Environmental and fate ecotoxicity models

CATALOGIC 301C (MITI) MODEL

Laboratory of Mathematical Chemistry, Bulgaria

Biodegradation CATALOGIC 301C model

Modeled phenomenon

Microbial aerobic degradation of organic chemicals, i.e. their conversion to CO_2, H_2O, and other non-organic molecules.

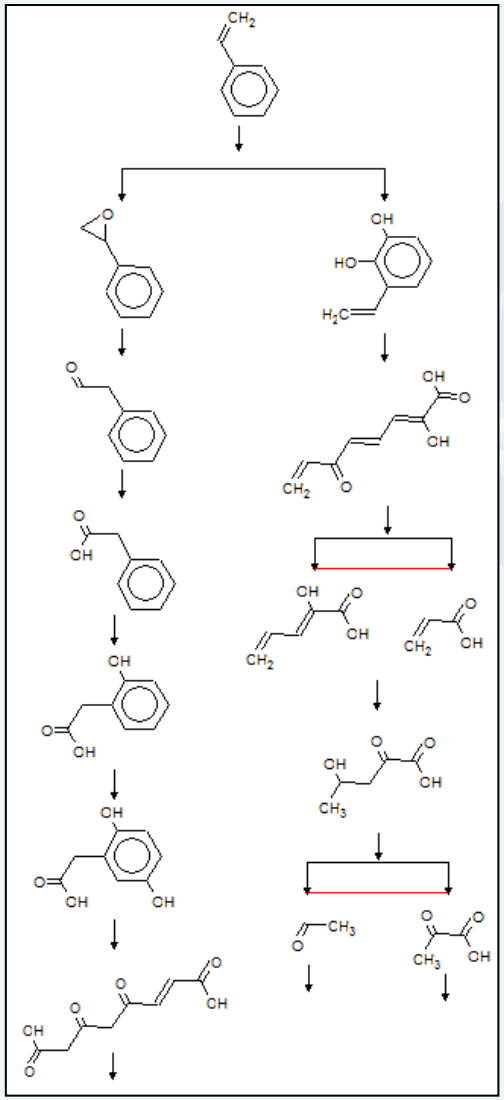
Modeled endpoint

The percentage of theoretical biological oxygen demand on 28^{th} day under MITI I (OECD 301C) test conditions :

$$BOD,\% = \frac{\text{Observed oxygen demand}}{\text{Theoretycal oxygen demand}} 100$$

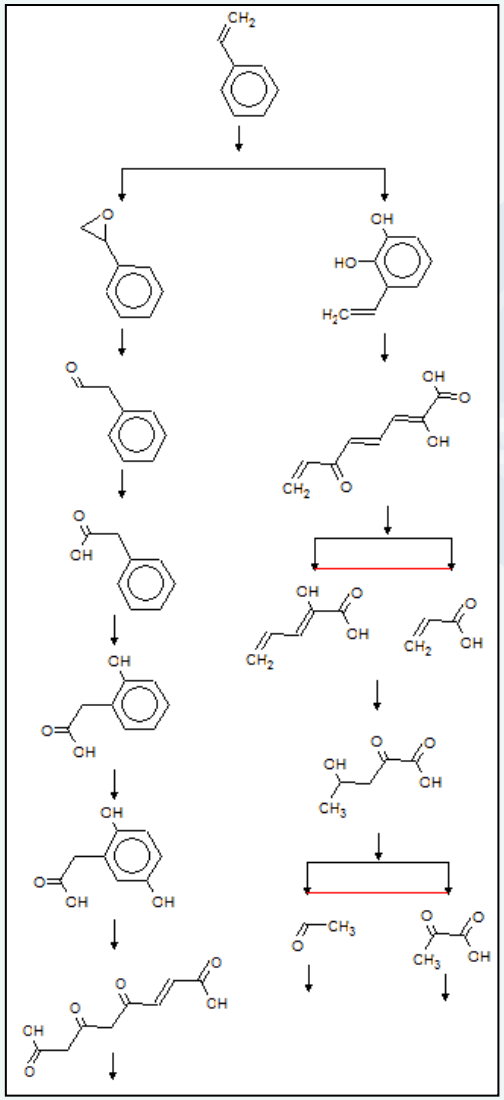
Mechanistic background

1. Biodegradation is a process of consecutive catabolic transformations.



Mechanistic background

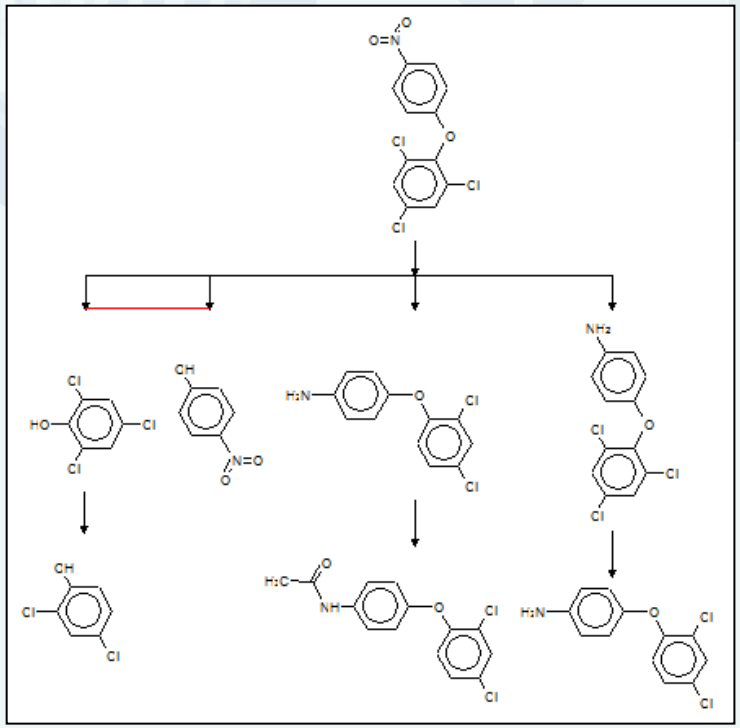
Obs. BOD = 100%



1. Biodegradation is a process of consecutive catabolic transformations.

2. The rate of transformations is different and have to be quantified.

Obs. BOD = 0%



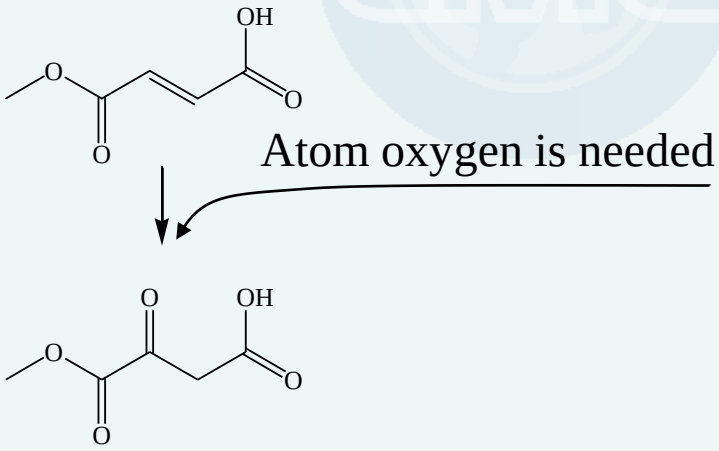
Mechanistic background

Aerobic biodegradation is conversion of organic compounds to CO_2 and H_2O.

