COMMENTS ON THE 3rd INTERNATIONAL WORKSHOP ON QSAR IN ENVIRONMENTAL TOXICOLOGY

by

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Management Perspective

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3rd International Workshop on QSAR in Environmental Toxicology

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Perspective:

This report describes major findings and conclusions of the 3rd International Workshop on QSAR in Environmental Toxicology, held at Knoxville, Tennessee, May 23-26, 1988.

Overall, the workshop was considered highly successful by most particpants. QSAR in environmental toxicology is expected to play an increasing role in the development and regulation of new chemicals, particularly those intended to find their way into the environment.

PERSPECTIVE-GESTION

Ce rapport décrit les principaux résultats et conclusions du 3e Atelier international sur les RQSA en toxicologie environnementale, qui a eu lieu à Knoxville, au Tennessee, du 23 au 26 mai 1988.

La plupart des participants ont considéré que dans l'ensemble, l'atelier était pleinement réussi. On prévoit que les RQSA en toxicologie environnementale joueront un rôle accru dans la mise au point et la réglementation de nouveaux produits chimiques, notamment ceux qui sont destinés à se retrouver dans l'environnement.

RÉSUMÉ

On présente les principales constatations et conclusions du 3e Atelier international sur les relations quantitatives structure-activité en toxicologie environnementale, qui a eu lieu à Knoxville, au Tennessee, du 23 au 26 mai 1988. Au nombre des sujets traités figurent les descripteurs expérimentaux et calculés relatifs aux corrélations structure-activité, l'utilisation des données et les statistiques, les modes d'action, et les intercorrélations entre descripteurs et espèces.

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ABSTRACT

Major findings and conclusions of the 3rd International Workshop on QSAR in Environmental Toxicology, held at Knoxville, Tennessee, May 23-26, 1988, are presented. Subjects dealt with include experimental and computed descriptors for structure-activity correlations, data use and statistics, modes of action, descriptor and species inter-correlations.

INTRODUCTION

This workshop followed two earlier workshops on the same subject held at McMaster University, Hamilton, Ontario in 1983 and 1986, respectively. Proceedings of these were published as *"QSAR in Environmental Toxicology"* (ISBN 90-277-1776-1) and *"QSAR in Environmental Toxicology - II"* (ISBN 90-277-2555-1), respectively, by the Kluwer Academic Publishers Group.

The present workshop was sponsored by the University of Tennessee (UoT) and the Oak Ridge National Laboratory (ORNL), with additional financial support from the US Department of Energy and the US Environmental Protection Agency. Organizers were M.W. England (ORNL), T.W. Schultz (UoT) and J.E. Turner (ORNL).

The workshop brought together some 60 participants from the Netherlands, France, Great Britain, Federal Republic of Germany, Canada and the USA. A mixer on Sunday evening gave participants a chance to get acquainted and adjust. An excursion to the Smokey Mountains provided a great opportunity for relaxation and discussion in small groups.

PROGRAM

The workshop was divided into a kenote address and six major sessions (including one panel discussion) with 16 invited speakers and 16 contributed posters. There was ample time for discussion following each presentation, a most beneficial and required arrangement for a successful workshop. The following gives the titles of the sessions:

Statistical considerations in QSAR
Molecular descriptors
QSAR in fish systems
QSAR in non-fish systems
Poster session
Panel discussion

KEYNOTE ADDRESS

The keynote address was given by Gilman D. Veith of the US-EPA Environmental Research Laboratory at Duluth, Minnesota on a "Historical Prospective of QSAR in Environmental Toxicology". Having been the driving force in the US on QSAR in environmental work for nearly a decade, this speaker was eminently suited for his task. Veith summarized the progress todate and outlined research directions and needs for the next decade. His review included a list of typical, environmentally important endpoints, such as bioaccumulation, acute lethal concentration (for aquatic species), biodegradation (e.g. biochemical oxygen demand), metabolic profile, alkylation profile. He demonstrated the need for a better understanding of "analogy" of structures by showing a slide with some 20,000 chemicals in a 12-dimensional property space, where some chemicals are very close in one space but quite distant in another. He went on to review nonpolar and polar mechanisms of toxicity for fathead minnows (*Pimephales promelas*), rat inhalation studies, respiration rate versus BOD, and fish acute toxicity syndromes (FATS).

In his outlook for the next decade of research on QSAR in environmental toxicology, Veith mentioned the need for better structure quantification methods (topology, geometry and reactivity), mathematical concepts, development of reference databases for biodegradation, chronic toxicity values, carcinogenicity and other long-term effects. In part, development in these areas requires first a resolution of outstanding questions on the definition and quantitation of some of such terms.

MAJOR WORKSHOP FINDINGS

The results of the wokshop can be summarized by the following major areas of research and their important findings.

Data Reporting and Use

- For QSAR purposes, toxicity data should be reported only as logarithms of the inverse molar (or milli- or micromolar) concentrations.

