

Skin Sensitisation Examples

Introduction to OECD QSAR Toolbox

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Purpose of ECHA examples:

- To address specifically the REACH registrants
- To try to translate the science into regulatory language
- To increase the transparency of a complex tool
- To re-iterate the Toolbox philosophy for a prediction
- To illustrate the Toolbox flexibility
- To facilitate the development of adaptations
- To promote the use of alternatives for REACH

Outline of this presentation

On prediction of skin sensitisation

- 1) A straight-forward example
- 2) Example with activation:
transformations including skin
metabolism and auto-oxidation



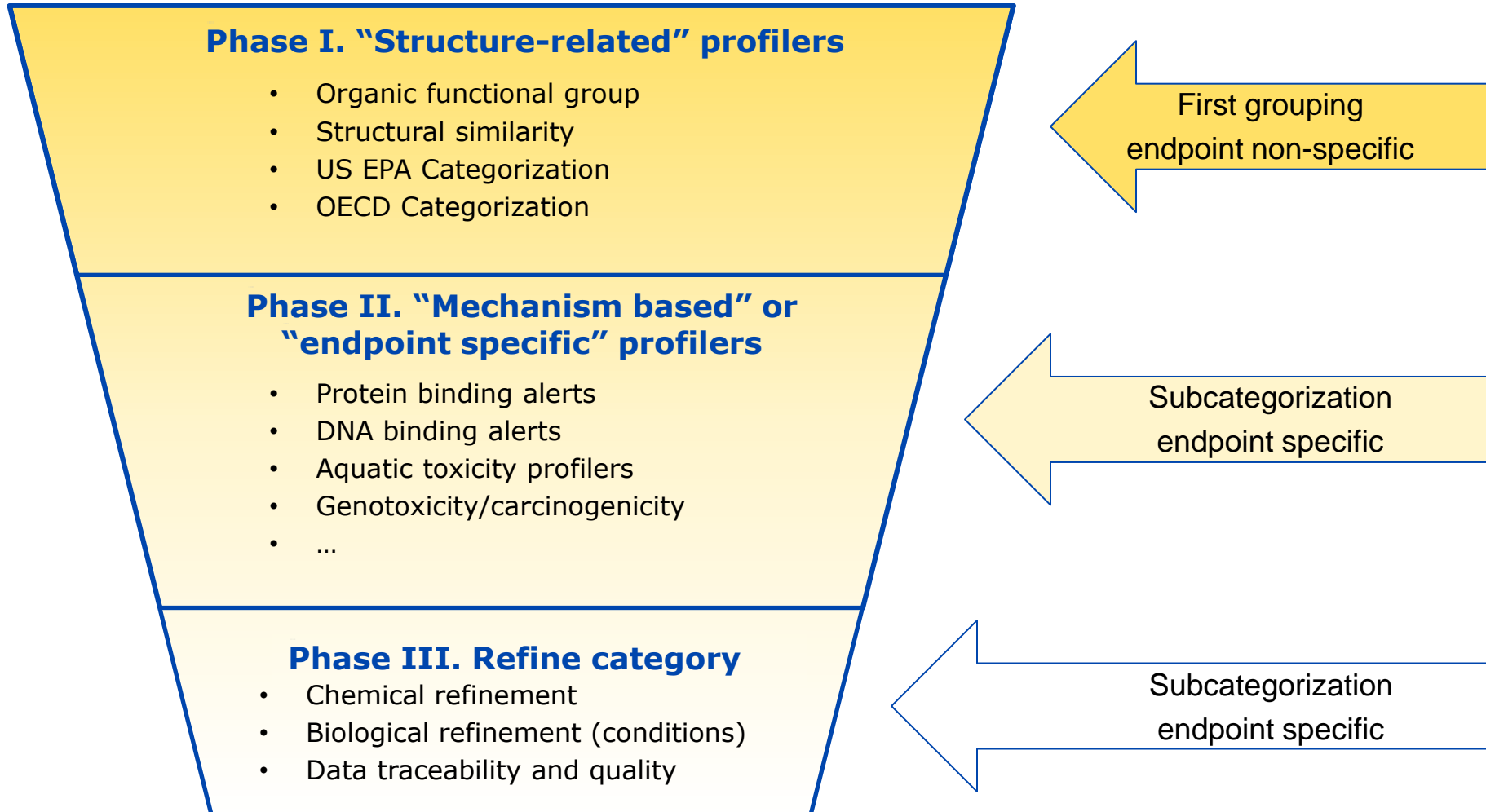
Objectives of this presentation:



To demonstrate the following:

- Input and profiling the target chemical
- Identifying analogues of the target chemical
- Filling data gaps for target chemical by read-across
- Profiling target chemical taking into account its (a)biotic activation (by simulating skin metabolism and auto-oxidation products)
- Collect mechanistic analogues depending on the products
- Filling data gaps by read across when (a)biotic activation is taken into account (final structural refinement)

Recommended Category formation process



The skin sensitisation endpoint

- In Annex VII of REACH (for more than 1 tpa)
- The information requirement can be adapted:
 - According to column 2 of the Annex
 - According to Annex XI
- The Murine Local Lymph Node Assay (LLNA) is recommended
- Guinea Pig Maximisation Test (GPMT) is still sometimes used
- No requirement for testing proposal in Annex VII, BUT
- New animal studies to be conducted only as a last resort

Relevant databases and profilers

Relevant databases:

- “Skin sensitisation”, which includes more than 1 035 chemicals (includes the OASIS skin sensitisation database)
- “Skin sensitisation ECETOC”, with 39 chemicals
- ECHA Chem currently brings more than 1 000 studies to the Toolbox

For classification purposes, the thresholds in the **CLP** Regulation and the respective guidance should be checked.

Relevant profilers:

- Protein binding by OASIS (101 categories)
- Protein binding by OECD (102 categories)
- Protein binding potency (90 categories)
- Protein binding alerts for skin sensitisation by OASIS (100 categories)

A straight-forward example

Step-by-step example on how to predict the skin sensitisation potential approach of a chemical by read-across based on an analogue approach (for beginners)

[pdf](#)

[video](#)

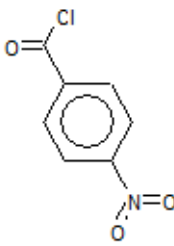


Input of chemical (CAS 122-04-3)

Search by CAS #

122043 Tautomeric sets

Select All Clear All Invert Selection Selected 1 of 1

Selected	CAS	Smiles	Depiction	Names	CAS/Name	2D/Name	CAS/2D
1. Yes	122-04-3	O=C(Cl)c1ccc([N+](=O)[O-])cc1		1: p-nitrobenzoyl chloride 2: benzoyl chloride, 4-nitr 3: 4-nitrobenzoyl chloride 4: benzoyl chloride, p-nitr	1: Bacte 2: DSST 3: Geno 2: High Qua 1: Cana 2: METI 3: NICN 4: Phys- 5: TSCA 6: US H 3: High Qua 1: ECHA 2: EINE 3: METI 4: REAC 5: US H	1: Bacteri 2: Genoto 3: DSSTO 2: High Qualit 1: Phys-ch 2: Canada 3: TSCA 4: METI Ja 5: NICNAS 6: US HPV 3: High Qualit 1: REACH 2: ECHA P 3: METI Ja 4: EINECS 5: US HPV	1: High Qualit 1: Bact 2: Can 3: DSS 4: ECH 5: EINE 6: Gen 7: MET 8: NICI 9: Phy: 10: RE 11: TS 12: US 13: US

