

IN SILICO MODELS FOR THE REACH
AND THE FOOD REGULATION :
PERSPECTIVES FOR THE NEAR FUTURE

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WHICH REGULATIONS?

- **REACH** (industrial chemicals); ECHA
- **Food** (and related substances: ingredients, additives, contaminants, pesticides, veterinary products, feed); EFSA
- Pharmaceuticals; EMA
- Cosmetics products; SCCS
- Biocides; ECHA
- Pollutants; EEA
- ...

NB: Ingredients are under REACH

CONTEXT FOR IN SILICO

Assessment of substances

This covers:

- Hazard
- Environmental properties
- Phys-chem
- Toxicokinetics
- Exposure (internal and external)
- Risk assessment

NB: Other features not covered by in silico (substance identification, registrant, etc.)

1S1A

NB: Europe is moving towards one substance - one assessment

Individual regulations will remain, but much better harmonisation, and one single database

GHS - CLP

REGULATIONS AND IN SILICO MODELS (i)

In silico models can be used for different purposes

Different models are preferable for different purposes (assessment: conservative; prioritization; balanced)

The documentation should clarify the context and intended use

Not covered today:

In silico models for «**research**» (strange endpoints, new approaches, etc.)

In silico models for **R&D** for industrial purposes (different properties, confidential data, etc.)

REGULATIONS AND IN SILICO MODELS (ii)

- Cosmetics products (SCCS): **NO** in vivo data
- Food (EFSA): moving towards NAMs (new alternative methodologies); in vivo data on parental compound; in silico can be used for degradation products, etc.
- REACH / Biocides (ECHA): in silico can be used (a few percent of registered substances; 25% read across; < 30% experimental data)
- Pharmaceuticals (EMA): in vivo requested; in silico for impurities
- In silico for prioritization

REACH

About 50 different properties:

- Phys-chem
- Environ
- Ecotox
- Tox

Different requests depending on the tonnage of substance on the market (from 1 tonn/year, up; if > 1000 all properties)

QSAR: key study or weight-of-evidence

Weight of evidence (WoE): EFSA Guidance

SCIENTIFIC OPINION



ADOPTED: 12 July 2017

doi: 10.2903/j.efsa.2017.4971

Guidance on the use of the weight of evidence approach in scientific assessments

EFSA Scientific Committee,
Anthony Hardy, Diane Benford, Thorhallur Halldorsson, Michael John Jeger,
Helle Katrine Knutsen, Simon More, Hanspeter Naegeli, Hubert Noteborn, Colin Ockleford,
Antonia Ricci, Guido Rychen, Josef R Schlatter, Vittorio Silano, Roland Solecki,
Dominique Turck, Emilio Benfenati, Qasim Mohammad Chaudhry, Peter Craig,
Geoff Frampton, Matthias Greiner, Andrew Hart, Christer Hogstrand, Claude Lambre,
Robert Luttik, David Makowski, Alfonso Siani, Helene Wahlstroem, Jaime Aguilera,
Jean-Lou Dorne, Antonio Fernandez Dumont, Michaela Hempen, Silvia Valtueña Martínez,
Laura Martino, Camilla Smeraldi, Andrea Terron, Nikolaos Georgiadis and Maged Younes

<https://www.efsa.europa.eu/en/efsajournal/pub/4971>

EFSA Guidance on WoE

Approach for WoE

1. Gather all info
2. Evaluate individual lines of evidence
3. Integrate the results

EFSA Guidance: integration

Criteria for integration

1. Relevance
2. Reliability
3. Agreement

In silico and read-across: integration

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Review article

Integrating *in silico* models and read-across methods for predicting toxicity of chemicals: A step-wise strategy



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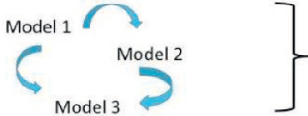
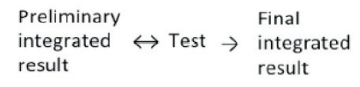
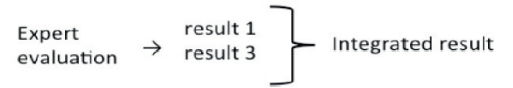
ARTICLE INFO

Handling Editor: Da Chen

ABSTRACT

In silico methods and models are increasingly used for predicting properties of chemicals for hazard identification and hazard characterisation in the absence of experimental toxicity data. Many *in silico* models are available and can be used individually or in an integrated fashion. Whilst such models offer major benefits to toxicologists, risk assessors and the global scientific community, the lack of a consistent framework for the integration of *in silico* results can lead to uncertainty and even contradictions across models and users, even for the same chemicals. In this context, a series of methods for integrating *in silico* models have been proposed and evaluated to assess their

