Simulating autoxidation kinetics for safety assessment of industrial chemicals

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ABSTRACT

Autoxidation (AU) is a spontaneous, air-induced oxidation of organic molecules. It is a free- radical chain reaction of a chemical with molecular oxygen, resulting in the formation of oxidation products. Among the latter, organic hydroperoxides are regarded as the most important with respect to eliciting adverse effects such as contact allergy [1]. AU significantly increases sensitizing potency by the formation of highly allergenic oxidation products. Allergic contact dermatitis is one of the most common health problems in the industrialized world, and an estimated 20% of the normal population in Western Europe is sensitized to one or more chemicals in the environment [3]. However, current *in silico* models to predict skin sensitization fail to identify compounds, forming sensitizing products by AU (pre-haptens). Therefore the model AU kinetics is developed for predicting the extent of AU at different time frame.

INTRODUCTION

AU is abiotic (non-enzymatic) process affected by both the chemical molecular structure and the experimental conditions. The aim of this work is the development of:

- AU simulator for prediction of the AU products and pathways
- Kinetic AU model for predicting the quantities of parent chemicals and their products as function of time, assuming the first-order kinetics

MATERIALS AND METHODS

Database consisting of experimentally observed (documented) AU pathways for 60 chemicals was used as training set.
Structurally diverse chemicals were included in the training set such as terpenes, simple aliphatic and polyethyleneglycol ethers, aldehydes, aminophenols, etc., among which:

- 57 chemicals with observed AU pathways and quantitative data for the parents and AU products
- 3 chemicals with observed AU maps only

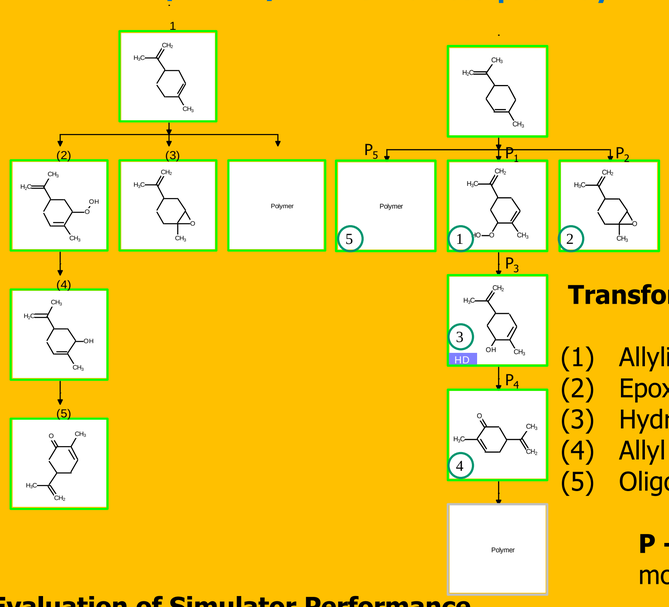
Experimental conditions, under which the published experiments were performed were as follows: air or oxygen exposure, room temperature, atmospheric pressure, AU in bulk or in the presence of different solvents, nearly neutral (pH 7 - 7,5) or slightly alkaline (pH 8 - 9) medium, duration of AU from a few hours to several months.

DEVELOPMENT OF AU MODELS: RESULTS AND DISCUSSION

Model 1: **AU simulator** containing generalized molecular transformations, extracted from the observed AU pathways, and rules for their application

Simulation of AU pathway of Limonene

Documented pathway **Simulated pathway**



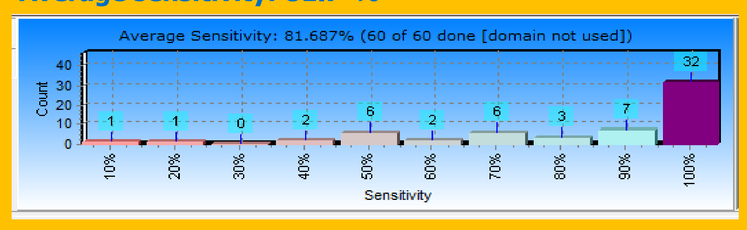
Transformations used:

(1) Allylic Hydroperoxide Formation; P_1 =0.03
(2) Epoxidation; P_2 =0.03
(3) Hydroperoxide Decomposition; P_3=0.26
(4) Allyl Alcohol Oxidation; P_4=0.38
(5) Oligomer Formation; P_5=0.38

P - probability of occurrence of each molecular transformation

Evaluation of Simulator Performance

Average sensitivity: 81.7 %



Model 2: **AU Kinetics** is based on experimental kinetics data for the chemicals from the training set.

Mathematical Formalism: [2]

$$Pj(k) = 1 - \exp(-k\,jt)$$

where P_j is the probability and k_j is surrogate of the first-order kinetic constant of the j [th] transformation

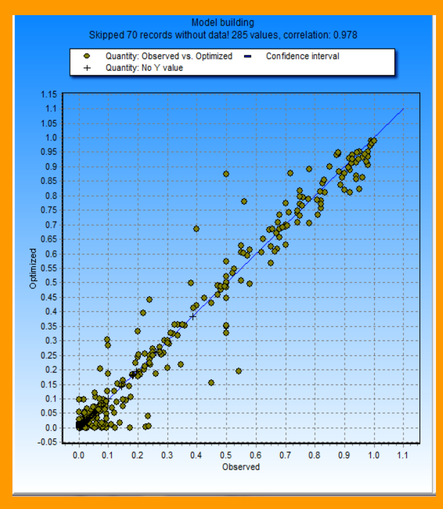
Model Parameterization – kinetics parameters are optimized statistically by the least square method.

