OAK RIDGE NATIONAL LABORATORY

OPERATED BY MARTIN MARIETTA ENERGY SYSTEMS, INC.
POST OFFICE BOX 2008, OAK RIDGE, TENNESSEE 37831-6285

ORNL/FTR--3768

DE91 000874

ORNL
FOREIGN TRIP REPORT

ORNL/FTR-3768

DATE: October 4, 1990

SUBJECT: Report of Foreign Travel of J. E. Turner, Group Leader, Analytic Dosimetry and Surface Physics Group, Health and Safety Research Division

TO: Alvin W. Trivelpiece

FROM: J. E. Turner

To participate in the Fourth International Workshop on QSAR in Environmental Toxicology, Veldhoven, the Netherlands, September 16-20, 1990

SITES

VISITED: 9/15-20/90 Workshop, Veldhoven, the Netherlands J. Hermens

ABSTRACT: The traveler attended the Fourth International Workshop on QSAR (Quantitative Structure-Activity Relationships) in Environmental Toxicology. He was an author or co-author on one platform and two poster presentations. The subject of the workshop offers a framework for analyzing and predicting the fate of chemical pollutants in organisms and the environment. QSAR is highly relevant to the ORNL program on the physicochemical characterization of chemical pollutants for health protection.

DISCLAIMER

This report was prepared as an account of work sponsored by an agency of the United States Government. Neither the United States Government nor any agency thereof, nor any of their employees, makes any warranty, express or implied, or assumes any legal liability or responsibility for the accuracy, completeness, or usefulness of any information, apparatus, product, or process disclosed, or represents that its use would not infringe privately owned rights. Reference herein to any specific commercial product, process, or service by trade name, trademark, manufacturer, or otherwise does not necessarily constitute or imply its endorsement, recommendation, or favoring by the United States Government or any agency thereof. The views and opinions of authors expressed herein do not necessarily state or reflect those of the United States Government or any agency thereof.

**PARTICIPATION IN THE FOURTH INTERNATIONAL WORKSHOP
ON QSAR IN ENVIRONMENTAL TOXICOLOGY
VELDHOVEN, THE NETHERLANDS
SEPTEMBER 16-20, 1990**

The traveler participated in the Fourth International Workshop on QSAR in Environmental Toxicology, September 16-20, 1990, in Veldhoven, the Netherlands. The itinerary is given in Appendix A. "QSAR," which stands for "Quantitative Structure-Activity Relationships," deals with molecular structures and structural differences as related to their properties and functioning under various conditions. Such studies are important and relevant for a number of purposes, such as pharmacology, understanding the fate and retention of chemicals in organisms and the environment, the mutagenic and carcinogenic properties of chemicals, and the prediction of certain physical characteristics (e.g., melting points and vapor pressures). In recent years, QSAR has become increasingly applied to environmental toxicology. The first two workshops in this series took place in 1983 and 1986 in Burlington, Ontario, Canada. The third was hosted by Oak Ridge National Laboratory (ORNL) and the University of Tennessee and was held in Knoxville, Tennessee, in 1988. Approximately 125 attendees were on hand at this fourth workshop, with some 16 different countries represented. The largest number of participants, 45, were from the Netherlands. This number is not surprising, in view of the fact that (1) the workshop was hosted there and (2) the Dutch are very active in the field. The United States was second in the number of attendees with 29, followed by the Federal Republic of Germany (15), and the United Kingdom (8). The other countries had five or less. Eastern European countries represented were Czechoslovakia (3), Bulgaria (1), and the German Democratic Republic (1). There were no participants from Japan, but one each from Australia and South Africa. This fourth workshop was organized by Joop L. M. Hermens (chairman) and Antoon Opperhuizen (co-chairman) of the Research Institute of Toxicology, University of Utrecht, Utrecht, the Netherlands.

At this fourth workshop, the traveler was a co-author of one platform presentation, "Inorganic Concepts Relevant to Metal Binding Activity, and Toxicity in a Biological System," James D. Hoeschele, James E. Turner, and M. Wendy England. The paper was presented by Dr. Hoeschele. In addition, the traveler was a co-author on two posters, "Metal-Ion Toxicities Relative to Normal Metal-Ion Concentrations in an Organism," M. Wendy England, James E. Turner, and K. Bruce Jacobson and "Calculated Distortions Induced by Metal-Ion Binding to Simple Oligonucleotide Systems: Implications for Toxicity," James E. Turner, Brian E. Hingerty, M. Wendy England, and K. Bruce Jacobson. Abstracts of these presentations are given in Appendix B. These contributions reported on research conducted in ORNL's program, Studies of Physical Parameters for Health Protection from Chemical Pollutants (ERKP158). The objective of the program is to develop physical and biological concepts and principles on which a system of health protection from chemical pollutants can be based. It seeks to identify physicochemical quantities that can be measured and used in predicting the toxicity of chemicals to man. These objectives are akin to those of QSAR studies, many of which seek empirical relations to predict the behavior of chemicals in various surroundings.

