ACUTE ORAL TOXICITY MODELING ACCOUNTING FOR MECHANISM AND TOXICOLOGICAL MODE OF ACTION

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Laboratory of Mathematical Chemistry

A.Detroyer et al.

INTRODUCTION

As part of its global strategy to develop and use non-animal alternative methods, a collaboration between L'Oréal R&I and OASIS LMC is ongoing to construct an in *silico* model for acute oral toxicity (AOT) classes of chemicals.

CHALLENGE

The challenge when developing an alternative method in the AOT area lies in the combination of the numerous mechanisms of action and considerations of the complexity of the chemical space covered by industrial compounds.

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DATA

The training set of the current version of the AOT modeling system consists of 2580 public domain chemicals with observed LD50 data (Test duration – 24 hours).

The chemicals of the training set belong to 50 chemical classes:
1. *alpha, beta* - Unsaturated aldehydes – 22 chemicals
2. Acrylic acid esters – 51 chemicals
3. Coumarins and chromenes – 96 chemicals
……
16. Imidazoles and Triazoles with benzofuranyl residues – 94 chemicals
17. Isocyanates and isothiocyanates – 32 chemicals…….

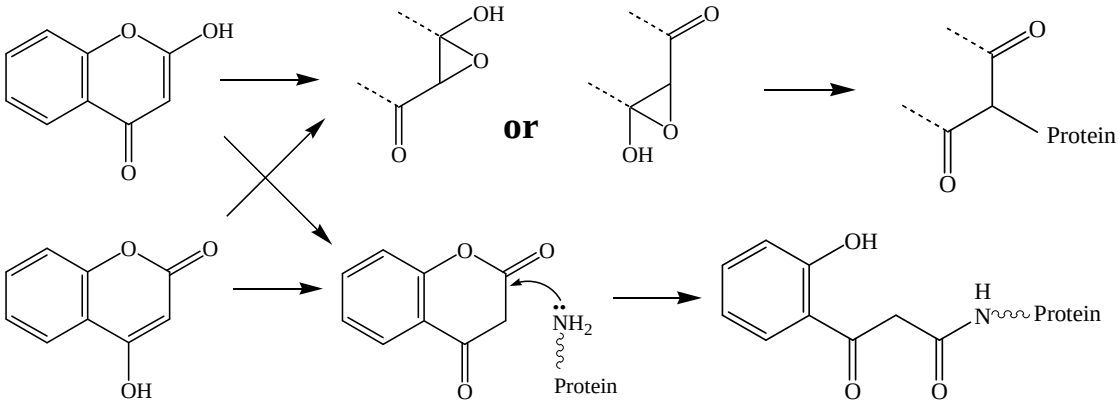
PROPOSED MODELLING : 1- CATEGORY APPROACH

Chemicals are grouped in the same acute toxicological category based on their known or hypothetical interaction mechanism and toxicological mode of action (assembled in a knowledge base).

Example : Coumarins and chromenes

Mode of action – Anticoagulants inhibiting the recycling of vitamin K from its (inactive) metabolite, vitamin K-2,3-epoxide.

Mechanism of action (hypothesized) – epoxide of lactone group (activated by β-carbonyl group)



PROPOSED MODELLING : 2- QSAR MODELS

Toxicological category

- Each toxicological category forms a local QSAR training set associated with similar functional groups.

