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PRIORITY SETTING FOR EXISTING CHEMICALS: AUTOMATED DATA SELECTION ROUTINE

ANNIEK G. VAN HAELST* and BJORN G. HANSEN
European Commission, European Chemicals Bureau, Joint Research Centre, Institute for Health and Consumer Protection, Ispra, Italy

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Abstract—One of the four steps within Council Regulation 793/93/EEC on the evaluation and control of existing chemicals is the priority setting step. The priority setting step is concerned with selecting high-priority substances from a large number of substances, initially starting with 2,474 high-production-volume chemicals. In order to be able to efficiently carry out the priority setting step, an automated priority setting method was developed, the so-called European Union risk ranking method (EURAM). The EURAM produces rankings among the high-production-volume chemicals appearing in the International Uniform ChemicaL Information Database (IUCLID). As part of a publication series, this paper deals with the data selection criteria used in EURAM and furthermore with data validation of the selected data. To validate the selected data in EURAM, comparisons are made with validated data of priority chemicals for which European Union risk assessment reports have been completed or with data of priority chemicals from the Screening Information Data Set initial assessment reports of the Organization for Economic Cooperation and Development. Regression analysis between the selected data in EURAM and the data selected by expert judgment in the assessment procedure resulted in good correlation for physicochemical properties and aquatic toxicity data. In addition, the type of biodegradation (i.e., readily biodegradable, inherently biodegradable, or nonbiodegradable) selected by EURAM also was in agreement with the type of biodegradation selected by expert judgment in the risk assessment procedure. Hence, the good correlation between the automated data selection procedure of EURAM and the data selection by expert judgment indicates that the data selection criteria of EURAM, which are developed in order to select data for priority purposes among high-production-volume chemicals in IUCLID, seem to perform well.

Keywords—Chemical ranking Priority setting Risk assessment Data selection

INTRODUCTION

In order to systematically evaluate the risks of the 100,195 so-called existing chemicals, that is, those substances that were deemed to be on the European market before September 18, 1981, and, therefore, that were listed in the European Inventory of Existing Commercial Substances, the European Union (EU) adopted on March 23, 1993, Council Regulation 793/93/EEC [1] (hereafter referred to as the regulation). The regulation establishes a binding framework for the data gathering, priority setting, risk assessment, and proposals for the risk management of chemicals in the European Inventory of Existing Commercial Substances that are produced or imported in quantities in excess of 10 tonnes per year. The regulation is initially concerned with the so-called high-production-volume chemicals, which are listed in the European Inventory of Existing Commercial Substances and which have been imported or have been produced in quantities exceeding 1,000 metric tonnes per year, at least once between March 23, 1990, and March 23, 1994. Producers and importers were obliged to submit a harmonized electronic data set (HEDSET) on the high-production-volume chemicals. All HEDSETs are stored in the International Uniform ChemicaL Information Database (IUCLID) [2], which is the basic tool for the priority setting step, in order to set priorities for in-depth risk assessment, but is also valuable during the risk assessment step under the regulation.

In order to set the priorities as efficiently as possible the EU developed the European Union risk ranking method (EURAM), which represents the EU method for ranking of the high-production-volume chemicals. The EURAM calculates values representing the concern for the environment through a score for environment effects and environmental exposure, and concern for humans through a score for human health effects and a score for human exposure. The EURAM has been described in detail in a previous paper [3]. The risk assessment phase, which focuses on an absolute evaluation of the life cycle of a chemical, is based at a minimum on the base set (Annex VIIA of Directive 67/548 [4]), but also on all available data, which in some cases goes far beyond the base set. Requests for testing and more exposure information are integrated parts of the risk assessment. Contrary to this, the priority setting step is focused only on the relative concern for chemicals, with no direct tools for collecting more data. As a consequence, the priority setting step must be based on a data set even smaller than the base set, in order to make comparisons possible between chemicals. Because validating all the data stored in IUCLID of the 2,474 high-production-volume chemicals would be an impossible task, pragmatic decisions are made before the priority setting stage begins on how to select representative data from IUCLID, to be used as input to the EURAM.

