Letters

Risk Assessment Reappraisals

Frederica Perera expressed concern in a recent letter (11 Mar., p. 1227) that the Environmental Protection Agency (EPA) has moved to lower its assessments of cancer risk for "many" chemicals by invoking mechanistic theories and pharmacokinetic models that are not scientifically justified. The facts and informed scientific opinion are at variance with her views.

For example, in the case of methylene chloride, a chemical cited by Perera, a large body of pharmacokinetic information clearly describes the nature and significance of two distinct metabolic pathways for the compound, the demonstrated species differences in metabolism, and the comparative metabolic parameters in humans and rodents which affect the disposition of a specific metabolite at the target site. Incorporation of this information into the risk assessment for methylene chloride results in an eightfold risk reduction when compared with an earlier EPA estimate. In reviewing the EPA's position, the EPA Science Advisory Board—a congressionally mandated group of independent scientists from outside EPA—stated that our analysis "was one of the best documents it has reviewed in terms of its clarity, coverage of the data and analysis of scientific issues. This document clearly demonstrates the potential utility of pharmacokinetic data in risk assessments. EPA should continue to use this approach in future risk assessments, whenever scientifically possible" (*1*).

Perera further suggests that a policy is being established at EPA to divide carcinogens into genotoxic and nongenotoxic categories. She cites EPA's recent reanalysis of the "dioxin" (2,3,7,8-tetrachlorodibenzo-*p*-dioxin, or TCDD) risk assessment to illustrate her allegation. The problem is that the evaluation of a single chemical cannot be equated with the formation of broad policy. TCDD is an intensively studied compound, and research has revealed important facts about its mechanism of toxic action. Nearly 2 years ago a prestigious group of non-EPA scientists reviewed the accumulated scientific evidence (*2*) and concluded that mechanistic models should be employed to estimate TCDD risks. This recommendation was synthesized from a variety of research observations that include (i) the necessity of reversible TCDD binding to an intracellular receptor as a step in its toxic mechanism; (ii) the demonstrated potent promotional activity with no evidence of initiation in at least two different tissues in two separate laboratory models; (iii) the absence of genotoxic activity in short-term tests; and (iv) the wide variation in toxic responses and differences in pharmacokinetics across species.

The existing EPA estimate of cancer potency for TCDD derives from use of a conservative (linear) extrapolation model and is the highest, by a factor of more than 1000 in some cases, of the various national and international estimates. In the proposed reassessment, EPA's potency estimate was still within the more conservative group, albeit 16-fold less than its original position. The point of the TCDD reanalysis was not simply to change the risks; it was an attempt to use the composite knowledge on the chemical in developing an estimate of risk.

EPA reevaluations of procedures and specific chemicals do not evolve in a vacuum. In addition to input from outside scientific groups (as noted above), EPA is conscientious (perhaps to a fault) in soliciting comments on draft assessments, guidelines, and policies. For example, EPA sent the preliminary reassessment of TCDD to more than a dozen persons from a broad segment of the scientific community for comment. We are taking responses to the proposal into account in developing a final position.

Regulatory agencies have the responsibility of making reasoned societal decisions about chemical safety. It is my strong view that to serve the public well these agencies have an obligation to remain current with scientific advances. This means they should periodically revisit the validity of the assumptions they use in evaluating risks. Many traditional risk assessment procedures represent default positions that are used in the absence of data. As new information is developed, these original positions need to be reviewed on a case-by-case basis for possible replacement or modification. I strongly agree with Perera that agencies need to set rigorous standards for the evaluation of the adequacy of new approaches in risk assessment. However, it is unrealistic to require scientific "proof" before making use of this information. In fact, there is no "proof" of the existing default procedures; they simply represent judgments based on available knowledge at the time.

The goal of reassessing regulatory approaches and assumptions is to reduce uncertainties, thereby increasing the accuracy of evaluations of the nature and degree of chemical risk. In contrast with Perera's implication that reappraisal results uniformly in the direction of lessening risk estimates, I believe it cuts both ways. Granted, there are cases like methylene chloride where new findings have resulted in reduction in risk estimates; but in others, like lead, there has been a one-way and continual increase in our concern over time about the risks of this metal to children.

