OASIS TIMES Skin sensitization model

Predicting pre- and pro- electrophilic activation of chemicals in skin sensitization assessment

Laboratory of Mathematical Chemistry
University Prof. Assen Zlatarov, Bourgas, 2015

Outline

- TIMES Skin sensitization model
- Predicting skin sensitization in TIMES:
  - ✓ Mechanism of Skin sensitization
  - ✓ Main concept of the model
  - ✓ Simulators for (a)biotic transformations
  - ✓ Model reliability and mechanistic justification
- Summary

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TIMES Skin Sensitization model

Short description

TIMES Skin Sensitization (SS) model is an expert system describing **structure-toxicity** and **structure-metabolism** relationships through a number of transformations simulating skin metabolism and interaction of generated reactive metabolites with skin proteins.

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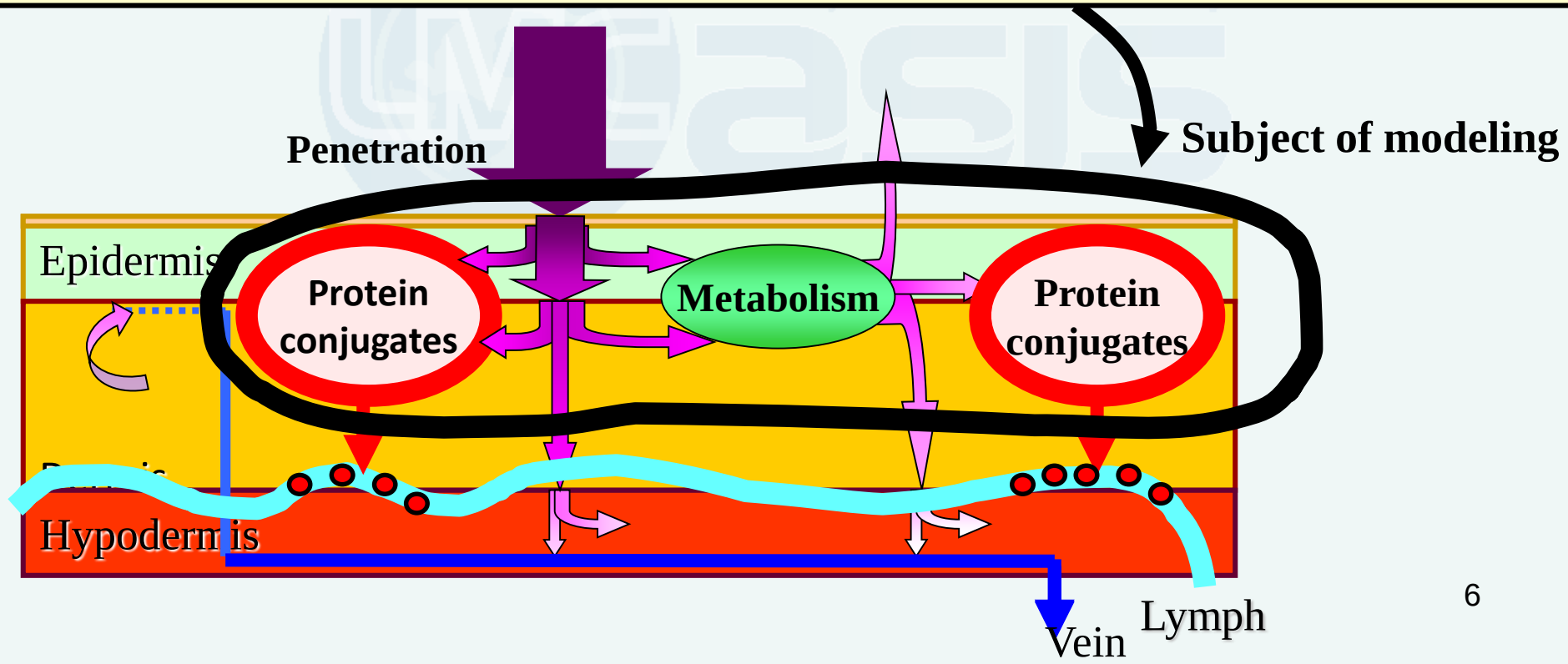
Predicting skin sensitization in TIMES

Mechanism of skin sensitization

Assumptions:

1. Chemicals always penetrate stratum corneum
2. Formation of protein conjugates is a premise for ultimate effect
3. Metabolism may play significant role in skin sensitization



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Predicting skin sensitization in TIMES

Main concept

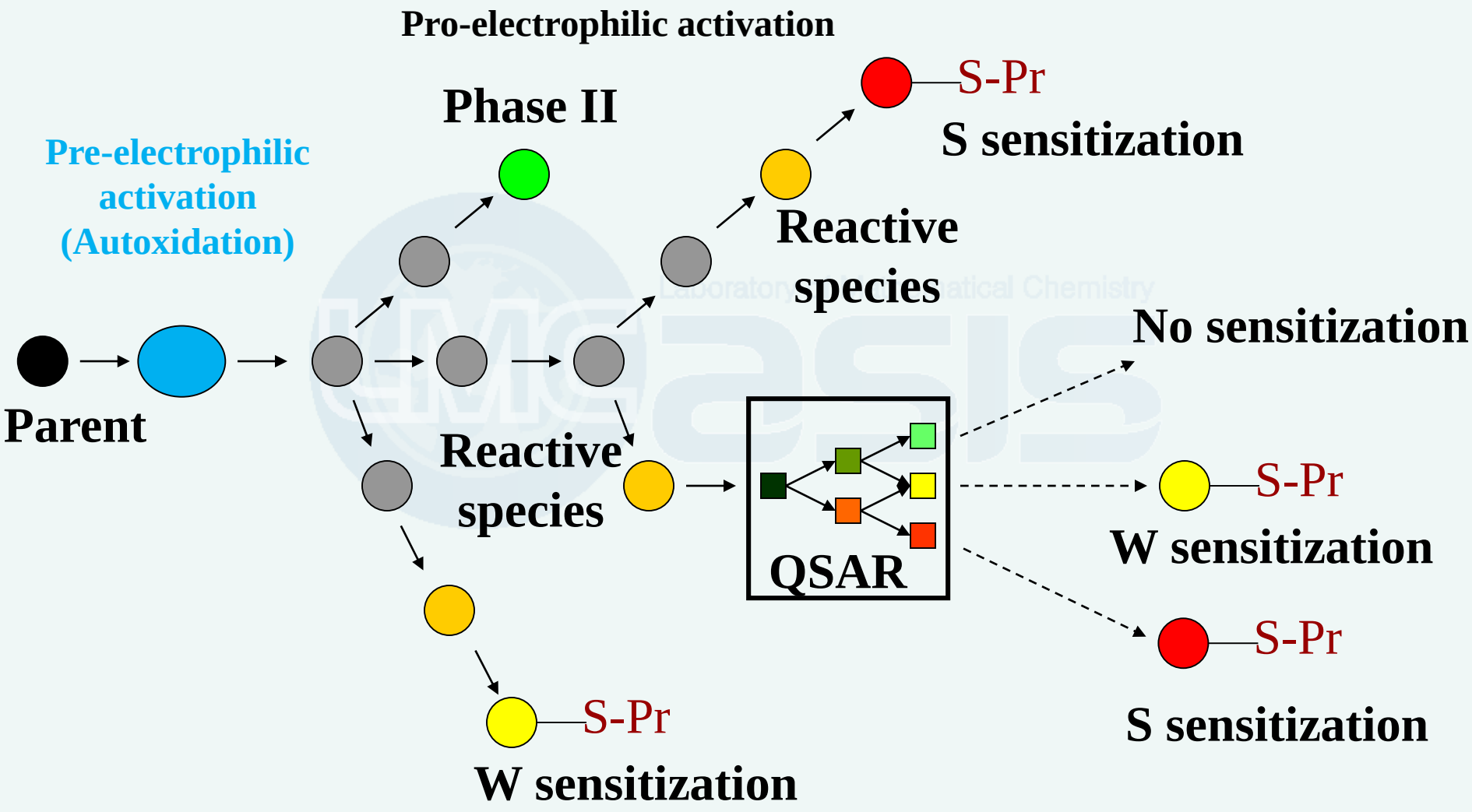
In order to predict skin sensitisation effect taking into account metabolic activation of chemicals in same platform are combined:

- ***Toxicokinetics*** – specific metabolism
  - ✓ Pre-electrophilic activation – Autoxidation reactions
  - ✓ Pro-electrophilic activation – *Phase I* and *Phase II* reactions
- ***Toxicodynamic*** – interaction with macromolecules

Dimitrov, et al., Skin sensitization: Modeling Based on Skin Metabolism Simulation and Formation of Protein Conjugates, *Internatational Journal of Toxicology*. 24, 189-204, 2005.

Predicting skin sensitization in TIMES

Basic scheme illustrating the model concept



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Predicting skin sensitization in TIMES

Simulators for (a)biotic transformations

LMC has published several papers where we shared our experience in the computerized management of metabolic data and the development of simulators of metabolism for predicting toxicity of chemicals.

SAR and QSAR in Environmental Research
2011, 1–20, iFirst

Taylor & Francis
Taylor & Francis Group

Simulation of chemical metabolism for fate and hazard assessment. I. Approach for simulating metabolism

S. Dimitrov[a], T. Pavlov[a], G. Veith[b] and O. Mekenyan[a]*

[a]*Laboratory of Mathematical Chemistry, University 'Prof. As. Zlatarov', Bourgas, Bulgaria;*
[b]*International QSAR Foundation, Two Harbors, MN, USA*

SAR and QSAR in Environmental Research
Vol. 23, Nos. 5–6, July–September 2012, 553–606

Taylor & Francis
Taylor & Francis Group

Simulation of chemical metabolism for fate and hazard assessment. V. Mammalian hazard assessment

O. Mekenyan*, S. Dimitrov, T. Pavlov, G. Dimitrova, M. Todorov, P. Petkov and S. Kotov

Laboratory of Mathematical Chemistry, University "Prof. As. Zlatarov", Bourgas, Bulgaria

Predicting skin sensitization in TIMES

Simulators for (a)biotic transformations

The toxicokinetic part of the TIMES-SS model is represented by two simulators:

- Abiotic Autoxidation (AU) simulator
- Skin metabolic (SM) simulator

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Simulators for (a)biotic transformations

- Abiotic Autoxidation (AU) simulator

  It represents a set of more than 260 generalized autoxidation molecular transformations developed on the basis of chemicals with documented AU pathways including *terpenes*, *simple aliphatic* and *polyethylene glycol ethers*, *aldehydes*, *aminophenols*, etc.

