

The ANTARES project

An evaluation of non-testing methods for REACH

Chiara Milan¹, Alessandra Roncaglioni¹, Leonello Attias², Silvia Alivernini², Ralf Knauf³, Giuseppina Gini⁴, Frank Lemke⁵, Emilio Benfenati¹

1 IRFMN, Istituto di Ricerche Farmacologiche Mario Negri, Via Giuseppe La Masa 19, 20156 Milan, Italy
2 ISS, Istituto Superiore di Sanità, Viale Regina Elena 299, Rome, Italy
3 FEDERCHIMICA, Federazione Nazionale dell'Industria Chimica, Via Giovanni da Procida 11, Milan, Italy
4 POLIMI, Politecnico di Milano, Dipartimento di Elettronica e Informazione, Piazza Leonardo da Vinci 32, Milan, Italy
5 KM, KnowledgeMiner Software Frank Lemke, Duererstrasse 40, Panketal, Germany

Objective

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

to EVALUATE and VALIDATE existing NON-TESTING METHODS (NTM) for their application according to REACH needs

The Identification of CRITERIA for Models Evaluation

ANTARES has the main target to analyze the use of NTM in accordance to REACH, and to identify suitable methods.

The study is organized as follows:

- to identify relevant criteria for comparing QSAR methods.
A list of criteria has been established. They are divided into *main* (see *Table 1*) and *additional criteria*.
- to set a score for each criterion according to its importance.
- to identify available QSAR models which could be used for REACH.
- if available, to rank different models for the same endpoint, using the proposed scoring system.
- for equally scored models to evaluate also the additional criteria.

Table 1 : the main criteria for model validation

NAME	DESCRIPTION	SCORE
1. DATA QUALITY	To consider if the data set is the best quality for a specific endpoint.	0-3
2. NUMBER OF CHEMICALS	To consider the number of compounds.	0-3
3.DEScriptors/FRAGMENTS	To give preference to models where explicit descriptors/fragments are defined.	0-3
4. EXPLICIT AND VERIFY THE ALGORITHM	To give preference to models where explicit algorithm is defined.	0-3
5. APPLICABILITY DOMAIN	Description of the AD of the model. Method used to assess the AD. Limits of AD.	0-3
6. PERFORMANCE	Statistical description.	0-3
7. VALIDATION	Internal and external validation.	0-3
8. OUTPUT	To explicit its format, to verify it and to test the comprehension for the user. To give preference to models where input is clearly defined, and how to use the results for REACH is explicated.	0-3
9. COST	To give preference to models which are less expensive.	0-3

Example of the Application of Criteria for Some Endpoint

ENDPOINTS	Data quality	number	descriptors	algorithm	AD	Performance	validation	output	cost
7.2. Melting/freezing point	3	0	3	3	0	3		3	3
7.3. Boiling point	3	2	3	3	0	3		3	3
8.3. Skin sensitisation	3	1	3	3	2	3	3	3	3
8.9.1. Carcinogenicity study	3	2	3	3	2	3	3	3	3
9.1.1. short-term toxicity testing on invertebrates (preferred species Daphnia)	3	1	3	2	2	2	2	3	3
9.1.3. short-term toxicity testing on fish	3	2	3	2	2	2	1	3	3
9.3.2. Bioaccumulation in aquatic species, preferably fish	3	2	3	3	3	2	2	3	3

Table 3 : Global overview of models characteristics for some selected endpoints

- On the basis of the criteria (*Table 1*), for a set of endpoints (from *Table 2*) we scored the models.
- This study will be applied to all endpoints to identify the most useful QSAR models.
- Then, we will evaluate read across on a set of selected cases, to evaluate also this approach.
- NTM will be validated using new chemicals.

- no suitable models about the specified endpoint;
- + some suitable models about the endpoint;
- ++ it is possible to find a certain number of models concerning the specified endpoint.

YELLOW: endpoints belonging to physical chemical group;
ORANGE: to toxicological properties;
BLUE: to ecotoxicological properties;
GREEN: to environmental properties.

