

SECTION 1

**SOCIETAL INTERACTIONS WITH
VETERINARY PHARMACOLOGY**

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Promoting Human Health: The Role of Veterinarians in Risk Assessment

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Introduction

In this paper I will offer a commentary on the role of veterinarians in risk assessment using as examples research results from the Chemical Industry Institute of Toxicology (CIIT). As a prelude to the discussion of risk assessment, I will briefly describe the Research Triangle Park environment in which CIIT is located and then describe CIIT. The comments I offer are based on the perspective I have gained from my own training as a veterinarian, more than thirty years of experiences as a scientist and research manager investigating the toxicity of radiation and chemicals, and service on a wide range of advisory bodies.

The Research Triangle Park and Veterinarians

The Research Triangle Park in North Carolina was established in 1959, and covers over 6000 acres. It is in close proximity to three doctoral granting-research universities with over 60,000 students--Duke University, North Carolina State University and the University of North Carolina at Chapel Hill. More than 50 corporations and institutions are located in the Research Triangle Park today with over 30,000 employees. A substantial number of organizations that have a strong life science orientation are located in the Park, including BASF Agricultural Research Center, Becton Dickinson, Burroughs Wellcome, Chemical Industry Institute of Toxicology, CIBA-GEIGY Biotechnology Corporation, Compuchem Corp., Glaxo, National Center for Health Statistics, National Institute of Environmental Health Sciences, North Carolina Biotechnology Center, The Research Triangle Institute, Rhone-Poulenc Ag Co., and the US Environmental Protection Agency Research Laboratories. A number of veterinarians are associated with almost every one of these organizations. These veterinarians combined with

those associated with the North Carolina State University College of Veterinary Medicine result in the Research Triangle Park area having one of the nation's largest concentrations of veterinarians engaged in research and educational activities. Veterinarians are playing a key role in these organizations as research scientists and managers. Many of the veterinarians employed by organizations in Research Triangle Park also hold adjunct appointments in the North Carolina State University College of Veterinary Medicine, the medical schools at University of North Carolina - Chapel Hill and Duke University, and in other university departments.

Overview of CIIT

CIIT is a private, not-for-profit research institute, supported by 48 member companies. The Institute's creed is to perform science in the public interest. Its mission is to provide an improved scientific basis for understanding and assessing potential adverse effects of chemicals, pharmaceuticals and consumer products on human health.

Over the past year and a half, member company support has grown from 30 to 48 member companies. A very large number of these corporations have been a part of CIIT since its founding in 1976. These founding companies had the foresight to recognize the importance of pooling their financial resources to assure that an improved understanding of the toxicity of a variety of compounds could happen for the common good. CIIT's member companies provided financial support in the amount of approximately \$12.6 million to CIIT this year, augmented by approximately \$2 million in revenue from investments and grant support from various trade associations, making CIIT one of the more substantial comparative toxicology research institutions in the world.

The urgent need for the testing of

commodity chemicals originally brought these organizations together. During the early years of the Institute, the acute and chronic toxicity of a number of chemicals was tested, with particular reference to carcinogenicity. Substantial emphasis was also given to the development of new testing methodologies. As those results came in, it became apparent that increased emphasis was needed on the development of a clear understanding of the mechanisms by which these agents acted. Simply to have a knowledge of an association between exposure and a health outcome was not sufficient. One had to understand why and how that health outcome came to be. That was the thrust of CIIT's research program through the 1980's.

During the past two years substantial effort has been directed to assess our research program and its future direction. Out of that assessment has come the decision to continue the emphasis on understanding mechanisms of toxicity, but also, to give increased emphasis to using a risk assessment approach to focus the studies on mechanisms of toxicity, to yield the greatest impact in understanding the potential health risks of chemicals, pharmaceuticals, and consumer products.