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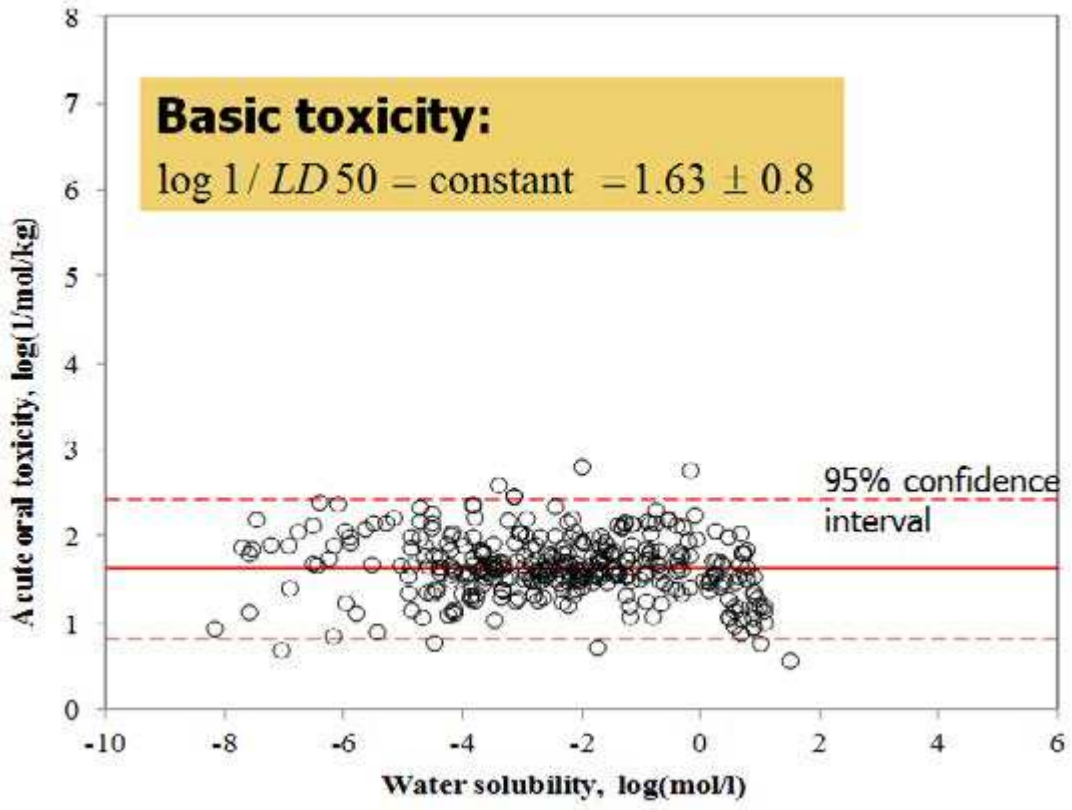
- Each toxicological category forms a local QSAR training set associated with similar functional groups.

- QSAR model according to the toxicological category's type of toxicity.

- a result of affecting the most basic functions of cells; characteristic of non-reactive chemicals acting by narcosis mechanism.

- a result of destroying critical processes of the cells or the whole organism due to enhanced chemical reactivity

BASIC TOXICITY FINDINGS



A result of affecting the most basic functions of cells; characteristic of non-reactive chemicals acting by narcosis mechanism.

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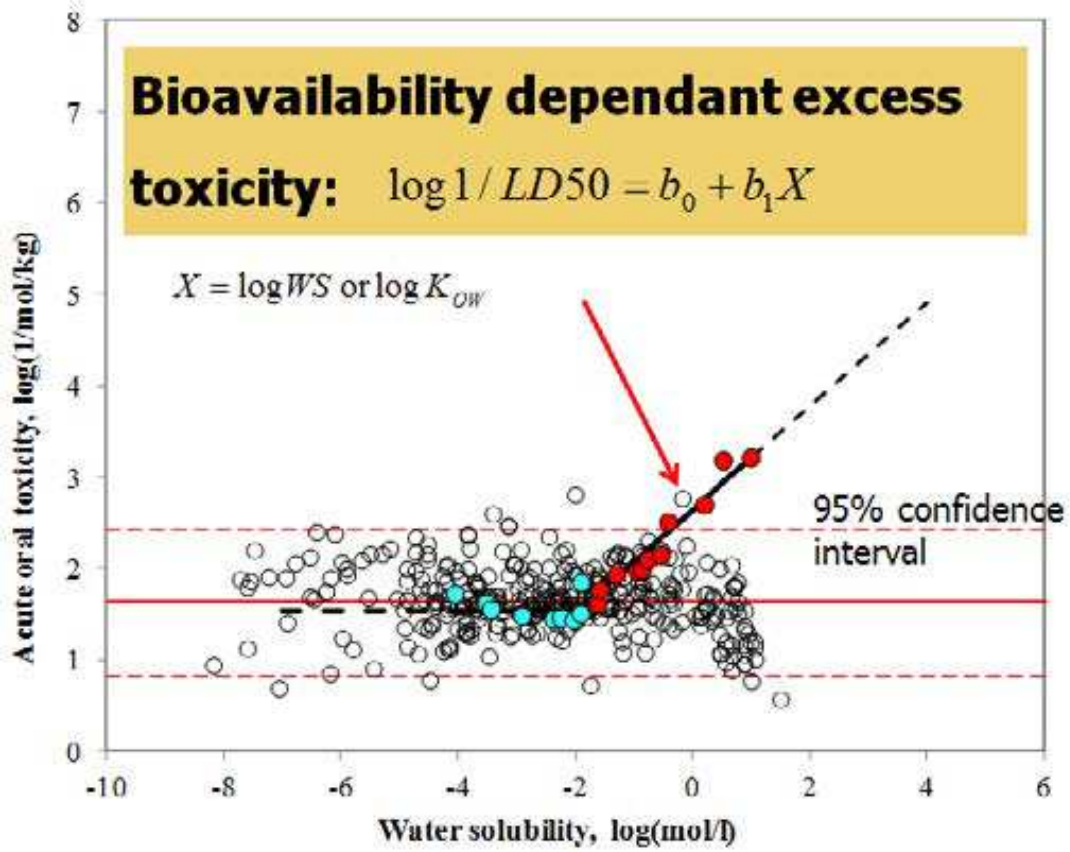
EXCESS TOXICITY FINDINGS



