

# ABSTRACTS

## **Species Differences with Regard to the Therapeutic Activity, Toxicity, and Carcinogenicity of Xenobiotics.** RICHARD H. ADAMSON, *Laboratory of Chemical Pharmacology, National Cancer Institute, National Institutes of Health, Bethesda, Maryland 20014*

Species differences with regard to the therapeutic activity, toxicity and carcinogenicity of various xenobiotics may be attributed to many factors which have been classified as internal environmental factors, external environmental factors, or xenobiotic administration factors [Dearborn, E. H., *Fed. Proc.* 26: 1075 (1967)]. Examples of internal environmental factors are sex, age, weight, nutritional state, and pregnancy; examples of external environmental factors are temperature, sound, time of day, or ambient atmosphere composition; examples of drug administration factors are route and rate of administration, particle size, or vehicle in which administered. Even when these types of factors are properly controlled, species exhibit differences with regards to their response to xenobiotics. Among the reasons for these differences are: differences in xenobiotic disposition, i.e., absorption, distribution, metabolism and excretion (Adamson, R. H., and Davis, D. S. In: *International Encyclopedia of Pharmacology and Toxicology*, M. J. Michelson, Ed., Pergamon Press, Oxford-New York, 1973, Section 85, Chapt. 9, pp. 851-911); anatomical and physiological differences; differences in binding to plasma protein and at the receptor site; interaction with virus, especially oncogenic virus present in inbred species; differences with regard to DNA repair and differences in amount of repair enzymes; and differences in the diet and the amount of nucleophils in the diet which may protect against electrophilic attack and thereby modify the potential clastogenic, mutagenic, teratogenic and carcinogenic potential of the xenobiotic.

Examples of these differences are given when possible and areas in which little data exists and research is needed is also stressed. In particular, it is suggested that, in species in which xenobiotics exhibit only weak carcinogenic effects as compared to untreated control animals, the potential role of interaction which "C" type particles must be examined, and that these data cannot always be extrapolated to humans.

## **Chemokinetics.** DANIEL S. ZAHARKO, *Laboratory of Chemical Pharmacology, National Cancer Institute, Bethesda, Maryland 20014*

In order to extrapolate results of laboratory animal data to man with reasonable expectations of validity, certain factual scientific information must be known. Scientists and regulatory agencies have primarily used dose-effect relationships in animals as the basis for extrapolation to expected effects in man. Such data with arbitrary "safety" factors included most often provide the estimated safe level of exposure. There are other kinds of information which can be used to increase predictive reliability. If a substance is toxic to an animal species it is important to understand the biochemical mechanism by which this toxicity is created. Does the substance compete with normal substrates for an enzyme or bind to an enzyme? Does the substrate react with

essential macromolecules (nucleic acids, membranes or cytoplasmic organ, by inducing an enzyme or by chelation of an essential trace metal)? These examples are just a few of many possible ones to illustrate the potential variety of mechanisms. Knowledge of the mechanism of action alone however is far from sufficient to predict toxic effects within a species at different doses or from species to species. This has been thoroughly demonstrated with antimetabolites in cancer research (Zaharko, D. S. In: *Pharmacological Basis of Cancer Chemotherapy*, Williams & Williams, Baltimore, 1975, p. 69).

Another important consideration is the chemokinetic behavior of the substance within an animal. Such information with many drugs has been collected and several important principles have been elucidated. The importance of proper scaling from species to species is one factor which is frequently neglected. There are still scientific reports which criticize toxicity studies in small animals as being nonrelevant to man because of the much larger dose (usually expressed in mg/kg) used in the small experimental animal study. There is still a lack of appreciation for the higher metabolic rates and higher clearances that generally exist in experimental animals as compared to man. (Schmidt-Nielsen, K. *How Animals Work*. Cambridge Univ. Press, New York, 1972, p. 54). These factors affect the rate of delivery of substances to tissues in intact animals. Other factors affecting delivery to intracellular compartments are blood flow, mixing volumes, membrane permeability and binding. Computer models can simulate such factors and give insight concerning their relative significance in determining concentration and exposure time at the actual site. [Lutz, R. J., et al. *J. Pharmacokin. Biopharm.* 3: 77 (1975)].

If concentrations at the active site can be predicted and the biochemical mechanism is known, then ways of counteracting the effect may be considered. When environmental exposure is inevitable or accidental, use of another substance to protect against toxicity might be effective.

## **Variability of Risk Extrapolation in Dose-Response Experiments.** CHARLES C. BROWN, *National Institutes of Health, Bethesda, Maryland 20014*

The number of chemicals in the environment which are found to be associated with carcinogenic activity is increasing at a rapid pace. For the carcinogens which cannot be easily eliminated, an estimate of the risk to the population should be made before any decisions can be taken. Since information on human populations exposed to the chemical is not available in most cases, data from animal experiments conducted at high doses are used to estimate the cancer risk at low dose levels.

