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Quantitative Structural activity relationships (Q)SAR's and their application to SDS and PIDS

John Morrison 23/11/16

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(Quantitative) Structural activity relationships (Q)SAR's

1. Download suggested QSAR software (VEGA and ECHA/OECD QSAR toolbox) to see what they do.

2.What do we want to use them for? KEY QUESTION !!!

For Risk assessment of unknowns for transport no simple guidance found for use of the software packages to assist in our chemical transportation problems. (so several false starts throughout, particularly on ECHA).

3. Try worked examples:- Drop in our structures and see what comes out. Easy on VEGA but huge data mass. ECHA remarkably complex.

4. Assimilation of findings.

(Quantitative) Structural activity relationships (Q)SAR's

1. Download suggested QSAR software (VEGA and ECHA/OECD QSAR toolbox) to see what they do. Both free after giving a few details.

VEGA (http://www.vega-qsar.eu/download.html) is server based so not much to download. Got it working reasonably quickly then failed. Needs old version of Java to operate.

ECHA/OECD (http://toolbox.oasis-lmc.org/?section=download&version=latest) has server and standalone versions. Both are massive (3.7GB for server version). To date have not seen any tutorials for server version but many for stand alone.

For this would really need training eg
http://oasis-lmc.org/products/software/toolbox/training.aspx

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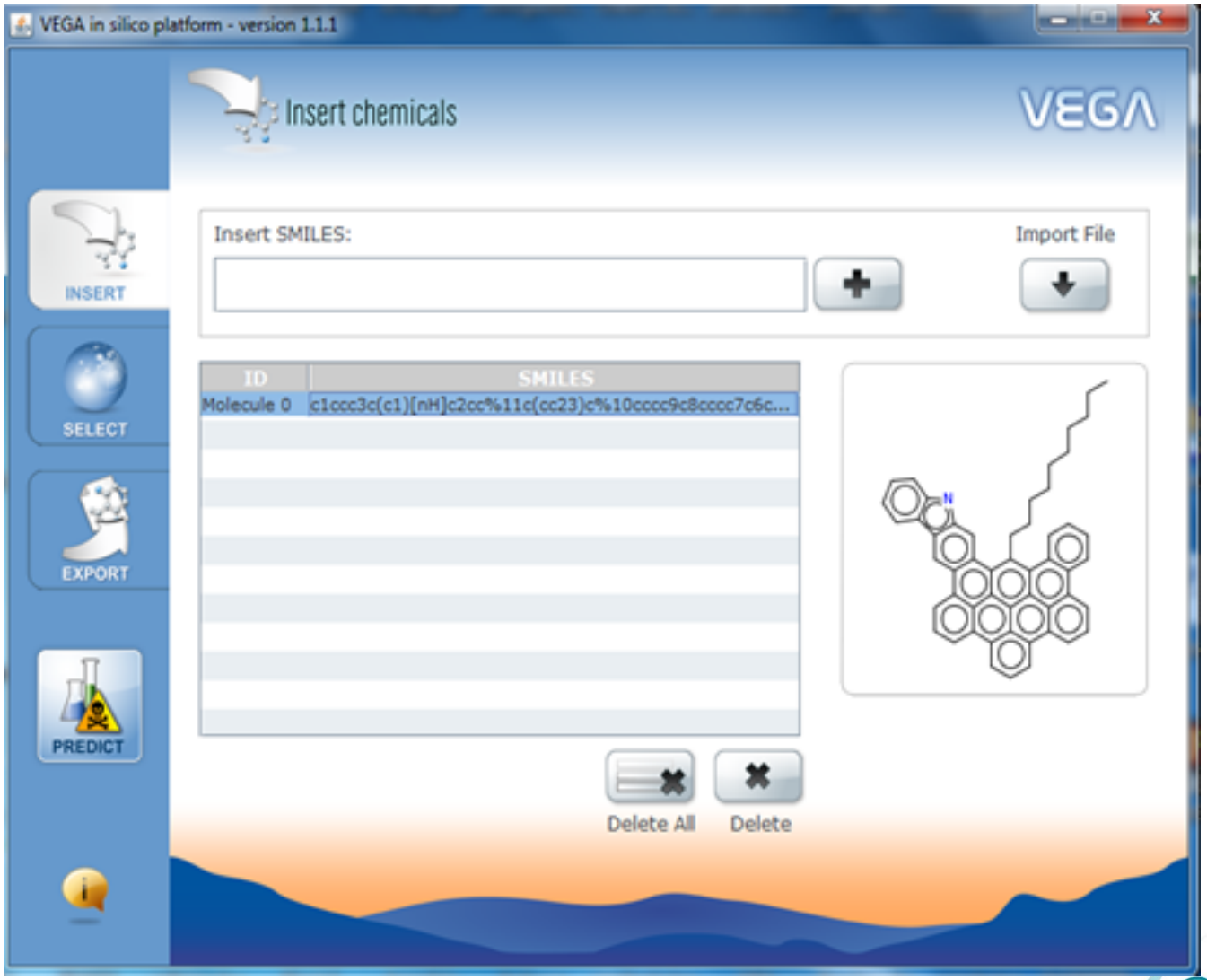
VEGA (Q)SAR's



