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ENVIRONMENTAL CONTAINMENT PROPERTY ESTIMATION USING QSARs IN AN EXPERT SYSTEM

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EXECUTIVE SUMMARY

Mathematical models are often used to estimate the fate and impact of organic chemicals in the environment. Use of these models requires a variety of parameters describing site and chemical characteristics. Aqueous solubility (S), the octanol/water partition coefficient (Kow), the organic carbon norn:alized soil/water sorption coefficient (Koc), vapor pressure (Pv), Henry's Law constant (H), and bioconcentration factor (BCF) are considered key properties used to assess the mobility and distribution of a organic chemical in environmental systems.

One major limitation to the use of environmental fate models has been the lack of suitable values for many of these properties. The scarcity of data, due mainly to the difficulty and cost involved in experimental determination of such properties for an increasing number of synthetic chemicals, has resulted in an increased reliance on the use of estimated values.

Quantitative Property-Property Relationships (QPPRs), based on the relationship between two properties as determined by regression analysis, are used to predict the property of interest from another more easily obtained property. Quantitative Structure-Property Relationships (QSPRs) often take the form of a correlation between a structurally derived parameter(s), such as molecular connectivity indices (MCIs) or total molecular surface area (TSA) and the property of interest.

Selection and application of the most appropriate QPPRs or QSPRs for a given compound is based on several factors including: the availability of required input, the methodology for calculating the necessary topological information, the appropriateness of correlation to chemical of interest and an understanding of the mechanisms controlling the property being estimated.

Incorporation of QPPRs and QSPRs into a computer format is a logical and necessary step to gain full advantage of the methodologies for simplifying fate assessment. A Property Estimation Program (PEP), utilizing MCI-property, TSA-property and property-property correlations and UNIFAC-derived activity coefficients, has been developed for the Apple Macintosh microcomputer to provide the user with several approaches to estimate S, Kow, Pv, H, Koc and BCF depending on the information available.

Structural information required for the MCI and UNIFAC calculation routines can be entered using either Simplified Molecular Identification and Line Entry System (SMILES) notation or connection tables generated with commercially available two-dimensional drawing programs. The TSA module accepts 3-D atomic coordinates entered manually or directly reads coordinate files generated by molecular modeling software. The program's built-in intelligence helps the user choose the most appropriate QSPR based on the structure of the chemical of interest. In addition, the statistical information associated with each QSPR in PEP can be displayed to help the user determine the model's validity. For the regression-based modules, assessments of accuracy based on the 95% confidence interval and estimated precision of the experimental values are also provided along with the estimated property value.

PEP also provides a batch mode that provides users with a method for the convenient, unattended calculation of MCIs, TSA and UNIFAC activity coefficients and the subsequent estimation of physical properties for large numbers of compounds.

A chemical property database, containing experimental values of S, Kow, H, Pv, Koc, and BCF complied from a variety of literature sources and computerized databases was used for developing the MCI-property, TSA-property and property-property relationships used in PEP. This database, which currently contains over 800 chemicals, is linked directly to PEP.

The property estimation modules in PEP are also linked directly to the Level 1 and 2 Fugacity Models. The combination of the various property estimation methods, chemical property database, and simple environmental fate models provides users with a methodology for predicting the environmental distribution of an organic chemical in a multi-phase system requiring only the structure of the chemical of interest as input.

OBJECTIVES OR STATEMENT OF WORK

The primary goal of this project was to develop a microcomputer-based decision support system utilizing Quantitative Structure Property Relationships (QSPRs) and Quantitative Property Property Relationships (QPPRs) to predict the physical/chemical properties of an organic chemical which are necessary to model its environmental fate. The following specific properties were investigated: aqueous solubility (S), octanol/water partition coefficient (Kow), vapor pressure (Pv), organic carbon normalized soil/water partition coefficient (Koc), Henry's Law constant (H), and bioconcentration factor (BCF).

In order to achieve the primary goal of this research, the following specific objectives were accomplished:

- 1. A database of experimentally determined values of S, Kow, Pv, Koc, H and BCF was compiled for over 800 organic compounds exhibiting a broad range of properties and expected mobility.
- Algorithms to calculate molecular connectivity indices (MCIs), total molecular surface area (TSA) and UNIFAC activity coefficients were adapted/developed to run in a microcomputer environment using SMILES notation, connection files, or coordinate files to input required structural information.
- 3. Using the database described in Objective 1 and the computational methods developed in Objective 2, a variety of QSPRs and QPPRs for estimating S, Kow, Pv, Koc, H and BCF were developed.
- 4. Created a microcomputer-based decision support system that uses chemical structure information to aid the user in choosing the most appropriate QSPR or QPPR.
- 5. Linked property estimation routines and property database to simple environmental fate models (the Level 1 and 2 Fugacity Models) to provides users with a methodology for predicting the environmental distribution of an organic chemical in a multi-phase system requiring only the structure of the chemical of interest as input.

BACKGROUND AND SIGNIFICANCE

Mathematical models are often used to estimate the fate and impact of organic chemicals in the environment. These models often idealize the environment as a system of connected compartments, i.e. water, soil, sediment, air and biota. The complexity of these models range from simple steady state models to non-steady state models which include a large number of compartments, transport between compartments and degradation processes.

Use of these models requires a variety of input parameters which describe site and contaminant physical-chemical and biological characteristics. Aqueous solubility (S), octanol/water partition coefficient (Kow), the organic carbon normalized soil/water sorption coefficient (Koc), vapor pressure (Pv), Henry's Law constant (H), and bioconcentration factor (BCF) are considered key properties used to assess the mobility and distribution of a chemical in environmental systems.

One major limitation to the use of environmental fate models has been the lack of suitable values for many of these properties. The scarcity of data, due mainly to the difficulty and cost involved in experimental determination of such properties for an ever increasing number of synthetic chemicals, has resulted in an increased reliance on the use of estimated values. Quantitative Property-Property Relationships (QPPRs) and Quantitative Structure-Property Relationships (QSPRs) have been used by environmental scientists and engineers to obtain estimated values for a variety of physical/chemical properties for use in environmental fate and assessment modeling.

QPPRs, based on the relationship between two properties as determined by regression analysis, are used to predict the property of interest from another more easily obtained property without a specific concern for molecular structure. Frequently, the regression expressions are expressed in terms of the log of the two properties. Researchers have found that a number of environmental properties can be related to one another in this manner. For example, QSPRs have been developed to estimate S, Koc and BCF from Kow and Koc and BCF from S [1-3].

QSPRs are methods by which the properties of a chemical can be inferred or calculated from a knowledge of the structure of a molecule. QSPRs often take the form of a correlation between a structurally derived parameter(s) and the property of interest. For example, relationships between structurally derived parameters, such as molecular connectivity indices (MCIs) and total molecular surface area (TSA) and properties such as S, Kow, BCF, and H have been reported.

Molecular connectivity developed by Randic⁷ [4] and refined and expanded by Kier and Hall [5-7] is a method of bond counting from which topological indices, based on the structure of the compound, can be derived. For a given molecular structure, several types and order of MCIs can be calculated. Information on the molecular size, branching, cyclization, unsaturation and heteroatom content of a molecule is encoded in these various indices [5]. MCI have been used to predict Koc [8,9], S [1], Kow [10], H [11] and BCFs [12].

A direct estimation of molecular surface area based on the concept of van der Waals radius, TSA has been correlated with S, Kow, Pv and H [13-22]. Several different algorithms, requiring the 3-D atomic coordinates of the solute molecule and the van der Waals radii of solute and solvent molecules as input [19,23], have been developed to calculate TSA.

Group contribution or fragment constant methods are another important category of QSPRs. The basic idea of a group contribution method is that while there is an enormous number of chemical compounds, both synthetic and naturally occurring, the number of functional groups that make up these compounds is much smaller. A single numerical value is assumed to represent the contribution of each functional group (i.e. a specified atom, a group of atoms bonded together or structural factor) to the physical property of interest. It is also usually assumed that the contributions made by each group are independent of each other. By summing up the values of the various fragments or groups the property of interest can be directly calculated.

The UNIFAC (UNIQUAC Functional Group Activity Coefficient) group contribution method [24-26] has been used by environmental researchers to estimate S and Kow [27-31]. The UNIFAC method was developed to estimate liquid phase activity coefficients in mixtures of nonelectrolytes [25]. In this technique, the activity coefficient is divided into two parts, a combinatorial part which reflects the size and shape of the molecule present and a residual portion which depends on functional group interactions. Various parameters, such as van der Waals group volumes and surface areas and group interaction parameters, are input into a series of equations from which the combinatorial and residual parts are calculated. Values for the group parameters have been tabulated and can be found in the literature[25,26]. UNIFAC is specifically designed to take into account interactions between groups and is appropriate for multiple solute/solvents systems. UNIFAC also permits estimates to be made as a function of temperature.

In most cases, more than one estimation method is available for a particular property. Estimation methods however, have widely varying accuracies and indiscriminate use of these techniques can result in large errors. Selection and application of QSPR or QPPR methods requires varying degrees of expertise that depend on the structure of a particular chemical of interest, knowledge of the mechanism of the process, the extent of the database used to develop the QSPR or QPPR and the complexity of the structural analysis required to relate structure to the property. For example, some QSPR and QPPRs are broader than others in the range of chemicals that are covered, and some methods have been established with a better understanding of the mechanisms or properties involved. In many cases estimation methods are developed from empirical or semiempirical correlations. The success of the correlation is dependent on many factors including the type and number of compounds used in its development.

Incorporation of QSPR and QPPRs into a computer format is a logical and necessary step to gain full advantage of the methodologies for simplifying fate assessment. A practical computerized property estimation program, utilizing QSPR and QPPRs, should include the following attributes: be simple and flexible to use for both experts and non-experts, include sufficient statistical information regarding the development of the QSPRs and QPPRs so that the range of applicability of such models can be evaluated, and provide an indication of the accuracy of the estimated property.

A microcomputer based Property Estimation Program (PEP), utilizing MCI-property, TSAproperty and property-property correlations and UNIFAC derived activity coefficients, was developed to provide both experts and non-experts with a fast, economical method to estimate a compound's S, Kow, Pv, Koc, H, and BCF for use in environmental fate modeling. The user can input the required structural information for the MCI and UNIFAC calculation routines using either SMILES notation or coordinate files (connection table or "Molfile" formats) generated with commercially available two-dimensional drawing programs such as ChemDrawTM [45], Chemintosh [™], or ISIS/Draw [™]. The TSA module accepts 3-D atomic coordinates entered manually or directly reads coordinate files generated by molecular modeling software such as Alchemy III[™] or Chem3D Plus[™]. For property-property, TSA-property and MCI-property modules, the user can select from either "universal" or class specific regression models. To aid the user in choosing the most suitable regression model, the program automatically suggests the most appropriate regression model(s) based on the structure of the compound. In addition, the statistics associated with each model can be displayed along with the list of compounds used in developing the model. For the regression based modules, assessments of accuracy based on the 95% confidence interval and estimated precision of the experimental values are provided along with the estimated property value. Additional correlation models can be easily added to PEP by the user.

A chemical property database, containing experimental values of S, Kow, H, Pv, Koc, and BCF complied from a variety of literature sources and computerized databases was used for developing the MCI-property, TSA-property and property-property relationships used in PEP. This database, containing over 800 chemicals, is linked directly to PEP and provides the means for the user to search for chemical compounds by full or partial name or synonym, to sort the compounds by name, boiling point, melting point, ω molecular weight, and the ability to transfer to any of the property estimation modules.

In addition to the physical properties, the database was recently modified to allow the user to enter information pertaining to a compound's persistence and toxicity. Biodegradation rates, hydrolysis rates, photolysis rates and LC 50 values, along with the references and comments associated with each property, can be stored in the database. To illustrate the potential application of PEP, the property estimation modules are linked directly to the Level 1 and 2 Fugacity Models developed by Mackay [32]. These simple models calculate the equilibrium distribution of an organic chemical between water, air, soil, sediment, suspended sediment and biota phases in a user defined world. The combination of PEP and Fugacity models provides users with a methodology for predicting the environmental distribution of an organic chemical in a multi-phase system requiring only the structure of the chemical of interest as input. The development and use of the PEP system will be described.

