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STUDY 237: Development and Use of QSARs for Regulatory Screening and Prioritization of Chemicals: Evaluation of Environmental and Toxicological Endpoints.

I. INTRODUCTION

Various aquatic toxicity data are required as a condition of pesticide registration per USEPA OPPTS Group *A* Aquatic Fauna Test Guidelines. These include acute toxicity to *Daphnia magna, gammarid, mysid*, Eastern oyster *(Crassostrea virginica)*, Fathead minnow *(Pimephales promelas),* rainbow trout, bluegill sunfish, and an alga *Selenastrum*. However, these data are often inadequate for evaluating aquatic risks from pesticides or prioritizing pesticides for monitoring. For example, proposed California water quality objectives for diazinon are based on acute and chronic toxicity endpoints for a number of sensitive organisms including the water flea *Ceriodaphnia dubia* (CVRWQCB, 2003). Many of these data were not required for diazinon or other organophosphate pesticide registrations. Potential sediment toxicities of recent pyrethroid detections have been evaluated using the sensitive sediment organism *Hyallela azteca* (Amweg et al., 2005). *H. azteca* data were not required for pyrethroid registrations, and data for many pyrethroids are not yet available from the literature. Therefore, methods to estimate aquatic toxicities of these and many other pesticides are needed to conduct screening level aquatic toxicity evaluations in determining monitoring priorities, and for identifying additional toxicity data needs for certain pesticides.

In addition, computational procedures for predicting aquatic toxicities of pesticides and other organic chemicals, including pesticide formulation constituents, are rapidly developing (Danish EPA, USEPA ASTER program, European Commission Directorate General, Joint Research Centre). Many of these procedures are based on quantitative structure-activity relationships (QSAR, Appendix A), where environmental behavior or effects of chemicals are predicted based on group contribution methods, molecular electronic structure and/or topology (Appendix A). In the long term, DPR will need expertise and knowledge in this area as more sophisticated methods and techniques are devised. This knowledge will also allow DPR to critically evaluate future data submissions based on QSAR and new approaches for characterizing aquatic toxicity.

II. OBJECTIVES

The general objectives of this study are to (a) evaluate the overall use of QSAR modeling for predicting different aquatic toxicological and environmental endpoints for use in a screening and/or prioritizing pesticides of concern in surface water, (b) develop QSAR models for predicting aquatic toxicities and environmental fate for

selected pesticide classes, (c) compare the developed models to current QSAR modeling approaches for predicting aquatic toxicities and environmental fate, and (d) validate the QSAR models to characterize prediction accuracy and capability. The specific tasks are to:

A. Compile a variety of environmental fate and aquatic toxicity data for different pesticide classes.
B. Calculate various quantum chemical parameters (e.g., electron density, charge distribution, chemical hardness/softness, molecular conformation, etc.) and chemical topology parameters (e.g., bond distances, connectivity, molecular size and shape, etc.), which have already been shown to be meaningful predictors of chemical behavior (Sullivan, et al, 2000; Karelson, et al, 1996; Gross and Seybold, 2001, Vaz, 1997).
C. Develop QSAR models based on data from (i) and (ii) above for predicting aquatic toxicity using established statistical procedures, including goodness of fit analysis on model development data, bootstrap (cross-validation) analysis based on the "leave one datum out" approach, and external validation on an independent data set where possible (Wold and Dunn, 1982; Walker, et al, 2003).
D. Compare results generated from the validated models to those derived from empirical models such as ECOSAR (US EPA Exposure Assessment Tools and Models Software Suite).
E. If possible, provide a mechanistic interpretation of derived relationships in selected cases, perhaps adding insight into little known toxic modes of action and degradative pathways.
F. Employ validated models to provide predicted values to fill data gaps when feasible and appropriate. "Appropriate" refers to screening-level applications such as prioritizing pesticides for monitoring and/or obtaining further aquatic toxicity data for further study.

