Use of Rodent Carcinogenicity Test Results for Determining Potential Cancer Risk to Humans

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A high proportion of "human" and "probable human" carcinogens as categorized by the International Agency for Research on Cancer have been identified through observations in workers. The excess cancer risk has often been quite high. Most substances known to cause cancer in humans are now known to cause cancer in animals. In the past two decades, an increasing number of substances first shown to cause cancer in animals are now known to cause or are highly suspected of causing cancer in humans (and quite often in workers). The observations necessitate the use of rodent cancer test results for identifying and regulating potential environmental carcinogens. The role of cell proliferation (CP) in the carcinogenic response is important from a regulatory view in terms of both qualitative and quantitative evidence. If CP influences the carcinogenic response, the use of such data to modify dose response in the low-dose range is another factor that needs to be considered. Presentations at this symposium, however, indicate that CP data at the present time should not be incorporated into cancer risk assessments. More simple concepts that affect quantitative dose response and that may result in an artificially low estimated risk but could be adjusted for in the bioassay protocol have usually been ignored. A balanced approach would be to incorporate all known factors that influence quantitative estimates of cancer risk when conducting animal cancer bioassays and extrapolating those results to humans.

Introduction

During the past decade, advances have been made toward understanding the mechanisms of carcinogenesis. As part of this research, attention has been focused on the potential role of cellular proliferation (CP) in chemical carcinogenesis. Some researchers believe that CP per se is a cause of cancer (1-3). Some argue that the standard cancer bioassay protocol is a poor surrogate for identifying human carcinogens because the cancer response observed in these studies is simply a reflection of increased CP related to the high dose used (2). Others have been more cautious in their interpretation of data on CP as it relates to a carcinogenic response (4-6).

The resolution of these arguments is important to regulatory agencies. Qualitative evidence of carcinogenicity plays a major role in hazard communication requirements related to toxicologic information that must be included on material safety data sheets or on labels for specific chemicals and products. Quantitative evidence is used to determine dose response, which in many cases leads to establishment of permissible exposure limits. If CP influences the carcinogenic response, the use of such data to modify dose response in the low-dose range is another factor that needs to be considered.

The above argument leads to the following questions: Can animal bioassays be used to predict carcinogenic responses in humans? Are there alternatives to animal studies for identifying carcinogens? Should CP data be used to modify cancer dose response in experimental studies? To answer these questions, one first needs to review the type of data that have been available for identifying human carcinogens on a qualitative basis to determine whether the use of animal cancer results bear any relation to cancer response in humans. Second, one needs to evaluate data for cancer dose response in experimental animals and in humans for the same substances to determine whether the experimental protocols result in a quantitative overestimate or underestimate of cancer risk to humans. Whether CP should be used for modifying dose response as car-
ried out by regulatory agencies has been the subject of this symposium. Below, I deal with each of the questions raised above with emphasis on occupationally related cancer.

**Occupational Cancer**

To evaluate the benefits of animal cancer tests to identify carcinogens, one has to look historically at the data used to classify agents as carcinogens. Most substances now categorized as “human carcinogens” were initially identified through case reports and more recently through epidemiologic studies of industrial workers who were unknowingly exposed to high levels of a large variety of toxic substances and physical agents.

The bladder carcinogenicity of several aromatic amines [2-naphthylamine, benzidine, 4-aminobiphenyl (7) and more recently ortho-toluidine (9)] was identified through the study of industrial workers. Based upon epidemiologic studies and case reports, several additional aromatic amines that have been shown to induce cancer in experimental animals have subsequently demonstrated an association between their exposure and bladder cancer in workers. For example, workers exposed to 4,4'-methylenedianiline (MDA) have demonstrated a significant proportional increase in mortality from bladder cancer (9). Case reports have indicated an association between bladder cancers and industrial exposure to 4,4'-methylenedis-2-chloroaniline (MOCA) (10). Several of the benzidine-based dyes are known to metabolize back to benzidine in both animals and humans (11); on the basis of this information it is not unreasonable to consider all of the benzidine-based dyes as human bladder carcinogens.

A large number of petrochemicals are also known to be human carcinogens based on case reports and epidemiologic study of workers. For example, a causal connection between chemical exposure and cancer has been demonstrated among workers exposed to petrochemicals such as vinyl chloride [brain, liver, lung cancer (7)], bischloromethyl ether [lung cancer (7)], benzene [leukemia and lymphoma (12)], automotive gasoline [leukemia and lymphoma (13,14)], and formaldehyde [nasal and lung cancer (15)].

