Animal and Human Carcinogens

Lewis et al. (1) state that compared to the fairly large number (≥ 400) of known rodent carcinogens, only a relatively small number of compounds (~20–30) have been shown to be carcinogenic in humans.

From this comparison, the authors seem to infer that animal bioassay cancer findings overpredict for human carcinogens. Of course, for most animal carcinogens there are no available epidemiologic data, and none planned, or for a few the findings are either inadequate or of limited value. In addition, few studies are under way or even planned on many known and potent animal carcinogens. Thus, one should realize that any conclusions about comparative numbers between animals and humans that are based on an apparent absence of data from humans can only be misleading and basically unusable for making any meaningful comparisons. A more relevant correlation to be made centers on the number of chemicals known to cause cancer in humans that have also been tested either prospectively or retrospectively in laboratory animals.

In any event, the numbers reported by these authors regarding known human carcinogens should be updated and modified using more current information. A proposed updated revision follows.

Utilizing data from the International Agency for Research on Cancer (IARC Monographs on the Evaluation of Carcinogenic Risks to Humans, volumes 1–73) and the National Toxicology Program (NTP: Report on Carcinogens, editions 1–8), there are approximately 75 agents known to be causatively associated with cancer in humans and another 60 considered "probably carcinogenic to humans" (Table 1). With few exceptions, agents in both these categories have varying evidence of cancer in humans. While attempting to plan or implement cancer prevention strategies, the additional 225 agents considered by IARC as "possibly carcinogenic to humans" and the 169 agents judged by the NTP as "reasonably anticipated to be carcinogenic to humans" must be given close public health attention as well. Of course both lists must be compared to account for any duplications.

I have no particular disagreement with the number of 400 chemicals as being carcinogenic in animals, other than to emphasize that not all carcinogens are equal. That is, some chemicals cause multiple site cancer in both sexes of each strain and species, whereas others may induce tumors in a single organ in one sex of only one strain of rodent (2). Thus, one must evaluate the carcinogenicity data for each chemical rather than simplistically group chemicals that have been tested into two clusters by "positive" or "negative" results. In the NTP for example, of the 500 chemicals evaluated for carcinogenicity:

- 14% caused cancer in each of the four sex/species groups used for testing (female rats, male rats, female mice, and male mice)
- 8% caused cancer in three of four experimental groups
- 18% caused cancer in two of four experimental groups
- 12% caused cancer in one of four experimental groups
- 48% caused cancer in none of four experimental groups.

Thus, using this data set, roughly 25% of these 500 (or 125 chemicals) would be considered as positive in two species, and therefore meeting established guideline criteria to be evaluated by IARC and/or the NTP as representing a possible cancer risk to humans. This does not mean that all 125 chemicals would be listed, only that this number would be considered for listing. At this interval, all available data on each agent must be scrutinized to decide whether the agent should be to listed or not. If, for the moment, all 125 were listed, then this would not be too different from the 135 agents listed by IARC as carcinogenic to humans or probably carcinogenic to humans. Interestingly, IARC evaluated nearly 850 agents and listed only 135 in these two categories, or 16%, not dissimilar from that posed by Fung et al. (3).

Consequently one should be more clear and more precise when using numbers of chemicals considered to be carcinogenic to rodents or to humans. To designate all chemicals that induce cancer in animals as being equal and representing similar and significant risks to humans is incorrect and improper, and should be avoided (4). Likewise, even though bioassays are indeed excellent surrogates for humans, not all chemicals shown to cause tumors in animals will, or should be expected to, prove to be carcinogenic to humans. Many reasons can be given for this lack of concordance, but a main one is that we should not expect the animal-to-human concordance to be perfect, largely for the reason mentioned: not all animal carcinogens are equal (that is, not equally potent or equally carcinogenic). Thus, chemicals such as d-limonene or allyl isothiocyanate that induce tumors only in the male rat kidney or urinary bladder are not in either the IARC or the NTP listings of carcinogens and clearly do not represent the likely cancer hazards that than do other more striking multigain, multistrain, and multispecies carcinogens do. Conversely, we know that all human carcinogens that have been tested adequately in animals are also carcinogenic to laboratory animals (5).

As shown in Table 1, the NTP has reviewed more than 800 chemicals as candidates for their Reports on Carcinogens, and only 198 agents have been judged as "known to be carcinogenic to humans" (29 agents) or as "reasonably anticipated to be carcinogenic to humans" (169 agents). IARC has reviewed and evaluated close to 850 agents in their Monographs program and found most of these (474 agents) inadequate for evaluation. Likewise for the

Table 1. Numbers of chemicals (~2,000 total), groups of chemicals, and exposure circumstances evaluated for carcinogenicity by the International Agency for Research on Cancer (IARC) and the National Toxicology Program (NTP).

