

UNITED STATES ENVIRONMENTAL PROTECTION AGENCY
WASHINGTON, D.C. 20460

JUN 5 1992

OFFICE OF
PESTICIDES AND TOXIC
SUBSTANCES

FILE COPY

Dr. Kenneth Olden
Director, National Toxicology Program
P.O. Box 12233
Research Triangle Park, NC 27709

Dear Dr. Olden:

The National Toxicology Program (NTP) has responsibility for developing the Annual Report on Carcinogens, a list of substances that are either known or reasonably anticipated to be human carcinogens. Given the general lack of adequate information in humans to impact these determinations, the bulk of the chemicals listed are based upon cancer findings in experimental animals, where the underlying premise is that agents that produce cancer in animals are likely to do so in humans.

Although it is reasonable to presume that animal carcinogens are human carcinogens, the position is rebuttable. Mechanistic and exposure information may modulate significantly the case for human carcinogenicity. Several of the chemicals listed in the 6th Annual Report demonstrate the problem with relying exclusively on animal tumor studies. Some of them include the following: (1) butylated hydroxyanisole, nitrilotriacetic acid and saccharin seem to cause tumors at laboratory doses associated with target organ toxicity and far beyond expected human exposure; (2) chloroform production of hepatic and renal tumors is greatly affected by specific pharmacokinetic considerations; (3) diethylhexylphthalate may produce tumors by processes not relevant to humans; and (4) iron dextran complex may present a hazard from parenteral exposure but should pose little or none via dermal, inhalation and oral exposure. Although these cases do not necessarily demonstrate the absence of any human cancer potential, they illustrate the complexities that are part of such decisions and point to the problems of using animal cancer data alone.

BFG27345

1007002

2

Without developing some appreciation of the uncertainties for human cancer potential for each chemical in the Report, the naive reader is forced to conclude that all listed substances have the same hazard potential. Certainly that is not the case. Likewise, the listing of chemicals in the Report has implications for potential regulatory action by states and certain federal authorities. Therefore, we urge you to produce more analytical evaluations of listed chemicals. This Agency has learned over the years the importance of going beyond the animal cancer studies in making hazard determinations, and the International Agency for Research on Cancer is beginning to recognize the significance of mechanistic information in their classification decisions. We urge the NTP to do likewise. Implementing these recommendations are in keeping with your laudable desire to strengthen the National Toxicology Program by conducting mechanistic studies to augment results from chronic studies and make outputs more meaningful to regulatory agencies and the public.

Sincerely,



Victor J. Kinn
Deputy Assistant Administrator
Office of Prevention, Pesticides
and Toxic Substances



William H. Farland, Ph.D.
Director, Office of Health
and Environmental Assessment
Office of Research and Development

23812002

AUG 12 '92 15:07

BFG27346

TOTAL P.05
PAGE.005