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The Paradoxical Lack of Interspecies Correlation between Plasma Concentrations and Chemical Carcinogenicity

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Several chemicals have been shown, within the limits of epidemiology, to be thus far not carcinogenic in humans at systemic exposure levels similar to those associated with carcinogenicity in rodents. The data are discussed in terms of mechanisms which appear to operate in rodents but not in humans. Pharmacokinetic methods for interspecies comparisons must always be validated by a complementary scrutiny of the pharmacodynamic processes involved, i.e., by considering the responsiveness of the species in question to a given systemic concentration of xenobiotic. For carcinogenesis this validation step is usually beyond reach, due to the time frame for the onset of cancer in humans. For these reasons it is argued that, in the absence of knowledge of mechanisms, there is usually no scientific basis for using the concentrations of a xenobiotic that occur in body fluids or tissues during a rodent carcinogenicity test to make a quantitative carcinogenic risk assessment in humans. © 1993 Academic Press, Inc.

Concern is sometimes expressed that a life-span toxicology study in rodents which provides no evidence of carcinogenicity cannot be valid as a predictor of human risk if the plasma concentrations of the test substance are relatively low in rodents when compared with those in humans. The author attempts to demonstrate that this concern is misplaced, for reasons which are, at first sight, paradoxical.

Over 50% of the many hundreds of chemicals tested for carcinogenic potential in lifetime rodent tests have given a positive result (Ashby and Tennant, 1991; Gold *et al.*, 1989; Huff *et al.*, 1991). Yet, only about 35 chemicals or groups of chemicals have been identified as being carcinogenic to humans (IARC, 1987; Vainio *et al.*, 1991). One obvious explanation for this apparent oversensitivity of the rodent test system is that the animals may simply be subjected to exposures of the test chemicals which are much higher than those that humans experience (Ames and Gold, 1990). Thus, even if the species possess an intrinsically similar response to a carcinogenic insult, one would expect a much lower incidence of cancer in humans. This exposure discrepancy is exacerbated, of course, by the usual practice of dosing animals at the maximum tolerated dose, thereby creating conditions which do not occur in humans, but which may predispose to carcinogenesis in animals by virtue of reparative hyperplasia in response to chronic irritation or organ damage.

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However, one must also consider whether rodents might be intrinsically more sensitive than humans to some carcinogenic insults. In general, rodents metabolize xenobiotics many times faster than do humans and for this reason plasma concentrations after a given dose are usually much lower in rodents than in humans. A growing number (now about 20) of rodent carcinogens are putatively noncarcinogenic in humans exposed at essentially similar dose levels (Goodman and Wilson, 1991; IARC, 1985) and where data are available (see later), the concentrations of these substances in body fluids or tissues of humans sometimes exceed those associated with carcinogenicity in rodents. This suggests that there must be differences in response between rodents and humans to these particular carcinogenic challenges and that, therefore, one cannot assume that a given systemic exposure in rodents and in humans corresponds to an equivalent carcinogenic response in each species.

The lack of carcinogenicity of some chemicals in humans despite circulating concentrations greater than those in rodents can often be reconciled by an understanding of the mechanisms involved. Evidence contributing to this viewpoint is reviewed in this paper.

THE RODENT IS ONLY A SURROGATE MODEL

It is salutary to recall that the rodent is only intended as a model for human risk assessment and it is pertinent to address its validity and limitations in meeting this objective. There are many types of scientific models and an investigator must generate his/her own criteria for a model. In the present context one must examine how well the data fit the model. First, how well does the pattern of tumor incidence observed in humans correspond to that which occurs spontaneously or by chemical treatment in rodents? And does one understand why the correspondence is good for some organs and not for others? Without such understanding one can have little confidence in using our model in a predictive sense.

The incidences of some common and other relevant tumors, estimated for the United States for 1990, are presented in Fig. 1. It is arguable, of course, as to what proportion of these tumors is "spontaneous" (since cancer is a degenerative disease associated with aging) and what proportion arises from external causes. Also presented in Fig. 1 are the incidences of tumors which occur spontaneously in untreated control animals from one strain of rat and one strain of mouse commonly used in carcinogenicity studies by the pharmaceutical industry. The generally poor concordance between humans and rodents is disconcerting, in several senses: some tumor types with a high incidence in humans (even though those may be partially preventable) occur rarely in animals and, conversely, some tissues with a high spontaneous tumor incidence in animals seem to be only slightly susceptible in humans.