STATUS OF RESEARCH EFFORT

General Programming Description

HyperCard

HyperCard is a program that was developed for the Apple Macintosh series of personal computers to enable novice Macintosh programmers to write user friendly computer applications. HyperCard, which is provided with every Macintosh sold, offers graphics, information storage, and the means to display information in a variety of formats. HyperTalk is a high-level, interpreted language used to establish links between related information and perform simple calculations within HyperCard. HyperCard also allows the programmer to create extensions of HyperTalk in a lower level language (i.e., C or Fortran). These extensions, called external functions (XFCN) and external commands (XCMD), greatly increase the speed of repetitive and calculation intensive algorithms over using HyperTalk itself. XFCNs and XCMDs can also be used to implement custom Macintosh features such as popup menus and custom dialog boxes.

Cards

Each screen of information in HyperCard is termed a card. Each card can contain graphics, fields, and buttons. The data on a card is held in the fields, and the buttons are used to initiate action procedures that operate on the data. The fields and buttons allow the standard Macintosh interface to be used without the direct use of the cumbersome Macintosh toolbox routines. To create a user interface the HyperCard programmer simply draws, or creates the buttons and fields. The link between buttons, fields and cards is done through HyperTalk scripts. A script is a set of HyperTalk statements linked to a button, field, card, or stack.

Stacks

Cards are put together in HyperCard files called stacks. A stack can contain from 1 to 16,000 cards depending on the amount of memory each card requires. Usually each stack contains cards that are related either by purpose or visual similarity. The movement from stack to stack is rapid and easy to accomplish using either the standard Macintosh menus or HyperTalk scripts.

External functions and commands

Some of the custom features used to enhance PEP were implemented using commercial XFCNs and XCMDs. Table 1 lists the commercial XFCNs and XCMDs that were used, their creator, and action.

XFCN or XCMD	Creator	Use
рорUр	Adrian Freed (1989a) [42]	makes a pop up menu
ShowDialog	Jay Hodgdon (1988a) [40]	shows a modal Dialog
Progress	Jay Hodgdon (1988b) [41]	shows a dialog box with a progress pointer

Table 1. The commercial XFCNs and XCMDs used

The XFCNs and XCMDs that were used in PEP were created using Think C versions 4.0 and 5.0 from Symantec Corporation (1991) [44]. "Glue" routines are used to facilitate the communication between HyperCard and XFCNs or XCMDs. HyperCard glue is furnished with Think C. XTRA Shell by Adrian Freed (1989b) [43] was also used to develop XFCNs and XCMDs. XTRA also contains HyperCard glue plus a simple to use set of functions that can be called from Think C.

Algorithms

TSA algorithm

Total Surface Areas (TSA) are calculated using a modified version of the SALVO2 algorithm developed by Pearlman [16]. SALVO2, a FORTRAN program designed to run on main frame computers, was translated to the C computer language using Cobalt Blue's [46] FOR_C translator version 2.9 (1989). This translation enabled the SALVO2 algorithm to be made into an XFCN and linked directly to a HyperCard stack.

MCI calculation method

A C language program was written for the calculations of the MCIs based on code described by Frazier [35]. The algorithm currently calculates 54 (0 to 6 order) bond, valance, and path indices, and 7 (0 through 6 order) Δ valence indices if the molecule contains any nitrogen or oxygen atoms. A more detailed discussion of the MCI calculation procedure is provided in the literature review section.

UNIFAC calculation method

The UNIFAC procedure, as described by Grain [38], was incorporated into HyperTalk scripts and XFCNs. The group contribution factors were also taken from Grain [38] and are derived from vapor-liquid equilibria data.

Fugacity level 1 model

The Fugacity level 1 model, described by Mackay [32, 39], was implemented in HyperTalk. This model is used to estimate the distribution of a chemical in a user defined environment consisting of a maximum of six compartments: air, water, soil, sediment, suspended solids, and biota. The default compartment volumes and densities were also taken from Mackay [32].

The graphs which show the distribution of the chemical are drawn using routines from GraphMaker a HyperCard stack included with version 2.0 of HyperCard. A detailed description of the PEP implementation of the Fugacity level 1 model is provided later.

Development of QSPRs and QPPRs

The QSPRs and QPPRs utilized in PEP were developed using both statistical and intuitive criteria. The QSPRs were first derived using the stepwise regression features in StatView II, a statistical analysis package by Abacus Concepts Inc. (1988) [47]. The results from the stepwise regression procedure were analyzed and the variables containing theoretical information were left in the regression equation. The final regression equation was chosen to include both a size term and a measure of the polar nature.

After the regression equations were chosen the final calculations of the Analysis of Variance table and the graphs were obtained using Data Desk by Odesta Corporation (1989) [48]. Both universal and class specific equations for each property were developed and evaluated. All of the universal relationships and the class specific relationships that were found to be significant to the 90 percent level were incorporated in PEP.

PEP Hardware/software Requirements

PEP requires the following system configuration to run: a Macintosh Classic, LC, II series, or PowerBook computer, with a hard disk; HyperCard 2.0 or greater software; Macintosh system software version 6.0.5 or greater, running under MultiFinder; and a minimum of 2 megabytes of memory (RAM), with 1000 kBytes of memory allocated for HyperCard.

PEP overview

The PEP system currently consists of four HyperCard stacks: PEP Processor, PEP Models, PEP Help and Chemical Property Database. A flowchart illustrating the overall operation of PEP is provided in Figure 1.



Figure 1. Flow chart illustrating the overall operation of PEP

Typically, users would first look for the required property information in the PEP database. If the information is not contained in the database, the user can then estimate the property using one or more of the four property estimation modules provided. Choosing the most appropriate property estimation module would depend on what information regarding the chemical is available. The function and use of each stack in PEP will be described in the following sections.

PEP Processor

This stack, divided into four sections or modules, contains the algorithms for data input, calculations and output of the estimated physical-chemical properties. Each stack will be described in detail in the following sections.

MCI Module The overall operation of the MCI module is illustrated in Figure 2.



Figure 2. Flow chart describing operation of PEP MCI module.

The user interface of this module, shown in Figure 3, is designed in the form of a flow chart. Upon entering the MCI module the user must first input the necessary structural information using either SMILES [33,34] notation or connection files generated from ChemDraw[™], Chemintosh[™], or ISIS/Draw[™], commercially available, Macintosh compatible two-dimensional (2D) drawing programs.

SMILES is a chemical notation language specifically designed for computer use. It is a method of "unfolding" a 2D chemical structure into a single line of characters containing the structural information.



Figure 3. Screen display of PEP MCI module

After the structural information is entered, MCIs can then be calculated using a set of HyperCardTM external functions (XFCN) written in the programming language C based on code described by Frazier [35]. The MCI calculation routine in PEP calculates simple, bond and valence indices of several types (path, cluster, chain, and path/cluster) and orders (0 through 6), if possible, for each molecule, resulting in a maximum of 54 index values for each molecule which can be displayed on screen and/or output to a printer. To account for non-dispersive force effects on aqueous solubility and solubility related properties, zero through six order Δ valence path indices ($\Delta \chi$), as described by Bahnick and Doucette [36], are calculated by PEP, in addition to the 54 indices described above. To calculate $\Delta \chi$ indices, a nonpolar equivalent is made by substituting C for O or N atoms. MCIs are calculated for the nonpolar equivalent and values for $\Delta \chi$ can be computed for each type of index by:

$$\Delta \chi = (\chi) np - \chi \tag{1}$$

After the MCIs are calculated, they can be displayed or printed if desired and the user can then choose which properties are to be estimated. For each property, two categories of MCI-property relationships are displayed. MCIs property relationships, both class specific and "universal", that were developed in this project using the experimental values reported in the PEP property database are preceded with the word PEP. "Universal" MCI-property relationships were developed using all available experimental data for a given property regardless of chemical class. "Class-specific" MCI-property relationships were developed if property values were available for a sufficient number (10 or greater) of compounds within a particular chemical class (PCBs, PAHs, ureas, etc.). In addition, several multi-class MCI-property relationships available to the user for the predicting the potential hierarchy of MCI-property relationships available to the user for the predicting the vapor pressure (Pv) of a polychlorinated biphenyl (PCB) is shown below. There are three MCI-property relationships, one developed using only PCBs, one using halogenated aromatics including PCBs and one using all compound types:

$\log Pv = 5.814 (nc5) - 2.428 (np3) + 9.479$	(PCBs)
$\log Pv = -1.559 (bp1) + 6.622$	(Halogenated aromatics)
$\log Pv = -1.275 (np3) + 5.261$	(Universal)

Generally, the use of a "class-specific" relationship, if available, should provide the best estimate (i.e. the estimate associated with the least amount of uncertainty).

By looking for a group of atoms and bonds that distinguish a chemical class, PEP uses the structural information contained in the SMILES string or connection file input to aid users in choosing the most appropriate MCI-property relationships. The number of appropriate relationships or chemical classes that are chosen by the program, denoted with a diamond in the popup menu, is determined by the number of different distinguishing subgroups that are found. In addition, a summary of the regression statistics and list of compounds used to develop and evaluate each MCI-property relationship can be displayed by clicking the "eye" or "view statistics option"

found at the left of each regression model. Information displayed on the statistics card includes: the MCI-property regression equation, the list of chemicals used in developing the regression model, the standard errors of the coefficients in the regression equation, the Analysis of Variance (ANOVA) table, the r^2 value, a graph of the the predicted vs. estimated values, a graph of the residuals vs. the predicted values, a graph of the residuals vs. the number of standard deviations and appropriate reference. An example of the statistical information provided for each MCIproperty relationship is shown in Figure 4.



Figure 4. Example statistics card from PEP

The 2nd category of MCI-property correlations, located below the PEP relationships, were complied from various literature sources. Clicking on the "book" icon will display the reference and information regarding the number and type of compounds included in the correlation if it was available in the original literature. After choosing the most appropriate regression, estimates for the selected properties can be made. As shown in Figure 5, the MCI module results card provides an estimate of the property along with its calculated accuracy based on both the 95% confidence interval calculated from the regression and the estimated precision associated with the experimental determination of the property. In addition, the user has the option to search the property database for actual experimental values if they are available for comparison.

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					1999 - 1 - 1 - 1 - 1 - 1 - 1 - 1 - 1 - 1						
		<u>Estima</u>	ited Properti	<u>es</u>							
Chemical	Name: 2.2'.6	.6'-tetraci	nlorobiphenul								
Method:	MCI										

			Regression	View	Look for values						
Property	* <u>Value</u>	<u>Units</u>	Equation Used	<u>stats</u>	h Prop.Db						
log/antilog											
log \$	-6.17 ± 0.38	moles/L	PEP : PCBs		NA						
log Kow	5.42 ± 0.43		PEP : PCBs		5.936						
log Pv	-2.34 ± 1.04	Pascals	PEP : PCBs		NA						
log H	-1,30 ± 0.28	dimension	les: PEP : PCBs	•	-1.648 dimensionless						
log Koc	3.92 ± 1.20	L/kg	PEP : PCBs		NA						
log BCF	4.69 ± 0.43		PEP : PCBs		NA						
X 11		luce eter	n and antimated a		the						
	*Note: the values shown are estimated at 25°L ± the										
93	w hisnicri		ar for the regress	ion useu.							

Figure 5. Results card from PEP MCI module.

<u>TSA module</u> The TSA module is similar in operation to the MCI module. However, unlike molecular connectivity, the calculation of TSA requires information describing the geometry of the molecule in terms of its 3-D atomic coordinates. The TSA module, shown in Figure 6, accepts 3-D atomic coordinates entered manually or directly reads coordinate files generated by commercially

available, Macintosh compatible, molecular modeling software such as Alchemy III[™] or Chem3D Plus[™].



Figure 6. TSA module card from PEP

The TSA module is also designed to accept files generated by other hardware/software combinations including UNIX or VAX versions of CONCORD (Tripos Associates, Inc.), a hybrid expert system and molecular modeling software designed for the rapid generation of high quality approximate 3-D molecular structures. In addition to the 3-D molecular structure, the user must also input van der Waals radii for each of the atoms. A editable table of van der Waal radii, obtained from Bondi [37] for most common atoms, is provided within the TSA module. Once the molecular geometry and the van der Waal radii are input, TSA can be calculated using a XFCN which was adapted from the SALVO2 algorithm developed by Pearlman [19]. This algorithm

represents each atom of a molecule by a sphere centered at the equilibrium position of the nucleus. The radius of the sphere is equal to that of the van der Waals radius. Planes of intersection between spheres are used to estimate the contribution to surface area from the individual atoms or groups. The program computes the surface area of individual atoms or group by numerical integration, and the overlap due to intersecting spheres is excluded from the calculation. TSA is calculated by the summation of individual group contributions. The program also allows the TSA of the solute molecule to be calculated after the addition of a suitable solvent radius. A more detailed description of the TSA calculation method is provided by Pearlman [19].

