Cr^{6+} versus Cr^{3+})
- Mineral structure (e.g. crystalline versus non-crystalline silica)
- Particle size (e.g. nanoparticles versus particles of μm size)
- Organometallic form (e.g. Hg versus CH_3Hg)

- Good scientific justification is crucial!

- Documentation of scientific approach!

⇒ Investment for the future to prevent future misclassifications

Read-across, a coin with two sides...

- ⇒ Required according Art 8(1)
- ⇒ Avoids the need to test every substance for every endpoint.
- ⇒ Cost-effective! 💰
- ⇒ Consortium covering multiple substances of the same element



BUT

- ✓ Be aware of classification of other analogue substances
- ✓ Be aware of consequences of classification
 - × Eg CMR or PBT, environmental classification,...



- ✓ Read-across to other substances in the category? 💣
(see next presentation Paola!)





ENM

QUESTIONS?