simplified molecular-input line-entry system (SMILES)

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VEGA (Q)SAR's


VEGA in silico platform - version 1.1.1
Select models
VEGA
INSERT
SELECT
EXPORT
PREDICT
Tox
Ecotox
Environ
Phys-Chem
Mutagenicity (Ames test) model (CAESAR) - v. 2.1.13
Mutagenicity (Ames test) model (SarPy/IRFMN) - v. 1.0.7
Mutagenicity (Ames test) model (ISS) - v. 1.0.2
Mutagenicity (Ames test) model (KNN/Read-Across) - v. 1.0.0
Carcinogenicity model (CAESAR) - v. 2.1.9
Carcinogenicity model (ISS) - v. 1.0.2
Carcinogenicity model (IRFMN/Antares) - v. 1.0.0
Carcinogenicity model (IRFMN/ISSCAN-CGX) - v. 1.0.0
Developmental Toxicity model (CAESAR) - v. 2.1.7
Developmental/Reproductive Toxicity library (PG) - v. 1.0.0
Relative Binding Affinity model (IRFMN) - v. 1.0.1
Skin Sensitization model (CAESAR) - v. 2.1.6
All models

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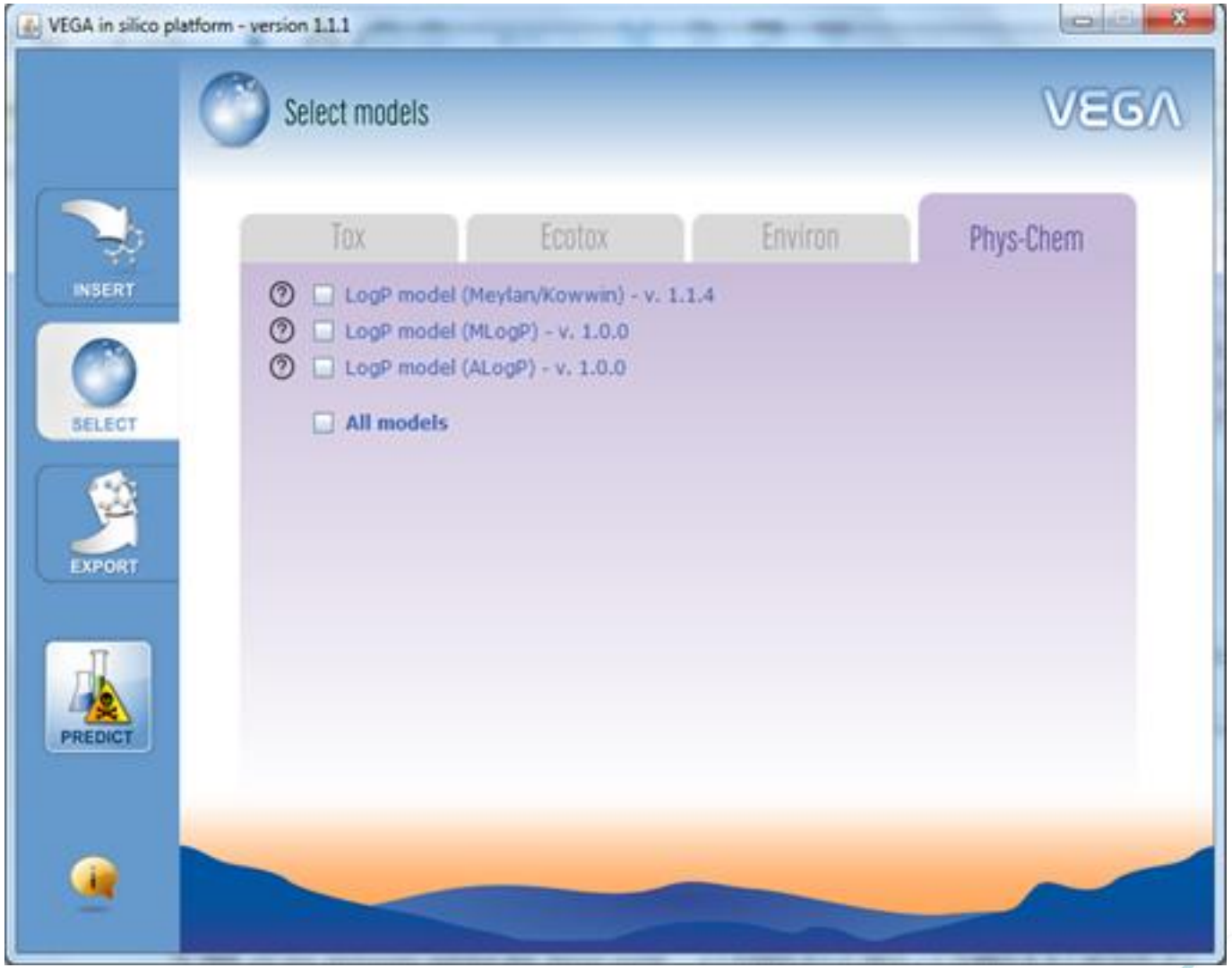
VEGA (Q)SAR's



