Human Health Models

Skin sensitization

Laboratory of Mathematical Chemistry, Bulgaria

Outline

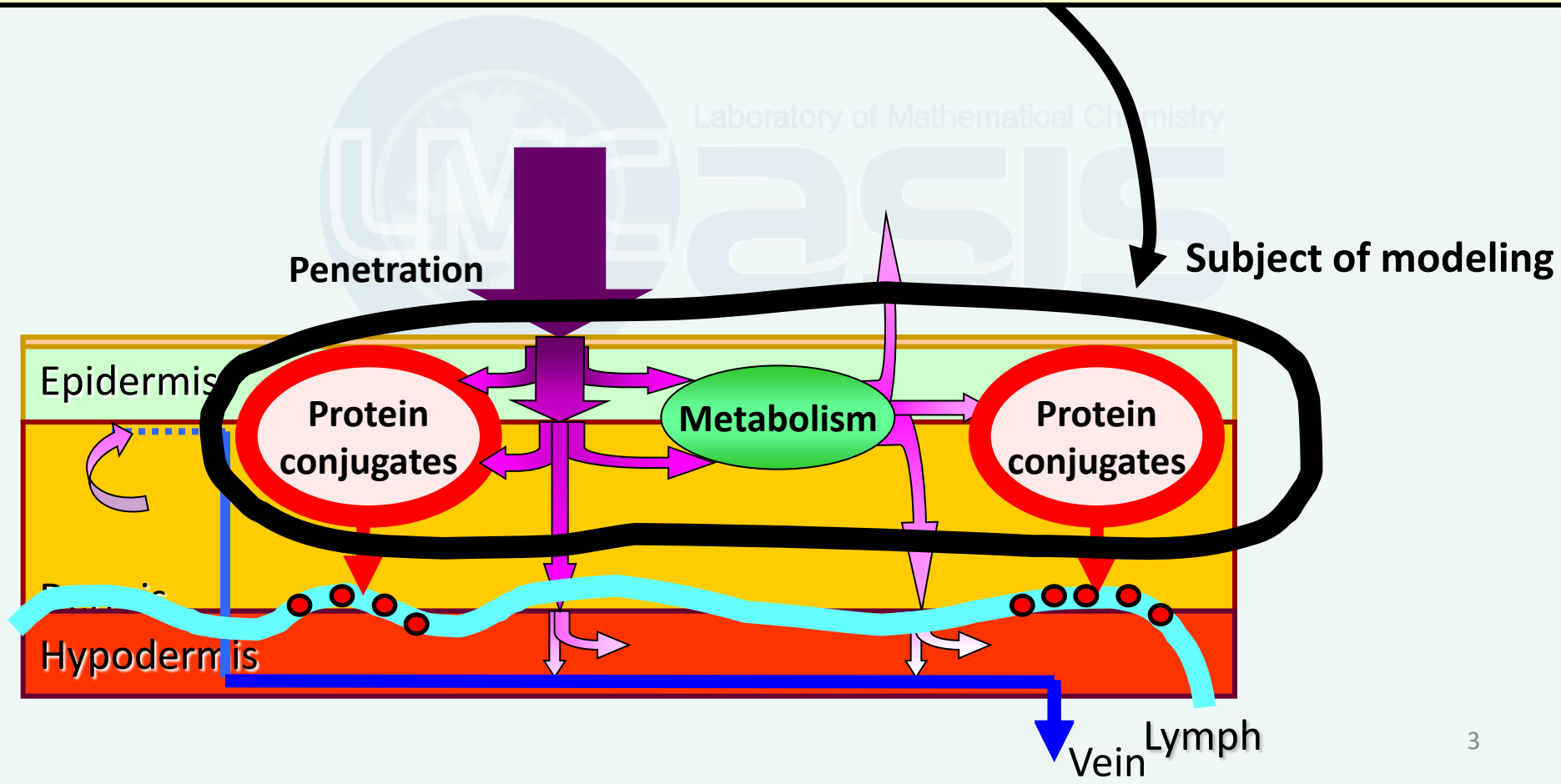
- Predicting skin sensitization in TIMES
- TIMES-SS model
- Applicability domain in TIMES (Q)SAR models
- Model performance
- Conclusions