Under our current program, CIIT's objectives place substantial emphasis on understanding the implications of molecular, cellular and animal toxicity data, in concert with available human data, for assessing exposure-related impacts on human health and disease - with specific concern for what might be viewed as two sides of a coin. Risk on one side, safety on the other. On one side of the coin lies human health risks from occupational and environmental exposure to materials while on the other side of the coin, species extrapolations used in product safety evaluations for humans and animals.

The underlying scientific information that is needed to make these assessments is similar.

Extrapolation issues, well known to pharmacologists, are the foundation upon which toxicology is continuing to build. These issues are related to exposures: from high to low, continuous to intermittent, single compounds to mixtures, route-to-route concerns, and animal species to man. Other issues are those related to extrapolating between individual compounds and classes of compounds. Emerging as the most significant extrapolation issue of the 1990's is the problem of bringing together information from molecular, cellular, tissue or organ system models of specific processes to understand what is happening in the

intact mammal. An additional major issue relates to the need to shift our concern from a laboratory orientation involving small homogeneous populations, to large heterogeneous populations of people or animals. For both of these issues an understanding of the relationships among exposure, dose and response (although a relatively simple and straightforward paradigm) provides a very sound underpinning for the conduct of research that offers the opportunity to make realistic assessments of health risks.

Veterinarians have much to offer in resolution of the issues identified above. They are trained to integrate information from the molecular, cellular, tissue and organ level to understand the normal biology and pathobiology of the intact mammal. Moreover, they have a strong population orientation.

In the past, much of the research in toxicology was concerned with the association between exposure and response. As one of my colleagues recently said, "We treated what was in the middle as a black box." We exposed animals, saw an outcome, and then proceeded in a very qualitative sense to make extrapolations across species. That kind of qualitative extrapolation may have been adequate in the past, but it is absolutely essential that we become more quantitative as we go forward. No longer can we consider banning a world of materials from commerce, or legislate against any potential contact with people, simply by classifying a compound as a carcinogen. Today, it is increasingly appreciated that at high levels of exposure many compounds may be shown to be carcinogenic in some particular animal species. The underlying mechanisms that cause the cancers may vary widely.

Two key inter-related questions emerge in considering the relevance of these findings to assessing human cancer risks; (1) are the mechanisms operative in the laboratory animal species operative in people and (2) are the mechanisms causing cancer at high levels of exposure operative at the low levels of exposure likely to be encountered by people?

An understanding of these mechanisms is essential for realistically appraising risks to people. Unrealistic assessments, either too high or too low can be costly in terms of human suffering or may deny society access to useful materials, including new pharmaceutical agents.

In our laboratory and in others, scientists are increasingly seeking to understand the mechanisms that underlie the relationship between the

concentration present in air, food, or water, and the dose that is delivered to critical biological units. This dose orientation has moved from the organ level down to tissues, cells and finally to the molecular level. In turn then we are trying to understand the role of these doses in putting in play a series of events at the molecular, cellular and, ultimately, organ level that may result in the manifestation of clinical disease.

CIIT's research program themes carry forward this paradigm of exposure, dose and response relationships. A significant risk assessment orientation is used to help guide the Institute's substantial programs in chemical carcinogenesis, respiratory toxicology, and lesser efforts in reproductive/developmental toxicology, neurotoxicology and immunotoxicology. The research approach being taken is strongly multidisciplinary with veterinarians having a promised role. At any given time about 25% of the doctoral staff at CIIT are Doctors of Veterinary Medicine, most of whom have specialty training in toxicology and pathology or are currently training in these specialties.

The Institute now puts about 75% of its resources into the studies of chemical carcinogenesis and about 15% into respiratory toxicology with lesser effort used for research on reproductive and developmental and neurological diseases that may be caused by toxicants. At CIIT, we are now in the process of carefully reviewing the resources being allocated to these latter areas and considering what is needed to achieve a critical mass of personnel in these areas in the future so we can have impact. Certainly, more research is needed in these areas. However, the level of effort must be significant to have a realistic chance of making progress.