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Predicting skin sensitization in TIMES

Simulators for (a)biotic transformations

- Skin metabolic (SM) simulator consisting of 420 hierarchically ordered transformations based on empiric and theoretical knowledge and peer-reviewed by experts:
  - ✓ Non-enzymatic transformations such as Hydrolysis of salts, Formaldehyde releasing, etc.
  - ✓ Enzyme-mediated reactions (*Phase I and Phase II*) such as C-hydroxylation, Glucoronidation, etc.
  - ✓ Protein binding reactions (PBR) illustrating the covalent interactions of chemicals/metabolites with skin proteins
- Currently, the skin metabolic simulator has been upgraded and adjusted to simulate the documented *in vitro* metabolism of 151 chemicals

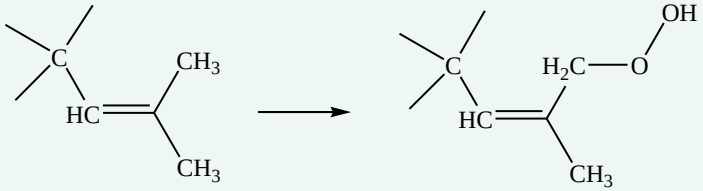
Predicting skin sensitization in TIMES

Simulators for (a)biotic transformations

Different types of principle transformations

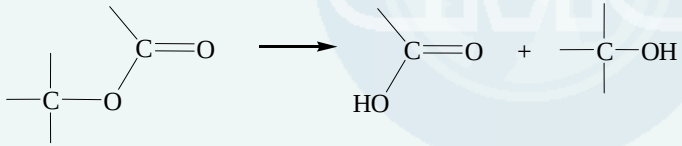
- **Autoxidation reactions**

  Allylic hydroperoxide formation



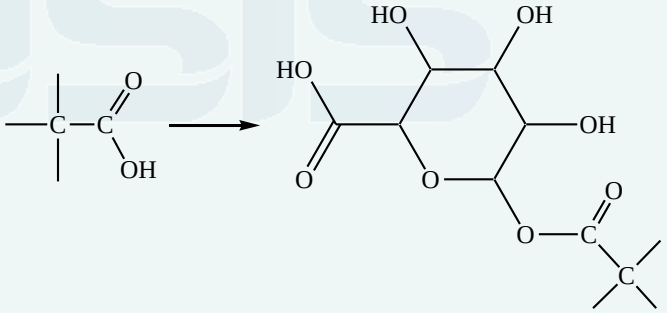
- **Phase I reactions**

  Ester hydrolysis



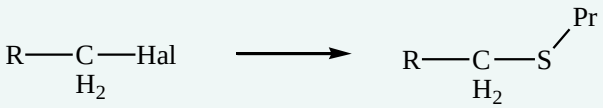
- **Phase II reactions**

  Glucoronidation



- **Proteins binding reactions**

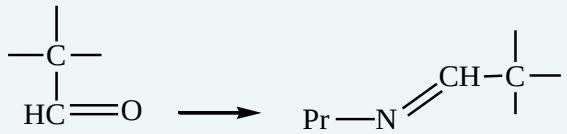
Nucleophilic substitution on halogenated C sp3 atom



R = -C≡C, -C≡N, -C=C, -C=S, -C=O, -NO_2

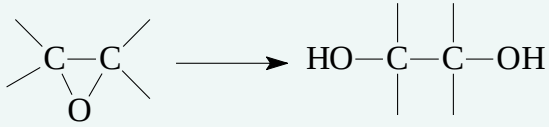
Hal = Cl, Br, I

Schiff base formation with aldehydes



Aliphatic C-oxidation

Epoxide Hydration



Epoxidation

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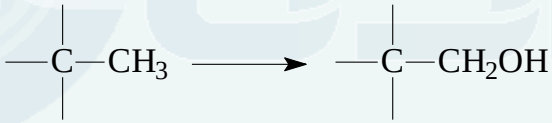

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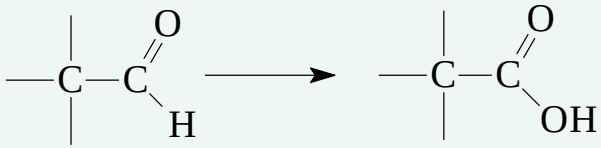
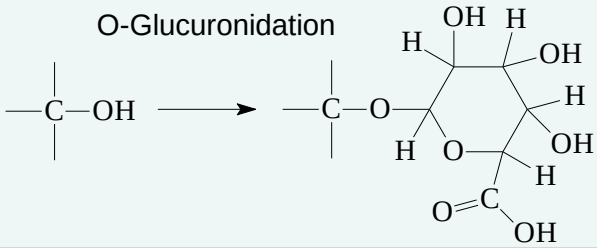


O-Glucuronidation



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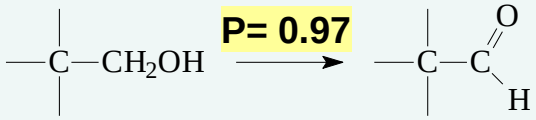

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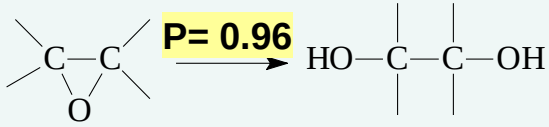

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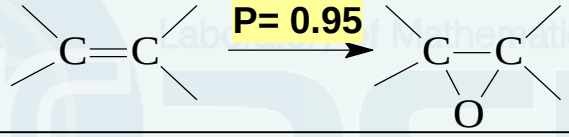

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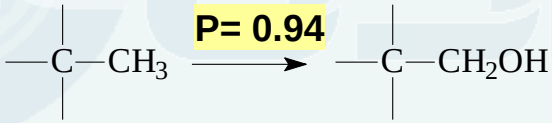

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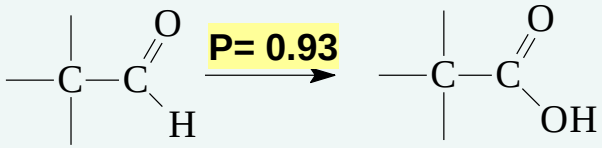

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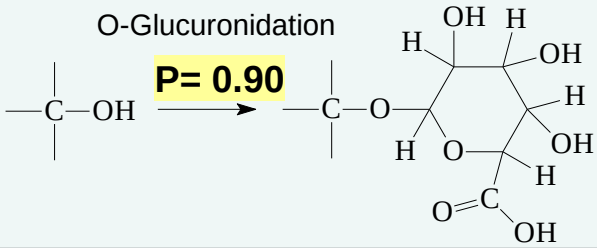
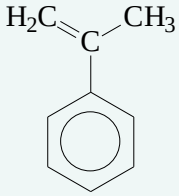


Substrate	Principle transformations	Metabolites

- Isopropenylbenzene



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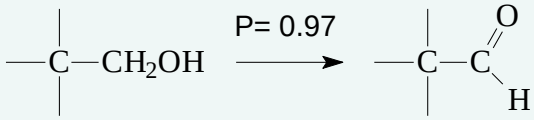

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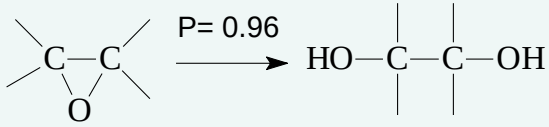

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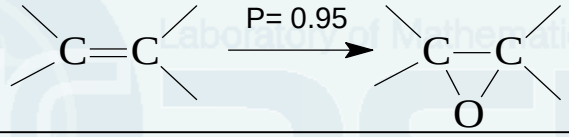

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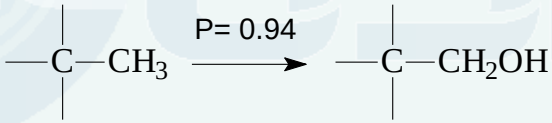

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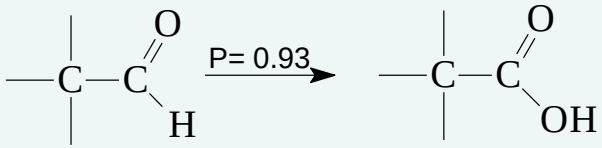

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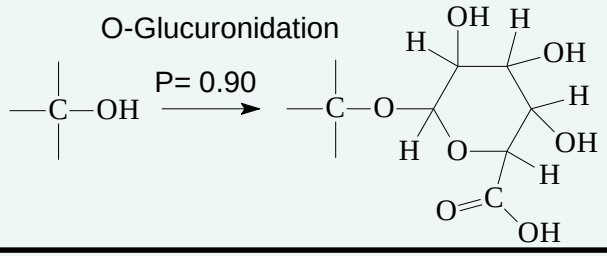
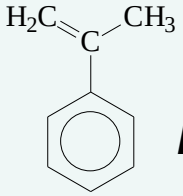


- Isopropenylbenzene



Match? - No!

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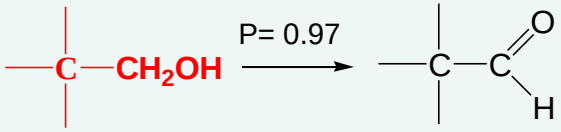

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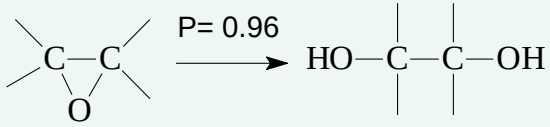

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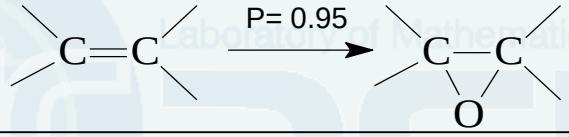

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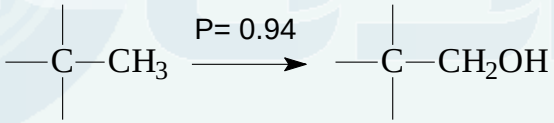

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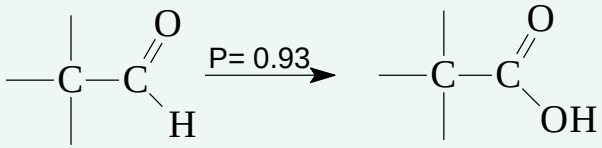
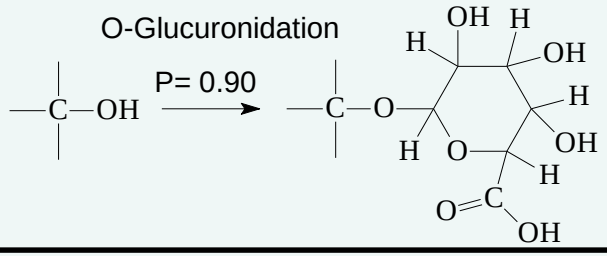


O-Glucuronidation



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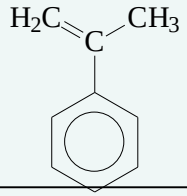

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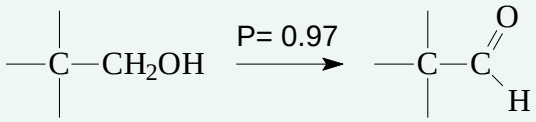

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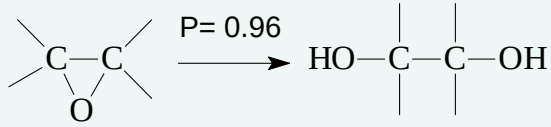
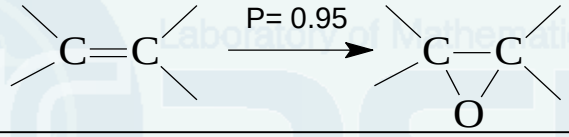


Epoxidation



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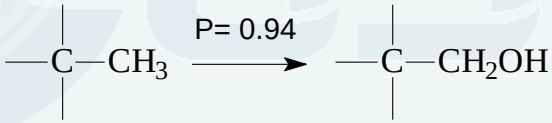