1. Biodegradation is a process of consecutive catabolic transformations.

2. The rate of transformations should be quantified.

3. Oxygen demand, produced CO_2, and quantity of metabolites could be determined by the material balance of transformations.



Mechanistic background

Aerobic biodegradation is conversion of organic compounds to CO_2 and H_2O.

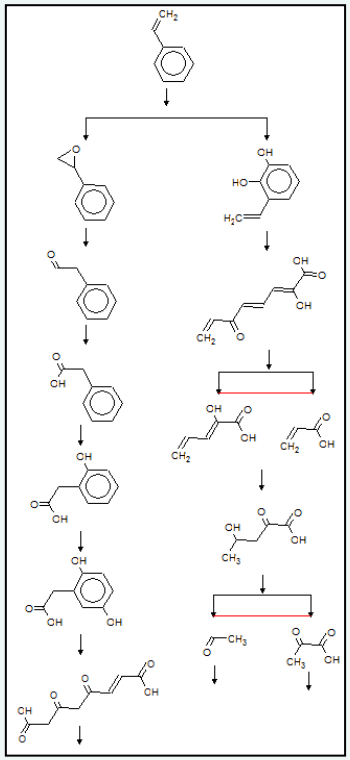
1. Biodegradation is a process of consecutive catabolic transformations.

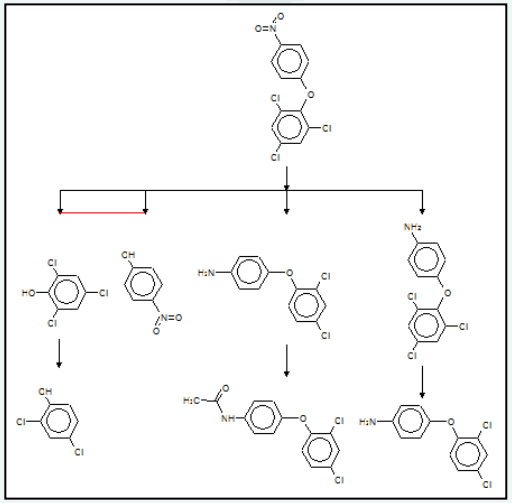
2. The rate of transformations is different and have to be quantified.

3. Oxygen demand, produced CO_2, quantity of metabolites could be determined by the material balance of transformations.

4.The catabolic pathway determines the overall material balance.

Different pathways - different material balances.





LMC modeling approach

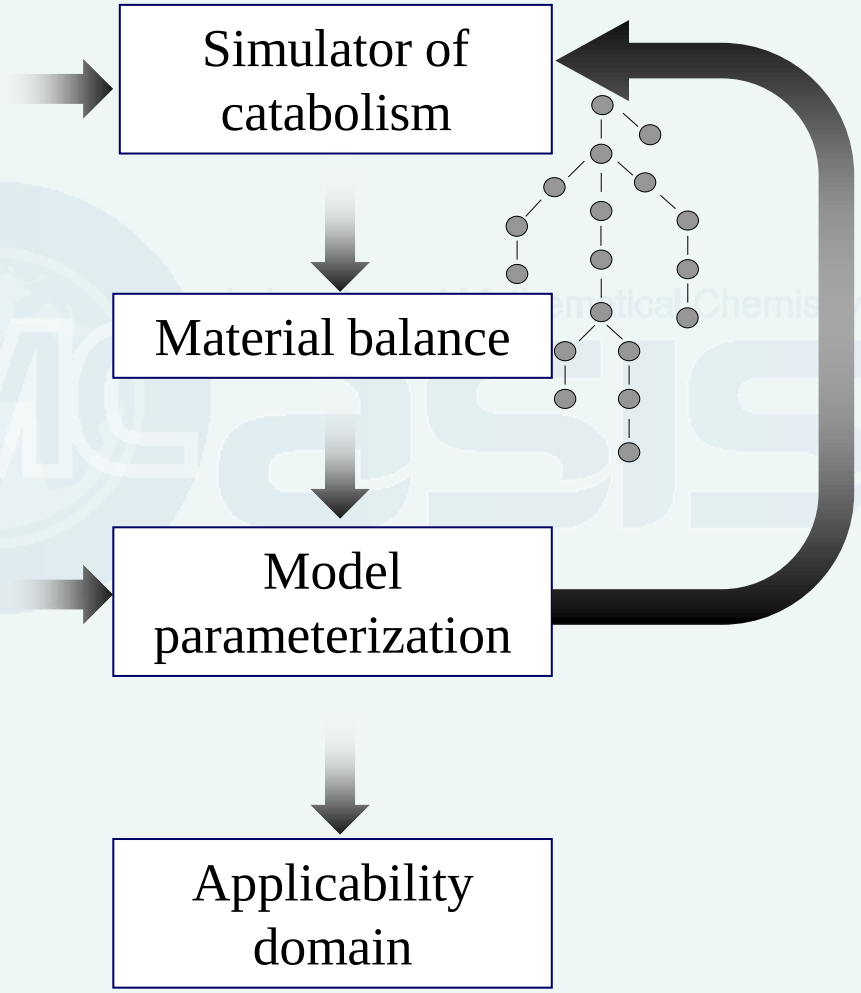
Observed microbial catabolism

550 chemicals

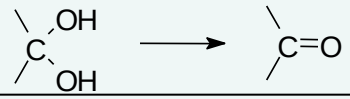
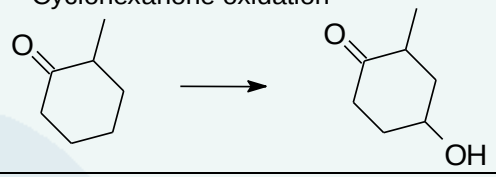
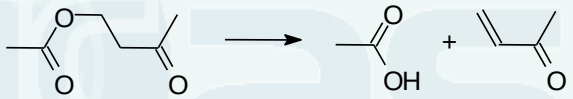
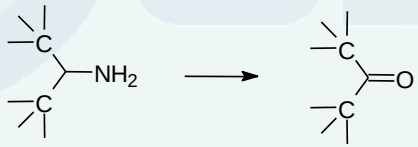
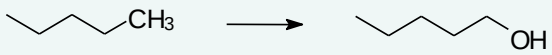
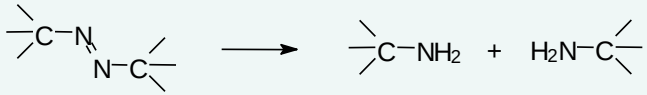
Observed BOD