The purpose of this paper is to bring into focus the data selection procedure for selecting the most appropriate data from IUCLID, to be used as input for the EURAM during the automated part of the priority setting step. For this reason, in addition to the description of the data selection procedure of EURAM, an attempt is made in this paper to validate the selected data. Therefore, the data extracted from IUCLID ac-

* To whom correspondence may be addressed (vanhaelst@voeding.tno.nl). The current address of A.G. van Haelst is TNO Nutrition and Food Research, Department of Toxicological Risk Assessment, P.O. Box 360, 3700 AJ Zeist, The Netherlands.

cording to the selection criteria of EURAM are compared with selected data in a limited number of risk assessments of priority substances already performed within the EU and within the Organization for Economic Cooperation and Development (OECD), Paris, France. The comparison is performed for the environmental endpoints (both exposure and effects). The comparison did not focus on human health endpoints, because human health exposure endpoints are similar to environmental endpoints and, because the data used for the human health effects scoring in the EURAM are to a large extent the so-called R-phrases (following Annex I to Directive 67/548 [4] or the provisional classification and labeling following Annex VI thereof). A general assumption is that the producer or importer has submitted the R-phrases in the HEDSET, which is a legal responsibility for companies. Hence, due consideration of the classification and labeling guide and, therefore, a considerable amount of expert judgment should be associated with the filling in of these phrases.

SELECTION CRITERIA

The selection criteria in EURAM are captured by two main factors: first, the selection of data as laid down in the technical guidance documents (TGDs) [5], and second, the handling of nonhomogeneity of the quality and quantity of the submitted data between substances.

Technical Guidance Documents

In the TGDs, guidance is given to data selection for risk assessment of existing chemicals. First, data that are invalid because of invalid test conditions or poorly reported test results should be rejected. Second, studies carried out according to currently accepted methods (e.g., EU, OECD, or other methods of standardized bodies and or those performed to good laboratory practice [6]) should have greater weight than those not carried out according to acceptable methods. Finally, preference should be given to consolidated data sets, that is, to HEDSET data generated by two or more cooperating companies.

Applying these data selection rules, guided by the TGD, the EURAM sorts the data according to the following criteria; first, the test method used to generate the data; second, whether the test result was generated using good laboratory practice; and finally, whether the data originate from a consolidated data set. The data for a specific substance and endpoint are divided into three sets: the set of not acceptable test results, the set of acceptable test results, and the set of preferred test results. The not acceptable test results are not further taken into account in the data selection procedure of EURAM. In general, test results generated using EU or OECD guidelines or certain other methods of standardized bodies will fall in the preferred test result category. Because no glossary code exists in HEDSET and hence in IUCLID, for some methods of standardized bodies, results from these methods will not be included in preferred test results. However, using these data will be possible through the expert judgment step of the ranking procedure. Estimated data for logK_{ow} and vapor pressure can be entered directly into the HEDSET/IUCLID; quantitative structure–activity relationship (QSAR) estimates can be used if no measured value is present in IUCLID. The use of QSAR estimates is flagged in the ranking results.

The preferred test results and not acceptable test results are divided into two categories, one with the data originating from a consolidated data set and one with the nonconsolidated data.

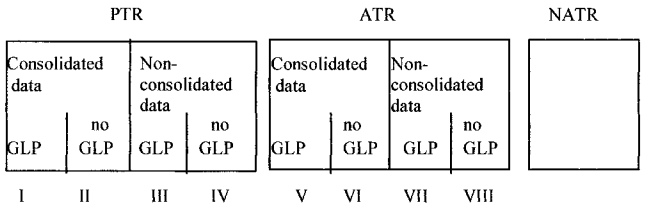

Fig. 1. Schematic overview of the division into eight preference classes (I–VIII) after applying the technical guidance document criteria within the data sets preferred test results (PTR) and acceptable test results (ATR). The not acceptable test results (NATR) are not divided in a preference class. GLP = good laboratory practice.

Within each of these two categories, the data are divided into two subcategories, depending on the application of good laboratory practice. The division of preferred test results and not acceptable test results according to the fulfillment of the requirements of the two categories results in eight preference classes. Figure 1 illustrates in schematic form the division into the eight preference classes (class I–VIII). Hence, for each endpoint the highest preference class is selected by the automated data selection procedure.