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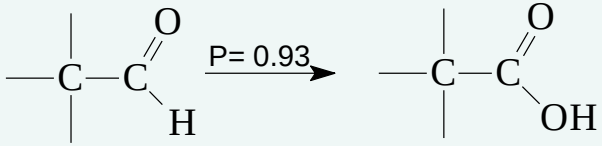
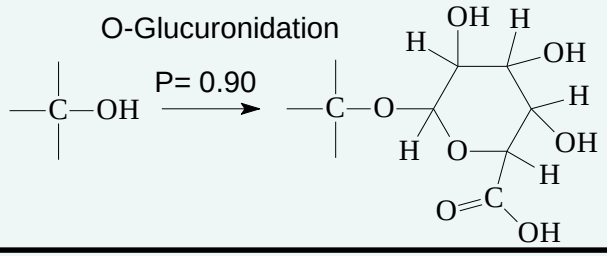
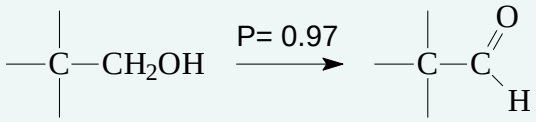


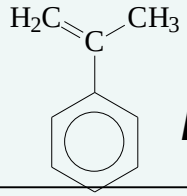
O-Glucuronidation



Substrate	Principle transformations	Metabolites

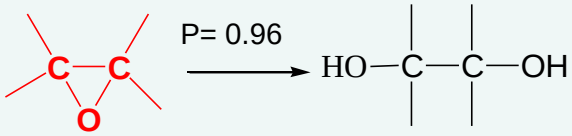
Aliphatic C-oxidation



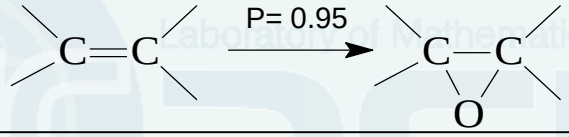


Match? - No!

Epoxide Hydration



Epoxidation



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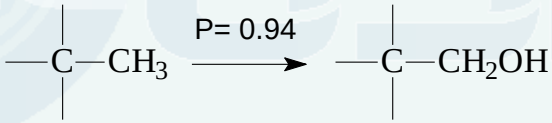

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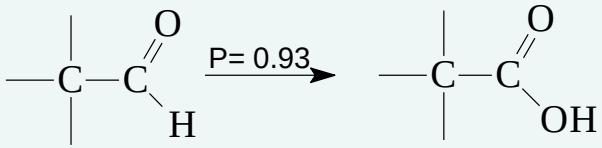
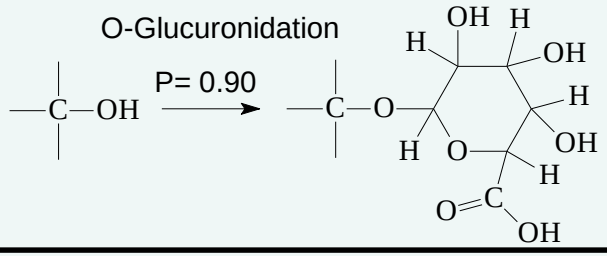
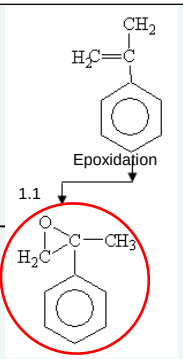


O-Glucuronidation



Generated map

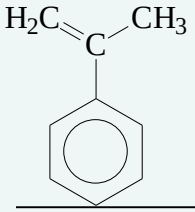


Aliphatic C-oxidation

P= 0.97

Epoxide Hydration

P= 0.96

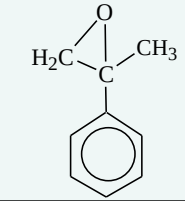


Match? - Yes!

Epoxidation

P= 0.95

RESULT



Aliphatic C-oxidation

P= 0.94

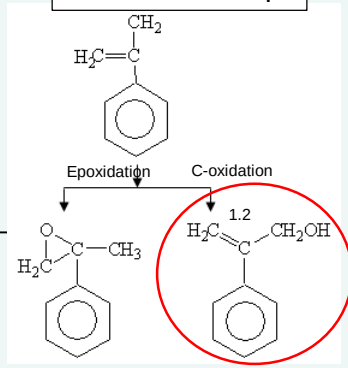
Aliphatic C-oxidation

P= 0.93

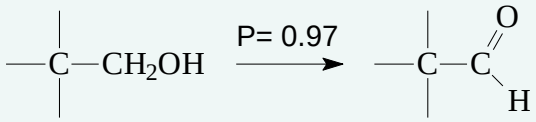
O-Glucuronidation

P= 0.90

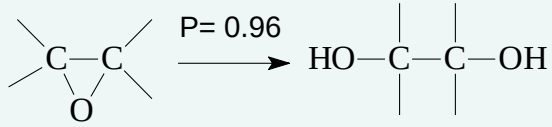
Generated map



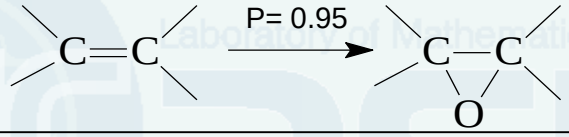
Aliphatic C-oxidation

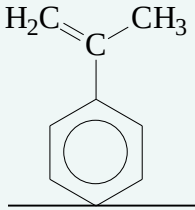


Epoxide Hydration



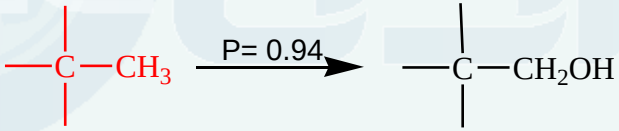
Epoxidation



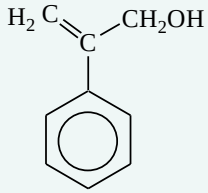


Match? - Yes!

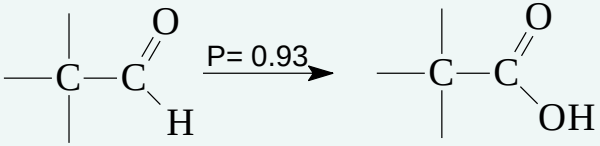
Aliphatic C-oxidation



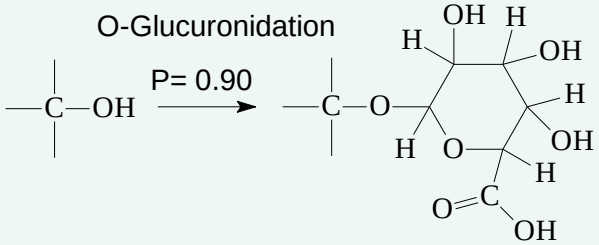
RESULT



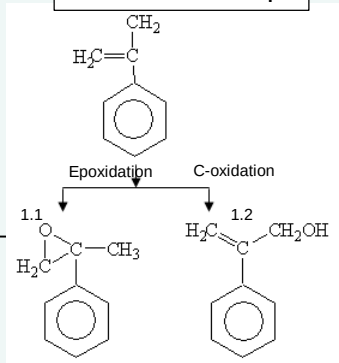
Aliphatic C-oxidation



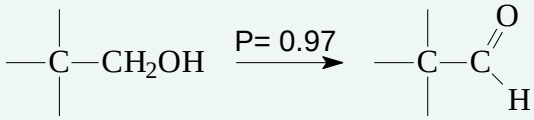
O-Glucuronidation



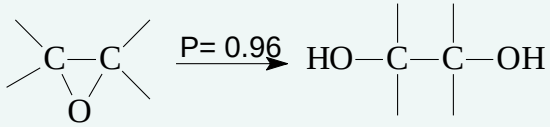
Generated map



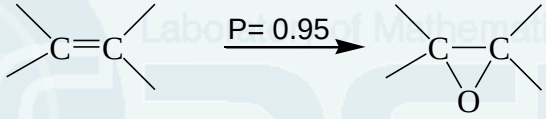
Aliphatic C-oxidation



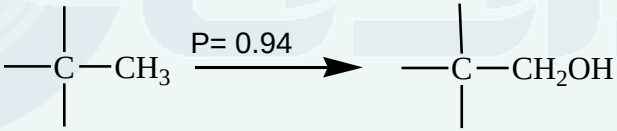
Epoxide Hydration

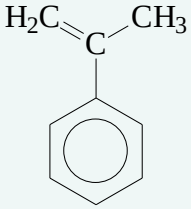


Epoxidation



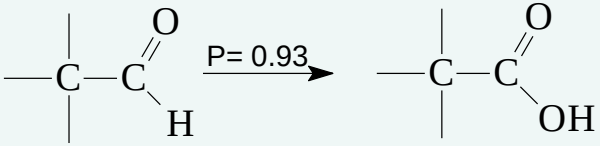
Aliphatic C-oxidation



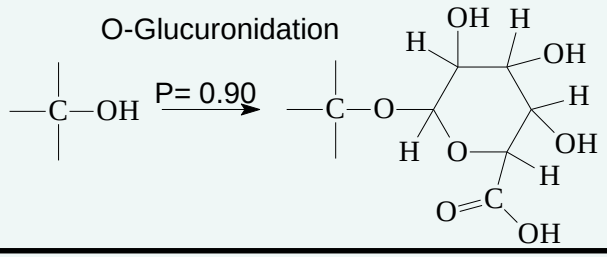


Match? - No!

Aliphatic C-oxidation

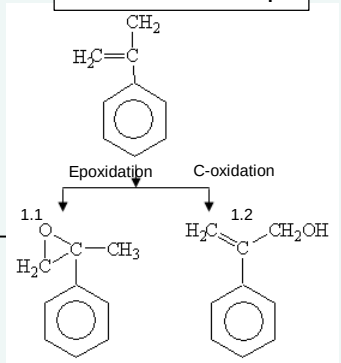


O-Glucuronidation

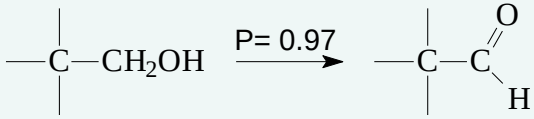


Substrate	Principle transformations	Metabolites

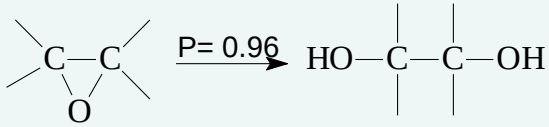
Generated map



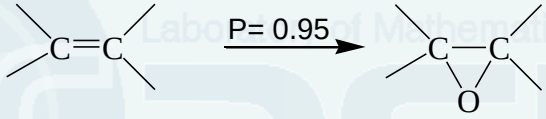
Aliphatic C-oxidation



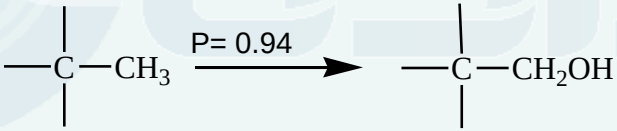
Epoxide Hydration



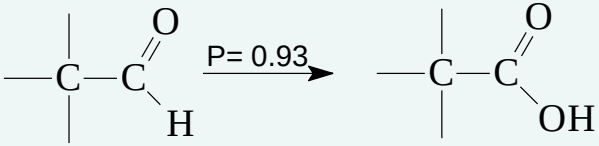
Epoxidation

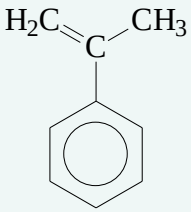


Aliphatic C-oxidation



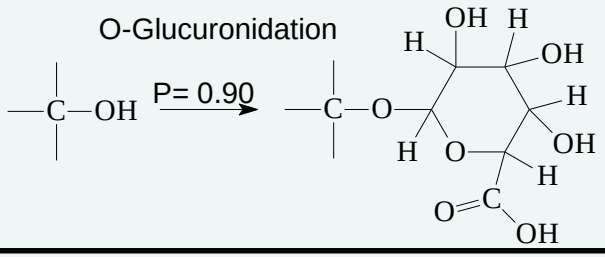
Aliphatic C-oxidation



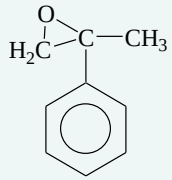


Match? - No!

