WORKSHOP ON QSAR MODELS FOR REACH

Mario Negri Institute, Milan, Italy - March 10-11, 2009

SIXTH FRAMEWORK PROGRAMME

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Use of QSAR models for REACH and the CAESAR approach

http://www.caesar-project.eu/

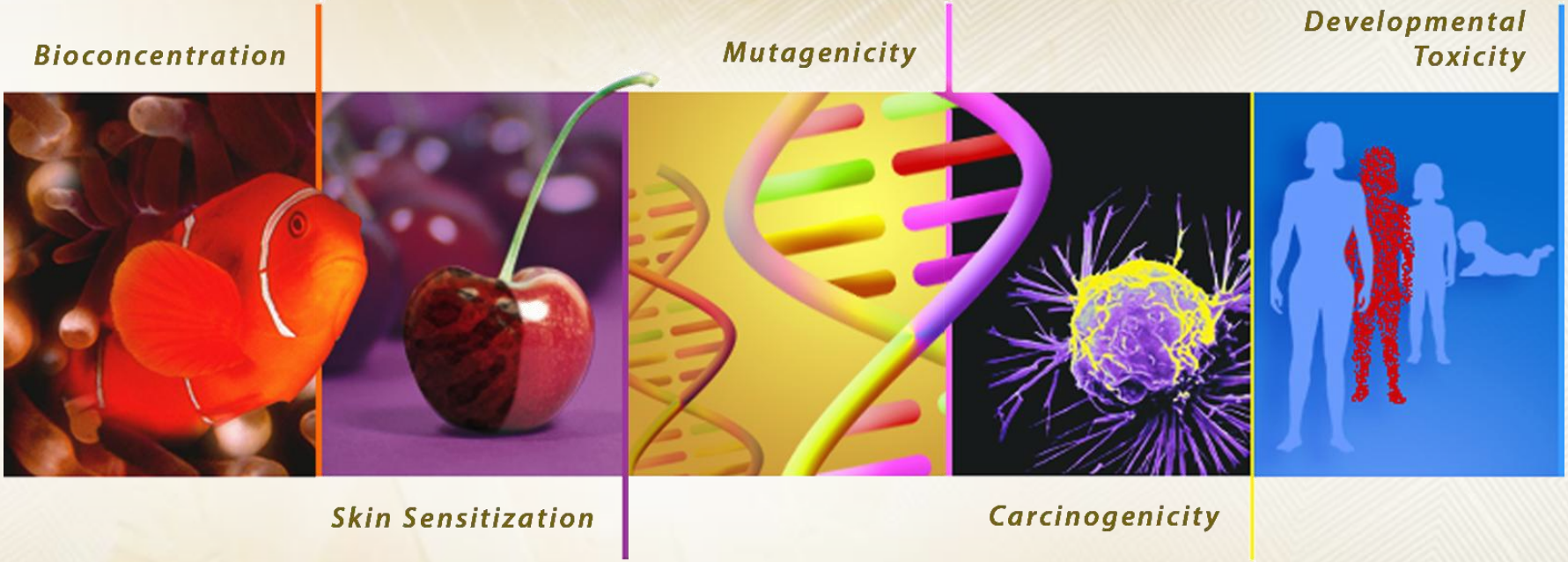
THE FOCUS OF THE WORKSHOP

- we will NOT discuss about QSAR theory in general
- we will NOT discuss the utility of QSAR for REACH in general
- **we will present the specific CAESAR approach and results**

- Our target is NOT to solve all the issues related to QSAR
- but to provide some tools useful for a SPECIFIC APPLICATION