Integration of in silico

Algebraic and voting methods	<p>Algebraic methods</p> <p>Model 1 → result 1 Model 2 → result 2 Model 3 → result 3</p> 
Weighing	<p>Weighing methods</p> <p>Model 1 → result 1 → transformed result 1 Model 2 → result 2 → transformed result 2 Model 3 → result 3 → transformed result 3</p> 
Hybrid	<p>Hybrid methods</p> 
Learning	<p>Learning methods</p> <p>Model 1 → result 1 Model 2 → result 2 Model 3 → result 3</p> 
Expert-based	<p>Expert-based integration</p> <p>Model 1 → result 1 Model 2 → result 2 Model 3 → result 3</p> 

Algebraic methods

Majority vote

Unanimity

Worst case

All models at the same level of reliability

Or you introduce thresholds (in / out: 2 levels or reliability)

Weighing methods

VEGA and mutagenicity is an example

Use of all models, in a quantitative way

(not in or out, binary, qualitative approach)

Consensus model (CNS-VEGA) : CAESAR + SARPY + TT-VEGA

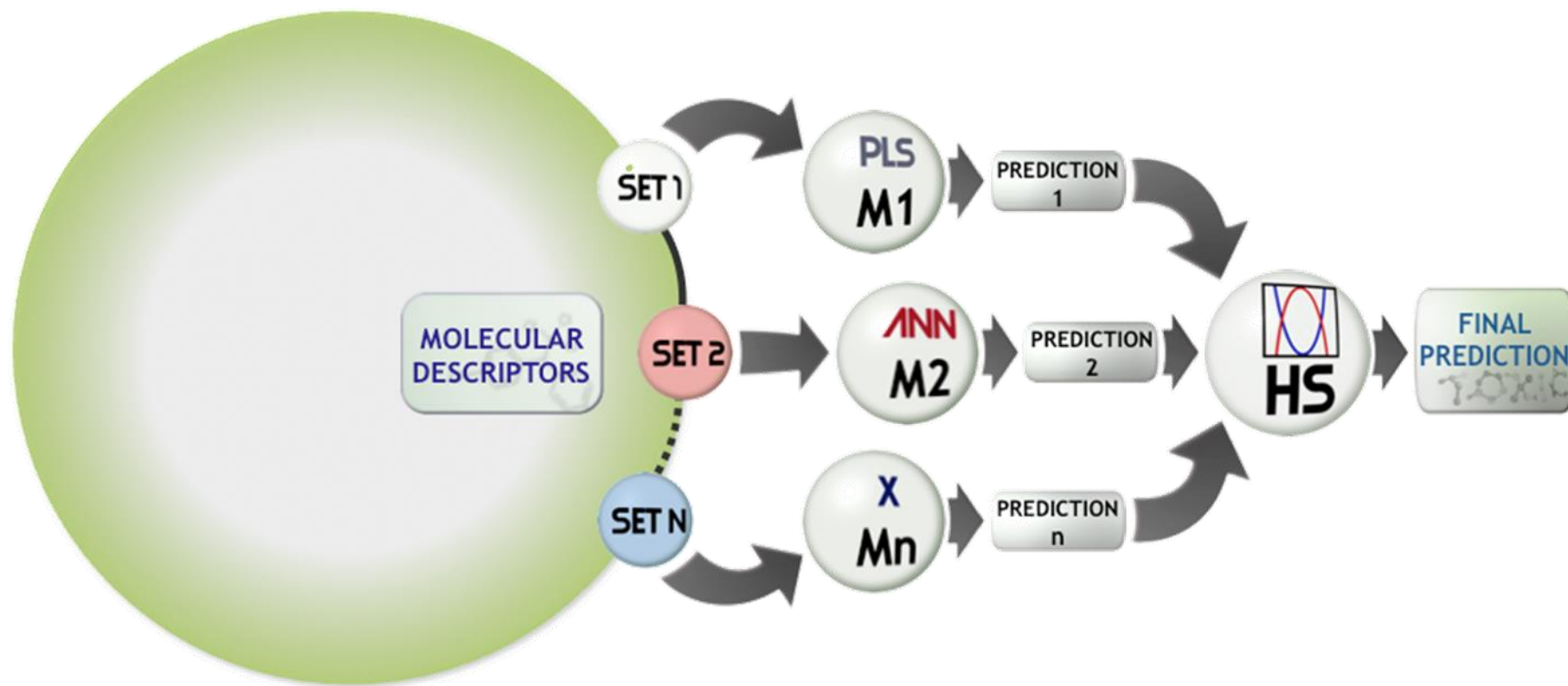
$$\text{CONSENSUS} = \frac{(\pm 1) * AD_{\text{CAESAR}} + (\pm 1) * AD_{\text{SARPY}} + (\pm 1) * AD_{\text{TTVEGA}}}{AD_{\text{CAESAR}} + AD_{\text{SARPY}} + AD_{\text{TTVEGA}}}$$

Algorithm extended now to 4 models



Hybrid models

The 5 CAESAR models in VEGA are hybrid models



Learning methods

Hybrid models are planned since their beginning to be within one single system

Learning methods takes pre-existing models, integrate them, and finds the best way to assemble them, ideally using a test set for this purpose.