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VEGA (Q)SAR's

9 Models gives 43 page report

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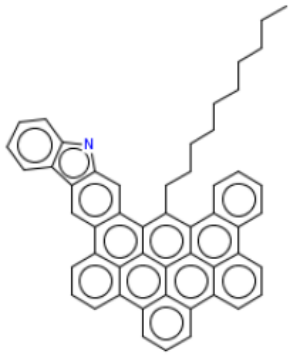
VEGA (Q)SAR's

1. Prediction Summary

Prediction for compound Molecule 0



Prediction: Reliability:

Prediction is NON-Carcinogen, 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:
- only moderately similar compounds with known experimental value in the training set have been found
- some similar molecules found in the training set have experimental values that disagree with the predicted value
- predicted substance falls into a neuron that is populated by no compounds of the training set

Compound: Molecule 0
Compound SMILES:
c1ccc3c(c1)[nH]c2cc%11c(cc23)c%10cccc9c8cccc7c6cccc5c4ccccc4c%12c(c56)c(c78)c(c9%10)c%11c%12CCCCC
CCCCC
Experimental value: -
Predicted Carcinogen activity: NON-Carcinogen
P(Carcinogen): 0.286
P(NON-Carcinogen): 0.714
Reliability: the predicted compound is outside the Applicability Domain of the model
Remarks:
none