Laboratory of Mathematical Chemistry

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



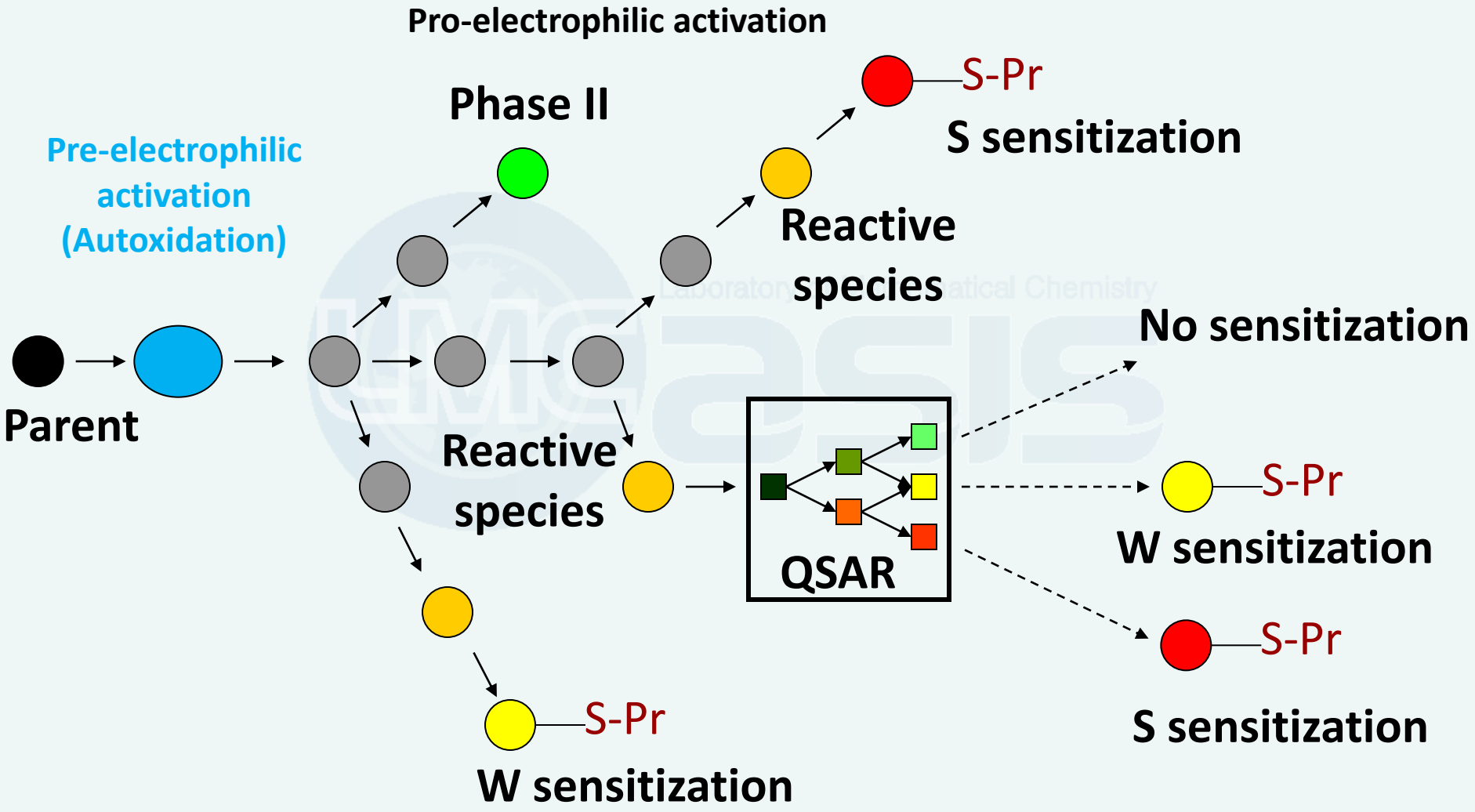
Predicting skin sensitization in TIMES
Main concept

- 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

Laboratory of Mathematical Chemistry

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



Predicting skin sensitization in TIMES
TIMES-SS model

1) Estimates skin sensitisation potency by integrating a simulator for skin metabolism with (Q)SARs.
2) Training set of 875 chemicals with experimental data from three sources (436 LLNA, 568 GPMT and 171 BfR).
3) Predicts potency as one of three classes: strong, weak or non sensitising.
4) A multi-step applicability domain is incorporated into the model.

