



# 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**
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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.

# Outline

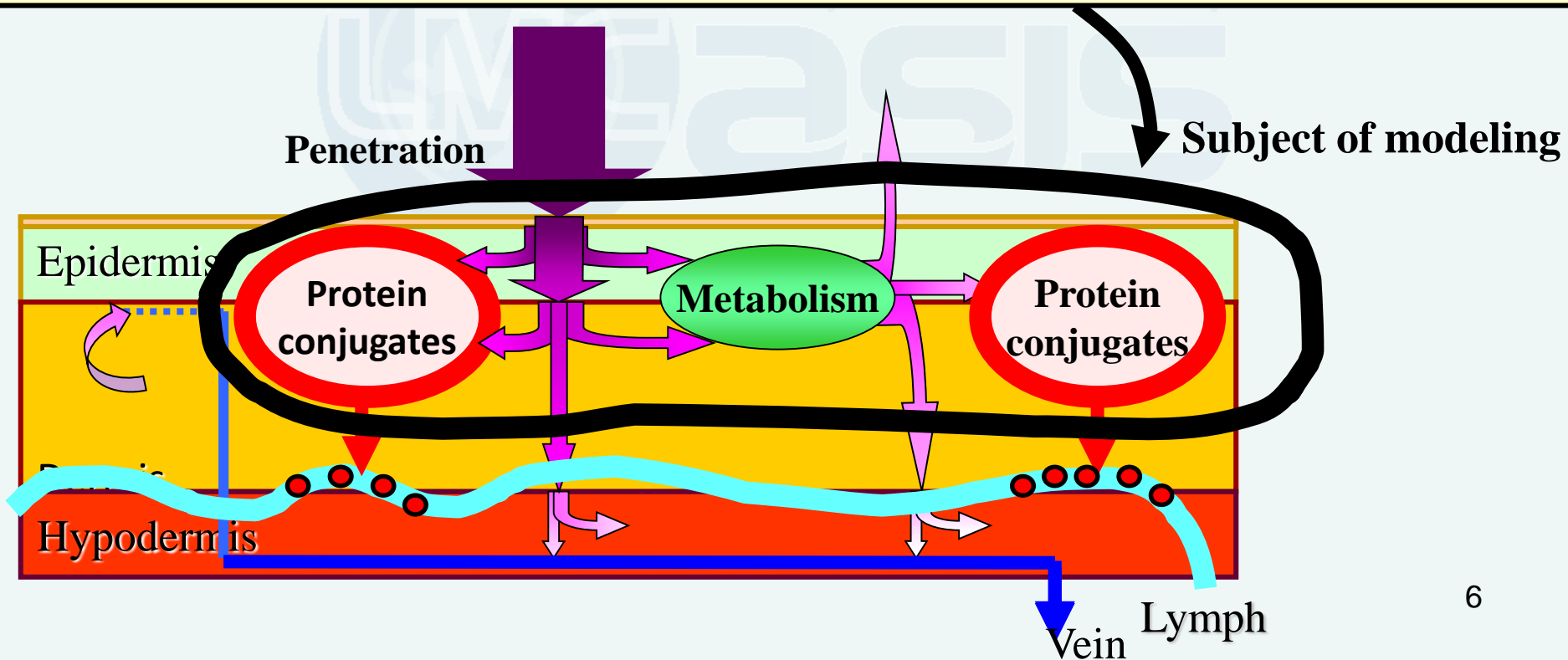
- TIMES Skin sensitization model
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# Predicting skin sensitization in TIMES

## 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

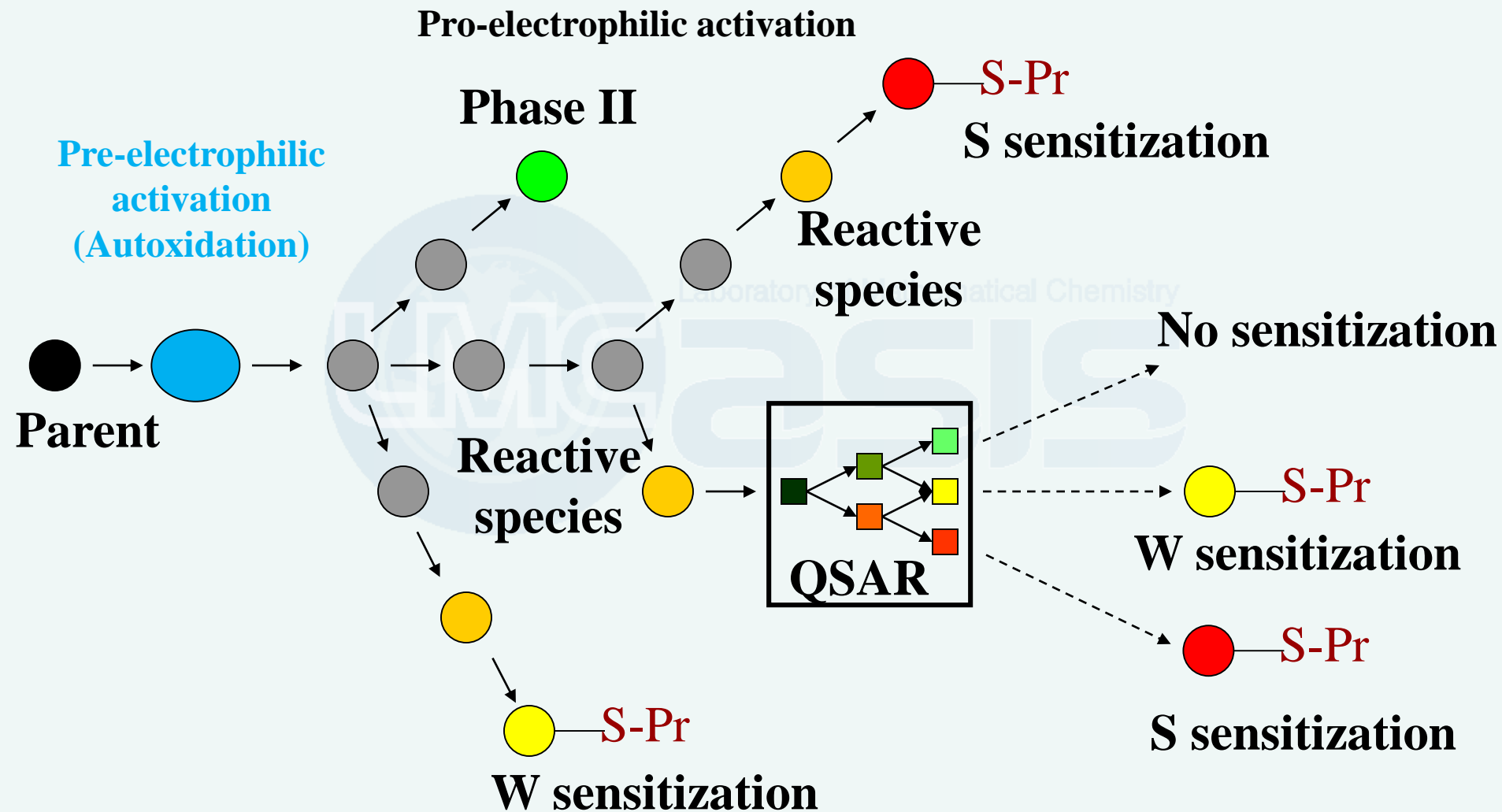
In order to predict skin sensitisation effect taking into account metabolic activation of chemicals in same platform are combined:

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



# 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



### **Simulation of chemical metabolism for fate and hazard assessment.**

#### **I. Approach for simulating metabolism**

S. Dimitrov<sup>a</sup>, T. Pavlov<sup>a</sup>, G. Veith<sup>b</sup> and O. Mekenyan<sup>a\*</sup>

<sup>a</sup>Laboratory of Mathematical Chemistry, University 'Prof. As. Zlatarov', Bourgas, Bulgaria;