III. PERSONNEL

Staff from the Registration and Environmental Monitoring Branch, Surface Water Protection Program, under the general direction of Kean S. Goh, PhD., Agricultural Program Supervisor IV, will conduct this study.

Key personnel are listed below:

Principal Investigator: Jonathan Sullivan, Ph.D.
Principal Investigator: Frank Spurlock, Ph.D.

To resolve questions concerning this monitoring project please contact Jonathan Sullivan at (916) 322-6767

IV. STUDY DESIGN

Aquatic toxicity data for a variety of classes of pesticides and other organic compounds will be collected from numerous regulatory, academic, and commercial database sources and organized by chemical class and endpoints. Principal

databases to be evaluated include the following:

1. US EPA ECOTOX (AQUIRE) Database (http://www.epa.gov/ecotox/): provides single chemical toxicity information for aquatic and terrestrial life. Peer-reviewed literature is the primary source of information encoded in the database. Pertinent information on the species, chemical, test methods, and results presented by the author(s) are abstracted and entered into the database.

2. PAN Pesticide Database (www.pesticideinfo.org): utilizes the data from the EPA ECOTOX database to calculate an average acute toxicity (LC50) value by organism type/species.

3. US EPA Office of Pesticide Programs Pesticide Ecotoxicity Database (http://www.ipmcenters.org/Ecotox/index.cfm): consists of data compiled from actual studies reviewed by EPA in conjunction with pesticide registration or reregistration and studies performed by USEPA, USDA and USFWS laboratories which have been reviewed by Ecological Effects Branch biologists and judged acceptable for use in the ecological risk assessment process.

4. Cal/Ecotox (http://endeavor.des.ucdavis.edu/calecotox/): collates species-specific information for 28 exposure factors (e.g., body weights, ingestion rates, seasonal activities and population dynamics) commonly used to estimate exposure to contaminants.

5. ORNL Benchmarks: (http://www.hsrd.ornl.gov/ecorisk/): Oak Ridge National Laboratory (ORNL) contains several databases of ecotoxicological information covering aquatic biota, terrestrial wildlife, terrestrial plants, sediment fauna, soil invertebrates and microbial processes. The benchmark criteria have been developed for a wide range of contaminants including metals, and organochlorine and organic compounds, and concentrate specifically on ecotoxicological criteria.

Within the selected chemical classes, compounds will be arranged into congeneric series' and, with associated endpoint values, comprise the training and testing sets. Training data will be chosen randomly based upon their endpoint activities, i.e., it is desirable to calibrate a model having as wide a range of activities as possible. Data not used for training purposes will be used for model validation. Model construction is the process that correlates the molecular descriptors to the activities. After the candidate model is derived, it will be internally validated, i.e., used to predict the activities of the molecules used to create the model (the training set) - this is a method of internally checking the model for robustness. For this study, cross-validation methods and the PRESS statistic (Predicted Error Sum of Squares) will be used for the internal validation of candidate models. If a training model is judged functional, it will be externally validated using an independent set of compounds (the testing set). Externally validated QSAR models will be utilized for prediction of endpoint values of unknowns (fill data gaps), to compare predictions with other regulatory models (e.g., the US EPA's ECOSAR) and to prioritize chemicals with respect to projected toxicity and environmental properties.

Both empirical and theory-based descriptors will be utilized in this study to encode structural variables, although the use of theoretical parameters will be emphasized. Empirical descriptors may be measured or estimated and include physicochemical properties or constitutional or geometrical terms. Non-empirical descriptors are typically structural properties based on topological or graph theory and as such they are so-called 2-D indices. Quantum chemical descriptors are based on an optimized 3-D structure of molecules. Some of the more profitable categories are listed below:

1. Constitutional Descriptors (e.g., total number of atoms, bonds, rings, molecular weight, atomic number, valence number, etc.)

