4.2. Detailed analysis of results

A detailed description of the end-point by end-point comparison of the values predicted by (Q)SAR and the values generated by experimental determination in the EC notification dossiers is given below. For ease of presentation the abbreviations "EC" or "EPA" have been used as a convenient short-hand to identify the approaches used in the European Community and the United States Environmental Protection Agency respectively.

4.2.1. Physico-chemical and environmental fate parameters

4.2.1.1. Boiling point

For predicting the boiling point, the EPA experts use estimation methods, e.g. PCGEMS (Meissner's method), data on analogues and experimentally determined data obtained from the published literature investigations. Impurities are in general neglected in the predictions. The application of the estimation techniques was not possible for all the chemicals within this study.

Even though the boiling point is required for notified chemicals at "base set" level in the EC, for many substances in this study experimentally determined boiling points were not available as it was technically not possible to conduct the tests.

The boiling point is used to characterize the material, it is not directly used for risk or safety evaluations. The boiling point may serve as an input parameter for estimating vapour pressure, if the latter is unavailable from experiment.

Only for 30 chemicals out of the 144 were measured/estimated boiling point values available for comparison. The following criteria were applied for the analysis:

- for all values assigned with < n or > n the signs are deleted and the values are directly compared;
- the values are considered to be in agreement if the difference between calculated and measured data does not exceed ± 50 degree C.

The comparison of the SAR and MPD data is given in Table 1; for detailed analysis of the boiling point data see Annex 4.

TABLE 1: Comparison of boiling point data

	N° of chemicals	%
Total	30	100
Agreement	15	50
Disagreement	15	50

If the literature data were included in the analysis, an additional 11 chemicals would be added, for which the US boiling points were all in agreement with the EC data. The agreement was below 50% for solid substances.

- **Conclusions**

The data set for analysis was very small, so only limited conclusions are possible. The boiling point is not used directly in the hazard/risk assessment nor is it used in the classification schemes. On the other hand, the boiling point is a basic piece of information about a chemical which manufacturers should normally be aware of; furthermore boiling point determination by testing is relatively inexpensive. Thus, it is concluded that it is preferable, in the EC scheme, to continue to measure the boiling point when it is technically possible to do so.

4.2.1.2. Vapour pressure

The vapour pressure of the chemicals under consideration is predicted by the EPA using methods based on the Antoine equation or the Watson equation or by applying the PCNOMO-technique. The vapour pressure contributes indirectly to the EPA's risk assessment, as it is used as an input parameter to the exposure and fate analysis.

Also within the EC risk assessment, the vapour pressure serves as a basic parameter for human health and environmental exposure evaluation. Measured vapour pressure data are required at "base set" level in the EC; however, calculation methods can be used according to Annex V for range finding purposes, for justifying the non-performance of the test or for providing an estimate or limit value in cases where the experimental method cannot be applied due to technical reasons (including where the vapour pressure is very low) .

For 113 chemicals out of the 144 test chemicals measured data on vapour pressure were available, and predictions were available for all chemicals. The predictions are given in the majority of the cases as upper/lower bounds. In order to compare the SAR values with the measured data, all values were converted to like units (torr). The following criteria for comparison analysis were applied :

- for all values assigned with < n or > n the signs are deleted and the values are directly compared;
- the lower limit is set at 10^{-6} torr. All SAR and MPD values that are less than this value are arbitrarily set to 10^{-6} torr;
- the values are considered to be in agreement if they are within ± 1 log unit.

The results of the comparison of the SAR and MPD data are given in Table 2; the detailed analysis of the vapour pressure data is to be found in Annex 5.

TABLE 2: Comparison of vapour pressure data

	N° of chemicals	%
Total	113	100
Agreement (± 1 log unit)	71	62.8
Disagreement	42	37.2
- of these, predictions which were not at all in agreement (>3 log units difference)	[23]	[20]

The data pairs which show big deviations were more rigorously investigated: in some cases the disagreement can be put down to the fact that the material used for the experimental determination contained volatile impurities, whereas the predictions are carried out for the pure substance.

- **Conclusions**

The best agreement was observed between the PCNOMO estimates and the measured values. In general the predictions tend to underestimate the vapour pressure. Assessing the deviations with respect to chemical classes is not possible with the small data set available. Imprecise predictions of very high or very low vapour pressure do not affect the overall assessment, but more precise values are needed in the decision-relevant range. Vapour pressure contributes to the exposure portion of the risk assessment in the EC and the US; however, it is not normally used for the purpose of classifying chemicals within the EC classification scheme. Under/overstimation of vapour pressure can result in an under/overestimation of the exposure associated with a chemical and thus contribute to an under/overestimation of the risks. The majority of methods for the experimental determination of vapour pressure are relatively inexpensive, and therefore notification schemes based upon testing will probably continue to require experimental determination. Schemes based upon predictive methods may need to be adjusted to foresee a more systematic approach to the experimental determination of this parameter for some of the chemicals which are identified as being of concern on the basis of a preliminary hazard/risk assessment.