The test set has to contain new substances, never used by any of the pre-existing models. This is often very difficult.

Expert-based methods

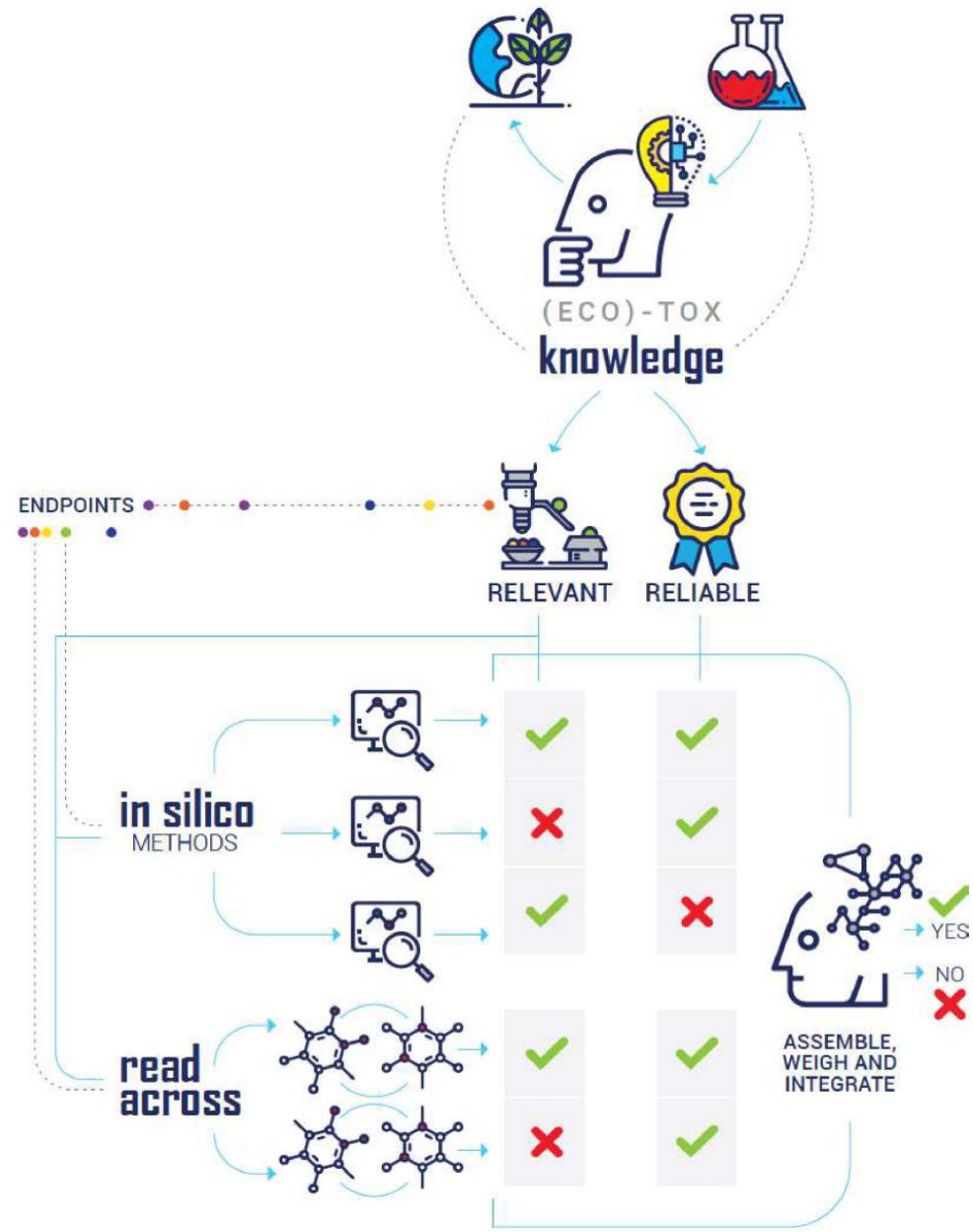
Experts may identify a preferred way to integrate results.

Pragmatic approach.

Often combining some criteria for reasoning, and introducing thresholds, and conservative assumptions.

Thus, the criteria are not only statistical. They should be declared.

