Excess Toxicity of Organic Electrophiles in the Tetrahymena pyriformis Bioassay Informs about Reactive Modes of Action

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ITS IN REACH

REACH is the European Directive on the Registration, Evaluation, Authorisation, and Restriction of Chemicals. It requires evaluation and classification of all chemicals with more than 1 tonne/year production or import toward their toxicological and ecotoxicological effects.

ITS Integrated testing strategies (ITS) use non-test and test information in a weight-of-evidence approach to meet the REACH requirements while following the 3 Rs principle (see on the right) concerning animal welfare. This is achieved by context- and substance-specific approaches using alternative methods (in vitro, in vivo, in silico, omics, TTC). There is still a lack of suitable methods and models, calling for targeted research and development in this field.

The 3 Rs

- Replacement
- Reduction
- Refinement

Alternative Methods

In vitro

This work

In silico

In chemico

MATERIALS AND METHOD

How can we measure the toxicity of quinone derivatives without using animals?

Narcosis baseline: \[ \log EC_{50} [M] = a \cdot \log K_{ow} + b \]

\( T_e > 1 \) \rightarrow high narcosis level

\( T_e < 1 \) \rightarrow low narcosis level

\( T_e = 1 \) \rightarrow narcosis level toxicity

\( T_e = 2 \) \rightarrow excess toxicity

\( T_e > 2 \) \rightarrow high excess toxicity

To assess the hazard of benzoquinones and hydroquinones and to unravel structural alerts to predicting reactive toxicity

CONCLUSIONS

In vitro toxicity screening as part of ITS

- Provides opportunities as efficient and information-rich non-animal ITS tool:
  - Rapid, cheap and sufficient analysis of toxic effects of organic electrophiles
  - Determination of EC50 (effect concentration 50%)
  - Evaluation in terms of excess toxicity vs. baseline narcosis
  - Analysis with emphasis on mechanisms of action

In this work we present an easy method for profiling organics with respect to excess toxicity and underlying mechanisms of action

REFERENCES

1) Von der Ohe PC et al. 2005. Structural alerts - a new classification model to discriminate excessive toxicity from non-acute effect levels of organic compounds in the acute daphnia assay. Chem. Res. Toxicol. 18: 204-215

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