While the tissue distribution pattern of the rodent tumors is itself a concern, the intrinsic variability of the incidence further reduces the investigator's confidence in the robustness of the model. Suggestions have been made that the variability might be related to an uncontrolled and variable incidence of unidentified dietary contaminants, but as researchers are continually learning, the process of carcinogenesis is subject to many, often poorly understood influences—diet (fat, fiber, anti-oxidants, calories, fungal metabolites), hormonal milieu, metabolism rate (environmental tem-

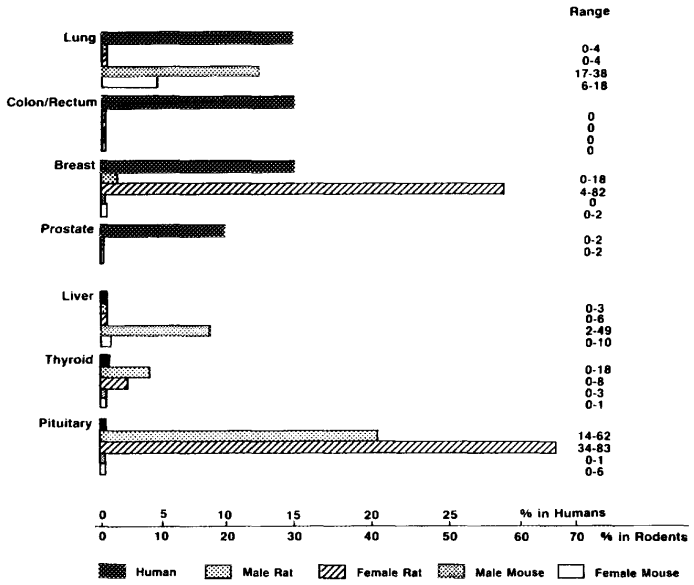

FIG. 1. The incidence of some human cancers (for 1990 in the United States) (data from Ries *et al.*, 1990) and the spontaneously occurring tumor incidence in Sprague–Dawley CD rats and CD-1 mice in the Pfizer laboratory, Amboise, France (data kindly supplied by Dr. B. Leblanc, derived from approximately 1500 control male and female rats and 1200 control male and female mice; about 50 or 100 animals/group). Reproduced, by permission of the publisher, from McAuslane *et al.* (1992).

perature, noise stress), etc. Against such an intrinsic variability researchers must be very cautious in the biological significance they attach to an increase in the incidence of a spontaneously occurring tumor.

Nevertheless, let us examine the frequency with which these same organs were deemed to be targets in a large survey of the literature, covering 341 studies in rats and 278 studies in mice (Gold *et al.*, 1989). The lack of concordance with human data remains disconcerting (Fig. 2). Worrisome, for example, is the fact that several important tumor sites in humans—the lower gastrointestinal tract and the prostate—are relatively rarely identified as target sites in rodents; by contrast, rodents could be said to be "overreacting" in respect of responses in the liver (especially), stomach and thyroid and of leukemia.

Another way to look at the problem is to consider recent trends, rather than the actual incidences of particular tumor types. If the continuing exposure to environmental chemicals is contributing to human cancer, one might expect that the pattern of the target organs in rodent studies would correspond to the changes in tumor incidences reported recently for humans. The changes in incidence of various tumors in humans in the United States over the period 1973–1987 are indicated in Fig. 3. It is recognized, of course, that in some cases the apparent increases in incidence may be a result of

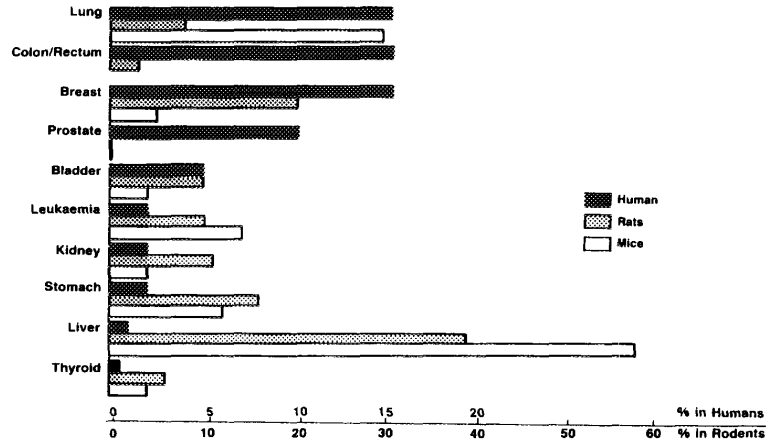

FIG. 2. The incidence of some human cancers (for 1990 in the United States) and the target site frequency of carcinogenicity in rodents (data from Ries *et al.*, 1990; Gold *et al.*, 1989). Reproduced, by permission of the publisher, from McAuslane *et al.* (1992).

