Quantitative and Qualitative Extrapolation of Carcinogenesis Between Species

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As currently conducted, standard rodent bioassays do not provide sufficient information to assess carcinogenic risk to humans at doses thousands of times below the maximum tolerated dose. Recent analyses indicate that measures of carcinogenic potency from these tests are restricted to a narrow range about the maximum tolerated dose and that information on shape of the dose–response is limited in experiments with only two doses and a control. Extrapolation from high to low doses should be based on an understanding of the mechanisms of carcinogenesis. We have postulated that administration of the maximum tolerated dose can increase mitogenesis which, in turn, increases rates of mutagenesis and, thus, carcinogenesis. The animal data are consistent with this mechanism, because about half of all chemicals tested are indeed rodent carcinogens, and about 40% of the positives are not detectably mutagenic. Thus, at low doses where cell killing does not occur, the hazards to humans of rodent carcinogens may be much lower than commonly assumed. In contrast, for high-dose exposures in the workplace, assessment of hazard requires comparatively little extrapolation. Nevertheless, permitted workplace exposures are sometimes close to the tumorigenic dose–rate in animal tests.

Regulatory policy to prevent human cancer has primarily addressed synthetic chemicals, yet similar proportions of natural chemicals and synthetic chemicals test positive in rodent studies as expected from an understanding of toxicological defenses, and the vast proportion of human exposures are to natural chemicals. Thus, human exposures to rodent carcinogens are common. The natural chemicals are the control to evaluate regulatory strategies, and the possible hazards from synthetic chemicals should be compared to the possible hazards from natural chemicals.

Qualitative extrapolation of the carcinogenic response between species has been investigated by comparing two closely related species: rats and mice. Overall predictive values provide moderate confidence in interspecies extrapolation; however, knowing that a chemical is positive at any site in one species gives only about a 50% chance that it will be positive at the same site in the other species.

Introduction

Current strategies to prevent human cancer use chronic rodent bioassays as the major source of information to predict the risk to humans from chemical exposures. Two types of extrapolation are required in such an undertaking: 1) a quantitative extrapolation is necessary from the maximum tolerated dose (MTD) administered in bioassays to human exposure levels that are usually hundreds of thousands of times lower and 2) a qualitative extrapolation is necessary between a short-lived species, such as rats or mice, to humans, a long-lived species. This paper addresses a variety of issues relevant to these two types of extrapolation. We discuss why standard rodent bioassays, as currently conducted, do not provide sufficient information to assess carcinogenic risk to humans at low doses. Such extrapolation should be based on knowledge of mechanisms of carcinogenesis and should reflect the importance of mitogenesis. We have postulated that chronic administration of chemicals at the MTD increases mitogenesis in cells that are not discarded which, in turn, increases rates of mutagenesis and carcinogenesis.[1–3] Therefore, at the low doses of most human exposures where cell killing does not occur, the hazards to humans of rodent carcinogens may often be much lower than has commonly been assumed.

Results from rodent bioassays are often used to predict qualitatively whether a chemical is a potential human carcinogen. Ideally, one would like to know the accuracy of prediction from rats or mice to humans, but because epidemiologic data are usually lacking and experiments cannot be conducted in humans, this knowledge is not available. The accuracy of prediction between the two closely related species, rats and mice is examined below. These data reflect results obtained under similar experimental conditions, including administration of estimated MTDs and laboratory diets fed *ad libitum*. Thus, qualitative prediction from one rodent species to another (i.e., prediction of positivity and prediction of target organ) can be examined without simultaneously having to address the issue of high to low dose extrapolation.[4,5] One would expect that the qualitative prediction of positivity and target organ from rats to mice would likely be much better than prediction from rats or mice to humans. The quantitative prediction from high dose in rodents to low dose in humans is much more uncertain.