<sup>b</sup>International QSAR Foundation, Two Harbors, MN, USA

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



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

O. Mekenyan<sup>\*</sup>, S. Dimitrov, T. Pavlov, G. Dimitrova, M. Todorov, P. Petkov and  
S. Kotov

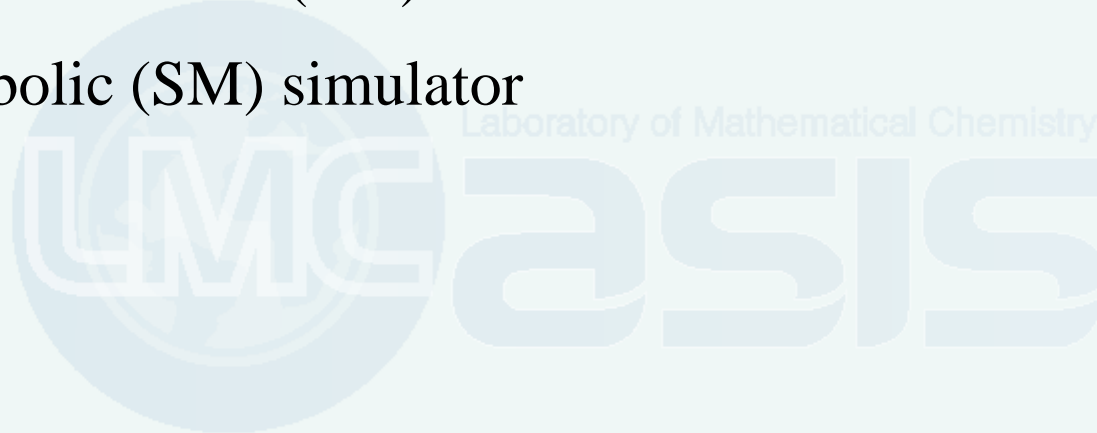
*Laboratory of Mathematical Chemistry, University "Prof. As. Zlatarov", Bourgas, Bulgaria*

# 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

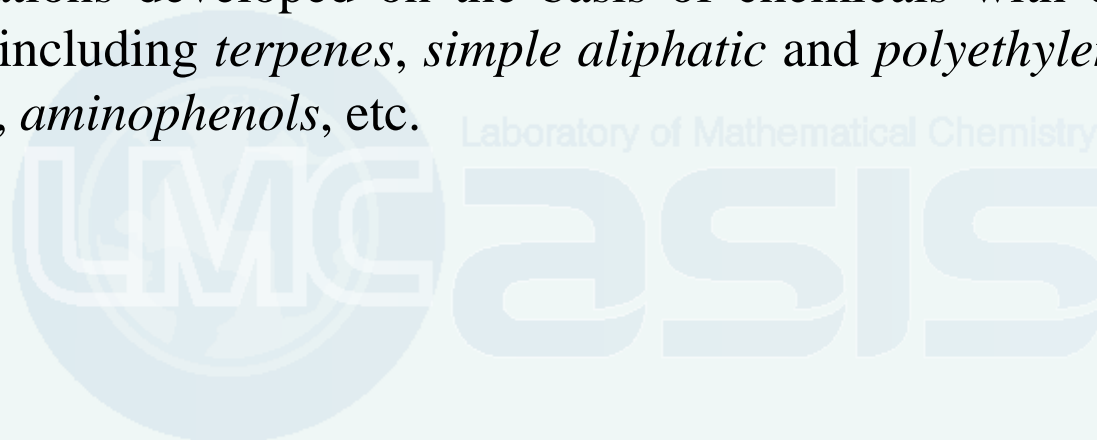


# Predicting skin sensitization in TIMES

## 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.



# 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

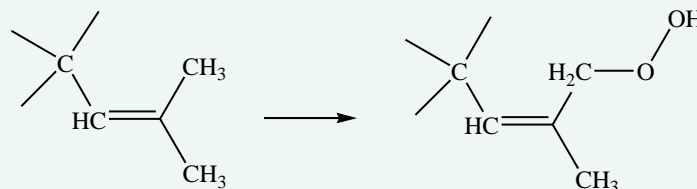
# Predicting skin sensitization in TIMES