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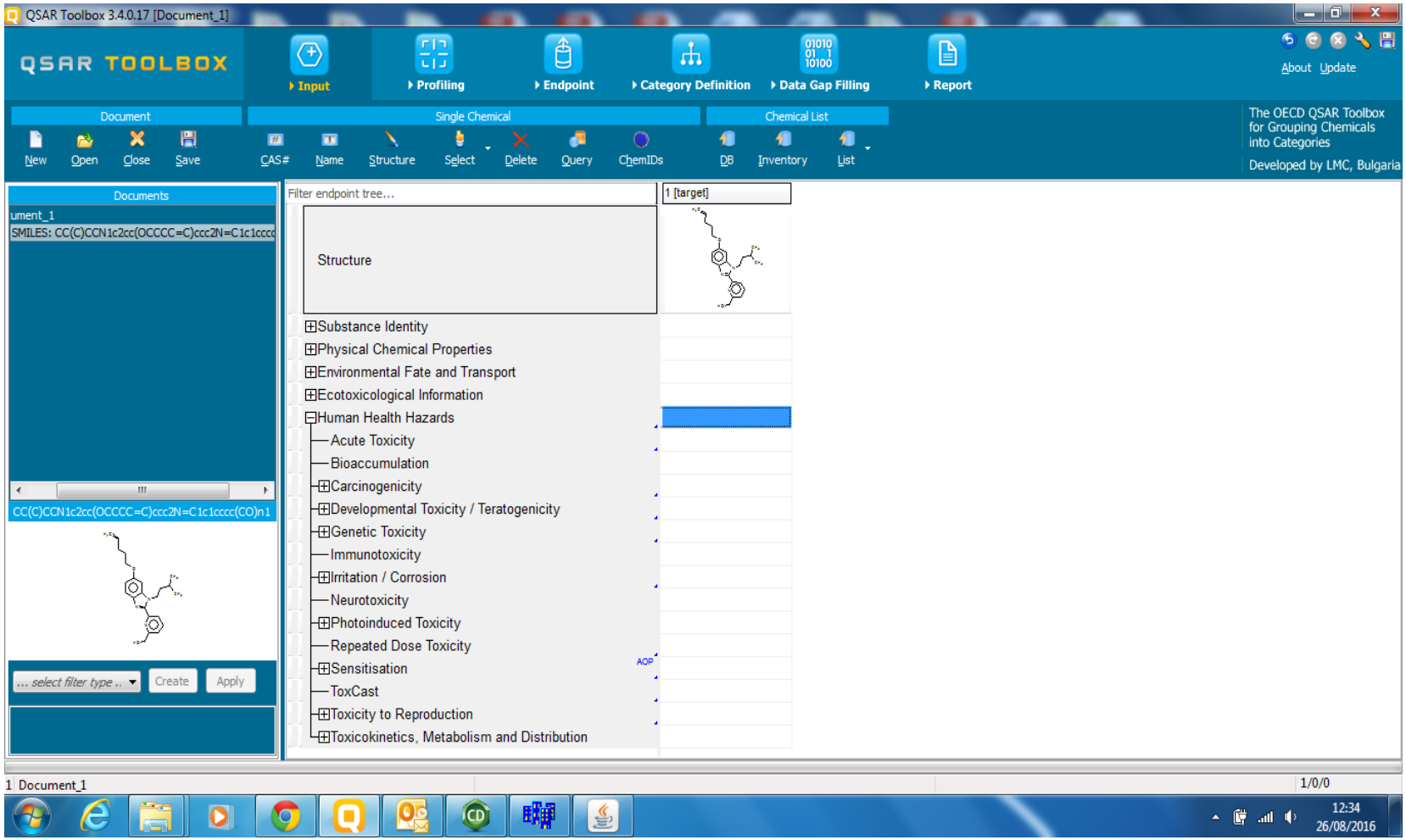
ECHA/OECD (Q)SAR's