2. Topological Descriptors (Wiener, 1947; Kier and Hall, 1986; Balaban, 1981, Kier, 1980)

3. Geometrical Descriptors (Karelson, 2000; Connolly, 1983; Richards, 1977)

4. Electrostatic Descriptors (Mulliken, 1955; Csizmadia, 1980; Osmialowski et al., 1985; Atkins, 1991; Politzer et al., 1991; Murray et al., 1990)

5. MO Related Descriptors (Csizmadia, 1976; Zhou and Parr, 1990; Pearson, 1989, Franke, 1984)

6. Quantum-chemical (Csizmadia, 1976; Bodor et al., 1989; Atkins, 1988; Clementi, 1980; Breneman and Martinov, 1996)

1) MATERIALS AND EQUIPMENT

   a) Software:
      i) Spartan ’04 (Wavefunction, Inc.): Molecular Modeling Software.
      ii) MDL QSAR (Elsevier MDL): QSAR Modeling System.
      iii) Molconn-Z (): Topological Indices Software).
      iv) ChemOffice Ultra 2004 (CambridgeSoft, Inc.): Chemical & Biological Publishing, Modeling, And Database Software.
      v) Norton SystemWorks Premier (Symantec, Inc.): Utilities & Security Software

   b) Books:
      i. Mati Karelson, Molecular Descriptors in QSAR/QSPR, Wiley-Interscience, 2000.
      ii. Mircea V. Diudea, Ivan Gutman, Jantschi Lorentz, Molecular Topology, Nova Science Pub Inc, 2001.
      iii. David B. Cook, Handbook of Computational Quantum Chemistry, Dover Publications, 2005.
      iv. Gary M. Rand, Fundamentals Of Aquatic Toxicology; Effects, Environmental Fate And Risk Assessment, CRC; 2nd edition.
      v. Wavefunction, Inc., Getting Started with Spartan 3rd Edition, 2004.
      vi. Wavefunction, Inc., Spartan'04 Windows Tutorial and User's Guide, 2001.
      vii. W.J. Hehre, A Guide to Molecular Mechanics and Quantum Chemical Calculations, Wavefunction, Inc., 2003.

viii. Wavefunction, Inc., Spartan Physical Chemistry, 2005.

2) PROCEDURES

a) Collect environmental/toxicological endpoint data from database resources.
   i) Organize according to chemical classes.
   ii) Arrange by structural congeners within classes.
b) Generate structural descriptors.
   i) Collect/calculate empirical descriptors per availability.
   ii) Calculate theoretical descriptors using purchased software packages.
c) Assemble and test training sets using rational descriptors, i.e., descriptors thought to encode for plausible mechanisms, modes of action, charge or orbital density distributions, molecular size and/or shape, etc.
d) Perform internal validation of derived models.
   i) Least squares fit (R^2).
   ii) Cross validation (q^2).
   iii) PRESS statistic.
e) Perform external validation of acceptable candidate models using structures and endpoint values not used in model calibration (training).
f) Employ validated models to
   i) Prioritize chemicals according predicted potential to elicit adverse toxic or environmental effects.
   ii) Fill data gaps where needed.
   iii) Compare predictions with those generated from other regulatory QSARs.
g) Write report(s).
h) Prepare manuscript(s) detailing study for publication.

V. TIMETABLE

1. Setup Computer/Install/Optimize Software: June 2006
2. Collect/Organize Chemical and Toxicological Databases: Ongoing From July 2006
3. Descriptor Calculation: Ongoing From September 2006
4. Develop Training Sets: Ongoing From September 2006
5. Model Validation: Ongoing From September 2006
6. Preliminary Memorandum: June 2008
7. Final Report: June 2009

VI. BUDGET

Software:

1. Spartan ’04 (Wavefunction, Inc.)…….. $1500
2. MDL QSAR (Elsevier MDL)……..……$2300
3. Molconn-Z ……..……$1500
4. ChemOffice Ultra 2004 (CambridgeSoft, Inc.)……...$2870
5. Norton SystemWorks Premier (Symantec, Inc.)…….…….$100
6. Upgrades and additional software ……..$5000