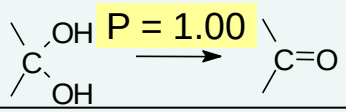
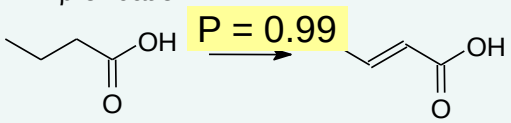
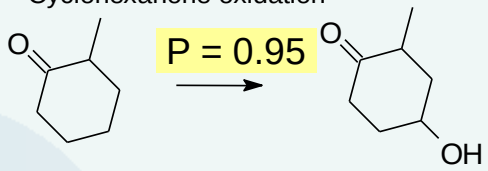
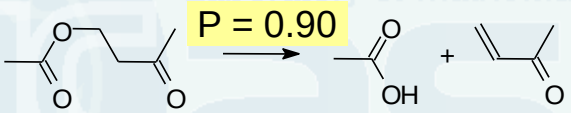
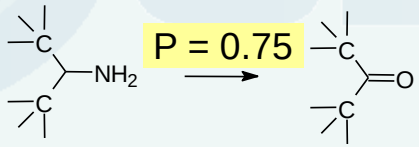
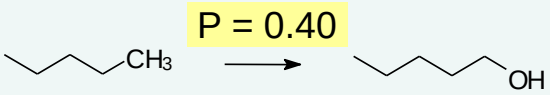
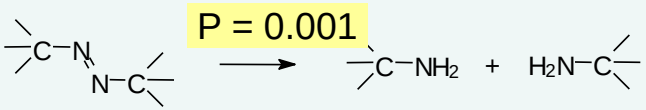
1078 chemicals

MITI I (OECD 301C) test



Simulation of catabolism

Principal transformations	Metabolites
Geminal diol decomposition 	
β-oxidation 	
Cyclohexanone oxidation 	
Ester hydrolysis 	
Amine decomposition 	
ω-Oxidation 	
Azo-bond cleavage 	

Substrate	Principal transformations	Metabolites
	Geminal diol decomposition 	
	β-oxidation 	
	Cyclohexanone oxidation 	
	Ester hydrolysis 	
	Amine decomposition 	
	ω-Oxidation 	
	Azo-bond cleavage 	

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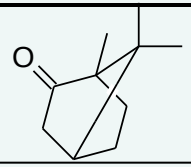
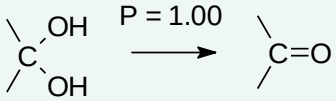
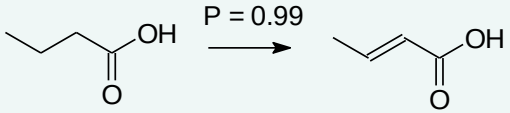
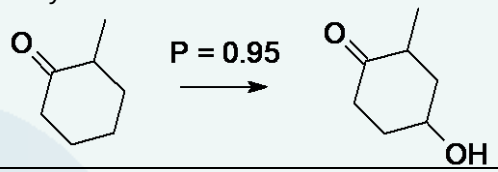
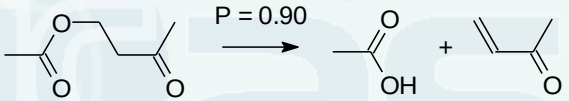
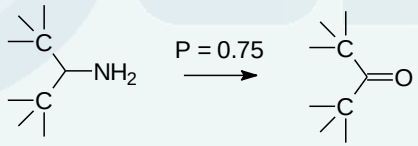
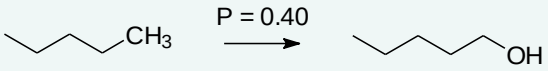
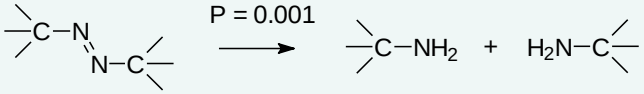
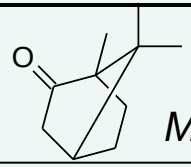
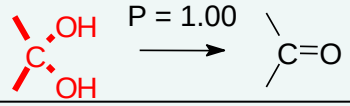
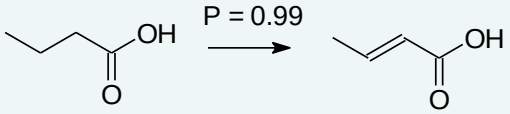
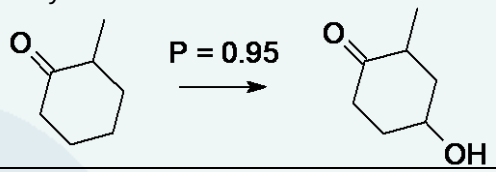
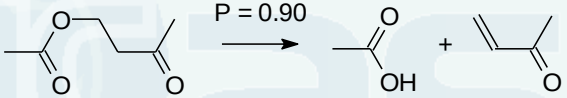
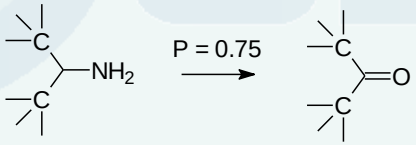
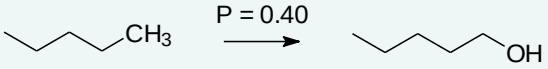
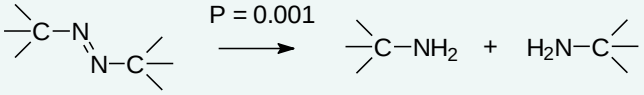
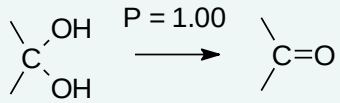
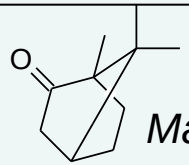
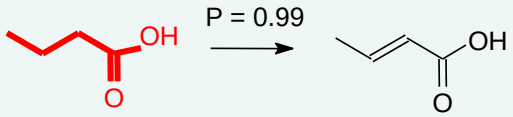
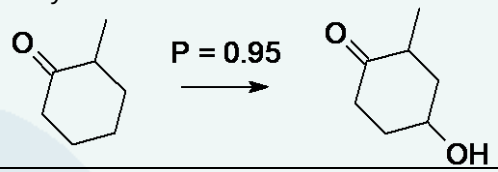
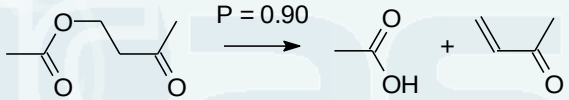
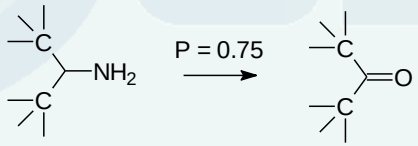
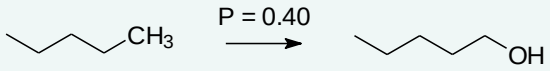
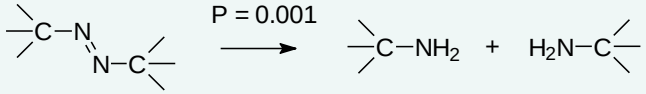
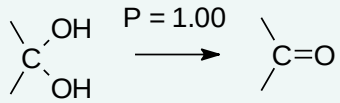
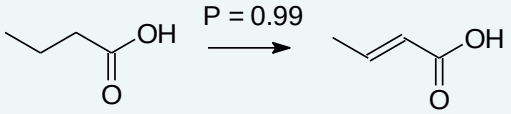
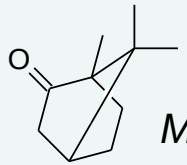
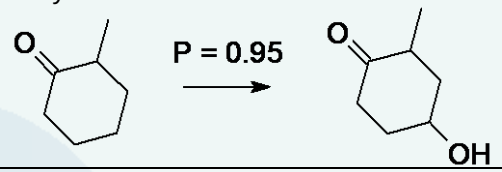
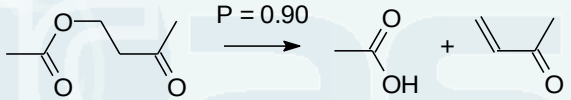
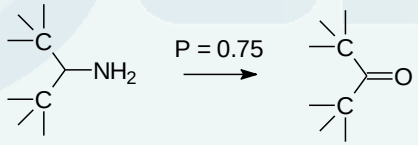
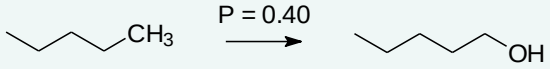
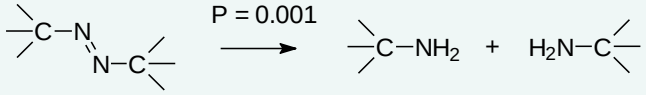
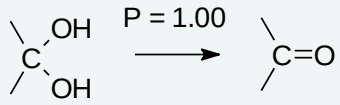
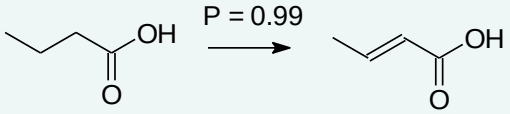
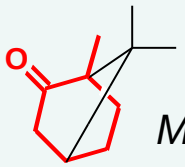
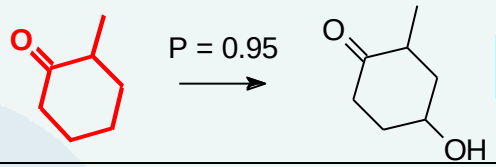
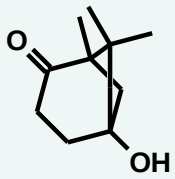
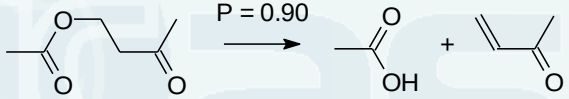
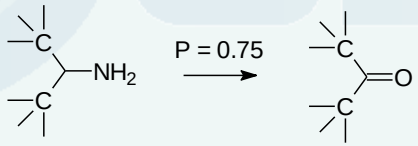
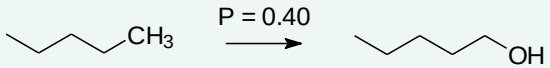
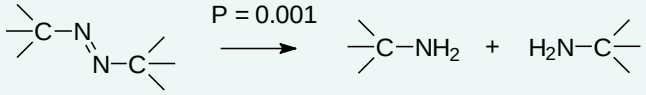
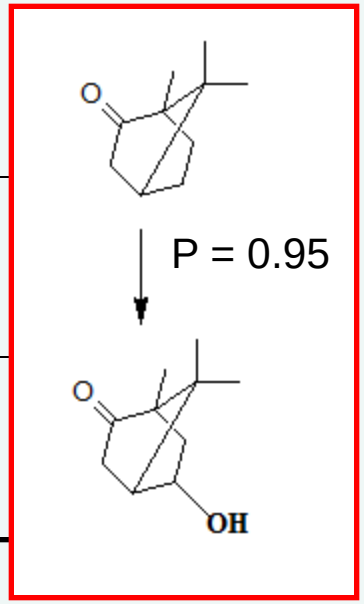
	Geminal diol decomposition 	
	β-oxidation 	
	Cyclohexanone oxidation 	
	Ester hydrolysis 	
	Amine decomposition 	
	ω-Oxidation 	
	Azo-bond cleavage 	