## Simulators for (a)biotic transformations

### Different types of principle transformations

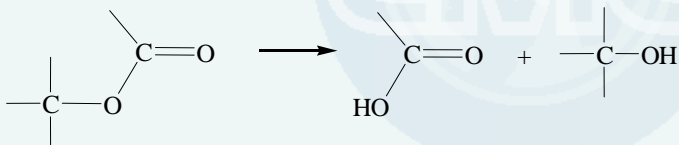
- **Autoxidation reactions**

*Allylic hydroperoxide formation*



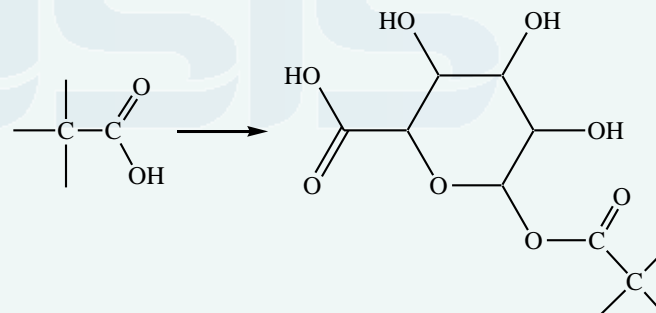
- **Phase I reactions**

*Ester hydrolysis*



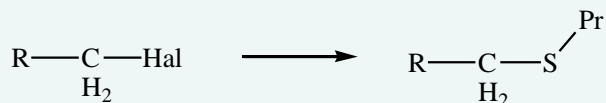
- **Phase II reactions**

*Glucuronidation*



- **Proteins binding reactions**

*Nucleophilic substitution on halogenated C sp<sup>3</sup> atom*



*Schiff base formation with aldehydes*

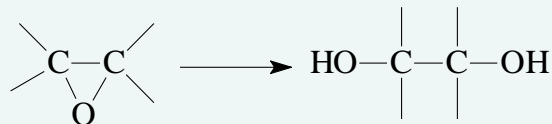


R = -C≡C, -CN, -C=C, -C=S, -C=O, -NO<sub>2</sub>  
Hal = Cl, Br, I

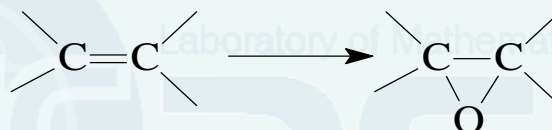
Aliphatic C-oxidation



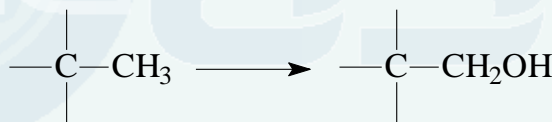
Epoxide Hydration



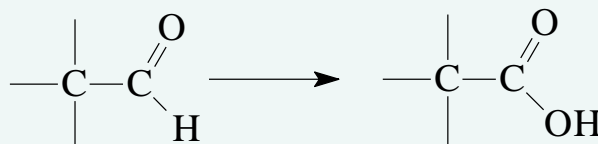
Epoxidation



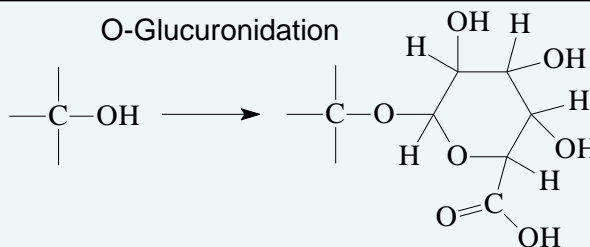
Aliphatic C-oxidation



Aliphatic C-oxidation

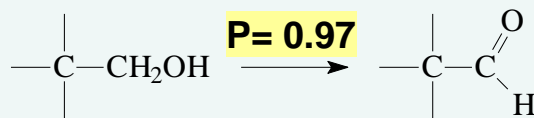


O-Glucuronidation

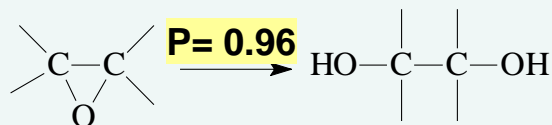




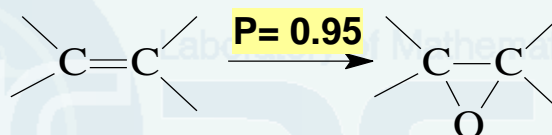
Aliphatic C-oxidation



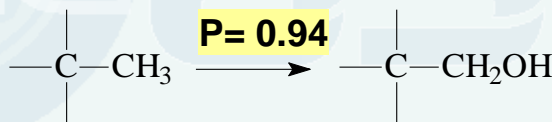
Epoxide Hydration



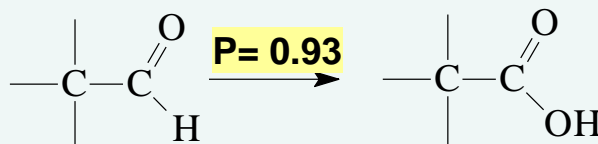
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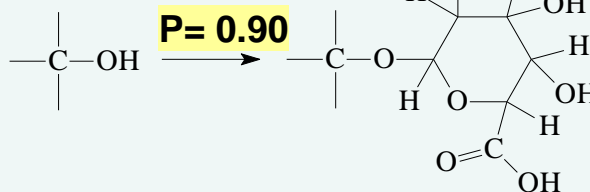
Aliphatic C-oxidation



Aliphatic C-oxidation

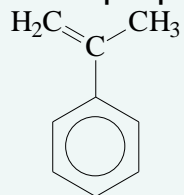


O-Glucuronidation

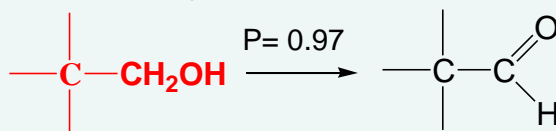




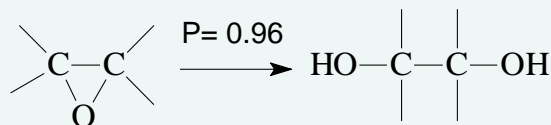
- Isopropenylbenzene

**Match? - No!**

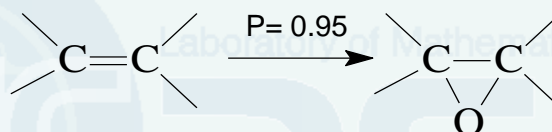
Aliphatic C-oxidation



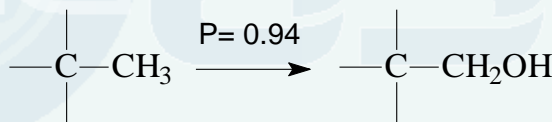
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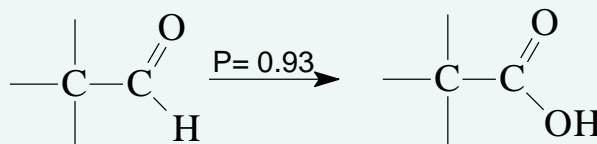
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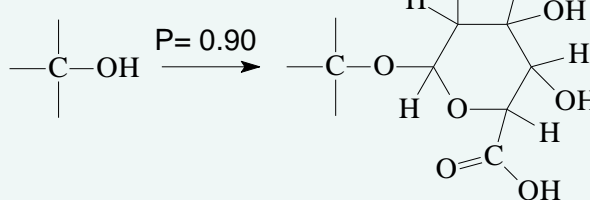
Aliphatic C-oxidation



Aliphatic C-oxidation

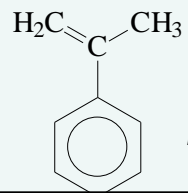
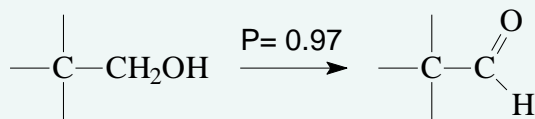


O-Glucuronidation

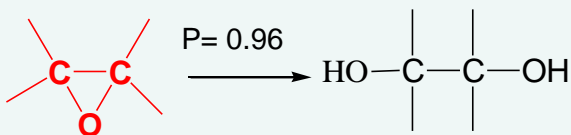




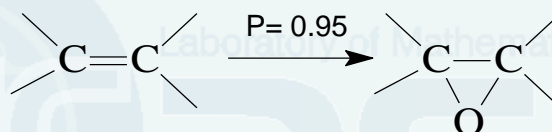
## Aliphatic C-oxidation

**Match? - No!**

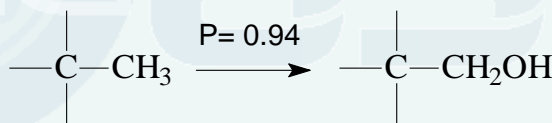
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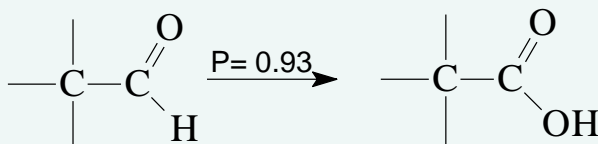
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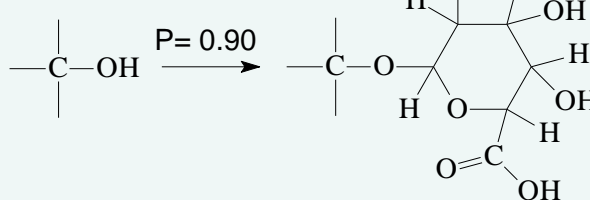
## Aliphatic C-oxidation



## Aliphatic C-oxidation

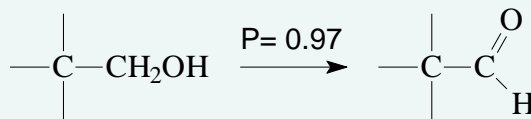


## O-Glucuronidation

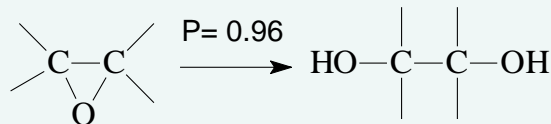




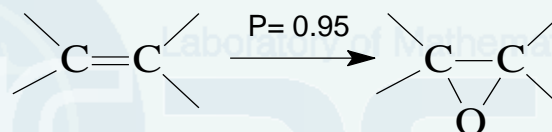
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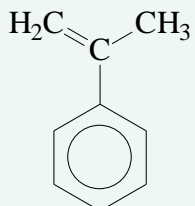
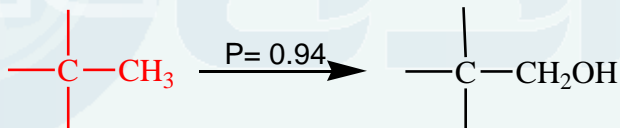
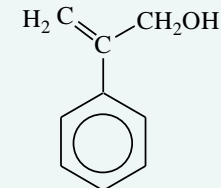
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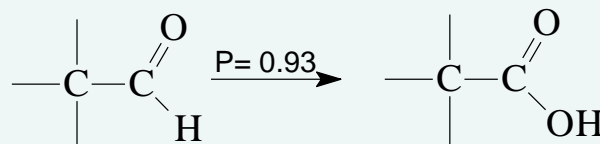
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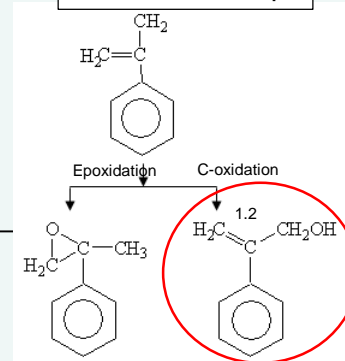
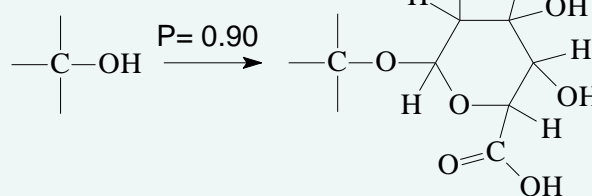
## Aliphatic C-oxidation