Profiling for protein binding

QSAR TOOLBOX

Input Profiling Endpoint Category Definition Data Gap Filling Report

Profiling Profiling Schemes

Apply New View Delete

The OECD for Group into Cate Develop

Profiling methods

Select All Unselect All Invert

- Ionization at pH = 9
- Protein binding by OASIS v1.2
- Protein binding by OECD
- Protein binding potency
- Superfragments
- Toxic hazard classification by Cramer (
- Toxic hazard classification by Cramer (
- Ultimate biodeg

Endpoint Specific

- Acute aquatic toxicity classification by
- Acute aquatic toxicity MOA by OASIS
- Aquatic toxicity classification by ECOS
- Bioaccumulation – metabolism alerts
- Bioaccumulation – metabolism half-lives
- Biodegradation fragments (BioWIN MI
- Carcinogenicity (genotox and nongen
- DNA alerts for AMES, MN and CA by O
- Eye irritation/corrosion Exclusion rules
- Eye irritation/corrosion Inclusion rules
- in vitro mutagenicity (Ames test) alerts
- in vivo mutagenicity (Micronucleus) ale
- Keratinocyte gene expression
- Oncologic Primary Classification
- Protein binding alerts for skin sensiti
- rTER Expert System ver. 1 - USEPA
- Skin irritation/corrosion Exclusion rules
- Skin irritation/corrosion Inclusion rules

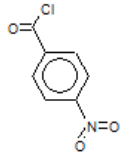
Empiric

- Chemical elements

Filter endpoint tree...

1 [target]

Structure



Substance Identity

Physical Chemical Properties

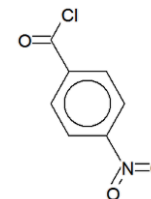
Environmental Fate and Transport

Ecotoxicological Information

Human Health Hazards

Profile

- General Mechanistic
 - Protein binding by OASIS v1.2
 - Acylation
 - Acylation >> Direct acylation involving a leaving group
 - Acylation >> Direct acylation involving a leaving group >> (Thio)Acyl and (thio)carbamoyl halides and cyanides
 - Protein binding by OECD
 - Acylation
 - Acylation >> Direct Acylation Involving a Leaving group
 - Acylation >> Direct Acylation Involving a Leaving group >> Acyl halides (including benzyl and carbamoyl deriv.)
 - Endpoint Specific
 - Protein binding alerts for sk...
 - Acylation
 - Acylation >> Direct acylation involving a leaving group
 - Acylation >> Direct acylation involving a leaving group >> (Thio)Acyl and (thio)carbamoyl halides and cyanides



MoA Explanation: Acyl halides

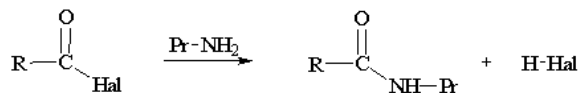
Mechanistic Domain: Acylation

Mechanistic Alert: Direct acylation involving a leaving group

Structural Alert: Acyl halides

This category includes chemicals that potentially can cause skin sensitization effect as a result of protein conjugation via **Nucleophilic substitution on acyl halides**.

The possible structural alert acting by this mechanism is illustrated below:

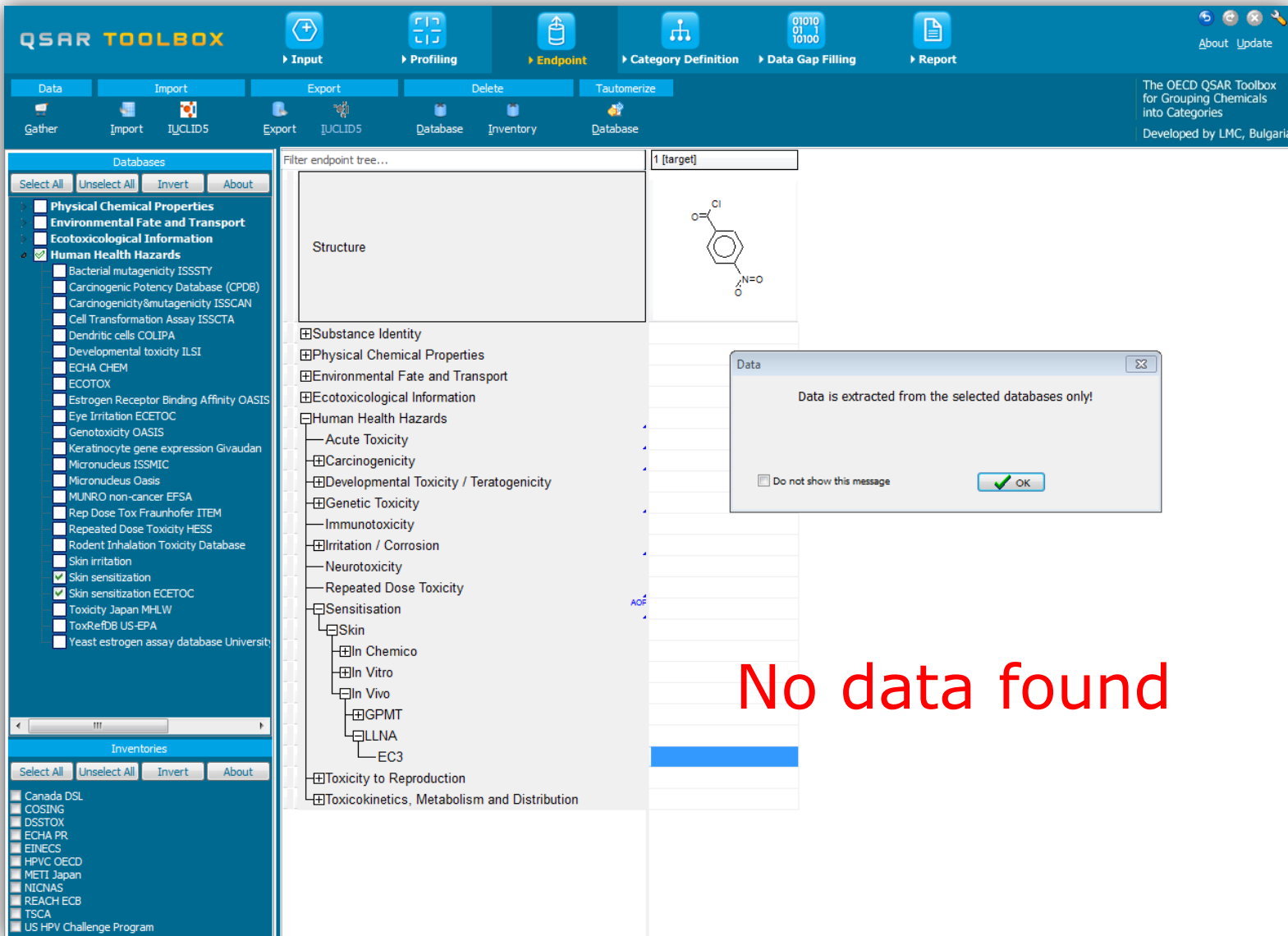


Hal = F, Cl, Br, I

R = alkyl, aryl

Acyl halides are compounds that have a halogen atom in place of OH group of acids. The nucleophile attacks the carbonyl carbon forming a tetrahedral intermediate. When the tetrahedral intermediate collapses, the weaker base is eliminated. If the nucleophile is neutral, the mechanism has an additional step. A proton is lost from the tetrahedral intermediate formed in the first step, resulting in a tetrahedral intermediate equivalent to the one formed by negatively charged nucleophiles. This tetrahedral intermediate expels the weaker of the two bases- the newly added group after it has lost a proton or the group that was attached to the acyl group in the reactant. Halogen ions are weaker bases than the amino groups in proteins.