REACH

THE CAESAR ENDPOINTS



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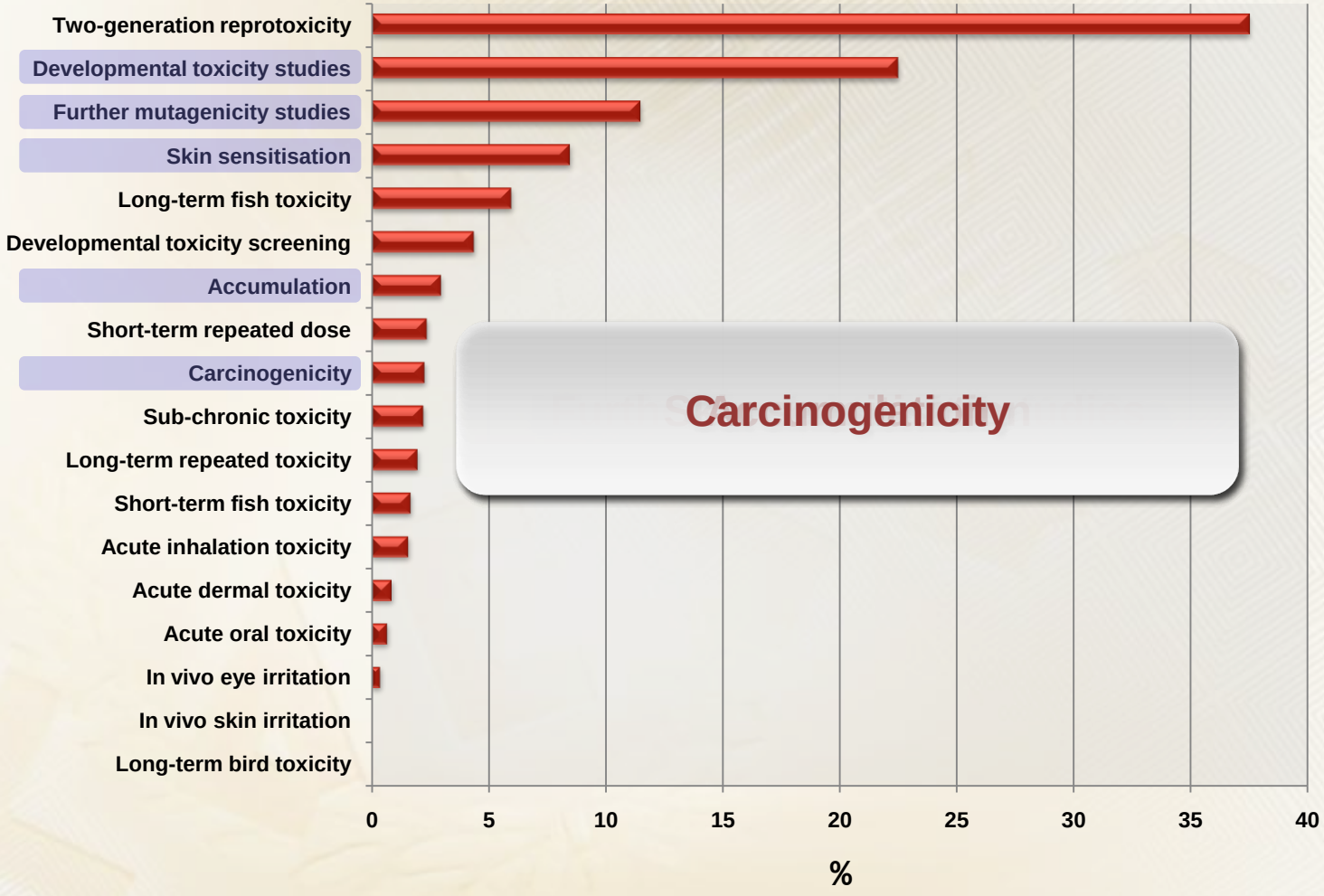
NUMBER OF ANIMALS TO BE USED FOR REACH

Test animal need (%) for different end-points

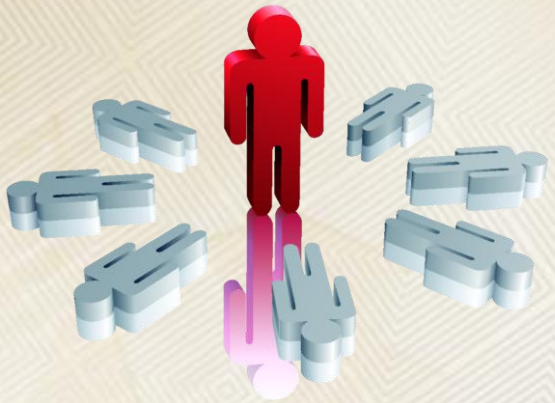


WHY THESE ENDPOINTS?