Like CIIT, all the various institutions that involve veterinarians must assess how the resources at hand can be used to achieve the most impact. This is very difficult to do in any setting and especially when veterinarians, who tend to be highly individualistic, are involved. The situation is especially difficult for teaching institutions, where responsibilities extend across a profession as broad as veterinary medicine. But I think it must be recognized that for schools to excel, we (laboratory scientists, clinicians and administrators) must prioritize and focus our collective resources. Real discipline on the part of the institutions and the people associated with them will be required. Certainly, not every school of veterinary medicine in the United States can excel in any given area such as

veterinary toxicology or pharmacology. I would hope, however, that by the turn of the century we would have four or five schools serving as prime resources in areas such as these from which knowledge could flow to other institutions. The time has long passed when a given institution could expect to excel in all facets of veterinary medicine. Assessment of our resource base helps us put in perspective what we have to do if veterinary medicine is going to effectively compete and be a part of the broad scene of comparative medicine in the United States and the world.

CIIT's Educational Program

CIIT contributes to the educational process in several ways, particularly through its very extensive postdoctoral program, currently with some 25 individuals participating. A large number of these participants are veterinarians. CIIT postdoctoral fellows, on finishing training at the Institute, are positive contributors to industry, government and academia. Over one-half of our former postdoctoral fellows accepted industrial positions, principally with pharmaceutical and chemical companies, while others have filled important positions in government and academic institutions. Certainly from the standpoint of compensation and professionalism, I can assure you that their level within organizations and compensation fits in on the right side of the bell-shaped frequency distribution of starting salaries and advancement. Students should be made aware, both before entering and during the time that they are in veterinary school, of the broad range of opportunities that are available in both traditional clinical practice and research. We need to redefine the practice of veterinary medicine to include research. And when the right candidates are selected to enter Colleges of Veterinary Medicine, there will be no question about their ability to enjoy a satisfying professional career with an appropriate level of compensation.

CIIT also hosts a significant number of visiting scientists including some who are veterinarians. This program is designed to acquaint senior scientists from industry, academia and government with contemporary toxicologic research methods as well as to provide an infusion of specialized skills into our institute. I think there is a particular need today to encourage people from various sectors of society; industry, academia and the government, to work together. I can think of no

better way to accomplish this goal than to facilitate a fluid exchange of scientists with their specialized knowledge between the various sectors.

CIIT is a unique organization in terms of its industrial funding, which permits the Institute to meet long-term collective needs rather than the proprietary or immediate regulatory requirements of companies. This funding provides a stable base of support for high risk, long-term interdisciplinary team research. We can focus on resolution of real-life issues using contemporary technology, and we can use research approaches that range from the molecular and cellular level to long-term animal studies and epidemiological investigations.

Risk Assessment and Risk Management

The need for a risk assessment and risk management orientation became increasingly apparent and prominent in the late 1980's, as the nation focused on approaches to managing health risks. In 1983, a committee of the National Research Council looked at the interface between research, risk assessment, and risk management, and how information can flow between investigators in the laboratory or the field into the area of risk assessment. That is, how do we proceed from the qualitative assessment of the potential hazard of a material to a quantitative understanding of the

relationship between exposure, dose, and response? These relationships are illustrated in Fig. 1. In the original publication of the National Research Council, (NRC, 1983) "dose" was used as a surrogate for "exposure." I have taken the liberty of expanding that paradigm in Fig. 1 because I think it emphasizes the importance of understanding the interior of the "black box" that lies between exposure and response. Clearly, even a highly toxic material may not pose a risk to people if there is no exposure. So to characterize the risk, we need not only an understanding of exposure-dose response relationships, but an assessment of the exposure itself. And finally, there are a number of other factors that have to be weighed along with risk, such as public health, economical, social and political issues. All must be considered as we move forward to make decisions and to take actions to manage the risk associated with those materials.

Veterinarians, as comparative medicine specialists, have a unique opportunity to participate in the risk assessment process as key players. Work on formaldehyde at our institute may be used as a case study to illustrate the kinds of information being developed. The reader interested in details on the toxicity and carcinogenicity of formaldehyde is referred to a recent review by Heck et al. (1990).