The Model Availability

On the basis of the set of the identified criteria it is possible to analyze all endpoints. Not all models are fully representative of REACH endpoints. For instance, for reproductive toxicity models exist, which however do not completely fit with the characterization of the endpoint, as reported using classical methods.

ENDPOINTS	MODELS
7.1. State at 20°C and 101,3 kPa	-
7.2. Melting/freezing point	++
7.3. Boiling point	++
7.4. Relative density	+
7.5. Vapour pressure	++
7.6. Surface tension	+
7.7. Water solubility	++
7.8. Partition Coefficient n-octanol/water	++
7.9. Flash-point	+
7.10. Flammability	+
7.11. Explosive properties	-
7.12. Self-ignition temperature	-
7.13. Oxidising properties	-
7.14. Granulometry	-
7.15. Stability in organic solvents ...	-
7.16. Dissociation constant	++
7.17. Viscosity	+
8.1. Skin irritation or skin corrosion	
8.1.1. In-vivo skin irritation	+
8.2. Eye irritation	
8.2.1. In-vivo eye irritation	+
8.3. Skin sensitisation	++
8.4. Mutagenicity	
8.4.1. In-vitro gene mutation study in bacteria	++
8.4.2. In-vitro cytogenecity or micronucleus study in mamm. cells	-
8.4.3. In-vitro gene mutation study in mammalian cells	-
8.4.4. In-vivo mutagenicity study	+
8.5. Acute toxicity	
8.5.1. Acute toxicity - by oral route	++
8.5.2. Acute toxicity - by inhalation	+
8.5.3. Acute toxicity - by dermal route	-
8.6. Repeated dose toxicity	+
8.6.1. Short-term repeated dose toxicity (28 d)	+
8.6.2. Sub-chronic toxicity study (90 days)	+
8.6.3. A long-term repeated dose toxicity (> 12 m)	-
8.7. Reproductive toxicity	++
8.7.1. Screening for reproductive/developmental toxicity	-
8.7.2. Pre-natal developmental toxicity study	-
8.7.3. Two-generation reproductive toxicity study	-
8.8. Toxicokinetics	++
8.8.1. Assessment of the toxicokinetic	-
8.9.1. Carcinogenicity study	++
9.1. Aquatic toxicity	
9.1.1. short-term toxicity testing on invertebrates (Daphnia)	++
9.1.2. Growth inhibition study aquatic plants (Algae preferred)	+
9.1.3. short-term toxicity testing on fish	++
9.1.4. Activated sludge respiration inhibition testing	+
9.1.5. Long-term toxicity testing on invertebrates (preferred Daphnia)	+
9.1.6. long-term toxicity testing on fish	+
9.1.6.1. Fish early-life stage (FELS) toxicity test	-
9.1.6.2. Fish short-term toxicity test on embryo and sac-fry stages	-
9.1.6.3. Fish juvenile growth test	-
9.2. Degradation	
9.2.1. Biotic	
9.2.1.1. Ready biodegradability	++
9.2.1.2. Simulation testing on ultimate degradation in surface water	-
9.2.1.3. Soil simulation testing	-
9.2.1.4. Sediment simulation testing	-
9.2.2. Abiotic	
9.2.2.1. Hydrolysis as a function of pH	+
9.2.3. Identification of degradation products	+
9.3. Fate and behaviour in the environment	
9.3.1. Adsorption/desorption Screening	+
9.3.2. Bioaccumulation in aquatic species, preferably fish	++
9.3.3. Further information on adsorption/desorption	-
9.3.4. Info on the environ. fate and behaviour of the substance	-
9.4. Effects on terrestrial organisms	
9.4.1. short-term toxicity to invertebrates	-
9.4.2. Effects on soil micro-organisms	-
9.4.3. short-term toxicity to plants	-
9.4.4. Long-term toxicity testing on invertebrates	-
9.4.6. Long-term toxicity testing on plants	-
9.5.1. Long-term toxicity to sediment organisms	-
9.6.1. Long-term or reproductive toxicity to birds	-