O-Glucuronidation

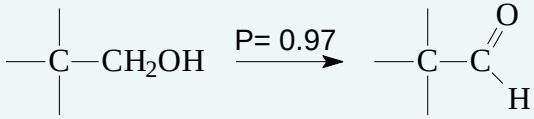


- Metabolite 1.1

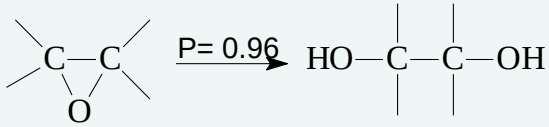


Match? - No!

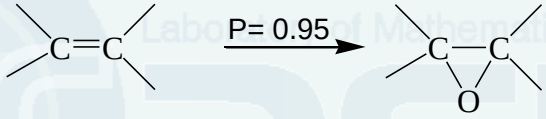
Aliphatic C-oxidation



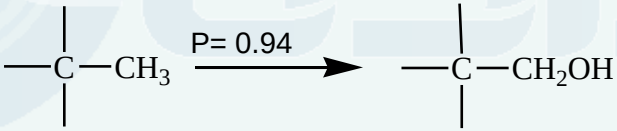
Epoxide Hydration



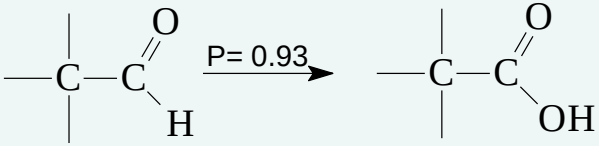
Epoxidation



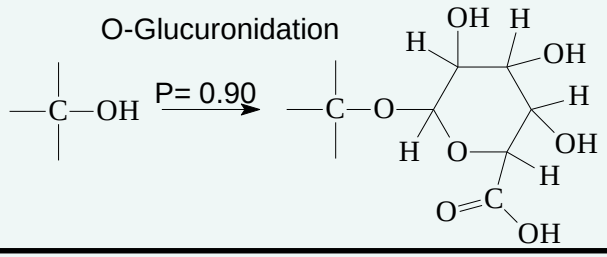
Aliphatic C-oxidation



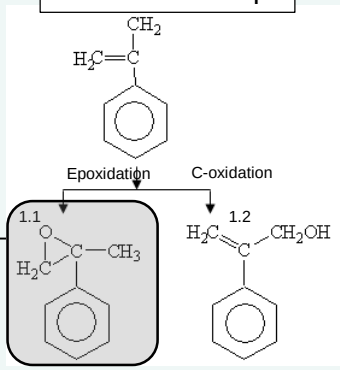
Aliphatic C-oxidation



O-Glucuronidation

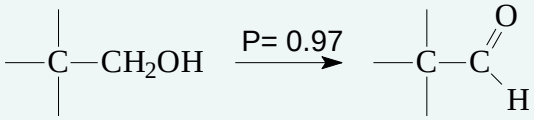


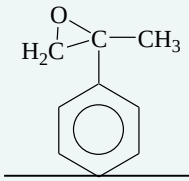
Generated map



- Metabolite 1.1

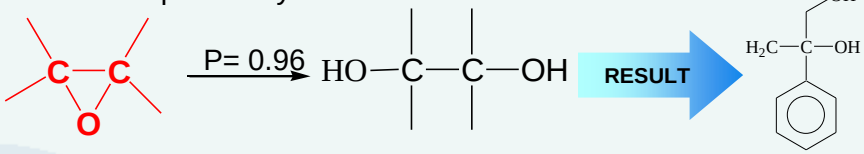
Aliphatic C-oxidation



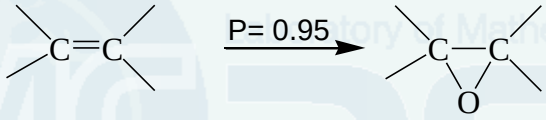


Match?- Yes!