These reactions are called nucleophilic acyl substitution reactions because a nucleophile (protein molecule) has replaced the substituent that was attached to the acyl group in the reactant. It is also called an acyl transfer reaction because an acyl group has been transferred from one group to another.



The screenshot shows the QSAR TOOLBOX interface. The top menu bar includes options like Input, Profiling, Endpoint, Category Definition, Data Gap Filling, and Report. The toolbar below has buttons for Gather, Import, Export, Delete, and Tautomerize. The left sidebar contains a 'Databases' section with a tree view where 'Human Health Hazards' is selected, and an 'Inventories' section with a list of various databases. The main window shows a 'Filter endpoint tree...' on the left and a '1 [target]' search result on the right, which displays the chemical structure of 1-chloro-4-nitrobenzene. A dialog box in the foreground reads 'Data is extracted from the selected databases only!' with an 'OK' button. The text 'No data found' is overlaid in red on the right side of the interface.









Structure based grouping and profiling of the analogues

QSAR TOOLBOX

Input Profiling Endpoint Category Definition Data Gap Filling Report

Apply New View Delete

The OECD QSAR Toolbox for Grouping Chemicals into Categories
Developed by LMC, Bulgaria

Filter endpoint tree...	2	3	4	5	6	7	8	9
Structure								
Substance Identity								
Physical Chemical Properties								
Environmental Fate and Transport								
Ecotoxicological Information								
Human Health Hazards (8/8)	M: 0.23 %	M: Strongly ...	M: 1.8 %	M: Strongly ...	M: 8.8 %	M: 2.3 %	M: 2.7 %	M: 2.7 %
Profile								
General Mechanistic								
Protein binding by OASIS v1.2	Acylation Acylation >... Acylation >...	Acylation Acylation >... Acylation >... SN2 SN2 >> Nu... SN2 >> Nu...	Acylation Acylation >>... Acylation >>...	Acylation Acylation >>... Acylation >>...	Acylation Acylation >> ... Acylation >> ...	Acylation Acylation >... Acylation >...	Acylation Acylation >... Acylation >...	Acylation Acylation >... Acylation >...
Protein binding by OECD	Acylation Acylation >... Acylation >...	Acylation Acylation >... Acylation >... SN2 SN2 >> SN... SN2 >> SN...	Acylation Acylation >>... Acylation >>...	Acylation Acylation >>... Acylation >>...	Acylation Acylation >> ... Acylation >> ...	Acylation Acylation >... Acylation >...	Acylation Acylation >... Acylation >...	Acylation Acylation >... Acylation >...
Endpoint Specific								
Protein binding alerts for skin...	Acylation Acylation >... Acylation >...	Acylation Acylation >... Acylation >...	Acylation Acylation >>... Acylation >>...	Acylation Acylation >>... Acylation >>...	Acylation Acylation >> ... Acylation >> ...	Acylation Acylation >... Acylation >...	Acylation Acylation >... Acylation >...	Acylation Acylation >... Acylation >...

QSAR TOOLBOX

Input Profiling Endpoint Category Definition Data Gap Filling Report

The OECD QSAR Toolbox for Grouping Chemicals into Categories
Developed by LMC, Bulgaria

Filter endpoint tree... 1 [target] 2 3 4 5

Structure

Substance Identity
Physical Chemical Properties
Environmental Fate and Transport
Ecotoxicological Information
Human Health Hazards
Acute Toxicity
Carcinogenicity
Developmental Toxicity / Teratogenicity
Genetic Toxicity
Immunotoxicity
Irritation / Corrosion
Neurotoxicity
Repeated Dose Toxicity
Sensitisation
Skin
In Chemico
In Vitro
In Vivo
GPMT
LLNA
EC3
Undefined Assay
Toxicity to Reproduction
Toxicokinetics, Metabolism and Distribution

Starting gap filling ...

(8/8) M: 8.8 %

Possible data inconsistency

Scale/Unit

Gap filling scale/unit

- Skin sensitization EC3(ratio)
- Skin sensitisation I (Oasis)
- Skin sensitisation II (ECETOC)
- Skin Sensitization (Danish EPA)

Selected [6/8] points

2.7 %

OK Cancel









Structure based grouping (acyl halide) and prediction

Data Gap Filling Method

- Read-across
- Trend analysis
- (Q)SAR models

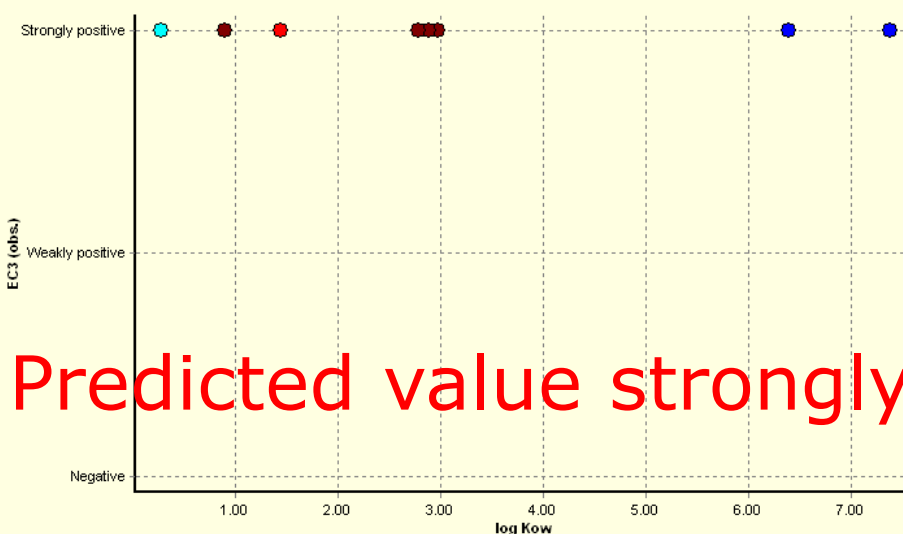
Target Endpoint

Human Health Hazards Sensitisation Skin In Vivo LLNA

Structure	2	3	4	5	6	7	8	9
Structure								
	LLNA (8/8)	M: 0.23 %	M: Strongly ...	M: 1.8 %	M: Strongly ...	M: 8.8 %	M: 2.3 %	M: 2.7 %

Descriptors | Prediction

Read across prediction of EC3,
taking the highest mode from the nearest 5 neighbours, based on 5 values from 5 neighbour chemicals,
Observed target value: 'Strongly positive', Predicted target value: 'Strongly positive'



Descriptor X:

Accept prediction

Return to matrix

- Select/filter data
- Selection navigation
- Gap filling approach
- Descriptors/data
- Model/(Q)SAR
- Calculation options
- Visual options
- Information
- Miscellaneous

Predicted value strongly positive

An example with (bio)activation

Step-by-step example for
predicting skin sensitization
accounting for skin metabolism

[pdf](#)

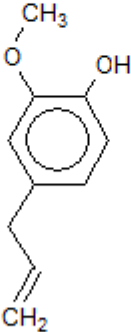


Input of chemical (CAS 97-53-0)

