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COVER An Asian cobra. Snake and insect venoms provide experimentalists with proteins for the study of biological action at the membrane surface. Venom phospholipase A<sub>2</sub> from a Chinese cobra, which is closely related to the one shown here, forms crystals of an inhibitor complex, the structure of which reveals the molecular mechanism of interfacial catalysis. See page 1560. [Photograph by Jessie Cohen, courtesy of National Zoological Park, Smithsonian Institution]

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## Incorporation of New Science into Risk Assessment

The Clean Air Act will eventually have some limited beneficial effect in reducing chemical risks to human health. It will be implemented at considerable expense to consumers. They will pay a subtle regressive tax, because industry will pass on to them increased costs. The act will have substantial hidden costs in creating numbing uncertainty in corporate planning and will probably lead to job losses in this country and weakened ability to compete globally. The act will enhance greatly the bureaucratic clout of the Environmental Protection Agency in its relations with industry. Principal beneficiaries of the act will be lawyers and entrepreneurial engineers.

Congress recognized that implementation of the bill will require enormous expenditures. Key members wished to be assured that the best science base available will be applied when costly standards are imposed. Their concerns were manifested in provisions in the act that stipulates, "The Administrator of EPA shall enter into appropriate arrangements with the National Academy of Sciences to conduct a review of . . . risk assessment methodology used by the Environmental Protection Agency to determine the carcinogenic risk associated with exposure to hazardous air pollutants. . . ." The act also states, "In conducting such review, the National Academy of Sciences should consider . . . the techniques used for estimating and describing the carcinogenic potency to humans of hazardous air pollutants. . . ."

The study and report produced by the National Academy of Sciences could have consequences in other areas requiring risk assessment, including Superfund and the Resource Conservation and Recovery Act. Based on its current modes of risk assessment, EPA is embarked on programs that will cost hundreds of billions of dollars but will have little impact on human health. The questionable cornerstone of EPA policy is its dependence on studies involving administration of huge levels of chemicals to rodents and highly conservative modes of extrapolations to low doses in humans with the further assumption that at trivial doses a carcinogenic effect exists. The current guidelines select the most cancer-sensitive species as the yardstick despite the fact that it is known that biochemical and other processes often differ greatly between animal species and humans.

The NAS review is to be completed not later than April 1993. It is to be submitted to relevant congressional committees, to the administrator of EPA and to a new, high-level Risk Assessment and Management Commission. Three members are to be appointed by the President, six by leaders of Congress, and one by the president of the National Academy of Sciences. The act directs this commission to make an investigation of policy implications and appropriate uses of risk assessment in regulatory programs under federal laws to prevent cancer and other chronic health effects that may result from exposure to hazardous substances. The commission is directed to consider the report of NAS on risk assessment. The commission is also, among other things, directed to evaluate "the accuracy of extrapolating human health risks from animal exposure data. . . ."

The Clean Air Act also stipulates that the risk assessment report of NAS be considered by the administrator of EPA. Before taking certain actions "the Administrator shall publish revised Guidelines for Carcinogenic Risk Assessment or a detailed explanation of reasons that any recommendations contained in the report of the National Academy of Sciences will not be implemented."

Considerable evidence is already available that the standard EPA approach is outdated and more will be forthcoming as detailed studies of metabolic and physiological processes are made. Bruce Ames and his colleagues have produced substantial evidence that results of effects of huge doses of chemicals in rodents are often misleading. A major study at the Chemical Industry Institute of Toxicology has shown that carcinogenicity of formaldehyde is nonlinear; it decreases far more rapidly than dose. Studies on dioxin have shown that the high level of carcinogenicity manifested in some animals is of doubtful relevance to humans. Thirteen important substances including D-limonene (a constituent of citrus) and unleaded gasoline, cause kidney tumors in male rats but do not similarly affect other rodents or humans.

The EPA still sets guidelines on carcinogenic risks based on the limited information available during the 1970s. The agency needs to update its regulations as new facts are discovered. The study by NAS should lead to improved ways of identifying which substances are innocuous and which are truly dangerous and to better methods of making risk assessments in the light of scientific advances.—PHILIP H. ABELSON