The human carcinogenicity of a number of metals was also determined through the study of industrial workers. Arsenic is known to cause lung and skin cancer and angiosarcoma of the liver (7); chromium is known to cause lung cancer (7), and nickel is known to cause lung and nasal sinus cancer (7) among industrial workers. Other metals such as beryllium and cadmium were first identified as carcinogens in experimental animals and are also known to cause cancer in humans based on the study of workers (16–18). A recent study of workers manufacturing inorganic lead for use in gasoline demonstrates a significantly elevated risk of rectal cancer (19).

The International Agency for Research on Cancer (IARC) has identified 56 substances or workplaces as being causally connected to human cancer. Of these, the majority have been identified through observations in industrial workers. If one were to add to this list the substances classified by IARC as category 2A carcinogens—mostly substances that have demonstrated cancer in experimental animals and for which there is some evidence in humans (though not considered conclusive by IARC)—an additional 46 substances and workplaces could be added to the list as probably carcinogenic to humans. A large number of this latter group were also identified through observations in workers.

Given that such a disproportionately high number of human carcinogens have been identified in the workplace and that such a large number of animal carcinogens are found at high exposure levels in the occupational setting, how much of environmental cancer can be attributed to occupation? Is it 2–5%, as suggested by Doll and Peto in 1981 (20)? Is it 2%, as mentioned by Ames at this symposium (21)? Or is it 10–33%, as suggested by Stallones and Downs (22)? The answer is not known because data are not available to make such a determination for the occupational contribution, nor for the contribution from other factors as well. But what is known is that a variety of occupational groups have a high relative risk for site-specific cancers.

With knowledge of this high cancer risk among workers, the Occupational Safety and Health Administration (OSHA) promulgated a standard in 1980 to lay out the groundwork for identifying, classifying, and regulating potential occupational carcinogens (23). It was the intention of this policy to rely on animal cancer tests when available to identify and control carcinogens in the workplace. In its carcinogen policy, OSHA stated that the problems of regulatory agencies concerning regulation of human exposure to possible carcinogenic substances was most eloquently phrased by Richard Bates (23):

...it is often necessary to control exposure for which there is some evidence of hazard before that evidence has reached the point that scientists would universally regard as conclusive. The alternative, to continue exposure until there is conclusive evidence of human hazard, is a form of human experimentation that our society finds increasingly unacceptable.

**Can Animal Bioassays Be Used for Predicting Potential Carcinogenic Responses in Humans?**

**Qualitative Evidence of Cancer in Humans and Test Animals**

Since the publication of the OSHA cancer policy in 1980, evidence supporting the use of animal cancer tests as a surrogate for identifying human carcinogens appears to be even stronger. As shown by Tomatis et al. in 1989 (24), 91% of the substances classified by
IARC as “human carcinogens” show sufficient evidence of carcinogenicity in one or more animal species. The three human carcinogens for which there was no evidence of carcinogenicity in experimental animals were ethanol, soot, and asbestos-containing talc. The sensitivity may be even better than the 91% indicated by Tomatis et al. (24). Although ethanol has not demonstrated carcinogenicity in experimental animals, the epidemiologic data relate to alcoholic beverages, and it is not clear whether the cancer response in the latter studies is a result of the ethanol or contaminants in the beverages. For soot and asbestos-containing talc, experimental carcinogenicity studies have not been conducted.

Likewise, there is a growing number of substances that were first identified as being carcinogenic in experimental animals and were later confirmed to cause cancer in humans (24). If one adds to this list the number of substances that IARC has categorized as demonstrating sufficient evidence in animals and limited evidence in humans (25) (most of the 46 substances listed in IARC category 2A), the list is much longer. Therefore, the sensitivity of animal cancer studies for identifying human carcinogens and the ability to predict human carcinogens based on the rodent bioassay support the use of animal cancer tests to identify carcinogens.

Quantitative Evidence of Cancer

With regard to the extrapolation of quantitative evidence of cancer in experimental animals to humans, difficulties are recognized. OSHA has a preference for determining dose response based on epidemiologic studies when they provide good information on exposure and relative risk of cancer. However, such data are lacking for a majority of carcinogens that need to be regulated. Thus, it often has been necessary for OSHA to rely on experimental data to estimate dose response for humans. In doing so, OSHA uses mathematical models that give a statistical fit to the experimental data. The agency makes a dose adjustment based on differences in body weight between animals and humans. The maximum likelihood estimate (MLE) is used to provide the best estimate of risk, though reference has been made to the upper 95% confidence limit.

