CADASTER

CAse studies on the Development and Application of in-Silico Techniques for Environmental hazard and Risk assessment

Grant agreement no.: 212668

Collaborative Project

Sub-Priority ENV2007 3.3.1.1: In-silico techniques for hazard-, safety-, and environmental risk-assessment

CADASTER – 4.3 Assessing ECETOC's TRA tool and comparison with other risk assessments and evaluation

Due date of deliverable: 31 December 2010
Actual submission date: 27 December 2010

Start date of project: 1 January 2009 Duration: 4 years

Lead Contractor: National Institute of Public Health and the Environment (RIVM), Laboratory for Ecological Risk Assessment

Corresponding authors of document: Linus Bergfors[1], Fredrik Persson[1]

1. IVL Swedish Environmental Research Institute, Box 210 60 SE- 100 31 Stockholm, Sweden (linus.bergfors@ivl.se)

Deliverable no.: 4.3 Assessing ECETOC's TRA tool and comparison with other risk assessments and evaluations
Nature: Public

Project co-funded by the EU Commission within the Seventh Framework Programme		
Dissemination Level		
PU	Public	X
RE	Restricted to a group specified by the consortium (including the Commission Services)	
CO	Confidential, only for members of the consortium (including the Commission Services)	

General

CADASTER is a project that was granted within the 7th Research Framework Programme of DG Research of the European Commission. CADASTER aims at providing the practical guidance to integrated risk assessment within REACH by carrying out a full hazard and risk assessment for chemicals belonging to four compound classes. The main goal is to exemplify the integration of information, models and strategies for carrying out safety, hazard and risk assessments for a selected number of compounds within four specific chemical domains. Real hazard estimates will be delivered according to the basic philosophy of REACH of minimizing animal testing, costs, and time. CADASTER will show how to increase the use of non-testing information for regulatory decision whilst meeting the main challenge of quantifying and reducing uncertainty.

CADASTER has officially started on the 1st of January, 2009. The project officer on behalf of DG Research of the European Commission is Dr. Georges Deschamps, the project is coordinated by Dr. Willie Peijnenburg (RIVM).

Table of Content

1. Objective

The first objective is to evaluate the ECETOC's (European Centre for Ecotoxicology and Toxicology of Chemicals) TRA (Targeted Risk Assessment) tool concerning the ability to identify chemicals of concern at varying levels of data/information. This will be a potentially powerful approach for smaller companies without the skills or expertise often available to large companies and if the tool is suitable, it will quickly help such companies identify whether they have a need for further higher tiered assessments.

Also ECETOC's TRA tool will be evaluated on the CADASTER chemical classes for a set of different scenarios and information levels. Accuracy and probability will be compared with other tools or working methods for TRA, for instance EUSES or literature review.

Finally the usability and accessibility of the tool especially from an SME point of view is to be evaluated.

2. Evaluation output

2.1. Conclusions

- To automatically identify chemicals of concern there is a lot of input data needed. Not only the physico-chemical data but also tonnage, Environmental Release Class and at least one PNEC (Predicted No Effect Concentration) -value. There would be much to be gain from cutting down the information needed for the first scope and simplify the use. For instance just by looking at K_{ow} (Partitioning coefficient of octanol-water), water solubility and vapour pressure it can be established whether a compound is likely to reach high concentrations or not.
- Due to the lack of performed risk assessments and lack of the data within the CADASTER compound groups the accuracy was hard to evaluate. A comparison with the results in Howe (2005) was performed but it is hard to draw any significant conclusions since total amounts for distribution in the different compartments are not available from that article.
- There is great room for improvement when discussing the usability of the tool. Much of the criticism in this report is due to the bad usability. In this tool there is a lot of bad programming practice and the usability seems to have been greatly neglected.
- Data availability is a key factor

2.2. Suggested improvements

- Write a proper manual.
- Consider changing programming language perhaps to open-source which does not require licenses.
- Compile REACH (Regulation of registration, evaluation, authorisation and restriction of chemicals) report automatically.
- Divide interface into several steps (sheets) concerning different endpoints (worker, consumers and environment) and present output separately.
- Hide the internal operations from the user while running!
- Add exception handling for error identification!
- Consider dividing tool depending on scope (tier 0, I, II). It could be split into two separate tools, tier 0 and higher tiered risk assessment. Perhaps the user can choose the scope when using.
- Additional documentation added to the input fields would be nice. Suggestions on where to find data, which is often difficult, would be very useful. Try to provide some hints and tips on the effect of data input.
- Remove quick fixes from the program and have another go at finding bugs.
- Supply documentation on importance and sensitivity of input parameters.
- The release area is of importance and need better consideration.

- Compile an overview sheet of hidden parameters, which are set automatically by SpERCs (Specific Environmental Release Class) etc. The user needs to know under which circumstances the results are valid.

3. ECETOC's TRA tool Introduction

3.1. Tool Background

The first TRA tool developed by ECETOC was launched as a web tool in 2004 and has since then been improved and redesigned as a downloadable MS-excel based tool (European Centre for Ecotoxicology and Toxicology of Chemicals).

Since the first of June 2007, the Regulation of registration, evaluation, authorisation and restriction of chemicals (REACH) is to be applied to imported and production chemicals. One objective with the ECETOC TRA tool is to provide a user friendly step-by-step tool for non-experts to use when register chemicals under REACH. The developed tool considers how consumers, workers and the environment are exposed to a compound. (European Centre for Ecotoxicology and Toxicology of Chemicals)

The bases of the calculations in the assessment tool are conservative assumptions. By considering these assumptions it is possible to identify when a more thorough assessment of the risks is needed. According to the ECETOC TRA home page this is what the main scope of the tool is. (European Centre for Ecotoxicology and Toxicology of Chemicals)

In this evaluation only the environmental assessment of the Revised integrated ECETOC TRA tool was considered. This version was released by ECETOC on 4th of May, 2010.