After the TSA has been calculated, the user then chooses the properties of interest and a regression equation for each using the same approach as described in the MCI module. If the SMILES string or the connection table is also input, the most appropriate TSA-property relationship(s) will be flagged in the popup menu. The operation of the TSA module from this point on is identical to that of the MCI module.

<u>UNIFAC module</u> Like the MCI module, the UNIFAC module, illustrated in Figure 7, requires either a SMILES string or a connection table as input. An XFCN converts the structural information provided by the SMILES string or connection file into valid UNIFAC subgroups and counts the number of each subgroups present. In order to break the structure into the proper subgroups, the SMILES string or the connection file is interpreted and the information is put into a matrix. Each row and column in the matrix represents an atom in the chemical. The matrix contains the bond order between the two atoms that correspond to each entry in the matrix. If two atoms are not connected then a 0 is placed in the corresponding entry in the matrix. After the matrix is built the algorithm then "asks" specific questions about each atom, its neighbors, and how it is connected. If the answers to a set of questions are all true then a subgroup was found, the atoms are put together, and the matrix is reduced. The questions are then asked over again and the next subgroup is chosen, this repeats until no more subgroups are found. The questions are asked in a specific sequence so that the resulting subgroups are independent of the order of the atoms in the matrix.



Figure 7. PEP UNIFAC module.

The UNIFAC method for calculating activity coefficients, as described by Grain [38], is implemented using both HyperTalk and an XFCN. The functional group interaction parameters, presented by Gmehling et al. [26] and derived from vapor-liquid equilibria (VLE), are used in the calculation routine but can be changed by the user. After the activity coefficients are calculated they can be displayed along with relevant intermediate values and used to estimate S and Kow by the following expressions (Arbuckle, 1986):

$$Kow = 0.115 \gamma \infty w /\gamma \infty 0 \tag{2}$$

$$S (mol/L) = 55.6 / \gamma \infty w$$
(3)

where $\gamma \infty w$ is the activity coefficient of the chemical infinitely dilute in water and $\gamma \infty o$ is the activity coefficient of the chemical infinitely dilute in octanol [27].

<u>Property/Property Module</u> Input for the Property/Property module, shown in Figure 8, depends on the the properties to be estimated and the regression models used. Thus, the user must

select the properties to be estimated and the property-property relationships (regression equations) to be used before any input values are requested. The program keeps track of the inputs required and provides the appropriate input fields. If available, the required properties can be imported directly from the associated chemical property database. Information regarding the regression statistics, if available, is also provided as previously described in the MCI module. After the necessary properties are entered into the corresponding input fields, the properties of interest can be estimated and the results, along with the 95% prediction interval (if the necessary data is available) can be viewed.



Figure 8. PEP Property/Property correlation module.

PEP Models

To illustrate the practical application of PEP, an additional stack called PEP Models was developed. This stack, which contains the algorithms for the Level 1 and 2 Fugacity Models [32], is linked directly to the the PEP Processor, but can also be used independently.

The Level 1 Fugacity Model considers a unit world consisting of six compartments: air, water, soil, suspended solids, sediment, and biota as illustrated below in Figure 9. The model predicts the equilibrium concentrations of the chemical of interest in each compartment using the fugacity approach described by Mackay [32, 39]. The model requires the input of K_{OC} , H and BCF which can be read directly from the PEP processor or the PEP chemical property database, if available. In addition to the chemical specific properties, the density and volume of each compartment must be specified along with the organic carbon content of the soil, sediment and suspended sediment. An editable set of default values for compartment density, volume and organic carbon content, as suggested by Mackay, is provided.



Figure 9. Representation of Fugacity Level 1 Model compartments.

The Level 2 Fugacity Model (Figure 10) allows for the chemical of interest to degrade in each compartment, move by advection through the water and air phases, and be emitted into the unit world. The rate values for each of these processes must be entered by the user. The degradation rates for each compartment can be entered either by t1/2 values in hours or by first order reaction rate constants in 1/hours. The advection rate data can be entered either by residence time or flow rate and the concentration or by directly entering the mass flow rate in moles per hour. The emission rate is entered in the units of moles per hour.

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Fugacity Model											
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1. Input Property Values	2. Input Enviro	nmental (Compartm	ent Values							
Look for Values in Prop.DB	Compartment	Density kg/m ³	Volume m ³	% Organic Carbon							
	🖾 Air	1.19	1e10		5. Calculate Distribution						
	🖾 Water	1000	<u>7e6</u>		OR						
(dimensionless)	🖾 Soil	1500	<u>9e3</u>	2	Input Fugacity						
-1.648	🛛 Susp. Solids	1500	35	4	Level 2 Data						
log BCF 🔲	🖾 Sediment	1500	2.1e4	4							
4.69	🖾 Biota	1000	3.5								
indicates value from DB											
	and a second										

Figure 10. PEP Models card

After the user inputs all the required information and hits the "calculate distribution" button, the model calculations are performed in HyperTalk and the results are presented in both in tabular and graphical form as illustrated in Figure 11. The graphical display can be changed from bar

(concentration of the chemical in each phase) to pie (percent of the chemical in each phase) chart forms using the "Graph:" popup menu. The values of the distribution coefficients that were used in the calculations are also shown on the results card. A complete description of these models has been given by Mackay [32,39]



Figure 11. PEP Models results card

PEP Help

Information regarding the operation of the chemical property database and the property estimation, models and batch modules is available in the PEP Help stack. This stack easily accessed at any time within the PEP system. The organization and layout of each help card is similar to that illustrated in Figure 12 for the MCI module. The user can select the topic of interest

by clicking on the appropriate radio button and the information on that subject will be displayed in the scrolling field.

	PEP Help
🔹 File Edit Go Pi	rint 🙆 🙀
	MCI Module
MCI Options	Molecular connectivity developed by Randic (1972) and refined and expanded by (Kier and Hall,
🖲 overview	1976, 1980, 1986) is a method of bond counting from which topological indexes, based on the
() input structure	structure of the compound, can be derived. For a
🔿 calculate MCIs	orders of molecular connectivity indexes (MCIs)
O choose properties & regression equations	can be calculated. Information on the molecular size, branching, cyclization, unsaturation, and
() estimate properties	heteroatom content of a molecule is encoded in these various indices (Kier and Hall, 1976).
() limitations	Molecular connectivity has been used to predict Koc (Sabliic, 1984, Sabliic, 1987, Bahnick and
	Doucette, 1988), S (Doucette, 1985, Nirmalakhandan and Speece, 1988a), Kow (Doucette 🕞

Figure 12. Example Help card from PEP

Chemical Property Database

Experimentally determined physical property data for about 800 compounds, having at least one value of aqueous solubility (S), octanol/water partition coefficient (Kow), vapor pressure (Pv), organic carbon normalized soil sorption coefficient (Koc), bioconcentration factor (BCF), or Henry's law constant (H), was complied from a variety of literature sources and computerized databases. Using this information, a chemical property database was constructed using HyperCardTM and subsequently used for developing MCI-property, TSA-property and propertyproperty relationships. In addition to the properties listed above, the database includes the following information: compound name and synonyms, a diagram of the 2-D chemical structure, SMILES notation, uses, CAS number, chemical formula, molecular weight (MW), boiling point (BP), melting point (MP), and appropriate references for each value. A built-in unit conversion utility enables users to quickly view property values in a variety of commonly used units. The database is directly connected to the PEP Processor stack.

The Chemical Property Database also provides the means for the user to search for chemical compounds by full or partial name or synonym, to sort the compounds by name, boiling point, melting point, or molecular weight, and the ability to transfer to any of the property estimation modules. In addition, the user can easily edit exiting values, add new values or export information to a text file or another database.

In addition to the physical properties, information describing the environmental persistence and toxicity of specific chemicals can also be entered into the database. Placeholders for biodegradation rates, hydrolysis rates, photolysis rates and LC50s, along with the appropriate references and comments have been incorporated into the database. This feature was added to the database after requests from test users, however at the time of this report no degradation or toxicity data has been entered into the database. The chemical property database is illustrated in Figures 13 and 14.

PEP Batch

PEP Batch provides users with a method for the convenient, unattended calculation of MCIs, TSA and UNIFAC activity coefficients and subsequent estimation of physical properties for large numbers of compounds via the PEP processor described earlier. Like the PEP Processor, PEP Batch is divided into MCI, TSA and UNIFAC modules. Each module, as illustrated in Figure 15 for the MCI module, requires the user to select the appropriate input file (i.e. SMILES string, connection table or 3-D atomic coordinates), choose to information to be sent to the output file (i.e. chemical name, SMILEs string, properties) and start the batch driver.

Chemical Pro	perty D	lata Base 📰	2 .
🔹 File Edit Go Find Sort Values	Print	Export (
2,2',6,6'-tetrachlarobiphenyl		View:	Structure
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Formula:NY:292 MP:°C BP:°C Synonyms:		$\langle \circ \rangle$	\rightarrow
	신 ()	CI	C1
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log/antilog Physical/Chemical Properties	Values	; Temp*C	units Ref
log Aqueous Solubility (S)			
log Octanol/Water Partition Coefficients (Kow)	5.936	25	. 🗨
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log Soil/Water Sorption Coefficient (oc-based) (Koc))	\ I	-
log Bioconcentration Factor (BCF)			
log Acid Dissociation (Ka)			

Figure 13 Example card from the Chemical Property Data Base

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Dhotohnia					-	\bigcirc
1009313						
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Biodegradation						0

Figure 14. PEP database degradation properties.



Figure 15. Example card for PEP Batch, MCI module.

The MCI and UNIFAC modules require the two-dimensional molecular structure of the chemical to be entered using either SMILES strings or connection tables.

To enter SMILES strings into the MCI or UNIFAC batch modules, you must create a text file containing name of the chemical and its corresponding SMILES strings in columns separated by tabs and hard returns at the end of each row. The text file can contain additional tab-delimited information, but the SMILES strings and chemical names must be in the first or second column. You indicate the column order when you select the type of input. The text file can be created with word processing or spreadsheet programs or you can also edit or create a file containing the SMILES strings and chemical names within PEP by selecting SMILES from the "input structure type" popup menu.

To input connection table files into the MCI or UNIFAC batch modules, you must first place them in a single folder. Select the "Connection tables" option from the "Select Input Type" popup button and choose the folder that contains the connection table files using the standard "open file" dialog box that appears. Highlighting any one of the files in the folder selects all of the files in that folder and allows you to view or delete specific files. The files can be any valid type for the MCI module as they will be converted if possible (see MCI module helps). After selecting the input files, click on the advance arrow located at the upper right of the card to advance to the next step.

The TSA batch module operates in the same manner as the MCI and UNIFAC modules except that the calculation of TSA requires the three-dimensional cartesian coordinates for each atom in the chemical of interest. The TSA batch module accepts Cartesian Coordinates or Alchemy files. Alchemy files contain both the two-dimensional chemical structure and the coordinates. This allows PEP to calculate the chemical's TSA and determine the most appropriate TSA-property relationship based on chemical class. From within the standard dialog box, you can click on any file in a folder to select all of the files in that folder. The files will then be displayed. You can also view or delete files.

Once the input files have been selected, the "output option" step becomes active. This allows the user to select the properties to be calculated and any additional information that is available (i.e. chemical name, SMILES string, MCIs, TSA, or UNIFAC activity coefficients) to be exported by to a tab-delimited text file.