better methods of detection. Disregarding lung tumors (because of the dominant role played by tobacco in humans), it is clear that several of the important trends in human cancer—increases in cancer of the prostate, testis, and kidney and decreases in leukemia

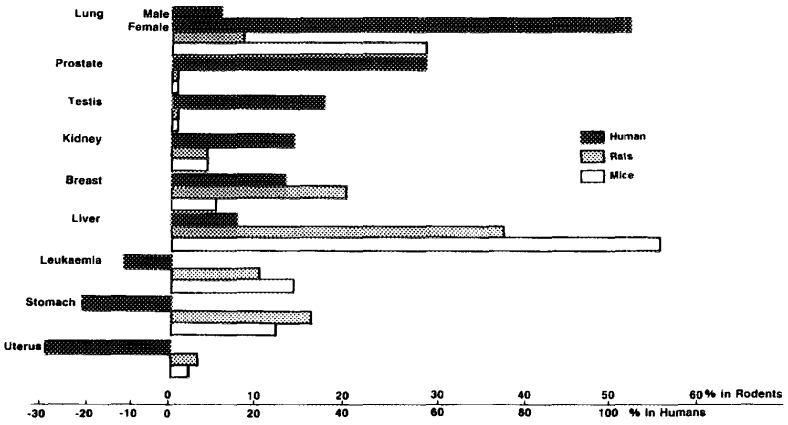

FIG. 3. Trends in the incidence of some human cancers (1973–1987 in the United States) and frequency of target sites for carcinogenicity in rodents (data from Ries *et al.*, 1990; Gold *et al.*, 1989). Reproduced, by permission of the publisher, from McAuslane *et al.* (1992).

and in cancer of the stomach—are not replicated by the tests in rodents. Examination of target organs for a more limited group of pharmaceutical agents (Marselos and Vainio, 1991), the use of which has also increased dramatically in the past 15 years, gives no better correspondence. Overall, these analyses suggest that if chemicals are contributing to the load of human cancer, the target sites in humans would be poorly predicted from the results of chronic rodent bioassays as presently conducted.

Thus, it is clear that the rodent model has some serious defects. The discrepancies in tumor patterns between humans and rodents suggest that there are some important differences in the susceptibility to spontaneous cancer in these species. It is against this background that researchers have to assess whether the study of plasma concentrations can improve their rodent model for the purpose of making risk assessments in humans.

CAN PHARMACOKINETICS IMPROVE THE MODEL?

It is clear that if one wishes to examine the various steps between the administration of a dose and production of a biological response, one must incorporate both pharmacokinetics (PK) and pharmacodynamics (PD) into the model (Fig. 4). The first phase comprises the processes of absorption, distribution, metabolism, and excretion (ADME), which determine how much and with what time/concentration profile the active moiety is present at the site of action. Data derived from plasma concentrations are inevitably limited in this respect, since they do not represent the concentration at the site of action; in addition, subtle differences in plasma protein binding can obscure potentially important interspecies differences in tissue distribution patterns. Furthermore, there is often little reason to assume that the parent xenobiotic, which is usually the first target of measurement, is itself the potentially carcinogenic substance (see later discussion). However, the second step—the pharmacodynamic one—presents a major impediment to interspecies comparisons. As is being increasingly recognized, the significant advances being made in biologically based pharmacokinetic (PBPK) models, while excellent in helping to better determine the delivery of the parent drug

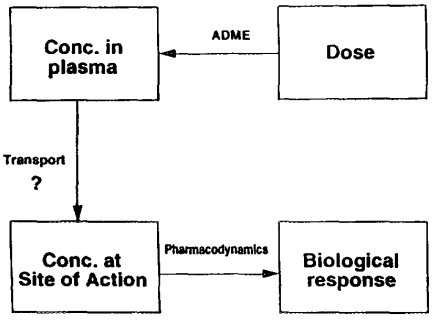

FIG. 4. The pharmacokinetic and pharmacodynamic steps relating the administered dose to biological response. Reproduced, by permission of the publisher, from McAuslane *et al.* (1992).

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