3.2. Tool input

For the environmental assessment there are five different physico-chemical properties needed as input to the tool:

1. Molecular weight (MW)
2. Vapour pressure (VP)
3. Water solubility (WS)
4. Partitioning coefficient between octanol and water (K_{ow})
5. Biodegradability test

Following the physico-chemical properties the next step is to identify the used tonnage and fraction of the tonnage, which is released to the environment. The use of the chemical also needs to be defined by an Environmental Release Class (ERC) or by a Specific ERC (SpERC). These release classes are estimates of how the release is distributed. For instance the dilution of the release is given by ERCs or SpERCs and whether release is mainly to water or air etc.

3.3. Tool output

The outputs from the environmental part of the tool are the predicted environmental concentration (PEC). These are calculated for the same compartments as presented in the input section for the Predicted No Effect Concentration values, PNECs. The PECs are then compared to the reference values (PNEC) and used to assess the risk involved with the chemical. The PEC -values differ between different compartment depending on the release and the physico-chemical properties. Six PEC -values are calculated by the tool:

1. Concentration in sewage treatment plant
2. Concentration in freshwater
3. Concentration in freshwater sediment
4. Concentration in soil
5. Concentration in marine water
6. Concentration in marine sediment

To complete the environmental risk assessment the tool needs ecotoxicological data represented by the PNEC values to compare with the PECs. To be fully populated the tool requires PNEC values to be accounted for the same compartment as the PEC values:

1. PNEC for microorganism in sewage treatment plant
2. PNEC for freshwater aquatic organisms
3. PNEC for freshwater sediment organisms
4. PNEC for marine water aquatic organisms
5. PNEC for marine water sediment organisms
6. PNEC for the terrestrial compartment organisms

It should be mentioned that many of these PNEC values may be estimated from the fresh water aquatic PNEC, given that relevant partitioning coefficients are available for the compound.

4. Model evaluation

The aim was to understand the model in the TRA tool in order to perform a complete evaluation. Originally some of the QSAR models developed in work package 3 were to be used as input to the model. However, due to the lack of data, no QSAR models for ecotoxicological effects have so far been developed within the project. This has limited the evaluation to include only predicted environmental concentration without any relation to estimated effect reference values. We collaborated with the Chemitecs project to retrieve more data and also to have a case study to compare with.

The model evaluation was performed following mainly two different strategies. A comparison with risk assessments made in the project Chemitecs was done and the results evaluated. And secondly, the case molecules involved in the CADASTER project were all assessed in the tool and the results evaluated. In the evaluation of the case molecules a Design of Experiment (DoE) for each chemical group (BDE, PFC, (B)TAZ) was also included.

4.1. Case studies

Three of the four chemical groups within CADASTER were chosen to be pin-pointed in the evaluation. The group of fragrances was not included due to lack of data. The group with most extensive data was (B)TAZ and the evaluation is therefore much reliant on this group. It is also the group with most reliable results.

4.1.1. Method

The molecule data from the CADASTER data base was used to populate the ECETOC TRA tool. All molecules with available data from the CADASTER molecule groups BDE, PFC and BTAZ) were used. The data was exported from the CADASTER data base and filtered for physico-chemical properties. To acquire molecular weight the constitutional descriptors in dragon was applied.

After data was exported it was manually sorted in excel to be sure that we had all essential data to be used for ECETOC calculations. The exported data comes in single rows for each new value so all single instances needed to be gathered in a usable format to write into the ECETOC TRA tool.

The DoE was compiled as a full factorized three point design. It consisted of 84 points each consisting of molecular weight, vapour pressure, water solubility and the octanol-water partitioning constant. Due to the lack of data the biodegradability was set to the most conservative value, since this is often the case in reality when data is missing. However this completely excludes the effect of biodegradability from this evaluation.

Table 1 The parameter extreme points for each evaluation group

	BDE		PFC		BTAZ	
	Min	Max	Min	Max	Min	Max
Molecular weight	173	722	88	461	84.1	460
Vapour pressure	5E-07	1.56	5.91E-05	2.3E+07	4.00E-14	0.012
Water solubility	389	1.9E+07	2.57	3160000	0.107	20000
Kow	9E-07	14000	0.02	1000000	0.12	1600

For each group a common specific environmental release class was chosen (Cefic, 2010). This was done through a thorough review of the molecules within the groups and their area of use. The most represented area of use was chosen to represent the entire group in the analysis.

Table 2 The SpERC chosen for evaluation

Evaluation group	Chosen area of use	Chosen SpERC
BDE	Flame retardant in various industries such as textile, furniture, electronics, etc..	TEGEWA 4 (textile)
PFC	Production of chemicals was chosen due to the wide variations of use.	ESVOC 1(Production of chemicals)
BTAZ	Use of pesticides	ESVOC 26

The tonnage was chosen as an estimate based on the use one of the BDEs in EU. This was for all molecules. It was estimated to 610 tonnes per year.

No environmental reference values were used in the evaluation due to lack of data. However that is merely a value for comparison.

4.1.2. Results

By evaluating plots of each parameter against each output a first analysis of the different groups of chemicals was conducted. In overall it showed the concentration in sediment and soil often escalated with an increased value on the partitioning coefficient for octanol-water (K_{ow}). In the same manner high water solubility was often connected to high concentrations in the water based compartments. The effect of vapour pressure is harder to discern from the univariate analysis. In some cases the results could be interpreted as a reduced vapour pressure correlates with reduced concentrations in the water based compartments, whereas it is the opposite correlation to the concentration in sediment and soil. For instance this is clearly the case when studying the BDE case molecules (Figure 1).