With regard to quantitative extrapolation of cancer results in animals to humans, the appropriateness of such procedures can only be determined through a comparison of toxicologic and epidemiologic study results. There is a limited number of substances, however, for which adequate study results with good dose information is available for both animal and human studies. Nonetheless, analyses by Allen et al. (26), in general, show a good correlation between the test results in animals and humans.

For substances regulated under Section 6(b) of the OSHA Act since the Supreme Court decision on benzene in 1980, data indicate that the risks estimated from animal and human data are similar. For benzene (27) and ethylene oxide (28), the risks projected from epidemiologic data were about 10 times higher than those based on experimental data. For formaldehyde, the risk projected from epidemiologic data also appeared higher (15). On the other hand, the risk of cancer estimated from epidemiologic data for cadmium is both higher and lower than the range of risks projected from experimental data (29).

Significance of Cancer Risks to Workers

Ames has also raised the issue of regulating insignificant risks (21). Such a situation, however, does not arise in relation to the occupational setting. If one considers the new permissible limits (PELs) that have been set for occupational carcinogens based on human data (in order to avoid any argument about extrapolation of risks from experimental data) since the Supreme Court decision on benzene in 1980, the remaining risk is still very high (30). The permissible exposure limit (PEL) of 1 ppm for benzene was associated with an occupational lifetime (45 years) excess cancer risk (based on leukemia only) of 10 per 1000 employees; the new arsenic PEL of 10 μg/m³ was associated with an excess lung cancer risk of 8–12 per 1000 workers; the new asbestos PEL of 0.2 fibers/cm³ was associated with an excess cancer risk (lung, gastrointestinal, mesothelioma) of 6.7 per 1000 workers, plus an additional risk of asbestosis of 5 per 1000 employees (30).

Because of economic feasibility, the agency concluded that it was not possible to set a low PEL for these substances. Perhaps some of the ancillary provisions of the standards will help to further reduce risk. For example, with the benzene standard, the ancillary provisions include an action level of one-half the PEL which serves as an incentive for employers to achieve this limit, thereby eliminating costs for compliance with other provisions of the standard; medical surveillance to identify and remove workers who develop various cytopenias; training, education, and exposure monitoring requirements to inform workers of the hazards and to identify and reduce fugitive emissions. Thus, cancer risks to workers are extremely high before regulation and, although significantly reduced as a result of regulation, still remain high in comparison to risks regulated by other Federal agencies.

Are There Alternatives to Animal Studies for Identifying Carcinogens?

There are some people who object to the use of animal cancer tests to identify and regulate carcinogens to protect the health of the public (1,2,31). The alternative is to rely on evidence in humans. Given the pro-
portion of human carcinogens that have been identified among workers in the past, as indicated above, the requirement of confirmatory evidence of carcinogenicity in humans would translate to relying on the identification of excessive cancer risks in workers more than 50% of the time. There are obvious problems with relying on observations in humans: the data arrive too late, if at all, resulting in unnecessary death from preventable causes of cancer; should an occupational cohort be identified for study, exposure data are often lacking, making dose–response analyses impossible to conduct; the latency period for most forms of cancer is long, necessitating years of follow-up during which time a tremendous cancer burden can accrue to workers and other individuals, resulting in great medical, administrative, and social costs to the public (32).

Even at the completion of an epidemiologic study, scientists may argue for a long time about whether the evidence is conclusive or suggestive. Given the high correlation between animal cancer test results and evidence of cancer in humans, a delay in taking regulatory action based on animal data until there is universal agreement on the epidemiologic evidence could be considered a form of human experimentation (23), particularly in reference to occupational exposures where such high relative risks of cancer continue to be identified.

There also has been discussion about reducing the doses in animal cancer tests because of the concern that toxicity and increased CP is responsible for the tumors observed in the animals tested at high doses. However, elimination of the high-dose level in the testing protocol will ultimately result in lessened sensitivity in the tests and further reliance on human studies to identify carcinogens.

**Should CP Data Be Used to Modify Cancer Risk Assessments?**

Two of the questions raised at the beginning of this symposium were: Should CP data be used to modify quantitative estimates of cancer risk? How should such data be used (33)? From presentations and discussions of this issue, it seems too early to answer these questions. However, if, in the future, data on CP appear to be relevant for modifying quantitative cancer risk assessments for specific chemicals, regulatory agencies would presumably make such adjustments (and seek public comment) provided that mechanistic information is available to indicate how such data affect the cancer dose response and agreement is reached on how such data are to be incorporated into risk assessments.

