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LETTERS

Assessing dangers

Should laboratory animals be used to test the possible toxicity of substances? How do the differences between these animals and humans affect the assessment of risk to humans? Should test animals be fed as much as they want, or should their diets be limited? What is risk assessment? These questions, and more, were raised by Philip H. Abelson's editorial of 13 October, "Flaws in risk assessments." Other letters discuss tamoxifen carcinogenicity, Lyme disease research, and the electromagnetic field controversy.

Test Animals and Risk

Philip H. Abelson's editorial of 13 October (p. 215) points out the trends in test animals which lead to conservative Environmental Protection Agency (EPA) risk assessments. Often chemical toxicities are determined in a sensitive strain of the most sensitive animal species using the most absorbable chemical species for the contaminant under study. When there are no human data, two factors of 10 are applied to extrapolate to humans and to allow for individual sensitivity. Another factor of 5 can be applied for "deficiencies in the data." It is difficult to understand how we humans ever survived to develop forebrains. To make matters worse, exposure scenarios are computed using 95 percentiles of multiplicitive parameters for the most vulnerable subpopulations. Monte Carlo simulations use the same biased reference doses to justify the results.

On the Lower East Fork Popular Creek site in Tennessee contaminated by the Department of Energy with mercury, the above factors reached a bias estimated at 500,000. In a public meeting, EPA justified this, stating that their procedure comprised two steps: (i) remediation assessment and (ii) risk management. They further stated that they viewed the Comprehensive Environmental Response, Compensation, and Liability Act as a mandate from the people through Congress to propose unquestionably safe remediation levels regardless of cost and that this in turn justified the use of conservatively biased data. If it so wished, the public could oppose the proposed level in the risk management step. Unfortunately the complexities of risk assessment and the magnitude of the task are well beyond the average lay person. Oak Ridge was fortunate to save 90% of the original cost estimate, $270 million. Lacking technically trained residents, the EPA procedure will most likely fail.

I fear that if attention is focused solely on the test animals we will be choking on the gnat and swallowing a procedural elephant and we will continually be defending ourselves against the extravagances of our government.

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Abelson characterizes toxicological experiments as risk assessment studies and experiments. Risk assessment is an analytical discipline that integrates data from many sources, with expert opinions and judgments, to arrange at a risk estimate. I have no disagreement with Abelson's critique of the experiments themselves, but usually these experiments are not conducted by risk assessors. The data from the described rodent experiments may be used in risk assessments, but each assessment should in turn describe the uncertainty each set of data contributes to the result. Risk assessment is an evolving field in which feedback from risk assessors should help laboratory and field investigators to provide appropriate information for the risk assessment process.

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In the book (*1*) cited by Abelson, it is made clear that dietary restriction results in major physiological alterations in restricted animals affecting the physiological response to drugs and drug-metabolizing enzyme expression, intermediary metabolism, and antioxidant systems. Alterations occur in the transcriptional apparatus of cells, DNA polymerase alpha function and fidelity, oncogene expression and cellular transformation, the regulation of growth hormone and insulin-like growth factor–1 and consequent protein synthesis, the rate of cellular replication in young mice, and the rate of pro-

grammed cell death. The institution of dietary restriction at a level that will reduce or delay the appearance of tumors and extend life span will thus provide a test animal that will be far different in its responses to drugs and toxic agents than that which has been used as a standard for the past 40 to 50 years. Any change from the ad libitum–fed animal to one kept on any degree of dietary restriction should be preceded by a careful and extensive set of comparison studies for the two conditions in all categories of drugs or toxic agents to be tested. The underlying response baselines will have been strongly altered at several levels, and not necessarily to the same degree for each category.

As for test animal-versus-human comparisons, we should remember that there are a great many more ad libitum–fed, obese Americans out there than dietary restricted ones.

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References

1. R. W. Hart, D. A. Neumann, R. T. Robertson, Eds., *Dietary Restriction: Implications for the Design and Interpretation of Toxicity and Carcinogenicity Studies* (ILSI Press, Washington, DC, 1995), pp. 127–140, 167–196, 213–228, and 245–326.

Tamoxifen Ruling in California

The decision in May to list tamoxifen as a carcinogen in California was not "preliminary," as stated in the ScienceScope item "Anticancer drug under scrutiny as carcinogen" (6 Oct., p. 19), but was simply the expert committee decision required by Proposition 65. It was based, like all such decisions, on the weight of available peer-reviewable evidence. The finding was made at a public meeting, held to review the literature and consider information believed by any member of the public to be pertinent. Legal counsel representing Zeneca Pharmaceuticals, tamoxifen's manufacturer, indicated at that meeting that the company did not challenge the finding that tamoxifen use is followed by and is likely to cause endometrial cancer. The predominant concern expressed by Zeneca's representatives, appropriately, was in relation to the occurrence of other, particularly gastrointestinal, neoplasms.

There is no intent to "deliberate for 6 months" before making a final decision; the original decision was intended to stand. It now is presumed that the compound will be listed unless additional information submitted by 31 October shifts the weight of evidence. Any compound listed can be removed from the list should stronger pertinent information to the contrary become available at a later date.

This legally mandated process of hazard identification does not address the issue of the compound's net benefit. Important commercial chemicals are listed, as are useful and widely used (and accepted) drugs, including chemotherapeutic agents, analgesics, and a best-selling formulation, conjugated estrogens. Evidence that neoplasms are produced in humans under conditions of treatment makes the listing of tamoxifen unavoidable.

Doctors who make case-by-case medical decisions weigh the costs against the benefits and, with the help of informed consent, allow the recipient of an agent to review the decision. Others who distribute carcinogenic chemicals may be less prudent. In the larger context of informing the public (in this case at the voters' request) about all the carcinogens they may come in contact with, it should be the duty of industry and consumer representatives to provide the most accurate information available, and it is the inescapable duty of government to digest and summarize that information with as much insight and objectivity as can be mustered. Insight and objectivity are often enhanced by outside scientific advisers,