Search by CAS #

97530 Tautomeric sets

Select All Clear All Invert Selection Selected 1 of 1

Selected	CAS	Smiles	Depiction	Names	CAS/Name	2D/Name	CAS/2D
1. Yes	97-53-0	COc1cc(CC=C		1: eugenol (4 2: eugenol 3: 4-allyl-2-m 4: 1-allyl-3-m 5: phenol, 2-r 6: phenol, 4- 7: 2-methoxy- 8: 2-methoxy- 9: 4-allyl-2-m 10: p-allylgua	14: Micro 15: Micro 16: Phys- 17: REAC 18: Skin s 19: Skin s 20: US HF 21: USER 3: Low Qualit 1: Experim 2: USER I 4: Low Qualit 1: Genoto 2: USER I 5: High Quali	14: Chem 15: Dendr 16: Kerat 17: Carcin 18: Cell T 19: Micro 20: Skin s 21: ECHA 3: Low Qualit 1: USER I 2: Experim 4: Low Qualit 1: USER I 2: Genoto 5: High Quali	6: Ce 7: Ch 8: DS 9: De 10: E 11: E 12: E 13: E 14: E 15: E 16: G 17: K 18: M 19: M 20: M 21: M

Profiling and data gathering

QSAR TOOLBOX

Databases

Select All Unselect All Invert About

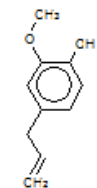
- Physical Chemical Properties
- Environmental Fate and Transport
- Ecotoxicological Information
- Human Health Hazards
 - Bacterial mutagenicity ISSSTY
 - Carcinogenic Potency Database (CPDB)
 - Carcinogenicity&mutagenicity ISSCAN
 - Cell Transformation Assay ISSCTA
 - Dendritic cells COLIPA
 - Developmental toxicity ILSI
 - ECHA CHEM
 - ECOTOX
 - Estrogen Receptor Binding Affinity OASIS
 - Eye Irritation ECETOC
 - Genotoxicity OASIS
 - Keratinocyte gene expression Givaudan
 - Micronucleus ISSMIC
 - Micronucleus Oasis
 - MUNRO non-cancer EFSA
 - Rep Dose Tox Fraunhofer ITEM
 - Repeated Dose Toxicity HESS
 - Rodent Inhalation Toxicity Database
 - Skin irritation
 - Skin sensitization
 - Skin sensitization ECETOC
 - Toxicity Japan MHLW
 - ToxRefDB US-EPA
 - Yeast estrogen assay database University

Filter endpoint tree...

Structure

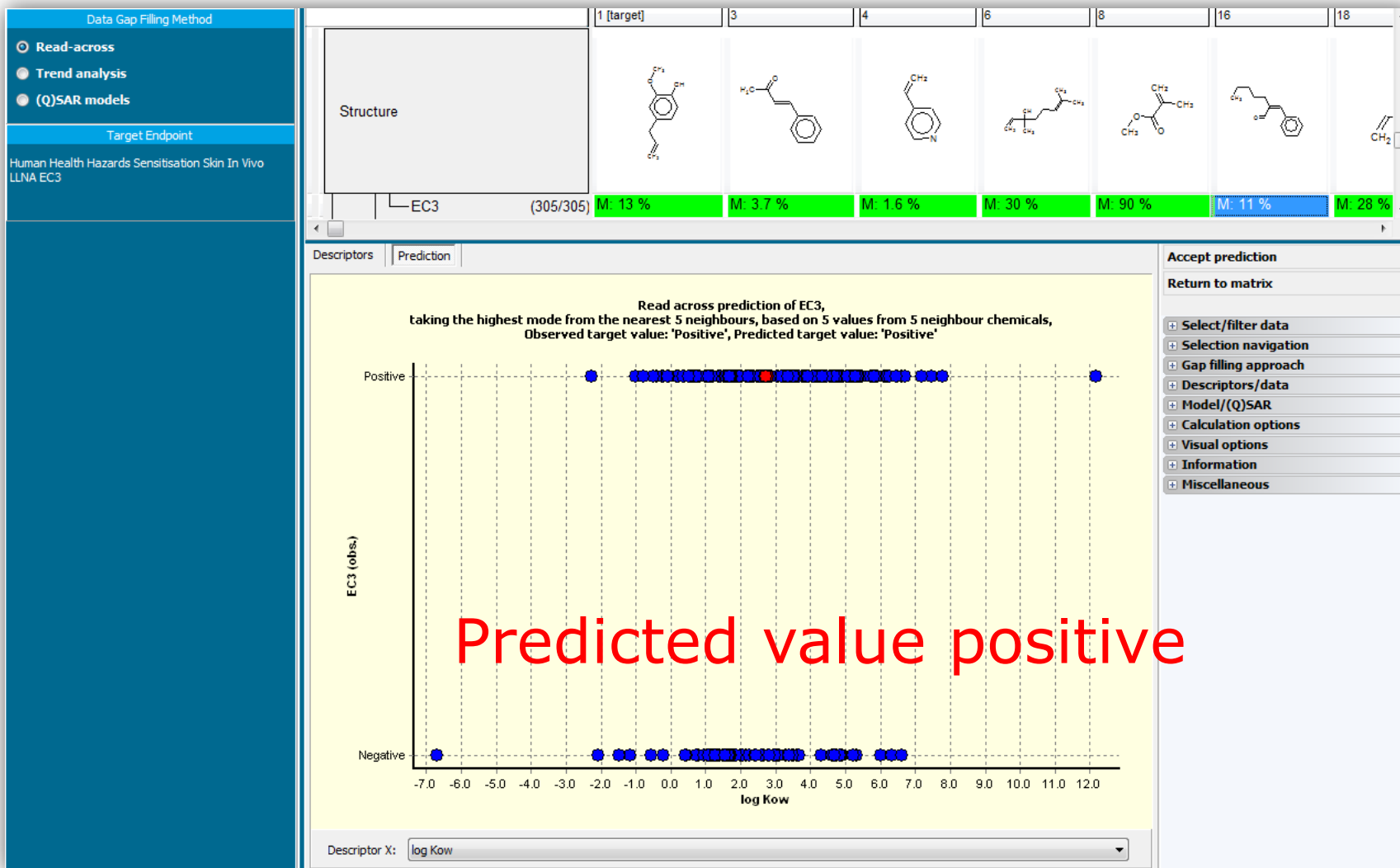
- Substance Identity
- Physical Chemical Properties
- Environmental Fate and Transport
- Ecotoxicological Information
- Human Health Hazards
- Profile
 - General Mechanistic
 - Protein binding by OASIS v1.2
 - Protein binding by OECD
 - Endpoint Specific
 - Protein binding alerts for skin sensitization by OASI...