Integrating in silico and read-across



Use all lines of evidence

1. VEGA in silico models
2. Read-across
3. Reasoning
 - Check agreement

Welcome to the VEGA HUB

Offering a family of tools to evaluate chemical hazard: VEGA, ToxRead, ToxWeight, ToxDelta, and JANUS.

VEGA is the QSAR software with tens of models for individual properties.

ToxDelta

ToxWeight

ToxRead

VEGA



Do you need assistance for a property prediction?

CONTACT US

JANUS



VEGA HUB ▾ QSAR ▾ Download ▾

VEGAHUB

Community News Contacts Login

Our philosophy

The In silico methods can be very useful,
if correctly applied

VEGA and ECHA



Preparation of an inventory of
substances suspected to meet
REACH Annex III criteria

Technical documentation



Practical guide

How to use and report (Q)SARs

Version 3.1 – July 2016

EFSA and OECD QSAR Toolbox

VEGA linked to the OECD QSAR Toolbox

From OECD TB you can make the predictions using the VEGA models

However:

- No access to the graphical info for the ADI
- Less models (57 not 80)

EFSA and VEGA



SCIENTIFIC OPINION

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FILE

Please, use one search field at a time and click on "Apply". If more than one filter is used, the tool will intersect all searched data. If you wish to see the alternative names (synonyms) of a substance please, select the substance name in the Substance characterisation table.

Substance Characterisation

Substance	has	Component	CAS number	EC Ref No	Molecular formula	Smiles	Synonym
Boron compounds	not part of group assessment	Borate	11113-50-1		(B(O3)3-	B([O-])[O-][O-]	Boron compounds
Boron compounds	not part of group assessment	Boric acid	7440-42-8		BH3O3	B(O)(O)O	E 284
Boron compounds	not part of group assessment	Boron	7440-42-8		B	[B]	FCM No. 981
Boron compounds	not part of group assessment	Sodium borohydride	16940-66-2		BH3.Na	[Na+].[BH3-]	

EFSA outputs

Substance	Author	Published	Output Id	Title	Output Type	Legal Basis	Url
Boron compounds	EFSA NDA	08/17/2004	2	Opinion of the Scientific Panel on Dietary Products, Nutrition and Allergies on a request from the Commission related to the Tolerable Upper Intake Level of Boron (Sodium Borate and Boric Acid)	EFSA opinion	Directive (EC) No 46/2002	http://dx.doi.org/10.2903/j.efsa.2004.80
Boron compounds	EFSA CONTAM	07/13/2005	43	Opinion of the Scientific Panel on Contaminants in the Food Chain on a request of the Commission related to concentration limits for boron and fluoride in natural mineral waters	EFSA opinion	Regulation (EC) No 178/2002 (amended)	http://dx.doi.org/10.2903/j.efsa.2005.237
Boron compounds	EFSA AFC	07/05/2006	377	Statement of the Scientific Panel on Food Additives, Flavourings, Processing Aids and Materials in Contact with Food on a request from the Commission related to Boric Acid and Sodium borate as nutrient sources of boron.	EFSA statement	Regulation (EC) No 178/2002 (amended)	http://dx.doi.org/10.2903/j.efsa.2005.1044

Hazard Characterisation: Reference points

Substance	Author	Year	Output Id	Study	Test Type	Species	Route	Duration (days)	Endpoint	Qualifier	Value	Unit	Effect	Toxicity
Boron compounds	EFSA NDA	2004	2	Human health	reproduction toxicity	Rat	oral; feed	21	NOAEL	=	9.6	mg/kg bw/day	body weight	teratogenic
Boron compounds	EFSA CONTAM	2005	43	Human health	reproduction toxicity	Rat	oral; feed	21	NOAEL	=	9.6	mg/kg bw/day	body weight	teratogenic
Boron compounds	EFSA AFC	2006	377	Human health	reproduction toxicity	Rat	oral; feed	21	NOAEL	=	9.6	mg/kg bw/day	body weight	teratogenic

Hazard Characterisation: Reference values

Substance	Author	Year	Output Id	Assessment	Qualifier	Value	Unit	Population
Boron compounds	EFSA NDA	2004	2	UL	=	0.16	mg/kg bw/day	Consumers - Adult women, lactating
Boron compounds	EFSA NDA	2004	2	UL	=	0.16	mg/kg bw/day	Consumers - Adult women, pregnant
Boron compounds	EFSA NDA	2004	2	UL	=	0.16	mg/kg bw/day	Consumers - Adults

Genotoxicity

Substance	Author	Year	Output Id	Genotoxicity
Boron compounds	EFSA NDA	2004	2	Negative
Boron compounds	EFSA CONTAM	2005	43	No data
Boron compounds	EFSA AFC	2006	377	No data
Boron compounds	EFSA CEF	2012	472	No data
Boron compounds	EFSA CEF	2013	2392	No data