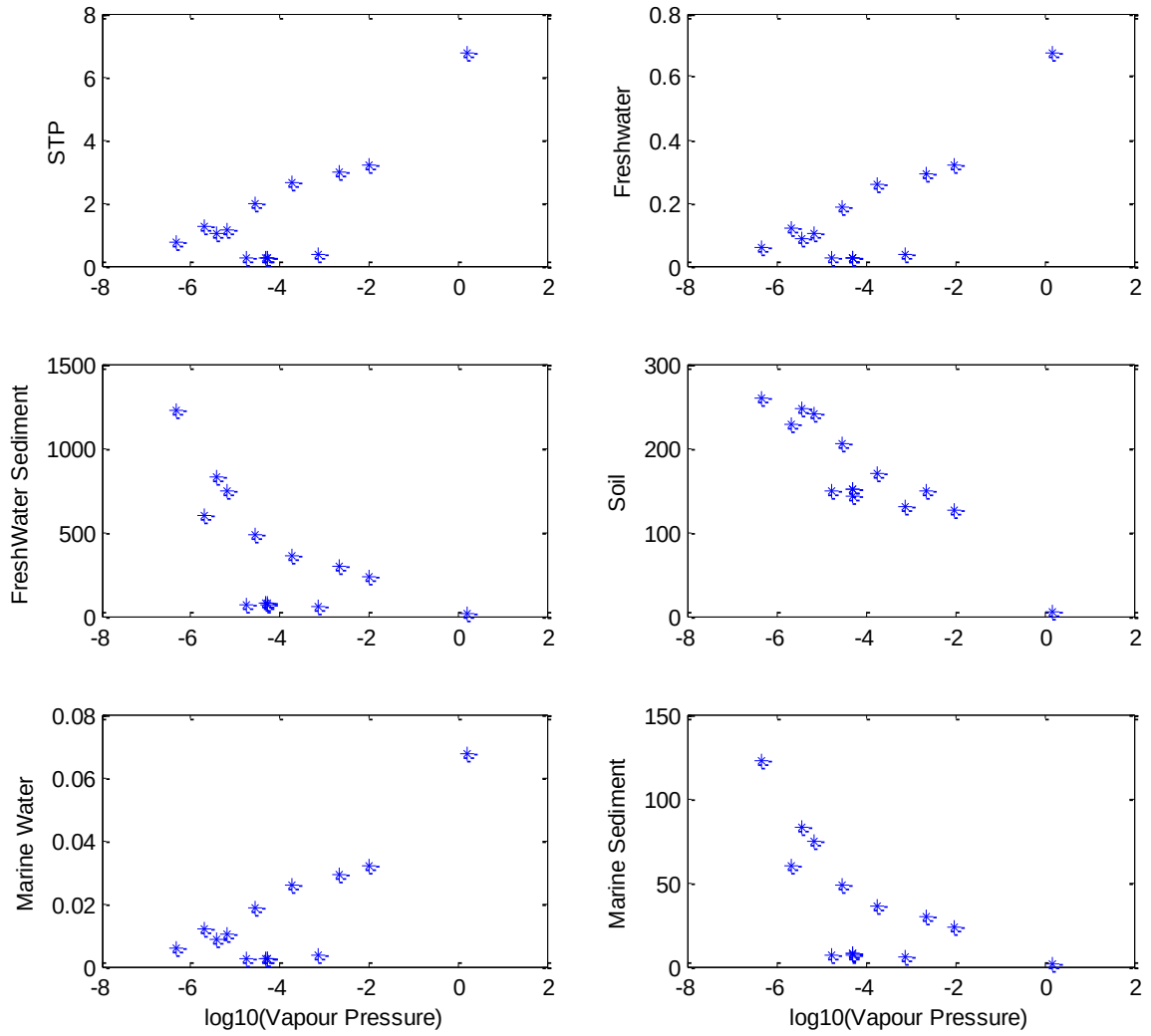

Figure 1 visualizes the correlation between vapour pressure and the concentrations in different compartments for the brominated flame retardants.

In the case of molecular weight it is hard to distinguish any real trend. In some cases a great molecular weight seems to have similar effects as K_{ow} (Figure 2). However, this may very well be a correlation between molecule weight and K_{ow} rather than real effects from the molecular weight itself (Figure 2).

