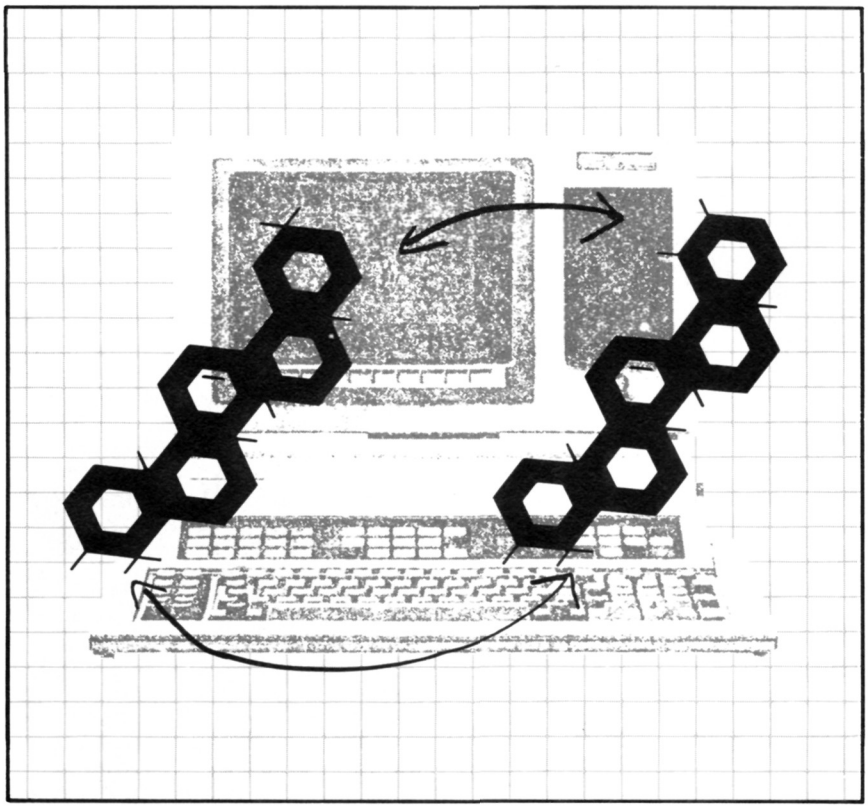
Structure–activity relationships

Are they predictors of toxicity and potential regulatory tools?



Structure–activity relationships (SARs) are a concept in chemistry that has been proposed as a means of predicting a substance's toxicity. Indeed, some environmental chemists believe that SARs have potential as a regulatory tool. SARs entail a comparison of the structure and properties of a chemical with those of known toxicants and nontoxicants. Theoretically, some indication as to whether or not a chemical is toxic is obtained.

Inner-space exploration

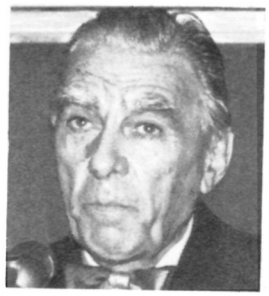
Corwin Hansch of Pomona College (Claremont, Calif.), who, with Toshio Fujita and other colleagues, has published more than 200 papers on SARs, referred to them as "the exploration of inner space." They could give chemists greater insight about chemical activity in biological systems. But, Hansch told *ES&T*, "While SARs can be very helpful to regulatory agencies in deciding which chemicals should be subject to special testing—EPA is doing this now—I believe that you cannot yet base regulations on SARs. In other words, SARs are not yet ready to use for confirming or denying market access to any given chemical, but they are of use, and are being used to *guess* which may be especially toxic or relatively safe.

"In the last 10–20 years, SARs have become a reputable field of research," Hansch continued. "But there are still many problems which are far greater than those of mere terminology. We simply do not know enough about all aspects of SARs to base laws [and regulations] upon our current understanding," he said to the Conference on Structure–Activity Relationships and Toxicity Assessment, of which he was chairman. Held at Gaithersburg, Md., in June, the conference was sponsored by the National Bureau of Standards, six groups within the American Chemical Society, and five other organizations.

"Another problem with SARs is that you have to educate people up to that science or bring it down to an understandable level so that there is a meeting of the minds between academia, industry, and government regulatory personnel," Hansch continued. "Otherwise, according to the poet W.H. Auden, 'intellectual disgrace stares from every face.' " Other problems with SARs with respect to toxicology are that their "track record" involves mainly acute toxicity. There is less knowledge about how to apply them to mutagenicity, carcinogenicity, and mammalian toxicity. As Hansch put it, "SARs suffer from a great shortage of biological data."

More descriptors needed

If SARs are to be useful as a means by which to predict toxicity, "a re-



Hansch: *SARs not yet ready for regulatory agencies*

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The development of biological SARs

Biological SARs date back to the late-19th-century work of H. Meyer and E. Overton. They showed that partition coefficients could be used to rationalize the narcotic action of simple organic chemicals.