Quantitative Extrapolation to Low Dose from Bioassays Conducted at High Dose

Limitations of Carcinogenesis Bioassay Data for Risk Estimation

Several recent analyses indicate that measures of carcinogenic potency estimated from standard rodent bioassays are restricted to a narrow range about the maximum dose tested for each chemical.[6–9] This narrow range contrasts with the 10 million-fold range in the test doses (MTDs) of different chemicals. In our comprehensive, standardized database of chronic, long-term bioassays, the Carcinogenic Potency Database (CPDB), we use TD_{50} based on the one-hit model as the measure of potency (i.e., the tumorigenic dose rate for 50% of the animals at the end of a standard lifespan).[10–15] One reason for choosing the TD_{50} was that the concept is easily understood, particularly by analogy to the widely reported LD_{50}. Importantly, the TD_{50} is often within the range of doses tested; thus, the experimental results do not have to be extrapolated far to estimate TD_{50}. The statistical methods used to estimate TD_{50} do not matter greatly. There is substantial agreement between TD_{50} estimated by lifetable and summary analyses.[16] Additionally, among chemicals that are positive in more than one test in a species, the single, most potent TD_{50} value from among all positive tests in the species is, with few exceptions, similar to other measures that average TD_{50} values (harmonic mean, geometric mean, or arithmetic mean).[17]

Several years ago, we showed that the potency (TD_{50}) calculated from bioassays, as currently conducted, is constrained to be within a narrow range (~32-fold) about the maximum dose tested (in the absence of 100% tumors in all dosed animals).[6] Several papers that appeared later all confirmed this restriction.[18–20] Recently, Krewski, et al.[21] showed that across chemicals, regardless of whether one uses the one-stage, multistage, or Weibull model to estimate TD_{50}, the correlation between the MTD and carcinogenic potency is greater than 0.9. Thus, potency estimates are constrained to a limited range when one knows the MTD.

TD_{50} does not provide information about low-dose exposures. Thus, we have not attempted to say anything about the doses estimated to give tumors to one rat in a million. In contrast to TD_{50}, vastly different results would be obtained for such an undertaking, depending on what particular statistical model was fitted.[22] Whereas TD_{50} is close to the doses tested, an estimate of the dose to give tumors to a maximum of one animal in a million based on the linearized, multistage model widely used for regulatory purposes, averages 380,000 times below the bioassay high dose.[8] This enormous toxicological "leap in the dark" emphasizes the point that carcinogenesis bioassays were not designed to determine one-in-a-million risks.

A further limitation of bioassay data for quantitative extrapolation to low dose is the minimal information available about dose–response from an experiment with only two doses and a control. Even at the two high doses tested (MTD and 1/2 MTD), it is difficult to interpret the shape of the dose–response curve with three data points. A recent study[23] tested for consistency of the dose–response with three different curves: linear, square-root, and quadratic. Results of bioassays from the National Cancer Institute/National Toxicology Program (NCI/NTP) indicate that two-thirds of the curves are consistent with all three models, and 83% are consistent with at least two models. More of the best fits are consistent with a quadratic model than either a linear or square-root model. An additional complication is the finding that the best fit curves for more than half the chemicals are not the same for different sex-species groups or different target organs within a single experiment. This variation in curves for the same chemical was also discussed earlier.[6,16]

The good correlation in carcinogenic potency between rats and mice at the high doses tested has been interpreted as a justification for quantitative extrapolation from rodents to humans. However, the MTDs of rats and mice for different chemicals are also very highly correlated; as previously stated, they span a 10-million-fold range across chemicals, whereas the potency for a given chemical is constrained to a narrow range about the MTD.[6] These facts imply statistically that the potencies of chemicals positive in rats and mice will be highly correlated. Thus, the study of potency correlations between rats and mice does not shed much light on the issue of quantitative prediction between species. The biological basis for these correlations lies, in part, in the high correlation in the MTDs of the two species and, in part, in the experimental finding that it is uncommon to observe either a plateau in the dose–response curve or a tumor incidence of 100% in experiments conducted using the standard bioassay design. These results are consistent with the hypothesis that mitogenesis induced by the near toxic doses administered is important in the carcinogenic response. The limitations of bioassay data for use in risk estimation underscore the importance of understanding mechanisms of carcinogenesis.

Several recent analyses have shown that quantitative risk assessments as currently conducted by regulatory agencies are also constrained to a narrow range about the MTD. Using data from the CPDB, Krewski et al.[9,21] have shown that the unit risk factor Q_1^* derived from the linearized, multistage model is restricted to a limited range about the MTD, that empirically the Q_1^* values for different chemicals are highly correlated with the MTD, and that linear extrapolation from the TD_{50} usually results in low-dose slope estimates that are similar to those based on the linearized, multistage model. Gaylor[8] estimated the risk specific dose (RSD) corresponding to a maximum risk of one cancer in a million based on the multistage model and found that RSD averages 380,000 times below the MTD and that 90% of the estimates are within a factor of 10 of that number.