The platform papers were presented under five general groups. The first, which occupied the entire first day, was entitled QSAR Techniques/Molecular Descriptions. From the standpoint of the traveler's background in physics, two papers were of particular interest. John C. Dearden from the United Kingdom presented "QSAR Prediction of Melting Point, a Property of Environmental Relevance." Like aqueous solubility, melting point is a related factor of potentially great environmental importance. It reflects intermolecular forces and the strength of crystal lattice binding.

Dearden found hydrogen-bond donor ability to be the most important parameter for correlating with melting points for a series of anilines. The second paper, "Estimation of Vapor Pressures for Organic Compounds," was given by Samuel H. Yalowsky of the University of Arizona. He presented an equation, based on entropies of vaporization and melting and the changes of heat capacity that accompany these changes of phase, that enables one to predict vapor pressures over a wide temperature range.

One-half day was devoted to a second group of papers on Environmental Fate. QSAR has been successful in studies of a range of relevant quantities, including chemical transformation rates, biodegradation, oxidation rates, and soil sorption coefficients. The Dutch and Swiss appear to be particularly active in these fields.

The third group, Toxicokinetics/Bioaccumulation, occupied another half day. The transport and fate of foreign chemicals in biosystems was emphasized. For example, one paper by Markus Riederer (Federal Republic of Germany) dealt with the transport and partitioning of organic compounds in the leaf/atmosphere systems of plants.

Group four, which occupied one and one-half days, was devoted to Toxicity/Mechanism of Action. The parameters one identifies in QSAR studies will often suggest mechanisms of action, which may underlie toxicity. This session was the most closely related to the traveler's own program. The paper he co-authored with Dr. Hoeschele was given in this group. Our own efforts seek to relate distortions in simple DNA subunits caused by metal-ion binding to metal-ion toxicity that we have measured in mice. Calculations show that the binding of the more toxic metals cause greater distortion in these molecular structure. To date, our efforts to relate distortions quantitatively (e.g., by changes in base plane angles) to toxicity have met with limited success.

The fifth group was headed Application of QSAR in Practice/Data Bases. This session had papers dealing with the role and uses of QSAR in regulatory functions. Robert S. Boethling of the U. S. Environmental Protection Agency (EPA, Washington, DC) described the "Development and Validation of a Predictive Model for Biodegradability Based on BIODEG, the Evaluated Biodegradation Database." Under the Toxic Substance Control Act, the Agency is obligated to provide risk assessments for thousands of existing and new chemical substances each year. EPA thus has a great need for guidance in rapid screening of large numbers of chemicals, guidance which QSAR studies can potentially help provide. J. Vincent Nabholz, also of EPA, presented a paper on "Environmental Hazard and Risk Assessment Under the United States Toxic Substances Act." "Chemical Structure Searching to Select Chemicals for Priority Testing" was the subject of another paper by John D. Walker of the Interagency Testing Committee. The committee, which consists of members from eight U.S. government organizations, selects and recommends chemicals to EPA for priority testing for health and environmental effects. Screening tests are necessary in performing this function.

A plenary session was held for general discussions on the last evening of the workshop.

Posters were set up on the first day and left standing for the duration of the workshop. Forty-seven (47) posters were accepted, and all but a few were presented. In addition, two two-hour periods were allotted in the program for poster viewing and discussion with the authors present.

To summarize, QSAR covers broad areas of research that relate structure and activity of materials. The workshop focused on QSAR in the field of environmental toxicology. Here QSAR plays a role in offering models and guidance for the screening of hazardous and potentially hazardous chemicals. These must be classified, categorized, and selected for priority testing in vast, overwhelming numbers. Going beyond the discovery of correlations between structure and activity as manifested in various ways, QSAR offers insight into mechanisms of toxic effects. Specific structural effects often suggest target sites as a basis for toxicity. The subject of the workshop is directly related to both basic research programs of the Department of Energy (DOE) on chemical

pollutants and the regulatory responsibilities of various state and federal agencies, principally EPA.

