



Alternative Non-Testing methods Assessed for REACH Substances

LIFE08
ENV/IT/000435

antares

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Promotion of non testing methods (NTM) for their use in the REACH context linking *scientists*, *regulators* and *industries*

to **evaluate** and **validate** existing NTM for their application according to REACH needs

Beneficiaries



POLITECNICO
DI MILANO



Beneficiary 1 : Istituto di Ricerche Farmacologiche Mario Negri

Beneficiary 2 : Istituto Superiore di Sanità

Beneficiary 3 : Federazione Nazionale dell'Industria Chimica

Beneficiary 4 : Politecnico di Milano, Dipartimento di Elettronica e Informazione

Beneficiary 5 : KnowledgeMiner Software Frank Lemke

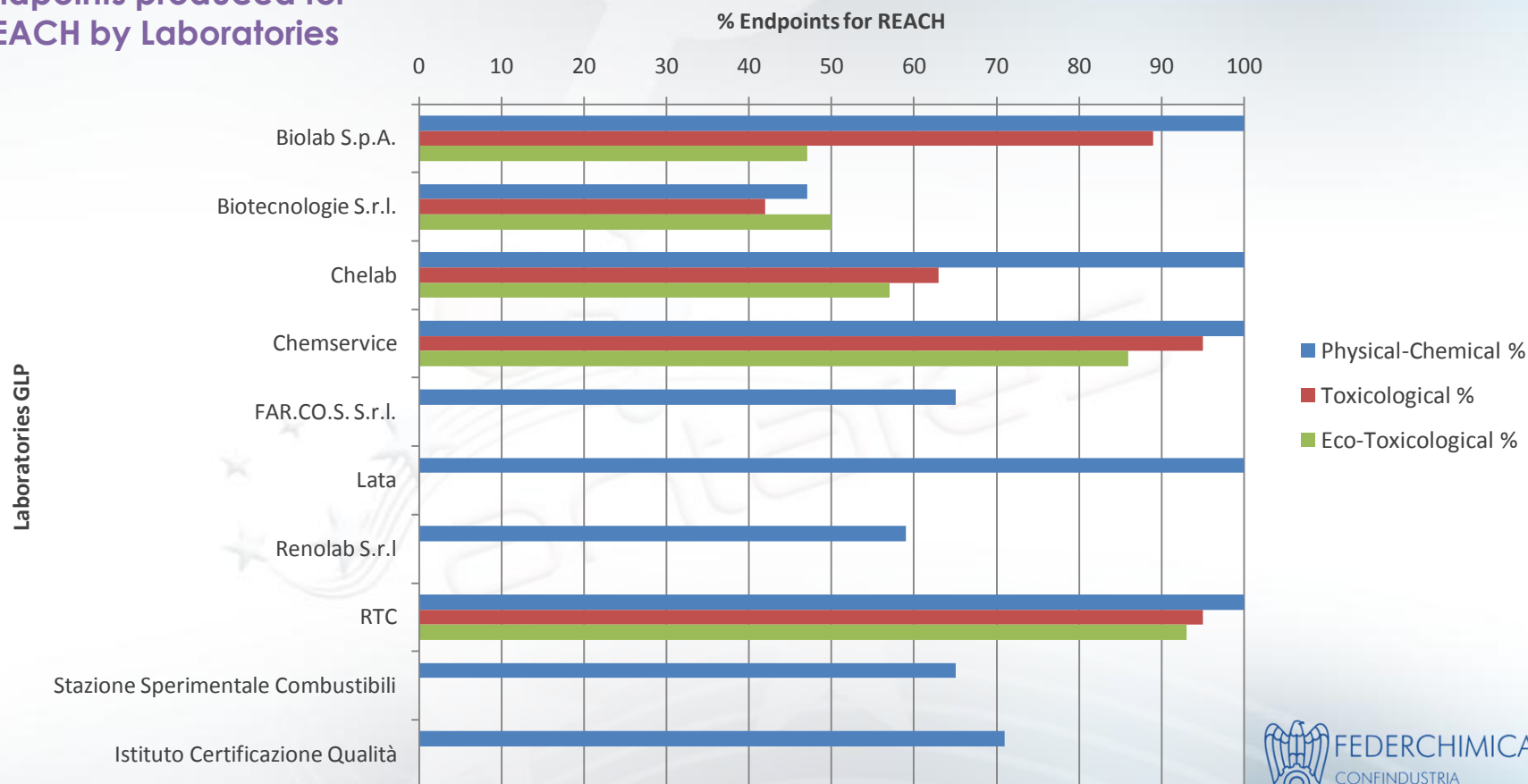
- Action 1** **Survey of current methods** for the compliance to the REACH legislation
- Action 2** Identification of the **criteria for the non-testing methods** for the REACH legislation
- Action 3** **Identification of** suitable **experimental databases/data sets** for the ecotoxicological, toxicological and environmental endpoints for REACH
- Action 4** **List of (Q)SAR models** for the ecotoxicological, toxicological and environmental endpoints for REACH, and their review
- Action 5** **Validation** of non-testing methods (incl. read-across)
- Action 6** Identification of **boundaries for best use** of models (applicability domain) **and** of the **assessment factors**