TIMES-SS model
Skin metabolic simulator

- Skin metabolic simulator contains around 380 hierarchically ordered transformations based on empiric and theoretical knowledge and peer-reviewed by human experts:
  - Non-enzymatic transformations:
    - Hydrolysis of salts
    - Autoxidation reactions
  - Enzyme-mediated reactions (*Phase I and Phase II*):
    - C-hydroxylation
    - Glucoronidation
    - .....
  - Protein binding reactions (PBR)

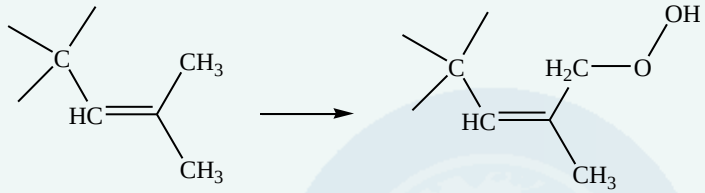
Laboratory of Mathematical Chemistry

TIMES-SS model

Different type of principal transformations

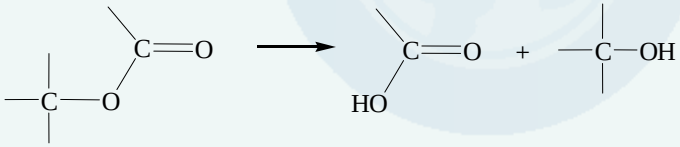
- **Autoxidation reactions**

  Allylic hydroperoxide formation



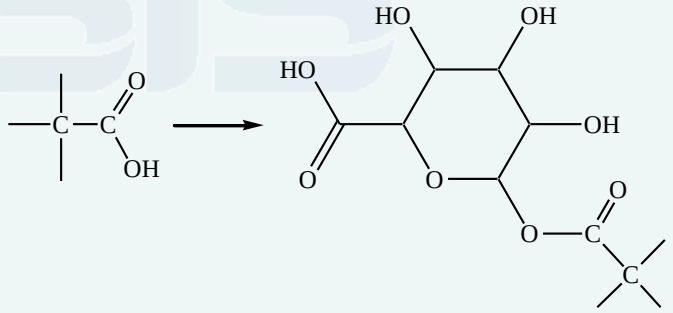
- **Phase I reactions**

  Ester hydrolysis



