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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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-

aration from immediate family members, and most have long been denied the right to work in their profession or at all.

Physicist Yuri Cherniak, suffering from heart disease, has been in refusal for 10 years, although his last exposure to state secrets was 16 years ago; the mathematician Benjamin Charny, a cancer patient, has been in refusal for 8 years, despite the fact that he has not worked with sensitive material since 1971; entomologists Igor Uspenskii and Inna Ioffe, both refuseniks for 7 years, have never done classified work; Vladimir Raiz, a young biochemist in Vilnius, was first refused an exit visa 14 years ago, just after completing work on his unclassified doctoral thesis; Vladimir Kislik, a radiation physicist who last worked with sensitive materials in 1966, has served part of his 14 years of refusal in a labor camp and in a psychiatric hospital; and the physical chemist Emil Mendzheritsky has been separated for close to 10 years from his children and grandchildren who live in the United States, despite the letter he holds from his former place of employment stating that the work he did there would no longer be considered sensitive after 1983.

There are now at least 805 scientists, engineers, and physicians (and their families) who have been denied exit visas. Of these, 122 have waited for more than 10 years, and 659 for between 5 and 10 years.

We appeal to the government of the U.S.S.R. to grant our colleagues their basic human rights, thus allowing them to emigrate and to take up their professional lives once again.

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Aurora Hypotheses

Richard A. Kerr's Research News article (28 Aug., p. 974) and the letter from Robert McPherron with Kerr's reply (4 Dec., p. 1340) concerning interpretation of the finding of Bruce Tsurutani and Walter Gonzalez (*1*) that high intensity long duration continuous aurora events (HILDCAAs) are caused by large-amplitude Alfvén waves was a stimulating discussion.

The idea that the southward turnings of the interplanetary magnetic field associated with the wave fluctuations lead to magnetic reconnection between the interplanetary and the Earth's magnetic fields is highly plausible and was discussed in depth by Tsurutani and Gonzalez. However, in testing this hypothesis, they obtained inconclusive results. It was determined that although data from the NASA/ESA (European Space Agency) International-Sun-Earth Explorer (ISEE)-3 satellite orbiting about the sun-Earth libration point made a fundamental contribution to the discovery of the relation between HILDCAAs and Alfvén waves, it was inadequate for the determination of details of the solar wind–magnetosphere energy transfer mechanism. This is because ISEE-3 was located at distances ($\sim 1.5 \times 10^6$ kilometers) from the Earth-sun line and Earth's magnetosphere that were large in comparison with the Alfvén wave lengths under consideration. Thus, Tsurutani and Gonzalez suggested using Earth-orbiting satellite data to determine the details of the energy transfer mechanism.

Meanwhile, other ideas (*2*) involving auroral energization processes that are alternatives to magnetic reconnection should not be ignored or left untested. Even if magnetic reconnection is found to be the principal cause of HILDCAAs, it is still possible that reconnection may not be of the classical type (*3*) during these very intense auroral events. In this aspect, qualitative coupling function studies, such as those involving impulse response functions (*4*) that use data from spacecraft placed immediately upstream of Earth's bow shock will be very helpful to elucidate basic differences among possible reconnection modes that are alternatives to the classical picture and the relative importance of other energization processes.

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Murine, Not Human, Cell Line

It has come to our attention that one of the cell lines examined in our report "Hormone conjugated with antibody to CD3 mediates cytotoxic T cell lysis of human melanoma cells" (22 Jan., p. 395) is of murine, not human, origin. By means of fluorescent antibodies to transplantation antigens and flow cytometry we have examined the two principal cell lines used in that study and it appears that one (B16F10) is murine; the other (M1313) is clearly human. Although our mistake is regrettable, it in no way affects the validity or significance of the reported observations. The point of the paper is that a chemically coupled complex, formed by linking a hormone to an antibody to the antigen-specific receptor complex on T cells, activates cytotoxic T cells and targets them on cells having receptors for the hormone. Like other peptide hormones, melanocyte-stimulating hormone is specifically bound by cell receptors of diverse vertebrate species; thus whether the targeted cells are mouse or human is immaterial. Indeed, the effectiveness of the conjugate in mediating destruction of murine cells by human cytotoxic T lymphocytes (CTLs) [and, reciprocally, of humans cells by murine CTLs with the use of a different targeting arrangement (*1*)] emphasizes the potential power of this general approach. We are particularly chagrined by our error because B16F10 is so widely known and appreciated for its value in studies on tumor metastases (*2*).

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Erratum: In the Research News article "Solutions to Euler equation" by Barry A. Cipra (29 Jan., p. 464), the equation in the first line of the fourth paragraph was incorrectly printed. It should have been "$x^4 + y^4 + z^4 = u^2$."