Letters

EPA Cancer Risk Assessments

Recently, the Environmental Protection Agency (EPA) has moved to lower its risk assessments for many environmental carcinogens, including dioxin and methylene chloride (*1*). In support of these revisions, the Agency has invoked theories about the mechanisms of chemical carcinogenesis and recently developed pharmacokinetic models; yet there is little scientific consensus that these approaches are justified.

Traditionally, EPA and other federal agencies have taken a conservative (health-protective) approach in regulating cancer-causing chemicals. Because conclusive data from human epidemiologic studies are seldom available, they have relied on results of experiments in laboratory animals to predict carcinogenicity in humans. In extrapolating from tumor incidence in animals to that expected in humans at lower levels of exposure, federal agencies have preferred conservative mathematical models (such as the linearized multistage model) which account for the possibility that a carcinogenic chemical can "add on" to the background of cancer. They incorporate low-dose linearity and do not permit estimation of a no-effect level or threshold.

In its proposed revised risk assessment for dioxin, EPA has departed from this conservative approach on the basis that the chemical might act by means of a mechanism resulting in lower cancer risk for humans. Several times since 1980, expert groups have reviewed the question of whether chemical carcinogens can be classified, for purposes of regulation, into separate categories on the basis of their presumed mechanism of action, that is, whether they are "genotoxic" and initiate normal cells by causing genetic mutation capable of predisposing the cell to uncontrolled growth or whether they are "nongenotoxic" and promote the malignant process by stimulating initiated cells to replicate at an increased rate, increasing the possibility of malignancy. These experts have asked: "Could nongenotoxic chemicals be considered to have thresholds below which there is virtually no risk? Could less stringent guidelines for regulation of this class of carcinogens be scientifically justified?" All of these groups, including those convened by the International Agency for Research on Cancer (1983) and the Office of Science Technology and Policy (1985), have rejected this approach as scientifically unsupported and premature.

Therefore, it is surprising that EPA has apparently decided that the process of chemical carcinogenesis is well enough understood to support a policy distinction between genotoxic and nongenotoxic carcinogens. According to the EPA proposal (*1*), on the basis of the possibility that dioxin might be a promotor in humans, the Agency would abandon its earlier traditional risk assessment for dioxin in favor of one 16-fold lower. A simplistic mathematical approach was devised in which the midpoint of six different risk assessments was taken. At one end of the spectrum was the EPA original estimate from the linearized multistage model; at the other end were estimates based on the concept that dioxin is a "threshold" carcinogen that does not cause cancer at low doses. These values vary by more than 1000-fold. A practical consequence of this revision is that, for purposes of standard-setting, the estimated dose of dioxin that would be associated with a maximum plausible human cancer risk of one case per million persons during a human's lifetime would be 0.1 picogram per kilogram of body weight per day rather than 0.006 picogram per kilogram per day.

EPA acknowledges that this is primarily a policy decision, not one based on new knowledge or new data. Noting that dioxin is a complete carcinogen that causes tumors by itself as well as a powerful promotor in test animals and that most but not all short-term tests for genotoxicity have been negative, EPA concludes that there is considerable uncertainty and controversy about the mechanism by which it causes cancer. Nevertheless, the agency has opted for the mathematical risk assessment approach.

While the new risks of dioxin are still very high (the estimated U.S. average daily dose is 1 picogram per kilogram of body weight per day), implementation of this proposal could set a precedent that would substantially relax regulation of a large fraction of manmade carcinogens in the air, water, and food supply.

Also in various stages of review at EPA are new risk assessments for cancer based on pharmacokinetic models (which mathematically describe the movement and fate of chemicals in the body) for two widely used solvents, methylene chloride and perchloroethylene (*1*). Both new risk assessments are substantially lower than previous estimates. Although pharmacokinetic modeling is an exciting and active area of research, some general caveats are appropriate regarding its application to risk assessment.

First, before a pharmacokinetic model can be developed, there is the formidable task of identifying the active species, which is rarely the parent carcinogen itself. Second, to accurately model the amount of activated carcinogen at the target site(s) extensive data are needed both in the rodent and the human regarding a large number of parameters (including activation, detoxification, excretion, binding to cellular macromolecules, replication, and repair of lesions). For most chemicals, these data are fragmentary. Perhaps most important, pharmacokinetic risk assessments are frequently based on limited data in genetically homogeneous experimental animals that have been exposed to fairly high concentrations of a test substance over a short period of time. This is very different from the common human situation involving intermittent, fluctuating exposures to a chemical, often over a lifetime. Even when some human pharmacokinetic data are available, small numbers of individuals have usually been studied over a short period of time. Thus, in general, the available experimental animal and human data cannot accurately reflect the wide interindividual variability in human response to carcinogenic chemicals.

These proposed precedent-setting changes in science policy could have a great impact on human health. It is therefore incumbent on EPA to set rigorous scientific standards for review of "new" approaches in risk assessment.

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REFERENCES

1. P. Shabecoff, *New York Times*, 4 January 1988, p. A1.
2. "A cancer risk specific dose estimate for 2,3,7,8-TCDD: Review draft" (Environmental Protection Agency, Washington, DC, 1987).

Refuseniks Still in U.S.S.R.

Last year brought many hopeful developments for human rights in the U.S.S.R. We are pleased with the release of prisoners of conscience and with an increase in emigration that has included some well-known, veteran refusenik scientists, engineers, and physicians. But we must remember that there are still many more who remain trapped in the U.S.S.R. against their will.

We were surprised by General Secretary Gorbachev's statement on American television, during a presummit interview, that "only those who cannot leave because of state security reasons" are denied exit visas. On the contrary, we know that many of them have never done classified work and that some did so only in the remote past. Some are sick, many endure wrenching sep-