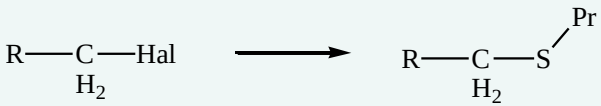
- **Phase II reactions**

  Glucoronidation



- **Proteins binding reactions**

Nucleophilic substitution on halogenated C sp3 atom



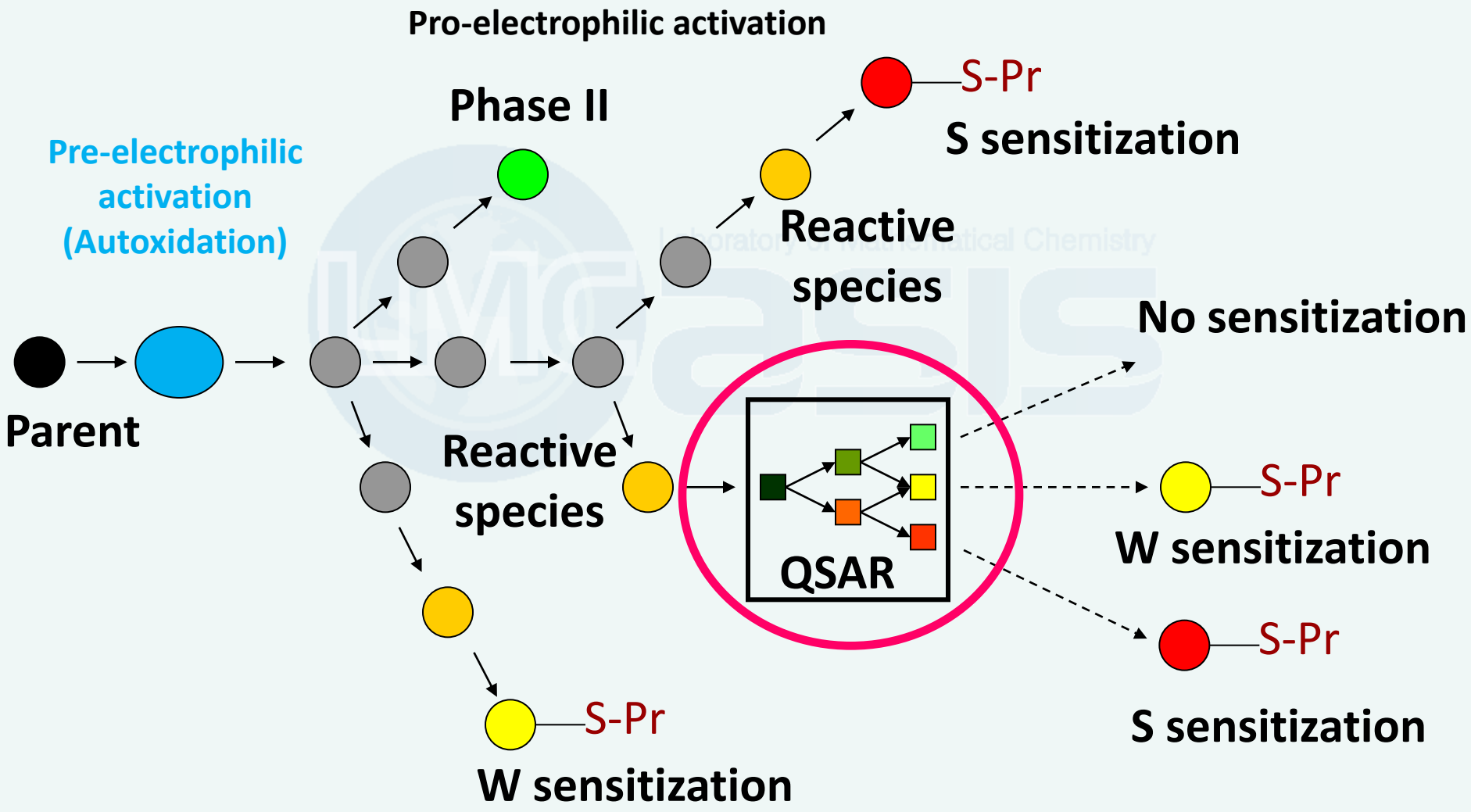
R = -C≡C, -C≡N, -C=C, -C=S, -C=O, $-NO_2$
Hal = Cl, Br, I

Schiff base formation with aldehydes

TIMES-SS model
Protein binding reactions

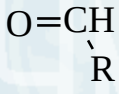
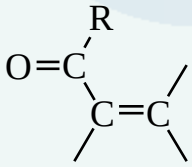
- Covalent interactions of chemicals/metabolites with skin proteins are described by almost 160 protein binding reactions (transformations).
- 3D-QSARs are applied for some of these transformations.
- Transformations characterized by same mechanism of interaction are combined in 97 alerts.
- The reliability of the reactions and alerts is assessed