These are striking findings with broad implications for

risk assessment: the dose usually estimated by regulatory agencies to give a maximum of one cancer in a million can be approximated merely by knowing the MTD, and a reasonable estimate of the Q_1* can be made from the TD_{50} values in our published CPDB. Proposals based on these findings have been made to facilitate the regulatory process. Although these proposals address the question of facilitating regulation as it is currently done, they do not resolve the fundamental question of the vast biological uncertainties in extrapolating 380,000 times below the bioassay dose. Rather, they assume that the current methodology should be approximated.

Gaylor[8] has proposed dividing the MTD by 400,000 to estimate the virtually safe dose; then, if the intended human exposure to a chemical is greater than the lowest virtually safe dose, the chemical cannot be accepted as safe. If the intended human exposure is below the lowest virtually safe dose, then conducting a bioassay may not be necessary because the predicted maximum risk will be below one in a million at the intended exposure level.[8] Rulis[24] proposed a threshold of regulation for safety assessment of packaging materials based on the distribution of TD_{50} values in the CPDB. This requires assuming that a substance is no more toxic than the most potent chemical carcinogen and inferring a theoretical upper bound on potency below which risks would be trivial. The California Department of Health Services has proposed that regulations for Proposition 65 be expedited by using the adjusted TD_{50} values for those chemicals that do not yet have a Q_1* from either their agency or the U.S. Environmental Protection Agency (EPA). Zeise[25] has shown that potency estimates derived from TD_{50} are reasonable estimates of potency values proposed for Proposition 65.

Ranking Possible Carcinogenic Hazards

Our approach has been to acknowledge the enormous limitations and uncertainties in quantitative risk assessment and to begin by ranking possible carcinogenic hazards to humans from typical exposures for a wide variety of chemicals.[26,27] This ranking can help to set priorities when selecting chemicals for chronic bioassay or mechanistic studies, for epidemiological research, and for regulatory policy. The current regulatory process needs to take into account several points that we have previously discussed in detail:[1–3,26–29]

1. An extrapolation from high to low doses should be based on an understanding of the mechanisms of carcinogenesis.
2. Testing at the MTD can frequently cause chronic cell killing and consequent cell replacement, a risk factor for cancer that can be limited to high doses. Ignoring this mitogenesis effect can greatly exaggerate many low-dose risks.
3. About half of the chemicals tested at the MTD are positive, and about 40% of the positives are not mutagenic. This would be expected if mitogenesis is important in the carcinogenic response at the MTD.
4. About half of the *natural* chemicals tested chronically in rats and mice at the MTD are positive, and the natural world of chemicals makes up the vast proportion of chemicals to which humans are exposed. Thus, human exposures to rodent carcinogens (as defined by testing at the MTD) are likely to be common.
5. The toxicology of synthetic and natural toxins is not fundamentally different.

Together, these five points indicate that cancer–prevention strategies aimed at chemical carcinogens as potential causes of human cancer need to take a broad overview of chemical exposures to put possible hazards into perspective and to focus on those exposures that rank highest in possible hazard. If there is an enormous natural background of "potential human carcinogens" as defined by rodent tests, then smaller exposures to synthetic chemicals are not likely to be significant causes of human cancer. Ames et al.[28] have recently shown, for example, that even though only 52 of the 5000 or more naturally-occurring plant pesticides in our diet have been tested, the 27 that are rodent carcinogens are present in many common foods and at concentrations that are commonly thousands of times higher than the concentrations of synthetic pesticide residues. It is probable that almost every fruit and vegetable in the supermarket contain plant pesticides that are rodent carcinogens. A chemical pollutant should not be a high priority for concern with respect to carcinogenicity if its possible hazard seems far below that of many common food items.[28] This is not to say that these dietary exposures are necessarily of much relevance to human cancer; rather the background of exposures to natural rodent carcinogens may cast doubt on the relevance of far lower levels of exposures to synthetic rodent carcinogens.