Computer Software Subtotal…….…….$10800
Tax/Shipping……$900
Software Total……..……..$13,900

Books:

1. Molecular Descriptors in QSAR/QSPR……..……$240
2. Molecular Topology……...…...$105
3. Handbook of Computational Quantum Chemistry……..……...$29
4. Fundamentals Of Aquatic Toxicology; Effects, Environmental Fate And Risk Assessment…….…..$89
5. Getting Started with Spartan 3rd Edition……$30
6. Spartan'04 Windows Tutorial and User's Guide……....$35
7. A Guide to Molecular Mechanics and Quantum Chemical Calculations… $25
8. Spartan Physical Chemistry……..$75

Book Subtotal…….……$670
Tax/Shipping……$150
Book Total……..……..…….$820

TOTAL……..……..$22,382

VII. REFERENCES

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Danish EPA: QSAR and pesticide risk assessment. *Available:* http://www.mst.dk/homepage/default.asp?Sub=http://www.mst.dk/udgiv/publications/2004/87-7614-434-8/html/kap02_eng.htm

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US EPA Exposure Assessment Tools and Models (EPI) Software Suite. Includes ECOSAR (Ecological Structure-Activity Relationships), Which Estimates The Toxicity Of Single Chemicals Using Quantitative Structure-Activity Relationships (QSARs). *Available:* http://www.epa.gov/oppt/exposure/docs/episuitedl.htm

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APPENDIX A: QSAR AND REGULATORY APPLICATIONS

Introduced by Hansch (1962) as an extension of the pioneering work of Hammett (1940), the Quantitative Structure-Activity Relationship (QSAR) paradigm is based the intuitive notion that the molecular structure of a given chemical determines its activity

$$Activity = f(Structure) \qquad (1)$$

where the term "activity" is a specific end-point measurement that may represent a biological, physicochemical, physiological, or chemical process. The QSAR approach relies on the development of statistical models that relate variations in activity to changes in molecular structure using molecular descriptors. A descriptor is defined as the mathematical representation of the information content encoded in a molecule and may embody empirical, quantum chemical or non-empirical parameters. Empirical descriptors maybe measured or estimated and include physicochemical properties such as hydrophobic, electronic, and steric terms. Non-empirical descriptors are typically structural properties based on 2-D topological or graph theoretical parameters. Quantum chemical descriptors are based on an optimized 3-D structure of molecules.

A QSAR model is first trained (calibrated) by mathematically quantifying the structures of sets of compounds and comparing them to the measured values of a biological or chemical activity or property. To ensure derived models have adequate interpolative capabilities, training sets contain measured end-point values extending over a broad range of activities. Descriptor information and the measured activity are then processed into a mathematical model using a variety of statistical methods. Typically, a QSAR takes the form of a linear equation

$$Activity = y = b_0 + b_1x_1 + b_2x_2 + \ldots b_nx_n \qquad (2)$$

where the independent variables x_n are descriptors derived from molecular structure or some readily measurable or calculable physicochemical property and the dependent variable y is a specific chemical or physical property of interest. The constants b_0, b_1, etc., are determined statistically. The statistical conditions for each of the data analytical methods commonly applied in QSAR analyses has been rigorously formulated (Wold, 1991).

After a QSAR is developed, it undergoes extensive internal and external validation. This process is necessary to test the predictive capability of the derived relationship, examine the restrictions of its application, and to evaluate its mechanistic hypotheses (Walker, et al, 2003). Internal validation involves generating goodness-of-fit statistics and performing cross-validation studies to establish goodness-of-prediction parameters. External validation is achieved by assessing the QSAR in terms of its predictive power by using data that were not used in the development of the model (the testing set). Employing the same descriptors used to encode the independent variables in the training set, end-point values for the testing set are generated from the derived model and analyzed statistically. A variety of statistical methods have been developed for the external validation process in QSAR studies

(Aptula, et al, 2005, Eriksson, et al, 2003).