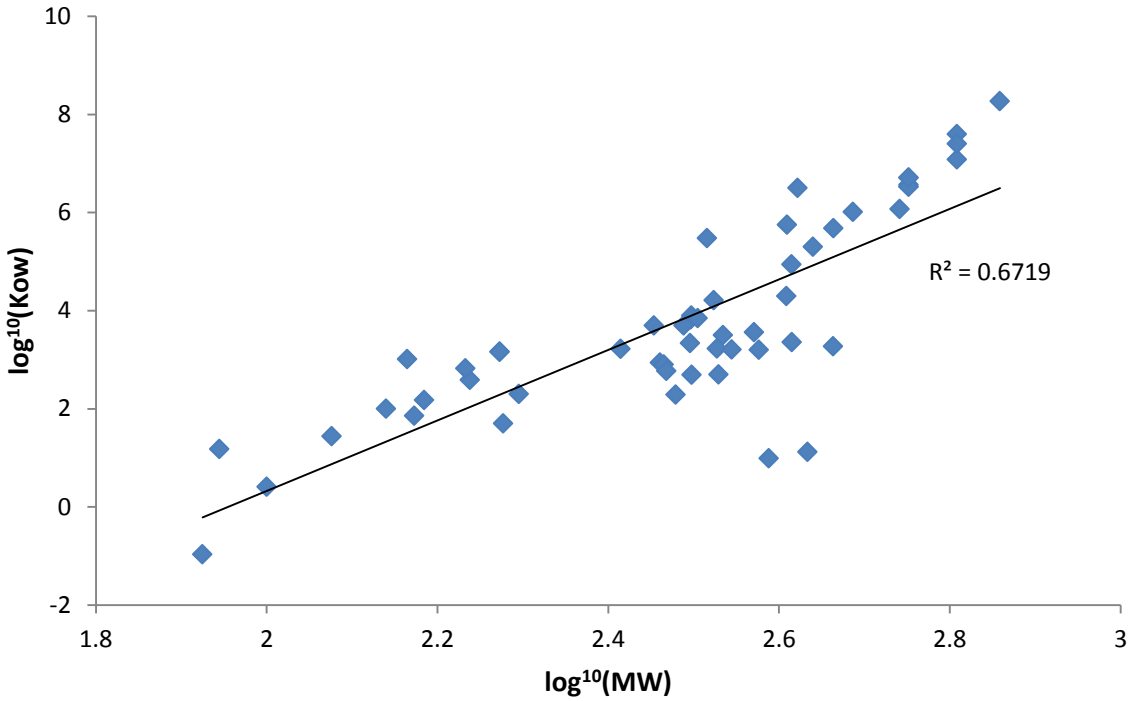

Figure 2 Molecular weight of all the case molecules within CADASTER, which have been used in the evaluation, plotted against $K_{ow.}$ Both are logarithmically transformed.

Looking at the actual output, it often seems to be a mere scaling difference between the compartments with similar matrices (Figure 3)

Studying Figure 3 more closely shows that the Freshwater sediment and Marine sediment actually seems to be separated only by a scaling factor. The concentration in soil however follows the same pattern as the two sediment compartments but seem to have a tendency to large differences when the concentration is low. Common for those molecules where the concentration in soil is deviating are low K_{ow} values and in some cases combined with high water solubility.

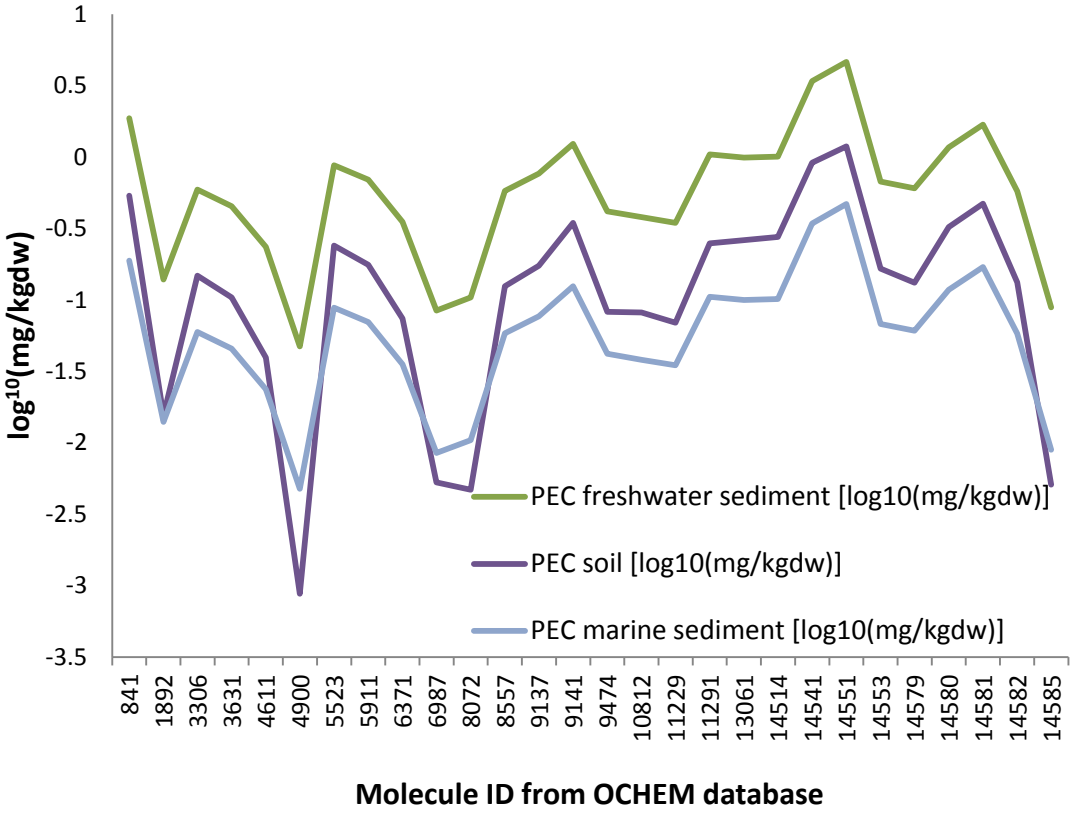

Figure 3 shows the logarithmic concentration in the organic compartments molecule by molecule within the BTAZ group.

Looking at the water based compartments shows the scaling effect even more clearly (Figure 4). The concentrations in freshwater seem to be about a fifth of the concentration in the sewage treatment plant (STP) for the studied chemical group, i.e. PEC(STP) times 0.2, and the concentration in marine water seem to be about a tenth of the concentration in freshwater, i.e. PEC(freshwater) times 0.1.