Substance Browser Reference Values Reference Point Background Documents

EFSA and CEFIC and Danish (Q)SAR DB

CEFIC: AMBIT

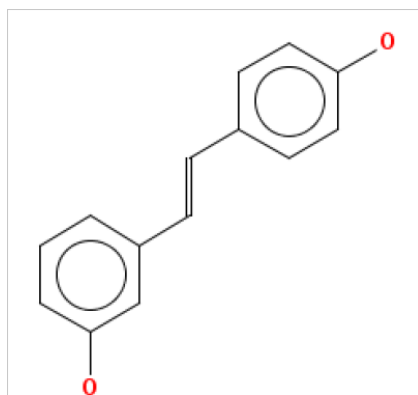


A screenshot of the Danish (Q)SAR Database website. The header is a dark blue gradient with the text "Danish (Q)SAR Database" in white. Below the header, there is a paragraph of text in a smaller font. Underneath the text, there are three buttons: "Search", "User manual", and "Contact". At the bottom of the page, there are six logos for partner organizations: MUXCASE, Leadscope, SciMatics, ACD/Labs, EPI, and QASIS.

ADI parameters

- ✓ **Visualization of similar substances**
 - ✓ **Similarity index** (*chemical; sub-indices*)
 - ✓ **Chemometric check** (*descriptor space*)
 - ✓ **Atom centered-fragment** (*chemical*)
- Chemical input space
- ✓ **Check of the descriptor sensitivity** (*algorithm*)
 - ✓ **Uncertainty** (*algorithm*)
- Characteristics of the algorithm
- ✓ **Fragments for outliers** (*output space*)
 - ✓ **Prediction Accuracy** (*output space*)
 - ✓ **Prediction Concordance** (*tox exploration*)
- Input and output toxicological space

ADI concordance



Prediction: Reliability:

Prediction is Possible NON-Mutagenic, but the result shows some critical aspects, which require to be checked:
 - similar molecules found in the training set have experimental values that disagree with the predicted value



Global AD Index

AD index = 0.719

Explanation: the predicted compound could be out of the Applicability Domain of the model.



Similar molecules with known experimental value

Similarity index = 0.901

Explanation: strongly similar compounds with known experimental value in the training set have been found.



Accuracy of prediction for similar molecules

Accuracy index = 1

Explanation: accuracy of prediction for similar molecules found in the training set is good.



Concordance for similar molecules

Concordance index = 0.33

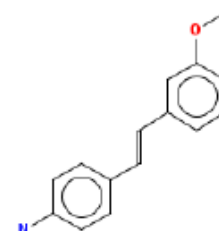
Explanation: similar molecules found in the training set have experimental values that disagree with the predicted value.



Atom Centered Fragments similarity check

ACF index = 1

Explanation: all atom centered fragment of the compound have been found in the compounds of the training set.



Compound #1

CAS: 154028-32-7

Dataset id: 2989 (Training set)

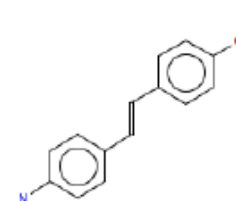
SMILES: O(c2cccc(C=Cc1ccc(N)cc1)c2)C

Similarity: 0.907

Experimental value: Mutagenic

Predicted value: Mutagenic

Alerts (not found in the target): SM44; SM104



Compound #2

CAS: 7570-37-8

Dataset id: 1345 (Training set)

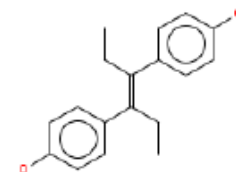
SMILES: O(c1ccc(cc1)C=Cc2ccc(N)cc2)C

Similarity: 0.905

Experimental value: Mutagenic

Predicted value: Mutagenic

Alerts (not found in the target): SM44; SM104



Compound #3

CAS: 56-53-1

Dataset id: 2731 (Test set)

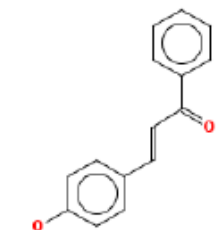
SMILES: Oc1ccc(cc1)C=C(c2ccc(O)cc2)CC)CC

Similarity: 0.893

Experimental value: NON-Mutagenic

Predicted value: NON-Mutagenic

Alerts (not found in the target): SM158



Compound #4

CAS: 20426-12-4

Dataset id: 561 (Test set)

SMILES: O=C(C=Cc1ccc(O)cc1)c2ccccc2

Similarity: 0.888

Experimental value: NON-Mutagenic

Predicted value: NON-Mutagenic

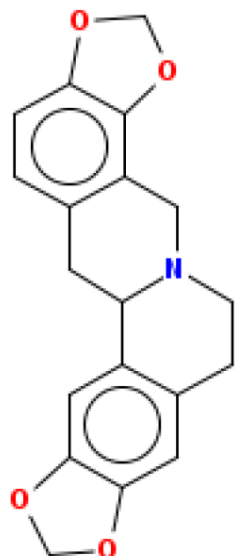
WoE mutagenicity


In silico model higher reliability than initial

Read-across: choice based on relevance

Reasoning about mechanism used

Elements of warning indicated by VEGA appropriate



Prediction: 

Prediction is NON-Mutagenic with a consensus score of 0.5, based on 4 models.