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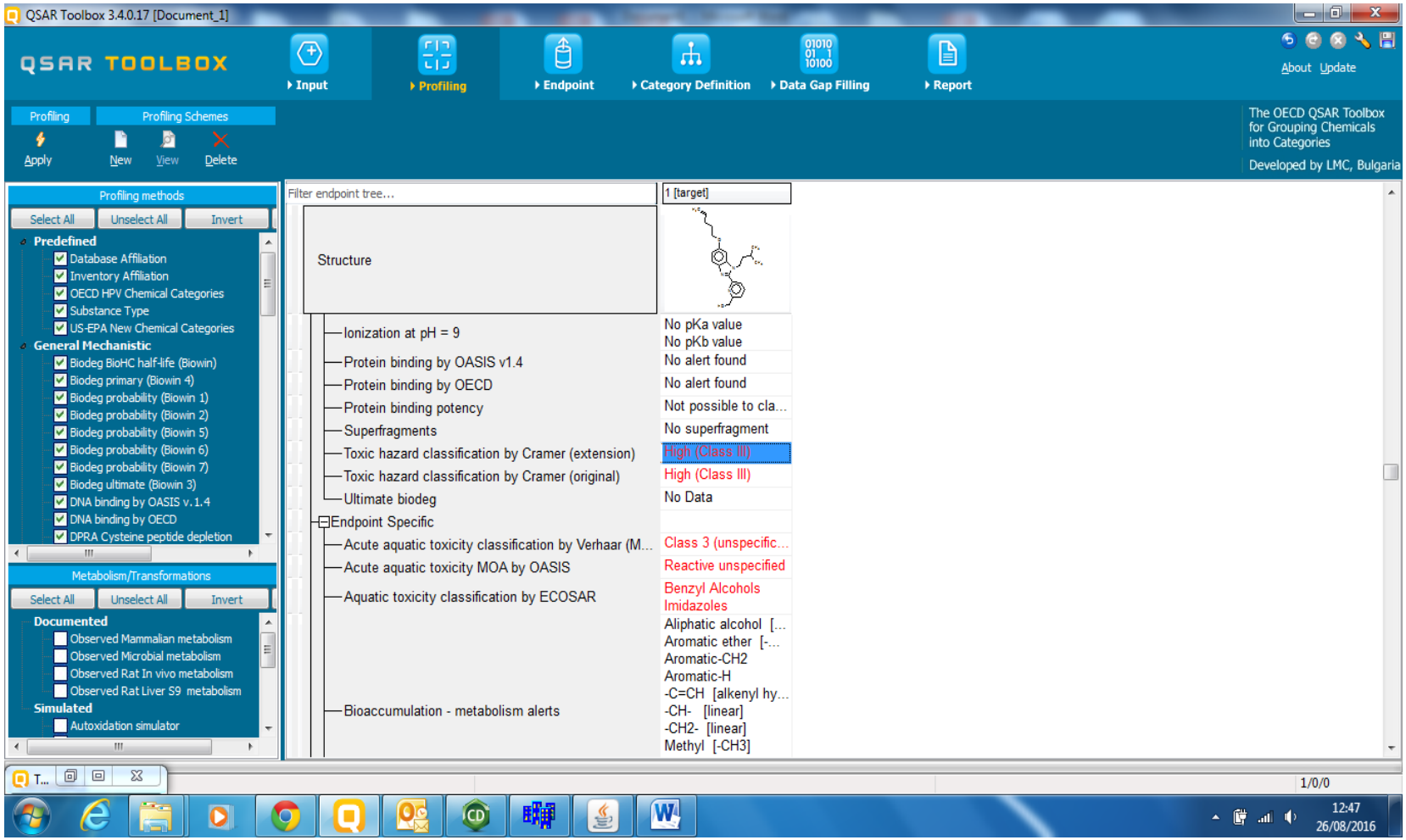