1 [target]



(1/2) M: 13 %, Moderate sensitizer
No alert found
No alert found
No alert found

Grouping by organic functional groups (OFG)



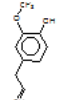
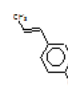
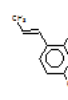
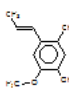
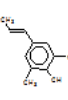

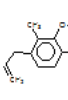
Grouping by OFG (nested)

Data Gap Filling Method

- Read-across
- Trend analysis
- (Q)SAR models

Target Endpoint

Human Health Hazards Sensitisation Skin In Vivo LLNA EC3

	1 [target]	2	3	4	5	6	7	
Structure								
EC3	(10/10)	M: 13 %	M: 1.2 %	M: 3.6 %	M: 0.3 %	M: 1.6 %	M: 0.6 %	M: 32 %

Descriptors Prediction

Read across prediction of EC3,
taking the highest mode from the nearest 5 neighbours, based on 7 values from 7 neighbour chemicals,
Observed target value: 'Negative', Predicted target value: 'Positive'

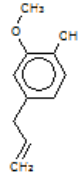
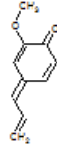
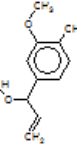
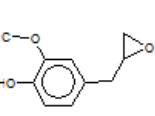
Predicted value positive

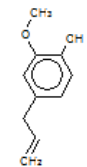
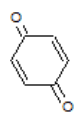
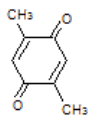
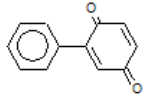
Descriptor X: log Kow

Accept prediction

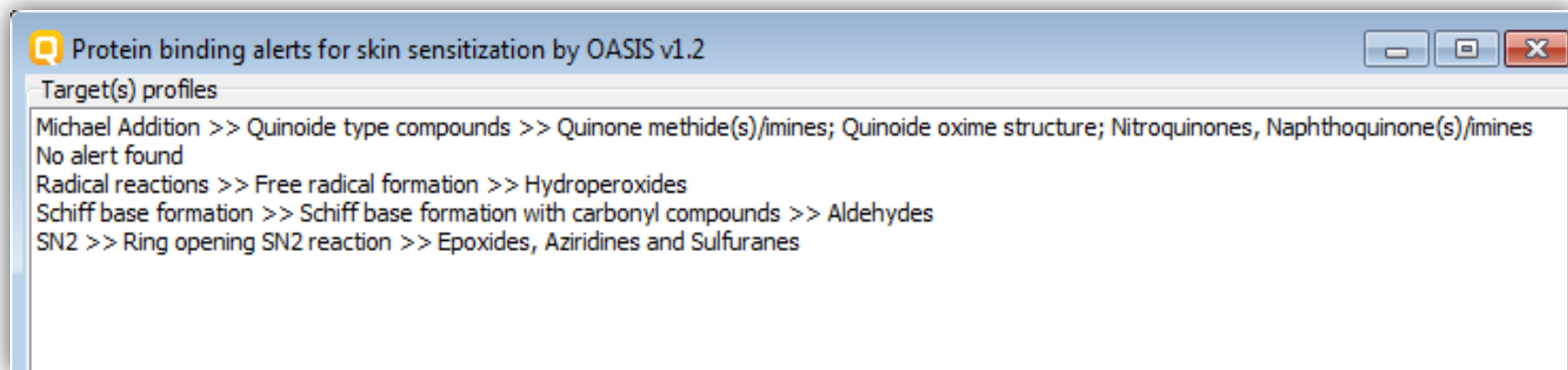
Return to matrix

- Select/filter data
- Selection navigation
- Gap filling approach
- Descriptors/data
- Model/(Q)SAR
- Calculation options
- Visual options
- Information
- Miscellaneous

Filter endpoint tree...	1 [target]	2 [target,transf. product]	3 [target,transf. product]	4 [target,transf. product]
Structure				
<input type="checkbox"/> Substance Identity				
CAS Number	97-53-0	N/A	N/A	N/A
Chemical IDs	Einecs Number:2025891	NA	NA	NA
Chemical Name	eugenol (4-allyl-2-methoxyph... eugenol 4-allyl-2-methoxy-phenol 1-allyl-3-methoxy-4-hydroxy... phenol, 2-methoxy-4-(2-prop... phenol, 4-allyl-2-methoxy- 2-methoxy-4-(prop-2-en-1-yl)... 2-methoxy-4-(2-propenyl)pheno 4-allyl-2-methoxyphenol p-allylguaiacol			
Structural Formula	<chem>COc1cc(CC=C)ccc1O</chem>	<chem>COC1=CC(=CC=C)...</chem>	<chem>COc1cc(C(C=C)O)...</chem>	<chem>COc1cc(CC2CO2)ccc1O</chem>
<input checked="" type="checkbox"/> Physical Chemical Properties				
<input checked="" type="checkbox"/> Environmental Fate and Transport				
<input checked="" type="checkbox"/> Ecotoxicological Information				
<input checked="" type="checkbox"/> Human Health Hazards	(2/96) M: Negative, Negative, Nega...			M: Positive, Positive, ...
<input type="checkbox"/> Profile				
<input type="checkbox"/> General Mechanistic				
Protein binding by OASIS v1.2	No alert found	Michael Addition Michael Addition >... Michael Addition >...	Radical reactions Radical reactions >... Radical reactions >...	SN2 SN2 >> Ring opening ... SN2 >> Ring opening ...
Protein binding by OECD	No alert found	Michael addition Michael addition >... Michael addition >... Michael addition >... Michael addition >...	No alert found	SN2 SN2 >> Epoxides and... SN2 >> Epoxides and...
<input type="checkbox"/> Endpoint Specific				
Protein binding alerts for skin sensitization by OASI...	No alert found	Michael Addition Michael Addition >... Michael Addition >...	Radical reactions Radical reactions >... Radical reactions >...	SN2 SN2 >> Ring opening ... SN2 >> Ring opening ...
<input type="checkbox"/> Empiric				