Nonhomogeneous data

The second factor taken into account by the data selection criteria is the handling of nonhomogeneous data. Because the resources vary considerably from data submitter to data submitter, both the quality and the quantity of the data in IUCLID vary considerably from substance to substance. To handle these nonhomogeneous data the most conservative value among the data in the highest preference class is selected. The most conservative value means the value that results in a worst-case calculation of the environmental exposure and effect scores within EURAM, as is described in detail in a previous paper [3]. For the calculation of the environmental exposure score (which includes the use of a Mackay level I model) the most conservative value of the endpoints boiling point, vapor pressure, and K_{ow} are the lowest values, whereas for the aqueous solubility the most conservative value is the highest value. Only data generated under environmental conditions are used. For boiling point this means measurements at a pressure between 950 and 1,050 hPa; for vapor pressure, aqueous solubility, and K_{ow} this involves measurements performed at temperatures between 15 and 25°C. Any tests indicating that they are not to be measured under environmental conditions will be included in the not acceptable test results.

The most conservative biodegradation test result is the glossary value (readily biodegradable, inherently biodegradable, or nonbiodegradable), which gives rise to the lowest fraction degraded, using the table for fraction degraded in Hansen et al. [3]. However, if only readily biodegradable and inherently biodegradable test results are in the highest preference class, then the substance is seen as being readily biodegradable. If no glossary entry exists in IUCLID for biotic degradation in soil, water, sediment, and sewage treatment plant, then the entries must be extrapolated from available standardized laboratory tests in IUCLID, namely biochemical oxygen demand (BOD) and chemical oxygen demand (COD) using BOD/COD. The test results in IUCLID will be converted into readily biodegradable, inherently biodegradable, and nonbiodegradable according Annex VI of Directive 67/548 [4], that is, if the BOD/COD is greater than 50%, a substance is classified as readily biodegradable; if the BOD/COD is in between 20 and

Table 1. Upper and lower limits of duration and percentage adverse effect at two screening levels (I, II) in aquatic toxicity tests in order to convert the test into standard toxicity endpoints within European Union risk ranking method

	Duration				% Adverse effect			
	I		II		I		II	
Standard endpoint[a]	Lower limit	Upper limit	Lower limit	Upper limit	Lower limit	Upper limit	Lower limit	Upper limit
96-h LC50 fish	48 h	96 h	48 h	∞	10	50	10	50
48-h LC50 *Daphnia*	24 h	48 h	24 h	∞	10	50	10	50
72-h EC50 algae	48 h	72 h	48 h	∞	10	50	10	50
28-d NOEC fish	14 d	∞	14 d	∞	—	—	0	10
14-d NOEC *Daphnia*	14 d	∞	14 d	∞	—	—	0	10
72-h NOEC algae	72 h	∞	24 d	∞	—	—	0	10

[a] LC50 = median lethal concentration; EC50 = median effective concentration; NOEC = no-observed-effect concentration.

50%, a substance is classified as inherently biodegradable; and finally, if the BOD/COD is smaller than 20%, a substance is classified as nonbiodegradable.

For the calculation of the environmental effect score, in addition to the aquatic toxicity data, the endpoints bioconcentration factors (BCFs) and K_{ow} also are involved [3]. If no measured BCF is present, then the highest log K_{ow}, hence the most conservative, will be used following the test result selection rules described above, as an indication for the substance to bioaccumulate. Within EURAM the use of a measured log K_{ow} is not considered to be a QSAR, because the use of the implicit QSAR ($\log(BCF) = -1.0 + \log K_{ow}$) is consistent with the approach in the TGD and with the Classification and Labeling Guide of Annex VI of Directive 67/548 [4]. The most conservative aquatic toxicity results for the calculation of the environmental effect score [3] are the lowest values. The EURAM considers six standard aquatic toxicity endpoints, namely 96-h LC50 fish, 48-h LC50 *Daphnia*, 72-h EC50 algae, 28-d no-observed-effect concentration (NOEC) fish, 14-d NOEC *Daphnia*, and 72-h NOEC algae. These aquatic toxicity endpoints are selected as standard endpoints, according to the TGD [5], in order to obtain comparable test data. The standard organisms are representatives of the three tropic levels, primary producer (algae), primary consumer (*Daphnia*), and secondary consumer (fish). If for any of the six aquatic toxicity endpoints all the acute and chronic aquatic toxicity data in IUCLID are less than x and x is less than 10 mg/L for the acute data or less then 1 mg/L for the chronic data, then the lower value cannot be established and a default value is given for that endpoint. If x is greater than 10 mg/L, then the data point is rejected. Furthermore, many tests results on existing chemicals were not performed with a standard test duration or an adverse effect, but can still be considered as a compatible test. Where possible these results will be converted into the six standard endpoints following specified criteria. In Table 1 these criteria, namely the values of lower and upper limits for the duration and for the adverse effect, are listed. The selection criteria for duration and adverse effect are given for two screening levels. The second screening level is an expansion of the first level, based on the idea that extending the time of the experiment, and, hence, of the adverse effect rate, will give a more conservative value than the first screening. Therefore, using the conversion criteria at both screening levels is a better alternative than using default values, which are in general considered as being too conservative.