The estimation of this low dose risk attributable to the agent under test consists of extrapolation from the observable dose-response relationship at high dose levels to doses close to zero. This extrapolation procedure must, by necessity, be based on some assumption concerning the dose-response relationship at these lower dose levels. This assumption is generally arbitrary, since little is known about the carcinogenic process in this low dose region. Because of this lack of knowledge, the current approaches to risk estimation have tended to be conservative in

nature. These current approaches do not embody good statistical practice in that there is no measure of the variability of the estimated risks or extrapolated "safe" dose levels. Everyone agrees that these methods lead to conservative answers, and, from the aspect of public safety, this is a reasonable goal. If public safety is of predominant concern, however, then the most conservative approach would simply be to ban the use of all such chemicals shown to be carcinogens and the concern over estimating "safe" dose levels would be a moot question. Therefore, if we are going to accept extrapolation as a necessary evil, the only prudent decisions can be made on risk estimation procedures that are not completely arbitrary and assumption-dependent but include some measure of the uncertainties inherent in these estimates. The purpose of this paper is to suggest methods of measuring the two components of this uncertainty, variability due to sampling and due to dependency on a specific dose-response model.

Two techniques are proposed for measuring these components of variation, a relative likelihood analysis to measure sampling variation combined with a general multiparameter dose-response model to measure the model-specific variation. Experimental data on dimethylnitrosamine fed to female rats are used to illustrate these techniques and to point out the practical difficulties of fitting models to dose-response data. Threshold models and the difficulty in distinguishing between threshold and nonthreshold models are also discussed.

**Qualitative Extrapolation from Laboratory Assay to Humans as Seen Through the Carcinogenicity, Mutagenicity or Teratogenicity of Vinyl Chloride, and Anesthetic Gases.** JOSEPH K. WAGONER, *Occupational Safety and Health Administration, Washington, D. C. 20210*, and PETER F. INFANTE, *Industry-Wide Studies Branch, Division of Surveillance Hazard Evaluation Field Studies, National Institute for Occupational Safety and Health, Cincinnati, Ohio 45226*.

Historically, most toxic agents which have been documented by observations both in humans and experimental animals, were first identified post hoc in man, through fortuitous clinical impressions, explosive surfacing of rare diseases or structured epidemiologic investigations. Subsequently, these observations were confirmed repeatedly by animal bioassay over a wide range of doses and species. Certainly this pathway has been the case for most identified carcinogenic or embryotoxic agents. Such is true for soot, tar, aromatic amines, asbestos, chromates, nickel carbonyl, lead, thalidomide, and many other agents. This high concordance of toxicity between man and animal for these agents has suggested to many the value of screening of chemicals prior to their introduction into the environment. This same high concordance has been argued by others to be an artifact arising from tests of chemicals already known to be toxic to man.

Recent observations, however, with regard to DES, BCME, vinyl chloride and anesthetic agents, now demonstrate and fortify the unbiased value of animal bioassay and other short-term *in vitro* test systems as powerful qualitative predictive tools for assessing the spectrum of carcinogenic, mutagenic and teratogenic hazards to man. Evidence for the carcinogenicity and mutagenicity of vinyl chloride is presented going from the laboratory assay to observation in man. The teratogenicity of anesthetic agents is presented, first in animals and then among humans.

**Dose-Response Relationships in Radiation Carcinogenesis.** FREDERICK P. LI, *Boston Field Studies Section, Epidemiology Branch, National Cancer Institute, Boston, Massachusetts 02115*

Extrapolation of carcinogenesis data from intensely exposed persons to populations exposed at low levels is often complicated by problems of individual susceptibility, inaccurate dose measurement, long latency, and inadequate numbers for study. In this discussion, findings are presented of two recent studies of patients given therapeutic irradiation in childhood. One group of 414 persons was intensely treated, and developed excess cancers. The absolute risk was 1.8 cancers in exposed tissues per million person-year-rads. The relative risk was 20-fold above expectation. In contrast, the second series of 4,746 patients received much lower doses of irradiation, and showed no increase in cancer mortality rates. The studies suggest a dose-response relationship, but the two series differ for many risk factors other than the nominal dose of radiation. Data from the literature also show evidence of dose-response, despite the diverse conditions of exposure to ionizing radiation. For leukemia, studies of atomic bomb survivors and of irradiated spondylitis patients show increasing risk of the neoplasm with increase in dose. For the thyroid gland, the frequency of nodularity, including carcinoma, rises proportionally with dose. In patients exposed to several radionuclides, a dose-response is also demonstrable. These and other studies constitute the data resource from which judgements are made regarding the hazards to the general population of much lower doses of radiation. A number of reports suggest a linear dose-response effect for carcinogenesis under conditions of exposure to very high levels of radiation at a high dose rate. However, in several studies, a nonlinear model is also possible. With either model, dose-response relationship beyond the range of measurement is based on extrapolation. There are biologic reasons to suspect that at high doses of ionizing radiation lethality predominates oncogenic effects, so that fewer tumors are produced. At low doses cells may repair radiation injuries, so that the carcinogenic effect is also diminished. With the uncertainties of estimating risk of cancer following exposure at low doses, safety recommendations are often made on pragmatic grounds that take into account cost versus benefit considerations. For radiation carcinogenesis, linear interpolation into the low-dose range appears to be a prudent method for deriving approximate numerical estimates of cancer risk for man. However, risk estimates are not inviolable, and should be modified as relevant new data are accumulated.