Profiling methods	Filter endpoint tree...	1 [target]	2	3	4
<p>Select All Unselect All Invert</p> <ul style="list-style-type: none"> <input type="checkbox"/> Ionization at pH = 9 <input checked="" type="checkbox"/> Protein binding by OASIS v1.2 <input checked="" type="checkbox"/> Protein binding by OECD <input type="checkbox"/> Protein binding potency <input type="checkbox"/> Superfragments <input type="checkbox"/> Toxic hazard classification by Cramer (<input type="checkbox"/> Toxic hazard classification by Cramer (<input type="checkbox"/> Ultimate biodeg <p>Endpoint Specific</p> <ul style="list-style-type: none"> <input type="checkbox"/> Acute aquatic toxicity classification by <input type="checkbox"/> Acute aquatic toxicity MOA by OASIS <input type="checkbox"/> Aquatic toxicity classification by ECOS <input type="checkbox"/> Bioaccumulation – metabolism alerts <input type="checkbox"/> Bioaccumulation – metabolism half-lives <input type="checkbox"/> Biodegradation fragments (BioWIN MIT <input type="checkbox"/> Carcinogenicity (genotox and nongenod <input type="checkbox"/> DNA alerts for AMES, MN and CA by O <input type="checkbox"/> Eye irritation/corrosion Exclusion rules <input type="checkbox"/> Eye irritation/corrosion Inclusion rules <input type="checkbox"/> in vitro mutagenicity (Ames test) alerts <input type="checkbox"/> in vivo mutagenicity (Micronucleus) ale <input type="checkbox"/> Keratinocyte gene expression <input type="checkbox"/> Oncologic Primary Classification <input checked="" type="checkbox"/> Protein binding alerts for skin sensitiza <input type="checkbox"/> rTER Expert System ver. 1 - USEPA <input type="checkbox"/> Skin irritation/corrosion Exclusion rules <input type="checkbox"/> Skin irritation/corrosion Inclusion rules <p>Empiric</p> <ul style="list-style-type: none"> <input type="checkbox"/> Chemical elements 	<p>Structure</p> <p>Environmental Fate and Transport</p> <p>Ecotoxicological Information</p> <p>Human Health Hazards (12/191)</p> <p>Profile</p> <ul style="list-style-type: none"> General Mechanistic <ul style="list-style-type: none"> Protein binding by OASIS v1.2 Protein binding by OECD Endpoint Specific <ul style="list-style-type: none"> Protein binding alerts for skin sensitization by OASI... 	<p>1 [target]</p> <p>[6] [M]</p> 			
		M: Negative, Negative, Nega...	M: Equivocal, Nega...	M: Negative, Negat...	M: Negative, Negative,...
		<p>Michael Addition</p> <p>Michael Addition >> Quinoid...</p> <p>Michael Addition >> Quinoid...</p> <p>No alert found</p> <p>Nucleophilic addition</p> <p>Nucleophilic addition >> Add...</p> <p>Nucleophilic addition >> Add...</p> <p>Schiff base formation</p> <p>Schiff base formation >> Dir...</p> <p>Schiff base formation >> Dir...</p> <p>Schiff base formation >> Sc...</p> <p>Schiff base formation >> Sc...</p>	<p>Michael Addition</p> <p>Michael Addition >...</p> <p>Michael Addition >...</p>	<p>Michael Addition</p> <p>Michael Addition >...</p> <p>Michael Addition >...</p> <p>Nucleophilic addition</p> <p>Nucleophilic addition...</p> <p>Nucleophilic addition...</p>	<p>Michael Addition</p> <p>Michael Addition >> Q...</p> <p>Michael Addition >> Q...</p> <p>Nucleophilic addition</p> <p>Nucleophilic addition ...</p> <p>Nucleophilic addition ...</p>
		<p>Michael addition</p> <p>Michael addition >> Polarise...</p> <p>Michael addition >> Polarise...</p> <p>Michael addition >> Quinone...</p> <p>Michael addition >> Quinone...</p> <p>No alert found</p> <p>Schiff Base Formers</p> <p>Schiff Base Formers >> Dire...</p> <p>Schiff Base Formers >> Dire...</p> <p>Schiff Base Formers >> Dire...</p>	<p>Michael addition</p> <p>Michael addition >...</p> <p>Michael addition >...</p> <p>Michael addition >...</p>	<p>Michael addition</p> <p>Michael addition >...</p> <p>Michael addition >...</p>	<p>Michael addition</p> <p>Michael addition >> P...</p> <p>Michael addition >> P...</p> <p>Michael addition >> Q...</p> <p>Michael addition >> Q...</p>
		<p>Michael Addition</p> <p>Michael Addition >> Quinoid...</p> <p>Michael Addition >> Quinoid...</p> <p>No alert found</p> <p>Schiff base formation</p> <p>Schiff base formation >> Sc...</p>	<p>Michael Addition</p> <p>Michael Addition >...</p> <p>Michael Addition >...</p>	<p>Michael Addition</p> <p>Michael Addition >...</p> <p>Michael Addition >...</p>	<p>Michael Addition</p> <p>Michael Addition >> Q...</p> <p>Michael Addition >> Q...</p>

Combining transformation products



Combining compounds with the same mechanisms as the target products from skin metabolism and auto-oxidation resulted in:

- More than 900 structures, and
- More than 1 000 data points

After chemical refinement OFG (allyl, phenol, ether), ECETOC

QSAR TOOLBOX | Input | Profiling | Endpoint | Category Definition | Data Gap Filling | Report | About Update

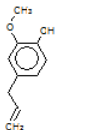
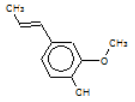
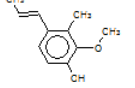
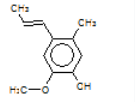
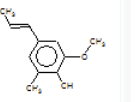
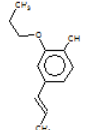
The OECD QSAR Toolbox for Grouping Chemicals into Categories
Developed by LMC, Bulgaria

Data Gap Filling Method

- Read-across
- Trend analysis
- (Q)SAR models

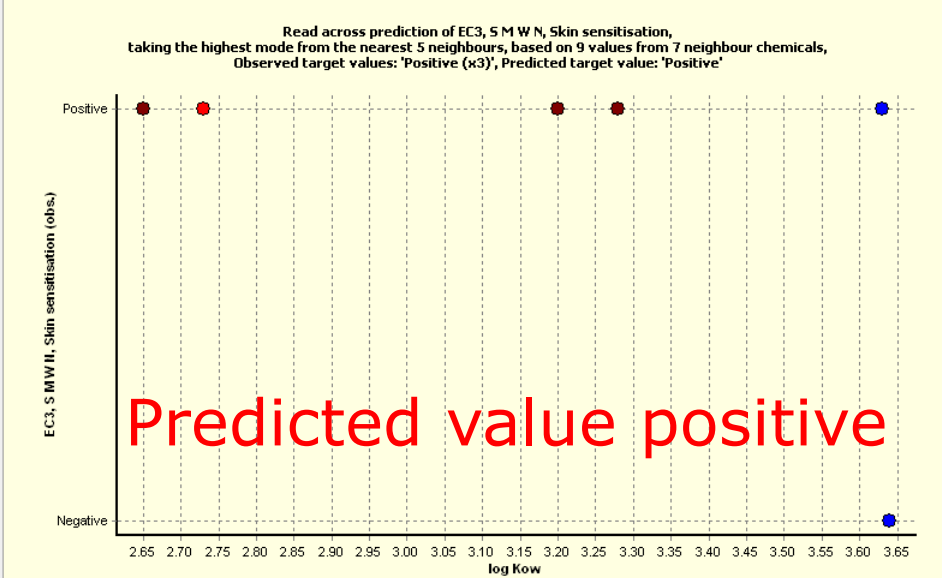
Target Endpoint

Human Health Hazards

Structure	1 [target]	2	3	4	5	6
						
	M: 13 % Moderate s...	M: 1.2 % Strong se...	M: 3.6 %	M: 0.3 %	M: 1.6 %	M: 0.6 %

Descriptors | Prediction

Read across prediction of EC3, 5 MW N, Skin sensitisation, taking the highest mode from the nearest 5 neighbours, based on 9 values from 7 neighbour chemicals, Observed target values: 'Positive (x3)', Predicted target value: 'Positive'



Predicted value positive

Descriptor X: log Kow

Accept prediction

Return to matrix

- Select/filter data
- Selection navigation
- Gap filling approach
- Descriptors/data
- Model/(Q)SAR
- Calculation options
- Visual options
- Information
- Miscellaneous

After chemical refinement OFG (allyl, phenol, ether), EC3 (%)

QSAR TOOLBOX | Input | Profiling | Endpoint | Category Definition | Data Gap Filling | Report | About Update

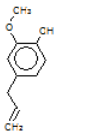
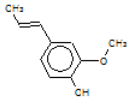
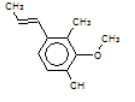
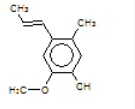
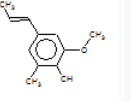
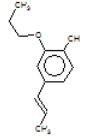
The OECD QSAR Toolbox for Grouping Chemicals into Categories
Developed by LMC, Bulgaria