Actions

- Action 7** **Architecture for integration** of different non-testing methods for best performances and coverage of applicability
- Action 8** **Communication** and **dissemination** initiatives
- Action 9** **Web portal**
- Action 10** **Project management**
- Action 11** **Monitoring**
- Action 12** **Audit**
- Action 13** **After-LIFE Communication plan**

LIST OF ITALIAN LABORATORIES WHICH CAN PRODUCE THE EXPERIMENTAL RESULTS REQUESTED FOR REACH

Endpoints produced for REACH by Laboratories



THE REQUIREMENTS FOR DATA

Criteria: what kind of DATA?

preferably from OFFICIAL PROTOCOLS

What kind of USE?

depends on the TONNAGE, etc: C&L, Risk Assessment

Endpoint (for REACH)?

data preferably from OFFICIAL PROTOCOLS:

Carcinogenicity, Mutagenicity, Skin Sensitization, Reprotox, Toxicity for plants, invertebrates, fish and mammals...

CRITERIA FOR THE IDENTIFICATION OF EXPERIMENTAL DATABASES/DATA SETS

- DB identification
- *ENDPOINT* identification
- Data source characterisation
- Quality check on the value
- Presence of multiple/single values, uncertainty
- Number of **COMPOUNDS**
- Type of input required for the query
- Export capabilities
- Type of query: single or batch
- Dissemination level (public/private)
- **OTHERS?**

SOME DATABASES

- **IRIS** <http://toxnet.nlm.nih.gov/cgi-bin/sis/htmlgen?IRIS>
- **Hazardous Substances Data Bank (HSDB®)**
<http://toxnet.nlm.nih.gov>
<http://toxnet.nlm.nih.gov/cgi-bin/sis/htmlgen?HSDB>
- **The PubChem Project**
<http://pubchem.ncbi.nlm.nih.gov/>
- **CPDB** <http://potency.berkeley.edu/>
- **DSSTox** <http://www.epa.gov/ncct/dsstox/index.html>
- **ISSCAN Database**
<http://www.iss.it/ampp/dati/cont.php?id=233&lang=1&tipo=7>
http://www.epa.gov/NCCT/dsstox/sdf_isscan_external.html
- **TOXCAST** <http://www.epa.gov/ncct/toxcast/>
- **PAN** <http://www.pesticideinfo.org>
- **ACToR** <http://www.alttox.org/spotlight/023.html>
- **Ecotox DB** http://cfpub.epa.gov/ecotox/ecotox_home.cfm

CRITERIA FOR THE IDENTIFICATION OF EXPERIMENTAL DATABASES/DATA SETS

Chemical Carcinogenesis Research Information System (CCRIS)