**Match? - Yes!****RESULT**

## Aliphatic C-oxidation



## O-Glucuronidation

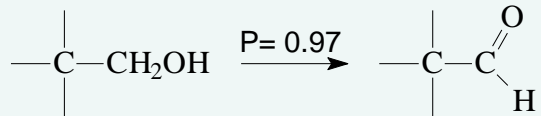




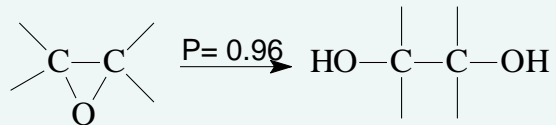


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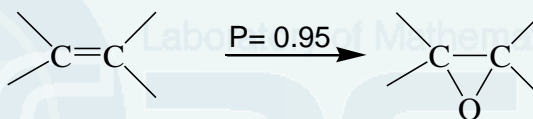
Aliphatic C-oxidation



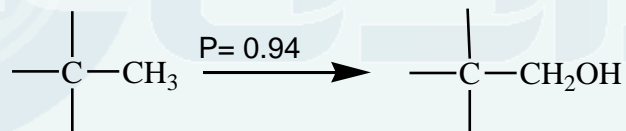
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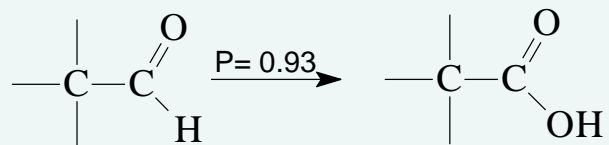
Epoxidation



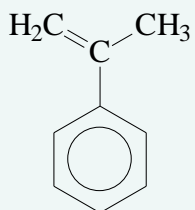
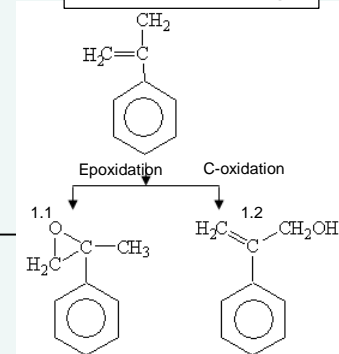
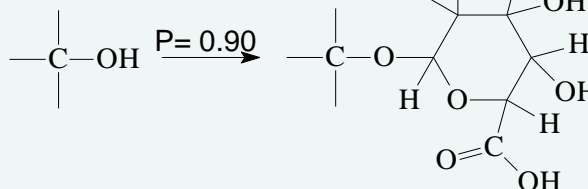
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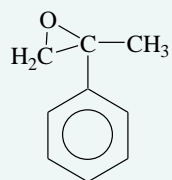
Aliphatic C-oxidation



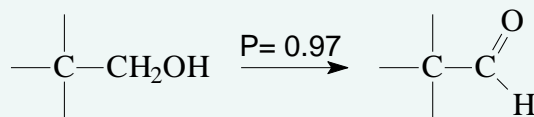
O-Glucuronidation

**Match? - No!**

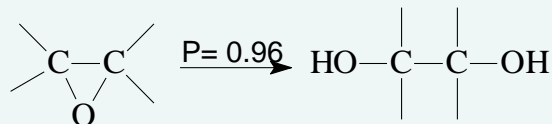
- Metabolite 1.1

**Match? - No!**

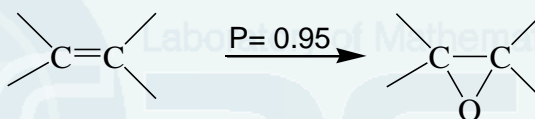
Aliphatic C-oxidation



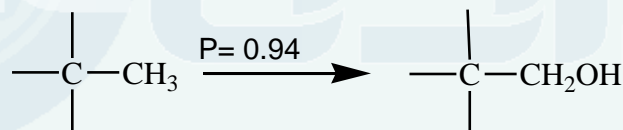
Epoxide Hydration



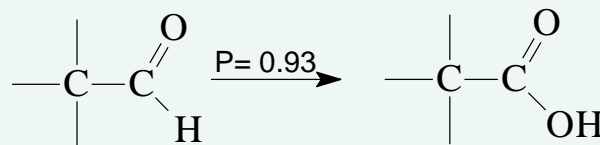
Epoxidation



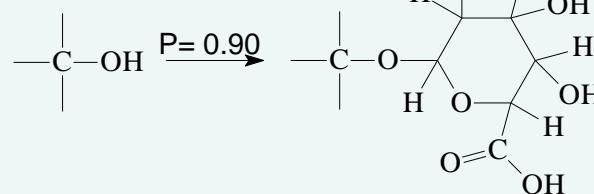
Aliphatic C-oxidation



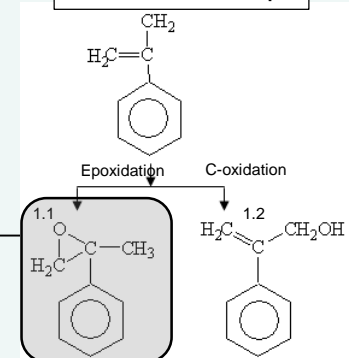
Aliphatic C-oxidation



O-Glucuronidation



Generated map



## Substrate

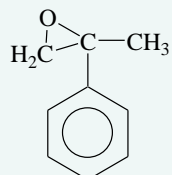
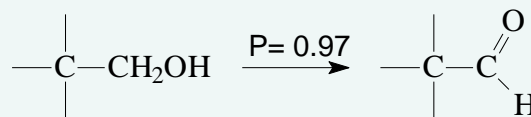
## Principle transformations

## Metabolites

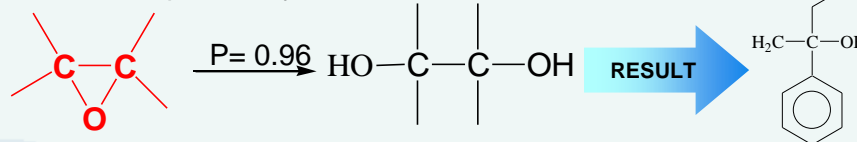
- Metabolite 1.1

Generated map

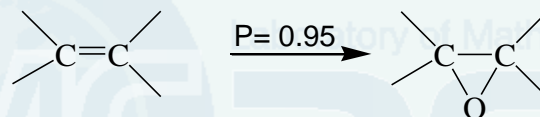
Aliphatic C-oxidation

**Match?- Yes!**

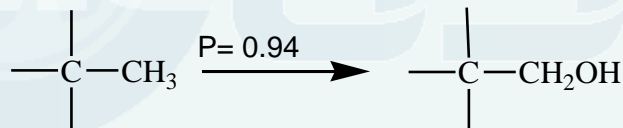
Epoxide Hydration



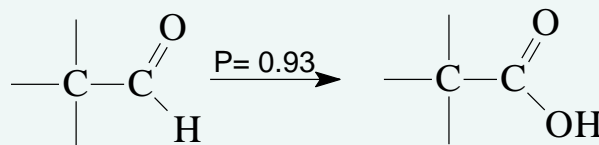
Epoxidation



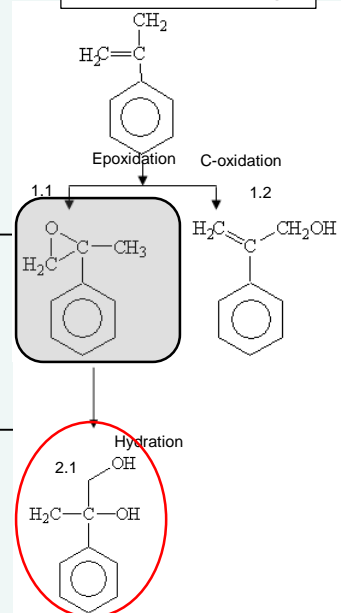
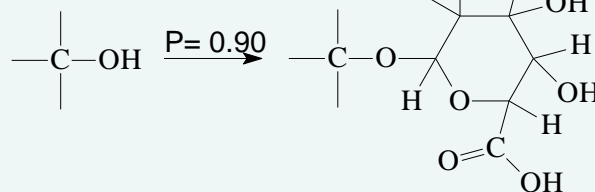
Aliphatic C-oxidation



