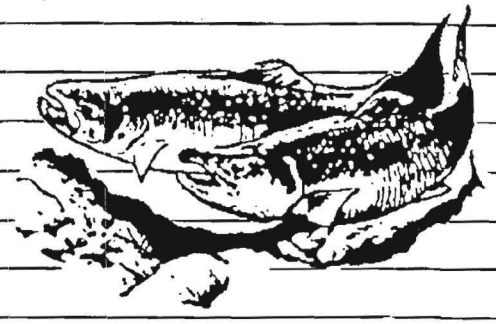
Research
Information bulletin
U.S. DEPARTMENT OF THE INTERIOR
NATIONAL BIOLOGICAL SURVEY



Number 61
1994

Linear Solvation Energy Relationship (LSER) Model Predicts the Response of a Biochemical Marker to Contaminant Exposure

The results of the H4IIE rat hepatoma cell bioassay, which is increasingly being used as a biomarker of contaminant exposure in fish and wildlife, can now be quickly and inexpensively estimated with three simple linear solvation energy relationship (LSER) equations (RIB 91-77) developed primarily for planar halogenated aromatic hydrocarbons. Contaminant enzyme induction and binding affinity for the A_h regulatory protein can now be estimated using only a contaminant's structure. These LSER equations quickly and accurately predicted relative behavior for numerous polychlorinated and polybrominated dibenzo-p-dioxins (PCDDs and PBrDDs), dibenzofurans (PCDFs), biphenyls (PCBs), and representative metabolites.

Bioassay Endpoints Indicate Contaminant Cellular Interaction

Binding affinities and enzyme induction activities are independent bioindicators of contaminant exposure and stress on an organism. Binding affinity, measured as a competition with 2,3,7,8-tetrachlorodibenzo-p-dioxin (dioxin) for interaction with the A_h regulatory protein, is an indicator of degree of contaminant-A_h protein interaction and dioxin-like activity. Similar regulatory A_h-type proteins have been identified in a wide variety of fish and wildlife. Another popular bioindicator, the dioxin-equivalent, is calculated from enzyme induction potentials. Both assays have relevance to field and laboratory investigations of the effects of contaminants on fish and wildlife.

Predictive Equations Used LSER Values and Literature Data

We correlated the LSER values for the individual compounds with literature data for binding affinities and enzyme induction using multiple linear regressions. Correlation coefficients (r^2) relating chemical structure to an endpoint ranged from 0.93 to 0.95. Relative enzyme induction activity and binding affinities for

PCBs, PBrDDs, and numerous PCDDs and PCDFs were differentiated well according to class and structure. As expected, nonplanar PCBs were not well predicted by these equations.

Enzyme induction and binding affinity data need to be collected to generate analogous predictive equations for a range of fish and wildlife species. Software already exists that will compute contaminant LSER values and predict acute contaminant toxicities for representative aquatic species (RIB 89-28).

LSER Equations Estimate Induction Potentials and Dioxin-like Activity

We generated three predictive equations that allow estimation of two types of enzyme induction activity and a measure of dioxin-like binding for a contaminant. LSER predicted relative binding affinities for many halogenated aromatic compounds related to PCDDs, PCDFs, and PCBs and their metabolites by using only molecular structures.

Compounds That Bind to Proteins May Cause Tumors in Fish

The binding affinity model using LSER is novel, indicating the likelihood of fitting a dioxin-like contaminant into the A_h receptor site on a protein. This protein then transports the contaminant into the nucleus, where DNA-contaminant interaction and subsequent carcinogenesis in fish can occur.

Compounds That Induce Enzyme Activity Linked to Chronic Conditions Such as Impaired Reproduction

Predicted induction activity for nonplanar PCBs suggested mechanisms other than the model for planar halogenated aromatics developed here. Most of the tested PCBs were ortho-substituted or nonplanar compounds, which are toxic to fish and wildlife and are more often associated with toxic effects such as neurological damage or impaired reproduction.

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