Our ranking of possible carcinogenic hazards is based on a simple measure, Human Exposure/Rodent Potency (HERP), that indicates what percentage of the TD_{50} in mg/kg/day a human gets from a daily lifetime exposure to a given chemical. We have also ranked possible carcinogenic hazards in the workplace based on the Permitted Exposure/Rodent Potency (PERP) index, using the Occupational Safety and Health Administration (OSHA) Permissible Exposure Limit (PEL) as a surrogate for estimates of exposure.[27] The HERP or PERP index uses the same animal results and similar statistical methods as the usual low-dose linear estimation of risk; however, our purpose is to *compare* possible carcinogenic hazards from a variety of naturally–occurring and synthetic chemicals, not to perform risk assessments. As more theory is developed and more evidence is produced about the mechanisms of carcinogenesis, the ranking of hazards by the simple HERP index can be improved (as can risk assessment) by taking into account information on a given chemical, i.e., mechanism, shape of the dose–

response curve, and mutagenicity.

Our analysis of possible carcinogenic hazards suggests that the possible hazards of synthetic chemicals ingested from pesticide residues or water pollution appear to be trivial relative to the background of rodent carcinogens from natural and traditional chemicals (e.g., from the cooking of food or nature's pesticides in plant foods).

For occupational exposures, there is a 100,000-fold range in possible carcinogenic hazard for rodent carcinogens that have PELs.[27] For several compounds, the permitted exposures to workers are close to the TD_{50} value in rodents, indicating that these should be a high priority for regulatory attention. For high occupational exposures, little extrapolation is required from the doses used in rodent bioassays; therefore, assumptions about extrapolation are less important. This contrasts with the large extrapolations required for the low doses of human exposures to pesticide residues or water pollution.

Only a tiny fraction of the chemicals to which humans are exposed will ever be tested in rodent bioassays. One strategy for choosing chemicals to test is to prioritize chemicals according to how they might rank in possible hazard *if* they were to be identified as rodent carcinogens. A useful first approximation is the analogous ratio Human Exposure/Rodent Toxicity (HERT). HERT would use readily available LD_{50} values rather than the TD_{50} values used in HERP. LD_{50} is related to the MTD and the TD_{50},(30,31) and we have found that the ranking of possible carcinogenic hazards by HERP and HERT is similar.[32] The number of people exposed is also relevant when attempting to prioritize systematically among chemicals. Chemicals with high HERT and population exposure could then be investigated in more detail as to mutagenicity, mitogenicity, pharmacokinetics, and the like. Natural and synthetic chemicals should both be ranked. If natural chemicals in foods (e.g., chlorogenic acid in coffee, psoralens in celery, or indole carbinol in broccoli) turned out to be important, they might be bred out; for processed foods such as coffee, they might be extracted.

It is unlikely that the high proportion of carcinogens in rodent studies is due simply to selection of suspicious chemical structures: most chemicals were selected because of their use as industrial compounds, pesticides, drugs, or food additives. Moreover, historically our knowledge to predict carcinogenicity has been inadequate.[4] We have examined the proportion of chemicals in the CPDB that are positive for ten different data sets, and in each case, roughly half of the chemicals are positive according to the published author's opinion in at least one test (Table I): all chemicals in the CPDB, NCI/NTP chemicals, NCI chemicals reported before 1979, literature other than NCI/NTP, chemicals tested in both rats and mice (and among these, natural chemicals only and synthetic chemicals only), natural pesticides, mold toxins, and 22 chemicals in coffee.[1,2,4,17,26,29] Even if there is some selection bias, these results indicate that we are likely to be living in a sea of rodent carcinogens as defined by testing at the MTD.

Mechanisms of Carcinogenesis: Mutagenesis, Mitogenesis, and Carcinogenesis

The study of the mechanisms of carcinogenesis is a rapidly developing field that can improve regulatory policy. Both DNA damage and mitogenesis are important aspects of carcinogenesis, and increasing either substantially can cause cancer.[26,33–37]

Mutagens are often thought to be only exogenous agents; however, endogenous mutagens cause DNA damage (oxidative and other adducts) that can be converted to mutations during cell division. Endogenous rates of DNA damage are enormous. We estimate that the DNA hits per cell per day from endogenous oxidants are normally 10^5 in the rat and 10^4 in the human.[38–40] This promutagenic damage is effectively

TABLE I. Proportion of Chemicals Evaluated as Carcinogenic[A] for Several Data Sets in the CPDB[B]