Participation in the workshop was very valuable for the traveler and the ORNL program in the physicochemical characterization of chemical pollutants. It provided the opportunity to present ORNL work at an international gathering of researchers and practitioners. Discussions that the traveler had with numerous other participants indicated that the ORNL work given in the three presentations was well received. The workshop also provided the traveler with a survey and update on the relevance of the ORNL program to the concerns of environmental toxicology. This series of workshops is one of the relatively few forums in which there is a common and natural link between chemical toxicity and the kinds of physical studies that match the background of physics in the traveler's group at ORNL. The traveler strongly recommends continued ORNL participation in the series. The fifth workshop is planned for 1992 in Duluth, Minnesota.

APPENDIX A**ITINERARY****1990**

9/14-15	Travel from Oak Ridge, Tennessee, to Veldhoven, the Netherlands
9/16-20	Veldhoven, the Netherlands, participation in Fourth International Workshop on QSAR in Environmental Toxicology
9/20	Travel from Veldhoven to Amsterdam, the Netherlands
9/21	Travel from Amsterdam, the Netherlands, to Oak Ridge, Tennessee

PERSONS CONTACTED

Dr Joop L. M. Hermens

Research Institute of Toxicology
Utrecht, the Netherlands**APPENDIX B****ATTACHED ABSTRACTS**

CALCULATED DISTORTIONS INDUCED BY METAL-ION BINDING TO SIMPLE OLIGONUCLEOTIDE SYSTEMS: IMPLICATIONS FOR TOXICITY.¹

J. E. Turner*, B. E. Hingerty*, M. Wendy England*, and K. Bruce Jacobson**

*Health and Safety Research Division and **Biology Division, Oak Ridge National Laboratory, P. O. Box 2008, Oak Ridge, TN 37831-6123

We have previously published detailed results of calculations of the binding of the metal ions, Cd^{2+} and Ca^{2+} , to the dinucleoside monophosphate GpC in water [QSAR in Toxicology and Xenobiochemistry, M. Tichy, Ed., Elsevier, Amsterdam, pp. 171-178 (1985); Hingerty et al., *Biopolymers* 24:427-439 (1985)]. These ions, which have the same charge and radius, differ enormously in their toxicity to man and other biological systems. Our calculations showed contrasting behavior in the binding of these two metal ions to GpC. Whereas Ca^{2+} binds most strongly to the phosphate moiety of GpC, Cd^{2+} has the greatest affinity for the electron-rich sites that are available - notably the N3 of guanine, the O2 of cytosine, and the O2' of the guanine sugar. Furthermore, the bonds formed by Ca^{2+} are largely electrostatic in character, as contrasted with the strong covalent bonds formed by Cd^{2+} . Because of the directional symmetries required for electron sharing with Cd^{2+} , the binding of this ion greatly distorts the standard A form of GpC. The planes of the guanine and the ribose are rotated relative to one another by the bound Cd^{2+} , which has a full complement of d-state electrons ($4d^{10}$). In contrast, the binding of Ca^{2+} , which is isoelectronic with the noble gas atom, Ar, entails negligible change in the original conformation of the GpC. We suggest the hypothesis that structural distortions calculated for metal ions binding to simple nucleic-acid systems might serve as an indicator of an ion's potential ability to alter molecular activity and hence to be toxic to an organism. Furthermore, the degree of distortion might be correlated with the degree of toxicity as measured by some suitable criteria. The present paper reports the results of binding calculations for a number of other metal ions, of different valence states, with several dinucleoside monophosphates in water. A general trend of distortion with the type of binding of the metal ions is found. We are seeking quantitative measures of distortion to correlate with indicators of acute toxicity that we have measured for 24 metal ions using mice, *Drosophila*, and CHO cells [Williams (now England) et al., *Toxicol. Appl. Pharmacol.* 63:461-469, 1982; Tan et al., *Toxicol. Appl. Pharmacol.* 74:330-336, 1984].

¹Research sponsored by the Office of Health and Environmental Research, U.S. Department of Energy, under contract DE-AC05-84OR21400 with Martin Marietta Energy Systems, Inc.

"The submitted manuscript has been authored by a contractor of the U.S. Government under contract No. DE-AC05-84OR21400. Accordingly, the U.S. Government retains a nonexclusive, royalty-free license to publish or reproduce the published form of this contribution, or allow others to do so, for U.S. Government purposes."