Aliphatic C-oxidation



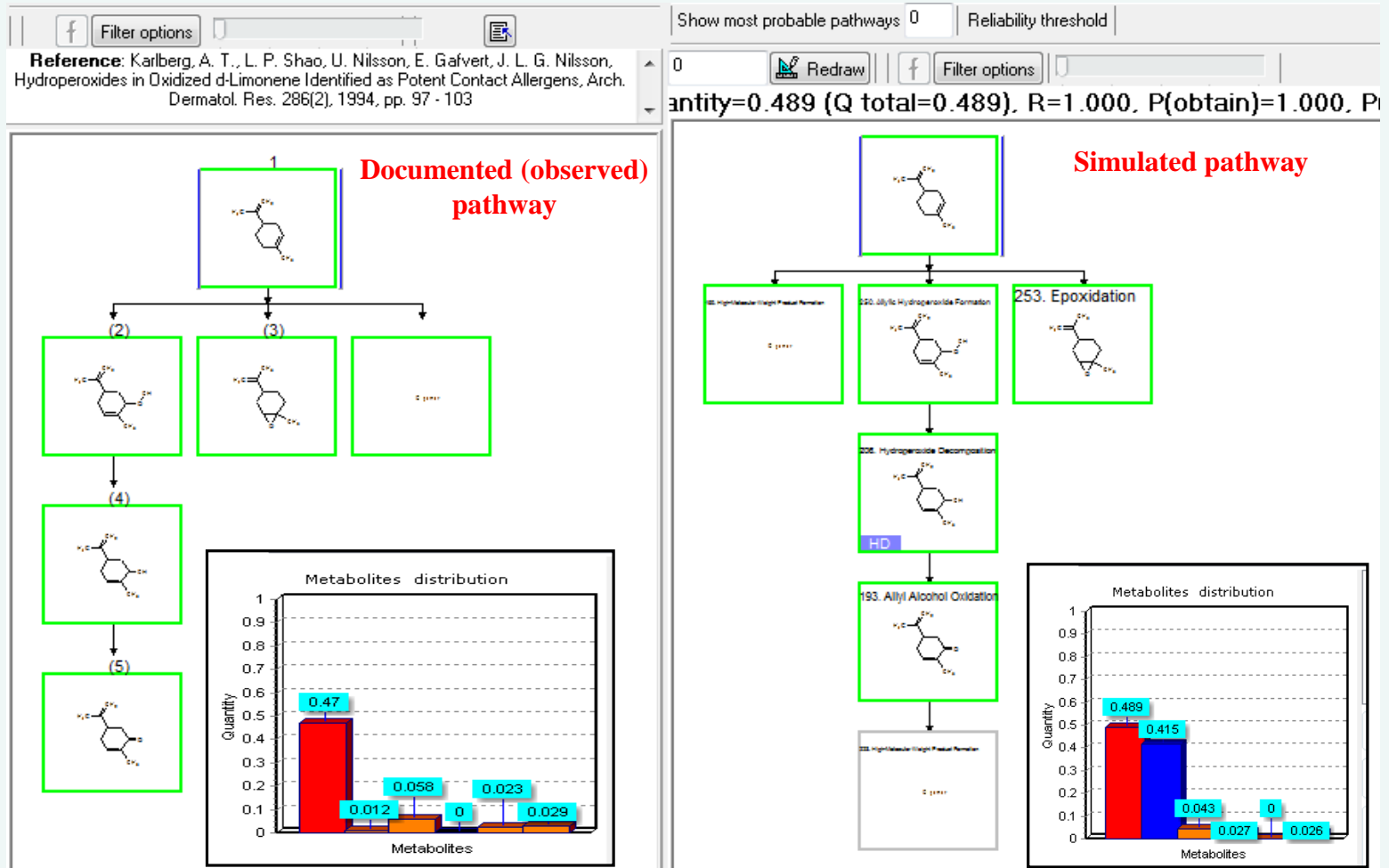
O-Glucuronidation



# Documented and OASIS simulated metabolism

## Autoxidation simulator

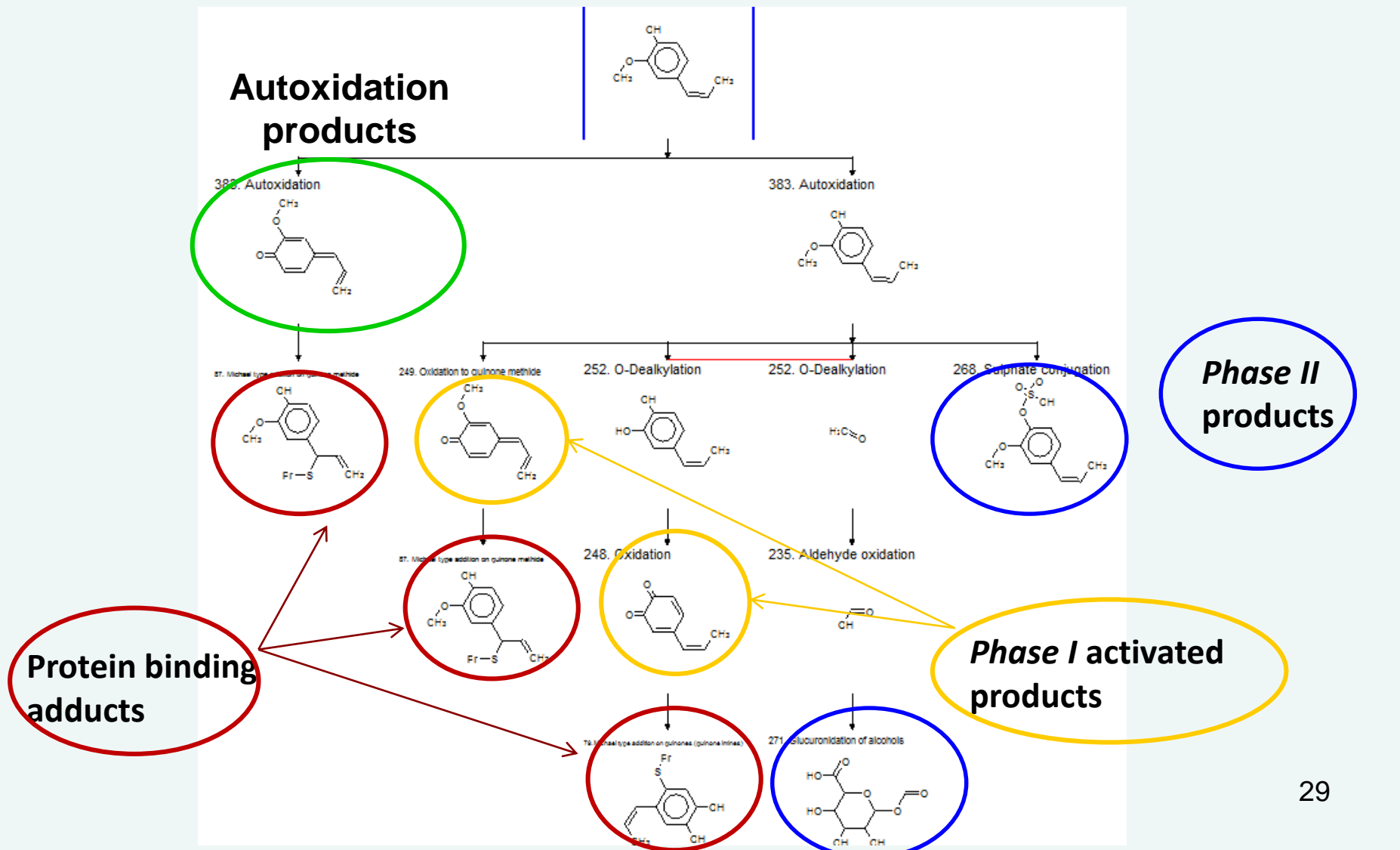
### *Autoxidation pathway of Limonene*



# Predicting skin sensitization in TIMES

## Simulators for (a)biotic transformations

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



# Outline

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# 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