After the output information is selected, the "Start Batch Driver" button becomes active. Clicking this button brings up the standard Macintosh "save file" dialog box that allows the user to specify the name of the data file to be exported by PEP batch and the location that the file will be sent.
SUMMARY

A microcomputer program for estimating physical/chemical properties of organic chemicals for use in environmental fate modeling has been described. The Property Estimation Program (PEP) and associated physical property database was developed using HyperCard for the Apple Macintosh series of computers. The PEP system utilizes both QSPRs and QPPRs to provide the user with several approaches to estimate S, Kow, Pv, H, Koc and BCF depending on the information available. While QPPRs have been used by both experts and non-experts for estimating properties, one of the major limitations in using QSPRs has been the difficulty in using the necessary software tools. The graphical interface and flow chart design of PEP leads the user through a series of logical steps designed to provide even non-experts with a economical, easy to use software system for property estimation. The structural information for the MCI and UNIFAC modules can be input using Simplified Molecular Input Line Entry System (SMILES) notation or connection tables generated from a commercially available two-dimensional drawing program. The TSA module accepts 3-D cartesian coordinates entered manually or directly reads coordinate files generated by molecular modeling software. For each property the user can select from either "universal" or class specific regression models. The program's built in intelligence helps the user choose the most appropriate QSPR based on the structure of the chemical of interest. In addition, sufficient statistical information is provided to allow the user to determine on the validity of the QSPRs and QPPRs utilized in PEP. Designed to make the program both practical and educational, on line documentation is provided not only for the operational characteristics of the program but also for the theory associated with the property estimation techniques.

The combination of the various property estimation methods, chemical property database, and simple environmental fate models provides users with a methodology for predicting the environmental distribution of an organic chemical in a multi-phase system requiring only the structure of the chemical of interest as input.

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- Frazier, J.D. 1990. Estimation of Chemical/Physical Properties Using Molecular Connectivity Indices for Application in Modeling the Environmental Fate of Organic Compounds. M.S.thesis, Utah State University.
- Holt, M. S. 1992. Microcomputer Program for the Estimation of Properties for Use in Environmental Fate and Transport Models. M.S.thesis, Utah State University.
- Denne, D. 1993 (expected completion, March 1993). Investigating the Relation Between Molecular Structure and Parameters Important in the Environmental Fate of Organic Chemicals. M.S.thesis Utah State University.
- Miles, R. 1993 (expected completion, May 1993). A simple and inexpensive method for measuring biodegradation rates in soil. M.S.thesis, Utah State University

LIST OF PAPERS/POSTERS PRESENTED AT PROFESSIONAL MEETINGS

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- Li, A., W.J. Doucette, A.W. Andren. 1992. UNIFAC estimation of environmental parameters for PCBs. Presented in a platform session at the 13th Annual SETAC meeting, November 8-12, Cincinnati, OH.
- Doucette, W. J. and M. S. Holt. 1992. PEP, a microcomputer program for estimating physical/chemical properties. Presented as a poster at the Fifth International Workshop on QSAR in Environmental Toxicology (QSAR 92), Duluth, MN (July 19-23):
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LIST OF GRADUATE STUDENTS ASSOCIATED WITH THE RESEARCH EFFORT

- Joe Frazier, M.S. 1990 Thesis title: Estimation of Chemical/Physical Properties Using Molecular Connectivity Indices for Application in Modeling the Environmental Fate of Organic Compounds.
- Mark Holt, M.S. 1992 Thesis title: Microcomputer Program For The Estimation Of Properties For Use In Environmental Fate And Transport Models
- Denne, D. J. expected March 1993. Tentative thesis title: Investigating the Relation Between Molecular Structure and Parameters Important in the Environmental Fate of Organic Chemicals. Utah State University.
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APPENDIX A

PEP Property Estimation Program and Chemical Property Database

PEP Property Estimation Program and Chemical Property Database

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DISCLAIMER

Utah State University and the authors of PEP make no warranties, either expressed or implied with respect to the operation or subsequent use of property values obtained through the use of PEP. In no event will Utah State University or the authors of PEP be liable for direct, indirect, or consequential damages resulting from the use of this software.

INTRODUCTION

Background

Mathematical models are often used by environmental scientists and engineers to estimate the fate and impact of organic chemicals in the environment. Use of these models requires a variety of parameters describing site and chemical characteristics. Aqueous solubility (S), the octanol/water partition coefficient (Kow), the organic carbon normalized soil/water sorption coefficient (Koc), vapor pressure (Pv), Henry's Law constant (H), and bioconcentration factor (BCF) are considered key properties used to assess the mobility and distribution of a organic chemical in environmental systems.

One major limitation to the use of environmental fate models has been the lack of suitable values for many of these properties. The scarcity of data, due mainly to the difficulty and cost involved in experimental determination of such properties for an increasing number of synthetic chemicals, has resulted in an increased reliance on the use of estimated values.

Quantitative Property-Property Relationships (QPPRs), based on the relationship between two properties as determined by regression analysis, are used to predict the property of interest from another more easily obtained property. Quantitative Structure-Property Relationships (QSPRs) often take the form of a correlation between a structurally derived parameter(s), such as molecular connectivity indices (MCIs) or total molecular surface area (TSA) and the property of interest.

Selection and application of the most appropriate QPPRs or QSPRs for a given compound is based on several factors including: the availability of required input, the methodology for calculating the necessary structural or topological information, the appropriateness of correlation to chemical of interest and an understanding of the mechanisms controlling the property being estimated.

Incorporation of QPPRs and QSPRs into a computer format is a logical and necessary step to gain full advantage of the methodologies for simplifying fate assessment.

PEP Overview

A Property Estimation Program (PEP), utilizing MCI-property, TSA-property and propertyproperty correlations and UNIFAC-derived activity coefficients, has been developed for the Apple Macintosh microcomputer to provide the user with several approaches to estimate S, Kow, Pv, H, Koc and BCF depending on the information available.

Structural information required for the MCI and UNIFAC calculation routines can be entered using either Simplified Molecular Identification and Line Entry System (SMILES) notation or connection tables generated with commercially available two-dimensional drawing programs. The TSA module accepts 3-D atomic coordinates entered manually or directly reads coordinate files generated by molecular modeling software. The program's built-in intelligence helps the user choose the most appropriate QSPR or QPPR based on the structure of the chemical of interest. In addition, the statistical information associated with each QSPR or QPPR in PEP can be displayed to help the user determine the model's validity. For the regression-based property estimation models, assessments of accuracy based on the 95% confidence interval and estimated precision of the experimental values are also provided along with the estimated property value.

PEP also provides a batch mode that provides users with a method for the convenient, unattended calculation of MCIs, TSA and UNIFAC activity coefficients and the subsequent estimation of physical properties for large numbers of compounds.

A chemical property database, containing experimental values of S, Kow, H, Pv, Koc, and BCF complied from a variety of literature sources and computerized databases was used for developing the MCI-property, TSA-property and property-property relationships used in PEP. This database, which currently contains over 800 chemicals, is linked directly to PEP.

The property estimation modules in PEP are also linked directly to the Level 1 and 2 Fugacity Models. The combination of the various property estimation methods, chemical property database, and simple environmental fate models provides users with a methodology for predicting the environmental distribution of an organic chemical in a multi-phase system requiring only the structure of the chemical of interest as input.

PEP was designed to be intuitive and user friendly. The easiest way to become familiar with the PEP is to try clicking on the buttons and pull down menus found on each card. Any comments or suggestions regarding improving the operation of PEP would be greatly appreciated by the authors.

• PEP Features

- Developed using Hypercard[™] for the Apple Macintosh series of personal computers
- Comprised of a chemical property database and four property estimation modules
- Uses standard Macintosh operations (buttons, menus, windows)
- Simple user interface based on flow chart design
- Four property estimation methods are available:
 - Molecular Connectivity Indices (MCIs)-property correlations
 - Total Surface Area Regressions (TSA)-property correlations
 - Property-Property Correlations
 - UNIFAC derived activity coefficients
- PEP can be used to estimate six chemical/physical properties
 - Solubility (S)
 - Octanol-water partition coefficients (Kow)
 - Henry's Law Constant (H)
 - Vapor Pressure (Pv)
 - Organic carbon normalized soil-water distribution coefficients (Koc)
 - Bioconcentration factors (BCF)
- Universal and class specific regression models are available
- PEP uses decision support for determination of chemical class.
- Estimates include 95% prediction interval for each regression based estimated value
- Statistical information readily available for each regression
- New regression models can be easily added
- Database contains over 800 chemicals having at least one property values
- Each chemical has at least one property and a two-dimensional SMILES string

• Chemicals in database can be search for by chemical name, CAS number, synonym, or selected from an alphabetized list

•Property estimation modules and property database are linked directly to the Fugacity Level 1 and 2 environmental fate models

- Published and on-line documentation
- Includes PEP tutorial

• Includes PEP Batch for estimating properties or calculating MCIs, TSA, or UNIFAC activity coefficients for large numbers of chemicals without continuous user input

• What Do I Need To Use PEP (i.e. Hardware requirements)?

- 1. Macintosh II computer or better with
- 2. 4,000 Kbytes (4 Megabytes) of usable hard disk space,
- 3. 3 Meg of RAM installed,
- 4. running system software 6.0.5 or higher, and
- 5. HyperCard 2.0 software or higher installed with the size allocated to 1500 MB.

• Installation of PEP

PEP is typically shipped on one 3.5 inch 1.44 Megabyte floppy disk. To install PEP:

1. Insert the PEP disk into the disk drive.

2. Drag the file PEP.sea to the hard drive that PEP is to be installed on. When the PEP.sea file has been copied to the hard drive you can eject the disk by dragging the "PEP" disk icon to the trash.

3. Double click on the icon of the "PEP sea" file. This will start the installation process by first creating a new folder called "PEP system" on the hard drive and then uncompacting five HyperCard stacks: (1) "Chemical Property Data Base", (2) "PEP Processor", (3) "PEP Help", (4) "PEP Models", and (5) "PEP Batch" (not necessarily in that order).

4. Drag the "PEP.sea" icon to the trash and remove it from your hard drive using the "empty the trash" command which can be found under the Special pull down menu located at the top of the screen.

The installation process is now complete. Test the installation by double clicking on the "PEP system" folder, then double clicking on the file "Chemical Property Data Base". If installation was successful the opening card of PEP will appear. If you have a problem with the installation please contact Mark Holt at (801)750-3916 or Bill Doucette at (801)750-3178. Note: PEP can also be sent on two 3.5 inch 800k floppy disks if requested.

General Programming Description

The PEP software system is a HyperCard[™] based program that runs on Apple Macintosh computers. HyperCard, which is bundled with most Macintosh computers sold, offers graphics, information storage, the means to display information in a variety of formats, the ability to establish links between related information, a high level language (HyperTalk), the ability to extend HyperTalk by writing new commands in a compiled language (i.e. C or Fortran) and a mechanism to transfer control to other Macintosh applications. The PEP system uses all these features.

HyperCard treats each screen full of information as a card and each set of related cards as a stack. Cards can contain fields for data and buttons for action procedures to operate on the data in the fields. This allows the standard Macintosh interface to be used without the direct use of the Macintosh toolbox routines, greatly simplifying programming. In order to create a user interface, the programmer simply draws, or creates the buttons or fields that are to be used. The link between buttons, fields and cards is done through HyperTalk. HyperTalk is an high–level, interpreted language used to establish links between related information and perform simple calculations within HyperCard. However, large repetitive tasks and complicated computations can be very slow if HyperTalk is used. HyperCard also allows the programmer to create extensions of HyperTalk in a lower level language. These extensions, called external functions (XFCN) and external commands (XCMD), greatly increase the speed of repetitive and calculation intensive algorithms over using HyperTalk itself and can also be used to implement custom Macintosh features such as popup menus and custom dialog boxes.

Starting the PEP Software System

If the installation of PEP (as described on the previous page) was successful, a new folder called "PEP system", containing five HyperCard stacks ("Chemical Property Data Base", "PEP Processor", "PEP Help", "PEP Models", and "PEP Batch"), should appear on your hard drive.

PEP is started from the Macintosh operating system by clicking twice (double clicking) on any one of the five stack icons, expect the PEP batch stack, shown in Figure 1. The five stacks must be in the same folder on a hard disk. This will open the PEP Processor stack and display the opening card shown in Figure 2. PEP can also be used by opening any HyperCard stack and then choosing "Open" from the "File" menu and selecting the "PEP Processor" stack.



Figure 1. PEP stack icons.



Figure 2. PEP opening screen.

Menus, Buttons and Icons

In Macintosh applications most cursor movements are accomplished by use of the mouse or trackball. Action buttons are operated by positioning the "hand" cursor over the button area and then depressing and releasing the mouse button. This is referred to as clicking. Popup and pull down type menus are operated by positioning the hand cursor over the button and then depressing and holding the mouse button. While holding down the mouse button move the cursor over the desired menu item and release (Note: on slower machines such as the Mac Plus, the menu selections may be slow to appear, but be patient, they will eventually show up.). Figure 3 shows the steps involved in using a menu for the selection of a command. The action of moving the mouse while holding down the mouse button is called dragging.



