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.

HENRY HURWITZ, JR.
827 Jamaica Road, Schenectady, NY 12309

REFERENCES AND NOTES

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.

JAMES D. WILSON
Monsanto Company,
800 North Lindbergh Boulevard,
St. Louis, MO 63167

REFERENCES AND NOTES

1. A. G. Knudson, *Adv. Viral Oncology* **7**, 1 (1987), and references therein.
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.

MARVIN E. JAFFE
10 Sentry Parkway, Blue Bell, PA 19422