Simple estimate of the influence of competitive inhibition on PBTK based risk assessment

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Simple estimate of the influence of competitive inhibition on PBTK based risk assessment

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Background: In recent years, increased focus has been on the development of methods for assessing health risks caused by exposure to mixtures of chemicals from food and the environment. It has been recommended by international bodies to consider physiologically based toxicokinetic (PBTK) modelling for higher tier cumulative risk assessment of chemicals. Another important area for the use of PBTK is risk assessment of aggregate exposure via different routes (dietary, dermal, etc.).

Method: The competitive inhibition was examined in a binary PBTK model. As an example simulations for a mixture of the R- and S-enantiomers of the pesticide tebuconazole was examined.

Results: Simulations made at different single oral doses in rat showed only minimal effect of inhibition at doses up to 1 mg/kg bw (0.5 mg/kg bw of each enantiomer) (graph A). Effect of inhibition was seen after a single oral dose of 10 mg/kg bw (graph B), but not after corresponding dermal exposure (graph C). Internal dose levels were affected by inhibition after 100 mg/kg bw dermal exposure (graph D).

Model validation: Good agreement between experimental and simulated half-lives for R- and S-tebuconazole in rat and rabbit:

Species | Experiment, R/S tebuconazole | T_{1/2} (exp.) [1, 2] | T_{1/2} (pred.)
--- | --- | --- | ---
Rat | in vitro, with inhibition | 36 min. | 50 min.
Rabbit | in vivo, with inhibition | 104 min. | 111 min.

Conclusion: The simulations for the two binary mixtures indicate that it is not necessary to include inhibition at realistic exposure levels for humans, i.e. for exposure due to pesticide residues in food and for dermal exposure due to professional use.

Further readings:
http://www2.mst.dk/Udgiv/publications/2014/02/978-87-93178-08-3.pdf

Sources for ADME data used in the development of the PBTK models. Abbreviations: JMPR: Joint FAO/WHO Meeting on Pesticide Residues. QSAR: Quantitative Structure Activity Relationship.

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--- | --- | --- | ---
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Dietary intake for an average consumer in the Danish population and a consumer eating ≥ 550 g fruit and vegetables a day.

Estimated occupational exposure by industrial wood treatment, brushing or spraying fields (data from Danish EPA).

0.013 – 0.026 μg tebuconazole/kg bw/day [3] 4.2 – 28 μg tebuconazole/kg bw/day [4]