Conference on Extrapolation of Data from Animals to Man

The increasing recognition that environmental toxicants have an impact on human health, particularly in various chronic diseases and cancer, has placed the burden of their control on Federal agencies. To make the necessary decisions, they need definitive evidence of human risk. Among the myriad agents to which we all are exposed, only a few hazards are established. These are occupational hazards, caused by extraordinarily high exposures, and of course cigarette smoking, but the effects of low, protracted exposures are unknown and probably unknowable. The problem is that animal assays for carcinogenesis with reasonable numbers of animals are statistically significant only with incidences of 5 to 10%. To achieve this incidence high doses must be administered, usually throughout a large proportion of the animals’ lifetime. To estimate risks to humans, whose exposure levels are orders of magnitude lower, it is necessary to extrapolate. The scientific bases, the methodology, and the validity of estimating human risks from animal assays were the subjects of a conference organized by the NIEHS1 at Pinehurst, N. C., March 10 to 12, 1976.

Presumptive tests for carcinogenesis based on mutations in microorganisms or eukaryotic cells, or on transformation, were described by W. G. Flamm (NCI); and on DNA damage and repair by T. Mitchell (NIEHS). These in vitro methods hold great promise as research tools and for screening but unfortunately are not yet ready to replace the costly and time-consuming animal assays. Much attention was devoted to the complexities and uncertainties inherent to both the assays and extrapolations. R. H. Adamson (NCI) dwelt on the many difficulties of evaluating species differences; internal and external factors; mode, site, and schedule of administration; and the possible effects of viruses that are ubiquitous in animals, especially mice. He felt that we are not yet ready to extrapolate animal tests to man and pointed out that DDT is carcinogenic in animals, but not in man. This was disputed by Marvin Schneiderman (NCI), however, who stated that human DDT data are not conclusive. He also made reference to an as yet unpublished report by M. S. Meselson, who analyzed the available data and concluded that 6 substances that are known to produce cancer in man, and for which human exposure data can be estimated, produce at the same exposure levels tumors of the same type and site in animals. D. Clayson (Eppley Institute), however, questioned the accuracy of the human exposure data in the Meselson report. H. L. Falk (NIEHS), Clayson, and D. P. Rall (NIEHS) emphasized other complexities. Falk stressed the difficulty of assessment of effects of promoters; Clayson cautioned on the differing effects in different species of diet, immune mechanisms, and activating enzymes on the number, nature, site, and time of tumor development. Rall pointed to the heterogeneity of human populations, which makes some people more susceptible than others. J. M. Brown (Stanford University), in a statistical analysis, emphasized the many uncertainties inherent in extrapolations from high to low dose effects.

Interspecies differences were discussed by others. R. T. Williams (St. Mary’s Hospital, London, England) pointed out marked differences in detoxication mechanisms that closely follow evolutionary relationships, and D. S. Zaharko (NCI) described differences in pharmacodynamics. W. Weber (University of Michigan) reported marked differences among humans in their ability to detoxify the drug, Isoniazid, by acetylation. L. Strong (M. D. Anderson Hospital and Tumor Institute) listed a series of human genetic abnormalities and emphasized their important role in elevating the risk of cancer to human subpopulations.

Despite these inherent complexities, much data emerged that lend confidence in animal assays as predictors of human risk. An important principle in extrapolation is that there is a simple mathematical relationship between dose and response over a wide dosage range. A linear dose-response relationship was shown by C. Nauman (Brookhaven National Laboratory) for mutation in Tradescantia by radiation or volatile chemicals. L. Dobson (Lawrence Livermore Laboratory) made similar findings with respect to neonatal damage to oocytes in mice by tritium radiation (at levels uncomfortably close to allowable human exposures). Similar linear dose-response relationships were reported by A. A. Infante (Wesleyan University) for human exposure to volatile halocarbons; and by P. Enterline (University of Pittsburgh) for asbestos. H. Guess (NIEHS) and K. Crump (Louisiana Technical University) also concluded, from available data on human exposures to chemicals or ionizing radiation, that the dose-response relationships are all linear. None of the dose-response data provided evidence for the existence of thresholds for carcinogenesis. Similar dose-effect relationships held for catastrophic radiation effects as reported by F. Li (Harvard University) and H. Jones (University of California). The latter, however, pointed out that, since the latent period for carcinogenesis incidence was proportional to the cube root of the dose, at low doses the latent period should extend beyond the normal lifespan. However, R. Peto (Oxford University, Oxford, England), who presented a persuasive mathematical analysis of the dose-effect-latency interrelationships in carcinogenesis, declared that, when one takes into consideration the “background” of multiple carcinogens to which we are exposed, we are compelled to accept the following “dogmas”: at low exposure rates the age distribution is independent of dose; the effects are linearly related to dose; and no thresholds exist.

The wealth of experimental, epidemiological, and mathematical data presented at this conference left no doubt that much work is needed to clear up the many complexities and uncertainties inherent in animal assays and their interpretation and in their application to estimate risks to the diverse and heterogeneous human population. Nevertheless, the

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1 The abbreviations used are: NIEHS, National Institute of Environmental Health Sciences; NCI, National Cancer Institute.

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"message" conveyed was that useful information can be provided by animal assays, from which reasonable approximations of human risk can be estimated. Concerning thresholds, Rall explained that, while they may exist, they must occur at some indeterminable low level; considering the already substantial and increasing influx of potentially carcinogenic chemicals into the environment, the concept of threshold is useless in the assessment of human risk of increased neoplasia and of damage to the genetic apparatus.

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