At lower solubility (estimated by WS or KOW) chemicals elicit basic toxicity. After reaching a certain solubility threshold a positive AOT vs. “bioavailability” relationship is observed.

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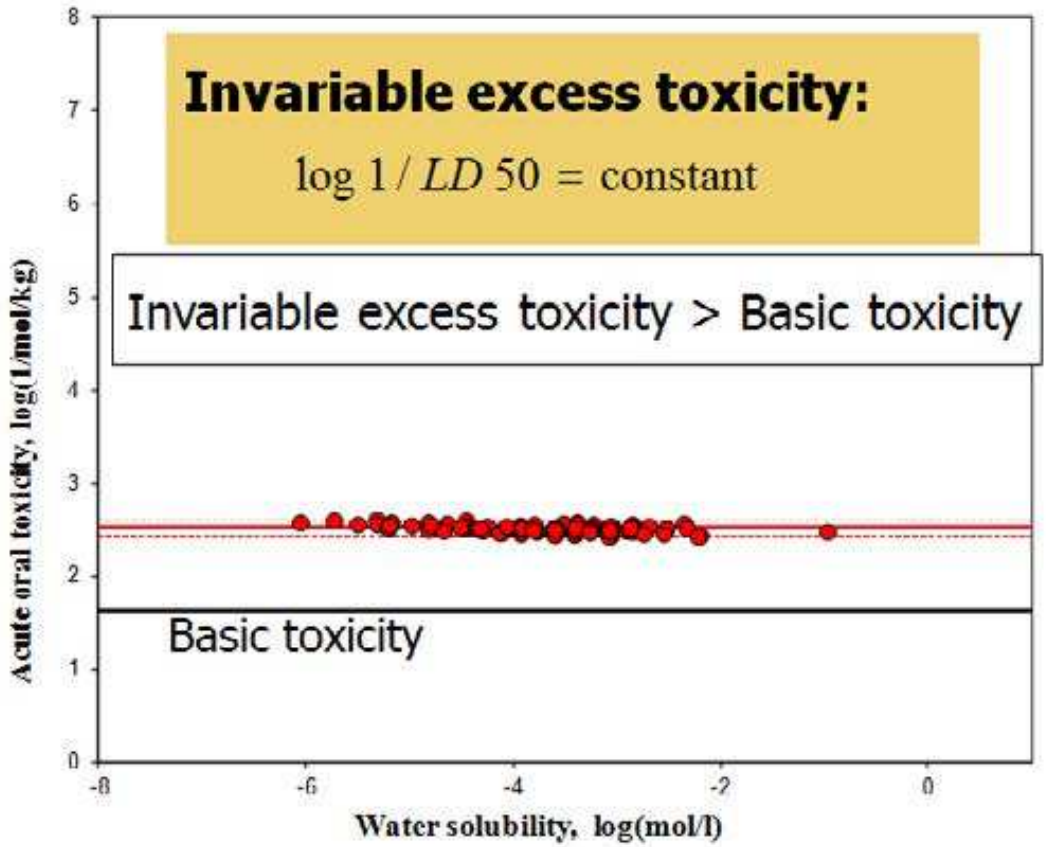
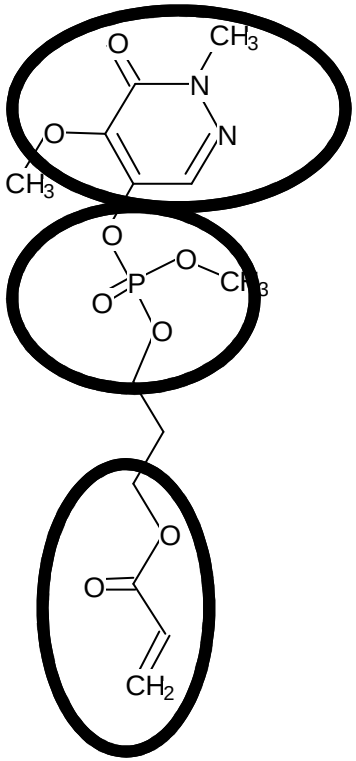