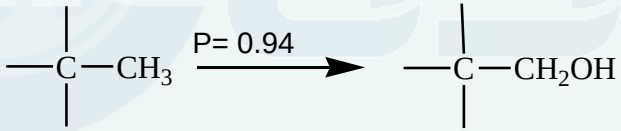
Epoxide Hydration



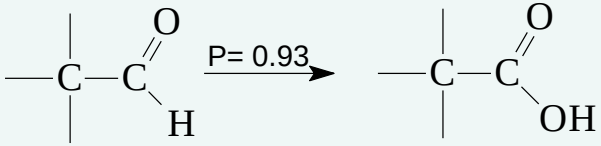
Epoxidation



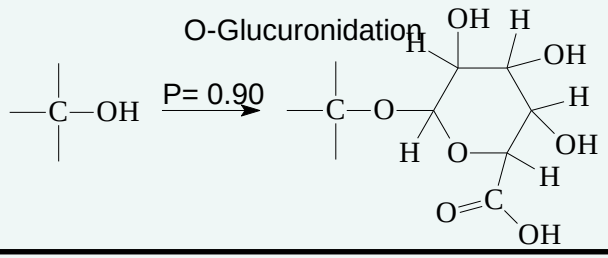
Aliphatic C-oxidation



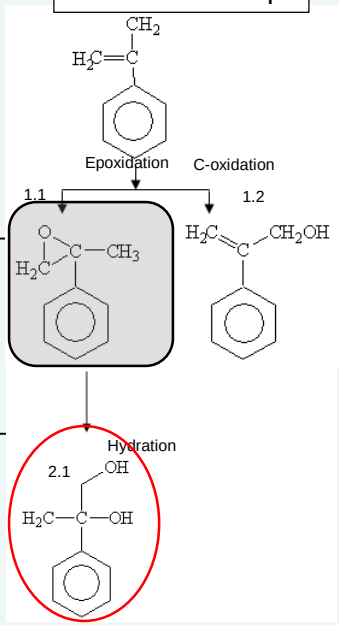
Aliphatic C-oxidation



O-Glucuronidation



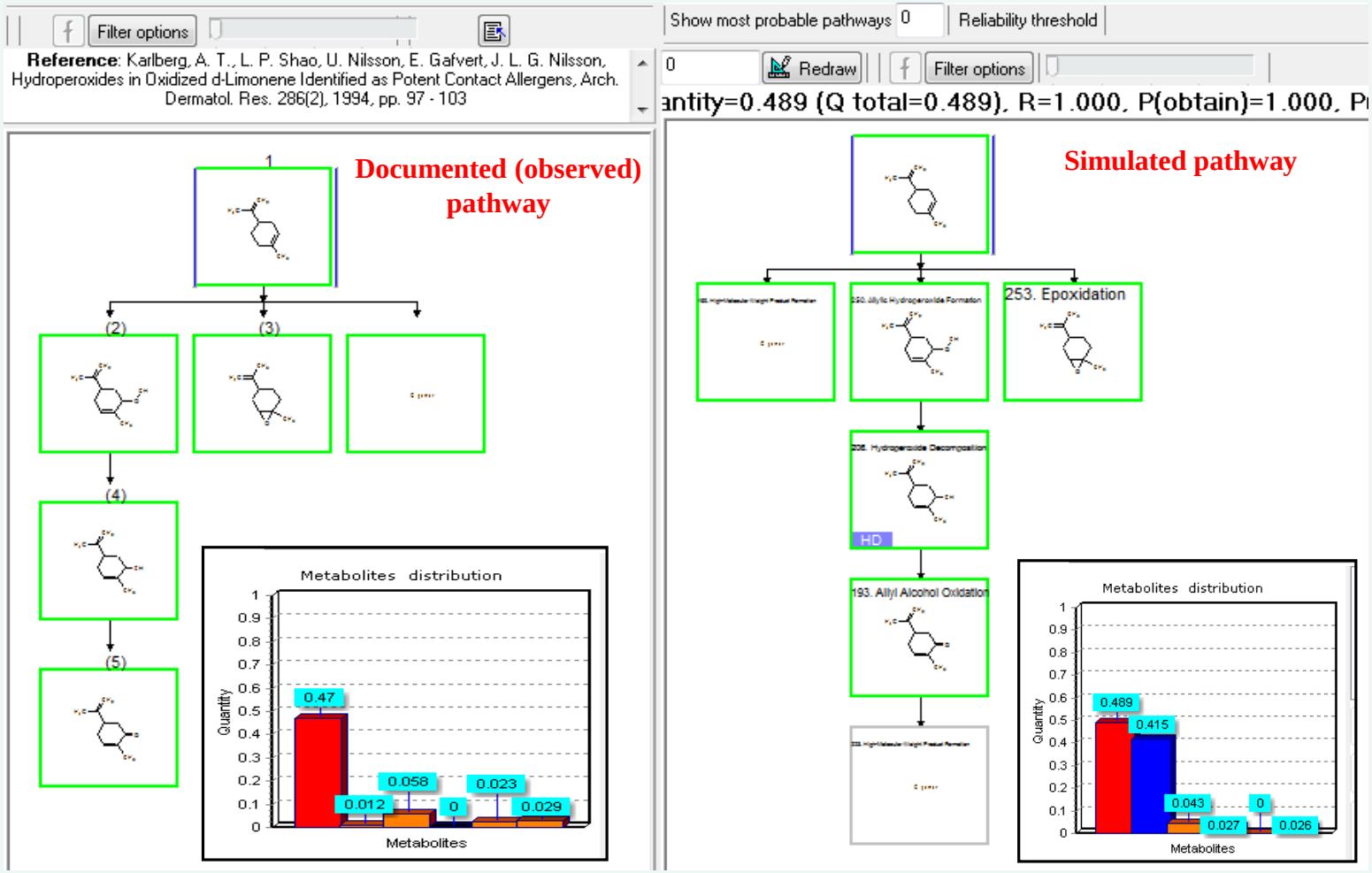
Generated map



Documented and OASIS simulated metabolism

Autoxidation simulator

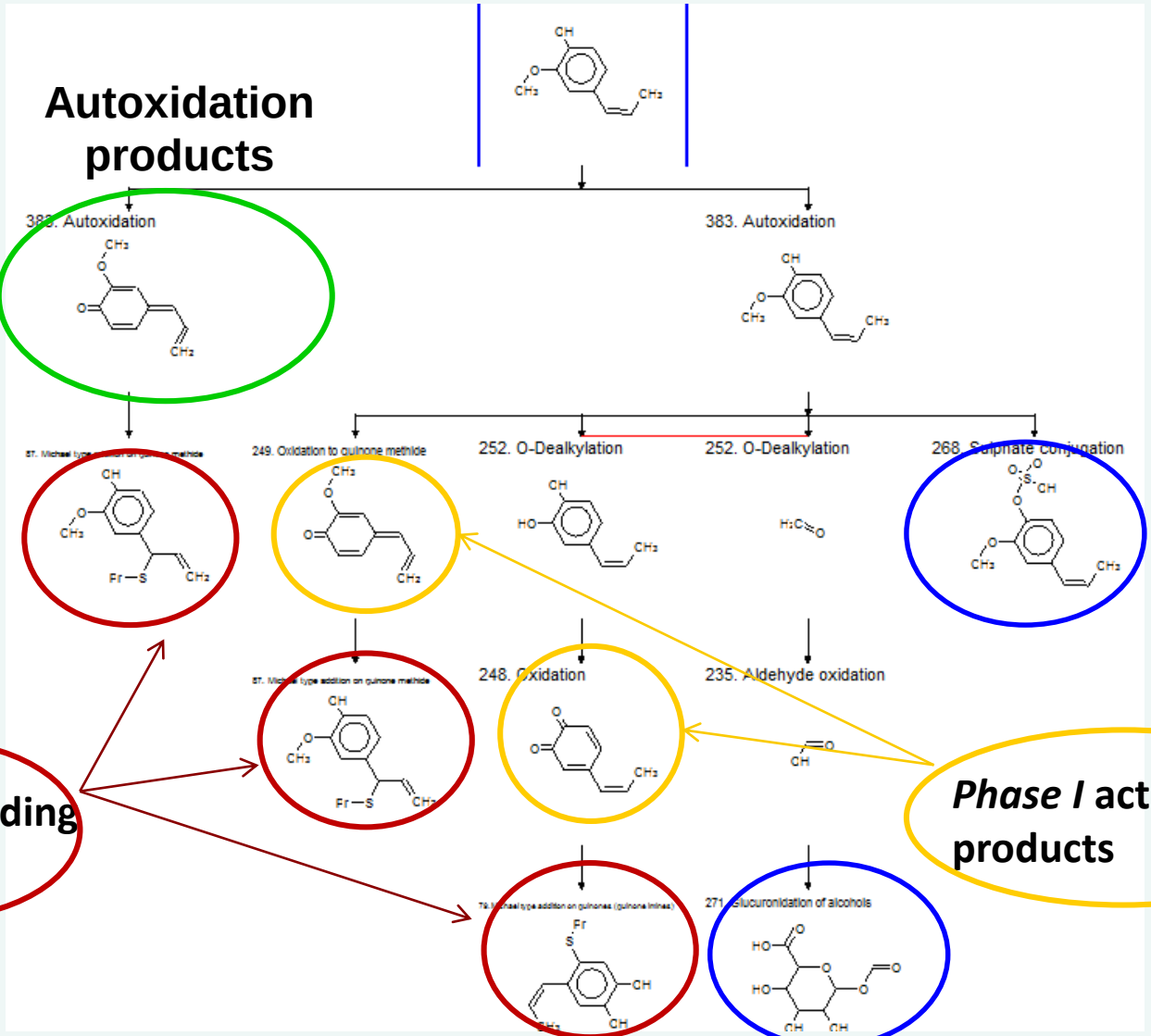
Autoxidation pathway of Limonene



Predicting skin sensitization in TIMES

Simulators for (a)biotic transformations

TIMES-SS Predicted metabolism of *Isoeugenol* accounting AU and SM activation



Outline

- TIMES Skin sensitization model
- Predicting skin sensitization in TIMES:
  - ✓ Mechanism of Skin sensitization
  - ✓ Main concept of the model
  - ✓ Simulators for (a)biotic transformations
  - ✓ Model reliability and mechanistic justification
- Summary

Laboratory of Mathematical Chemistry

Predicting skin sensitization in TIMES

Model reliability and mechanistic justification

TIMES-SS model reliability relies on:

1. Model applicability domain
2. Transformation/ Alert Performance - the ratio between the number of correct (Positive and Negative) predictions and the total number of chemicals within the local training set
3. Number of chemicals in the local training sets
4. Mechanistic justification

Predicting skin sensitization in TIMES

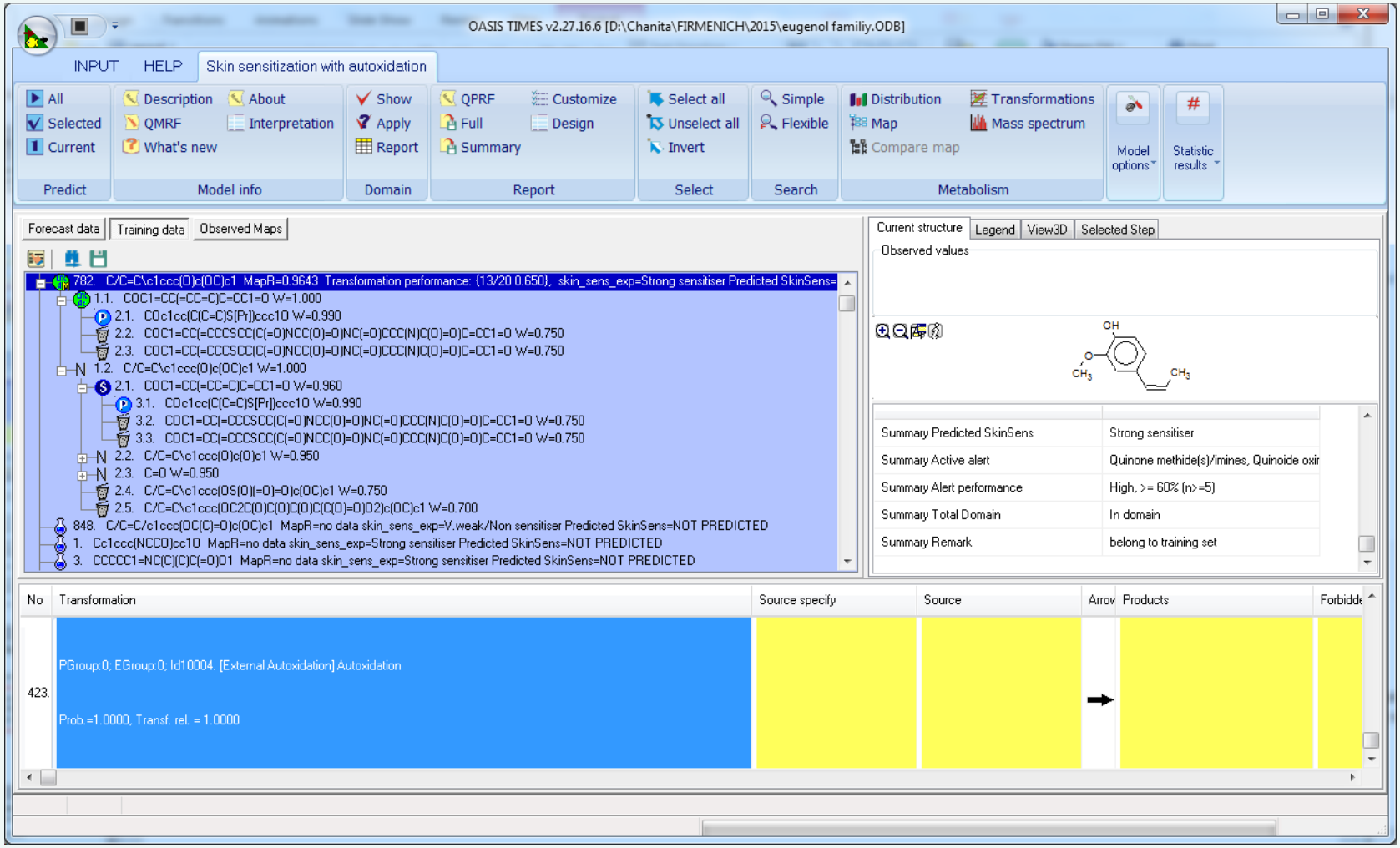
Applicability domain of TIMES-SS model is built following the step wise approach as described by *Dimitrov et.al.* and consists of:

- general parametric requirements - include ranges of molecular weight MW and log Kow defined on the basis of correctly predicted training set chemicals
- structural domain - based on atom-centered fragments extracted from correctly and incorrectly predicted training chemicals accounting for the atom type, hybridization and attached H-atoms
- mechanistic domain – characterizes specific functional group associated to skin sensitization effect

S. Dimitrov, G. Dimitrova, T. Pavlov, D. Dimitrova, G. Patlevisz, J. Niemela, and O. Mekemyan, A stepwise approach for defining the applicability domain of SAR and QSAR models, *J. Chem. Inf. Model.* 45 (2005), pp. 839–849.