1. Chemicals tested in both rats and mice	288/479 (60%)
1a. Naturally-occurring chemicals tested in both rats and mice	56/101 (55%)
1b. Synthetic chemicals tested in both rats and mice	232/378 (61%)
2. NCI/NTP chemicals[C]	
2a. NCI/NTP chemicals tested before 1979	60/117 (51%)
2b. NCI/NTP chemicals tested after 1979	105/198 (53%)
3. Chemicals tested in at least one species	
3a. Natural pesticides	29/57 (51%)
3b. Mold toxins	12/20 (60%)
3c. Chemicals in roasted coffee	19/26 (73%)

[A] A chemical is classified as positive if the author of at least one published experiment evaluated results as evidence that the compound is carcinogenic.
[B] CPDB = Carcinogenic Potency Database
[C] 94% (296/315) are tested by the National Cancer Institute/National Toxicology Program (NCI/NTP) in both rats and mice.

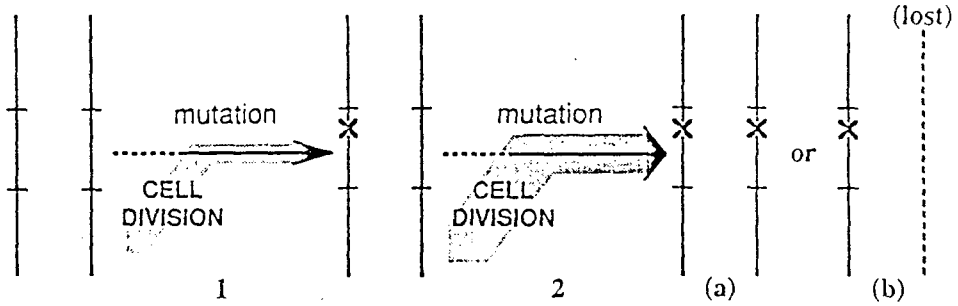

FIGURE 1. Mitogenesis increases mutagenesis. Mitogenesis (induced cell division) is a major multiplier of endogenous (or exogenous) DNA damage leading to mutation. The pathway to inactivating (x) both copies of a recessive tumor suppressor gene is shown (two vertical lines represent the pair of chromosomes carrying the genes). Cell division increases mutagenesis because of the following: DNA adducts are converted to mutations before they are repaired (1 & 2a); mutations owing to DNA replication (1 & 2a); and replicating DNA is more vulnerable to damage (1 & 2a). Mitotic recombination (2a), gene conversion (2a), and nondisjunction (2b) are more frequent, and the first two give rise to the same mutation on both chromosomes. This diagram does not attempt to deal with the complex mutational pathway to tumors.

but not perfectly repaired; the normal steady-state level of just 8-hydroxydeoxyguanosine (1 of about 20 known oxidative DNA adducts) in a 2-year-old rat DNA has been measured as 1/130,000 bases or about 90,000 per cell.[39] We have argued that this oxidative DNA damage is a major contributor to aging and to the degenerative diseases associated with aging such as cancer.[1,3] Thus, any agent causing chronic mitogenesis can be indirectly mutagenic (and consequently carcinogenic) because it increases the probability of converting endogenous DNA damage into mutations (Figure 1). Furthermore, endogenous rates of DNA damage are so high that it may be difficult for exogenous mutagens to increase the total DNA damage rate significantly by low doses that do not increase mitogenesis.

Geneticists have long known that cell division is critical for mutagenesis. If one accepts that mutagenesis is important for carcinogenesis, it follows that mitogenesis rates must be important. The inactivation of tumor suppressor genes is also known to be important in carcinogenesis, and recent evidence suggests that one of the functions of tumor suppressor genes is to inhibit mitogenesis.[41] When the first copy of a tumor suppressor gene is mutated, the inactivation of the second copy (loss of heterozygosity) is more likely to be caused by processes whose frequency is dependent on cell division (mitotic recombination, gene conversion, and nondisjunction) than by an independent second mutation.[1,2] Therefore, loss of heterozygosity will be stimulated by increased mitogenesis. Thus, while the stimulation of mitogenesis increases the chance of every mutational step, it is a much more important factor for tumor induction after the first mutation has occurred. This explains why mutagenesis and mitogenesis are synergistic[1,2] and why mitogenesis after the first mutation is more effective than before.