TIMES-SS model
3D QSAR models



TIMES-SS model
3D QSAR models

- COREPA models of reactivity

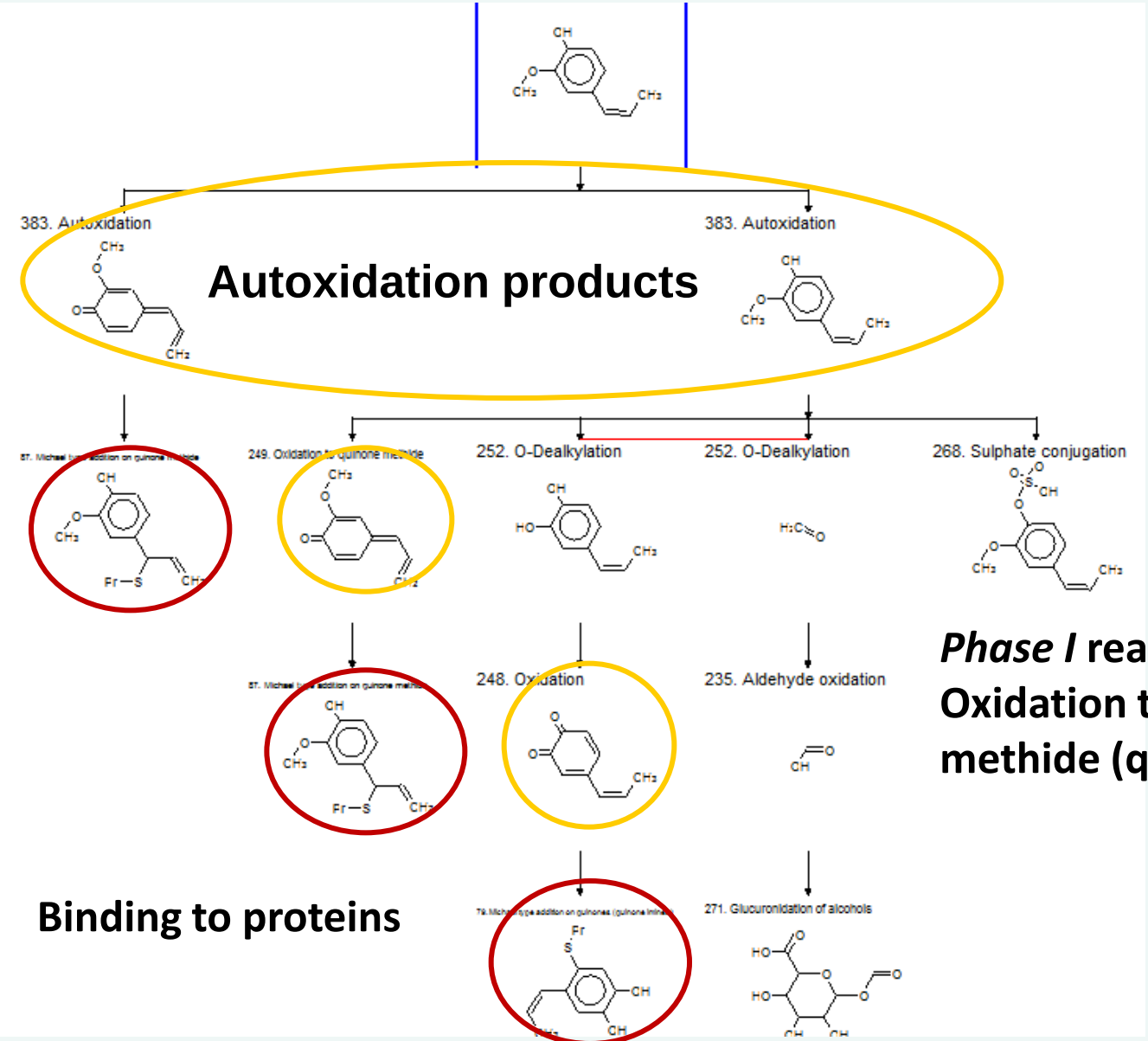
#	Alerting group	Chemical class	Descriptors in the corresponding COREPA model
1	 R = H, alkyl	Aldehydes	E_{HOMO} *MW*
2	 R = OC, C, N, S	Conjugated systems with electron withdrawing groups	Electronegativity E_{GAP} log K_{OW} *Accept DLC*

TIMES-SS model
Pre-electrophilic activation

- The Autoxidation reactions included in the skin simulator are “switched off”
- Autoxidation (AU) transformations are simulated by using an external AU simulator
- The external simulator containing more than 240 transformations, extracted from documented autoxidation pathways in the scientific literature, is applied on parent chemicals
- All generated unique autoxidation products are then submitted to skin sensitization model
- Parent structure is also submitted to skin model assuming that it is not fully autoxidyzed (kinetic data is not used)