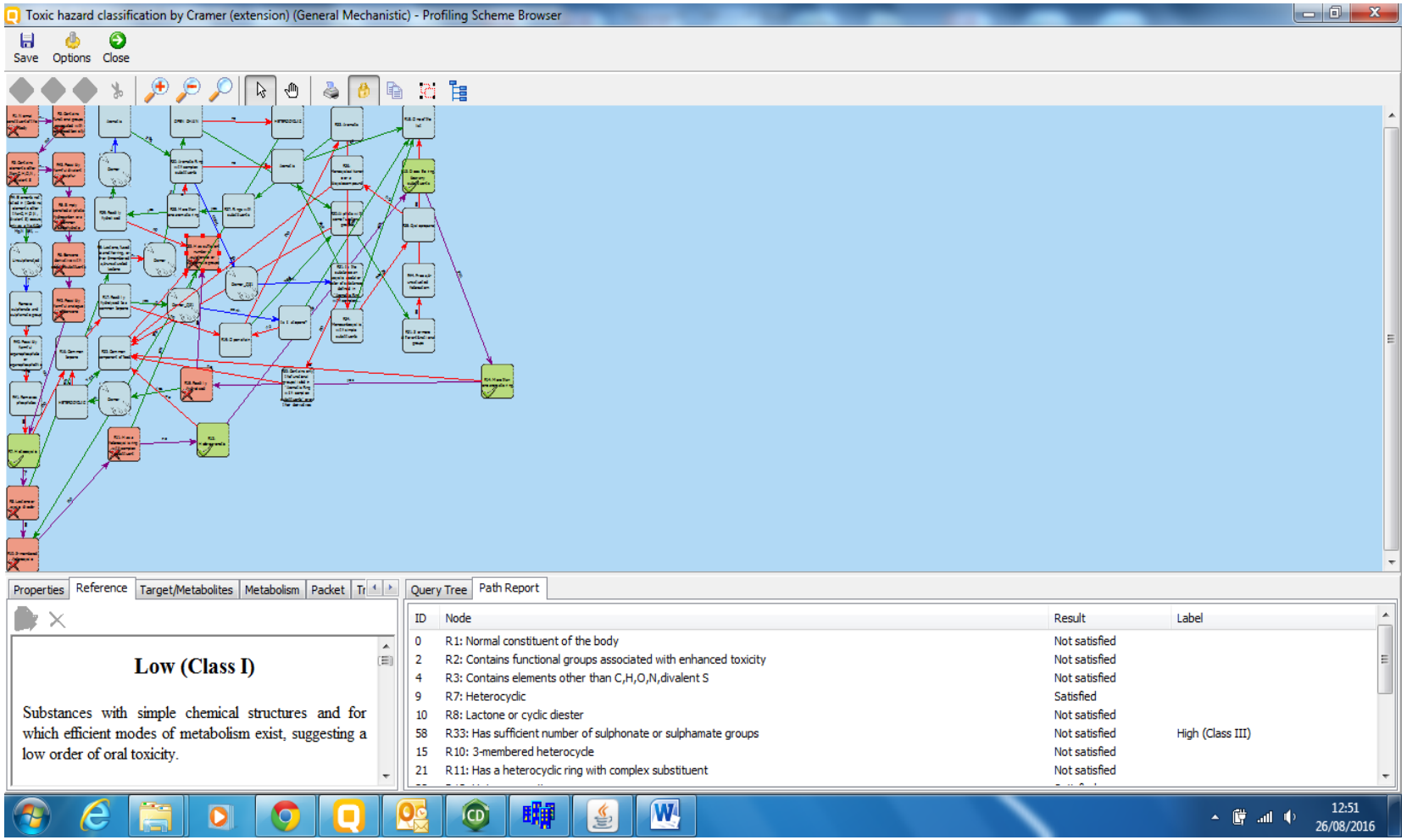
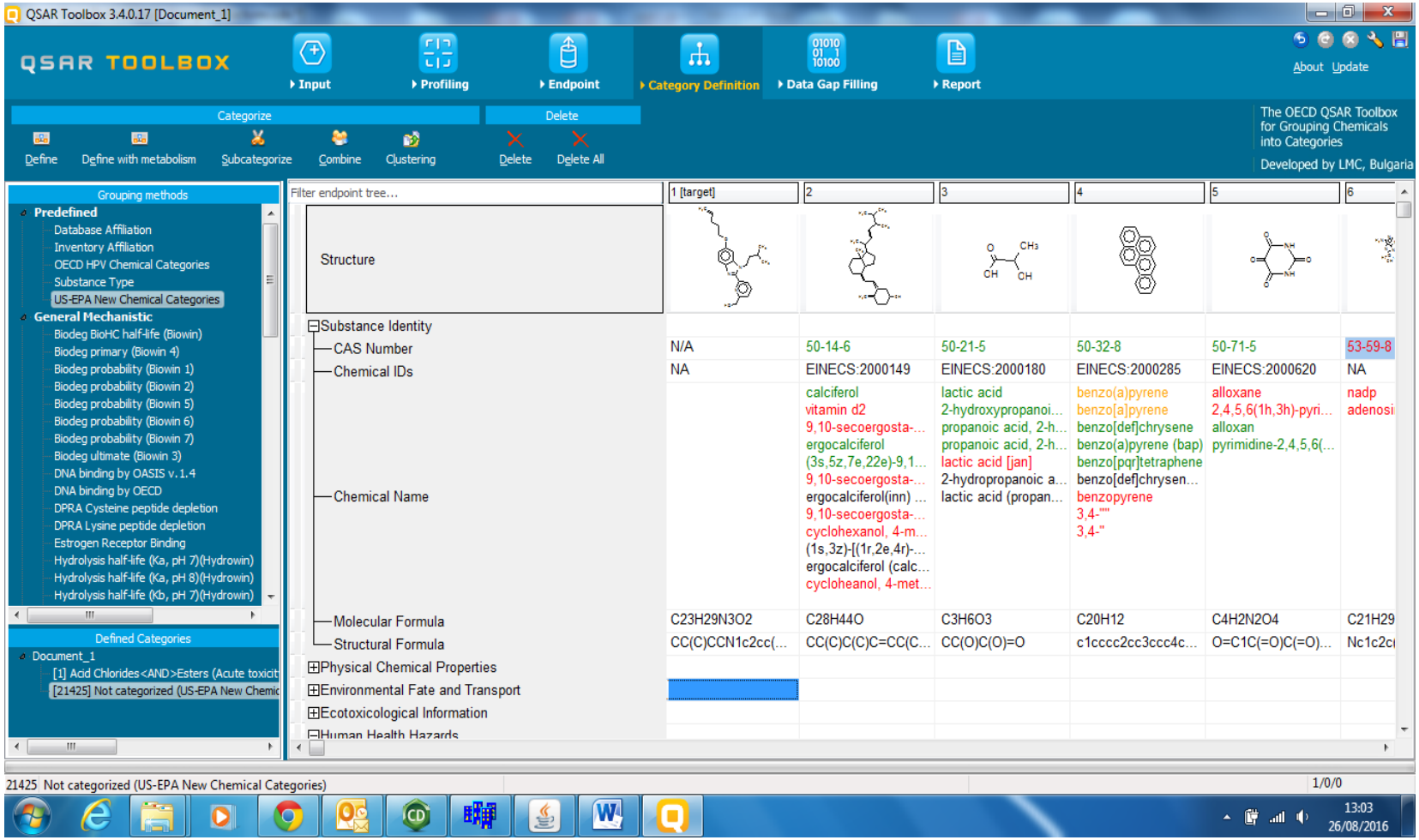
ECHA/OECD (Q)SAR's