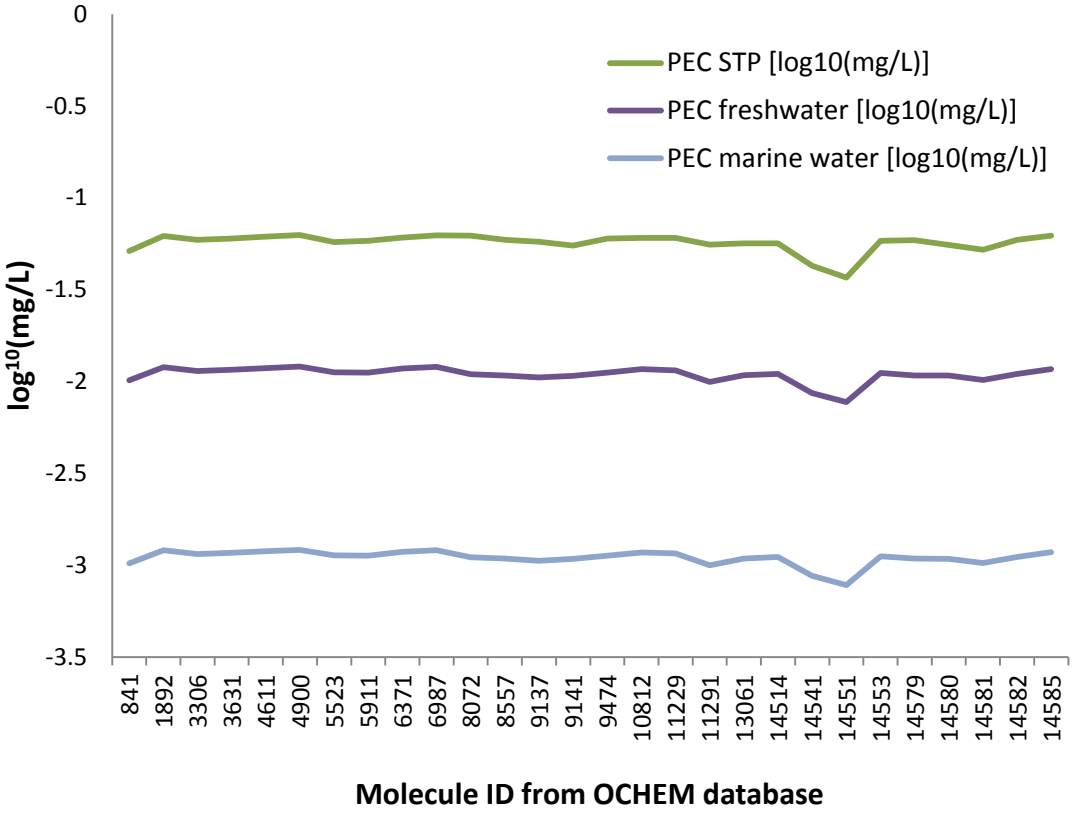

Figure 4 shows the logarithmic concentration in the water based compartments molecule by molecule within the BTAZ group.

Evaluating different Specific Environmental Release Classes (SpERCs) show similar scaling results as with the different compartments (Figure 5). If any difference at all it seems to be mostly scaling when comparing SpERCs developed from the same ERC. By calculating the coefficient or scaling separating the SpERCs Colipa 17 and Esvoc 26 for all molecules and comparing the variance and standard deviation, it could be analysed whether the difference is a mere scaling or not. Looking at the figures in Table 3 it can be concluded that except for the Soil compartment it seems to be a scaling. In the case of STP the deviation was actually in the magnitude of double precision machine epsilon (1.11* e-16), which can be considered as zero. Another interesting fact is that the relationship between the Colipa 17 freshwater and the Esvoc 26 freshwater is exactly the same as that of the freshwater sediment. The same is accurate for the marine and marine sediment relation. Yet another thing to be noted that in all cases except

for soil the variances are about one thousand times smaller or more than the average of the compartment output for this chemical group.

Table 3 the mean, variance and standard deviation of the coefficient from SpERC Colipa 17 to Esvoc 26

	STP	Freshwater	Freshwater sediment	Soil	Marine water	Marine water sediment
Mean	0.0267	0.4918	0.4918	0.2477	0.4953	0.4953
Variance	0.0000	0.0003	0.0003	0.0279	0.0004	0.0004
Standard devation	0.0000	0.0186	0.0186	0.1671	0.0188	0.0188