1. Menu Bar before the mouse is pressed

2. Menu Bar after the mouse is pressed

3. Menu Bar after the mouse is moved over the desired command but before the mouse button is released.

Figure 3. The steps for using a menu for command selection

The PEP software system is comprised of five HyperCard stacks that are linked together by various menus and buttons. The pull down menus, located at the top of each card and buttons positioned at various card locations allow the user to navigate through PEP.

The File and Edit menus at the top of each PEP card duplicate the general File and Edit menus in Hypercard (Please refer to the Hypercard manual for complete instructions.) The Go menu allows the user to move to the either of the four property estimation modules, the chemical property database, the fugacity model or the batch mode. In addition to the menu items found at the top of each PEP card, buttons, such as those displayed below, can be found on each of the various PEP cards. Figure 4 shows each button icon, its title and its action.

Icon	Title	Action
畿	PEP Icon	Shows Opening Screen of PEP
	Return Arrow	Takes you back to the card you were at prior to this one
?	Help	Shows Help for the current card
\mathcal{O}	Information	Shows general information
•	Eye	Shows the equations or statistics
	Book	Shows the reference
Kþ	First Card	Takes you to the opening card of HyperCard
Po	p Up Button	Lets the user choose from a popup menu list
80	tion Button	Initiated come patien or eplectation
		initiates some action of calculation

Figure 4. Buttons and icons used in PEP.

Tutorial

The "Click Here for Tutorial" button, accessible on the opening screen of PEP, takes the user to the opening screen of the tutorial. As shown in Figure 5, this screen takes the form of a flow chart depicting the overall design of PEP. Individual tutorials, available for the chemical property database and each of the four property estimation modules, can be activated by clicking on the appropriate button in the flow chart. Each tutorial automatically runs the chosen component of the PEP system while illustrating its operation in a step-by-step manner.



Figure 5. Opening screen of PEP tutorial (Flow chart illustrating overall design of PEP system).

REFERENCE SECTION

PEP Processor

The PEP Processor stack contains the algorithms for data input, calculations and output of the physical-chemical properties estimated using MCI-Property, TSA-Property, and Property-Property correlations and UNIFAC derived activity coefficients. The PEP Processor is divided into four modules, one module for each of these estimation methods.

The user interface for each module is designed as a flow chart consisting of a series of numbered steps or actions required to estimate the physical-chemical property(s) of interest. The steps are numbered sequentially from left to right and top down. Initially, all but the first step is dimmed. As the user completes the first step the next step will darken, indicating the appropriate progression. However, during any step a darkened, previously accomplished step can be redone or the selection changed. Figure 6 shows this progression of steps.



Figure 6. Example illustrating the use of the PEP Processor's flow chart interface.

MCI Module

Overview

The user interface of the MCI module, like the other property estimation modules in PEP, is designed in the form of a flow chart depicting the steps that must be completed in order to use the module. As illustrated in Figure 7 by the fully darkened MCI module card, the four steps that must be completed before the selected physical-chemical properties can be estimated using are: (1) input the necessary structural information for the chemical of interest using either SMILES notation or a connection file, (2) calculate and display the MCIs, (3) select the properties to estimate and (4) choose the most appropriate MCI-property regression model.



Figure 7. Screen display of PEP MCI module.

Entering Chemical Structure

Upon entering the MCI module, only the first step in the flow chart is active as indicated by its darkened status. The two dimensional molecular structure of the chemical of interest is needed to calculate the MCIs. You must first input the necessary structural information using either SMILES [33,34] notation or connection files before you can continue to the second step. Select either option from the "Input Structure" popup button.

If you select SMILES, two blank lines appear, one for the chemical name (optional) and one for the SMILES string. Once you have entered the SMILES string, click the "OK" button or the carriage return. The SMILES string must conform to the standard set by Anderson, Veith, and Weininger (1987) and Weininger (1988) with the following exceptions: a single bond connecting aromatic rings must be explicitly denoted by an "-", the SMILES string must be Hydrogen suppressed, and the SMILES string cannot contain any "{}" or "[]" qualifiers. SMILES is a chemical notation language specifically designed for computer use. It is a method of "unfolding" a 2D chemical structure into a single line of characters containing the structural information. For users unfamiliar with SMILES notation, a detailed description describing its use can be found in scrollable window directly below the SMILES string input line.

If a connection table is chosen as the input method, the standard Macintosh file selection dialog box, as shown in Figure 8, will be used to select the file. This requires that a connection table has already been created for the chemical of interest.



Figure 8. Standard Macintosh file selection dialog box.

Connection tables can be generated from commercially available, two-dimensional (2D) chemical drawing programs, such as ChemDrawTM, ChemintoshTM, or ISIS/DrawTM, that have the ability to save the structure as a connection table file. The connection table file must be formatted the same as a connection table from ChemDraw (1989). An example of a ChemDraw compatible connection table is shown in Figure 9.



Figure 9. Example connection table.

The first data line contains the title of the chemical or any other identifier. The second line consists of two numbers separated by a comma. The first number is the number of atoms in the connection table and the second is the number of connections described in the connection table. The remaining lines describe the type of atoms in the molecule and their location (atom information) and the atoms to which they are connected (connection information). The total number of lines depends on the number of atoms in the molecule and the number of connections.

Atom information is contained in four columns separated by one or more spaces. Columns one through three are the X,Y,Z coordinates of the atom (not used for calculation of MCIs) and column four contains the atom symbol (e.g. C, Cl, Br, N etc.). Connection information is contained in four columns of whole numbers. Columns one and two contain the atom numbers of the atoms that are connected (atoms are numbered consecutively), column three contains the bond type (1, 2, 3, or 4), and column four usually contains a 1 (not used). The bond type in column three can be either "1" for a single bond, "2" for a double bond, "3" for a triple bond, or "4" for an aromatic bond. (NOTE: The Macintosh compatible molecular modeling program, Alchemy IITM, generates files containing connection table information along with 3D atomic coordinates. To use alchemy files for input into the MCI module simply treat the alchemy file as a "ChemDraw Connection Table".)

As described in the next section, MCIs are calculated from the hydrogen suppressed structure of a chemical. Consequently, for the most efficient calculation of MCI, the connection tables created for input into the MCI module should be created from hydrogen suppressed structures. If the connection tables are not hydrogen suppressed PEP will automatically remove them. This can result in a significant increase in the time required to calculate the MCIs.

Calculating MCIs

As soon as the structure is entered, the second step becomes active. Clicking on the "Calc. MCIs" button starts the calculation of the MCIs. If the structure was entered as a SMILES string the "mciSmile" XFCN converts the SMILES string into the proper format for the "mcichi" XFCN which calculates the MCIs. Similarly, if a connection table was used for input the "mciConvert" XFCN converts the connection table into the proper format. The MCIs that are calculated are listed along with the variable names in Table 1. Once the MCIs have been calculated, they can be viewed, exported, or printed by using the "Display MCIs" button under the "Calc. MCIs" button.

MCI Title	Orders calculated
normal path	0 through 6
normal cluster	3 through 6
normal chain	3 through 6
normal path/cluster	4 through 6
bond path	0 through 6
bond cluster	3 through 6
bond chain	3 through 6
bond path/cluster	4 through 6
valence path	0 through 6
valence cluster	3 through 6
valence chain	3 through 6
valence path/cluster	4 through 6
delta valence path	0 through 6
	MCI Title normal path normal cluster normal cluster normal path/cluster bond path bond cluster bond chain bond path/cluster valence path valence cluster valence chain valence path/cluster delta valence path

Table 1. MCIs calculated by PEP.

How PEP calculates MCIs

To calculate the MCIs for a given compound, a delta (d) value are first assigned to each nonhydrogen atom in the structure. Three d values were computed in this study: normal, bond, and valence. Normal deltas are computed by summing the number of bonds (single, double, etc. are counted as one bond) connected to the atom whose delta is being calculated. The bond deltas are calculated the same as the normal deltas except the bonds were taken at their face value (single is one, double is two, etc.) instead of each bond being equal to one. Valence deltas for each atom are computed according to equations (1) and (2) (Kier and Hall, 1986):

$$\mathbf{d}_{\mathbf{V}} = \mathbf{Z}\mathbf{v} - \mathbf{h} \tag{1}$$

$$d_V = (Z_V - h)/(z - Z_V)$$
 (2)

where dv is the valence delta, Zv is the number of valence electrons in the atom, h is the number of hydrogen atoms bound to the atom, and Z is the atomic number of the atom. Equation (1) is used for those atoms in the first row of the periodic chart, and equation (2) is used for all other atoms.

Once the delta values have been calculated for each atom in the molecule, simple, bond and valence indices of different orders and types can be calculated. The order refers to the number of bonds in the skeletal substructure of fragment used in computing the index: zero order defines individual atoms, first order used individual bond lengths, second order uses two adjacent bond combinations, and so on. The type refers to the structural fragment (path, cluster, path/cluster or

chain) used in computing the index. A more detailed explanation of the calculation of MCIs can be found in Kier and Hall (1986).

The MCI calculation routine in PEP calculates simple, bond and valence indices of several types (path, cluster, chain, and path/cluster) and orders (0 through 6), if possible, for each molecule, resulting in a maximum of 54 index values for each molecule.

To account for non-dispersive force effects on aqueous solubility and solubility related properties zero through six order Δ valence path indices ($\Delta \chi$), as described by Bahnick and Doucette (1988), are calculated by PEP, in addition to the 54 indices described above. To calculate $\Delta \chi$ indices, a nonpolar equivalent is made by substituting C for O or N atoms. MCIs are calculated for the nonpolar equivalent and values for Δc can be computed for each type of index by:

$$\Delta \chi = (\chi)_{\rm np} - \chi \tag{3}$$

where $\Delta \chi$ is the delta index, $(\chi)_{np}$ is the index for the non-polar molecule and χ is the index for the original molecule.

Choosing the Properties

After the MCIs have been calculated, the third step becomes active. Select the property or properties you would like to estimate by clicking on the check box button next to it. You can simultaneously select all the properties by holding down the shift key and clicking any one of the property buttons.

Choosing the Regression Models and Chemical Classes

After the properties are selected, step four becomes active and the regression models available for each property are displayed in a popup menu. Two categories of MCI-property relationships are displayed for each property. The first category of MCIs property relationships, preceded with the word PEP, were developed in this project using the experimental values reported in the PEP property database. "Universal" MCI-property relationships were developed using all available experimental data for a given property regardless of chemical class. "Class-specific" MCI-property relationships were developed if property values were available for a sufficient number (10 or greater) of compounds within a particular chemical class (i.e. PCBs, PAHs, ureas). In addition, several multi-class MCI-property correlations were developed for more broad classes of compounds such as: halogenated aliphatics and halogenated aromatics. The second category of MCI-property relationships displayed for each property were obtained directly from the literature and are located below the PEP relationships, separated by a gray line, in the popup menu. By clicking the "book" found at the left of each literature MCI-property regression model, the coefficients r^2 value and the appropriate citation can be can be displayed

To illustrate the potential hierarchy of MCI-property relationships available to the user, an example for the predicting the vapor pressure (P_v) of a polychlorinated biphenyl (PCB) is provided below. The are three appropriate PEP-derived MCI-property relationships available to the user, one developed using only PCBs, one using halogenated aromatics including PCBs and one using all compound types:

 $\log Pv = 5.814 (nc5) - 2.428 (np3) + 9.479$ (PCBs) $\log Pv = -1.559 (bp1) + 6.622$ (Halogenated aromatics) $\log Pv = -1.275 (np3) + 5.261$ (Universal)

Generally, the use of a "class-specific" relationship, if available, should provide the best estimate (i.e. the estimate associated with the least amount of uncertainty). To automatically aid you in choosing the most appropriate MCI-property relationships, PEP looks in the SMILES string or connection file for groups of atoms and bonds that distinguish various chemical classes. The number of MCI-property relationships or chemical classes that are chosen by the program is determined by the number of different distinguishing subgroups that are found. For the example shown above, the most appropriate regression model, PCBs, would be made the default equation. The two other appropriate models, halogenated aromatics and Universal, would be denoted with a \blacklozenge in the popup menu. If the compound entered into PEP does not fit one of the class specific models the "Universal" equation is selected as the default. You may also choose to ignore the regression model chosen by PEP and select your own.