ECHA/OECD (Q)SAR's



ECHA/OECD (Q)SAR's



(Quantitative) Structural activity relationships (Q)SAR's

2.What do we want to use them for? KEY QUESTION !!!

https://echa.europa.eu/documents/10162/13655/pg_report_qsars_en.pdf

2.5 Strategy for using (Q)SAR results

In general, it is recommended to use (Q)SAR results as part of a weight of evidence (WoE) approach or as supporting information. For instance, (Q)SAR predictions can support results from tests that have not been performed according to good laboratory practice (GLP) or according to accepted guidelines, if those predictions concur with the experimental results. A compilation of several predictions with unassignable quality cannot provide an adaptation on its own.

When using (Q)SARs, it is recommended to run all (Q)SAR models available to the registrant for the endpoint to be fulfilled, especially when models are independent from each other (e.g. the algorithms are based on different descriptors, structural alerts or training sets). Agreement among predictions generated from independent and scientifically-valid (Q)SAR models increases the confidence in relying on the predictions.

Predictions that fulfil only some conditions specified in REACH Annex XI (1.3) should be disregarded or the reason for providing these predictions should be explained if it is considered that there are some benefits to providing these predictions. If the remaining (valid and adequate) predictions show small quantitative differences, the most conservative result should be chosen for further consideration. If those remaining predictions show significant quantitative differences, the registrant must decide if these differences could affect the risk assessment (for demonstrating safe use) and/or classification and labelling.