Data Gap Filling Method

- Read-across
- Trend analysis
- (Q)SAR models

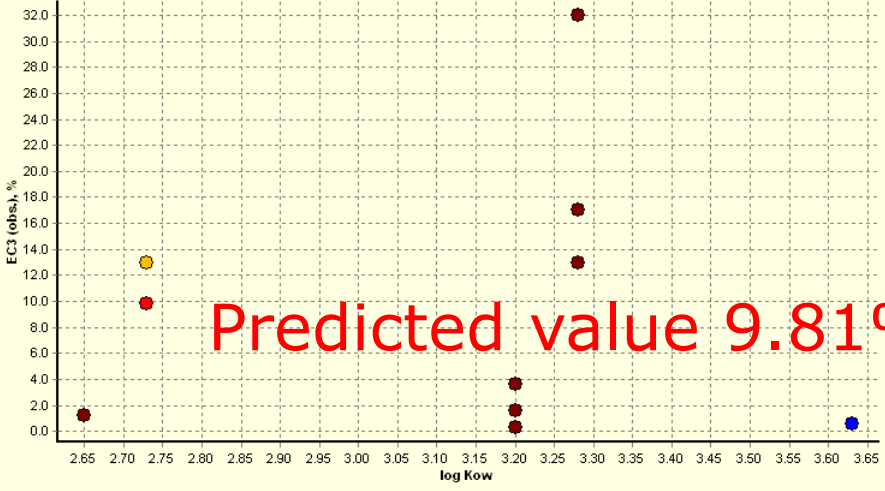
Target Endpoint

Human Health Hazards

Structure	1 [target]	2	3	4	5	6
						
Human Health H... (10/16)	M: 13 %, Moderate s...	M: 1.2 %, Strong se...	M: 3.6 %	M: 0.3 %	M: 1.6 %	M: 0.6 %

Descriptors | Prediction

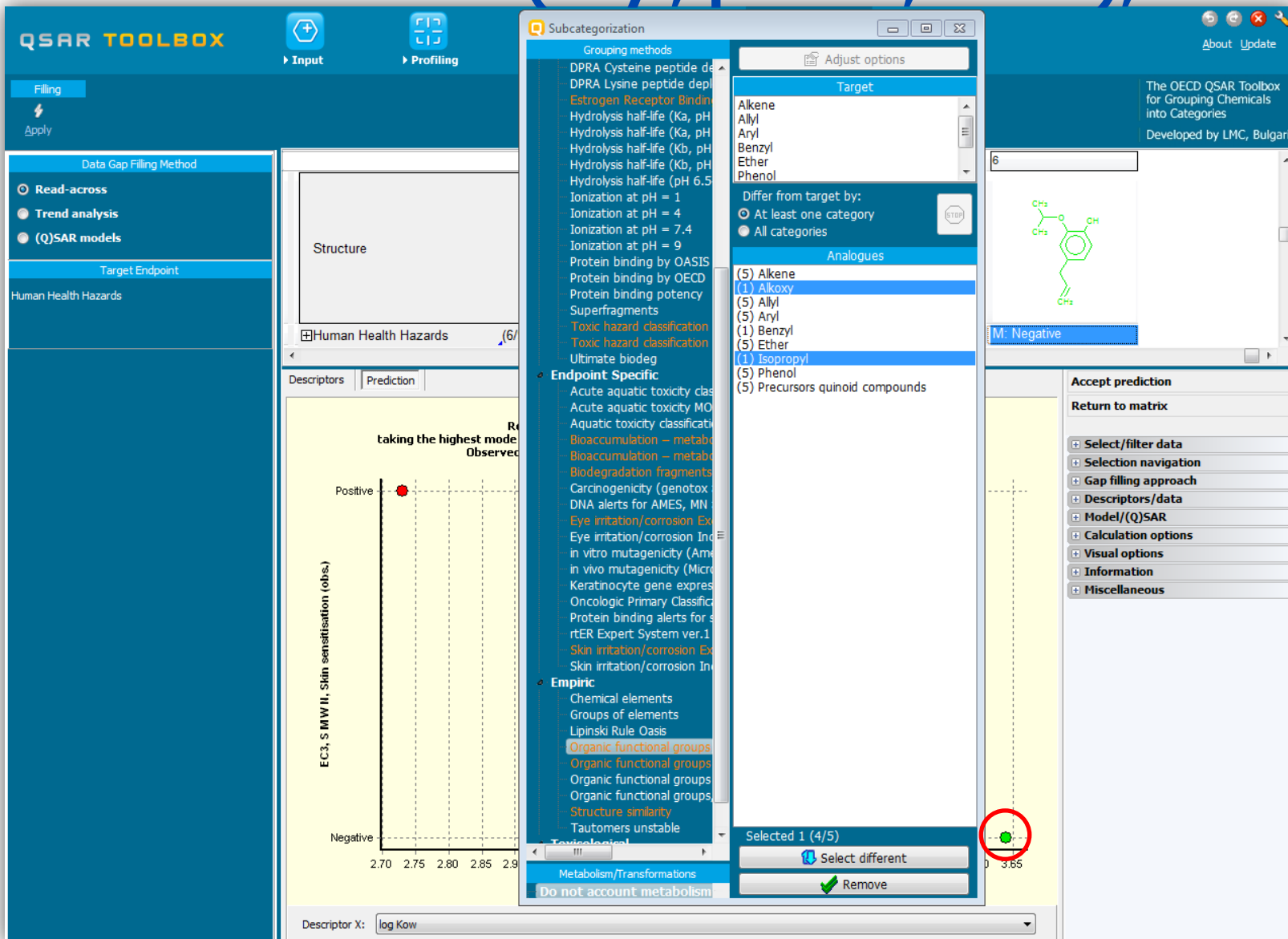
Read across prediction of EC3, taking the average from the nearest 5 neighbours, based on 7 neighbour chemicals, Observed target value: 13.0 %, Predicted target value: 9.81 %



Descriptor X: log Kow

Accept prediction
Return to matrix
Select/filter data
Selection navigation
Gap filling approach
Descriptors/data
Model/(Q)SAR
Calculation options
Visual options
Information
Miscellaneous

After chemical refinement OFG (allyl, phenol, ether), OASIS



The screenshot displays the QSAR Toolbox interface with the Subcategorization window open. The main window shows a graph of EC₃, S₁ MW II, Skin sensitisation (obs.) versus log Kow. A red dot is plotted at approximately (2.75, Positive). The Subcategorization window lists various grouping methods and shows a list of categories for the selected chemical. The chemical structure is shown as a benzene ring with an ether group and two allyl groups.