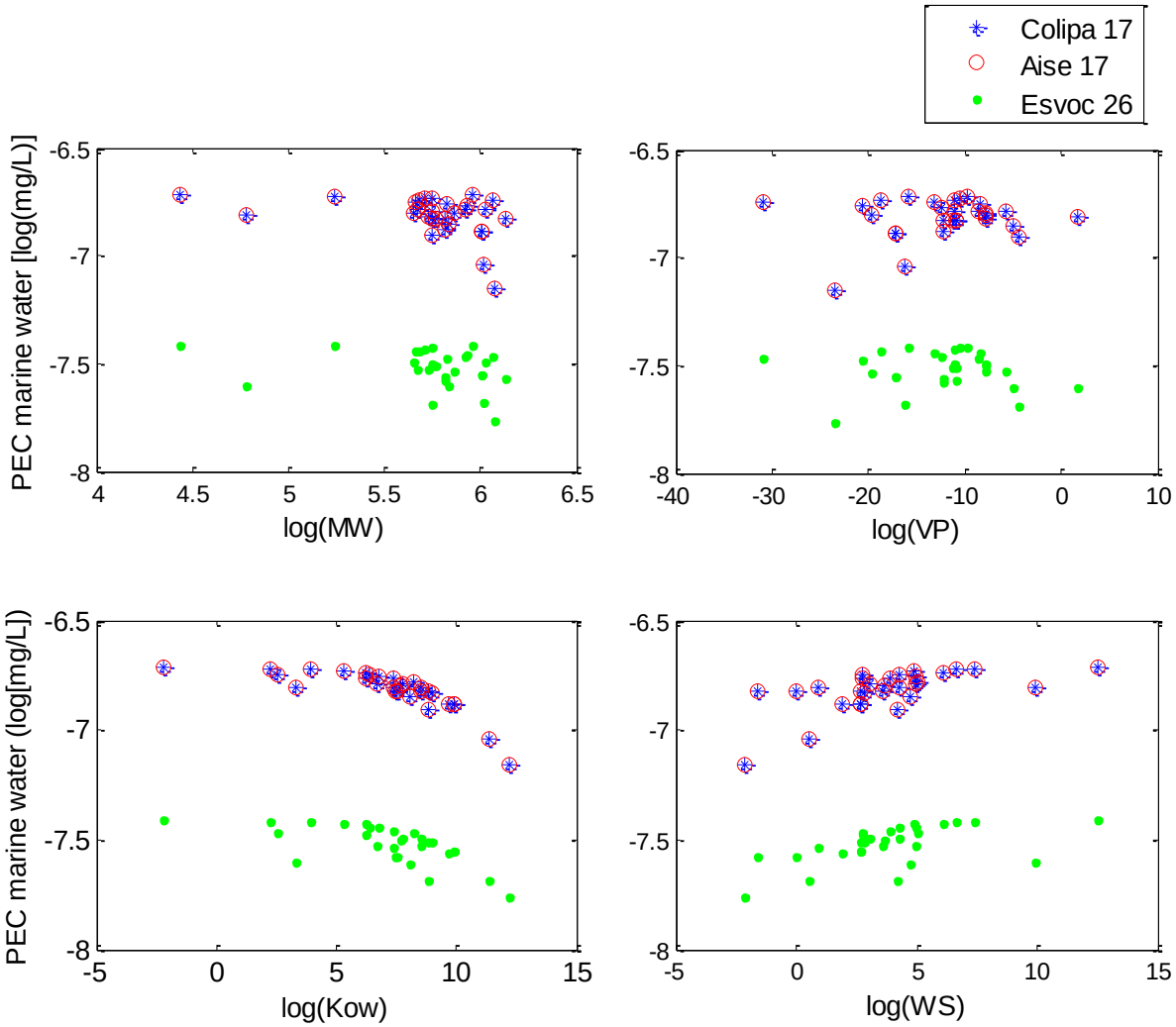

Figure 5 shows the predicted environmental concentration of marine freshwater when three different SpERCs (Colipa 17 (stars), Aise 17 (rings) and Esvoc 26 (dots)) were used and plotted agianst each input parameter.

In the multivariate analysis many of the described above can be confirmed. Large K_{ow} does indeed seem to be closely connected to high concentrations in sediment and soil. Water solubility has the same effect on the water based compartments although the effects seem to be greater when K_{ow} is small. This is visualised by the coefficients plots below, (Figure 6). K_{ow} and Water solubility are clearly the most influential of the four studied parameters in the experiment. A low vapour pressure seems to correlate with decreased concentrations in all compartments for the chosen interval. However, it seems to have a remarkably great strong negative correlation with the concentration in marine water.

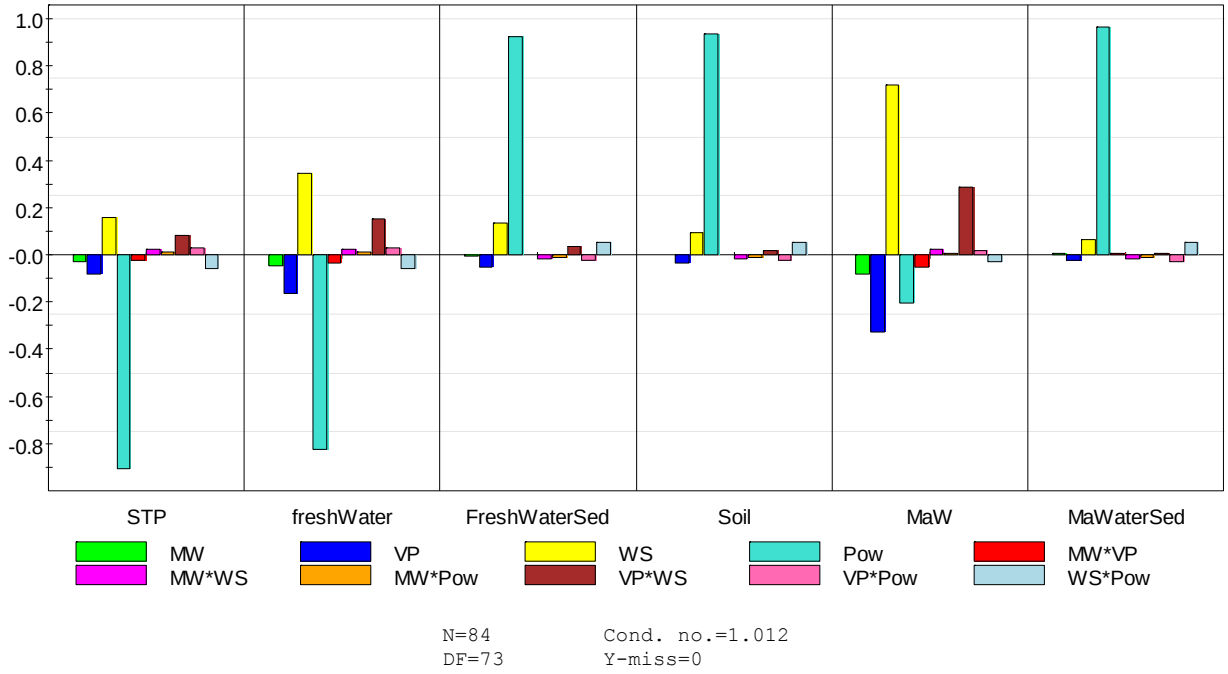

Figure 6 shows a plot of sizes the normalized coefficients for each compartment. The size of the column can be interpreted as the amount of influence. A negative coefficient indicates that the parameter has a reducing effect on the output. The parameters have been expanded with crossed parameters.

By studying the importance of the parameters for the concentration levels for all the compartments combined, the already noticed importance of K_{ow} and water solubility becomes even clearer (Figure 7). For the studied interval the partitioning coefficient octanol-water seems to be the by far the most important parameter to the model for this interval, followed by water

solubility. Vapour pressure has some influence whereas molecule weight has very little effect on the overall output. A result that is worth mentioning is that these results point towards that vapour pressure has a strictly reducing effect on the concentration if it is increased. However, the results from the univariate analysis showed that this was not the case for BDE.