The IUCLID provides data for boiling point, vapor pressure, log K_{ow}, aqueous solubility, BCF, aquatic effects, and the numeric data for biodegradation in several forms. Each form consists of an operator (=, ca., $<$ or $\leq$, $>$ or $\geq$) and the possibility to fill in two values, generally the upper and the lower values. If the operators are used for a given endpoint, then the reported value, or in the case that both fields have been filled in, both the reported values are used to determine the upper and lower values for the substance and endpoint. If the operators $<$ or $\leq$ have been used, then the reported value, or in the case that both fields have been filled in, both the reported values will be used to calculate the upper bound for the substance and the endpoint. Similarly the values corresponding to an operator of the type $>$ or $\geq$ will only be used to calculate the lower bound for the substance and the endpoint.

VALIDATION OF DATA SELECTION CRITERIA

To compare the automated data selection of EURAM and the data selected by expert judgment within the EU and OECD risk assessments, linear regression has been performed between these data sets for boiling point, vapor pressure, log K_{ow}, aqueous solubility, bioaccumulation, and the acute and chronic toxicity to fish, *Daphnia*, and algae. In addition, a regression is performed of the aquatic toxicity value selected for the derivation of the predicted no-effect concentration in the EU and OECD risk assessment [5] on the respective aquatic toxicity value selected by the automated data selection procedure in EURAM.

Table 2 lists 39 EU priority substances for which the risk assessment reports are currently available (European Chemicals Bureau, European Commission, Brussels, Belgium) and 32 OECD priority substances for which Screening Information Data Set (SIDS) initial assessment reports, discussed at the Fourth SIDS Initial Assessment Meeting (Tokyo, Japan, May 20–22, 1996), Fifth SIDS Initial Assessment Meeting (Arona, Italy, October 28–30, 1996), Sixth SIDS Initial Assessment Meeting (Paris, France, June 9–11, 1997), and Seventh SIDS Initial Assessment Meeting (Sydney, Australia, March 25–27, 1998), are available (United Nation Environment Program, Geneva, Switzerland).

The results of the regression analysis between data selected by EURAM and data selected by expert judgment in the EU and OECD risk assessment reports are shown in Table 3 and Figures 2 and 3. In Table 3 the square correlation coefficient r^2, standard error of regression (ser), the number of chemicals (n), the intercept, and the slope are listed. All the slopes were not significantly different from one at $\alpha = 0.05$. Similarly, the intercepts were not significantly different from zero at $\alpha = 0.05$. At this significance level, the distributions of the residuals of the regression line were normal, using either the Kolmogorov D test or Lillifors. It thereby follows that the standard

Table 2. European Union (EU) [7,8] and Organization for Economic Cooperation and Development (OECD) priority substances for which risk assessment reports are available