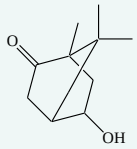
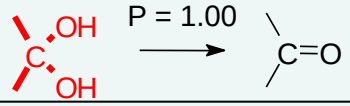
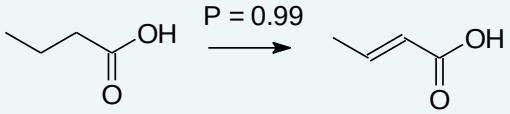
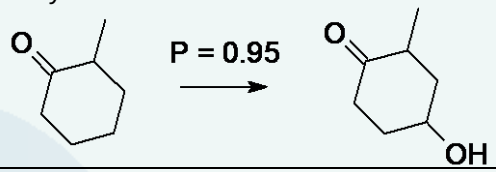
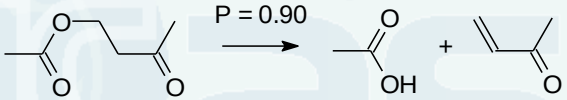
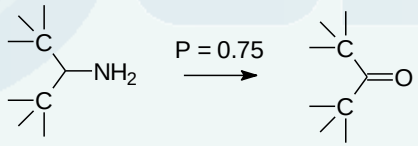
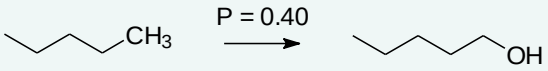
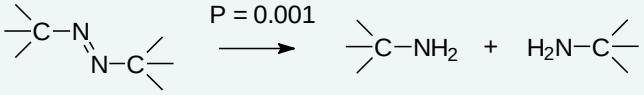
Substrate	Principal transformations	Metabolites
 *Match? - No!*	Geminal diol decomposition  P = 1.00	
	β-oxidation  P = 0.99	
	Cyclohexanone oxidation  P = 0.95	
	Ester hydrolysis  P = 0.90	
	Amine decomposition  P = 0.75	
	ω-Oxidation  P = 0.40	
	Azo-bond cleavage  P = 0.001	

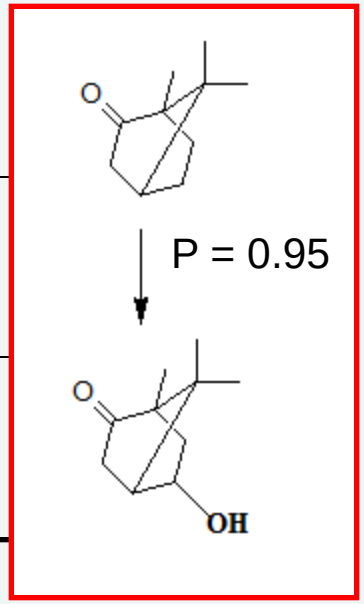
Substrate	Principal transformations	Metabolites
	Geminal diol decomposition 	
 *Match? - No!*	β-oxidation 	
	Cyclohexanone oxidation 	
	Ester hydrolysis 	
	Amine decomposition 	
	ω-Oxidation 	
	Azo-bond cleavage 	

