Modeling Mutagenicity and Carcinogenicity Accounting for Metabolic Activation and Detoxification of Chemicals

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Goals

❖ To predict *in vitro* mutagenicity accounting for metabolic activation of parent chemicals.

❖ To use the difference between *in vitro* and *in vivo* metabolism to inform the development of *in vivo* models which account for metabolic activation and detoxification.

❖ To bin chemicals into mutagenicity categories and to assess their performance in predicting genotoxic carcinogenicity.

The concept

❖ Basic difference between *in vitro* and *in vivo* genotoxicity effects is due to the following:

➢ *In vitro* (S9) generated metabolites are freely available to interact with DNA and/or proteins thus causing positive genotoxicity effects.
➢ *In vivo* generated metabolites are organized as a result of enzyme-catalyzed substrate channeling which prevents their potential positive genotoxicity effect in macromolecules.

❖ The substrate channeling may explain the *in vivo* detoxification of chemicals which could otherwise lead to a positive outcome *in vitro*.

❖ Combinations of positive *in vitro* and *in vivo* mutagenicity results could provide reliable predictions of genotoxic carcinogenicity.

Predicting in vitro mutagenicity

❖ TIMES system allows the mutagenicity of chemicals to be investigated by combining toxicokinetics and toxicodynamics into the same modeling platform.

❖ Hierarchically ordered transformations are used to reproduce observed *in vitro* metabolism of large number of chemicals.

❖ Parent chemicals and their metabolites are analyzed for reactivity to DNA and/or proteins by using structure activity rules.

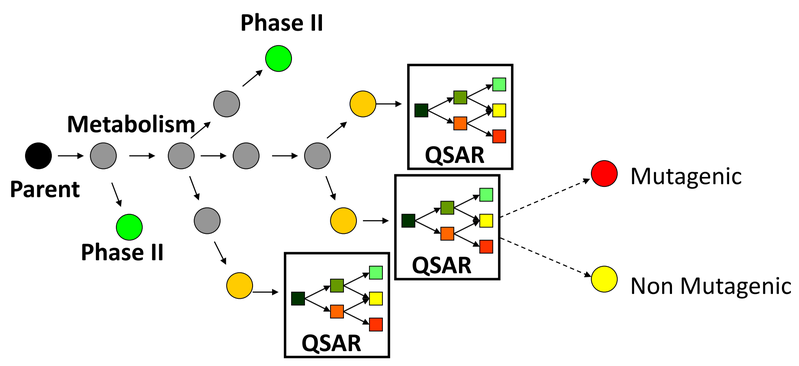

Figure 1. Predicting mutagenicity accounting for metabolic activation of chemicals

Predicting in vivo mutagenicity

❖ *In vivo* mutagenicity models are derived based on:
  ❖ DNA and protein binding reactivity
  ❖ *in vivo* metabolism simulator
  ❖ detoxification pathways

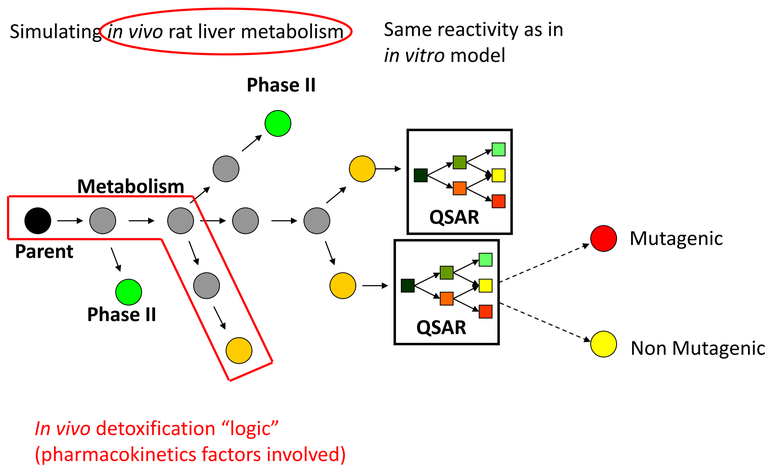

Figure 2. Predicting mutagenicity accounting for metabolic activation and detoxification

Predicting carcinogenicity

❖ Three categories of mutagens are defined based on logically ANDed combination of *in vitro* and *in vivo* mutagenicity assays.

❖ Mutagenicity categories are used to predict positive genotoxic carcinogenicity:

Combination of *in vitro* and *in vivo* tests	Defined Category mutagens	Sensitivity to positive carcinogenicity, (%)	Rate of false positive carcinogens, (%)	Total # chemicals
DLT	Category 1	82 (37/45)	18 (8/45)	45
Ames and TRM	Category 2	91 (10/11)	9 (1/11)	11
Ames and MNBM	Category 2	89 (17/19)	11 (2/19)	19
CA and CA	Category 2	100 (13/13)	-	13
CA and MNBM	Category 2	92 (36/39)	8 (3/39)	39
Ames and Comet	Category 3	87 (13/15)	13 (2/15)	15
CA and Comet	Category 3	88 (30/34)	12 (4/34)	34

Table 1 . Relating mutagenicity categories with genotoxic carcinogenicity

❖ For predicting negative genotoxic carcinogenicity, a combination of mutagenicity assays with different test capacities should be used to encompass all genotoxic mechanisms involved in cancer formation:

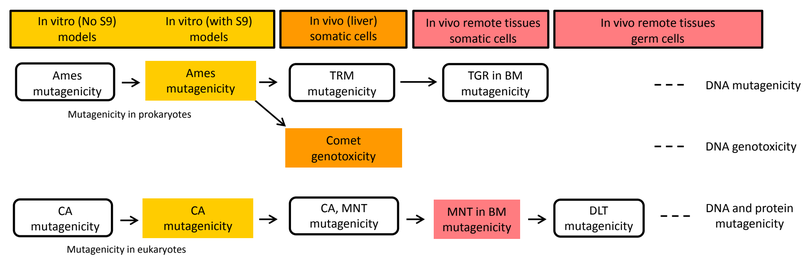

Figure 3. Combination of mutagenicity assays with different tests capacity

IATA for negative carcinogenicity

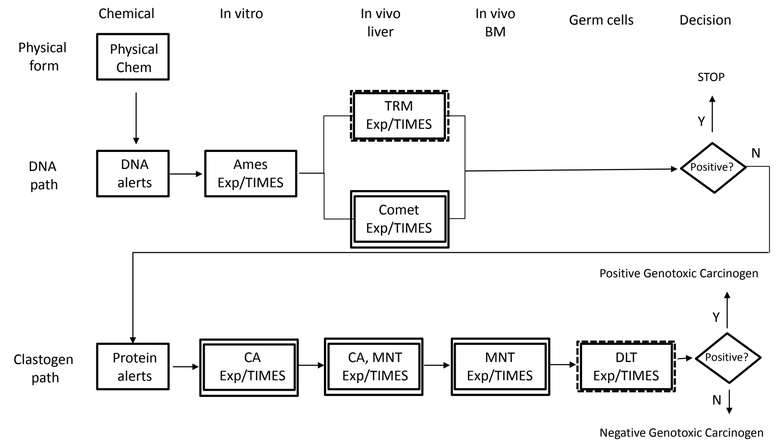

Figure 4. Integrated approach for testing and assessment of negative carcinogenicity

Acknowledgments

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