A constant excess toxicity is observed within the studied range of "bioavailability" due to the presence of reactive functionalities in chemicals.

AOT OF MULTIFUNCTIONAL CHEMICALS ?

Multifunctional target chemical



Profiler
Substituted pyridazinones: 4.96 log(1/mol/kg)
Maleimides: N/A
Methacrylic acid esters: N/A
Organophosphates: 4.70 log(1/mol/kg)
basic toxicity: N/A
Acrylic acid esters: 2.80 log(1/mol/kg)
…

$\log 1/LD_{50} = \max\{4.96;\ 4.70;\ 2.80\}$ **?**

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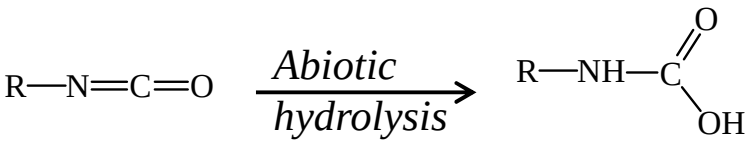
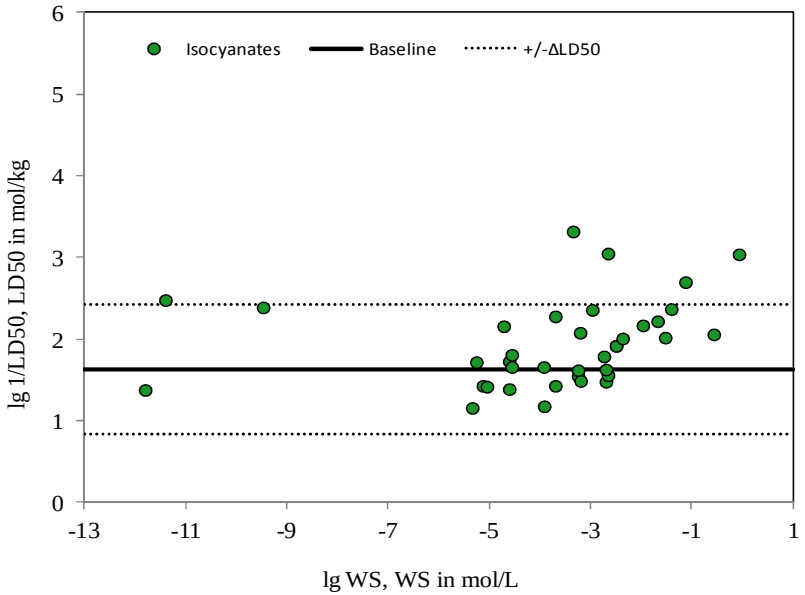
ADDING HYDROLYSIS SIMULATORS ?

Fast hydrolyzing chemicals having well known highly reactive groups which is a premise for significant excess toxicity have been analyzed :

Example by isocyanates:





Alteration of physical and chemical properties due to abiotic hydrolysis is expected to affect toxicity of chemicals including AOT.

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CONCLUSIONS

AOT model based on an original category approach

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model part of *in vitro/in silico* integrated AOT testing strategy ?

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CONCLUSIONS

Over 2500 chemicals grouped in over 76 toxicological categories (hypothetical chemical interaction mechanism and toxicological MOA).