Subcategorization Window:

- Grouping methods:**
 - DPRa Cysteine peptide depl
 - DPRa Lysine peptide depl
 - Estrogen Receptor Bindin
 - Hydrolysis half-life (Ka, pH
 - Hydrolysis half-life (Ka, pH
 - Hydrolysis half-life (Kb, pH
 - Hydrolysis half-life (Kb, pH
 - Hydrolysis half-life (pH 6.5
 - Ionization at pH = 1
 - Ionization at pH = 4
 - Ionization at pH = 7.4
 - Ionization at pH = 9
 - Protein binding by OASIS
 - Protein binding by OECD
 - Protein binding potency
 - Superfragments
 - Toxic hazard classification
 - Toxic hazard classification
 - Ultimate biodeg
- Endpoint Specific:**
 - Acute aquatic toxicity clas
 - Acute aquatic toxicity MO
 - Aquatic toxicity classific
 - Bioaccumulation – metabo
 - Bioaccumulation – metabo
 - Biodegradation fragments
 - Carcinogenicity (genotox
 - DNA alerts for AMES, MN
 - Eye irritation/corrosion Ex
 - Eye irritation/corrosion Ind
 - in vitro mutagenicity (Am
 - in vivo mutagenicity (Micro
 - Keratinocyte gene expres
 - Oncologic Primary Classif
 - Protein binding alerts for s
 - rTER Expert System ver.1
 - Skin irritation/corrosion Ex
 - Skin irritation/corrosion Ind
- Empiric:**
 - Chemical elements
 - Groups of elements
 - Lipinski Rule Oasis
 - Organic functional groups
 - Organic functional groups
 - Organic functional groups
 - Organic functional groups
 - Structure similarity
 - Tautomers unstable
 - Toxicological

Target List:

- Alkene
- Allyl
- Aryl
- Benzyl
- Ether
- Phenol

Analogue List:

- (5) Alkene
- (1) Alkoxy
- (5) Allyl
- (5) Aryl
- (1) Benzyl
- (5) Ether
- (1) Isopropyl
- (5) Phenol
- (5) Precursors quinoid compounds

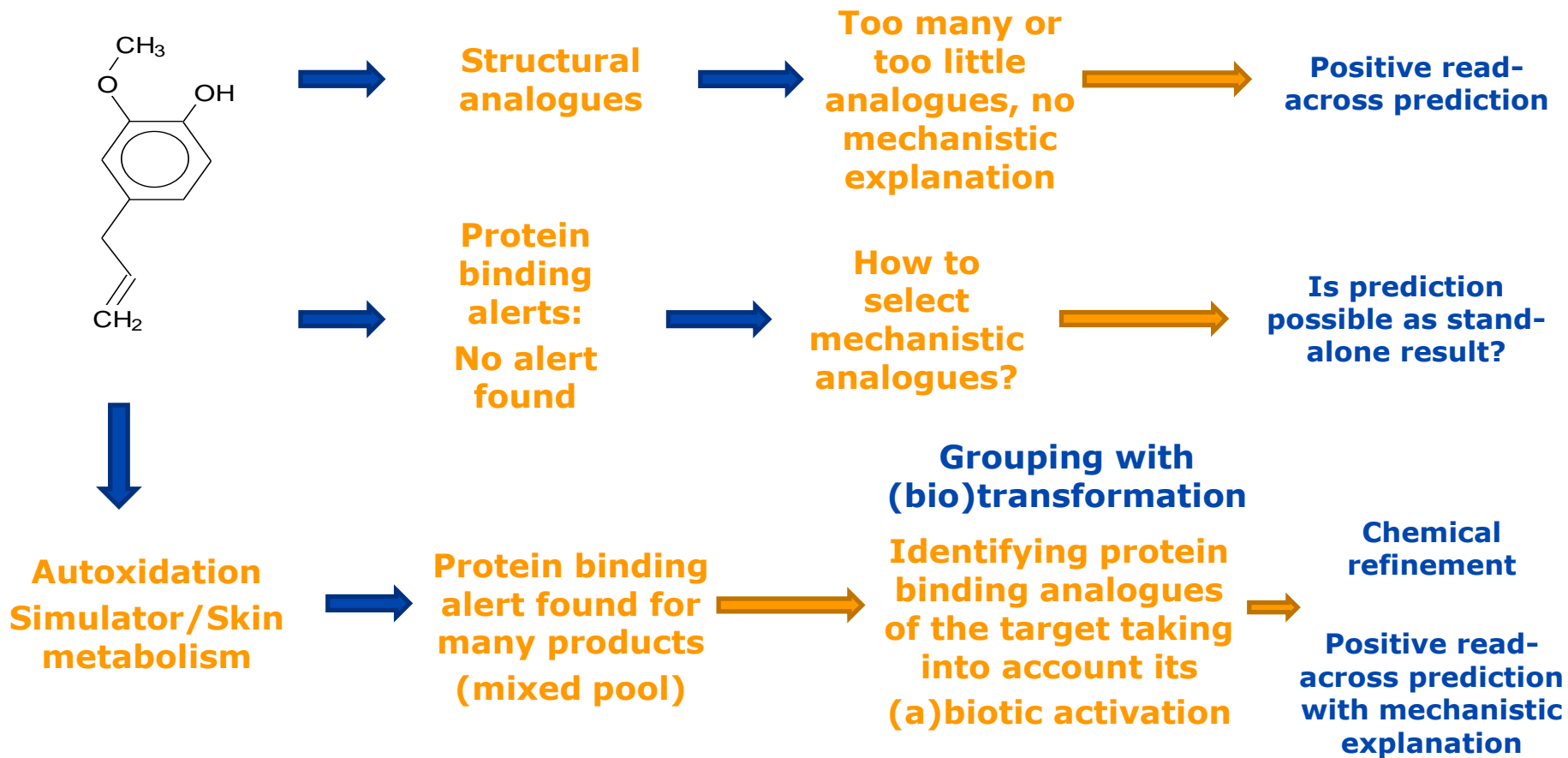
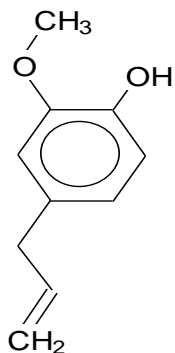
Chemical Structure: C=CC1=CC=C(C=C1)OCC=C

Graph: EC₃, S₁ MW II, Skin sensitisation (obs.) vs log Kow. The y-axis ranges from Negative to Positive. The x-axis ranges from 2.70 to 2.9. A red dot is at approximately (2.75, Positive). A green dot is at approximately (3.85, Negative).

Subcategorization Window Controls:

- Adjust options
- Target
- Differ from target by:
 - At least one category
 - All categories
- STOP
- Selected 1 (4/5)
- Select different
- Remove

Summary



Step-by-step example for how to use the Toolbox AOP workflow for Skin Sensitization(pdf)

QSAR TOOLBOX

Overview of implemented AOP scheme

Key node	Key event
1 Protein binding alerts	Protein binding – in silico/theoretical
2a <i>in chemico</i> Peptide depletion assay DPRA (Cys)	Protein binding potency in chemico
2b <i>in chemico</i> Peptide depletion assay DPRA (Lys)	
2c <i>in chemico</i> Glutathione depletion assay GSH (RC50)	
2d <i>in chemico</i> Adduct formation assay LC-MS	
3 <i>in vitro</i> Keratinocyte ARE (EC1.5, EC2, EC3)	Cellular response
4a <i>in vitro</i> Dendritic cell activity assay h-CLAT (expression of CD54 and CD86)	
4b <i>in vitro</i> Dendritic cell activity assay MUSST (expression of CD86)	
5 <i>in vivo</i> Organ response (LLNA)	Organ response
6 <i>in vivo</i> Organism response (GPMT)	Organism response

The OECD QSAR Toolbox for Grouping Chemicals into Categories 28.01.2014 8

Some learnings:

- The prediction could be relatively simple, sometimes is more difficult, and sometimes looks impossible.
- Check for experimental data (all data principle) first, EC3?
- Source of data should be traceable, data of good quality
- Select analogues by broad structural similarity first
- Consider further (sub)categorisation for consistent mechanism
- If the prediction seems negative, try transformation to check
- Check for data for the predicted transformation products
- Make a conservative estimation – **toxicological hazard should not be underestimated** and the prediction should be useful for C&L and/or risk assessment (consider cut-offs!)

Thank you!

tatiana.netzeva@echa.europa.eu

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