It is always attractive to incorporate new data into the quantitative risk assessment analyses. In this specific case, the use of CP data may give the superficial appearance that risk assessment methodology is being improved because information at the cellular and subcellular level is being used to modify dose response. However, the use of such data to modify dose response has not been justified.

**OSHA conducts risk assessment and promulgates permissible exposure levels in an open process before the public. Any individual with an interest in the subject of the regulation is invited to participate in the informal rule-making process. If information in the future indicates that CP data should be incorporated into risk assessment for a particular substances, the agency will go as far as the scientific data allow.**

**Some Factors in the NTP Bioassay That Result in Underestimation of Cancer Risk**

There may be some concern that lack of use of CP data may result in overestimation of cancer risks in the low-dose range when extrapolating from animals to humans. However, in addition to factors related to underestimation of cancer risks when extrapolating from animals to humans, as mentioned by Ballar et al. (32), there are a number of factors related to current bioassay procedures that result in underestimation of risk. These factors, as mentioned below, could be taken into consideration with data currently available. Adjustments for these factors, however, are not included in the estimates of cancer risk based on cancer bioassay data.

First, most risk assessments based on cancer bioassays do not take into consideration “wasted dose,” as they still employ the instantaneous cancer model. In the animal cancer studies, dose is usually counted until the animals die or until terminal sacrifice, at which time histopathology is conducted to evaluate tumor response. In this manner, dose is counted up to the time of death. Hence, one is indirectly making the assumption that the tumors developed at the time of terminal sacrifice or at the time of death. For this reason, the tumors are being considered as if they occurred instantaneously in relation to the final dose received by the animals. (This is also the case with risk assessments based on epidemiologic data, but the impact is not as great because most deaths occur when the worker is no longer exposed to the substance under study.) Thus, dose is usually overestimated in the dose–response analyses based on the rodent bioassay.

Second, the standard National Toxicology Program (NTP) bioassay protocol uses a 24-month sacrifice. This aspect of the protocol for the rat portion of the studies will usually underestimate the yield of tumors because many tumors induced by the test substances may not appear until after this time period in the life span of the rat. For example, if one looks to the cancer bioassay for cadmium, the first lung cancer was not observed in Wistar rats until age 22 months, and by the 31-month terminal sacrifice, 75% of the animals in the high-dose group developed lung carcinoma (35). In the low-dose group, 25% of the animals developed lung cancer. A 24-month sacrifice would have resulted in a nonsignificant increase in cancers, and it would have
been erroneously concluded that cadmium was not carcinogenic. One of the justifications for the 24-month sacrifice is that the background cancer rates rise to such an extent at 24 months that it becomes difficult after that age to conduct a proper histopathologic evaluation. Nevertheless, the current procedure still results in an underestimation of the cancer yield. A possible solution to the problem would be to restrict caloric intake of the animals and extend the terminal sacrifice to 30 months.

Third, most risk assessments have used a cumulative dose concept in estimating dose associated with cancer risk (36). Yet, this assumption may not be correct, resulting in overestimation of dose necessary for manifestation of the toxic effect. There is ample evidence with a well-studied substance such as benzene that cumulative dose is not the correct measure of dose. The degree of toxicity from benzene exposure is related to the mode in which the cumulative dose is received. Intermittent exposure to a lesser cumulative dose results in more aplastic anemia, red blood cell reduction, a greater suppression of polychromatic erythrocytes, and a greater incidence of cancer in experimental animals as compared to the full dose given on a more continuous basis (12). Most of the cancer risk assessments based on cancer bioassays or epidemiologic studies have used a cumulative dose concept.

Fourth, in the rodent bioassay, animals are exposed to a single test chemical at a time, and yet human populations are exposed from prenatal life through childhood to adult life to a large variety of carcinogens and other conditions that may amplify the carcinogenic response. Although relatively little research has been conducted to evaluate interaction of carcinogenic exposures with other factors (e.g., medications, immune deficiency, hormonal imbalances), additive and synergistic interaction between carcinogens and other toxic substances has been demonstrated repeatedly (37–39). Thus, single chemical administration to experimental animals will underestimate quantitative cancer risk when extrapolating to humans.

The above factors are known to underestimate cancer risk when conducting dose–response analyses based on the rodent bioassay. In some of these situations, it would be relatively simple to make the necessary corrections, yet they are not made. On the other hand, it seems there is a fair amount of discussion about using cell proliferation data to adjust quantitative risk assessments when the merits of such procedures are speculative. Prediction of cancer risk to humans by use of experimental data will only improve when all factors known to be related to cancer response are incorporated into the procedure.

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