Substrate	Principal transformations	Metabolites
	Geminal diol decomposition 	
	β-oxidation 	
 *Match?*	Cyclohexanone oxidation 	
	Ester hydrolysis 	
	Amine decomposition 	
	ω-Oxidation 	
	Azo-bond cleavage 	

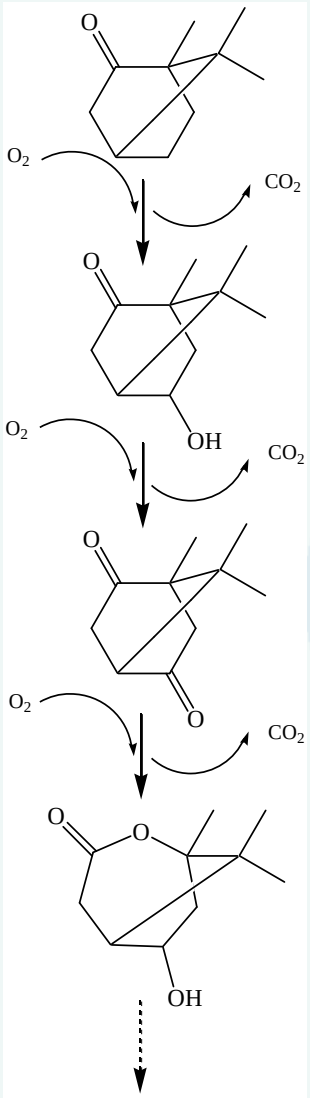
Substrate	Principal transformations	Metabolites
	Geminal diol decomposition 	
	β-oxidation 	
 *Match? - Yes!*	Cyclohexanone oxidation 	RESULT 
	Ester hydrolysis 	
	Amine decomposition 	
	ω-Oxidation 	
	Azo-bond cleavage 	



Substrate	Principal transformations	Metabolites
 *Match? - No!*	Geminal diol decomposition 	
	β-oxidation 	
	Cyclohexanone oxidation 	
	Ester hydrolysis 	
	Amine decomposition 	
	ω-Oxidation 	
	Azo-bond cleavage 	



Mathematical formalism



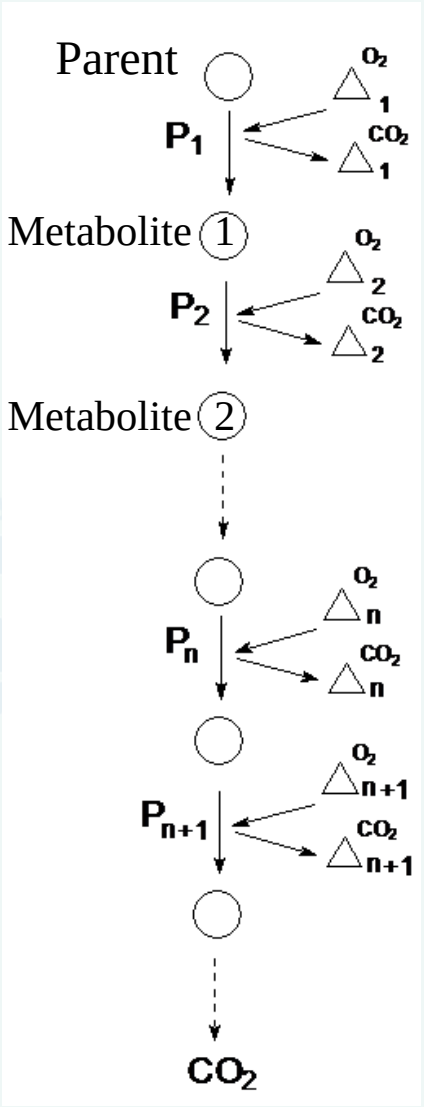
Formalization

Simulated catabolic pathways
Material balances
Transformation probabilities

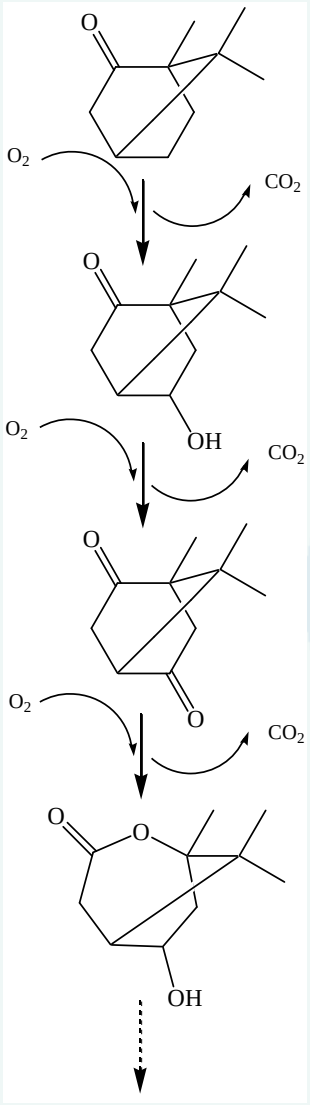
$$BOD,\% = \frac{\text{Predicted oxygen demand}}{\text{Theoretycal oxygen demand}} 100$$