Predicting skin sensitization in TIMES

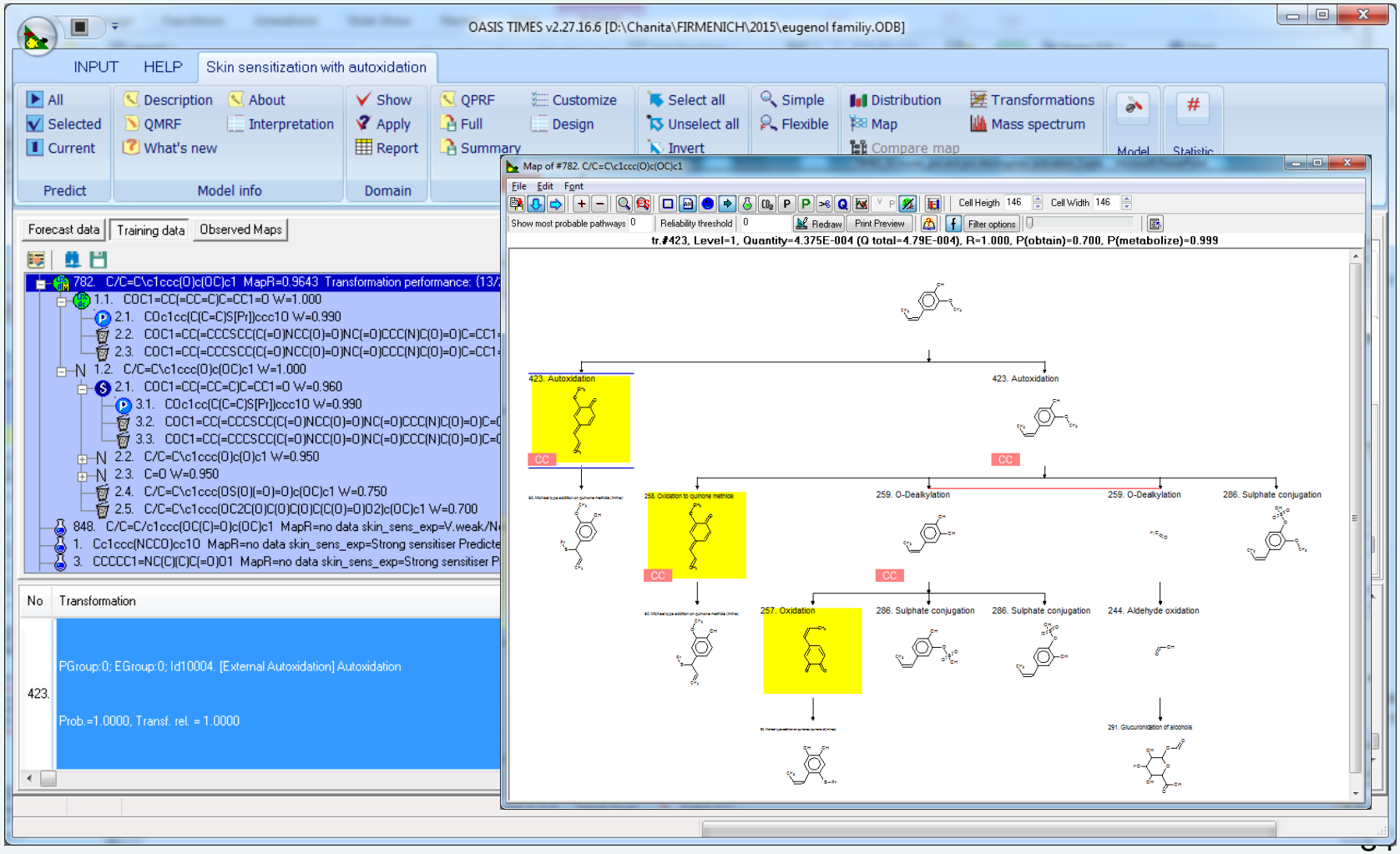
View of TIMES-SS model



Predicting skin sensitization in TIMES

View of TIMES-SS model

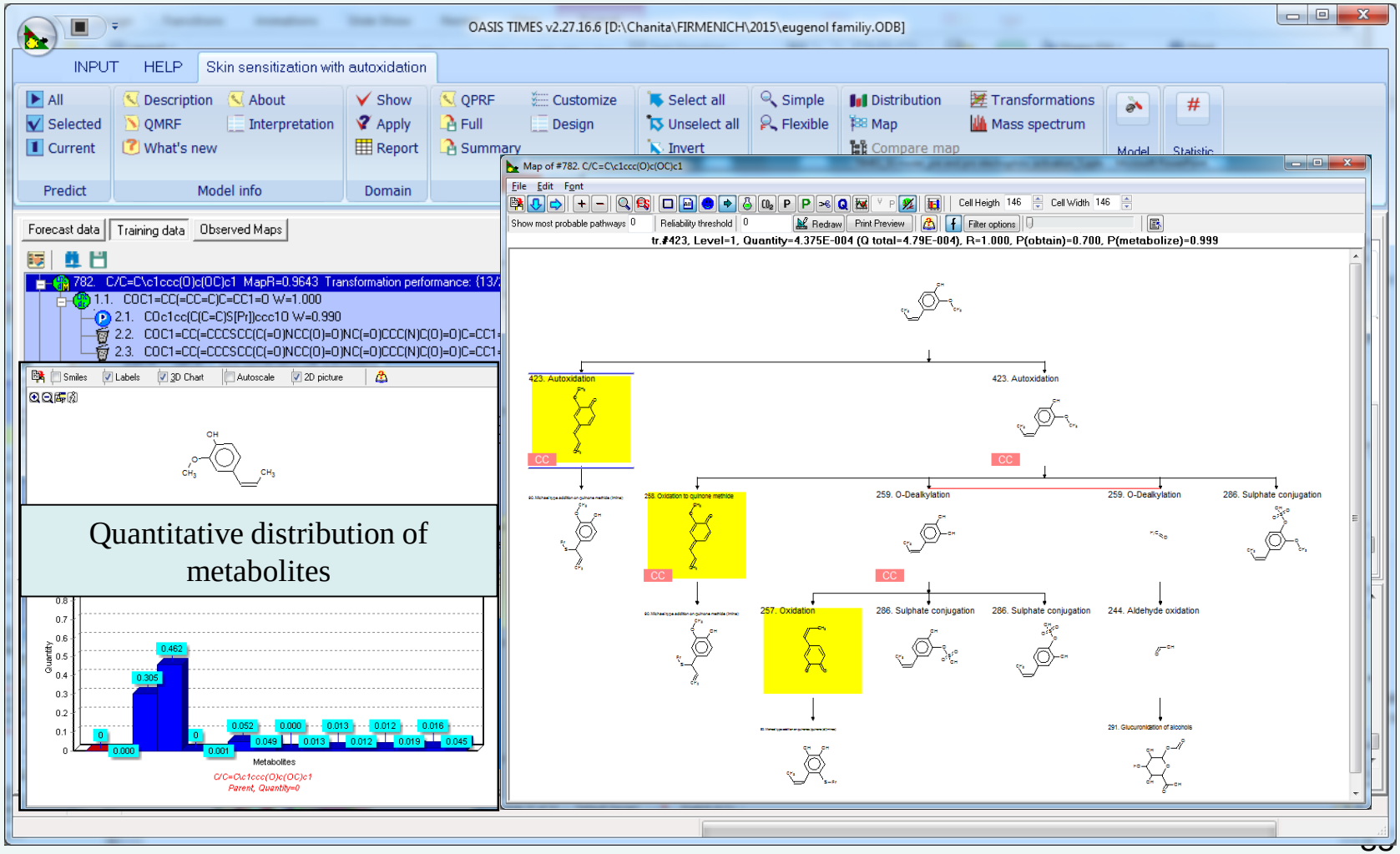
Generation of metabolic map with highlighted the activated metabolites



Predicting skin sensitization in TIMES

View of TIMES-SS model

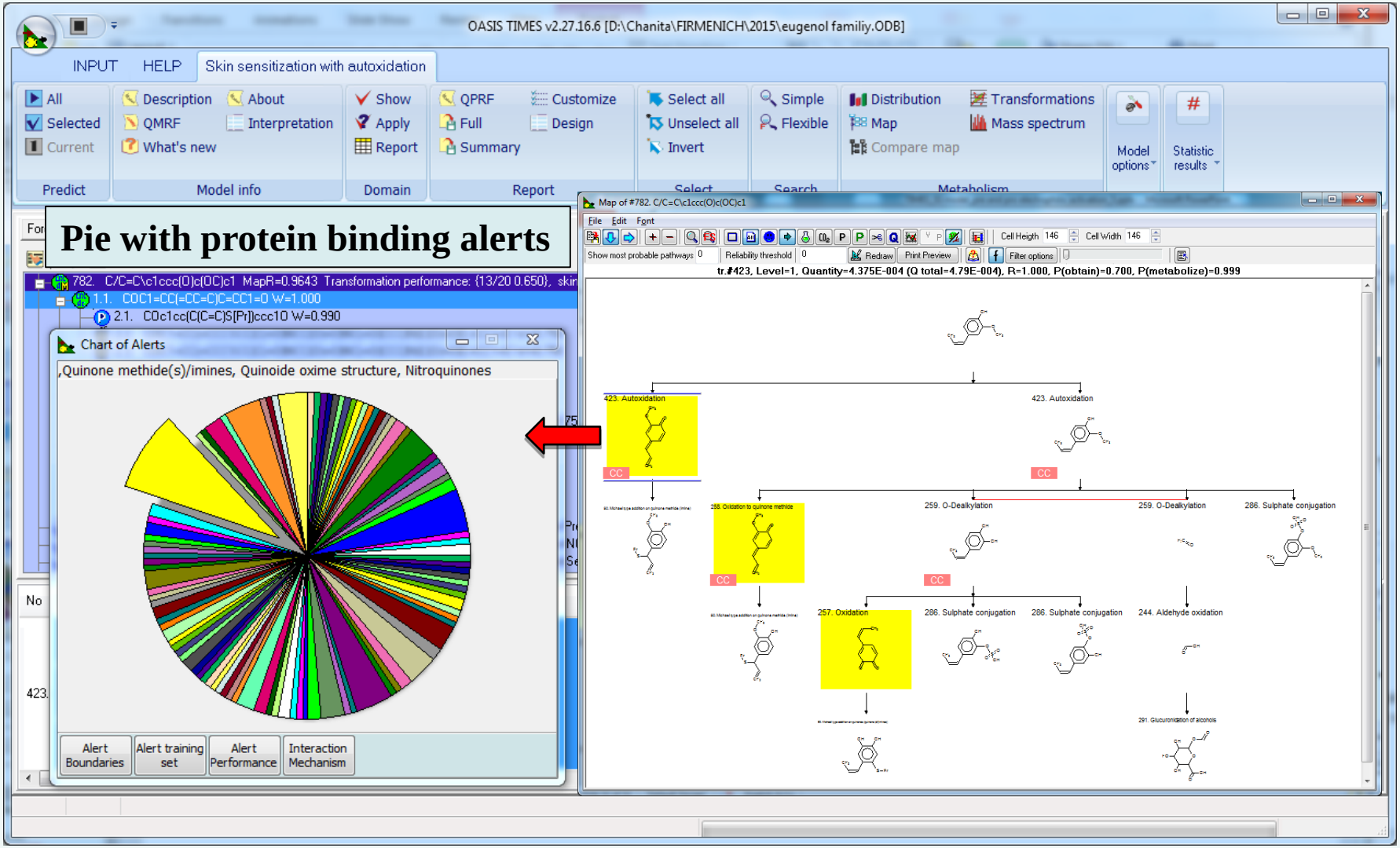
Generation of metabolic map with highlighted the activated metabolites