Database identification	http://toxnet.nlm.nih.gov/cgi-bin/sis/htmlgen?CCRIS
Endpoint identification	Carcinogenicity, mutagenicity, tumor promotion, and tumor inhibition
Data source characterisation	National Cancer Institute (NCI)
Quality check on the value	Test results have been reviewed by experts in carcinogenesis and mutagenesis
Presence of multiple/single values, uncertainty	Multiple values/uncertainty not solved
Availability on information on details of values	Fully referenced data
Number of compounds	9,000
Type of input required for the query	Combination of words, chemical names, and numbers, including Chemical Abstracts Service (CAS) Registry Numbers (RN). Structure search via ChemIDplus
Export capabilities	Text format download
Type of query: single or batch	Both
Dissemination level (public/private)	Free

REACH & QSAR

According to *REACH* regulation (Annex XI) a (Q)SAR is **VALID** if:

- the model is recognized scientifically valid;
- the substance is included in the applicability domain of the model;
- results are adequate for classification and labelling and for risk assessment;
- adequate documentation of the methods provided.

THE PROPOSED CRITERIA FOR MODELS EVALUATION

1. SCIENTIFIC VALIDITY:

Classifiers/ Regressions
Sensitivity/specificity/accuracy (or R2/Q2)
Test/training
In/out Applicability Domain
Updated versions
Efficiency connecting different components

3. ADEQUATE (Q)SAR RESULTS:

Endpoints for REACH
Input/output format for REACH

OTHERS:

Easiness
Comprehension
Usability/user friendly
Skill requested to run models
Skill requested to interpret results

Access
Cost
Platform/SW requirements
Connection problems
Time needed

2. APPLICABILITY DOMAIN (AD) OF THE (Q)SAR MODELS:

Discussion of AD Occurrence of specific tools
Efficacy of the tools

4. ADEQUATE AND RELIABLE DOCUMENTATION:

Transparency
Information
Instruction
Experimental biological data (availability; check; official guidelines; Klimish; uncertainty; ...)
Chemical (structure, descriptors, fragments, SW/version, ...)
Algorithm (given, ...)
Reproducibility