EU priority substances		OECD priority substances	
CAS[a] no.	Chemical name	CAS no.	Chemical name
75-56-9	1,2-Propylene oxide	4979-32-2	*n*-*n*-Dicyclohexyl-2-benzothiazolesulfenamide
79-01-6	Trichloroethylene	611-06-3	2,4-Dichloro-1-nitro-benzene
79-06-1	Acrylamide	81-11-8	2,2′-(1,2-Ethenediyl)bis(5-amino-benzenesulfonic acid)
79-10-7	Acrylic acid	82-45-1	1-Aminoanthraquinone
79-41-4	Methacrylic acid	836-30-6	4-Nitrodiphenylamine
80-62-6	Methyl methacrylate	89-61-2	2,5-Dichloronitrobenzene
87-74-2	Dibutyl phthalate	105-76-0	Maleic acid, dibutylester
90-04-0	*o*-Anisidine	105-99-7	Dibutyl adipate
91-20-3	Naphthalene	106-42-3	*p*-Xylene
98-82-8	Cumene	108-44-1	*m*-Toluidine
100-42-5	Styrene	111-76-2	*n*-Butoxyethanol
101-77-9	4,4′-Methylenedianiline	115-18-4	2-Methyl-3-buten-2-ol
106-46-7	*p*-Dichlorobenzene	121-14-2	2,4-Dinitrotoluene
106-99-0	1,3-Butadiene	128-39-2	2,6-Di-*tert*-butylphenol
107-02-8	Acrolein	156-43-4	*p*-Phenetidine
107-13-1	Acrylonitrile	1758-73-2	Aminoiminomethanesulfonic acid
107-64-2	Dimethyldistearylammoniumchloride	76-03-9	Trichloroacetic acid
110-65-6	2-Butyne-14-diol	78-40-0	Triethyl phosphate
110-82-7	Cyclohexane	111-69-3	1,4-Dicyanobutane
111-77-3	2-(2-Methoxyethoxy)ethanol	120-78-5	Mercaptobenzothiazole disulfide
112-34-5	2-(2-*n*-Butoxyethoxy)ethanol	26444-49-5	Diphenyl cresyl phosphate
127-18-4	Tetrachloroethylene	5392-40-5	Citral
141-97-9	Ethyl acetoacetate	101-72-4	*N*-(1-Methylethyl)-*N*′-phenyl-1,4-phenylenediamine
1163-19-5	Brominated diephenylether	108-24-7	Acetic acid, anhydride
1570-64-5	4-Chloro-2-methylphenol	109-69-3	1-Chlorobutane
7664-39-3	Hydrogen fluoride	11-42-2	Diethanolamine
67774-74-7	Benzene, C_{10-13} alkyl derivatives	67-64-1	Acetone
25154-52-3	Nonylphenol, isomers	77-73-6	Dicyclopentadiene
84852-15-3	*p*-Nonylphenol	85-68-7	Benzyl-*n*-butylphthalate
32536-52-0	Octabromodiphenylether	98-54-4	*p*-*tert*-Butylphenol
85535-84-8	Chloroalkanes (C_{10-13})	98-83-9	α-Methylstyrene
123-91-1	1,4-Dioxane	102-01-2	Acetoacetanilide
79-20-9	Methyl acetate		
77-78-1	Dimethyl sulfate		
75-05-8	Acetonitrile		
1314-13-2	Zinc oxide		
32534-81-9	Diphenylether, pentabromo derivative		
120-82-1	1,2,4-Trichlorobenzene		
88-12-8	*n*-Vinylpyrrolidone		

[a] CAS = Chemical Abstracts Service.

Table 3. Results of regression of data selected by expert judgement within the European Union and Organization for European Cooperation and Development risk assessment and data selected by the automated data selection procedure of European Union risk ranking method[a]

Endpoint	r^2	ser	*n*	Intercept	Slope
Log boiling point	0.978	0.039	54	0.044	0.980
Log vapor pressure	0.940	0.652	40	0.009	0.981
Log K_{ow}	0.970	0.354	50	0.051	1.052
Log solubility	0.879	0.695	41	0.148	0.908
Log BCF	0.711	0.712	31	0.231	0.769
Log LC50 fish	0.785	0.546	57	0.035	0.915
Log LC50 *Daphnia*	0.897	0.377	54	0.121	0.936
Log LC50 algae	0.974	0.243	20	−0.169	1.069
Log NOEC *Daphnia*	0.656	0.696	12	−0.256	0.756
Log NOEC algae	0.915	0.555	9	−0.390	1.071
PNEC	0.894	0.472	30	−0.086	0.957

[a] r^2 = square correlation coefficient; ser = standard error of regression; *n* = number of chemicals; BCF = bioconcentration factor; LC50 = median lethal concentration; NOEC = no-observed-effect concentration; PNEC = predicted no-effect concentration.

deviation is a good descriptor of the error between the data selected by expert judgment in the EU and OECD risk assessment reports and the data selected by EURAM.

Data derived by using QSAR and data for which default values are used are not included in the regression analysis. No linear regression was performed for the NOEC of fish, because of the use of QSAR and default values in EURAM and hence the lack of measured data ($n = 4$). Also, for the NOECs of both *Daphnia* and algae, the number of chemicals with measured data is relatively small ($n = 12$ and $n = 9$, respectively). Boiling point, log K_{ow}, and LC50s for fish and *Daphnia* showed relatively high amounts of measured data (Table 3) ($n = 54$, 50, 57, and 54, respectively).