MCI-property regression models are available for the following "classes" of chemicals: Universal, Universal Nonionizable, Universal Ionizable, Alcohols, Arilines, Carbamates, Halogenated, Aliphatics, Nonhalogenated Aliphatics, Halogenated Aromatics, PCBs, PAHs, Phenols, Triazines, and Ureas. Examples of representative chemicals for each of the classes can be found in the View menu. To see the structures of the chemicals click on the class name. Not all of the classes listed above are implemented for each property. The models not available for the properties to be estimated are dimmed in the popup menu.

Statistics Cards

A summary of the regression statistics and list of compounds used to develop and evaluate each MCI-property relationship can be displayed by clicking the "eye" or "view statistics option" found at the left of each regression model. Information displayed on the statistics card includes: the MCI-property regression equation, the list of chemicals used in developing the regression model, the standard errors of the coefficients in the regression equation, the Analysis of Variance (ANOVA) table, the r^2 value, a graph of the the predicted vs. estimated values, a graph of the residuals vs. the predicted values, a graph of the residuals vs. the number of standard deviations, a normal probability plot of the residuals, the X'X inverse matrix and appropriate reference. An example of the statistical information provided for each MCI-property relationship is shown in Figure 10.



Figure 10. Statistics card associated with the MCI module.

The ANOVA table contains the degrees of freedom, the residual sum of squares, the residual mean square, and the variance ratio (F) for regression, residual and the total source of errors.

The X'X inverse matrix is used in PEP to calculate the prediction interval of an estimate. The matrix is derived by pre-multiplying the X matrix by its transpose and then inverting the result. The X matrix has a column for each variable in the regression equation and a row for each observation used to calculate the regression equation. Each row contains the value used for each of the variables in the regression equation. For example, if the regression equation is

Yj = b0 + b1Xj1 + b2Xj2

where j is 1 to the number of observations, Yj is the estimated values for each observation, bi are the regression coefficients, and the Xji are the values of the variables used then the X matrix is

1	X11	X12
1	X21	x22
:	:	:
:	:	:
1	Xj1	Xj2.

The resulting X'X inverse is a square matrix with the number of rows and columns equal to the number of variables in the regression equations.

If the QSPR or QPPR was taken from the literature only the input variables and the statistical information provided in the original reference is included.

Estimating the Properties and Viewing the Results

Click the "Est. Property" button to calculate the selected properties. The results card displays the estimated properties and their respective 95% prediction interval Note: 95% prediction intervals are not available for MCI-property relationships taking from the literature. You can return to the previous card by clicking on the "return" button at the upper right corner of the results card. The "Go" menu can be used to move to another module. You can compare the estimate property values with those contained in the "Chemical Property Database", if available, by clicking on the "Look in DB" button. Clicking this button activates a database "search by name" routine. The name on the results card must match exactly the name in the database for the search routine to find the compound. If a property value is not found an NA will be displayed.

Adding or Deleting MCI-Property Regression Models

Additional MCI-projectly regression models can be added to the PEP MCI module through the statistics cards. Choosing the "New Stat. Card" option from the "Misc." menu of a statistics cards

while the type of statistics card that is to be added is the current card The statistics for a new regression equation can be added to PEP b. First the new card must be titled. This title will be used in the popup menus and on the results card. The first 28 characters of the title must be unique. The second step is to enter the regression equation. The user will be prompted for the number of terms in the equation, then prompted for each coefficient and the associated variable with the dialog box shown in Figure 11. The variables which are available for that type of statistics card will be in a popup menu for easy, consistent selection.

Choose MCI and Input Coefficient
Choose MCI : vp0
Coefficient: -2.3
Cancel OK

Figure 11. Example dialog box for the input of new MCI-property relationships

A relationship can easily be deleted from PEP by first making that statistic card the current card, and then choosing "Del. Stat. Card" from the "Misc." menu. The user will be prompted to confirm the deletion and then the regression list will be rebuilt.

Limitations of MCI-Property Regression Models

Selection of the most appropriate MCI-property relationship depends on the structure of a particular chemical of interest, knowledge of the mechanism of the process, and the extent of the database used to develop the MCI-property relationship. For example, some MCI-property relationships are broader than others in the range of chemicals that are covered, and some have been established with a better understanding of the mechanisms or properties involved.

One problem that has limited the widespread acceptance of MCI-property correlations is that the actual physical meaning associated with the individual indices is not well understood. Frazier
(1990) and Doucette and Holt (1991), however, have shown a strong correlation between calculated molecular surface area and several MCIs for a variety of organic chemicals. MCI-property correlations tend to be class specific and thus are highly dependent on the type and range of compounds that were used to derive a particular correlation. Indiscriminate use of such models without an examination of number and type of compounds used to develop the model can result in considerable error.

TSA Module

Overview

As shown in Figure 12, the TSA module is similar in design to the MCI module. However, unlike molecular connectivity, the calculation of TSA requires information describing the geometry of the molecule in terms of its 3-D atomic coordinates.

1

		PEP Processor		2
🔹 File Edit Go	Print V	iew		
		ТСА		
				naniinii aniiiiiii
Chemical Name: <u>2,2',6,</u> SMILES String:	6'-tetracl	nlorobiphenyl		
	3. Choose Prop.	4. Choose Regression	<u> </u>	
	⊠s	РСВз	۱	
	🛛 Kow	PCBs	۱	5. Estimate
Structure TSAs	🛛 Pu	PCB3	۱	Properties
	ЮH	Halogenated Aromatics	۱	(")
Edit van	🛛 Koc	Halogenated Aromatics	، ک	
Radii display TSAs	🛛 BCF	Universal	۱	

Figure 12. TSA module card from PEP

Three-dimensional coordinates can be obtained from X-ray crystallography data or from molecular modeling. Alchemy from Tripos Associates (1989) and Chem3D+ from Cambridge Scientific (1989) are examples of Macintosh compatible molecular modeling software that allows the user to draw a chemical structure, energy minimize the structure, and produce a file containing the three-dimensional coordinates. The TSA module is also designed to accept files generated by other hardware/software combinations including UNIX or VAX versions of CONCORD (Tripos

Associates, Inc., 1990), a hybrid expert system and molecular modeling software designed for the rapid generation of high quality approximate 3-D molecular structures.

Entering the Structural Information

To estimate properties using the TSA module, you must first input the necessary structural information by using one of the three options available under the popup menu titled "Input Structure": (1) Alchemy file, (2) cartesian coordinates file, or (3) manually entered cartesian coordinates. The preferred method of structural input is via Alchemy files because they contain both the three-dimensional structure and the connection information. This information allows PEP to calculate the chemical's TSA and determine the most appropriate TSA-property relationship based on chemical class. Therefore, if an Alchemy file is chosen for the input then only the file selection dialog box will be presented for selection of the file. However, if ether of the cartesian coordinate options are selected for input, both the standard file selection dialog box will be presented.

The format of an Alchemy file, shown in Figure 13, is similar to that of a ChemDraw connection table discussed previously. The first line of an Alchemy file contains the number of atoms followed by "ATOMS," the number of bonds followed by "BONDS," the number of charges followed by "CHARGES," and then the title of the file. The next set of lines contains six columns of information for each atom in the molecule including the hydrogen atoms. Column one contains the atom numbers, column two contains the atomic symbols, and columns three through five contain the X,Y,Z coordinates of the atom. The set of lines describing the atoms is followed by a series of lines containing four columns describing the bonds. The first column contains the bond number, the second and third columns contain the atom numbers of the two atoms connected, and the fourth column contains the type of bond either "SINGLE," "DOUBLE," "TRIPLE," or "AROMATIC."



Figure 13. Example Alchemy file.

PEP accepts cartesian coordinates files having the following format. The file has one header line indicating the number of atoms in the molecule. The rest of the lines in the file describe each atom in the molecule. Only the first five columns of each line are used. Column one contains the atom symbols, column two contains the atom numbers, and columns two through five contain the X,Y,Z coordinates of the atom. An example cartesian coordinates file is shown in Figure 14.

umber Atoms	Ato Sym	bols Numbers	X Y Z coord	dinates	Not use	d
6 Cl	1	1.658981	1.412048	0.220383	12	2
С	2	0.678864	0.010635	0.004303	2	1
С	3	0.661346	0.015198	0.109131	2	2
CI	4	1.498978	1.476791	0.333939	12	3
CI	5	1.607437	1.456451	0.031769	12	3
Н	6	1.277542	0.912277	0.055084	5	2

Figure 14. Example Cartesian coordinate file.

If the option to manually enter the coordinates is chosen then a card is presented, as shown in Figure 14, that allows the coordinates and atom symbol of each atom to be entered individually from the keyboard. The X,Y,Z, coordinate values and atom symbols for each atom in the molecule are entered in the appropriate labeled boxes one at a time. After the information for each line is correctly entered the "Line OK" button is clicked. This enters the information into the scrollable window below. This process is repeated for each atom in the molecule. When all the atoms have been entered clicking the "Done" button will send the structural information to the TSA module.

🗲 File Edit (Go Print	Misc.		?
Enter	XYZ coo	<u>rdinates</u>	s for the	chemical
Chemical Name: B	enzene	*******		
Fill in one atom it into the table. "All Done" when	at a time at . To Edit an . the table is	the bottom entry click o complete.	, type Return on the line in	or Tab to put the table. Click
Atom Symbol	X coord	Y coord	Z coord	
2 C				Line OK
1 C 1 1 1			<u>+</u> 	Clear Cancel All Done

Figure 15. Example card for the entry of atomic coordinates.

Calculating Total Surface Area (TSA)

In addition to the 3-D molecular structure, the user must also input van der Waals radii for each of the atoms before the TSA of the molecule can be calculated. PEP automatically enters a van der Waals radius for each atom using values from Pauling (1960). However, when the "Calc. TSA" button is clicked the user has the opportunity to edit the van der Waals radii using the dialog box shown in Figure 16.



Figure 16. Dialog box for editing van der Waal radii.

This dialog box also contains a place to enter a solvent radius. If it is left at "0.0" then the total surface area will be calculated. Some relationships from the literature require the solvent accessible surface area to be calculated. If this is the case, the desired solvent radius can be entered.

Once the molecular geometry and the van der Waal radii are input, the "Calc. TSA" button becomes active and TSA can be calculated using a XFCN that was adapted from the SALVO2 algorithm developed by Pearlman (1980). This algorithm represents each atom of a molecule by a sphere centered at the equilibrium position of the nucleus. The radius of the sphere is equal to that of the van der Waals radius. Planes of intersection between spheres are used to estimate the contribution to surface area from the individual atoms or groups. The program computes the surface area of individual atoms or group by numerical integration, and the overlap due to intersecting spheres is excluded from the calculation. TSA is calculated by the summation of individual group contributions. These areas are then imported to the "TSAs" card shown in Figure 17.

*	File	Edit Go	Print M	lisc.			<u>。</u> (1)
				TSAs			
Che	Chemical Name: Benzene.Alc						
TS	As Ca	culated	with 0.0	Solvent	radius		Using a 0.0
ato:	m sym.	isolated area	accessible area	isolated volume	accessibl volume	e	total area (A ²)
1 2 3 4 5 6	ArC ArC ArC ArC ArC ArC	36.317 36.317 36.317 36.317 36.317 36.317 36.317	15.391 15.397 15.382 15.394 15.390 15.394	20.580 20.580 20.580 20.580 20.580 20.580	12.027 12.028 12.023 12.027 12.027 12.026	수	92.348 total volume (Å ³) 72.158 Not Using a 0.0 Solvent Radius total area (Å ²) Not Calc.
N	-TSA	0-TSA	P-TSA	S-TSA	ArN-TS	ja ja	Not Calc.

Figure 17. Example TSA card.

To quantify the surface area attributed to the polar portions of the molecule the surface areas of nitrogen, oxygen, phosphorous, sulfur, and aromatic nitrogen atoms are individually separated from the TSA and placed on the "TSAs" card. A more detailed description of the TSA calculation method is provided by Pearlman (1980).