Compound: Molecule 0

Compound SMILES: O1c2ccc5c(c2(OC1))CN4CCc3cc6OCOC6(cc3C4C5)

Used models: 4

Predicted Consensus Mutagen activity: NON-Mutagenic

Mutagenic Score: 0

Non-Mutagenic Score: 0.5

Model Caesar assessment: NON-Mutagenic (low reliability)

Model ISS assessment: NON-Mutagenic (moderate reliability)

Model SarPy assessment: NON-Mutagenic (moderate reliability)

Model KNN assessment: NON-Mutagenic (moderate reliability)



VEGA

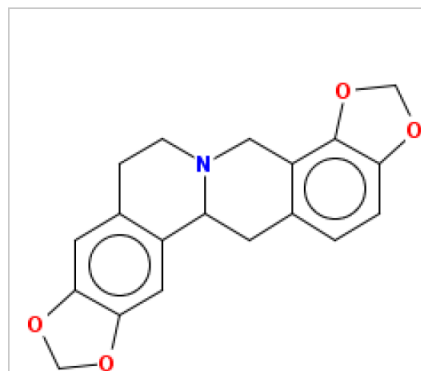
Mutagenicity (Ames test) model (CAESAR) 2.1.13





page 2

1. Prediction Summary



Prediction for compound Molecule 0



Prediction:  Reliability:   

Prediction is NON-Mutagenic, but the result may be not reliable. A check of the information given in the following section should be done, paying particular attention to the following issues:

- accuracy of prediction for similar molecules found in the training set is not adequate
- similar molecules found in the training set have experimental values that disagree with the predicted value

Compound: Molecule 0

Compound SMILES: O1c2ccc5c(c2(OC1))CN4CCc3cc6OCOc6(cc3C4C5)

Experimental value: -

Predicted Mutagen activity: NON-Mutagenic

Structural alerts: -

Reliability: the predicted compound is outside the Applicability Domain of the model

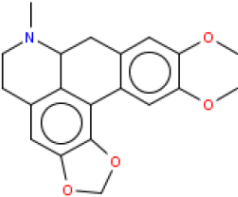
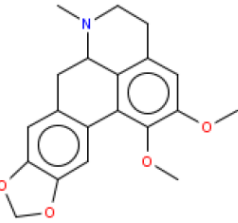
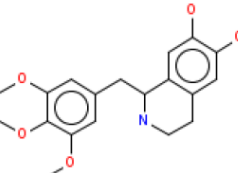
Remarks:

none



3.1 Applicability Domain: Similar Compounds, with Predicted and Experimental Values



	<p>Compound #1</p> <p>CAS: 517-66-8 Dataset id: 1275 (Training set) SMILES: <chem>O(c3cc4c1c5OCOc5(cc2c1C(N(C)CC2)Cc4(cc3(OC))))C</chem> Similarity: 0.909</p> <p>Experimental value: Mutagenic Predicted value: NON-Mutagenic</p>
	<p>Compound #2</p> <p>CAS: 2565-01-7 Dataset id: 2067 (Training set) SMILES: <chem>O(c1cc4c3c(c1(OC))c2cc5OCOc5(cc2CC3N(C)CC4))C</chem> Similarity: 0.908</p> <p>Experimental value: Mutagenic Predicted value: NON-Mutagenic</p>
	<p>Compound #3</p> <p>CAS: 30418-38-3 Dataset id: 4202 (Training set) SMILES: <chem>Oc1cc2c(cc1(O))C(NCC2)Cc3cc(OC)c(OC)c(OC)c3</chem> Similarity: 0.898</p> <p>Experimental value: NON-Mutagenic Predicted value: NON-Mutagenic</p>









VEGA

Mutagenicity (Ames test) model (CAESAR) 2.1.13

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3.2 Applicability Domain: Measured Applicability Domain Scores



	Global AD Index AD index = 0.547 Explanation: the predicted compound is outside the Applicability Domain of the model.
	Similar molecules with known experimental value Similarity index = 0.905 Explanation: strongly similar compounds with known experimental value in the training set have been found.
	Accuracy of prediction for similar molecules Accuracy index = 0.33 Explanation: accuracy of prediction for similar molecules found in the training set is not adequate.
	Concordance for similar molecules Concordance index = 0.33 Explanation: similar molecules found in the training set have experimental values that disagree with the predicted value.
	Model's descriptors range check Descriptors range check = True Explanation: descriptors for this compound have values inside the descriptor range of the compounds of the training set.
	Atom Centered Fragments similarity check ACF index = 1