# Predicting skin sensitization in TIMES

## View of TIMES-SS model

OASIS TIMES v2.27.16.6 [D:\Chanita\FIRMENICH\2015\eugenol family.ODB]

INPUT HELP Skin sensitization with autoxidation

All  Selected  Current  
 Description  QMRF  What's new  
 About  Interpretation  
 Show  Apply  Report  
 QPRF  Full  Summary  
 Customize  Design  
 Select all  Unselect all  Invert  
 Simple  Flexible  
 Distribution  Map  Compare map  
 Transformations  Mass spectrum  
 Model options  Statistic results

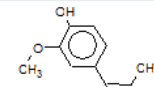
Forecast data | Training data | Observed Maps

782 C/C=Cvc1ccc(O)c(OC)c1 MapR=0.9643 Transformation performance: (13/20 0.650), skin\_sens\_exp=Strong sensitiser Predicted SkinSens=

- 1.1. COc1cc(C=C)S(Pr)ccc1O W=0.990
- 2.1. COc1cc(C=C)S(Pr)ccc1O W=0.990
- 2.2. COc1cc(C=C)S(Pr)ccc1O W=0.990
- 2.3. COc1cc(C=C)S(Pr)ccc1O W=0.990
- 1.2. C/C=Cvc1ccc(O)c(OC)c1 W=1.000
- 2.1. COc1cc(C=C)S(Pr)ccc1O W=0.960
- 3.1. COc1cc(C=C)S(Pr)ccc1O W=0.990
- 3.2. COc1cc(C=C)S(Pr)ccc1O W=0.990
- 3.3. COc1cc(C=C)S(Pr)ccc1O W=0.990
- 2.2. C/C=Cvc1ccc(O)c(OC)c1 W=0.950
- 2.3. C=O W=0.950
- 2.4. C/C=Cvc1ccc(O)c(OC)c1 W=0.750
- 2.5. C/C=Cvc1ccc(O)c(OC)c1 W=0.700
- 848. C/C=Cvc1ccc(O)c(OC)c1 MapR=no data skin\_sens\_exp=v.weak/Non sensitiser Predicted SkinSens=NOT PREDICTED
- 1. Cc1ccc(NC(=O)C)cc1O MapR=no data skin\_sens\_exp=Strong sensitiser Predicted SkinSens=NOT PREDICTED
- 3. CCCC1=NC(C)C(C)C(=O)O1 MapR=no data skin\_sens\_exp=Strong sensitiser Predicted SkinSens=NOT PREDICTED

Current structure Legend View3D Selected Step

Observed values



|                            |   |
|----------------------------|---|
| Summary Predicted SkinSens | Strong sensitiser                       |
| Summary Active alert       | Quinone methide(s)/imines, Quinoid oxir |
| Summary Alert performance  | High, >= 60% (n=5)                      |
| Summary Total Domain       | In domain                               |
| Summary Remark             | belong to training set                  |

| No  | Transformation   | Source specify | Source | Arrow | Products | Forbid |
|-----|--|----------------|--------|-------|----------|--------|
| 423 | PGroup:0; EGroup:0; Id10004. [External Autoxidation] Autoxidation<br>Prob.=1.0000, Transf. rel. = 1.0000 |                |        | →     |          |        |

# Predicting skin sensitization in TIMES

View of TIMES-SS model

Generation of metabolic map with highlighted the activated metabolites

OASIS TIMES v2.27.16.6 [D:\Chanita\FIRMENICH\2015\eugenol family.ODB]

INPUT HELP Skin sensitization with autoxidation

Forecast data Training data Observed Maps

782: C/C=C\c1ccc(O)c(OC)c1 MapR=0.9643 Transformation performance: (13/13)

- 1.1. COC1=CC(=CC=C)C=CC1=O W=1.000
- 2.1. COc1cc(C(C=C)S(PI))ccc1O W=0.990
- 2.2. COC1=CC(=CC=CC(C(=O)NCC(O)=O)NC(=O)CCC(N)C(O)=O)C=CC1=O W=0.990
- 2.3. COC1=CC(=CC=CC(C(=O)NCC(O)=O)NC(=O)CCC(N)C(O)=O)C=CC1=O W=0.990
- 1.2. C/C=C\c1ccc(O)c(OC)c1 W=1.000
- 2.1. COC1=CC(=CC=C)C=CC1=O W=0.960
- 3.1. COc1cc(C(C=C)S(PI))ccc1O W=0.990
- 3.2. COC1=CC(=CC=CC(C(=O)NCC(O)=O)NC(=O)CCC(N)C(O)=O)C=CC1=O W=0.990
- 3.3. COC1=CC(=CC=CC(C(=O)NCC(O)=O)NC(=O)CCC(N)C(O)=O)C=CC1=O W=0.990
- N 2.2. C/C=C\c1ccc(O)c(OC)c1 W=0.950
- N 2.3. C=O W=0.950
- N 2.4. C/C=C\c1ccc(OS(O)=O)c(OC)c1 W=0.750
- N 2.5. C/C=C\c1ccc(OC2C(O)C(O)C(O)C(O)O2)c(OC)c1 W=0.700
- 848. C/C=C\c1ccc(O)c(OC)c1 MapR=no data skin\_sens\_exp=V.weak/N
- 1. Cc1ccc(NCCO)cc1O MapR=no data skin\_sens\_exp=Strong sensitizer Predict
- 3. CCCCC1=NC(C)C(C)=O)O1 MapR=no data skin\_sens\_exp=Strong sensitizer P

No Transformation

PGroup:0; EGroup:0; Id10004. [External Autoxidation] Autoxidation

423. Prob.=1.0000, Transf. rel. = 1.0000

Map of #782: C/C=C\c1ccc(O)c(OC)c1

tr.#423, Level=1, Quantity=4.375E-004 (Q total=4.79E-004), R=1.000, P(obtain)=0.700, P(metabolize)=0.999