AOT model based on an original category approach

Specific QSAR models according to each toxicological category's type of toxicity :

basic (minimum) toxicity ; invariable excess toxicity; bioavailability dependent excess toxicity

Add a simulator of the abiotic (biotic) hydrolysis of target chemicals.

Predictions are to be supported by mechanistic justification for MOA, example chemicals and an applicability domain indication.

To be implemented in the TIMES platform.

AOT challenge is complex (not all mechanisms known) : model part of *in vitro/in silico* integrated AOT testing strategy ?

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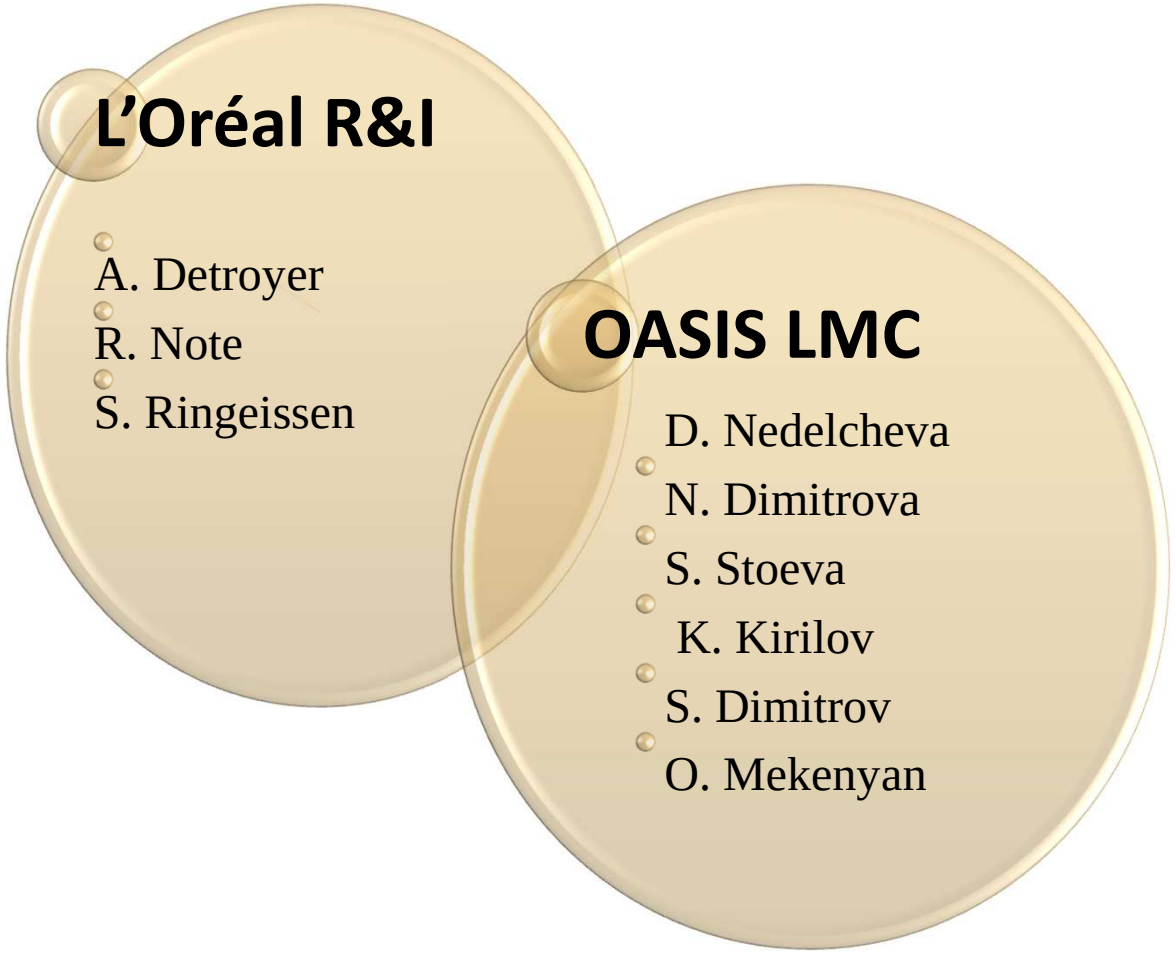
THANK YOU



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