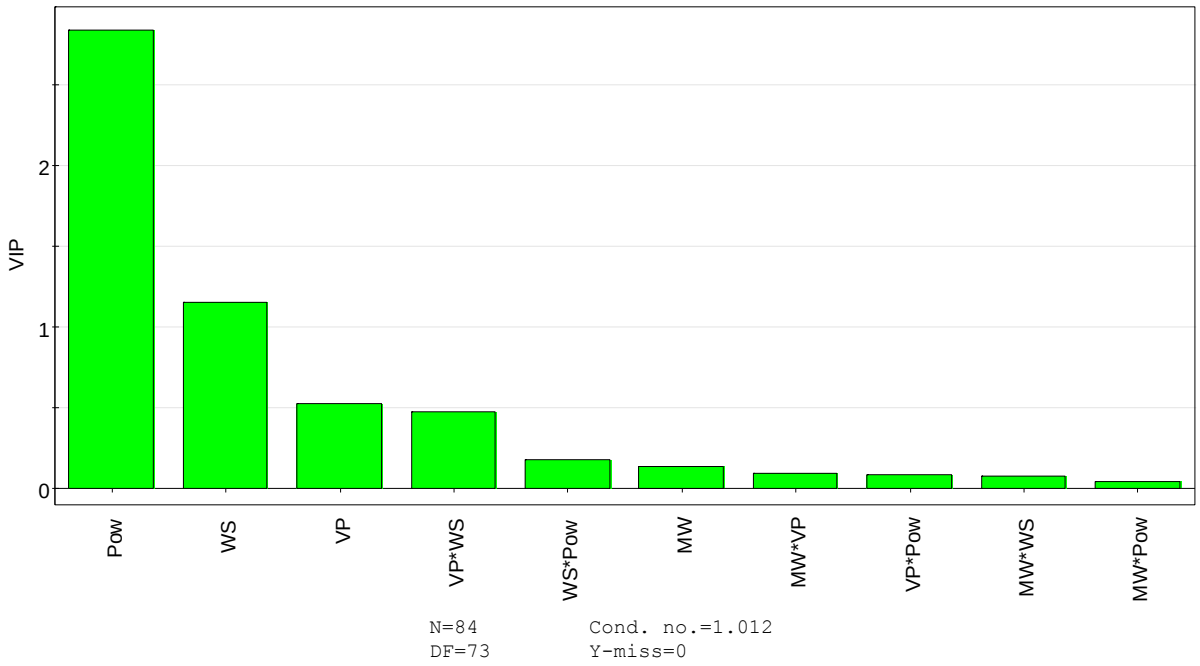

Figure 7 shows the variable importance plot. Parameters with a VIP above one is of great importance to the model.

4.2. Targeted risk assessment comparison

4.2.1. Method

Two chemicals were chosen for comparison from Chemitec 2,4-Dibromophenol and 2,4,6-Tribromophenol, (Chemitec 2010). Not all necessary physico-chemical properties was in the CADASTER database for these compounds so values were also used from the article "Water solubility and partitioning behaviour of brominated phenols" (Kuramochi, 2004). Unfortunately there are still no risk assessment results available within the Chemitec project to compare

results with instead PEC results from ECETOC was compared with distribution percentage in Howe (2005).

When there was no data for biodegradability of the compounds the recommendation is to choose the setting “Not biodegradable”. Therefore a comparison was made between the settings “Not biodegradable” and “Readily biodegradable”.

4.2.2. Results

The correlations between different compartments are comparable for the two compounds and reasonable for the chemical properties of the compounds. I.e. higher water solubility gives a higher contribution to the water phase. Looking at Table 4, less brominated phenols tend to stay in the water phase when released to water. In ECETOC calculations when using ERC8a which has a release distribution of 100 % to water and 100 % to air most of the 2,4-dibromophenol and 2,4,6-tribromophenol are ending up in the freshwater sediment, Table 5.

Table 4 Distribution of brominated phenols estimated by the Mackay Level III fugacity model (Howe, 2005)

Percent distribution				
Medium	**4-BP**	**2,4-DBP**	**2,4,6-TBP**	**PBP**
Release to water				
Air	<0.01	<0.01	<0.01	<0.01
Water	99.7	97.3	91.7	6.8
Soil	0.02	0.03	0.03	0.06
Sediment	0.3	2.7	8.3	93.2
Release to soil				
Air	<0.01	<0.01	<0.01	<0.01
Water	5.9	0.9	0.4	0.06
Soil	94.1	99	99.6	99.9
Sediment	0.02	0.03	0.04	0.09
Release to air				
Air	2.5	2.9	1.1	2.6
Water	7.8	2.9	2	0.3
Soil	89.7	94.1	96.7	93.5
Sediment	0.02	0.08	0.2	3.7

Changing the biodegradability from “Not biodegradable” to “Readily biodegradable” has the effect of a concentration decrease in all compartments with about a tenth (Table 5).

Table 5 ECETOC PEC values for 2,4-Dibromophenol and 2,4,6-Tribromophenol with impact from different biodegradability settings

Environmental Assessment	2,4-Dibromo-phenol	2,4-Dibromo-phenol	2,4,6-Tribromo-phenol	2,4,6-Tribromo-phenol
Biodegradability	Not Biodegradable	Readily Biodegradable	Not Biodegradable	Readily Biodegradable
PEC STP [mg/L]	48.78	6.30	43.80	5.88
PEC freshwater [mg/L]	5.52	0.69	4.92	0.65
PEC freshwater sediment [mg/kg_{dwt}]	292.97	36.80	741.57	97.39
PEC soil [mg/kg_{dwt}]	86.16	6.99	286.16	18.34
PEC marine water [mg/L]	0.55	0.07	0.49	0.06
PEC marine sediment [mg/kg_{dwt}]	29.33	3.67	74.24	9.72

5. Usability

The focus of the evaluation of ECETOC's TRA tool was to assess its usage potential especially for SMEs. The usability evaluation has been performed based on the experiences working with the tool. Having not used the tool before, it can be considered as the perspective of someone who does not work with risk assessment on a daily basis. The opinions of experienced risk assessors have been taken into account. Since, IVL have experience in software development that perspective has also been strongly influencing the evaluation.