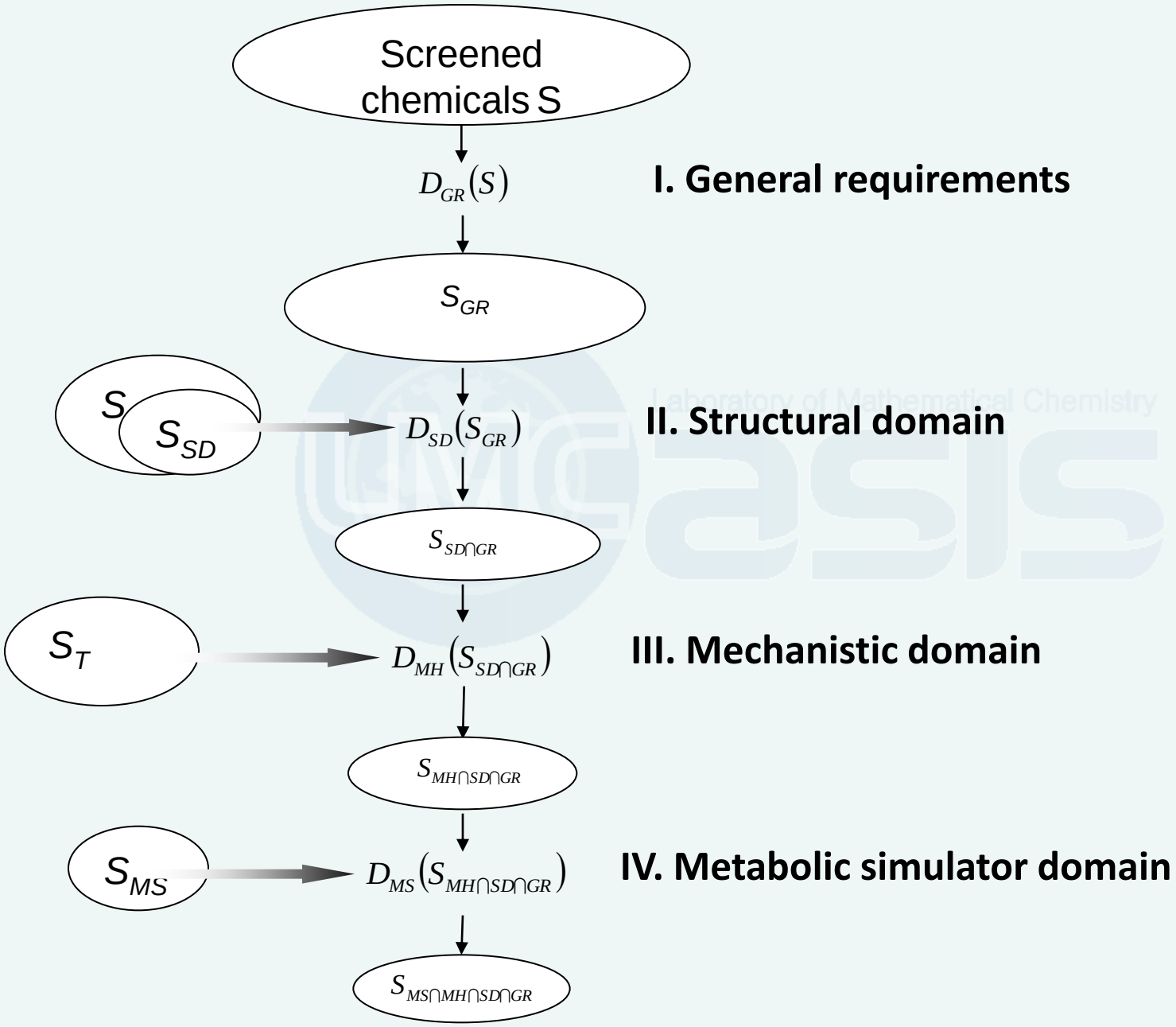
TIMES-SS using an external Autoxidation simulator

Predicted metabolism of isoeugenol



***Phase I* reactions: Oxidation to quinone methide (quinone)**

Applicability domain of TIMES (Q)SAR models



Laboratory of Mathematical Chemistry

Applicability domain of TIMES (Q)SAR models

DOMAIN:	Parents	Metabolites
• General Requirements	+	-
• Structural domain	+	-
• Mechanistic domain		
○ Interpolation space	+	+

Laboratory of Mathematical Chemistry

Applicability domain of TIMES (Q)SAR models

DOMAIN:	Parents	Metabolites
• General Requirements	+	-
• Structural domain	+	-
• Mechanistic domain		
○ Interpolation space	+	+

The ranges of the specified parameters (log K_{ow} and MW) are defined on the bases of parent structures from the training set which are correctly predicted by the model.

Laboratory of Mathematical Chemistry

Applicability domain of TIMES (Q)SAR models

DOMAIN:	Parents	Metabolites
• General Requirements	+	-
• Structural domain	+	-
• Mechanistic domain		
○ Interpolation space	+	+

Structural domain is represented by the list of atom-centred fragments (accounting for the first neighbours) extracted from the parent structures in the training set which were split into two subsets: chemicals correctly predicted by the model and incorrectly predicted chemicals.