METAL-ION TOXICITIES RELATIVE TO NORMAL METAL-ION CONCENTRATIONS IN AN ORGANISM.¹

M. Wendy England*, James E. Turner*, and K. Bruce Jacobson**

*Health and Safety Research Division and **Biology Division, Oak Ridge National Laboratory, P. O. Box 2008, Oak Ridge, TN 37831-6123

In our previous studies of metal-ion toxicity, we have shown that correlations exist between indicators of toxicity and selected physicochemical parameters of the metal ions [e.g. Williams (now England) et al., *Toxicol. Appl. Pharmacol.* 63:461-469, 1982; Tan et al., *Toxicol. Appl. Pharmacol.* 74:330-336, 1984; Turner et al., *Science Total Environ.* 28:343-354, 1983; 68:275-280, 1988]. This presentation will examine whether a better correlation can be obtained, for a given indicator of toxicity and physicochemical parameter, if the values of the indicator of toxicity are presented as a percentage of the normal metal-ion concentration in the organism. Supporting data for this approach are the existence of relatively high correlations between LC₅₀ *Drosophila* data and normal metal-ion concentrations [Turner et al., *Science Total Environ.* 28:343-354, 1983; Jacobson et al., *Science Total Environ.* 28:355-366, 1983; Christie et al., *Toxicol.* 26:295-312, 1983] and between interperitoneal LD₅₀s of metal oxides for mice and the normal body levels of the metals [Rabotnikova, 1965 in Filov et al., *Quantitative Toxicology*, Wiley-Interscience, 1979, p. 339]. This approach is also consistent with our observation, presented in the literature cited above, that strontium which is the least toxic metal in the mouse is relatively more toxic to *Drosophila*. *Drosophila* have a much lower normal body concentration of calcium than do mice. Thus the administration of strontium (which is similar chemically to calcium) to the organism may represent a major biochemical perturbation to *Drosophila* but not to mice. Problems, plus some limited results, will be discussed. If justified, these methods will be applied to the extrapolation of indicators of toxicity across species to man [England et al., *Health Phys.* 57(Sup. 1):115-119, 1989].

¹Research sponsored by the Office of Health and Environmental Research, U.S. Department of Energy, under contract DE-AC05-84OR21400 with Martin Marietta Energy Systems, Inc.

"The submitted manuscript has been authored by a contractor of the U.S. Government under contract No. DE-AC05-84OR21400. Accordingly, the U.S. Government retains a nonexclusive, royalty-free license to publish or reproduce the published form of this contribution, or allow others to do so, for U.S. Government purposes."

INORGANIC CONCEPTS RELEVANT TO METAL BINDING, ACTIVITY, AND TOXICITY IN A BIOLOGICAL SYSTEM.¹

James D. Hoeschele*, James E. Turner[†], and M. Wendy England[†]

*Parke-Davis Pharmaceutical Research Division, Warner Lambert Co., 2800 Plymouth Rd., Ann Arbor, MI 48106 and [†]Health and Safety Research Division, Oak Ridge National Laboratory, P. O. Box 2008, Oak Ridge, TN 37831-6123

The response elicited when a metal species (electrophile) interacts with a biological system is dependent upon a complex set of interrelationships involving physical, chemical, biological, and pharmacological effects. Physicochemical factors associated with both the intrinsic nature of the metal system and the type of biological ligands present are, to a first approximation, primary determinants in whether the interaction will be beneficial, innocuous, or detrimental to the organism. The purpose of this presentation is to examine selected physical and inorganic chemical concepts and factors which might be important in assessing and/or understanding the fate and disposition of a metal system in a biological environment. Hopefully, such inquiries will ultimately permit us to understand, rationalize, and predict differences and trends in biological effects and, in optimal cases, serve as input to a system of guidelines for the notion of "Chemical Dosimetry." The following factors and concepts will be discussed and illustrated with selected examples:

Metal System

- Kinetic reactivity/lability
- Affinity and thermodynamic stability of metal-ligand bonds
- Speciation
- Stereochemical aspects
- Periodic properties

Biological System

- Availability of ligands with high affinity for metal ions (S, N, and O donor atom systems)
- Capability for chelation

¹Research sponsored in part by the Office of Health and Environmental Research, U.S. Department of Energy, under contract DE-AC05-84OR21400 with Martin Marietta Energy Systems, Inc.

The submitted manuscript has been authored by a contractor of the U.S. Government under contract No. DE-AC05-84OR21400. Accordingly, the U.S. Government retains a nonexclusive, royalty-free license to publish or reproduce the published form of this contribution, or allow others to do so, for U.S. Government purposes.

- END -

DATE FILMED

10 / 31 / 90