Thinking of chemicals as "initiators" or "promoters" confuses mechanistic issues.[42] The idea that "promoters" are not, in themselves, carcinogens is not credible on mechanistic grounds and is not correct on experimental grounds.[1,2,42] Every classical "promoter" that has been tested adequately (e.g., phenobarbital, catechol, TPA) is a carcinogen. The very word "promoter" confuses the issue because mitogenesis may be caused by one dose of a chemical and not by a lower dose. Dominant oncogenes and their clonal expansion by mitogenesis can clearly be involved in carcinogenesis, adding complexity; however, these mechanisms are still consistent with the view that mitogenesis is an important factor in carcinogenesis. Nongenotoxic agents (e.g., saccharin) can be carcinogens at high doses just by causing cell killing with chronic mitogenesis and inflammation, and the dose–response would be expected to show a threshold.[2,35,36] Epigenetic factors are also involved in carcinogenesis. However, both mitogenesis (e.g., through mitotic recombination) and DNA damage can cause loss of 5-methylC or other epigenetic modification.[2] Chronic mitogenesis by itself can be a risk factor for cancer: theory predicts it and the literature supports it.[2,43] The 40% of rodent carcinogens that are not detectable mutagens should be investigated to see if their carcinogenic effects at high doses result from induction of mitogenesis; if so, then such rodent carcinogens would be unlikely to be a risk at low doses.

Genotoxic chemicals, because they hit DNA, are even more effective than nongenotoxic chemicals at causing cell killing and cell replacement at high doses. Because genotoxic chemicals also act as mutagens, they can produce a multiplicative interaction not found at low doses, leading to an upward curving dose–response for carcinogenicity.[2,35,36] Mitogenesis can often be the dominant factor in chemical carcinogenesis at the high, nearly toxic doses used in rodent bioassays, even for mutagens. Mitogenesis can be caused by toxicity of chemicals at high dose (cell killing and subsequent replacement), by interference with cell–cell communication

at high dose,[44–47] by substances such as hormones binding to receptors that control cell division,[43] by oxidants (the wound healing response), by viruses, and such.[2] The important factor is not toxicity, but increased mitogenesis in those cells that are not discarded.

The importance of chronic mitogenesis for many of the known causes of human cancer has been discussed (e.g., hormones in breast cancer, hepatitis B[34] or C viruses or alcohol in liver cancer; high salt or *Helicobacter (Campylobacter)* infection in stomach cancer; papilloma virus in cervical cancer; asbestos or tobacco smoke in lung cancer; and excess animal fat and low calcium in colon cancer).[2,43,48] For chemical carcinogens associated with occupational cancer, worker exposure historically was often at high doses that might be expected to induce mitogenesis.

In animal cancer tests, chronic dosing at the MTD may often be the equivalent of chronic wounding, which is known both to increase carcinogenesis in animals and to be a risk factor for cancer in humans.[49] In the usual experimental design of dosing at the MTD and 1/2 MTD, both dose levels are high and may result in mitogenesis. Even at these two high doses, we have found that 44% of the positive sites in NTP bioassays are statistically significant at the MTD but not at 1/2 the MTD (among 365 positive sites). It is clear that the mechanisms of action for all rodent carcinogens are not the same and that one cannot use a simple, linearized, risk assessment model for all of them. For some chemicals, there is evidence to support mitogenesis effects unique to high doses (e.g., formaldehyde, melamine, and saccharin). For others (e.g., butadiene), carcinogenic effects have been found 100 times below the MTD. Further studies of mechanism in rodent bioassays should help to clarify such differences. Adding routine measurements of mitogenesis to the 13-week toxicology study and the 2-year bioassay would provide information that would improve dose setting, interpretation of experimental results, and risk assessment. The work of Cunningham et al.[50,51] is a good example of how mechanism studies help to differentiate among chemicals. Their experiments showed that with pairs of mutagenic isomers (1- versus 2-nitropropane and 2,4- versus 2,6- diaminotoluene), one isomer is a carcinogen and the other is not; however, only the carcinogen was mitogenic.

Qualitative Extrapolation Between Species

Prediction of Positivity

How well can one predict carcinogenicity from rats to mice or from mice to rats? These closely related species both receive doses at or near the MTD in chronic bioassays. Because humans are less closely related to rodents, qualitative prediction from results in rats or mice to humans exposed at high doses is not likely to be more accurate than prediction between rats and mice.

TABLE II. Comparison of Carcinogenic Response for 479 Chemicals Tested in Both Rats and Mice

Not positive in either rats or mice	191
Positive in rats only	59
Positive in mice only	64
Positive in both rats and mice, no common target site	57
Positive in both rats and mice at same target site	108[A]

[A]For 47 of these 108 chemicals, the liver is the only site in common between rats and mice.