Quantity of metabolites

Ultimate half-life



Mathematical formalism



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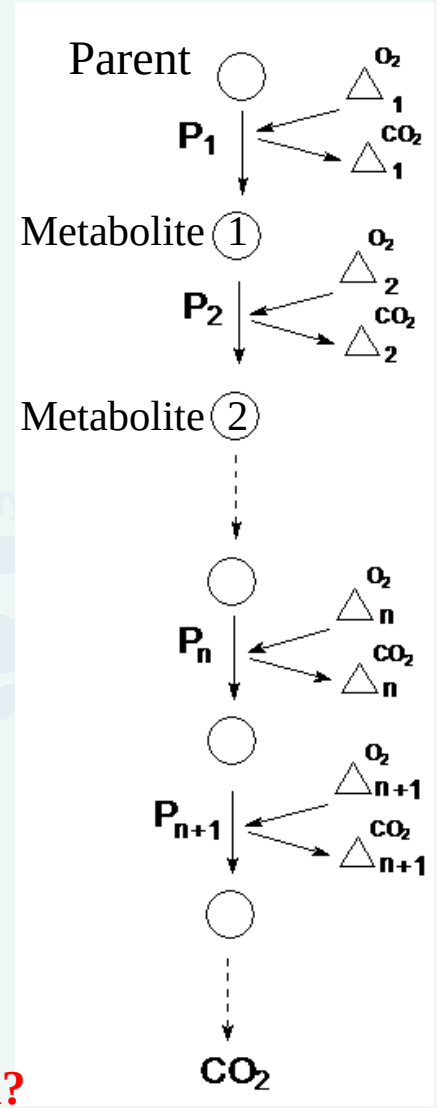
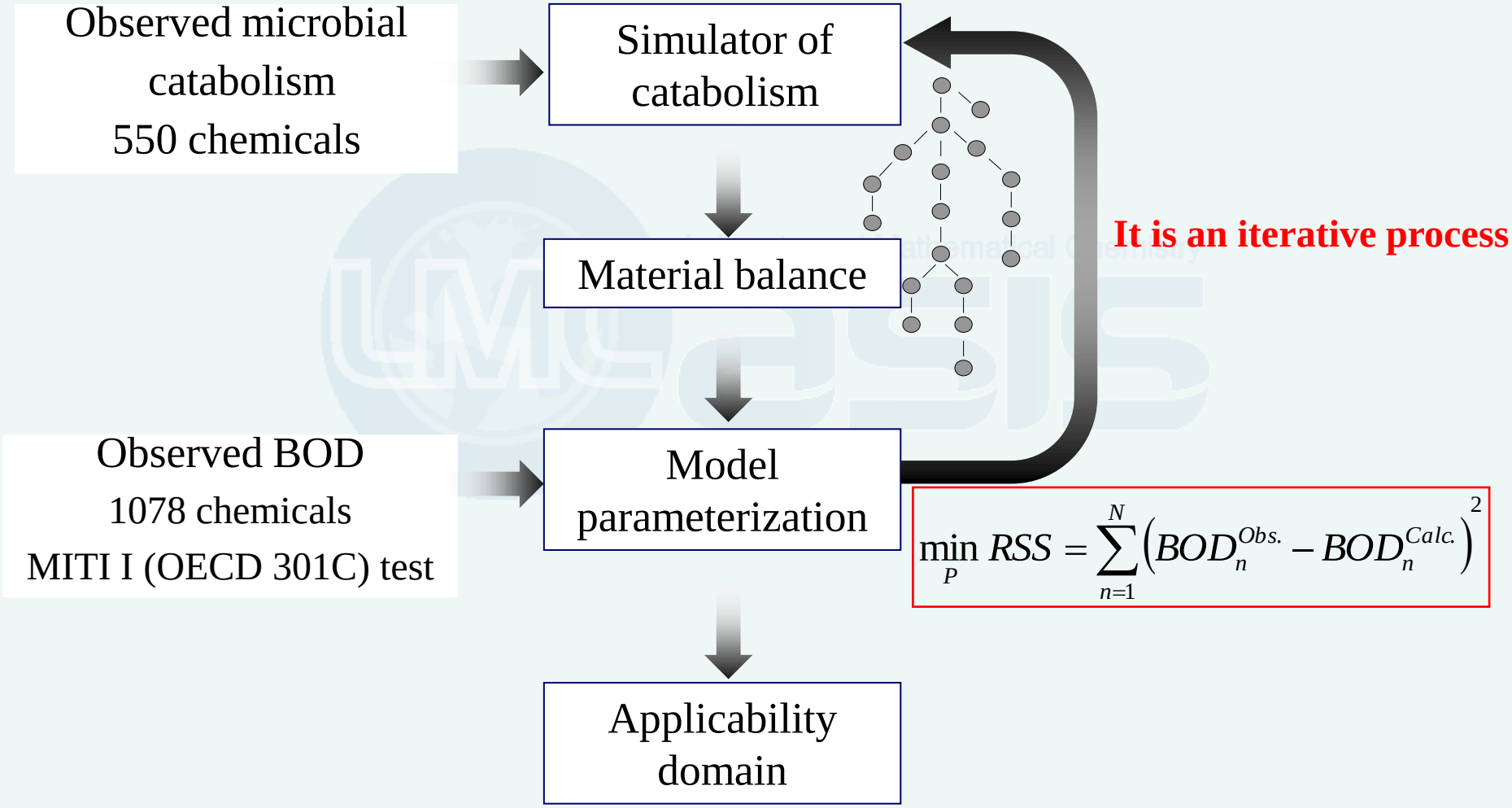
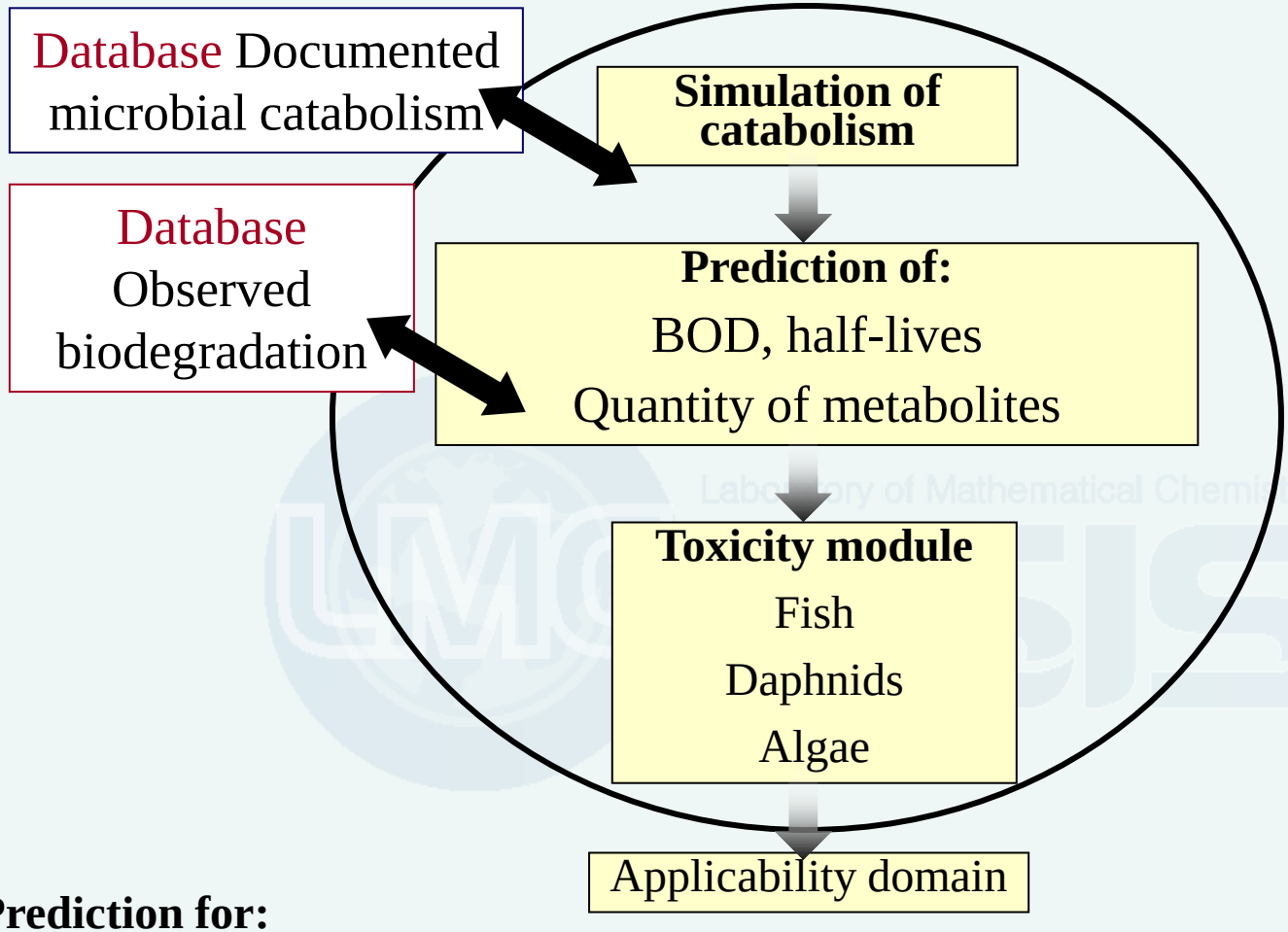