- CAESAR had a defined BUDGET and DURATION
- we wanted to OPTIMIZE the use of models
- we wanted to provide tools with maximum benefits for the USERS
- we focused our attention on these endpoints, because they are IMPORTANT and, hopefully, FEASIBLE

THE USER INTEREST IS OUR TARGET

- NOT a new algorithm
- NOT a new chemical approach
- NOT a new theory
- NOT a general approach
- NOT a proposal of models we had



- **All these targets are correct, but we aimed at SOMETHING ELSE**

THE REACH REQUIREMENTS

REACH
Registration, Evaluation,
Authorisation of Chemicals

to take into account the specific

REACH requirements

in addition to

QSAR model requirements

for REACH

Data -> Use

Experimental data
high quality

Use
C&L, prioritization, risk assessment

Data -> QSAR -> Use

QSAR evaluations have to increase their horizons

*not all **inputs** are equally good*

*not all **outputs** are equally good*

QSAR IS LIKE A BRIDGE

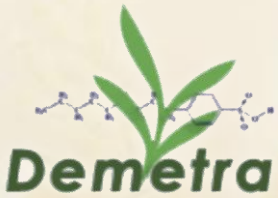
- between DATA and USE
- between INPUTS and OUTPUTS

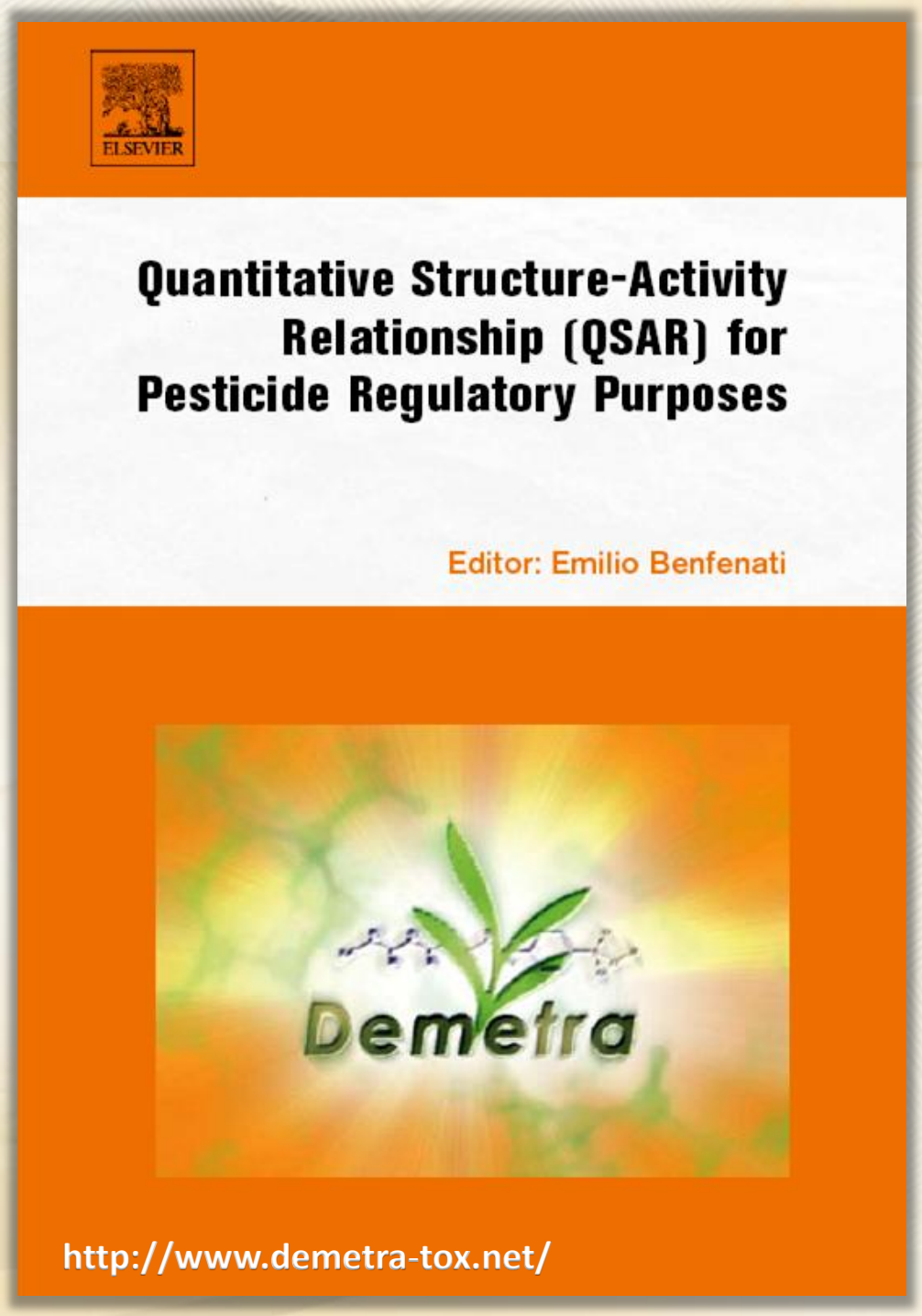
Are all the bridges the same?