Choosing the Most Appropriate TSA-Property Regression Model

After the TSA has been calculated, you can display the values and/or choose the properties of interest and a corresponding regression model using the same approach described in the MCI module. As discussed previously, "class-specific" regression models generally yield estimates associated with the least amount of uncertainty. If an Alchemy file is used to enter the 3D structure information or if a SMILES string or connection file is entered along with the cartesian coordinates, the decision support system in PEP will choose the most appropriate TSA-property regression model(s) as described in the MCI module. The most appropriate regression model will be made the default and a \blacklozenge will be place next to the other appropriate class name in the popup menu containing a list of the regressions. If no class specific regression models are available, the

"Universal" equation will be made the default. The operation of the TSA module from this point on is identical to that of the MCI module. Note: for solid solutes the melting point is needed to estimate the solubility. When the "S" button is clicked, the user is prompted with a dialog box to enter the melting point. Because the solubility will be estimated at 25° C, only if the melting point is above 25° C (solid solute) will the value be required. If the melting point is below 25° C it is set equal to 25° C. At this time only the " $\leq 25^{\circ}$ C" and "known" options are useable in the dialog box.

TSA-property regression models available within PEP are: Universal, Universal Nonionizable, Universal Ionizable, Alcohols, Anilines, Carbamates halogenated Aliphatics, Nonhalogenated Aliphatic, Halogenate Aromatics, Nonhalogenated Aliphatic, Halogenate Aromatics, PCBs, PAHs, Phenols, Triazine, and Ureas. Not all models are available for each property. The models not available for the properties to be estimated are dimmed in the popup menu. You can also view the statistical information associated with each model by clicking on the "eye" next to the regression equation.

Estimating the Properties

After the appropriate TSA-property relationships have been selected you can now click on the "Estimate Property" button to calculate the estimated properties. The estimated properties and their respective 95% prediction interval will be displayed on the results card. Return from the results card by clicking on the "Return arrow" button at the upper right hand corner of the results card. Use the "Go" menu to move to another module. View values in the Chemical Property Database by clicking on the "Look in DB" button. If a property value is not available in the database, an NA will be displayed in the property field.

Development of TSA-Property Relationships

The PEP TSA-Property relationships that were were developed using stepwise regression techniques and the data in the Chemical Physical Data Base. The stepwise regression was stopped when the coefficient of determination did not improve by at least 0.05 when the next variable was added.

For compounds containing polar functional groups, the addition partial TSA terms (i.e. nitrogen (N-TSA), oxygen (O-TSA), aromatic nitrogen (ArN-TSA), sulfur (S-TSA), or phosphorous (P-TSA)) significantly improved the TSA-property regression models. To view the regression information by clicking on the "eye" next to the regression title on the results card or on the TSA card.

Limitations of TSA-Property Relationships

A major factor in the solubilitzation process is the energy required to create a cavity in the solvent into which the solute is placed. The energy needed for the hole formation is considered to be proportional to the surface area of the solute. TSA has been found to be linearly related to the logarithm of solubility for many classes of non-ionizable organic chemicals.

As with the MCI module, selection of the most appropriate TSA-property relationship depends on the structure of a particular chemical of interest, knowledge of the mechanism of the process, and the extent of the database used to develop the TSA-property relationship. Some TSA-property relationships are broader than others in the range of chemicals that are covered and some have been established with a better understanding of the mechanisms or properties involved.

UNIFAC Module

Overview

The UNIFAC (UNIQUAC Functional Group Activity Coefficient) group contribution method for calculating activity coefficients, as described by Grain (1990), is implemented using both HyperTalk and an XFCN. The functional group interaction parameters, presented by Gmehling et al. (1982) and derived from vapor-liquid equilibria (VLE), are used in the calculation routine but can be changed by the user. After the activity coefficients are calculated they can be displayed along with relevant intermediate values and used to estimate S and K_{OW} by the following expressions (Arbuckle, 1986):

$$K_{OW} = 0.115 \,\gamma \infty w \,/\gamma \infty 0 \tag{2}$$

$$S (mol/L) = 55.6 / \gamma \infty w$$
(3)

where $\gamma^{\infty W}$ is the activity coefficient of the chemical infinitely dilute in water and $\gamma^{\circ \circ 0}$ is the activity coefficient of the chemical infinitely dilute in octanol.

The operation of the UNIFAC module, illustrated in Figure 18, is considerably different than the correlation modules previously described. To use the UNIFAC module the you must input structural information, calculate the activity coefficients, choose then choose the properties to be estimated. Currently the only properties that can be directly estimated using the UNIFAC module are S and K_{OW} .



Figure 18. Example card from the PEP UNIFAC module.

Entering Structural Information

Calculation of activity coefficients via the UNIFAC approach requires that the user input the valid UNIFAC groups that make up the chemical of interest and the number of each group present. PEP provides the user with three options for entering the appropriate UNIFAC groups using the popup menu under the button titled "Input Structure": (1) hand selecting the groups from a list in HyperCard, (2) using a connection table, and (3) using SMILES.

If the connection table option is chosen, a the standard file selection dialog box is presented where the user can select the desired connection table file. The "Struct" XFCN then uses the connection information to dissect the molecule into its UNIFAC groups.

If SMILES is chosen as the input method, the user is then prompted to input the chemical name and the SMILES string. The Struct XFCN uses the connection information contained in the SMILES string to build the UNIFAC input string. When the user chooses to hand select the UNIFAC groups, a card is displayed showing the first 37 groups as shown in Figure 19.

Main Groups				
(1) ⁻ CH ₂ ⁻	(4) "ACCH ₂ "	(10) (CHD	(15) CNH	
О СНЗ	O ACCH3	(11)*******	O CH3NH	
O CH2	○ ACCH2	O CH3C00	○ CHNH	
О СН	O ACCH	○ CH2C00	⊖ CH2NH	
00	(5) () 0H	(12)) HCOO		
(2) ⁻ C=C ⁻ ○ CH2=CH	(6) — CH30H	(13) °CH ₂ 0 °	(16)"(C) ₃ N"	More
O CH=CH	(7) O H20	○ снзо	⊖ CH2N	
⊖ CH2=C		○ СН20	O CH3N	DONE
O CH=C		🔿 СН-0		
O C=C	(9) -CH_CO-	○ FCH20	(17) O ACNH2	?
(3) "ACH" (3) 6 ACH	○ CH3C0 ○ CH2C0	(14) CNH ₂ \bigcirc CH3NH2 \bigcirc CH3NH2		

Figure 19. UNIFAC module card used to select UNIFAC groups.

This card is connected to two other similar cards showing the rest of the available groups. To select a group, the user clicks on the group symbol and a dialog box will then appear to enable the user to input the number of this group that is in the molecule. The user then continues to select groups until all the groups that are in the molecule have been selected. When the user clicks the "Done" button the UNIFAC input string is built and returned to the UNIFAC card. In addition, for users familiar with the UNIFAC approach, the appropriate subgroups can also be entered directly by simply typing the number of a group followed by a space then the symbol of the group for each group in the chemical.

The final form of the input is "# group # group". The # represents the number of the functional group in the molecule, the group is the group symbol of the functional group. For example the UNIFAC input string for Toluene is "5 ACH 1 ACCH3", meaning five aromatic carbons with one hydrogen atom (5 ACH) and one aromatic carbon connected to a methyl group (1

ACCH3). The UNIFAC groups available to PEP are shown in Table 2. Remember UNIFAC subgroups may not be available for every compound. In these cases the activity coefficient can not be calculated using the UNIFAC.

Group Name	Group Symbol	Group Name	Group Symbol
CH2	CH3 CH2	CCN	CH3CN CH2CN
C=C	CH CH2=CH CH=CH CH2=C	CCI	COOH HCOOH CH2CI CHCI
ACH	ACH	CCl2	CH2Cl2 CHCl2
ACCH2	ACCH3 ACCH2 ACCH	CCl3	CHCl3 CCl3 CCl2
OH CH3OH H2O ACOH CH2CO	OH CH3OH H2O ACOH CH3CO	CC14 ACC1 CNO2	CCI4 ACCI CH3NO2 CH2NO2 CH2NO2
CHO CCOO	CH2CO CH0 CH3CO	ACNO2 CS2 CH3SH	ACNO2 CS2 CH3SH
HCOO CH2O	CH2COO HCOO CH30 CH20 CH-O ECH20	Furfural DOH I Br	CH2SH Furfural (CH2OH)2 I Br CH=C
CNH2	CJ ¹ ^NH2 C ₁ .2NH2	C≈C DMSO	C≈C DMSO
CNH	CHNH2 CH3NH CH2NH CHNH	ACRY CICC ACF DME	ACRY Cl-(C=C) ACF
(C)3N	CH3N CH2N	CF2	DMF-2 CF3
ACHN2 Pyridine	ACHN2 C5H5N C5H4N C5H3N		CF2 CF

Table 2. UNIFAC groups

Calculate Activity Coefficients

After the functional groups are chosen, the activity coefficients can be calculated using the procedure described by Grain (1990) by clicking on the "Calc. Activity Coefficients" button. Once the activity coefficients have been calculated they can be displayed, along with values from several intermediate steps, by clicking on the "Display Act. Coeff." button. The equations used to calculate the activity coefficients can also be displayed by clicking the "balloon" on the "UNIFAC Calculations" card.

Editing Parameters

The UNIFAC group values can be edited by clicking on the "Edit Parameters" button. This will take you to an Index card containing a button for each group. To edit the value for that group, click on the corresponding group button. To edit the Q and R values, click on the left arrow at the bottom of the index card.

Estimating Properties

To estimate S and/or K_{OW} click on the "Estimate Properties" button. Clicking the "eye" next to the property will display the equations used to estimate S or K_{OW} . The results will be reported on the results card.

Limitations of UNIFAC Approach to Estimating S and Kow

The use of UNIFAC is limited to chemicals that have subgroups contained in a UNIFAC data base. If a chemical has subgroups for which no UNIFAC values are available, the activity coefficients cannot be calculated and, therefore, the properties cannot be estimated. In addition, it has been observed that the errors associated with estimating S and K_{OW} via the UNIFAC approach tend to increase as the compound becomes less solubility (larger K_{OW}). Correction factors have been presented in the literature to correct for this tendency.

Property/Property Module

Overview

Quantitative Property-Property Relationships (QPPRs), based on the relationship between two properties as determined by regression analysis, are used to predict the property of interest from another more easily obtained property without a specific concern for molecular structure. Frequently, the regression expressions are expressed in terms of the log of the two properties.

The operation of the Property-Property correlation module, illustrated in Figure 20, is considerably different than the other modules because the choice of the regression models used for the property estimation determines the required inputs.



Figure 20. Example card from PEP property-property module.

Selecting the Properties to be Estimated

Since the input for the Property/Property module depends on the properties to be estimated and the regression models used, the user must first select the properties to be estimated and the regression equations to be used before any input values are requested. The program keeps track of the properties required and provides the appropriate input fields. If available, the required properties can be imported directly from the associated chemical property database. Currently property-property relationships for the estimation of S, Kow, Koc, and BCF are available and will darken as the properties are selected.

Choosing the Property-Property Regression Model

The most appropriate model to use in estimating the property of interest depends on the class of the chemical and what property-property relationships are available. The property-property relationships that are available in PEP are divided into two general categories; regressions developed using data from the PEP Chemical Physical Data Base and regressions obtained from the literature. The two categories are separated by a grey line in the popup menu. To choose the property-property model, use the popup menu directly under the current regression by holding the mouse button down while over the title of the current regression. The "eye" icon to the right of the regression title will display the regression equation and statistics associated with the current relationship. The "book" icon will show the reference for the current regression if the regression is from the literature.

Viewing the Calculated Values

Once the properties and the relationships are chosen, the properties required for input need to be entered. The properties that are required are shown on the right side of the card with a line next to the symbol. The values can be retrieved from the PEP Chemical Property Database by making sure the property name is correct and clicking on the "Look in Prop. DB" button. The current units of the inputs will be shown if appropriate, and will be changed as needed by PEP for the different regression equations.

When the "Estimate Properties button is clicked the properties that were input will be used along with the chosen regression equations to estimate the selected properties. If the values for the input properties have not been entered on the Property-Property card the user will be prompted to supply the required values. The property estimates along with the calculated 95% prediction interval, if the statistical information is available, will be placed on the Results card.

Limitations of the Property/Property Module

One major limitation to the use of property/property relationships is the lack of suitable property values required for input into the regression models. For many new chemicals, no physical/chemical property information is available. In addition, the quality of the propertyproperty regression model depends on the extent of the database used to develop the relationship. For example, some property-property models are broader than others in the type and number of compounds used in its development.