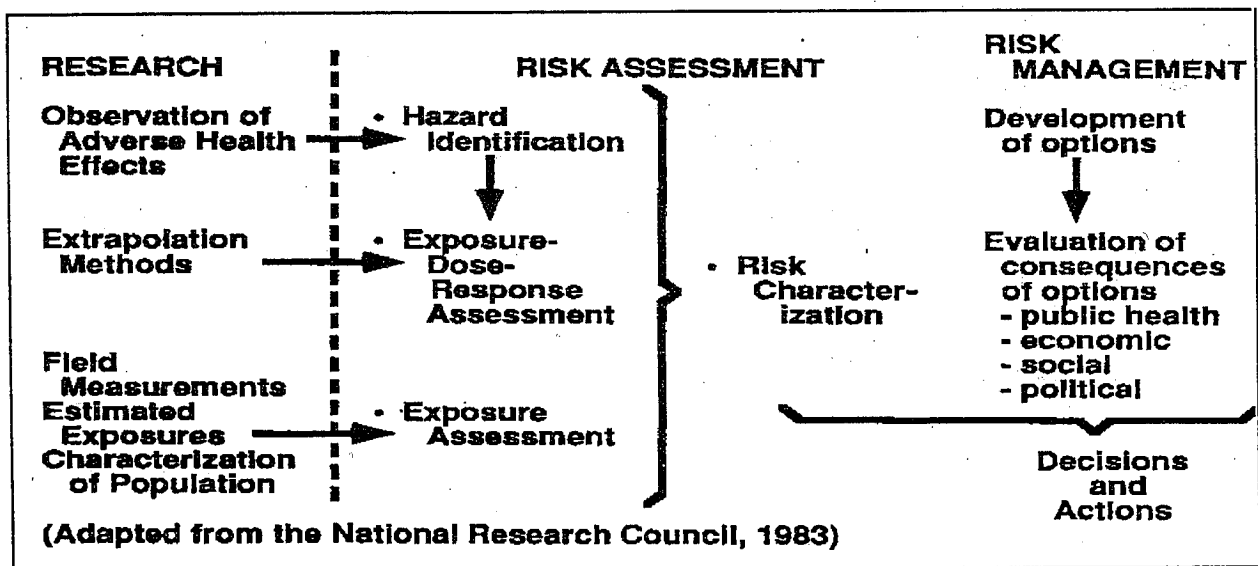


Figure 1. Schematic representation of the risk assessment/risk management process and the related research base.

A Brief Case Study in Risk Assessment

The hazard identification phase of risk assessment is illustrated with findings from a CIIT sponsored study with formaldehyde. In this long-term study, a high incidence (about 50%) of nasal cancers was observed in rats exposed to very high concentrations of formaldehyde (about 15 ppm) (Kerns et al., 1983). At 6 ppm, that incidence dropped down to a level that was marginally significant relative to the controls, while at 2 ppm, there was no evidence of nasal cancer in the rats. So there was a steep concentration-response. Furthermore, the tumors were located at specific regions in the nose. This research, in conjunction with equivocal findings from epidemiology studies as to the carcinogenicity of formaldehyde in man, triggered and stimulated a substantial research program designed to understand the mechanism by which formaldehyde induces cancer in laboratory rats and the relevance of the observations to people exposed to low concentrations of formaldehyde. Ultimately, this research will provide an improved basis for assessing human health risks. Veterinary pathologists are key participants in this research effort.

The next phase of the risk assessment process, exposure-dose-response relationships is illustrated in Fig. 2 with data presented on DNA-protein cross-links in nasal tissue related to exposure concentration. Data developed by Heck et al. (1989) are presented for both rats and monkeys. The selection of tissues for study was guided by the histopathological findings made by the veterinary pathologists. Covalent binding of formaldehyde in the nasal tissue is viewed as an appropriate measure of internal dose that is more relevant for quantitatively estimating the potential health effects of exposure to formaldehyde than is the external exposure concentration. Two aspects of the results deserve emphasis; first, the marked degree of non-linearity in the relationship between exposure and covalent binding and, second, the significantly lower amount of binding in the monkey versus the rat for a given exposure concentration. However, by using a pharmacokinetic model, the rat data could be adjusted to predict the results in monkeys, thereby enhancing our confidence that the data from rats and monkeys can be used to realistically estimate the situation for people.