NO

we also used previous experience

DEMETRA





- in the case of *drugs/pesticides* we need data **for ANIMALS**
- in the case of *cosmetics* we need data **from ALTERNATIVE METHODS**
- for REACH we use **ALL INFO**

DIFFERENT STRATEGIES

a) in case of **single QSAR**
b) in case of **COMBINED TOOLS**

- for **REGULATORY PURPOSES** it is important to ***minimize the false negatives***

INDUSTRY, during compound development, has other TARGETS

different  **different QSAR needed**

- the *balance* between **false positives** and **false negatives** depends on:

1. **THE USE OF THE METHOD**
   alone or combined, *see the legislation*
2. **POLITICAL AGREEMENT**
   it is not only scientific

SPECIFIC MODELS NEEDED FOR SPECIFIC LEGISLATION

- CAESAR developed a *strategy* to turn the model in one direction (*max accuracy*) or another (*max sensitivity*)

Typically QSAR models are evaluted using *square parameters* (R^2, Q^2)

- CAESAR developed new strategies for evaluation of *regression models*

- the **threshold values** are relative to the **LEGISLATION**
- ***false negatives*** are relative to **thresholds**
- **different optimization** depending on to the **LEGISLATION**

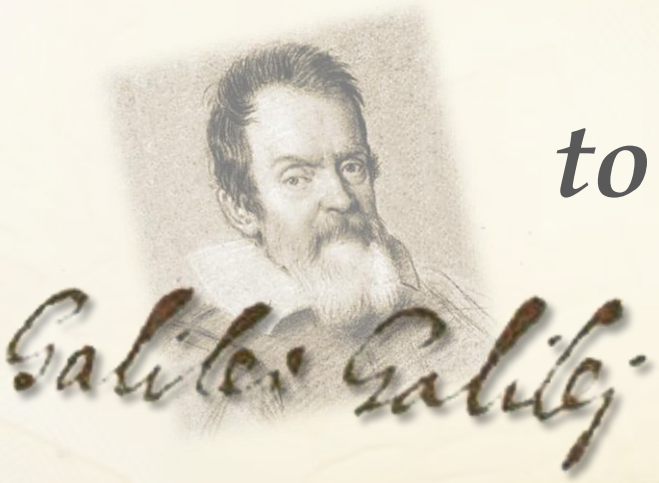
within REACH *different models* may be preferable, depending on the *tonnage*

- For **models for risk assessment**, we need *continuous values*, to be compared with the exposure level
- in **other cases** we need a *classification*: *different evaluations*

QSAR SHOULD FIT FOR THE PURPOSE

- it has to be demontrated that QSAR works in the specific case

- Proof of principle



"Any theory has to be demonstrated"

WORKSHOP: TO DISCUSS ABOUT FACTS

- CAESAR is a step in the direction of safer, more extensive use of QSAR for REACH

- **YOUR INPUTS** for **future steps** are very important

Important features for REACH

- **according to the *REACH regulation* (*Annex XI*) a QSAR is valid if:**
  - the model is recognized to be **scientifically valid**;
  - the substance is included in the **applicability domain** of the model;
  - results are adequate for **classification**, **labelling** and **risk assessment**;
  - adequate **documentation** of methods is provided.