5.1. Learnability

Sitting down for the first time with the tool one is overwhelmed by the amount of information which is presented. There are many fields, which could be used or not. Both input and output fields are presented in the same sheet. All different functionalities are presented still in the same sheet. As a user this inflicts confusion and resignation for the task. In an attempt at making the tool more easily understandable it has been colour coded. This is good and could probably be extended for further clarity.

The manual for using the tool is very insufficient. Following the manual the user only learns to perform the most basic calculations. There is not enough information on how the tool works, which would help the user making more accurate assumptions. The user needs to in some way be aware of the effect his/her decisions might have in order to take the correct actions to improve the situation.

Furthermore, when wishing to use the batch-mode there is almost no instructions at all in the manual even though this is more complex than the manual mode. The user needs to figure out a lot for him/herself how to use this mode where to fill in the data and where to find the outputs. Some instructions are written inside the tool, which helps. Either those should be extended or the manual should be written properly.

5.2. Efficiency

The tool efficiency is greatly dependent on the availability of data. If data is available the TRA runs rather smoothly when single chemicals are considered. However, when the tool is run in batch mode it rapidly becomes slower for each added compound. For example when the tool is run with the full 80 possible chemicals it needs several hours to complete the assessment. This could probably be much improved by choosing another programming language and adding more choices of what to calculate. For instance it seems unnecessary to go through even those fields which are left empty.

Since, the algorithm in the tool uses the copy and paste functions this creates problems if the user wishes to continue working while the tool is running. The copy/paste function is today greatly used in every day work often without even thinking about it. Using these function while the tool is running can cause errors in the calculations, cause the tool to crash, cause values from the tool to be pasted in to documents the user is working with, etc. It is a bad choice of method to use and bad programming practice and should be reconsidered in the future.

When having the tool open in the background the built-in autosave function causes interruptions in other work performed on the computer. While autosaving the tool uses a lot CPU which causes the other programs to stop.

5.3. Errors

It is hard to know when errors have been committed by the user, due to the fact that there is no exception handling. Furthermore, there is no function for checking if the values are realistic. By simply prompting the user when and where data is missing or deviating would greatly ease the evaluation of results and errors.

The colour code indicates that certain fields are compulsory and other is optional. However, even though fields, which are marked as compulsory is not filled in the calculation proceeds with no message to alert the user.

5.4. Satisfaction

A concern with all calculating/analysing software's is trust. When running the ECETOC TRA tool it rapidly switches between different rows and columns, datasheets and excel-documents in front of the eyes of the user. This causes confusion and mistrust. Calculations and operations should be hidden from the user.

The colour code of the output fields in the interface is very useful. It makes it easy to overview. However, it should be considered to present it in a separate sheet to minimize the size of the interface sheet.

As stated before, the main scope of the TRA tool is to provide an assessment to determine whether further investigation is necessary. At present state much more complex assessment can be made in the tool as well and depending on scope different amount of data needs to be entered but it is still mostly in the same sheets. A clearer scope orientation of the tool would be preferable.

6. Discussion

The user needs to understand how his choices will affect the output of the risk assessment. Therefore, gathering an understanding of how the model works is important from a non-developer point of view. If the tool is supposed to be used by an SME and perhaps personnel, which are not greatly experienced with risk assessments, the explanations of how the tool is working needs to be greatly improved. At the moment the documentation is mainly concerned with handling the tool.

The data analysis has shown that octanol-water partitioning constant and water solubility has a large effect on the output of the model. When compared to other tools this is not surprising. In the analysis, due to lack of data, the biodegradability was not included. This is unfortunate since the biodegradability is an important factor when performing risk assessments. It was harder to establish with certainty how influential the vapour pressure is on the model and how much effort needs to be spent at assessing this parameter.

The evaluation shows that the molecular weight has very little or no effect on the output. It is surprising that this parameter is a compulsory parameter anyway.

A surprising aspect of the ECETOC TRA tool is that the release area is not explicitly specified. In the tool the area is specified through the SpERCs, which seems like a very uncertain estimation.

When using different Specific release classes in the tool generally it seems as the only difference is a scaling. This has not been fully evaluated though but should be considered in the future. There could be other methods which might be more efficient for this target.

Data availability is a key factor to get accurate results. The greatest limitation when working with the tool is data. Especially when dealing with SMEs, this need to be attended to and the tool should be designed in a way, which keeps the input data at each different scope at the minimum.

7. Bibliography

Cefic. (2010, 7). CEFIC Guidance Specific Environmental Release Categories (SPERCs) Chemical Safety Assessments, Supply Chain Communication and Downstream User Compliance. Retrieved 12 14, 2010, from cefic.org: http://cefic.org/Files/Publications/SPERC%20Guidance%20100707%20FINAL.pdf

Cefic. (2010). Discalimer cefic. Retrieved 12 14, 2010, from Disclaimer cefic: http://cefic.org/files/downloads/SPERC-Overview-Table-Final-for-publication-April%202010.xls

European Centre for Ecotoxicology and Toxicology of Chemicals. (2004). TechnicalReport No. 93. Brussels: European Centre for Ecotoxicology and Toxicology of Chemicals.

European Centre for Ecotoxicology and Toxicology of Chemicals. (n.d.). ECETOC - Targeted Risk Assessment (TRA) tools. Retrieved 12 14, 2010, from http://www.ecetoc.org/tra

European Centre for Ecotoxicology and Toxicology of Chemicals. (n.d.). Targeted Risk Assessment (User Guide of the integrated tool). Retrieved 12 14, 2010, from ECETOC - Integrated tool - User guide: http://www.ecetoc.org/integrated-tool-user-guide

Howe, P. D. (2005). 2,4,6-Tribromophenol and other simple brominated phenols. Centre for Ecology & Hydrology. Geneva: World Health Organization.

Kuramochi, H. M. (2004). Water solubility and partitioning behavior of brominated phenols. Environmental Toxicology and Chemistry, 6(23), 1386-1393.