Heck et al. (1989) also looked at the distribution of covalent binding in various tissues of

the respiratory tract. In this case, taking advantage of the larger size of the monkey, they were able to study the distribution of the covalent bound formaldehyde in the turbinates and anterior nose, nasopharynx, larynx, trachea, carina, proximal conducting airways, and maxillary sinuses. It was of interest that the gradient of covalent binding from the anterior nasal cavity down to the proximal conducting airways paralleled the histopathological changes. It is also noteworthy that covalent binding of formaldehyde was not detected in the maxillary sinuses even at the 6 ppm exposure concentration suggesting this tissue is not at risk for cancer induction even with this high level of exposure.

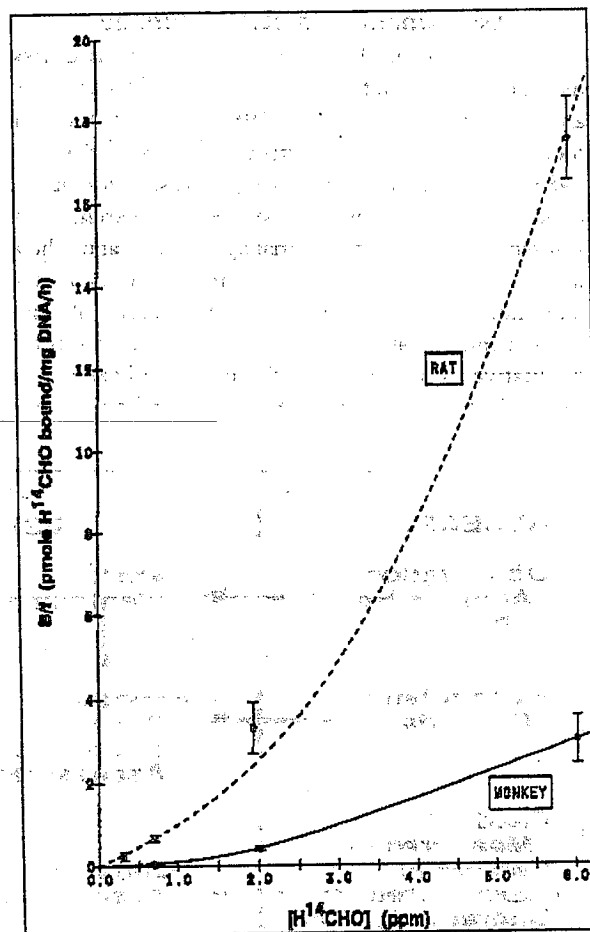


Figure 2. Relationship between concentration of DNA-protein cross-links in nasal tissue of rats and monkeys and formaldehyde exposure concentration. [From Heck, H. D'A., Casanova, M., and Starr, T. B. (1990). *Formaldehyde Toxicity - New Understanding*. CRC Crit. Rev. Toxicol. 20, 397-426.]