How the transformation probabilities are assessed?

Estimation of transformation probability



CATALOGIC 301C model



Prediction for:

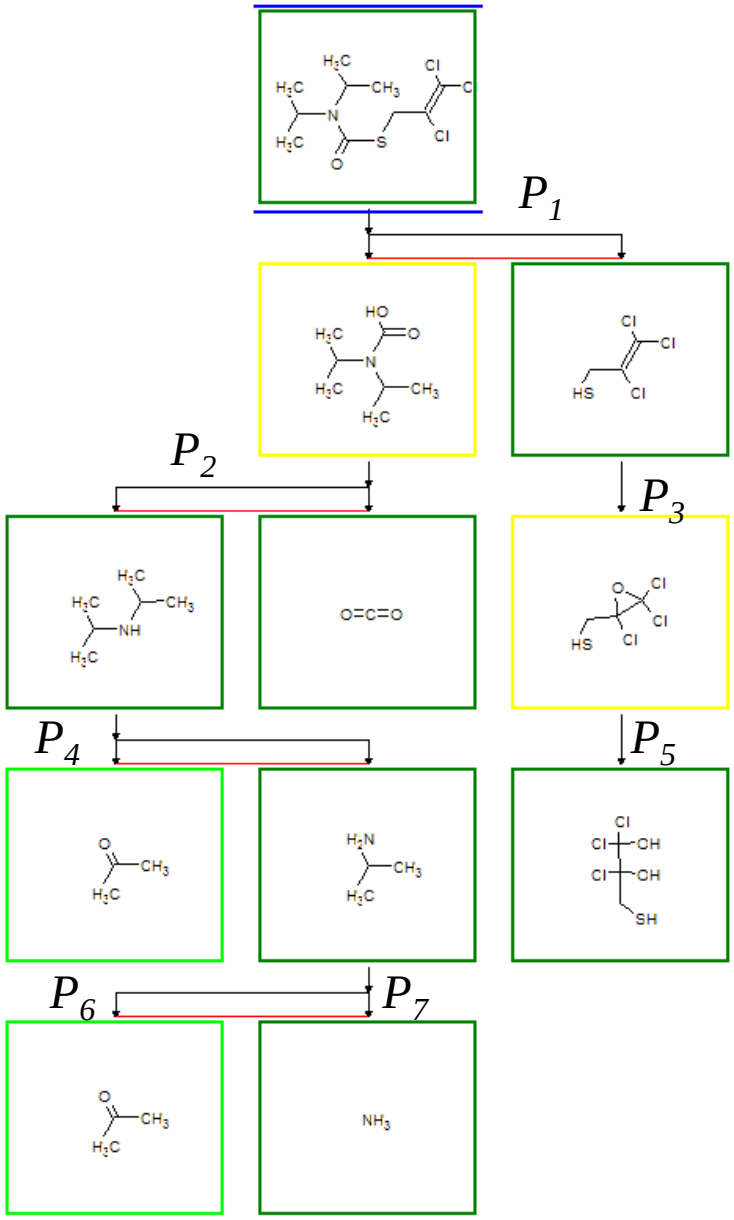
Overall biodegradation - BOD, $t_{1/2}$

Metabolites - Quantities, Probabilities to be formed, to be stable, or to metabolized

Toxicity - Parent chemical and selected metabolites

Search for analogues chemicals

Simulated catabolism



$P_m = 1.00$:

$$\text{Theoretical oxygen demand} = \sum_n \Delta_n^{O_2}$$

$$\text{Predicted oxygen demand} = \sum_n \Delta_n^{O_2} \prod_{m=1}^{n} P_m$$

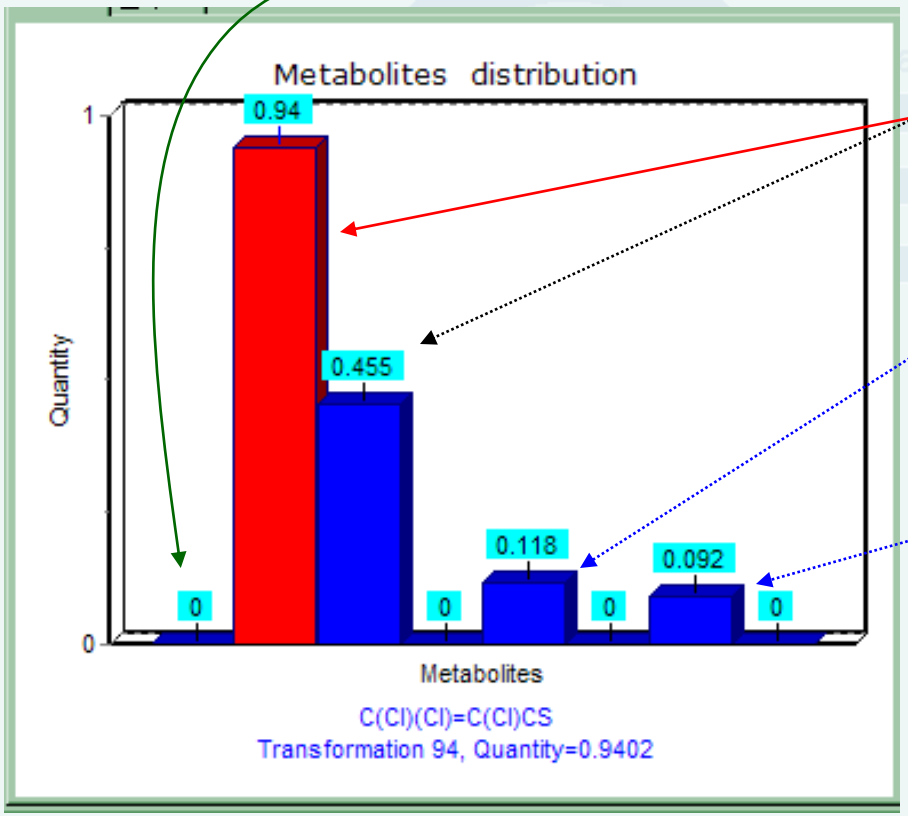
$$BOD^{Calc} = \frac{\sum_n \Delta_n^{O_2} \prod_{m=1}^{n} P_m}{\sum_n \Delta_n^{O_2}} 100$$

