QSAR models for aquatic toxicity of triazoles and benzo-triazoles: WP3 results within the FP7 European Project CADASTER

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INTRODUCTION & OBJECTIVES

Triazoles and benzotriazoles (BTAZs) are potentially hazardous chemicals that adversely affect humans and other non-target species, and are on the list of substances of very high concern (SVHC) in the European regulation of chemicals REACH. BTAZs are synthetic molecules used in various industrial processes (to obtain pharmaceuticals and agricultural products), and have a wide application as anti-cancerous, cleaning agents for textiles, flame retardants, photographic emulsions, etc. Furthermore they are abundantly used as components of liquid deicing agents for aircraft and airport runways. Because of their wide use they have been found distributed throughout the environment, mainly in water compartments. The amount of experimental data available for these molecules is insufficient for a comprehensive understanding of their environmental and toxicological behavior and they have been included among the four classes of chemicals studied in the European FP7 Project CADASTER (Case studies on the Development and Application of In Situ Techniques for Environmental hazard and Risk assessment) [1].

Objectives:

- Development of QSAR models, for different modeling approaches, for the three key organisms for the aquatic ecosystem (Algae, Daphnia and Fish), in order to define the potential aquatic toxicological profile of BTAZs. (Deliverable 3.5)
- Definition of Daphnia-Fish Interspecies Quantitative Correlation with a QAR approach.
- Future development of consensus models, based on WP3 results, for the aquatic toxicity of BTAZs. (Deliverable 3.6)

GENERAL MATERIALS & METHODS

- Endpoint: EC50, 96hr.
- External validation on different prediction sets: external parameters are related to split models

ALGAE TOXICITY

### Partner N Obj Descriptors N Descriptors R Q2 0.1 RMSErr. RMSEp QOut. CCC

| Partner | N Obj | Descriptors N Descriptors R | Q2 | 0.1 RMSErr. RMSEp QOut. CCC |
|---------|-------|-----------------------------|-----|--------------------------|------------------|
| UI      | 78 (28 BTAZ) | DRAGON 5.5, PaDEL | 2.2 5 0.78-0.80 0.79-0.79 0.48-0.51 0.71-0.87 * 0.83-0.93 |
| NL      | 20 DRAGON 6.0 | 7.27-0.08 0.86-0.54 - - |
| NL      | 10 DRAGON 6.0 | 0.94-0.91 0.98-0.98 0.94-0.98 0.94-0.98 |
| HMGU    | 76 (28 BTAZ) | ChemAxon | 0.63-0.63 0.68-0.68 0.60-0.60 0.97-0.97 |
| IDEA    | 75 (30 BTAZ) | DRAGON 5.5 | 0.83-0.80 0.80-0.81 0.58-0.60 0.46-0.49 0.77-0.79 * 0.89-0.93 |

- Endpoint: pEC50, 96hr.
- External validation on different evaluation set (EV, n=18 BTAZ)

FISH TOXICITY

### Partner N Obj Descriptors N Descriptors R Q2 0.1 RMSErr. RMSEp QOut. CCC

| Partner | N Obj | Descriptors N Descriptors R | Q2 | 0.1 RMSErr. RMSEp QOut. CCC |
|---------|-------|-----------------------------|-----|--------------------------|------------------|
| UI      | 78 (28 BTAZ) | DRAGON 5.5, PaDEL | 2.2 5 0.78-0.80 0.79-0.79 0.48-0.51 0.71-0.87 * 0.83-0.93 |
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- Endpoint: pLC50, 96hr.
- External validation on different prediction sets: external parameters are related to split models

UI PaDEL model

- pLC50 = 2.486 x 0.367 VP-1 – 0.047 SHBint2 - 0.312 maxHaaCH
- 94% interpolated predictions

UI ECOQSAR comparisons

- Predicted data, derived from the UI local models here proposed for aquatic toxicity of BTAZs, were compared with those obtained by the freely available tool ECOQSAR (9 triazoles included). The accuracy in toxicological predictions and UI ECOQSAR models was compared by calculating the parameter RMSWE (range of different UI models).

REFERENCES

[1] CADASTER PANDA PROJECT - www.cadaster.eu

Conclusions and future work

- Different robust and externally predictive QSAR models have been developed by WP3 partners, with different modeling approaches, to predict the aquatic toxicity of BTAZs in Algae, Daphnia and Fish.
- Quantitative Activity-Activity Relationship (QAR) based on Interspecies Correlation, externally validated, has been developed by UI to predict Fish acute toxicity from Daphnia toxicity data.
- Consensus modeling approach will be applied for the aquatic toxicity of BTAZ, considering all the results obtained by WP3 partners. This work will be presented in the Deliverable 3.6.