In conclusion, given the scientific standards and open review process used by EPA, I believe that this agency has been more attentive to the science than arbitrary with the facts. The EPA goal is responsive to current knowledge rather than reactionary to past procedures. Further, I believe objective observers will agree with that.

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1. N. Nelson, R. A. Greisemer, J. Doull, personal communication to L. M. Thomas, Environmental Protection Agency (9 March 1988).
2. "Dioxin update conference report" (Office of Pesticides and Toxic Substances, Environmental Protection Agency, Washington, DC, 1986).

The question of how scientific estimates of risk should be presented to the public is a common thread in Perera's letter "EPA [Environmental Protection Agency] Cancer Risk Assessments" and in Glennda Chui's News & Comment article on activist opposition to new biology laboratories (11 Mar., p. 1229). In the past, an influential sector of the scientific community has supported the "conservative approach" in which public policy is based on the most pessimistic risk assessment models. Much less emphasis has been placed on the need for placing risks in perspective by coupling consistent methodologies of hazard evaluation with consistent phraseology in presenting tentative conclusions to the public.

The "conservative approach" to risk assessment has catered to the desire of the news media and activists to sensationalize the dangers that can be hypothesized for virtually any technological activity, and the lukewarm support of consistency and perspective by the scientific community has allowed public misconceptions to persist and to escalate. The resulting juggernaut of public opposition and legal obstuctionism has mainly had an impact on industry, but, as Chui clearly shows, academic laboratories are no longer immune to opposition based on public concern over small hypothetical risks that cannot be completely excluded on the basis of present scientific knowledge.

As has been dramatically demonstrated in the context of indoor radon, individual members of the public are actually quite willing to accept small hypothetical risks if such acceptance reduces personal expense and inconvenience. Thus the EPA indoor radon "guideline" of 4 picoCuries per liter is universally regarded as "safe" despite the fact that EPA openly acknowledges that con-

servative methodologies would assign a risk as high as five lung cancer deaths per 100 individuals exposed to this level of indoor radon over their lifetimes (*1*). The public has apparently made the intuitive and probably correct judgment that risk estimates quoted by EPA are unrealistically large by at least an order of magnitude, so that indoor radon at or below the "guideline" level does not significantly alter quality of life or life expectancy.

While I do not disagree with present public attitudes toward indoor radon, I feel that it would have been more forthright for EPA and the scientific community in general to have focused attention on more realistic risk estimates, while at the same time insisting that risks be placed in proper relative perspective. The public would then be justified in not worrying about indoor radon levels within the "guideline," and might eventually be persuaded that other demonstrably smaller risks, such as those from low levels of dioxins, nearby nuclear waste repositories, nearby nuclear power plant accidents (*2*), and even nearby biological laboratories, should be of even less concern.

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1. *A Citizen's Guide to Radon* (Publ. OPA-86-004, Environmental Protection Agency, Washington, DC, 1986), p. 10.
2. The EPA 4 pCi/liter "guideline" level of indoor radon causes a whole body equivalent dose on the order of 1 rem per year. Thus, if one assumes that radiological health effects are cumulative, lifetime exposure to the "guideline" level of indoor radon is as hazardous as the 50- to 70-rem exposure experienced by evacuees from the 3- to 7-kilometer zone around the uncontained Chernobyl nuclear power plant accident. Radiological exposures to neighbors of the contained Three Mile Island nuclear power plant accident were smaller by a factor of approximately 7000.

Perera asserts that the science used by EPA as the basis for its recent revision of carcinogen risk assessment methodology is "scientifically unsupported and premature." That might have seemed so 5 years ago to the groups whose conclusions she cites; it is not so today. There now exists a theory of carcinogenesis (*1–3*) that provides a strong foundation for EPA's actions. That theory is supported by a wide variety of evidence from studies on inheritance of human cancer and on the age-specific incidence of certain cancers, from clinical observations, and from experimental systems. It is entirely appropriate for EPA and other regulatory bodies to recognize this progress in the science of carcinogenesis and to take it into account in developing exposure standards. Nevertheless, Perera is correct in calling for scientific review of the methodology: EPA should continue to seek comment on its proposed decisions from its several scientific advisory boards, as it has done in the decisions she criticizes, and continue to base its decisions on those boards' advice.

