In vivo Genotoxicity Models in TIMES

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Introduction

In vivo systems provide a better model for understanding the toxic potential of xenobiotics compared with *in vitro* systems since they account for substrate channelling effect which together with highly pronounced Phase II reactions hinder the generated metabolites from damaging DNA in target cells.

Aim

The aim of this work is to build mechanistically based *in vivo* genotoxicity models which accounts for metabolic activation and detoxification of chemicals.

Background

Three components are implemented in the *in vivo* genotoxicity models namely:

- ***a reactivity component:*** which accounts for interactions of chemicals with macromolecules;
- **an *in vivo metabolic simulator:*** which represents an electronically designed set of structurally generalized, hierarchically arranged in vivo biotransformation reactions;
- ***in vivo detoxification pathways:*** which consist of expertly defined sequences of metabolic transformations assumed to be involved in the detoxification of in vitro positive compounds.

Reactivity component

- Based on structural alerts (molecular fragments), which account for DNA and/or protein interactions.
- The predicted positive outcome is supported by an expertly assigned mechanistic justification.

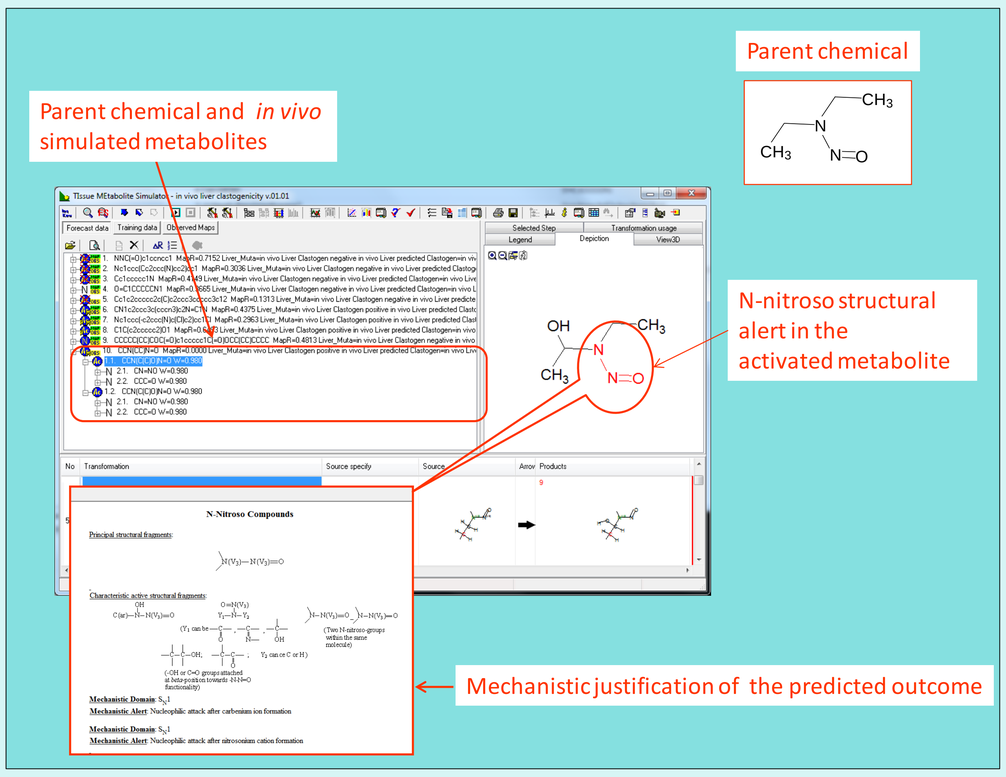

Figure 1. *In vivo* simulated metabolism of *N-nitrosodiethylamine.*

In vivo detoxification logic

In vivo, enzymes are aggregated in multi-enzyme complexes which protect cells from reactive metabolites by shuttling intermediates between consecutive enzymes.

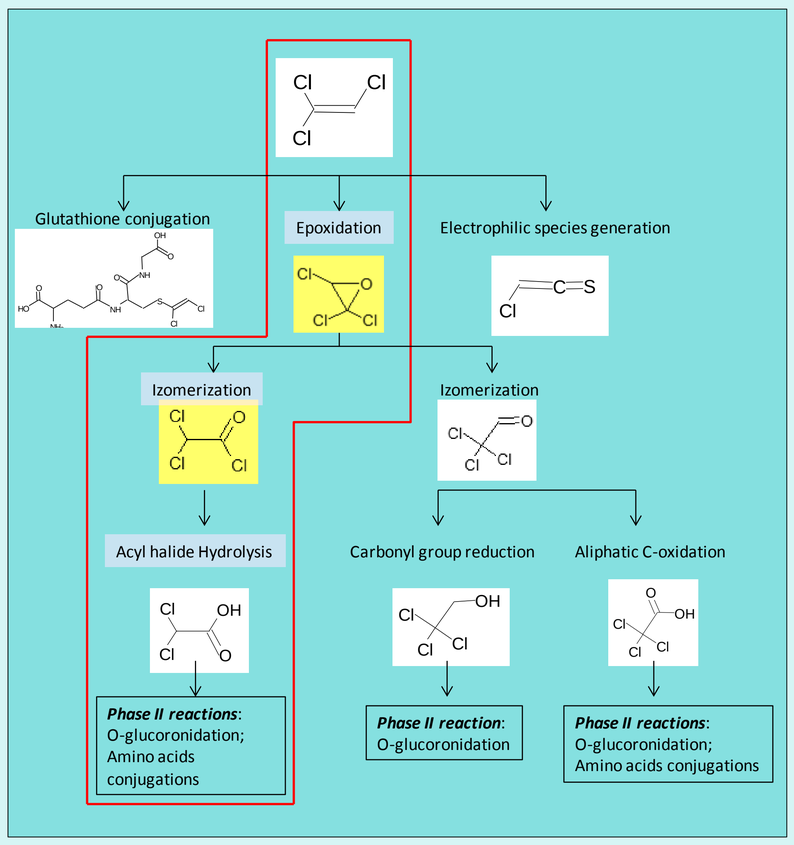

Figure 2. *In vivo* simulated metabolic activation and detoxification of Trichloroethylene. The activated metabolites (highlighted in yellow) are detoxified in the liver.

Conclusions

Three *in vivo* genotoxicity models are built within the TIMES platform.

- ***In vivo* Liver Clastogenicity model**
  - Identifies chemicals that could cause structural and numerical chromosomal aberrations in liver;
  - Training set consists of chemicals with integrated clastogenicity outcomes from the liver CA assay and liver micronucleus test.
- ***In vivo* Liver Genotoxicity model**
  - Identifies chemicals that could cause single- and double-strand breaks;
  - Based on an indicator test for genotoxicity (Comet assay), which detects long length DNA damage (20-30 nucleobases).
- ***In vivo* Micronucleus formation model**
  - Identifies chemicals that could cause structural and numerical chromosomal aberrations in bone marrow;
  - Based on data from the Mammalian Erythrocyte Micronucleus Test (OECD 474).

Acknowledgments

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This poster could be downloaded from : **http://oasis-lmc.org/news/events/qsar2014.aspx**