Good correlation is found between the selection of data of physicochemical properties by expert judgment within the EU and OECD risk assessments and with the automated data selection procedure of EURAM, as is shown in Table 3 and Figure 2. Boiling point and log K_{ow} show a high r^2, a low ser, and a slope and intercept approaching 1 and 0, respectively. Also, aqueous solubility and vapor pressure have a high r^2 and a slope and intercept approaching 1 and 0, respectively. However, the ser of these last two endpoints is relatively high. In

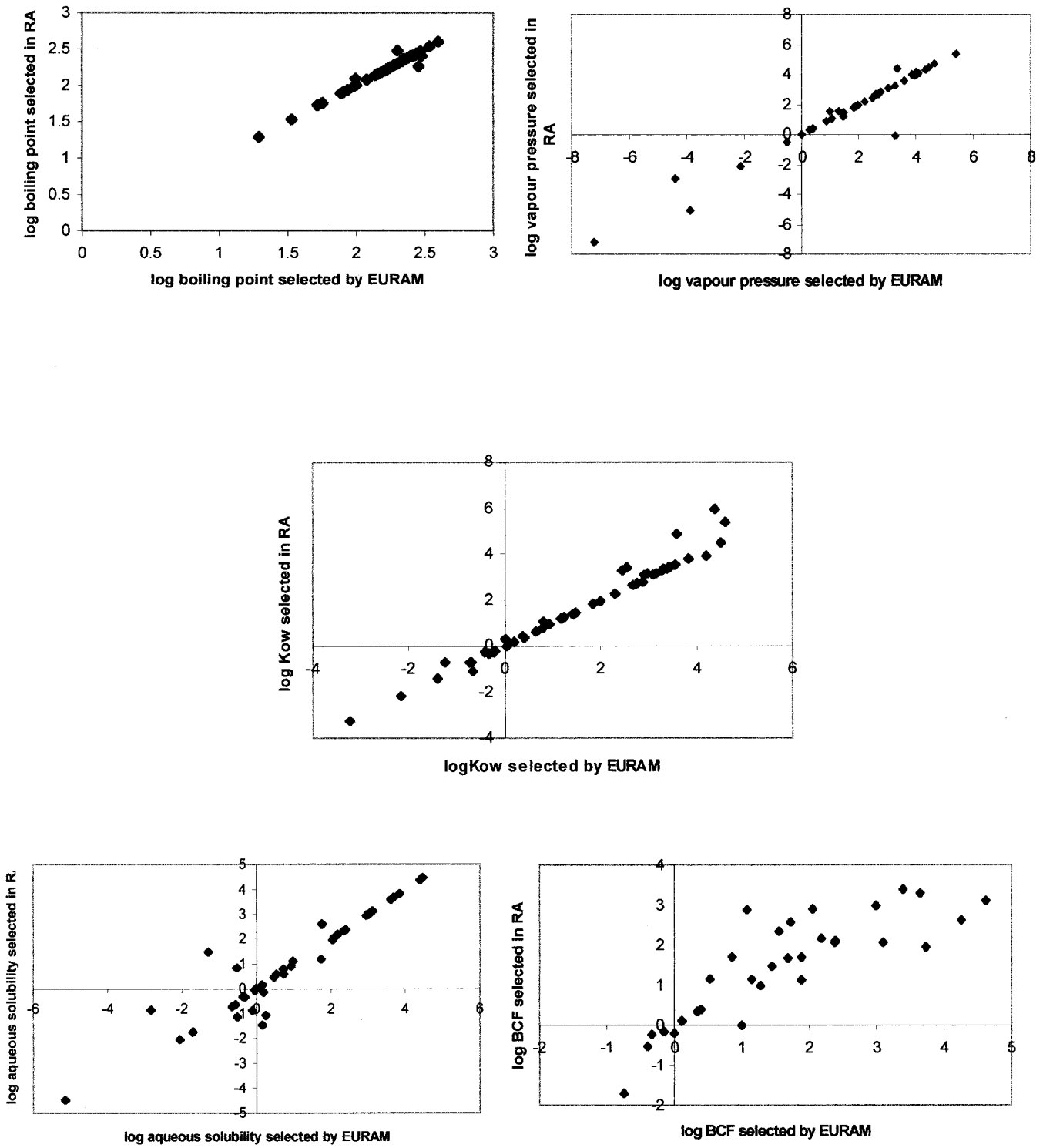

Fig. 2. Plot of regression of data on boiling point, vapor pressure, log K_{ow}, aqueous solubility, and bioaccumulation selected by expert judgment within the European Union and Organization for Economic Cooperation and Development risk assessments on data selected by the automated data selection procedure of the European Union risk ranking method (EURAM). BCF = bioconcentration factor.