Using results in the CPDB for the 479 chemicals that have been tested in both rats and mice, Table II indicates that if a chemical is positive in one of the species, it will be positive in the other species about 75% of the time. This is similar to results reported earlier for smaller numbers of chemicals.[4,5,52–54] Because about half of the test chemicals are positive in each species, by chance alone we would expect a positive predictive value between species of about 50%.[4,5] Thus, the overall predictive values of 75% between rats and mice provide only moderate confidence in interspecies extrapolation. We have also compared results for the limited number of compounds tested in hamsters and rats or hamsters and mice. Prediction from rats to hamsters or from mice to hamsters (about 65%) is similar to, but slightly less accurate than, prediction between rats and mice.

We have discussed three factors that influence the accuracy of prediction of carcinogenicity between rats and mice. Predictive values are more accurate for mutagens than nonmutagens and for chemicals that are toxic at lower doses compared to higher doses (as measured by the MTD). The accuracy of prediction also varies by chemical class.[4]

Prediction of Target Site

If a chemical is positive in one species, how often will it be positive in the other species and at the same target site? Because many chemicals induce tumors at multiple sites, there is often more than one target site that is potentially a common site for the two species, thus increasing the chance that there will be some target site in common.

Site-specific prediction between rats and mice is less accurate than overall prediction of positivity. Knowing that a chemical is positive at any site in one species gives about a 50% chance that it will be positive at the same site in the other species (Table II). For 47 of the 108 chemicals with a site in common between rats and mice, the liver is the only site in common. Site-specific prediction from rats or mice to hamsters is similar to that between rats and mice.

Ultimately, one wants to know whether chemicals that have been shown to be carcinogenic in experimental animals are also carcinogenic in humans. This question cannot be answered by reversing the question (i.e., by asking whether chemicals that are human carcinogens are also carcinogenic in a rodent species) because even if most human carcinogens

are rodent carcinogens, the converse does not necessarily follow, as can be demonstrated by a simple probabilistic argument.[55] However, some additional evidence about interspecies extrapolation can be obtained by asking how good a model the human is for the rat or the mouse, even though this will not provide direct evidence about how good a model the rat or mouse is for the human. The evaluations of the International Agency for Research on Cancer (IARC)[56] list 55 known human carcinogens including industrial processes, therapeutic combinations, single chemicals, and mixtures such as tobacco smoke.[56–58] For 35 of these, data in experimental animals have been evaluated by IARC.[57] The CPDB includes only results of experiments on single chemicals, administered by routes expected to result in whole-body exposure, that meet specified experimental-design criteria. A search of the CPDB indicates that results are included for 17 human carcinogens tested in rats and for 16 tested in mice. Using only these CPDB results, the overall predictive value from humans to rats is 76% (13/17) and from humans to mice is 75% (12/16). For some human carcinogens with only negative results[A] in the CPDB, positive results have been obtained in experiments not meeting CPDB inclusion criteria.[58] Prediction based on target organ is 47% (8/17) from humans to rats and 37% (6/16) from humans to mice. Thus, the overall predictive values are similar to those reported above between rats and mice for the CPDB; the value for target organ is slightly lower for mice.

Based on this experimental evidence from the CPDB involving prediction from rats to mice, from rats or mice to hamsters, and from humans to rats or mice, we conclude that one cannot assume that if a chemical induces tumors at a given site in one species it will also induce tumors at the same site in a second species; the likelihood is at most 49%.

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[A] In rats, 4 human carcinogens have only negative results in the CPDB: arsenic compounds, azathioprine, cyclosporin, and Myleran. All 4 are evaluated by IARC as having limited, not sufficient, evidence of carcinogenicity in experimental animals. In mice, 4 human carcinogens have only negative results in the CPDB. IARC evaluates 2 as having limited evidence in animals (arsenic compounds and cyclosporin) and 2 as having sufficient evidence (aflatoxin and nickel compounds). Some rodent experiments on human carcinogens are used by IARC in their evaluations but are not included in the CPDB because of route of exposure (e.g., skin painting, subcutaneous injection, intratracheal instillation, implant), nonchronic dosing, use of infant animals, lack of controls, cocarcinogenesis tests, and screening assays on the accelerated induction of tumors.

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