The ultimate and practical significance of QSAR is that it allows the prediction of the activity of interest of structurally related compounds (Walker, 2003). Toxicity and environmental fate tests with many chemicals have generated enough data to generate models that can be used to calculate toxicity and biodegradation based on chemical structure. Such models are not just predicting a chemical property, like the boiling point, but are actually predicting what the molecule will do in the environment. Accordingly, QSARs are highly amendable to regulatory applications. A number of domestic and international regulatory mandates have in recent years led to aggressive explorations into the use of QSAR to evaluate environmental and ecotoxicological data (Worth, 2003, Walker, et al, 2002, Bradbury, et al, 2003). In the United States, under Sections 4 and 5 of the Toxic Substances Control Act (TSCA, 1993), the TSCA Interagency Testing Committee (ITC) and the U.S. Environmental Protection Agency (EPA) employ QSAR to estimate the hazards existing and new chemicals. The TSCA chemical inventory currently lists over 72,000 chemicals, most of which have little or no ecotoxicity or fate data available. QSAR methods developed and supported by the EPA now provide predictions and crosschecks of test data for the regulation of existing chemicals. QSAR screening of the TSCA Inventory has prioritized thousands of existing chemicals for possible regulatory testing of: 1) persistent bioaccumulative chemicals, and 2) the high ecotoxicity of specific discrete organic chemicals. (Zeeman et al, 1995). Around the same time as TSCA, the European Union (EU) authorized the Existing Substances Regulation (ESR), a European-wide systematic approach to identifying and managing the risks of chemicals to human health and the environment. The ESR also supports and encourages the use of QSAR for data evaluation, test strategy identification, and the identification and filling of data gaps (Comber et al, 2003). Similarly, under the Canadian Environmental Protection Act, 1999 (CEPA 1999), Environment Canada uses QSARs for categorizing chemicals on the Domestic Substances List (DSL, currently containing more than 23,000 substances), and QSAR is often relied upon to fill data gaps (Robinson et al, 2004). As increasing numbers of QSAR methods are developed and validated to predict the ecological effects and environmental fate of chemicals, it is anticipated that more regulatory agencies and authorities will find them to be acceptable alternatives to chemical testing (Cronin, et al, 2003).

One of the most widely used QSAR models developed by the EPA is ECOSAR (Ecological Structure Activity Relationships), which predicts the aquatic toxicity of new industrial chemicals in the absence of test data. ECOSAR uses a number of Log*P*-based QSARs to estimate the ecotoxicity of organic compounds for several structural classes often resulting in ecotoxicity estimates of a variety of endpoints. However, the usefulness of ECOSAR and other QSAR models used for regulatory purposes is contentious due largely to their empirical nature. Structural descriptors for such models are typically generated experimentally, and since there is often considerable ambiguity in the interpretation of empirical evidence, insights and conclusions drawn from such evidence can only be rationalized by inference, chemical intuition, and experience. Empirical models are often plagued by persistent uncertainties in the quality of available experimental data and by the ambiguous chemical meaning of empirical terms. Clearly, there is a need to develop

and test QSAR models for regulatory screening based on a well-defined theoretical framework that provides explicit meaning to modeled results.

Quantum chemistry provides a more accurate and detailed description of structure than empirical methods. Quantum chemical methods can be applied to QSAR by direct derivation of descriptors from the molecular wave function. Because of the large well-defined physical information content encoded in computational expressions and because they are currently readily calculable, their use as descriptors in QSAR applications has become more appealing. The advantage in the use of such descriptors is that compounds and their various fragments and substituents can be directly characterized on the basis of their molecular structure and proposed behaviors can be accounted for directly in terms of chemical activities of the compounds under investigation. In addition, unlike experimental measurements there is no statistical error in quantum-chemical calculations (although there is inherent error associated with assumptions required to facilitate the calculations), thus structure-based models avoid the error associated with the measurement of molecular properties (Karelson, et al, 1996).

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