Figure 2 the plots of the regression for aqueous solubility show that the high ser is due to three outliers and due to four outliers for vapor pressure.

Concerning the BCFs, the data selected by expert judgment and by the automated data selection procedure do not show a good correlation (Table 3 and Fig. 2). One of the reasons for this moderate correlation might be the presence of a large database for a substance for bioaccumulation factors. Therefore, data can belong to similar preference classes in EURAM, hence increasing the possible choices for the selection by the automated data selection procedure.

Two of the three acute aquatic toxicity data, namely L(E)C50 for *Daphnia* and algae, showed a good correlation (Table 3). The correlations for the acute toxicity data are relatively high compared with the moderate correlation for the chronic toxicity data. However, for the chronic toxicity data,

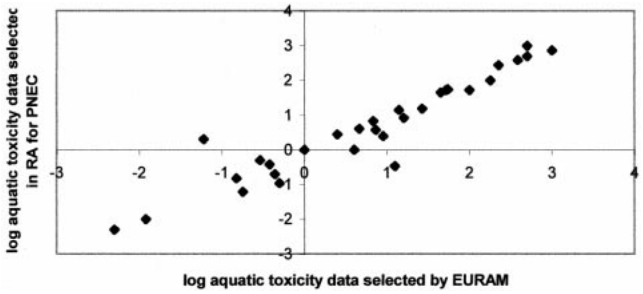

Fig. 3. Plot of the regression of the data on aquatic toxicity selected by expert judgment for the derivation of the predicted no-effect concentration (PNEC) in the European Union and Organization for Economic Cooperation and Development risk assessment on the aquatic toxicity values selected by the automated data selection procedure of the European Union risk ranking method (EURAM).

a limited amount of data is available, namely $n = 12$ and 9 for NOEC *Daphnia* and NOEC algae, respectively, and therefore the ser to the total variance in the parameter can be relatively high.

The comparisons of aquatic toxicity data selected by expert judgment for the derivation of the predicted no-effect concentration with the aquatic toxicity data selected by the automated data selection procedure are shown in Table 3 and Figure 3. Taking into account that the aquatic toxicity value, which is selected by expert judgment for the derivation of the predicted no-effect concentration, is chosen out of the six standard toxicity endpoints and considering the two outliers, as shown in the plot in Figure 3, the results of the regression are relatively high.

Because within the automated selection procedure of EURAM only descriptive values (i.e., readily biodegradable, inherently biodegradable, and not biodegradable) are available, no linear regression could be performed for this endpoint. However, the type of biodegradation selected by EURAM and selected by expert judgment within the EU and OECD risk assessments can be compared. After excluding the substances for which only QSAR and default values were available in IUCLID, the comparison was performed for 36 priority substances, as is shown in Table 4. Twenty-six of the 36 substances seem to have the same descriptive value, that is, readily biodegradable (14 substances), inherently biodegradable (2 substances), or nonbiodegradable (10 substances), selected by either method. Six of the remaining 10 substances seem to have a more conservative value when selected by EURAM, namely inherently biodegradable versus readily biodegradable. Therefore, for a majority of the substances (72%), the type of degradation selected by the automated selection procedure in EURAM is in agreement with the type of degradation selected by expert judgment. For 16% of the substances the value selected in EURAM is more conservative than the value selected by expert judgment.

CONCLUSION

The IUCLID has proven to be a good database for priority setting purposes, because the data in IUCLID, and hence selected by EURAM, are in agreement with or are similar to the data used in the EU and OECD risk assessment procedures. The data selection criteria for the automated selecting of data from IUCLID perform well, as shown by the good correlation with data selection by expert judgment in the risk assessment procedure. In particular, the selection of physicochemical properties and aquatic toxicity data shows a relatively high correlation. In addition, the selection of the type of biodegradation in EURAM also was in agreement with the data selected by expert judgment in the risk assessment procedures.

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Table 4. The number of priority substances having the same type of biodegradation selected by both the automated data selection procedure of European risk ranking method (EURAM) and by expert judgement in the risk assessment procedure

	Risk assessment procedure		
EURAM	Readily biodegradable	Inherently biodegradable	Nonbiodegradable
Readily biodegradable	14	1	1
Inherently biodegradable	6	2	1
Nonbiodegradable	0	1	10