PEP BATCH

Overview

PEP Batch provides users with a method for the convenient, unattended calculation of MCIs, TSA and UNIFAC activity coefficients and subsequent estimation of physical properties for large numbers of compounds via the PEP processor described earlier. Like the PEP Processor, PEP Batch is divided into MCI, TSA and UNIFAC modules. Each module, as illustrated in Figure 21 for the MCI module, requires the user to select the appropriate input file (i.e. SMILES string, connection table or 3-D atomic coordinates), choose to information to be sent to the output file (i.e. chemical name, SMILEs string, properties) and start the batch driver.



Figure 21. Example card for PEP Batch, MCI module.

Input Structure

The MCI and UNIFAC modules require the two-dimensional molecular structure of the chemical to be entered using either SMILES strings or connection tables.

To enter SMILES strings into the MCI or UNIFAC batch modules, you must create a text file containing name of the chemical and its corresponding SMILES strings in columns separated by tabs and hard returns at the end of each row. The text file can contain additional tab-delimited information, but the SMILES strings and chemical names must be in the first or second column. When you select the SMILES input option, you must indicate the column order on the "Explain SMILES file card shown in Figure 22. The text file can be created with word processing or spreadsheet programs or you can also edit or create a file containing the SMILES strings and chemical names within PEP by selecting SMILES from the "input structure type" pulldown menu.

	PEP Bat	ch En and Ch	<u> </u>
🔹 File Edit Go	Print Batch	<u>& "</u>	\Box
	Explain SMI	ES file	an ga tag ta ta
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View File Contents			
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Figure 22. PEP Batch, explain SMILES file card.

To input connection table files into the MCI or UNIFAC batch modules, you must first place them in a single folder. Select the "Connection tables" option from the "Select Input Type" popup button and choose the folder that contains the connection table files using the standard "open file" dialog box that appears. Highlighting any one of the files in the folder selects all of the files in that folder and allows you to view or delete specific files. The files can be any valid type for the MCI module as they will be converted if possible (see MCI module helps). After selecting the input files, click on the advance arrow located at the upper right of the card to advance to the next step.

The TSA batch module operates in the same manner as the MCI and UNIFAC modules except that the calculation of TSA requires the three-dimensional cartesian coordinates for each atom in the chemical of interest. The TSA batch module accepts Cartesian Coordinates or Alchemy files. Alchemy files contain both the two-dimensional chemical structure and the coordinates. This allows PEP to calculate the chemical's TSA and determine the most appropriate TSA-property relationship based on chemical class. From within the standard dialog box, you can click on any file in a folder to select all of the files in that folder. The files will then be displayed. You can also view or delete files.

Output Options

Once the input files have been selected, the "output option" step becomes active. This allows the user to select the properties to be calculated and any additional information that is available (i.e. chemical name, SMILES string, MCIs, TSA, or UNIFAC activity coefficients) to be exported by to a tab-delimited text file.

Start Batch Driver

After the output information is selected, the "Start Batch Driver" button becomes active. Clicking this button brings up the standard Macintosh "save file" dialog box that allows the user to specify the name of the data file to be exported by PEP batch and the location that the file will be saved.

CHEMICAL PROPERTY DATABASE

Overview

Experimentally determined physical property data for about 800 compounds, having at least one value of aqueous solubility (S), octanol/water partition coefficient (Kow), vapor pressure (Pv), organic carbon normalized soil sorption coefficient (Koc), bioconcentration factor (BCF), or Henry's law constant (H), was complied from a variety of literature sources and computerized databases. Using this information, a chemical property database was constructed using HyperCard[™] and subsequently used for developing MCI-property, TSA-property and propertyproperty relationships. In addition to the properties listed above, the database includes the following information: compound name and synonyms, a diagram of the 2-D chemical structure, SMILES notation, uses, CAS number, chemical formula, molecular weight (MW), boiling point (BP), melting point (MP), and appropriate references for each value. A built-in unit conversion utility enables users to quickly view property values in a variety of commonly used units. The database is directly connected to the PEP Processor stack.

The Chemical Property Database also provides the means for the user to search for chemical compounds by full or partial name or synonym, to sort the compounds by name, boiling point, melting point, or molecular weight, and the ability to transfer to any of the property estimation modules. In addition, the user can easily edit exiting values, add new values or export information to a text file or another database.

In addition to the physical properties, information describing the environmental persistence and toxicity of specific chemicals can also be entered into the database. Placeholders for biodegradation rates, hydrolysis rates, photolysis rates and LC50s, along with the appropriate references and comments have been incorporated into the database. This feature was added to the database after requests from test users, however currently no degradation or toxicity data has been entered into the database. The chemical property database is illustrated in Figures 23 and 24.



Figure 23 Example card from the Chemical Property Data Base



Figure 24. PEP database degradation properties.

Searching for Chemical Compounds in PEP's Database

Chemicals in the database can be found by full chemical name, partial chemical name, synonyms, or CAS number searches, or by selecting the chemical from a current list of compounds. The user selects the desired option from the "Find" menu.

Searching or Finding by either chemical name, partial chemical name, synonyms or CAS number is done using the finding tools built into HyperCard. When the finding option is chosen a standard dialog box is used to input the string that is to be found. Finding by full chemical name or CAS number requires that the entire contents of the appropriate field match the string of characters that was entered. Finding by partial chemical name or synonym requires that all of the string that was entered be present in the appropriate field.

The select from list option allows the user to select a compound from the current list of chemical names. The chemical names appear alphabetically sorted in a dialog box. Typing the first letter or number of the chemical will scroll the list to the first chemical starting with that character. The chemical card is located and displayed by clicking twice on the same chemical name or selecting the chemical name and then clicking the "Go There" button.

Sorting the Database

The "Sort" menu at the top of the card allows you to sort the database by name, melting point (MP), boiling point (BP), or molecular weight (MW). NOTE: the alphabetic sort function built into HyperCard places all chemicals with numbers preceding the letters in the chemical name before those chemicals having only letters in the chemical name. For example, after sorting by name, 1-octanol would come before acetone and 2-octanol, but after 1-decanol.

Adding or Deleting Data

New chemicals may be added to the data base by choosing "Add new card" option from the Values menu. The user will then be prompted for the chemical name, CAS number, molecular formula, melting point, boiling point, molecular weight, and the SMILES string.

Additional values for melting point, boiling point, S, K_{OW} , P_V , H, K_{OC} , BCF, and K_a can be added to a chemical already in the database using the "Add value" option accessed from the Value menu. As each new value is entered the user is prompted for the reference. The reference can be an existing reference or the user can add a new reference. If a new reference is to be added, the user will be prompted for the author, year, title, publication, volume, issue, and the page numbers. The user will also be given a chance to edit the new reference.

An entire card or specific values contained on a card can be deleted by choosing the appropriate item from the Value menu. A reference can also be deleted if it was entered incorrectly. The data will not be deleted until the user verifies the request through a standard dialog box.

Printing Information From the Database

The user can print the current card, or a series of cards using the print features built into HyperCard. To print a series of cards, first the user must select that option from the "Print" menu. Then while each card that is to be printed is the currently displayed card, the select "Print this card" option from the print menu must be chosen. When the desired cards have been printed, the user then selects "Stop printing" from the "Print" menu. The user can also print a list of all the references contained in the PEP data base.

Exporting Information From the Database

Information in the database can either be exported as text in a line or as a spreadsheet format using the "Export" menu. If the line format option is used, the data will appear with each data field on a line and each chemical separated by a solid line. This option is most appropriate if a word processor will be used to print or manipulate the exported data. If the spreadsheet format is used the data will be put in columns delimited by a tab.

Moving to Other PEP Modules

The "Go" menu at the top of the card allows you to move to any PEP module. To use the Go option, move the pointer to Go menu at the top of the card. Hold the pointer down on the button until the selections appear. Then move the pointer until the selection of choice is highlighted and release the mouse button.

Changing the Units of Measurement

The popup menu under each property's units allows you to change the units for solubility, Henry's law, and vapor pressure. All values of the property will be changed to reflect the new units.

PEP Models

Overview

To illustrate the practical application of PEP, an additional stack called PEP Models was developed. This stack, which contains the algorithms for the Level 1 and 2 Fugacity Models (Mackay, 1980), is linked directly to the the PEP Processor, but can also be used independently. The Level 1 Fugacity Model considers a unit world consisting of six compartments: air, water, soil, suspended solids, sediment, and biota (as shown in Figure 25).



Figure 25. Representation of Fugacity Level 1 compartments.

The model predicts the equilibrium concentrations of the chemical of interest in each compartment using the fugacity approach described by Mackay (1980). The model requires the input of K_{OC} , H and BCF which can be read directly from the PEP processor or the PEP chemical property database, if available. In addition to the chemical specific properties, the density and volume of each compartment must be specified along with the organic carbon content of the soil, sediment and suspended sediment. An editable set of default values for compartment density, volume and organic carbon content, as shown in Figure 26.

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Figure 26. PEP Models card, input for Fugacity Level 1

The Level 2 Fugacity Model allows for the chemical of interest to degrade in each compartment, move by advection through the water and air phases, and be emitted into the unit world. The rate values for each of these processes must be entered by the user. The degradation rates for each compartment can be entered either by t1/2 values in hours or by first order reaction rate constants in 1/hours, as shown in Figure 27. The advection rate data can be entered either by residence time or flow rate and the concentration or by directly entering the mass flow rate in moles per hour. The emission rate is entered in the units of moles per hour.



Figure 27. PEP Models card, input for Fugacity Level 2

Input Property Values

To calculate the environmental distribution of a chemical the user must enter the several physical-chemical properties along with the size and densities of each compartment. The physical-chemical properties that are need to be input for the six compartment unit world are Koc, H, and BCF. However, in step 2 the user may choose to eliminate one or more compartments to simplify the model cr to more closely examine the distribution of a chemical in a sub-environment such as the hypolimnion of a lake (i.e., water, air, biota). This would eliminate the need for a value for Koc. PEP determines which physical-chemical property values are needed depending on the unit world which the user has defined. The chemical-physical properties that are not needed will be dimmed.

When available, experimental values are preferred over estimated values in environmental fate modeling. Experimental values for the physical-chemical properties can be searched for in the Chemical Property Data Base by using the "Look for Values in Prop.DB" option. When clicked, a

full chemical name search is initiated, and if the chemical is found, the values of the three properties required by the Fugacity level 1 model will be displayed in a dialog box. The values can be copied to the Fugacity card using the buttons on the dialog box as illustrated in Figure 28. The check boxes next to the property names of the Fugacity card indicate if the property came from the data base.



Figure 28. Example dialog box resulting from the "Look for Values in Prop.DB" option

Input Environmental Values

The values used for the unit world can be changed in step 2. The available compartments are air, water, soil, suspended solids, sediment, and biota. Water must always be part of the unit world because of the partition coefficients are defined as the ratio of the chemical in the nonaqueous phase to the aqueous phase. The rest of the compartments can be eliminated by clicking the check box next the compartment name. The densities, volumes, and the percent organic carbon (if appropriate) of each compartment can be changed.

Different user defined environments or unit worlds can also be saved using the "Save Current Values" button and later recalled using the "Values:" popup menu. The "Delete Saved Values" button can be used to remove a saved set of values from the list that will popup when the "Values" button is used. The "Set Default Values" button can be used to set the unit world that is used when the PEP Models stack is opened.

Calculate Distribution

After the user inputs all the required information and hits the "calculate distribution" button, the model calculations are performed in HyperTalk and the results are presented in both in tabular and

graphical form as illustrated in Figure 29. The graphical display can be changed from bar (concentration of the chemical in each phase) to pie (percent of the chemical in each phase) chart forms using the "Graph:" popup menu. The values of the distribution coefficients that were used in the calculations are also shown on the results card.



Figure 29. PEP Models results card

PEP Help

Information regarding the operation of the chemical property database and the property estimation, models and batch modules is available in the PEP Help stack. This stack easily accessed at any time within the PEP system. The organization and layout of each help card is similar to that illustrated in Figure 30 for the MCI module. The user can select the topic of interest by clicking on the appropriate radio button and the information on that subject will be displayed in the scrolling field.

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Figure 30. Example card from PEP Help stack for MCI module.

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APPENDIX B

STATISTICAL, SUMMARY FOR MCI-PROPERTY, TSA-PROPERTY AND PROPERTY-PROPERTY RELATIONSHIPS INCORPORATED INTO PEP








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