Increasingly, we are coming to recognize the importance of understanding the dynamics of the target tissue and the progression of normal cells to cancer cells. A starting point for these studies is an understanding of histopathological changes. Histopathological changes were identified in the upper respiratory tract of rats and monkeys exposed to 6 ppm formaldehyde for six weeks (Monticello et al., 1989, Monticello and Morgan, 1989, Monticello, 1990). In the rat, these moderate to mild lesions are focused in a very small area at the anterior of the nasal cavity, with no changes in the more distal reaches of the respiratory tract. In the case of the monkey, lesions are found in the anterior portion of the nasal cavity and milder lesions extend down to the level of the carina. These changes need further exploration in view of similarities in the structure of the respiratory tracts of monkeys and man and recognizing it is in the lower reaches of the conducting airways in man where most lung cancers develop. Most of these lung cancers, well over 100,000 cases per year are attributed to cigarette smoking. The extent to which cigarette smoking induced cancers dominate the lung cancer incidences in the human population makes it extremely difficult to tease out potential interactive effects between cigarette smoking and exposure to occupational agents or environmental agents in human populations. Thus, even for materials for which there is human exposure experience it is necessary to use laboratory observations to understand the basic biology and pathobiology in exposed laboratory animals to aid in understanding potential human disease outcomes. Veterinary pathologists, working in collaboration with human pathologists, are ideally trained to make these difficult interspecies comparisons.

Toxicologists concerned with the mechanism of cancer induction by chemicals are increasingly recognizing cell proliferation in addition to damage to DNA as a key factor in chemical-induced cancer. Researchers at CIIT are investigating the influence of both exposure concentration and exposure duration on cell proliferation in the respiratory tract of rats and monkeys exposed to formaldehyde. Preliminary results indicate a non-linear relationship between exposure concentration and cell proliferation. The pattern of cell proliferation as a function of time following the beginning of repeated exposure, five days/week, is complex. Fig. 3 illustrates the increase in cell proliferation observed in respiratory tract epithelial cells at various locations following exposure of monkeys to 6 ppm of formaldehyde for 5 days per

week for either 1 or 6 weeks. In this example the level of cell proliferation increases with increased duration of exposure. In studies conducted with rats, Monticello (1990) observed a diminished cell proliferation response after 3 months of chronic exposure compared to 4 days. Ultimately, it will be necessary to obtain a profile of cell proliferation as a function of exposure concentration and time at multiple tissue sites if one is going to gain adequate insight into the potentially complex role of cell proliferation in the carcinogenic process.

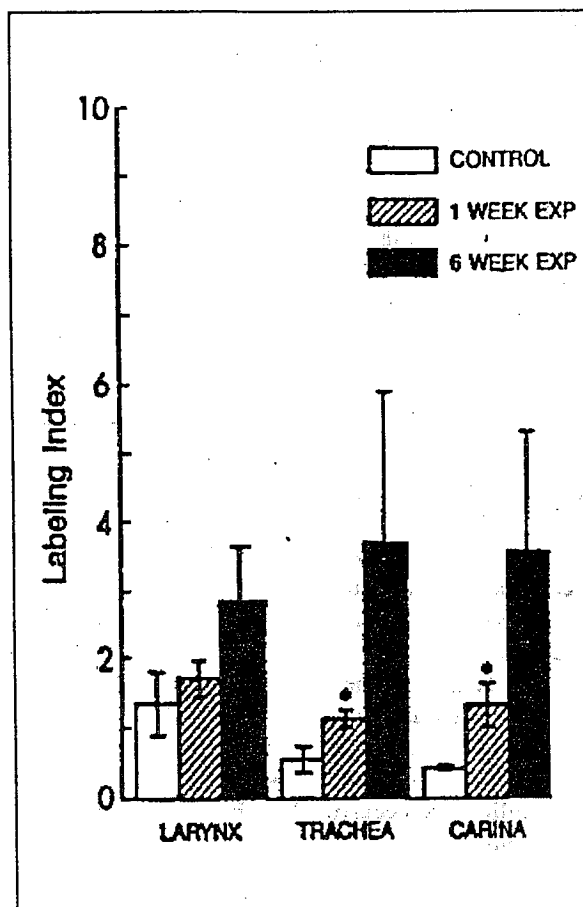


Figure 3. Mean labeling indices for the larynx, trachea, and carina of monkeys exposed to formaldehyde for 1 or 6 weeks compared to controls. (From Monticello, T. M., Morgan, K. T., Everitt, J. I., and Popp, J. A. (1989). Effects of formaldehyde gas on the respiratory tract of rhesus monkeys. *Am. J. Pathol.*, 134, (3), 515-527.)