In a series of papers starting in the mid-1970s, Knudson, Moolgavkar, and their collaborators outlined a theory of carcinogenesis that unifies most of the observations in this field. Developed from the 40-year-old "multi-stage" theory, it recognizes the crucial importance of mitotic rate in modulating the probability that the two "irreversible genetic events" necessary for conversion of normal cells to cancerous cells will occur. Knudson and co-workers showed (*1*) that only two such events are on the critical path for carcinogenesis from analysis of inheritance of childhood cancers. Moolgavkar and co-workers showed (*2*) that the age-specific incidence of breast cancer was consistent with the two-step theory when the timing of terminal differentiation of breast tissues is taken into account and discussed application of the theory to chemical carcinogenesis (*3*). Greenfield *et al.* showed (*4*) that saccharin causes bladder tumors in rats in proportion to the increase in mitotic rate in the bladder epithelium stem cells. Isaacs (*5*) found that two molecules of genotoxic carcinogen are required to convert normal rat memory cells to cancerous cells. The fact that almost all cancers of adult humans occur in tissues of epithelial origin has been widely noted, with tumors associated with healing of wounds the principal exception; only these tissues include populations of cells which regularly undergo mitosis and are thus vulnerable to mutation and carcinogenic transformation.

This theory has profound implications for low-dose extrapolation of carcinogenic action and thus for regulation of carcinogens. First, it establishes two different kinds of processes by which treatment can increase tumor incidence: (i) direct action on genetic material and (ii) indirect action, by means of modulation of mitotic rates. The distinction between "genotoxic" and "nongenotoxic" agents, previously made on phenomenological grounds, thus can be seen to have a strong theoretical basis.

Second, because all "genotoxic" agents can act through "nongenotoxic" means—increasing mitotic rate through cell killing at high dose rates, if nothing else—the term "complete carcinogen" becomes synonymous with "genotoxic carcinogen." Further, because most conventional lifetime bioassays have been carried out under conditions where some toxicity is observed, and thus where mitotic rate increases probably occur, extrapolation of results to low-exposure conditions is problematic.

Finally, because mitotic rate is normally controlled within limits by the organism, treatment with nongenotoxic agents that does not increase the mitotic rate outside those limits will not result in an increase in tumor incidence over background. That is, a real "threshold" will exist for these agents. Conversely, genotoxic agents may not exhibit such a threshold, unless the reaction with DNA is not a simple first-order one (*3*). The low-exposure hazard from genotoxic agents needs to be evaluated with the use of data from experiments in which mitotic rate increases do not occur.

It is true that these implications of the Knudson-Moolgavkar theory have not been widely discussed, but that does not affect their validity. It is also true that most regulation of carcinogens done to now has proceeded from the assumption that high-dose-rate experiments reliably predict low-exposure hazard, an assumption that we must now strongly question. The EPA has given close scrutiny to this assumption in the cases cited by Perera and has ample grounds for taking the actions it has taken. It seems to me that the EPA should be congratulated, not scolded, for introducing modern concepts about carcinogenesis into its risk assessment and risk management processes.

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2. S. H. Moolgavkar and A. G. Knudson, *J. Nat. Cancer Inst.* **66**, 1037 (1981); S. H. Moolgavkar and D. J. Venzon, *Math. Biosci.* **47**, 55 (1979).
3. S. Moolgavkar, *Env. Health Perspect.* **50**, 285 (1983).
4. R. E. Greenfield, L. B. Ellwein, S. M. Cohen, *Carcinogenesis* **5**, 437 (1984).
5. J. T. Isaacs, *Cancer Res.* **45**, 4827 (1985).

Macro, Not Macho

The letters concerning the extended workweeks of scientists as compared with those of the rest of the world, and the particular emphasis on the need for adequate child-care facilities, are broadly relevant to many disciplines. However, I think that a typographical error has crept into the correspondence of Djerassi (Letters, 1 Jan., p. 10) and the respondents (Letters, 5 Feb., p. 543 and 18 Mar., p. 1362).

In my opinion, the discussion is not of a "macho" workweek, but of a "macro" workweek. The micro-week, 40 hours, 9 to 5, is the mark of the hourly toiler, not the dedicated professional.

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