$$\min_k RSS = \sum_{i=1}^{N} \left(Q_i^{obs} - Q_i^{calc}(k) \right)^2$$ (Non-linear method of Marquardt)

The kinetic parameters k_i are optimized by minimizing the RSS (residual sum of squares)

N - number of fitted data
Q_i^{obs} - observed values of quantity, mol/mol parent
$Q_i^{calc}(k)$ - predicted values of quantity

$$C_i(k) = C_{oi} e^{-kt}$$



Model Performance

Availability of quantitative data:

Total number of available kinetic data points – 358:

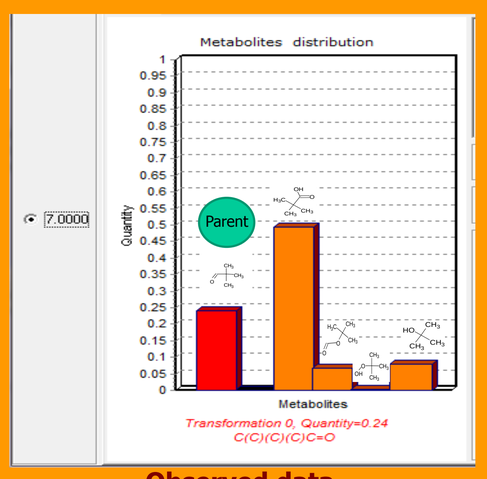
- 142 for parent chemicals
- 216 for AU products

Statistics of parent chemicals and products:

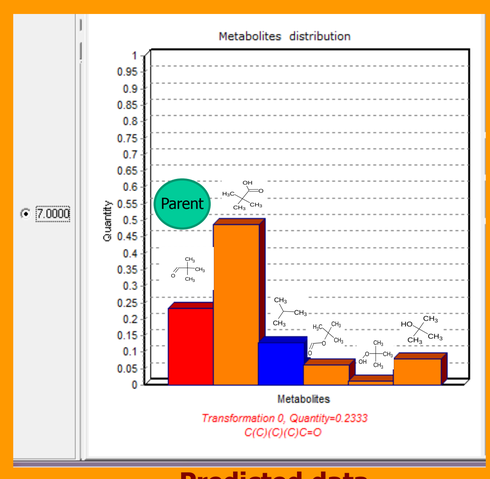
- **Fitted kinetic curves: 181**
- **Fitted quantitative data: 285**
- **Non-fitted quantitative data (expertly assigned probabilities) – 70**
- **Estimated kinetic constants: 178**

R^2 = 0,98 S^2 = 0.012

Predictability of observed quantities for 7 days of AU for Pivalaldehyde and its products

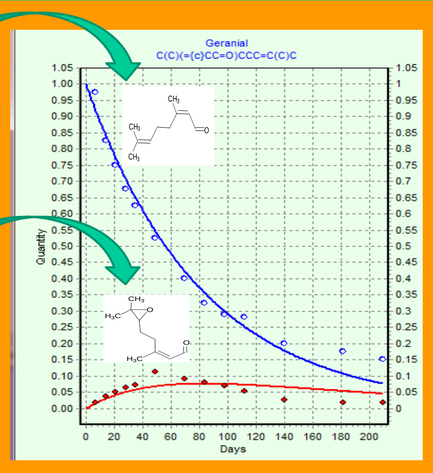


Observed data



Predicted data

Parent

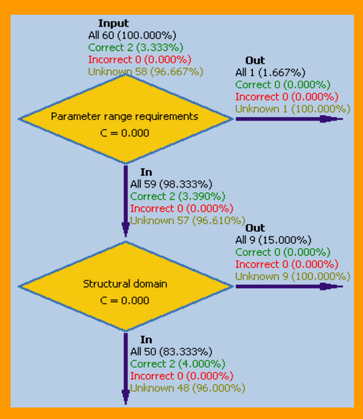


Product

Illustration of Model Predictions:

Predicted and observed quantitative AU data for Geranial:

- **-** observed quantity of Geranial (parent);
- - observed quantity of 6,7-Epoxygeranial (main oxidation product);
- - predicted quantity



Deriving Applicability Domain:

- Training chemicals (parents) were split into two subsets of correctly and incorrectly predicted chemicals, according to the 95% empirical confidence interval. Applicability domain is extracted on the basis of correctly predicted parent chemicals
- The applicability domain consists of two layers:
  - Parametric domain:
    MW ∈ [86.13 ; 616.80]
    log Kow ∈ [-2.33 ;17.64]
  - Structural domain

Conclusions

- **Two models for AU were developed: qualitative and quantitative**
- **The first model simulates the observed AU pathways:**
  - **Average sensitivity: 81.7%**
  - **Average predictability: 86,9 %**
- **The second model predicts the time variation of the observed quantitative data for parent chemicals and their AU products with good correlation: R^2 = 0,98**
- **Model predictions are accompanied by determination of applicability domains**

References:

1.Hagvall, L., , Doctoral Thesis, University of Gothenburg, **2009**, 1- 74
2.Dimitrov, S; Pavlov, T; *SAR and QSAR in Environmental Research*, 18, **2007**, 443- 457
3. Hagvall, L; Backtorp, C; Chem. Res. Toxicol. **2011**, 24, 1507–1515

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