Statistics

- Multiple linear regressions should always be accompanied by n (number of observations), s (standard error of the estimate) and the F ratio (ANOVA). In addition, the coefficient of determination (r^2) should be given rather than its root. Preferably, also adjusted r^2 values may be given (r^2 adjusted= $[(n-1)r^2 - (p-1)](n-p)$).

- Multivariate stastical analysis, such as principal component analysis and factor analysis can simplify QSARs through identification of redundant variables. Care should also be taken to identify influential observations and outliers.

QSAR Descriptors

- Computation of octanol/water partition coefficients (logP) has advanced with many new fragment values incorporated into the CLOGP program. In addition, such complicating factors as ortho substituent influences, intra-molecular hydrogen binding and conformational changes are now being treated effectively for the computations.

- Computation of acid dissociation constants (pK_a) are now available for several classes of chemicals, including aliphatic and aromatic systems. The models rely on some 1,700 experimental values.

- Position-dependent branching factors of alkyl chain substituents improve logP based toxicity QSAR of linear alkyl sulfonates. These "adjusted" partition coefficients may be relevant to other work.

- Topological shape and electronic descriptors, computed from an adjacency matrix, have been successfully used for the prediction of aquatic toxicity values and show great promise for other applications.

- Conformational changes in toxicant or receptor molecules are increasingly being computed from molecular mechanics and other programs and provide useful clues to molecular interaction mechanisms.

- Molecular connectivity indexes ($^{0}X^{v}$) predict the acute toxicity of alcohols, ethers, aldehydes, ketones, nitriles, aliphatic and aromatic amines, halogenated hydrocarbons, substituted benzenes and phenols to fish. Molecular size accounts for 85% of the measured toxicity variation.

- *Ab initio* and molecular mechanics calculated electronic parameters, such as LUMO, HOMO, chemical shifts and electron population densities at certain groups or atoms (e.g. NO_2, NH_2) are increasingly being used to correlate acute effects of polar, reactive compounds. Their power of prediction appears to combine varying modes of action.

Next generation effects

- Studies on developmental toxicity of substituted phenols on rat embryos were largely inconclusive in terms of QSAR.

Experimental QSAR Parameters

- Improved logP measurements (e.g. "slow stirring method") allows much easier experimental access to experimental values for highly lipophilic compounds.

- Octanol/water partition coefficients may be misleading when used for correlations of toxicity of certain groups of chemicals. Other partition coefficients (e.g. 2,2,4-trimethylpentane/water) may be better models for certain chemicals.

QSAR Descriptor Inter-correlations

- Molecular connectivity index values (after Kier and Hall) seem to reflect primarily the steric properties of molecules.

- Molecular volume and electronegativity (as computed from valence elctron numbers) are highly inter-correlated and therefore can be computed from each other.

- Ionization potentials of aromatic hydrocarbons are highly correlated with their computed molecular connectivity indexes.

- Aqueous solubilities and molecular connectivity indexes of substituted benzenes and polychloro-biphenyls are highly correlated with each other.

Inter-Species Extrapolations

- There is continuing progress in the inter-species extrapolation and correlation of toxicity data. Models exist to corrrelate mammalian with aquatic (fish) data. Extrapolations across species to man are being investigated.

Database developments

- New databases with "filtered" and normalized data are being developed and existing ones are expanded to provide compatible data sets for QSAR analysis and general use.

Expert System Approach

- A prototype knowledge based expert system has been developed to predict narcosis, polar narcosis, respiratory uncoupling and membrane irritation mode of action responses on the basis of number, position and type of substituents.

Modes of Action

- Narcosis and polar narcosis modes appear to be well in hand for a variety of aquatic species and endpoints for non-reactive compounds.

- Respiratory uncoupling mechanisms is modelled by logP for aniline and phenol toxicity to *Tetrahymena* sp.

- Acrylate and methacrylate esters have higher than baseline (narcotic) toxicity to fish, but their effects can also be modelled by logP dependent submodels for each chemical group.

Linear Solvation Energy (LSER) Parameters

- Significant advances in this field were made by the late Mortimer Kamlet. Their value has been demonstrated on models of acute toxicity of organics to *Daphnia* sp. Computer programs exist to calculate the LSER values for substances and their application allows the identification of more hazardous environmental contaminants.

Water treatment

- Lipophilicity (i.e. logP) is a reasonably good descriptor of the acute toxicity of monochloramines to fish.

General Observations

- There is an increased use of strictly computed "experimental" (logP, IP, LSER, etc.) and theoretical (HOMO, LUMO, dQox, $^{1}X^{v}$, etc.) descriptors.

- There is an increasing volume of work on more complex structures, e.g. multiple substituted compounds and polar, reactive compounds.

- There is an increasing interest in inter-species, inter-endpoint and inter-desriptor relationships.

CONCLUSIONS

Overall, the workshop was considered highly successful by most participants. The proceedings will be available in the near future in form of an US Department of Energy publication.

QSAR in environmental toxicology is expected to play an increasing role in the development and regulation of new chemicals, particularly those intended to find their way into the environment. A fourth workshop is in the early planning stage for 1990, to be held in the Netherlands.