IMPORTANT FEATURES FOR QSAR FOR REACH - 1

SCIENTIFICALLY VALID: proof, does it work?

within CAESAR validation done according to different procedures:

- **sound statistical internal validation;**
- **external test set(s);**
- **predictivity assessed.**

VALIDATION

- R^2, R'^2, slope, slope', leave-one-out;
- attention to false negatives;
- external test set: split of the data into a training and test (20%);
- when possible further test sets;
- Collaboration is welcome on validation and checking.

APPLICABILITY - RELIABILITY

- in most cases the target has been a model of wide applicability;
- specific limitations as common in QSAR: neutral form, no chirality, no polymers;
- boundaries also defined by descriptor range;
- limitations for individual models: rules for higher uncertainty for certain chemical classes.

APPLICABILITY - UNCERTAINTY

- **A PRIORI conditions, as typically performed:** ***chemometric tools, on model's basis/inputs*;**
- **A POSTERIORI conditions, on the basis of the results/outliers, identifying chemical groups with higher uncertainty;**
- **not black/white, but uncertainty is given.**

A POSTERIORI CHECK OF APPLICABILITY

- performances per chemical category;
- number of compounds;
- average error, compared with experimental value;
- number of false positives/negatives;
- presentation of the results for similar compounds.

DEFINITION OF INTENDED USE

- classification or continuous values;
- suitable for C&L or RA;
- attention to the EU thresholds.

ADEQUATE DOCUMENTATION - 1

- **Toxicity/property data on the web**

  All values given, including multiple values

- **Chemical structure given**

- **Chemical descriptors/fragment**

  This includes the formula for descriptor. In several cases it varies depending on the software or on the version.

ADEQUATE DOCUMENTATION - 2

- **Mathematical algorithm** of the *in silico* model is given;
- The **methodology** is provided and the **parameters** fixed;
- **Full results provided** (raw data and statistical evaluation).

Documentation, transparency, Reproducibility

- since the algorithm is given (including *chemical descriptors*) the model is fully transparent and reproducible
- the same value obtained in Italy, Finland, France, etc.
- the same model used by regulators and industry

CAESAR MODELS: ADVANTAGES

- Planned for **REACH**: reference to *legislation & QC*
- Planned to be **used**, **transparent**, **validated**
- Some models can replace **assays**, others are **supplementary info**
- Models for the future: **implementable**
- Modern **IT basis** (*Java*, *Python*, …)
- **Public**, **easy** access

FUTURE STEPS - 1

- Feed-back from USERS
- Your OPINIONS
- OPTIMIZATION of the models
- IMPLEMENTATION of more CAESAR models
- INTEGRATION of the models

FUTURE STEPS - 2

- collaboration with **US EPA**
- collaboration with **CHEMPREDICT**
- use and test within **OSIRIS**
- dissemination (**ORCHESTRA**)
- your **SUPPORT**, your **IDEAS**

CAESAR

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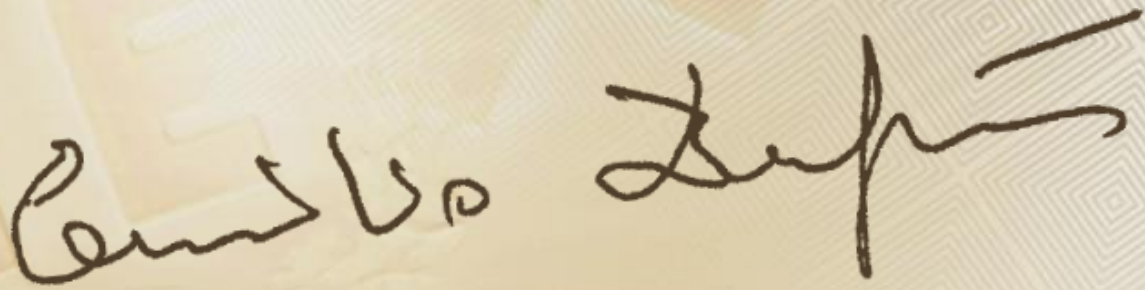
GRAZIE!



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