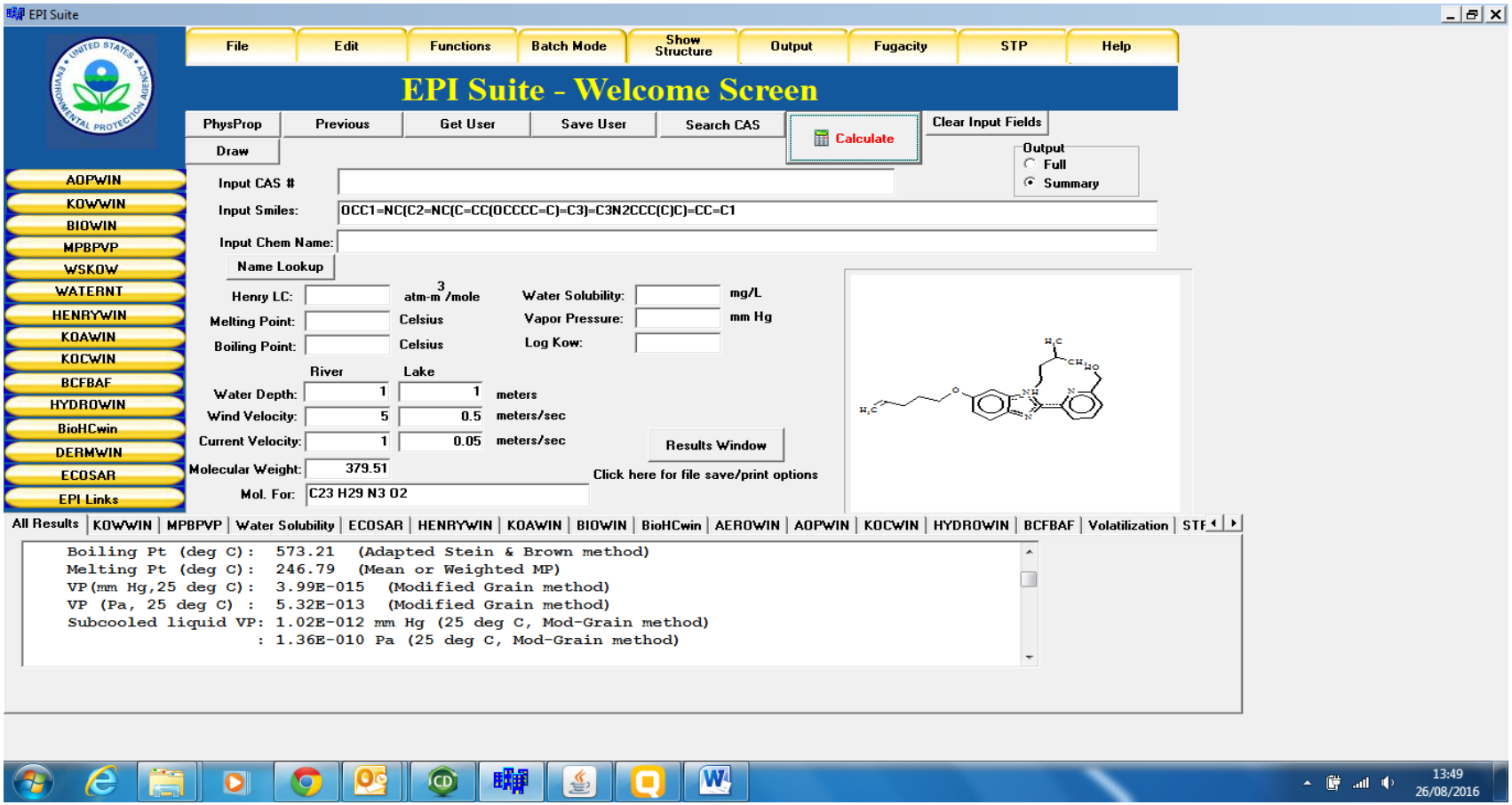
(Quantitative) Structural activity relationships (Q)SAR's

2. What do we want to use them for? KEY QUESTION !!!

How about simple physical constants for PID's?
Not available on VEGA.
Might be on ECHA toolbox (but not found so far).

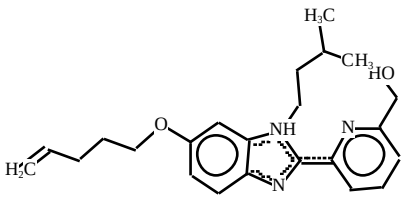
(Quantitative) Structural activity relationships (Q)SAR's

2. What do we want to use them for? KEY QUESTION !!!



(Quantitative) Structural activity relationships (Q)SAR's

2. What do we want to use them for? KEY QUESTION !!!



SMILES : OCc1nc(c2nc(ccc(OCCCC=C)c3)c3n2CCC(C)C)ccc1
Boiling Pt, Melting Pt, Vapor Pressure Estimations (MPBPVP v1.43):
Boiling Pt (deg C): 573.21 (Adapted Stein & Brown method)
Melting Pt (deg C): 246.79 (Mean or Weighted MP)
VP(mm Hg,25 deg C): 3.99E-015 (Modified Grain method)
VP (Pa, 25 deg C) : 5.32E-013 (Modified Grain method)
Subcooled liquid VP: 1.02E-012 mm Hg (25 deg C, Mod-Grain method)
: 1.36E-010 Pa (25 deg C, Mod-Grain method)
Water Solubility Estimate from Log Kow (WSKOW v1.42):
Water Solubility at 25 deg C (mg/L): 0.1373
log Kow used: 5.24 (estimated)

(Quantitative) Structural activity relationships (Q)SAR's

4. Assimilation of findings.

VEGA quite simple – but how do we generate an operating practice without resorting to best guess by whoever is interpreting the results?

ECHA toolbox is remarkably complex and would really be better to seek training once established what we want it for as it can give more output than VEGA and also allows Data gap filling and many other functions.

ECHA toolbox is developed specifically for REACH-IT classification and reporting. It can interface with the International Uniform Chemical Information Database (ICULID) in format ready for REACH-IT registration of chemicals.

EPI suite can supply a simple (but rough) guide to many physical constants which may be of use on supply of PIDS.

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