Applicability domain of TIMES (Q)SAR models

DOMAIN:	Parents	Metabolites
• General Requirements	+	-
• Structural domain	+	-
• Mechanistic domain		
○ Interpolation space	+	+

This stage of the applicability domain of the model holds only for chemicals which have an alert group however an additional COREPA model is required. This layer of model domain is applied on parents and metabolites because the alert groups interacting with proteins could be obtained after metabolism of the parent chemical.

Laboratory of Mathematical Chemistry

Performance of the PBR and alerts
Reliability Criteria

1. Performance:
   - Transformation Performance - the ratio between the number of correct (Strong, Weak and Non sensitizers) predictions and the total number of chemicals within the local training set associated with the transformation
   - Alert Performance - the ratio between the number of correct (Positive and Negative) predictions and the total number of chemicals within the alert training set
   - In general, the alert performance is higher than the performance of the constituting transformations, because chemicals are classified as:
     - ✓Strong/weak/non – when transformation reliability is determined
     - ✓Positive/negative – when alert reliability is determined
2. Number of chemicals
3. Mechanistic justification

Laboratory of Mathematical Chemistry

Performance of the PBR and alerts
Reliability Criteria

Based on their performance PBR/alerts have been classified with:

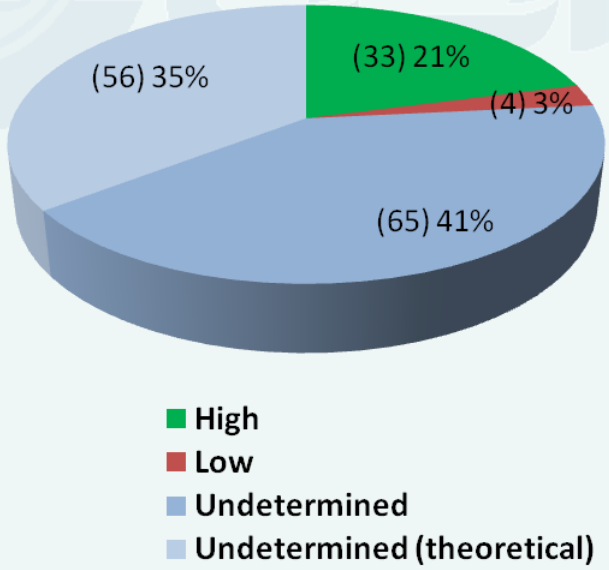
- **High** performance (perf. ≥ 60% and n ≥ 5)
- **Low** performance (perf. ≤ 60%)
- **Undetermined** (1< n <5)
- **Undetermined** theoretical

Laboratory of Mathematical Chemistry

Performance of the PBR and alerts
Reliability of PBR

Summary: Total number of PBR in the TIMES-SS model is 158

- **High** performance – 33
- **Low** performance – 4
- **Undetermined** (1< n <5) – 65
- **Undetermined** theoretical – 56



Performance of the PBR and alerts
Reliability of PBR

Options for minimizing the number of:

- PBRs with **low performance** - the PBRs will be reassessed by expert and adjusted in TIMES-SS if necessary.

- PBRs with **Undetermined performance** - If the expert is certain in the reactivity of the PBR it will be flagged as “Reliable according to 3rd party expert”.

Performance of the PBR and alerts

Reliability of PBR

PBRs have been review by Dr. David Roberts and coded by LMC in TIMES SS model

The following improvement have been reached

Performance of the TIMES-SS model

TIMES-SS - using the external Autoxidation simulator

Training set: 875 chemicals

Sensitivity:

Strong sens. 91%

Weak sens. 52%

Specificity: 70%

Concordance: 76%

Conclusions

- Prediction of skin sensitization is provided in a single modeling platform accounting for specific metabolism and protein adducts formation.
- Criteria for reliability of protein binding reactions have been introduced.
- Numbers of protein binding reactions with low and undetermined reliability have been reassessed by human expert (Dr. Roberts).
- Sets of protein binding reactions having the same mechanism of interaction have formed different alerting groups.

Laboratory of Mathematical Chemistry