CHT's formaldehyde studies are at a critical juncture. We are now in the process of formulating mathematical models based on the concepts of other researchers (Moolgavkar and Venzon, 1979; Moolgavkar and Knudson, 1981), to integrate information on DNA damage and cell proliferation into models that estimate cancer risks. The next important step is to test the validity of those models using nasal tumor incidence data of the kind that can be developed by veterinary toxicologists and pathologists.

To summarize, the essential determinants of carcinogenesis - not just for formaldehyde but for many chemicals - include the dose of the chemical and/or its metabolites that reach target sites and the rate of cell replication in those sites. There are significant species differences in both the dose delivered and cell proliferation in different species. There is no ideal surrogate for man. We must take advantage of both similarities and differences in species to provide an improved base of biological information to join with more limited data in man to estimate human health risks. At the same time, we must improve our understanding of the biology of any animal species being studied including man. Interspecies studies are essential to understand toxic mechanisms, to evaluate the validity of the models, and to ultimately estimate the risk to man for materials for which human data do not exist. All of the various specialty areas of veterinary medicine have much to contribute in understanding the biology and pathobiology of diverse laboratory animal species and how these relate to man.

Achieving the objectives of toxicology of the 1990's will require increasing input from veterinary medicine as a comparative medical science. Modern toxicology, oriented toward estimating low probability, late-occurring health risks for populations of people at low levels of exposure, is based on understanding the mechanisms of toxicity and disease. This knowledge base will be derived from integrating information of multidisciplinary teams, from studies at all levels of biological organization - macromolecules, cells, tissues, organs, various species, and finally, man. It is very important for us not to let appropriate societal concerns, such as for the use of laboratory animals, divide us into camps, each championing its own cause as to the models to be used. None of the model systems used alone; molecules, cells, whole animal, people on computer simulations, will be sufficient. Data from all of these

types of studies must be joined together to develop our best understanding of health risks to people.

One of the most vexing problems, yet one of the greatest opportunities, is the study of populations. Certainly we do not have any idealized standard to which we all conform. Some of us are tall, some are short, some are slightly underweight, some are overweight; there are males, there are females. We are a heterogeneous group of individuals. On an individual basis, risks are not equal for all of us. Risk is certainly influenced by life styles, by dietary habits, and, most significantly, by genetic background. The challenge that faces us as experimentalists is to take the extrapolative leap from studies of a dozen (or at best, hundreds) of animals to thousands (or millions) of people.

In the immediate future, assessments of human health risk will come from studies of laboratory animals and molecular and cellular studies, joined together with information gleaned from epidemiological studies. With dramatic steps taken in recent years to reduce human exposures, it's going to be very difficult to get full positive epidemiological data in the future. There will be relatively few materials judged to have such low potential for inducing late-occurring diseases such as cancer that the materials can be ethically evaluated in controlled human exposure studies.

In the absence of adequate human data, animals must be surrogates for people. Information from subanimal systems, molecules, cells and tissues must also be integrated with data of the intact individuals. Knowledge of comparative medicine is essential for extrapolating to people. Well-trained veterinarians have a unique opportunity to contribute to this important field.

Communicating Career Opportunities

Increased participation from the veterinary medical profession in biomedical research, and in particular from students, starts with an awareness of the spectrum of career opportunities that exist in veterinary medicine today. They have never been broader or more exciting. Students should be made aware of the long-term benefits to be gained from making a commitment to further training. Yet today in many of our training programs there is generally a paucity of suitable applicants. The answer to this problem lies in working together to make certain that students understand what these opportunities are, so that in-depth training in a biomedical science can be

provided while maintaining that comparative medicine orientation that they achieve through their professional curriculum. I am confident that professionals working in government, industry, and education "sitting at the same table" can arrive at mutually agreed-upon goals for approaches that will have lasting impact.

The profession of veterinary medicine is on the threshold of an era when extraordinary contributions can be made to society, particularly as specialists in comparative medicine in the area of risk assessment.

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