EXPLORATIVES EXAMPLES

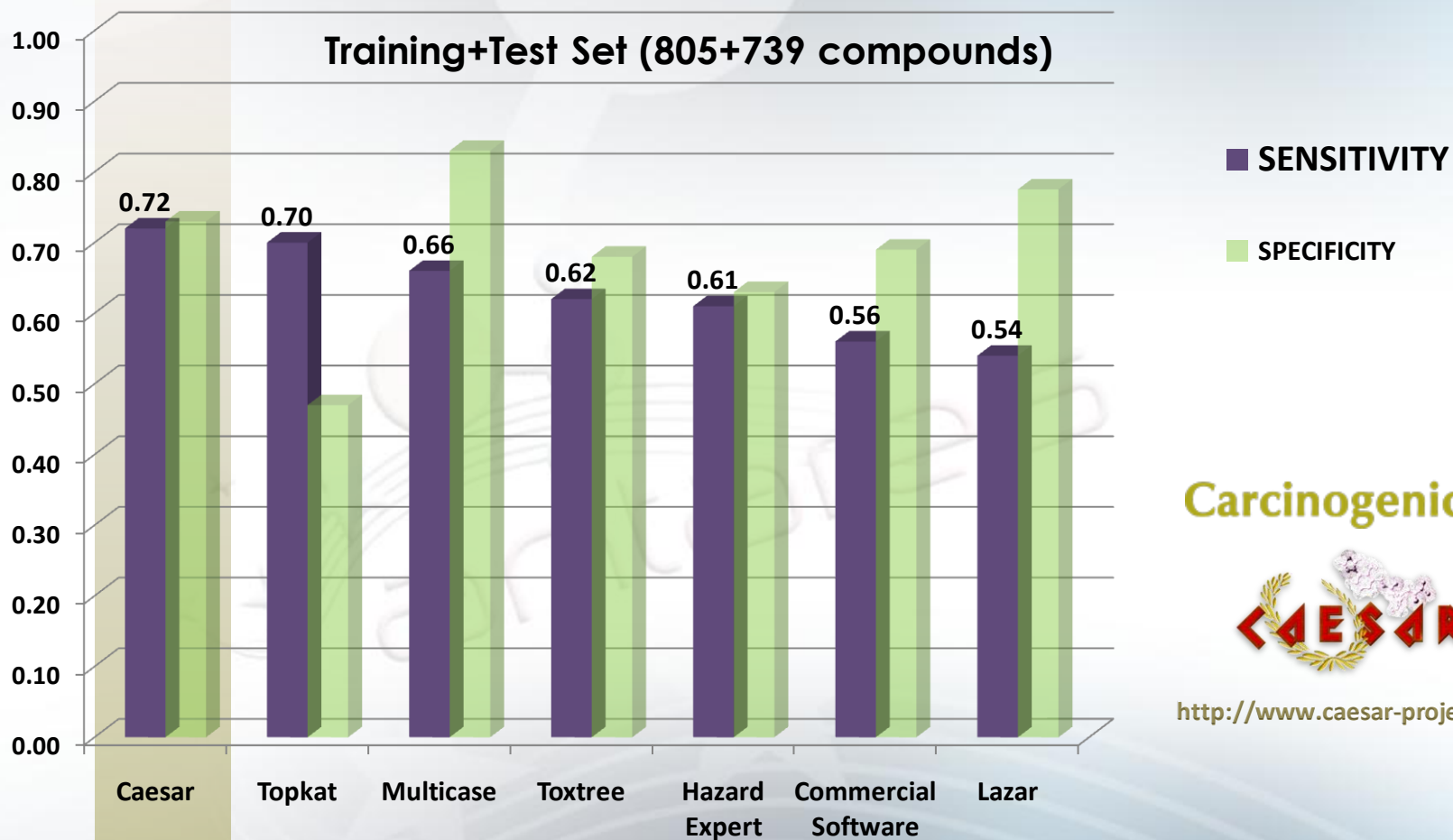
1

Comparison among different models

2

CAESAR's Applicability Domain (AD) for Pesticides

Comparison among different models

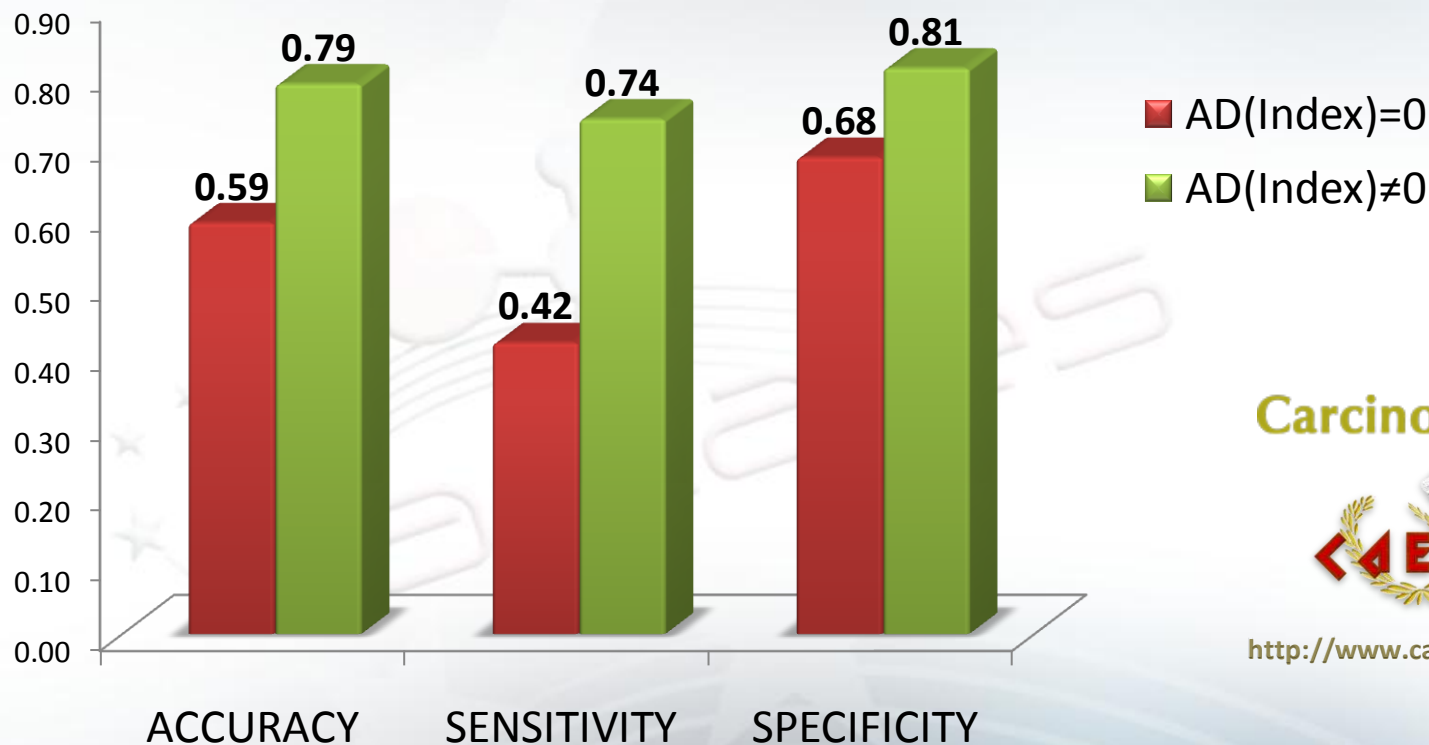


Carcinogenicity



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

CAESAR's Applicability Domain (AD) for Pesticides



Carcinogenicity



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

Main Outputs for FIRST YEAR

OUTPUT

Report on survey of methods for REACH

Report on criteria for non-testing methods

List of end users

List of databases

Evaluation on the model's performances (first model, preliminary report)

Evaluation on the model availability for 20 endpoints (preliminary report)

List and description of the dissemination activities

Production of info brochures, DVDs and newsletters

ANTARES Web portal

Action 4

LIST OF (Q)SAR MODELS FOR THE ECOTOXICOLOGICAL, TOXICOLOGICAL AND ENVIRONMENTAL ENDPOINTS FOR REACH, AND THEIR REVIEW

list the suitable non-testing methods and make an assessment of their quality searching in the internet, literature, etc

SUGGESTED MODELS?

Action 5

VALIDATION OF NON-TESTING METHODS (INCL. READ-ACROSS)

using methods from Action 4 and criteria from Action 3 for predicting the toxicity, ecotoxicity, environmental values, depending on the methods, of the new compounds from databases identified in Action 2, not used to develop the method.

In this way we will have a proof-of-principle of the performances of the methods.

Action 6

IDENTIFICATION OF BOUNDARIES FOR BEST USE OF MODELS (APPLICABILITY DOMAIN) AND OF THE ASSESSMENT FACTORS

establishing safety factors, to keep into account the uncertainty of the results

Action 7

ARCHITECTURE FOR INTEGRATION OF DIFFERENT NON-TESTING METHODS FOR BEST PERFORMANCES AND COVERAGE OF APPLICABILITY

Action 7 will analyze the results of the previous Actions defining a strategy on how to use multiple models in an intelligent way, taking advantages of strengths of each method. The user will be guided to the correct choice of the right method. Finally, the alternative method will be compared with the common one, in terms of costs, performances, applicability, easiness, availability, animal use, etc.

-  Possible collaborations
-  Models suggested for evaluation?
-  Suggestions on DB
-  Preferred endpoint?