STYLOPINE mutagenicity

Read-across prevails

Not possible to exclude mutagenicity of stylopine

In silico models contradicted by the similar compounds

Elements of warning indicated by VEGA appropriate

FOOD: THE VERMEER-FCM MODEL

EXPOSURE

X

HAZARD

=

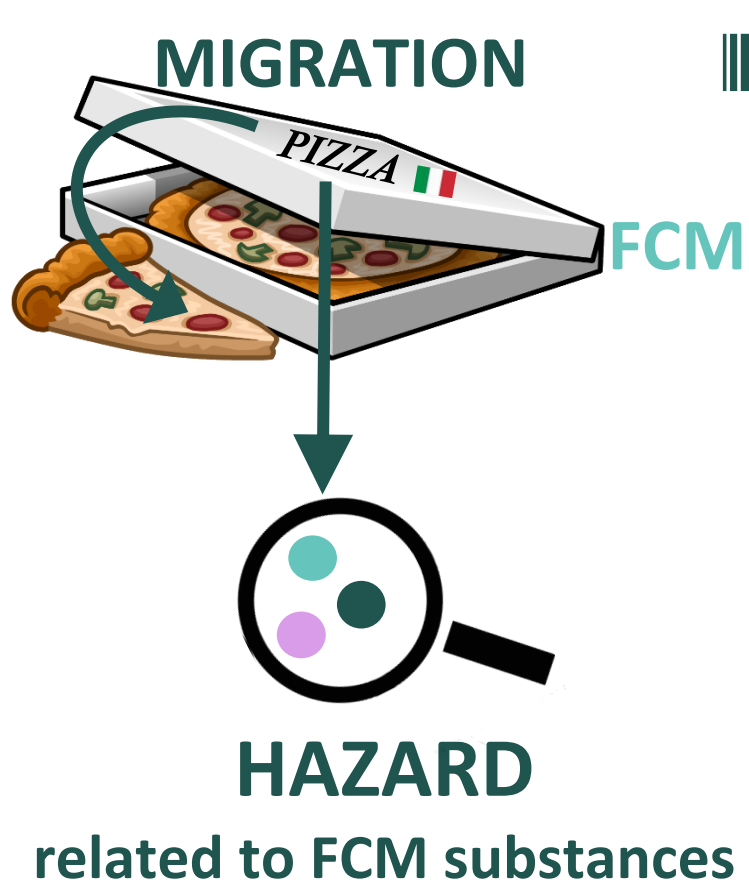
RISK



Several case studies including food contact materials - FCM



Background: FCM



Food contamination



Consumption

EXPOSURE

AIM: Combine information on exposure collected with MERLIN EXPO with information on hazards collected with VEGA to support risk assessment of FCM compounds

Regulations: FCM



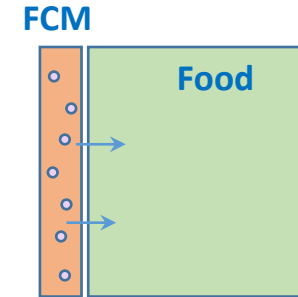
Plastic FCM: **positive list (Annex I of Regulation 10/2011)** (only starting substances such as monomers and additives)

Annex I provides overview of authorized substances to be used in plastic FCM
(with corresponding SML, if available)

(1)	(2)	(3)	(4)	(5)	(6)	(7)	(8)	(9)	(10)	(11)
FCM substance No	Ref. No	CAS No	Substance name	Use as additive or polymer production aid (yes/no)	Use as monomer or other starting substance or macromolecule obtained from microbial fermentation (yes/no)	FRF applicable (yes/no)	SML [mg/kg]	SML(T) [mg/kg] (Group restriction No)	Restrictions and specifications	Notes on verification of compliance
1	12310	0266309-43-7	albumin	no	yes	no				
2	12340	—	albumin, coagulated by formaldehyde	no	yes	no				

