United States
Environmental Protection
Agency

Environmental Research
Laboratory
Duluth MN 55804

Research and Development

EPA-600/S3-81-029 June 1981

EPA

Project Summary

State-of-the-Art of Structure Activity Methods Development

Gilman D. Veith

The overall objective of this project is to provide the Agency with the technical basis for estimating the toxicity and environmental behavior of organic chemicals from molecular structure. The project is directed toward the evaluation of quantitative structure-activity relationships (QSAR) for use by EPA Program Offices and toward the development of new data and QSAR methods to extend the technique to meet Agency needs.

Specifically, the objective of the Structure-Activity Project is to develop methods to predict the toxicity, persistence, and treatability of large numbers of untested chemicals using QSAR based on structural, chemical, and biological properties of representative reference data bases. Development of QSAR is being tailored of use in the (1) initial screening of chemicals under the Toxic Substances Control Act (TSCA), (2) development of risk assessment strategies, (3) prioritization of chemicals for Water Quality Criteria development, and (4) the optimization of national monitoring programs for toxic chemicals.

This report summarizes the progress during the first six months of the project. The report provides a literature review and perspective for applying structure-activity methods to aquatic toxicity of industrial chemicals. Experimental work centered on developing methods for estimating molecular descriptors such as log P and connectivity indexes and on the development of a systematic structure-activity data base for aquatic toxicity. A new program for entering structures into a computer and calculating connectivity indexes is discussed. A general model for predicting 96-hour LC50 for narcotic chemicals is presented.

This Project Summary was developed by EPA's Environmental Research Laboratory, Duluth, MN, to announce key findings of the research project that is fully documented in a separate report of the same title (see Project Report ordering information at back).

Introduction

Developing technology to predict the toxicity or reactivity of new and existing industrial chemicals from structure requires the simultaneous generation and compilation of endpoints to measure toxicity, etc. and of molecular descriptors for representative structures as well as the development of statistical methods of relating the two to form the predictive model. This report includes a literature review of statistical methods which indicates that methods are available for most models for QSAR deemed necessary for EPA purposes. A small effort by this project is aimed at compiling computer programs for the most useful statistical methods

into a QSAR modeling library which uses common input/output formats.

The limiting factor for use of QSAR in screening chemicals, therefore, is the availability of data on endpoints and molecular descriptors for industrial chemicals. Consequently, this project placed major emphasis on generating a systematic aquatic toxicity data base using the 96-hour LC50 for fathead minnows, and on generating a data base of important molecular descriptors such as the n-octanol water partition coefficients and molecular connectivity indexes.

Experimental Procedures

The chemicals initially selected for this study include a wide variety of alcohols, ketones, aldehydes, ethers, phenols, and chlorinated aliphatic and aromatic hydrocarbons. Toxicity tests were conducted in proportional diluters (Mount and Brungs, 1967) each with a dilution factor of 0.6. Test chambers were glass aquaria measuring 20 x 35 x 25 cm with a 9 cm standpipe, providing a 6.3 L volume. A 16-hr light, 8-hr dark photoperiod with no transition was used.

All tests were conducted with fathead minnows (*Pimephales promelas*) from the Environmental Research Laboratory—Duluth culture units. Fish were hatched and reared in Lake Superior water and fed live brine shrimp at least twice daily. Typical fish tested were 30 days old and weighed 0.12 g. Twenty-five fish were randomly assigned to each of 12 tanks in lots of five. Fish were not fed during the 96-hour tests. Deaths were recorded at hours 1, 3, 6, 12, and 24, and every 24 hours thereafter. Concentrations for toxicity in each test tank were determined by chemical measurements throughout the test.

Results

During the initial six months of this project, toxicity tests with more than 50 organic chemicals indicated that the majority of the chemicals caused death by non-specific physical toxicity-termed narcosis. The literature review on narcosis presented in the report showed that the toxicity data for fish are consistent with literature data in mammalian tests in that homologous series can be grouped together in QSAR models and that the chemical activity needed to produce narcosis in fish is similar to that which causes narcosis in mammals. The data showed that the 96-hour LC50 for industrial alcohols, ethers, alkyl halides, ketones, and benzene derivatives can be estimated by the equation:

$$\log \frac{1}{LC50} = 1.17 + 0.94 \log P$$

where log P is the logarithm of the n-octanol/water partition coefficient. However, this model is limited to chemicals with a log P less than 4.0 until more data can be generated. The data also showed that chemicals which do not behave as narcotics at lethal concentrations require additional QSAR for their specific mode of action.

An extensive computer program was developed which permits entry of chemical structure through either a graphics terminal or conventional TTY and calculations of 134 connectivity indexes for even polycyclic chemicals were developed. Preliminary results indicate that the toxicity of narcotics can be estimated from structure by the QSAR:

$$\log LC50 = 0.28 - {}^{1}X^{v}$$

where ${}^{1}X^{v}$ is the first order valence connectivity index of the chemical.

This approach has the advantage that the connectivity indexes are computed rather than measured values, which eliminates experimental error and the need for data other than structure. It has the potential for discriminating chemicals in terms of expected mode of action of lethality, other biological effects and chemical reactivity through cluster analysis in a multi-dimensional structure space.

Conclusion

QSAR can provide cost-effective methods of screening new and existing chemicals for potential hazards in the aquatic environment. The development of a comprehensive QSAR system for evaluating the 45,000 chemicals in the TSCA inventory is limited largely by the time needed to generate the training sets of toxicity data for the numerous classes of chemicals.

This Project Summary was authored by ***Gilman D. Veith*** *who was also the EPA Project Officer (see below).*

The complete report, entitled "State-of-the-Art of Structure Activity Methods Development," (Order No. PB 81-187 239; Cost: $11.00, subject to change) will be available only from:

National Technical Information Service
5285 Port Royal Road
Springfield, VA 22161
Telephone: 703-487-4650

The EPA Project Officer can be contacted at:

Environmental Research Laboratory
U.S. Environmental Protection Agency
Duluth, MN 55804

☆ U S GOVERNMENT PRINTING OFFICE: 1981-757-012/7149

United States
Environmental Protection
Agency

Center for Environmental Research
Information
Cincinnati OH 45268

Postage and
Fees Paid
Environmental
Protection
Agency
EPA 335