4.2.1.3. Water solubility

The methods used by the EPA experts for predicting water solubility are based on log P_{ow} values (PCGEMS). However, most new chemicals do not match the application criteria of the available QSARs, e.g. applicability recommended for liquid substances or only for certain log P_{ow} ranges. Within the EPA hazard/risk assessment scheme, water solubility serves as an input parameter for the environmental fate analysis and ecotoxicity assessment. The lower prediction limit for fate and ecotoxicity assessment is ≤1 μg/l; for some other purposes it may be around 1 mg/l. In cases of concern, e.g. for chemicals with higher production volumes, measured water solubility is required.

In the EC, experimentally determined water solubility data, which are required at "base set" level, are also used in environmental exposure assessment; they may also contribute to the classification "dangerous for the environment".

Measured numerical values were not available for 13 of the 144 chemicals, as their determination was technically not possible, but in 6 cases out of the 13, qualitative test data were available which could be used for comparison. In 4 further cases the SAR data cannot be used for the comparative analysis. This means there were 133 data pairs for comparison. An additional problem affecting meaningful comparison is the lack of precision in the data (both predicted and measured): many data, in particular the majority of the predicted data, are given as ranges or upper/lower bounds, in case of measured data the values given as bounds are mostly without an indication of detection limit.

The following criteria were applied for the comparison analysis:

- for all values assigned with < n or > n the signs are deleted and the values are directly compared;
- for data given as ranges, the average is taken for comparison;
- the lower limit is set at 0.01 mg/l and the upper limit at 10,000 mg/l. All SAR and MPD values that are less than the lower limit value, or above the upper limit value are arbitrarily set to 0.01 mg/l or 10,000 mg/l, respectively;

- the values are considered to be in agreement if they are within ±1 log unit.

Results of the comparison between SAR and MPD data is given in Table 3, the detailed analysis of water solubility data in Annex 6.

TABLE 3: Comparison of water solubility data

	N° of chemicals	%
Total	133	100
Agreement (± 1 log unit)	90	67.7
Disagreement	43	32.3

A rigorous scientific analysis of the estimated and measured data for water solubility was not possible due to the imprecise nature of both data sets. Tendencies of over or underestimation of water solubility are not observed. A relatively high rate of disagreement is detected for low solubility values (<1 mg/l).

- Conclusions

Water solubility is a significant parameter in risk assessment and might have a decisive impact on the classification "dangerous for the environment". Under/overestimation of water solubility can result in a under/overestimation of exposure and thus contribute to a under/overestimation of the risks. SAR based predictions may not always be of sufficient reliability, especially in the range of low solubility, i.e. <1 mg/l, due to the complexity of factors influencing a chemical's water solubility. The experimental determination of water solubility is relatively inexpensive, therefore notification schemes based upon testing will probably continue to require experimental determination. Schemes based upon predictive methods may need to be adjusted to foresee a more systematic approach to the experimental determination of this parameter for chemicals at higher production levels or which are identified as being of concern for the aquatic environment on the basis of a preliminary hazard/risk assessment.

4.2.1.4. Partition coefficient

The partition coefficient is a key parameter to evaluate a chemical's impact on the environment.

Furthermore, its particular importance is underlined as, in the SAR methodologies, several other predictions, e.g. ecotoxicity/toxicity, are based upon it. The SAR prediction methods applied by the EPA use the MedChem ClogP Software package; the respective estimations are based on a fragment method. In cases of missing fragments, their values are estimated from expert knowledge. The upper prediction limit applied by the EPA for fate assessment is log $P_{ow} \geq 6$. For ecotoxicity assessment no upper limit is considered for some chemical classes.

In the test driven, stepwise assessment scheme of the EC, the partition coefficient is also used in the decision taking process on further testing (e.g. for bioaccumulation potential); in addition, the log P_{ow} contributes to the criteria for classification as "dangerous for the environment" within the EC classification scheme: the log P_{ow} value 3 represents the cut off value for decisions on further testing and for classification. The EC notification scheme requires experimentally determined partition coefficient data at "base set" level. Nevertheless, Annex V recommends to estimate log P_{ow} for deciding which of the experimental methods is appropriate, for selecting appropriate test conditions and for providing a calculated log P_{ow} in cases where the experimental methods cannot be applied for technical reasons. Therefore, in a number of cases, only estimated values were available in the EC dossiers. Those values were not taken into consideration for the comparative analysis of the SAR/MPD data.

Eighty two chemicals with both measured and predicted log P_{ow} values are available for the comparative study. The analysis included the application of the following criteria for comparison :

- for all values assigned with <n or >n, the values are directly compared;
- for values given as ranges, the arithmetic average is used;
- the lower limit is set at log P_{ow} = 0, all values that are below 0 are arbitrarily set to 0;
- the upper limit is set to log P_{ow} = 6; all values above 6 are arbitrarily set to 6;
- the values are considered to be in agreement if they are within ± 1 log unit.