423. Autoxidation

258. Oxidation to quinone methide

257. Oxidation

259. O-Dealkylation

259. O-Dealkylation

286. Sulphate conjugation

286. Sulphate conjugation

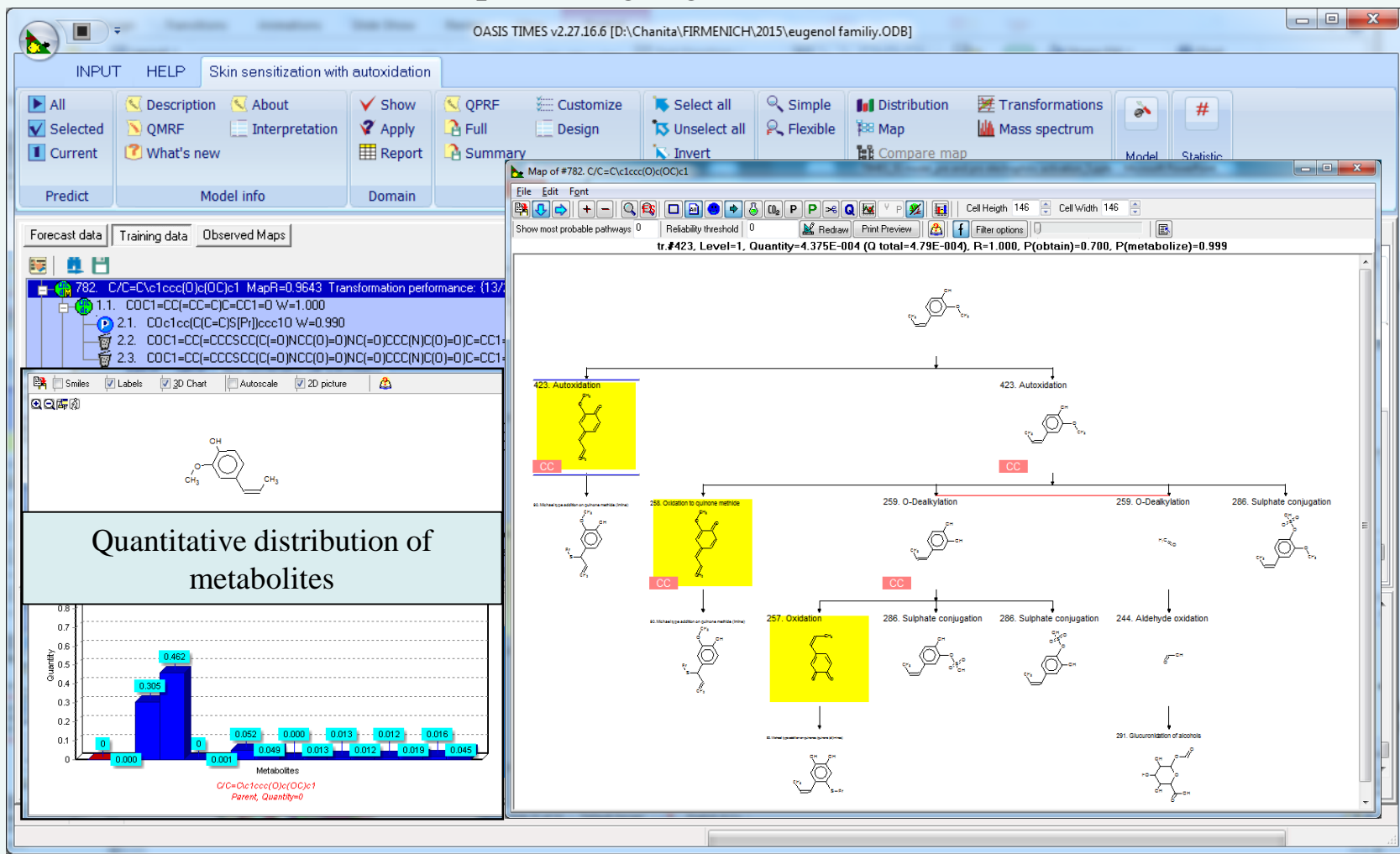
244. Aldehyde oxidation

281. Glucuronidation of alcohols

# 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

The screenshot displays the OASIS TIMES v2.27.16.6 software interface. The main window shows a metabolic map for the compound C/C=C/c1ccc(O)c(OC)c1 (tr.#423, Level=1, Quantity=4.375E-004). The map illustrates various metabolic pathways, with several metabolites highlighted in yellow, indicating they are activated. These include:

- 423. Autoxidation (highlighted)
- 257. Oxidation to quinone methide (highlighted)
- 259. O-Dealkylation (highlighted)
- 286. Sulphate conjugation (highlighted)

A red arrow points from the highlighted metabolite 423. Autoxidation in the metabolic map to a 'Chart of Alerts' window. This window displays a pie chart representing the distribution of alerts, with a legend listing: 'Quinone methide(s)/imines, Quinoid oxime structure, Nitroquinones'. The chart shows a significant portion of alerts corresponding to these categories. The interface also includes a top menu bar with 'INPUT' and 'HELP', a toolbar with various analysis tools, and a bottom panel with 'Alert Boundaries', 'Alert training set', 'Alert Performance', and 'Interaction Mechanism' buttons.

# Predicting skin sensitization in TIMES

## View of TIMES-SS model

The screenshot displays the OASIS TIMES v2.27.16.6 software interface. The main window title is "OASIS TIMES v2.27.16.6 [D:\Chanita\FIRMENICH\2015\ Eugenol family.ODB]". The interface includes a menu bar with "INPUT" and "HELP", and a toolbar with various icons for prediction, model information, domain, report, select, search, and metabolism. The main workspace shows a list of chemical structures with their SMILES and predicted skin sensitization values. The structure CC1=CC(=CC=C1)C=CC1=O is highlighted, with a predicted skin sensitization value of 1.1. A "Chart of Alerts" window is open, showing a sunburst chart with the text "Quinone methide(s)/imines, Quinoid oxime structure, Nitroquinones". A "Show Fragments" window is also open, displaying five chemical structures with RD4 labels. A red box highlights the "Alert Boundaries" button in the bottom left corner. A text box labeled "Alert Boundaries" is overlaid on the chart area. The "Current structure" window shows the chemical structure of the highlighted compound.

Forecast data | Training data | Observed Maps

782. C/C=C\c1ccc(O)c(O)c1 MapR=0.9643 Transformation performance: (13/20 0.650), skin\_sens\_exp=Strong sensitiser Predicted SkinSens=

1.1. COC1=CC(=CC=C1)C=CC1=O W=1.000

2.1. COc1cc(C[C=C]S[Pr])ccc1O W=0.990

Chart of Alerts

Quinone methide(s)/imines, Quinoid oxime structure, Nitroquinones

Alert Boundaries

Show Fragments

double click on the picture for more information

# Predicting skin sensitization in TIMES

## View of TIMES-SS model

The screenshot displays the OASIS TIMES v2.27.16.6 software interface. The main window shows a menu bar with 'INPUT' and 'HELP', and a toolbar with various icons. Below the toolbar, there are tabs for 'Forecast data', 'Training data', and 'Observed Maps'. A 'Chart of Alerts' window is open, showing a circular sunburst chart with many colored segments. The chart is titled 'Quinone methide(s)/imines, Quinoide oxime structure, Nitroquinones'. Below the chart, there are buttons for 'Alert Boundaries', 'Alert training set' (highlighted with a red box), 'Alert performance', and 'Interaction Mechanism'. The 'Alert Training set' window is also open, showing a table of chemical structures and their predicted values. The table has columns for '#', 'parent', and 'metabolite'. The first row shows a parent structure (a benzene ring with an amino group and a chlorine atom) and a metabolite (a quinone structure). The second row shows a parent structure (a benzene ring with an amino group and a chlorine atom) and a metabolite (a quinone structure with an imine group). The third row shows a parent structure (a benzene ring with an amino group and a chlorine atom) and a metabolite (a quinone structure with an imine group). The predicted values for all three rows are 'Strong sensitiser'. The observed values are also 'Strong sensitiser'. The window title is 'Alert Training set' and the subtitle is 'Quinone methide(s)/imines, Quinoide oxime structure, Nitroquinones, Local training set : 341 applications(number of parents and active metabolites)'. The window also has a 'References' button.

# Predicting skin sensitization in TIMES

## View of TIMES-SS model

The screenshot displays the OASIS TIMES v2.27.16.6 software interface. The main window shows a 'Chart of Alerts' with a sunburst chart representing the distribution of alerts. The chart is divided into many segments of various colors, with a prominent yellow segment. The chart is titled 'Quinone methide(s)/imines, Quinoide oxime structure, Nitroquinones'. Below the chart, there are buttons for 'Alert Boundaries', 'Alert training set', 'Alert performance', and 'Interaction Mechanism'. The 'Alert training set' button is highlighted with a red box.