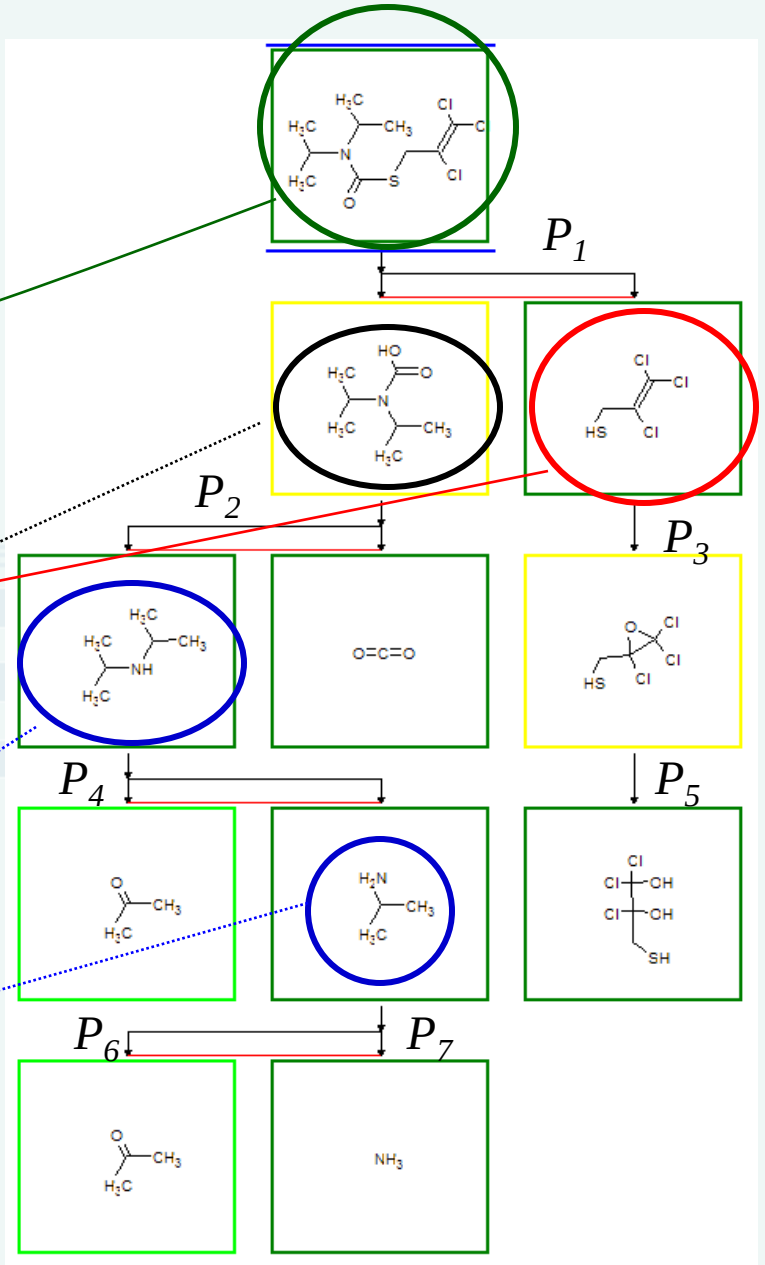
Quantities of metabolites

$$Q_n^{Calc} = Q_0^{Parent}\left(1 - P_{n+1}\right)\prod_{m=1\to n} P_m, \text{ mol}$$

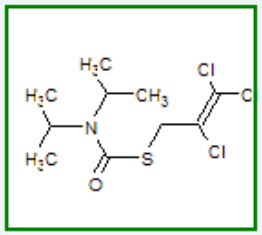
for $Q_0^{Parent} = 1\,mol$

$$Q_n^{Calc} = \left(1 - P_{n+1}\right)\prod_{m=1\to n} P_m, \text{ mol/mol parent}$$





Ultimate half-life: BOD = 50 %



Assumption: First order kinetics

$$BOD = 100\left(1 - \exp\left(-kt\right)\right)$$

$$BOD^{Calc} = 31\%$$

$$k = -\ln\left(1 - BOD_{28-d}^{Calc}/100\right)/28$$

$$t_{1/2}^{\text{Ultimate}} = \ln(2)/k$$

$$k = 0.013\,\text{day}^{-1}$$

Predicted ultimate half-life

$$t_{1/2}^{\text{Ultimate}} = \frac{\ln(2)}{-\ln\left(1 - BOD_{28-d}^{Calc}/100\right)/28}$$

$$t_{1/2}^{\text{Ultimate}} = 52\,\text{days}$$

Ultimate half-life: *BOD* = 50 %

Assumption: First order kinetics

$$BOD = 100\left(1 - \exp\left(-kt\right)\right)$$

$$k = -\ln\left(1 - BOD_{28-d}^{Calc}/100\right)/28$$

$$t_{1/2}^{\text{Ultimate}} = \ln(2)/k$$

Primary half-life: Q^{Parent} = 50 %

Assumption: First order kinetics

$$Q^{\text{Parent}} = 100\left(1 - \exp\left(-kt\right)\right)$$

$$k = -\ln\left(1 - Q_{28-d}^{Parent,Calc}/100\right)/28$$

$$t_{1/2}^{\text{Primary}} = \ln(2)/k$$

Reliability of generated metabolic pathway

$N_{i,succ}^{TR}$ - the numbers of successful applications of the transformation

$N_{i,fail}^{TR}$ - the numbers of unsuccessful applications of the transformation

Reliability of *i*-th transformation $$R_i^{TR} = \frac{N_{i,succ}^{TR}}{N_{i,succ}^{TR} + N_{i,fail}^{TR}}$$

Reliability of predicted *l*-th metabolite $$R_l^M = \prod_{j=1}^{J} R_j^{TR}$$

Reliability of *k*-th map $$R_k^{Map} = \frac{\sum_{j=1}^{K} R_k^M}{K}$$

Applicability domain

Consists of the following sub-domain levels:

- **General parametric requirements** - includes ranges of variation of log K_{OW} and *MW*,
- **Structural domain** - based on fragmentation of correctly predicted chemicals into fragments (atom-centered fragments ACFs),
- **Domain of simulator of metabolism** – simulation of catabolism is interrupted due to the lack of suitable transformation.

Conclusions

CATALOGIC 301 C model has

1. Strong mechanistic background ,
2. Clear algorithm and transparent predictions,
3. Defined applicability domain,
4. Appropriate measures of goodness-of-fit, robustness and predictivity.

Practically, these are OECD principles for use (Q)SARs for regulatory purposes