During the 1930s, Louis Hammett of Columbia University derived the classical physical–organic chemistry equation that bears his name. That equation rationalizes the electronic effects of substituents on rates of organic reactions. Later, Robert Taft developed a parameter for doing the same thing with steric effects of substituents. Then, Hansch and Fujita showed how a hydrophobic parameter for substituents could be combined with the Hammett and Taft constants to deal with biological SARs.

Since the 1960s SARs have been used in industry as a basis for the design of new drugs and pesticides. Hansch and Fujita began the pioneering work that led to practical uses of this concept, which is considered an extension of the Hammett equation. Nevertheless, because of their complex nature, SARs might have remained a purely academic topic were it not for the computer. This is what made possible their big leap from almost pure theory to potential application.

quirement is that one must have a great amount of data with biological end points," said Paul Craig of the National Library of Medicine. Once that requirement is met, "the octanol–water partition coefficient [log P] is the most significant single physical–organic chemical property for correlative purposes." Craig was the chairman of the first Gordon Research Conference on SARs, which took place in 1975. Interest in the field has increased so greatly that speakers had to be turned away from the 1981 conference, Craig recalled. Another such meeting on SARs is planned for next summer.

Important though it may be, log P is but one descriptor. The more descriptors one has—for instance, hydrophobicity, electron energy, and configurations—the more effective SARs might become as toxicity predictors.

William Dunn of the University of Illinois at Chicago suggested identifying compounds with known toxicological end points and projecting them into a high-dimensional coordinate system or grid in which they should cluster. It is possible that a group of chemicals with another end point may cluster on another portion of the system. Those compounds of a known toxic property would be called training sets, because they "train" the observer to discern this property in certain structural patterns (pattern recognition). The coordinate system and patterns are generated by computer.

Now, an unknown compound, not a cluster or set member, would be projected onto the grid through the computer program, which would also classify the substance as to its resemblance to compounds in a training set. But what if the substance is an *outlier*; that is, what if it does not fit in a training set? Dunn acknowledged that this situation "can appear to be a problem, but it is the natural result of the analysis." He expressed the hope that such outliers can be increasingly resolved with more relevant descriptors for training set members and unknowns.

To "crank in" additional descriptors, the computer works in mathematical domains of more dimensions. One scientist once described a carcinogenicity predictor scheme based on SARs that required a program involving 37 dimensions. Unaided, the human mind presently cannot comprehend such mathematics; SAR programs of this type work because appropriate statistical methods coupled with today's computers can perceive what the human mind cannot. However, Dunn says that a large number of descriptors can be used *if* the appropriate method of analysis is applied. The use of incorrect methods would lead to results having little or no predictive utility, he added.

A regulator's view

"I am not comfortable with this topic," EPA's John Moore told a dinner session of the conference. "SARs are continuing to yield useful information, and I think their future does look bright. I also think that we're being subjected to more than a little hype and hoopla by some of our overly enthusiastic colleagues who promise more than can be delivered.

"For example, some people talk about the state of the art being 'tell me what you want, and based on what I know, I'll go to my computer and design a chemical just to meet your needs.' Somehow this conjures up a picture of the computer doing for chemistry what Calvin Klein has done for jeans.

SARs and TSCA

Section 5 of the Toxic Substances Control Act (TSCA) requires companies proposing to manufacture chemicals not on the inventory of chemicals in commerce to submit a premanufacture notification (PMN) 90 days before they intend to commence manufacture or import. Charles Auer of EPA said that since PMNs do not require test data (though these data must be submitted if they exist), SARs could be used under Section 5(e) as a basis for a finding that a proposed chemical "may present an unreasonable risk." Essentially, the SAR could indicate that there is concern about the toxicity of the chemical and that EPA's Office of Toxic Substances (OTS) should seek more information.

Many of the conclusions based on SARs are drawn from the literature and OTS staff members' expertise and memories. Structural analogue identification is made in terms of functional groups and relies on automated substructure-searchable chemical dictionaries. If, on the basis of potential effects based on an SAR, a chemical causes concern, one looks for relevant biological data on a chemical analogous to that proposed in the PMN. But what if no such biological data exist? Then one must rely on the professional judgment of staff scientists.

Thus, at OTS, scientists look for data on substances with analogous structures and attempt to quantify SARs according to log P, regression equations, and other data points. Next, they try to predict hazard and list any data that are still needed.

SARs might also be useful in the implementation of Section 4 of TSCA, by which EPA may call for testing. Gilman Veith of the EPA Research Laboratory in Duluth, Minn., has developed preliminary methods to estimate metabolism, biodegradation rates, bioconcentration factors, and acute and chronic toxicities of certain chemicals in fish.

"Proponents suggest that SARs will soon be able to generate toxicity information without testing. Maybe that idea carries a germ of truth, but it promotes expectations among members of Congress and others that are destined to remain unfulfilled [at least over the near term]." Nevertheless, Moore added, "I look forward to . . . SARs making my job as a regulator easier."

—Julian Josephson