Predicting skin sensitization in TIMES

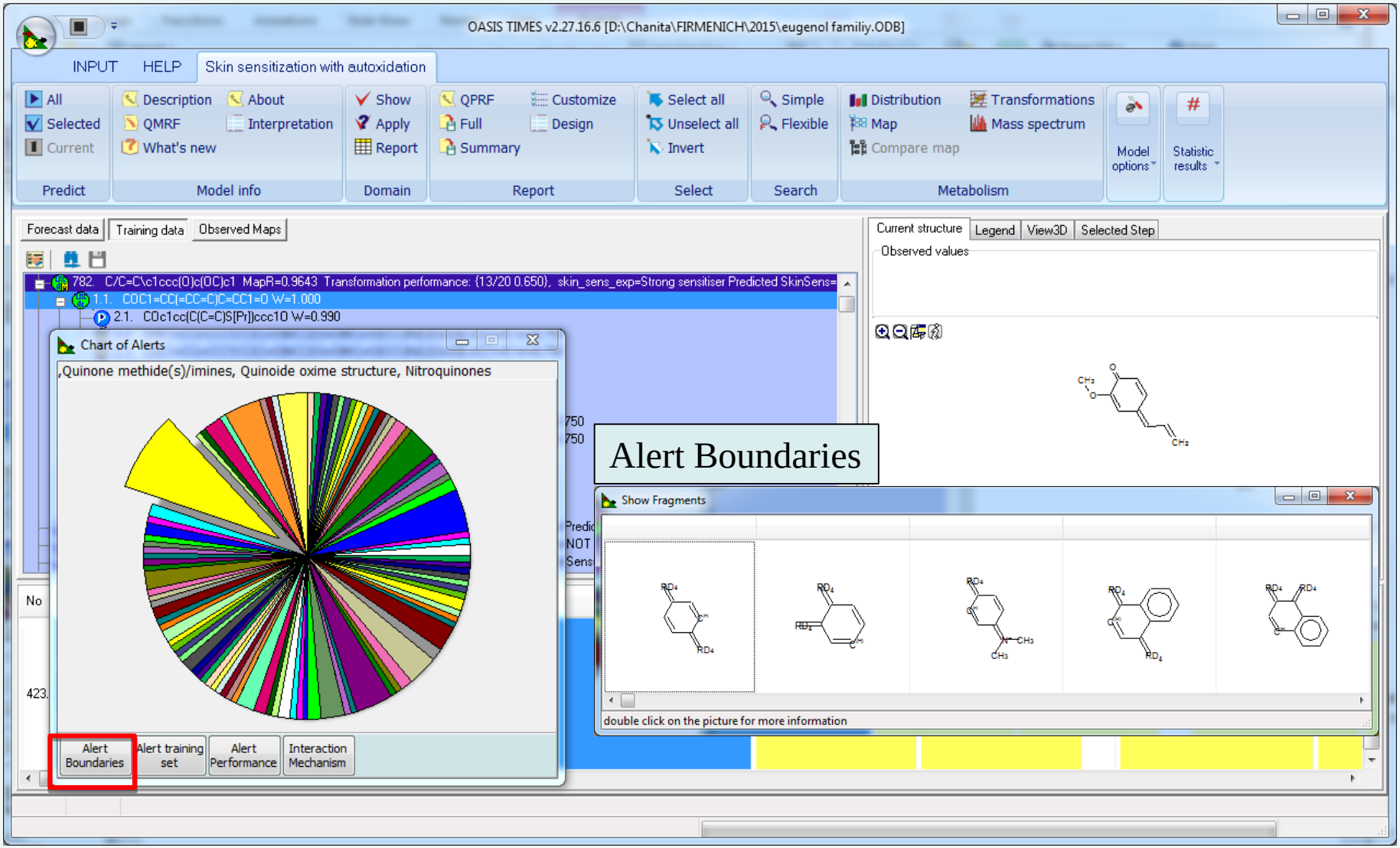
View of TIMES-SS model

Generation of metabolic map with highlighted the activated metabolites



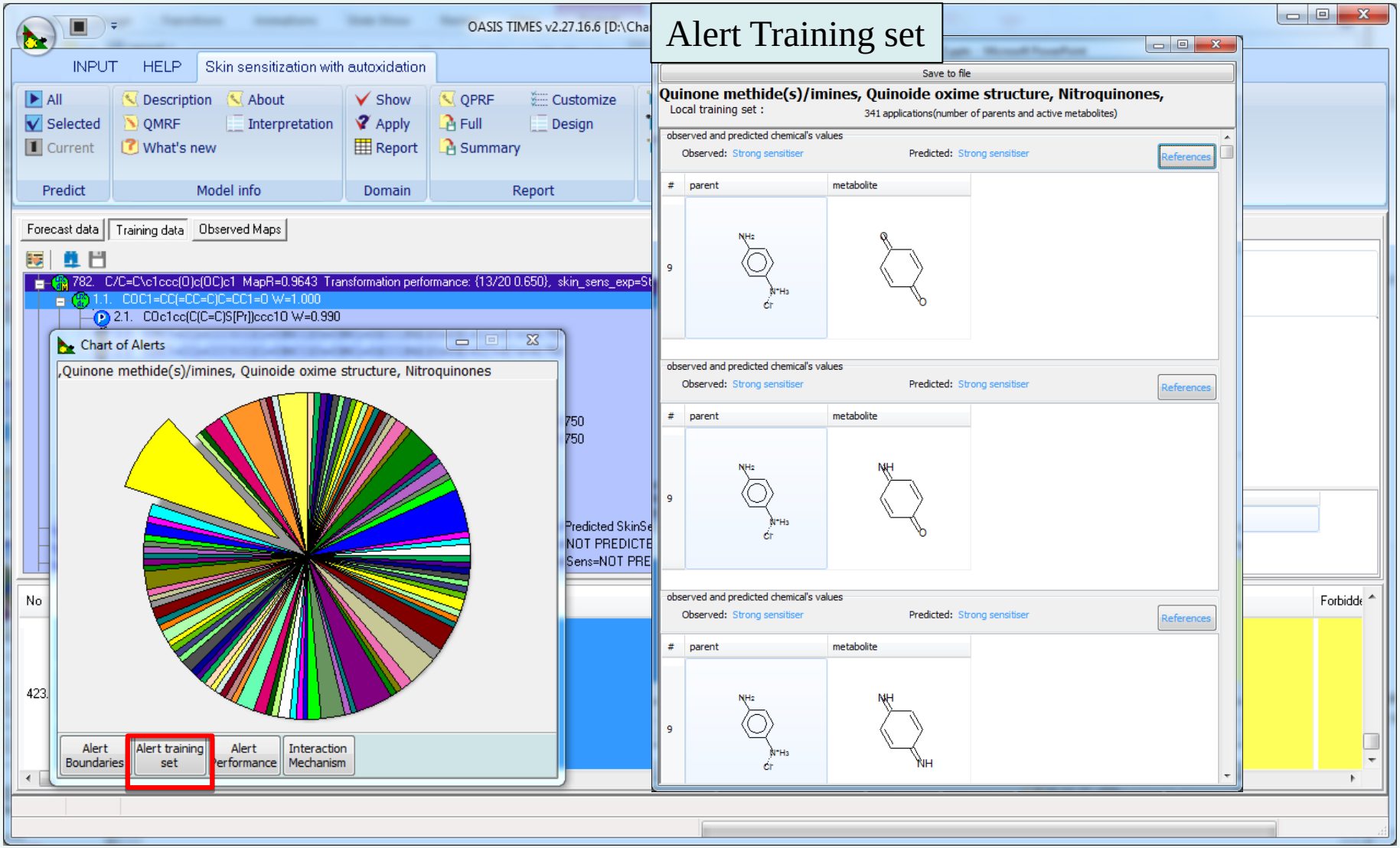
Predicting skin sensitization in TIMES

View of TIMES-SS model



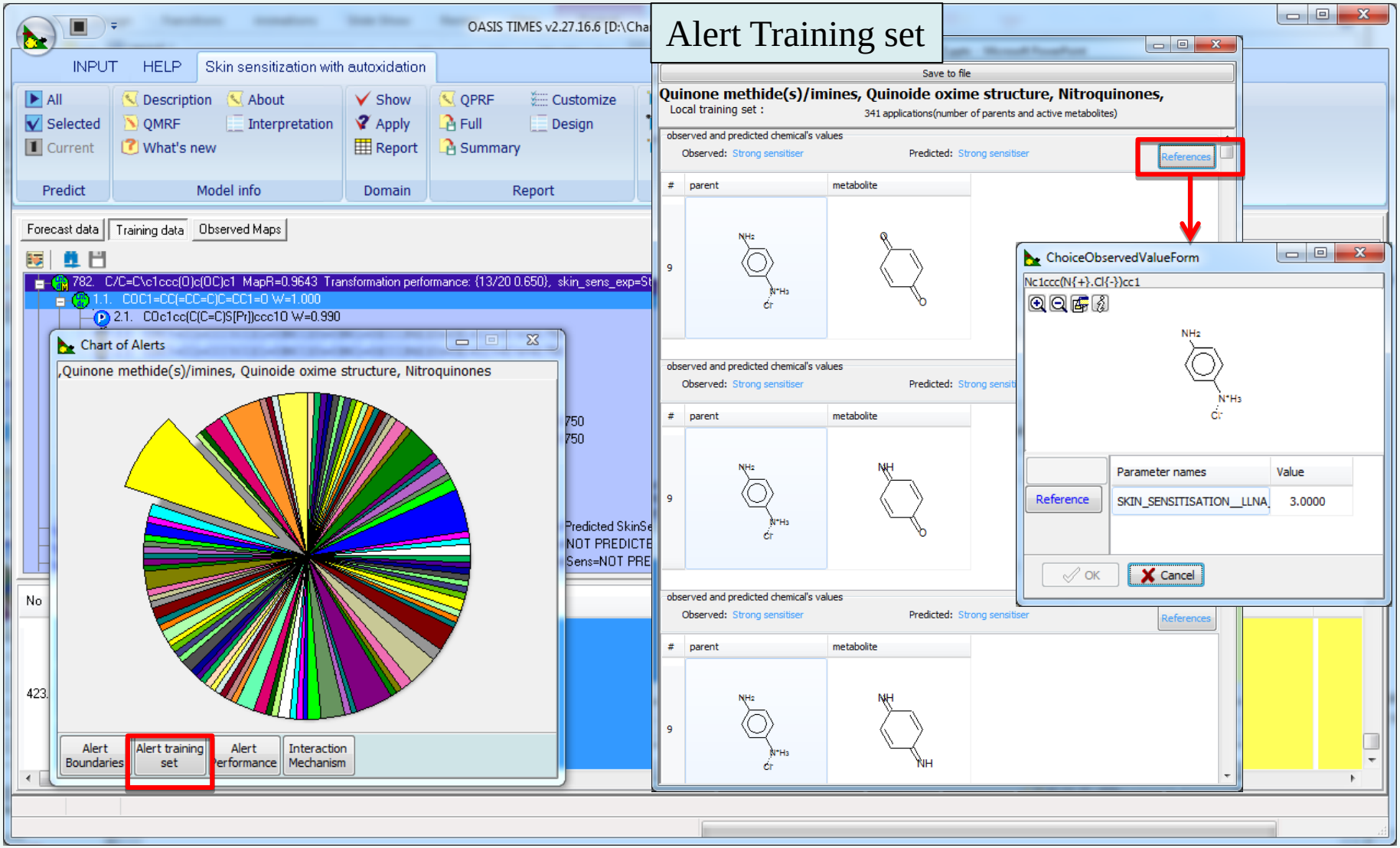
Predicting skin sensitization in TIMES

View of TIMES-SS model



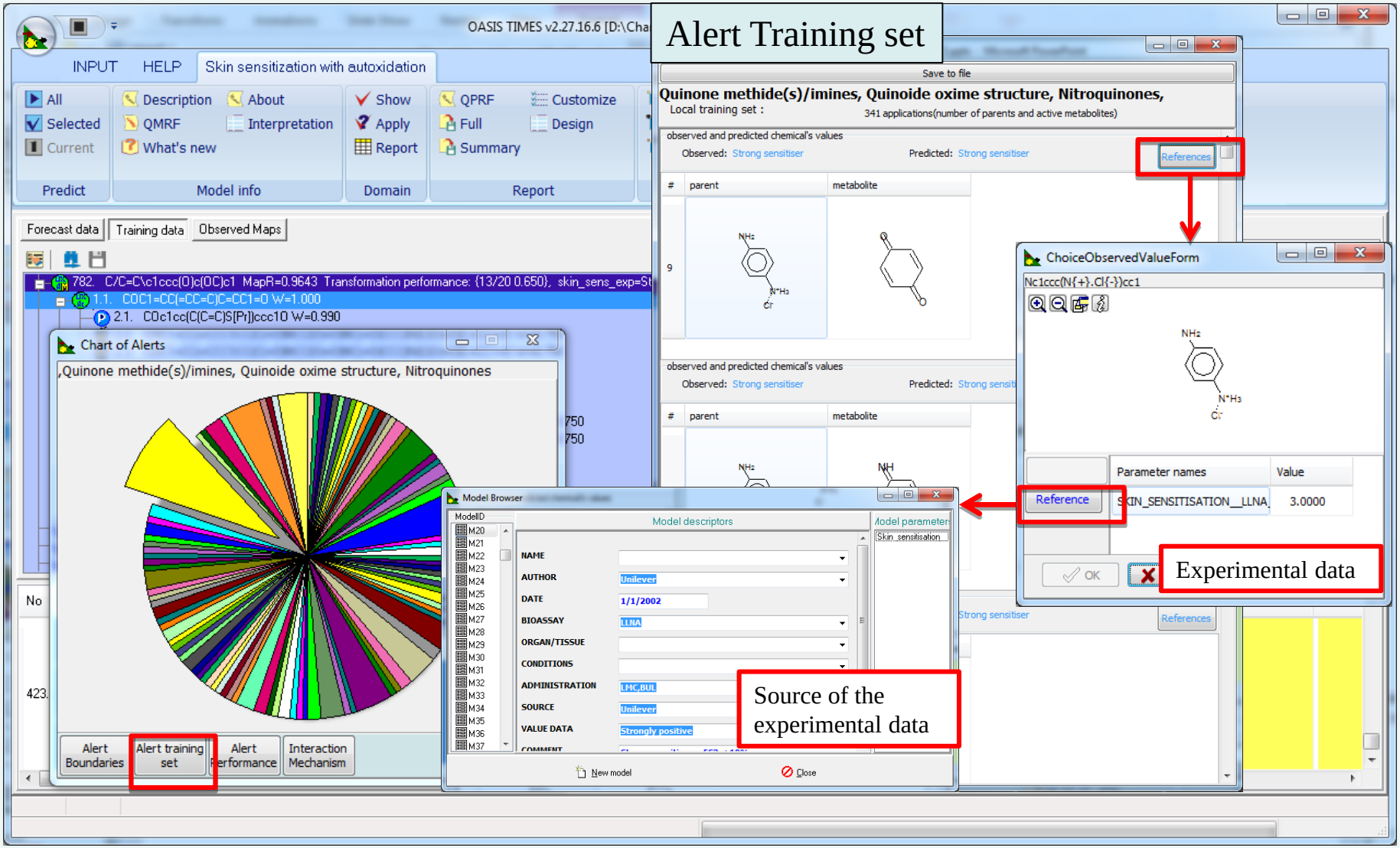
Predicting skin sensitization in TIMES

View of TIMES-SS model



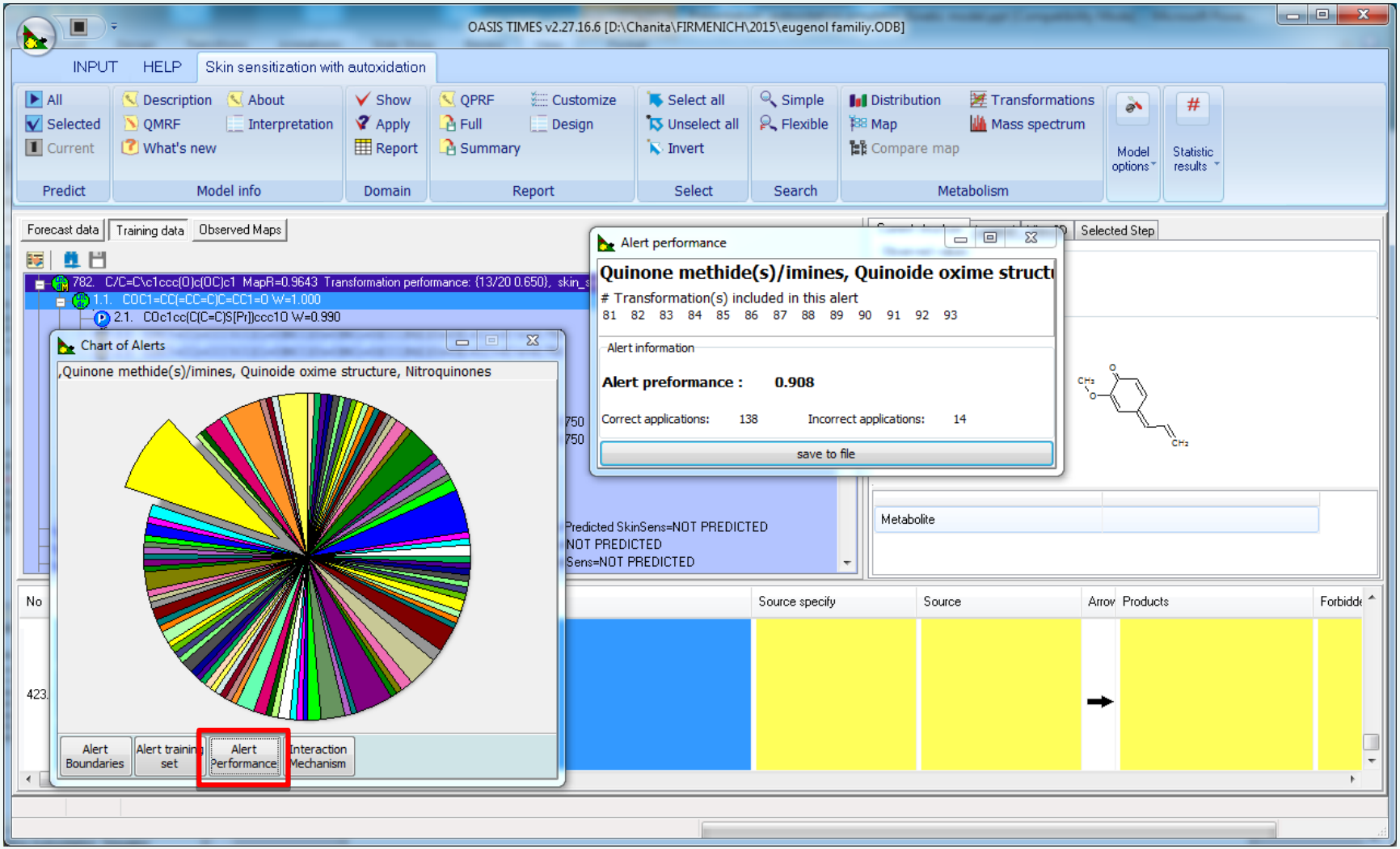
Predicting skin sensitization in TIMES

View of TIMES-SS model



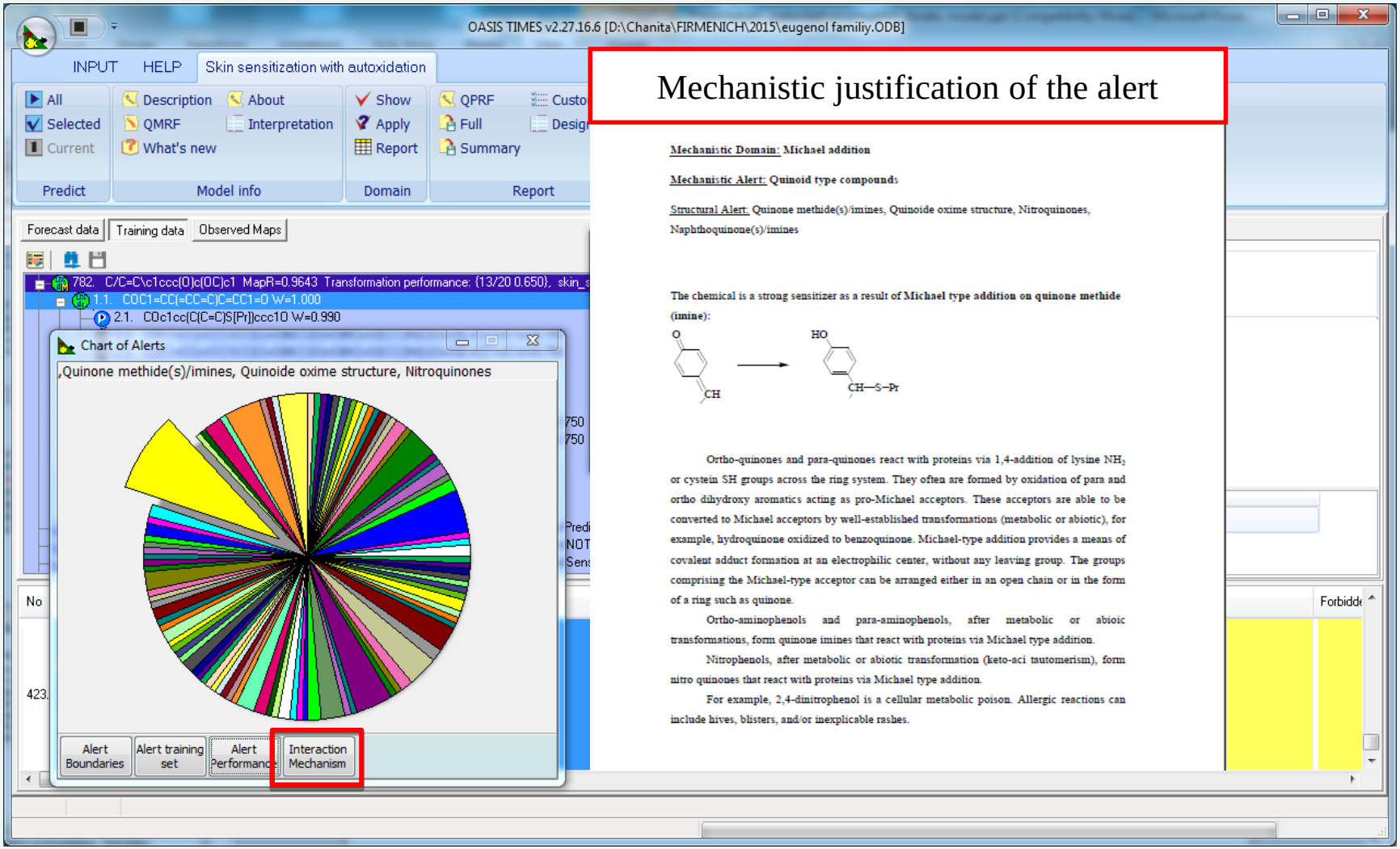
Predicting skin sensitization in TIMES

View of TIMES-SS model



Predicting skin sensitization in TIMES

View of TIMES-SS model



Predicting skin sensitization in TIMES

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TIMES-SS – Recent refinements resulting from an industrial skin sensitisation consortium[$]

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Outline

- TIMES Skin sensitization model
- Predicting skin sensitization in TIMES:
  - ✓ Mechanism of Skin sensitization
  - ✓ Main concept of the model
  - ✓ Simulators for (a)biotic transformations
  - ✓ Model reliability and mechanistic justification
- Summary

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TIMES Skin sensitization model

Summary

TIMES-SS model is an unique non-testing system:

- Simulating:
  - ✓ Pre- and Pro-electrophilic activation in skin
  - ✓ covalent interactions of activated metabolites with proteins
- Generating activation pathways with quantitative distribution of the metabolites
- Providing reliability of the prediction in terms of:
  - ✓ alert performance
  - ✓ mechanistic justification of protein binding
- Estimating belonging of chemicals in the parametric, structural and mechanistic boundaries of the model applicability domain

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