The results of the comparison of the SAR and MPD data are given in Table 4 , the detailed analysis of log P_{ow} is attached (see Annex 7).

TABLE 4: Comparison of partition coefficient data

	N° of chemicals	%
Total	82	100
Agreement (± 1 log unit)	50	61
Disagreement	32	39
- Overestimation	25	30.5
- Underestimation	7	8.5

- Conclusions

The log P_{ow} estimates are in general reasonably accurate. However, estimations are in poor agreement for certain classes of compounds (e.g. dissociated compounds, charged compounds, surfactants, chelating compounds, organometallics, organophosphorous compounds, compounds with unknown fragment values, UVCB compounds) and are not applicable for them. Calculated log P_{ow} values above 4 tend to overestimate. Calculations in the range of 0 - 2 possibly underestimate log P; however, the data set available is too small for exhaustive analysis. The EPA calculation methods are in general successful at calculating log P values <0.

The results of this exercise indicate that the predictive methods for log P_{ow} may be of further importance in the EC in future, i.e. submission of predicted log P_{ow} values by the notifiers instead of measured data might be regarded as a possible option. However, the log P_{ow} range around the value 3, which is of particular importance for the EC classification and stepwise risk assessment scheme, will anyhow have to be taken into special consideration and may continue to require experimental determination as well as in the case of suspected underestimation.

4.2.1.5. Biodegradation

The data on this end-point were difficult to compare because different scales /definitions are used. The biodegradation estimates are given in semi-quantitative terms, indicating the appropriate time for complete degradation ("days", "days to weeks", "weeks", "weeks to months", "months" or "months or longer", whereas the OECD-based standard 28-days tests, which are available in the EC at "base set" level, result either in the decision "readily biodegradable" or "not readily biodegradable".

The EPA predictions concern biodegradability in terms of primary and ultimate biodegradability using structural analogies with previously studied chemicals. The applied estimation methods are based on expert judgement. The biodegradation predictions are used within the EPA risk assessment scheme as an important factor of the environmental fate analysis.

Biodegradation data are required in the EC for risk assessment and also for the classification "dangerous for the environment".

115 substances were available for comparison of predicted with experimental data. By relating estimates of "days" and "days - weeks" to the definition "readily biodegradable", 5 of the 9 substances experimentally determined as being readily biodegradable have been identified as such by the predicting methods (=55.5%). The other 4 readily biodegradable substances are predicted to degrade in "weeks", "weeks-months" or "months or longer". At the same time, for 4 substances which did not pass the experimental criteria for ready biodegradability, a rapid degradation was predicted ("days-weeks"). In general, as the predictive methods indicated increasing time required for complete degradation, the better they correlated with test results indicative of a lack of ready biodegradability. The overall results of the comparative study are summarised in Table 5, the detailed analyses of the data is to be found in Annex 8.

TABLE 5: Comparison of biodegradation results

Test result	Prediction	
	correct	incorrect
Total	107 (93%)	8 (7%)
Readily biodegradable	5	4
Not readily biodegradable	102	4

- Conclusions

The EPA methods are likely to identify those substances which are not "readily biodegradable", i.e. slowly degrading chemicals. However, they do not appear to work as well in identifying chemicals which readily degrade. The use of biodegradation predictions as a tool for establishing suitable testing strategies within a stepwise assessment scheme is considered a possible option for the future in the EC. On the basis of the EPA results it appears that if the predicted biodegradability is "weeks" or longer, testing for "readily biodegradability" would not be indicated. Instead a test for inherent degradability or another suitable test that provides further information on the biodegradation process should be carried out. If the predicted biodegradability is "days" or "days-weeks" corresponding to "readily biodegradability", then a "ready biodegradability test" would be needed for confirmation.

4.2.1.6. Hydrolysis

The EPA dossiers include data hydrolysis only if it is likely to occur. The applied estimation methods evaluate the rate of hydrolysis if relevant (hydrolysable) functional groups are present in the molecule. For few compound classes the HYDRO-programme is applied. Hydrolysis tests are not mandatory in the EC at "base set" level; for 41 of the chemicals included in this study hydrolysis data were given. Only for 6 chemicals were both measured and predicted hydrolysis data available. A comparative analysis of this end-point was therefore not carried out.

4.2.1.7. Soil Sorption

The environmental fate analysis carried out by the EPA includes in general the prediction of log K_{oc}. For the majority of the chemicals within this study log K_{oc} predictions were available. The applied estimation methods are mostly based on log P_{ow}, but they are of limited applicability. The fragment method can be applied more widely, but it also does not satisfy all requirements.

Under the sixth amendment no tests on soil sorption are required in the EC; for notifications according to the seventh amendment a screening test on adsorption/desorption will be mandatory. For this study no test results were available for comparison.

4.2.1.8. Photodegradation

The environmental fate analysis of the EPA experts includes estimates of the photolysis of the substance (direct and indirect) in water. Measured photolysis data are not required at "base set" level and are therefore in general not available. A comparative study is not possible on the data available.