| IARC category of evidence | Total | Chemicals and physical agents | Biological agents | Mixtures | Exposure circumstances and occupations |
|--------------------------|-------|-------------------------------|------------------|---------|----------------------------------------|
| IARC evaluationsa (n = 833) |       |                               |                  |         |                                        |
| Carcinogenic to humans, Group 1 | 75    | 39                            | 11               | 12      | 13                                     |
| Probably carcinogenic to humans, Group 2A | 59    | 46                            | 4                | 5       | 4                                      |
| Possibly carcinogenic to humans, Group 2B | 227   | 207                           | 4                | 12      | 4                                      |
| Not classifiable as to its carcinogenicity to humans, Group 3 | 471   | 446                           | 6                | 12      | 7                                      |
| Probably not carcinogenic to humans, Group 4 | 1     | 1                             | -                | -       | -                                      |
| Totals | 833 | 739                           | 25               | 41      | 28                                     |
| NTP evaluationsb (n = 800) |       |                               |                  |         |                                        |
| Known to be carcinogenic to humans | 29    |                               |                  |         |                                        |
| Reasonably anticipated to be carcinogenic to humans | 169   |                               |                  |         |                                        |
| Agents or exposure circumstances evaluated and not listedc | -600  |                               |                  |         |                                        |

aData from the IARC Monographs on the Evaluation of Carcinogenic Risks to Humans, volumes 1–73 (International Agency for Research on Cancer, Lyon, France). bData from the Report on Carcinogens, editions 1–8 (National Toxicology Program, Research Triangle Park, NC). cConsidered not meeting guideline criteria as clearly carcinogenic in two species.
NTP, many have been considered but few have been selected. Because many of the chemicals evaluated by IARC and the NTP are the same, although many are unique as well, one cannot simply add numerical data from these two sources without individual comparisons. Unfortunately, neither organization lists the agents that were considered but not selected for formal review because the available data are not considered adequate; that is, there may be no cancer data on a chemical, or the available data are insufficient to meet either agency’s criteria for review.

Another issue posed by Lewis et al. (1) concerns the value of rodent bioassays. This has been an ongoing debate for many years. Some facts may be of interest. We know that all known human carcinogens that have been tested adequately in laboratory rodents are also carcinogenic to animals (2,4,6); for nearly 30 agents, the evidence of carcinogenicity was first observed in animals, ignored for the most part, and only subsequently detected in humans (7,8). These studies have all been accomplished using what some describe as the “maximum tolerated dose,” which is at best operational terminology that has been literally misapplied and distorted, and is obsolete (9,10). A more accurate term is “minimally toxic dose” (MTD), or “minimally toxic exposure” (MTE), because when long-term bioassays are conducted, one must be certain that some adverse effects of the chemical are occurring, or the time, resources, and efforts will be wasted. Further, there is little evidence to support a “high-dose only” phenomenon in carcinogenesis. That is, using an MTD concept of exposure cannot “make” a chemical a carcinogen when it is a noncarcinogen (11).

I agree with Lewis et al. (1) that in the safety evaluation of chemicals, we should be cautious in extrapolating results from experimental animal models to humans. Conversely, I do not agree that we should ignore long-term bioassay results or delay preventative strategies until we have definitive mechanistic data, such as, for example, species differences and similarities in cytochrome P450 isomorph carcinogen metabolic information, proposed by Lewis et al. (1). This does not mean such information will not be useful to the overall paradigm of quantifying carcinogenic risk in humans, but that equal caution must be recognized in considering another in a lengthy line of mechanistic discoveries. This information may only modify or extend quantitative estimates of risk. On this issue, the distribution of these enzymes may be most useful for evaluating interindividual differences in susceptibility.

Thus, the public health value and usefulness of the bioassay for identifying potential or likely human carcinogens has a long history of being quite relevant and predictive. Perhaps we should give more attention to these laboratory results when attempting to prevent human cancers resulting from exposures to environmental or occupational carcinogens (12).

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REFERENCES AND NOTES

1. Lewis DFV, Ioannides C, Parks DV. Cytochromes P450 and species differences in xenobiotic metabolism and activation of carcinogen. Environ Health Perspect 106:633–641 (1998).
2. Huff JE. Value, validity, and historical development of carcinogenesis studies for predicting and confirming carcinogenic risks to humans. In: Testing, Predicting, and Interpreting Chemical Carcinogenicity (Kitchin KT, ed). New York: Marcel Dekker, 1995:21–123.
3. Fung VA, Barrett JC, Huff JE. The carcinogenesis bioassay in perspective: application in identifying human cancer hazards. Environ Health Perspect 103:680–683 (1995).
4. Huff JE. Carcinogenesis results in animals predict cancer risks to humans. In: Maxcy-Rosenau-Last Public Health & Preventive Medicine (Wallace RB, ed). 14th ed. Norwalk, CT: Appleton-Lange, 1998:543–550, 567–569.
5. Huff JE. Chemicals causally associated with cancers in humans and in laboratory animals: a perfect concordance. In: Carcinogenesis (Waaikes MF, Ward JM, eds). New York: Raven Press, 1994:5–37.
6. Tomas L, Atto A, Whobourn J, Shaker L. Human carcinogens identified so far. Jpn J Cancer Res 80:795–807 (1989).
7. Tomas L. The predictive value of rodent carcinogenicity tests in the evaluation of human risks. Annu Rev Pharmacol Toxicol 19:511–530 (1979).
8. Huff J. Chemicals and cancer in humans: first evidence in experimental animals. Environ Health Perspect 100:201–210 (1993).
9. Bucher JR, Portier CJ, Goodman JI, Faustman EM, Lucier GW. Workshop overview. National Toxicology Program studies; principles of dose selection and applications to mechanistic based risk assessment. Fundam Appl Toxicol 31:1–8 (1996).
10. Huff JE, Haseman JK, Rall DP. Scientific concepts, value, and significance of chemical carcinogenesis studies. Annu Rev Pharmacol Toxicol 31:621–652 (1991).
11. Bucher JR. Doses in rodent cancer studies: sorting fact from fiction. Drug Metab Rev (in press).
12. Tomas L, Huff JE, Hertz-Picciotto I, Sandler D, Bucher J, Boffetta P, Axelson O, Blair A, Taylor J, Steynen L, et al. Avoided and avoidable risks in cancer. Carcinogenesis 18:97–105 (1997).