VERMEER FCM: Migration model

- One FCM layer



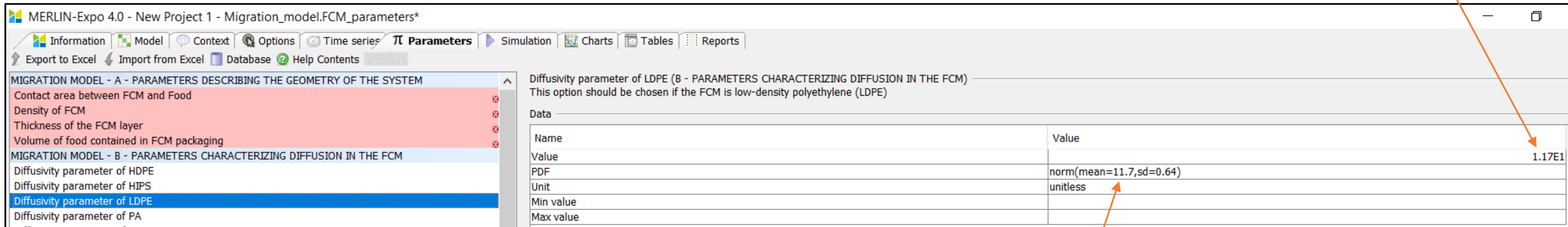
- One dimensional (1D) diffusion model between the FCM layer and Food

$$\text{Fick's law: } \frac{\partial C_i}{\partial t} = D_i \cdot \frac{\partial^2 C_i}{\partial x^2}$$

- When only one FCM layer is considered, mass-balance equation based on Fick's law → **analytical solution** (Crank, 1975 ; Piringer et al, 2008)

VERMEER FCM: Model available

It works within the MERLIN-Expo platform. Best estimate of the parameter



MERLIN-Expo 4.0 - New Project 1 - Migration_model.FCM_parameters*

Information Model Context Options Time series **Parameters** Simulation Charts Tables Reports

Export to Excel Import from Excel Database Help Contents

MIGRATION MODEL - A - PARAMETERS DESCRIBING THE GEOMETRY OF THE SYSTEM

- Contact area between FCM and Food
- Density of FCM
- Thickness of the FCM layer
- Volume of food contained in FCM packaging

MIGRATION MODEL - B - PARAMETERS CHARACTERIZING DIFFUSION IN THE FCM

- Diffusivity parameter of HDPE
- Diffusivity parameter of HIPS
- Diffusivity parameter of LDPE**
- Diffusivity parameter of PA

Diffusivity parameter of LDPE (B - PARAMETERS CHARACTERIZING DIFFUSION IN THE FCM)
This option should be chosen if the FCM is low-density polyethylene (LDPE)

Data

Name	Value
Value	1.17E1
PDF	norm(mean=11.7,sd=0.64)
Unit	unitless
Min value	
Max value	

First step: migration, then **toxicity**

<https://www.life-vermeer.eu/>

doi: 10.1016/j.fct.2022.113118

VERMEER FCM: Toxicity models (via VEGA)

Migration threshold	Toxicological data required	Models available in Vega
X < 0.05 mg/kg food	<ul style="list-style-type: none"> Genotoxicity data <ul style="list-style-type: none"> ➤ Gene mutations ➤ Structural and numerical chromosome aberration 	<ul style="list-style-type: none"> Mutagenicity (Ames test) CONSENSUS model (version 1.0.3) <i>In vitro</i> Micronucleus activity (IRFMN/Vermeer) (version 1.0.0)
	<ul style="list-style-type: none"> Genotoxicity data 	<ul style="list-style-type: none"> <i>See above</i>
	<ul style="list-style-type: none"> Subchronic oral toxicity data (90-day study) Data to demonstrate absence of accumulation potential in man 	<ul style="list-style-type: none"> NOAEL (IRFMN/CORAL) (version 1.0.0) LogP model (MLogP) (version 1.0.0)

VERMEER FCM: Hazard models

Migration threshold	Toxicological data required	Models available in Vega
5 mg/kg ≤ X < 60 mg/kg	<ul style="list-style-type: none"> • Genotoxicity data • Subchronic oral toxicity data (90-day study) • Toxicokinetic data 	<ul style="list-style-type: none"> • <i>See above</i>
	<ul style="list-style-type: none"> • Data on reproductive and developmental toxicity 	<ul style="list-style-type: none"> • Developmental Toxicity model (CAESAR) (version 2.1.7) • Developmental/Reproductive Toxicity library (PG) (version 1.1.0)
	<ul style="list-style-type: none"> • Data from long term toxicity/carcinogenicity studies 	<ul style="list-style-type: none"> • Carcinogenicity model (Antares) (version 1.0.0) • Carcinogenicity model (ISSCAN-CGX) (version 1.0.0) • Carcinogenicity model (CAESAR) (version 2.1.9) • Carcinogenicity model (ISS) (version 1.0.2) • Carcinogenicity consensus model • Carcinogenicity oral classification model (IRFMN) (version 1.0.0) + Carcinogenicity oral Slope Factor model (IRFMN) (version 1.0.0)

CONCLUSIONS

In silico models assisting experts

Integratation of models for the same endpoint

Integration hazard + exposure

Network between multiple systems

Plus prioritization

Transparency, documentation, reasoning, weight-of-evidence