An 'Alert Training set' window is open, showing a list of training sets. The first entry is 'Quinone methide(s)/imines, Quinoide oxime structure, Nitroquinones' with a local training set of 341 applications. The observed and predicted values are both 'Strong sensitiser'. A 'References' button is highlighted with a red box, and a red arrow points to a 'ChoiceObservedValueForm' dialog box. The dialog box shows the chemical structure of the parent compound (4-aminobenzene-1,3-diol) and the metabolite (4-aminobenzene-1,3-dione). The parameter name is 'SKIN\_SENSITISATION\_\_LLNA' and the value is '3.0000'. The 'Reference' button is highlighted with a blue box.

The 'ChoiceObservedValueForm' dialog box also shows the chemical structure of the parent compound and the metabolite. The parameter name is 'SKIN\_SENSITISATION\_\_LLNA' and the value is '3.0000'. The 'Reference' button is highlighted with a blue box.

The 'Alert Training set' window also shows a table with columns for '# parent' and 'metabolite'. The first entry shows the parent compound (4-aminobenzene-1,3-diol) and the metabolite (4-aminobenzene-1,3-dione). The observed and predicted values are both 'Strong sensitiser'. The 'References' button is highlighted with a blue box.

The 'Alert Training set' window also shows a table with columns for '# parent' and 'metabolite'. The first entry shows the parent compound (4-aminobenzene-1,3-diol) and the metabolite (4-aminobenzene-1,3-dione). The observed and predicted values are both 'Strong sensitiser'. The 'References' button is highlighted with a blue box.



# Predicting skin sensitization in TIMES

## View of TIMES-SS model

The screenshot displays the OASIS TIMES v2.27.16.6 software interface. The main window shows a 'Chart of Alerts' with a sunburst chart for 'Quinone methide(s)/imines, Quinoide oxime structure, Nitroquinones'. The 'Alert Training set' window is open, showing a table of parent and metabolite structures. The 'ChoiceObservedValueForm' window is also open, displaying a chemical structure and a table of parameter names and values. The 'Model Browser' window is open, showing a list of models and their descriptors.

**Alert Training set**

Quinone methide(s)/imines, Quinoide oxime structure, Nitroquinones,  
Local training set : 341 applications(number of parents and active metabolites)

observed and predicted chemical's values  
Observed: Strong sensitiser Predicted: Strong sensitiser

| # | parent                    | metabolite                    |
|---|---------------------------|-------------------------------|
| 9 | <chem>Nc1ccc(N)cc1</chem> | <chem>O=C1C=CC(=O)C=C1</chem> |

**ChoiceObservedValueForm**

Nc1ccc(N)cc1

| Parameter names         | Value  |
|-------------------------|--------|
| SKIN_SENSITISATION_LLNA | 3.0000 |

**Model Browser**

| ModelID | Model descriptors | Model parameters   |
|---------|-------------------|--------------------|
| M20     | NAME              | SKIN_sensitisation |
| M21     | AUTHOR            | Unilever           |
| M22     | DATE              | 1/1/2002           |
| M23     | BIOASSAY          | LLNA               |
| M24     | ORGAN/TISSUE      |                    |
| M25     | CONDITIONS        |                    |
| M26     | ADMINISTRATION    | LMC,BUL            |
| M27     | SOURCE            | Unilever           |
| M28     | VALUE DATA        | Strongly positive  |
| M29     | COMMENT           |                    |
| M30     |                   |                    |
| M31     |                   |                    |
| M32     |                   |                    |
| M33     |                   |                    |
| M34     |                   |                    |
| M35     |                   |                    |
| M36     |                   |                    |
| M37     |                   |                    |

**Experimental data**

**Source of the experimental data**



# Predicting skin sensitization in TIMES

## View of TIMES-SS model

The screenshot displays the OASIS TIMES v2.27.16.6 software interface. The main window shows a 'Chart of Alerts' with a sunburst chart and a list of alerts. A red box highlights the 'Alert Performance' button in the bottom left. An 'Alert performance' dialog box is open, showing details for the alert 'Quinone methide(s)/imines, Quinoide oxime structure'. The dialog includes a list of transformation IDs (81-93), alert information, and performance metrics: Alert performance: 0.908, Correct applications: 138, and Incorrect applications: 14. A chemical structure is shown on the right. Below the dialog, a table displays the predicted skin sensitization status for various source and product combinations.

Alert performance

**Quinone methide(s)/imines, Quinoide oxime structure**

# Transformation(s) included in this alert  
81 82 83 84 85 86 87 88 89 90 91 92 93

Alert information

**Alert performance : 0.908**

Correct applications: 138      Incorrect applications: 14

save to file

Chemical structure: CC1=CC(=C(C=C1)C=O)C=C

| No  | Source specify | Source | Arrow | Products | Forbidd |
|-----|----------------|--------|-------|----------|---------|
| 423 |                |        | →     |          |         |

# Predicting skin sensitization in TIMES

## View of TIMES-SS model

The screenshot displays the OASIS TIMES v2.27.16.6 software interface. The main window is titled "Mechanistic justification of the alert" and is highlighted with a red border. The interface includes a menu bar (INPUT, HELP), a toolbar with various icons, and a main content area. The main content area is divided into several sections:

- Mechanistic Domain:** Michael addition
- Mechanistic Alert:** Quinoid type compounds
- Structural Alert:** Quinone methide(s)/imines, Quinoid oxime structure, Nitroquinones, Naphthoquinone(s)/imines

The text explains that the chemical is a strong sensitizer due to Michael type addition on a quinone methide (imine). A chemical reaction scheme shows the reaction of a quinone methide (a benzene ring with a carbonyl group and a methylene group at the ortho position) with a protein residue (represented by a sulfur atom bonded to a proline ring, -S-Pr). The product is a Michael adduct where the methylene carbon has added to the carbonyl carbon, forming a new C-C bond and a C-S bond.

Ortho-quinones and para-quinones react with proteins via 1,4-addition of lysine NH<sub>2</sub> or cysteine SH groups across the ring system. They often are formed by oxidation of para and ortho dihydroxy aromatics acting as pro-Michael acceptors. These acceptors are able to be converted to Michael acceptors by well-established transformations (metabolic or abiotic), for example, hydroquinone oxidized to benzoquinone. Michael-type addition provides a means of covalent adduct formation at an electrophilic center, without any leaving group. The groups comprising the Michael-type acceptor can be arranged either in an open chain or in the form of a ring such as quinone.

Ortho-aminophenols and para-aminophenols, after metabolic or abiotic transformations, form quinone imines that react with proteins via Michael type addition.

Nitrophenols, after metabolic or abiotic transformation (keto-acid tautomerism), form nitro quinones that react with proteins via Michael type addition.

For example, 2,4-dinitrophenol is a cellular metabolic poison. Allergic reactions can include hives, blisters, and/or inexplicable rashes.

In the bottom left corner of the software interface, there is a "Chart of Alerts" window showing a sunburst chart with the text "Quinone methide(s)/imines, Quinoid oxime structure, Nitroquinones". Below the chart are several buttons: "Alert Boundaries", "Alert training set", "Alert Performance", and "Interaction Mechanism", which is highlighted with a red box.

# Predicting skin sensitization in TIMES

Patlewicz G, Kuseva C, Mehmed A, Popova Y, Dimitrova G, Ellis G, Hunziker R, Kern P, Low L, Ringeissen S, Roberts DW, Mekenyan O, **TIMES-SS--recent refinements resulting from an industrial skin sensitisation consortium**, SAR QSAR Environ Res. 2014;25(5):367-91

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## **TIMES-SS – Recent refinements resulting from an industrial skin sensitisation consortium<sup>S</sup>**

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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**

# 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