LETTERS

Mutagens and Carcinogens

Andrew Sivak (Letters, 23 July, p. 272) makes three criticisms about mutagenicity testing as an indication of potential carcinogenicity, and in particular about our test system of *Salmonella* bacteria and liver enzymes (*1*, *2*). We think he does not analyze any of the points clearly.

1) Sivak says that when we discuss our test results, which show an excellent correlation with animal carcinogenicity data, it is not clear whether we mean a qualitative or a quantitative correlation. Our articles are very clear; the correlation we discuss is qualitative (90 percent of 175 carcinogens are mutagenic in the test) and not related to potency. In our discussion of our data (*2*) (which Sivak does not quote), we point out (*2*, p. 951) some of the hazards of attempting to equate mutagenic potency with carcinogenic potency, and we discuss this subject briefly.

Sivak quotes some data for carcinogenic potency in an attempt to show that it does not correlate with mutagenic potency and states (without any qualifiers) that there is a "lack of correlation between microbial mutagenicity and rodent carcinogenicity results." His analysis is invalid for several reasons. (i) He gives a table of raw data on subcutaneous injections of chemicals in mice but does not say how to calculate the potency of a carcinogen from such data. Calculating the potency of a carcinogen is complicated even with the best of data, and data on subcutaneous injections (with tumors at the injection site and uncertainties as to the active dose) are inappropriate in any case. Such studies are not designed for that purpose (and are not particularly relevant to human exposure). (ii) Sivak also uses the Iball index of carcinogenic potency for polycyclic hydrocarbons, which is primarily of historical interest as an oversimplified view of what is now known to be a much more complex phenomenon. The Iball index makes no provision for dose and does not take into account the higher power relationship of the number of tumors with elapsed time (*3*). (iii) Sivak does not discuss the range of values necessary for a correlation. Carcinogenic potency (and mutagenic potency) varies over about a millionfold range (from an extremely weak substance such as chloroform to an extremely potent carcinogen such as aflatoxin B1). If, in addition to detecting 90 percent of carcinogens in a rapid and inexpensive test, one could also obtain mutagenic potency data that would en-

able one to predict the approximate potency of a carcinogen with some degree of probability, this would be extremely useful. One would like to be able to do this in drug development and in evaluation of the hazard of complex mixtures (such as water effluents, air pollution samples, and so forth), in which animal cancer tests are impractical. It is clear that by using a simplified system such as a rat liver homogenate and bacteria, one would *not* expect to be able to precisely predict carcinogenic potency in a rat (or a human). If one could predict it with a high probability within ± an order of magnitude this would be extremely useful, considering the range of carcinogenic potency. We believe the test may well be able to do this. Sivak chooses his carcinogenic potency examples from a much too narrow range where one could not see any correlation that existed.

Russell and Meselson (*4*) at Harvard are actively pursuing the area of the degree of quantitative correlation between a chemical's carcinogenic potency in animals and mutagenic potency in the *Salmonella* test, and following their lead we are doing the same. There are some animal carcinogenicity data from feeding experiments of appropriate quality for calculating carcinogenic potency and also some data on humans that meet the requirements.

2) Sivak says that we selected our strains to detect carcinogens and therefore the fact that they detect carcinogens is "self-fulfilling and not a true test." We selected our strains primarily on the basis of maximizing the detection of known mutagens (we did not think about carcinogenicity until much later), and fewer than 10 percent of the 175 carcinogens we actually tested in the validation of the method were used in the development of the strains. [In addition, the test has been independently validated (90 percent correlation) in a blind study of 120 chemicals (*5*).] Very few chemicals in general are mutagens or carcinogens, and the finding that more than 90 percent of carcinogens tested have been detected as mutagens (and that almost every mutagen that has been given an adequate cancer test is a carcinogen) may actually mean something. The chemicals known to be carcinogenic in humans represent an unselected sample, and the test detects almost all of them as mutagens (*2*).

3) Sivak questions the "equivalency" (we would not use that word) of mutation in bacterial DNA with "the multistep, multifactorial process of carcinogenesis in eukaryotic organisms." We have briefly discussed the idea of DNA damage (somatic mutation) as the initiator of most chemical and radiation carcinogenesis (*2*, *6*). This is a coherent theory that is supported by a wide variety of evidence. Sivak does not add any new arguments against it. We would welcome the presentation of a more specific alternative theory.

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References

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Sergei Kovalev: A Colleague in Trouble

Scientists in the United States are often unaware of real threats to their profession—the pursuit of truth—except for incidentals, such as the exigencies of budgets or the snarls of red tape. For some of our colleagues in the Soviet Union, merely raising what their political bosses deem the wrong questions can ruin their careers and threaten their very lives.

We are reminded of this most forcefully by the fate of the biologist Sergei Adamovich Kovalev, as described in an urgent message from academician Andrei Sakharov. If Kovalev had taken a narrow view of his profession, he might still be doing research in cellular physiology at his alma mater, Moscow State University. Instead, he is suffering from serious, untreated illnesses at "corrective labor colony number 36" near Perm.

Kovalev's "crimes," according to the laundry-list indictment on which he was tried last December, consist of embarrassing inquiries made on behalf of political dissidents in the Soviet Union. He has wanted to know, for example, why the cybernetician Leonid Plyushch was punished for his political heresies by 30 months in a psychiatric prison at Dnepropetrovsk amid violent criminals; why Alexander Solzhenitsyn was hounded from his homeland; why thousands of political and religious dissidents are being brutalized in camps and psychoprisons for attempting to exercise the rights guaranteed in the Soviet constitution.