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LETTERS

Risk from Low-Dose Exposures

Philip H. Abelson, in his editorial "Risk assessments of low-level exposures" (9 Sept., p. 1507), cites the case of the carcinogenic effects of dioxin when administered to female rats. When low doses were given, the tumor incidence in treated animals was lower than in controls; when high doses were given, the incidence of certain tumors was greater than in controls, while for the other tumors the incidence was lower. Abelson questions the assumptions made by government agencies that carcinogenic effects observed at high exposures are predictive of effects at minuscule exposures.

Examination of the totality of the tumor data from a series of rodent carcinogenicity studies shows that the phenomenon described by Abelson is widespread. We analyzed the results of 124 sex-species (male-female, rat-mouse) experiments carried out by the U.S. National Toxicology Program on 37 chemicals and found that tumor increases were observed in 41% of the experiments relative to controls and decreases were observed in 46%; in 22 experiments, simultaneous increases and decreases of tumors were observed (*1*). Decreases in the incidence of some tumors were observed for 30 of the 37 chemicals. While decreased body weight may have contributed to a low tumor incidence in some experiments, for 12 of 30 chemicals, tumor decreases occurred without any concurrent effects on body weight. In these experiments, the animals were exposed to the maximum tolerated dose of the test chemical and this dose, by definition, disturbs the normal physiology of the test animals. The disturbances could be quite diverse in nature and, because the process of carcinogenesis is multistage (with many possibilities for a chemical to intervene to accelerate or impede the process), it is not surprising that the tumor rates of untreated control animals are either increased or decreased by a test chemical.

Mutagenicity is widely regarded as a property that predisposes a chemical to display trans-species carcinogenic activity, often with multiple target organs (*2*). In our analysis, we noted that the five chemicals associated with multiple organ carcinogenicity were, as expected, all positive in the bacterial mutation (Ames) test; however, nine Ames-positive chemicals produced increases and decreases in tumor incidence, and three such chemicals produced only decreases in tumor incidence (*1*). As the Ames test uses prokaryotes as surrogates for a eukaryotic organism, this is also not surprising. A mammalian mutagenicity test in vivo appears to be a more reliable predictor of a carcinogenic hazard (*3*).

A fundamental tenet of governmental risk assessment is that a chemically induced increase in tumor increase in animals implies a carcinogenic risk to humans exposed to the chemical. Logically, it should follow that a chemically induced decrease in tumor incidence implies an anticancer effect in exposed humans. To decide which of these effects is more relevant to the overall well-being and survival of an individual may require further investigation of mechanisms, but to base a regulatory decision on analysis of only part of the data (tumor increases) is scientifically unsound. Given all the associated legal and socioeconomic implications, should one stigmatize a chemical that both increases and decreases tumor incidence as a "carcinogen"?

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Abelson questions the appropriateness of linear extrapolation for carcinogenic risk assessment. It is always a good idea to question the use of default methodologies in any scientific endeavor, and we commend Abelson for raising this issue once again. However, several misconceptions need correction to put this issue into proper perspective.

First, it is important to understand the meaning of the term "linear extrapolation" as used by the Environmental Protection Agency (EPA) for risk extrapolation. The EPA does not draw a line from high dose risks to low dose risks; they use a model that can be highly nonlinear (according to the usual mathematical definition) over the entire dose range. This model is flexible enough to account for metabolic saturation of detoxification pathways that may lead to a threshold-looking response. The term "linear" as it is applied by EPA concerns the slope of the dose-response curve very near the zero dose. If this slope is greater than zero at control, it implies that very small doses will result in increased risk and,

through a simple bit of arithmetic, risk can be shown to be well approximated in this region by a linear model. This does not imply or even require linearity over the entire dose range. In contrast, a "nonlinear" model in the jargon of risk assessment would have a zero slope at dose zero, implying there is no change in cancer risk for a range of doses near control. The "linearized multistage model" used by EPA allows for "nonlinearity" for the best estimate of risk, but requires the upper bound on risk to be "linear."

It is possible that the method of linear extrapolation of risks using dose-response from the experimental range could exaggerate risks at low environmental exposures. Several biological theories exist that support this contention, the most prominant of which suggests saturation of detoxication pathways resulting in a secondary effect that is only relevant at high doses. Situations may exist where intoxication pathways are saturated at lower doses than detoxication pathways. When this occurs, linear extrapolations from high to low doses may underestimate risk. There are also several biological theories that are better developed and much more convincing than the radiation hypothesis cited in Abelson's editorial that predict that "linearity" is adequate for low-dose extrapolation. The most plausible of these is that the chemical being studied adds to the process that spontaneously results in carcinogenesis. Numerous authors have illustrated the effect this "additivity of dose" would have on the "linearity" of a model by deriving the slope at dose zero and showing that this dose is positive when additivity holds.

Additivity is applicable to numerous biological processes related to carcinogenesis, including rates of oxidative damage, rates of DNA repair, and ligand-receptor binding. The examples cited by Abelson are the very situations that raise concern about additivity. For example, it is plausible that some spontaneously occurring human tumors result from natural oxidative damage. A chemical that adds oxidative damage to the mammalian system without a subsequent increase in the rate of repair would result in an increased cancer risk that is likely to be proportional to dose in the low-dose region.

Do "linearity" theories imply that "one molecule can cause cancer"? Yes and no. Under the additivity assumption, it is the total dose (the chemical agent and any endogenous biochemicals it is mimicking) that results in the tumor risk, not the chemical itself. However, "linearity" at low doses does imply that a single molecule of compound can increase risk. The large-scale repair of damaged DNA and the magnitude of spontaneous DNA damage do not preclude this possibility; this has no bearing on the issue unless the repair of spontaneous lesions is 100% perfect. The real issue is not whether a single molecule can cause cancer but the magnitude of risk for that single molecule. In the case of TCDD (tetrachlorodibenzodioxin), the EPA estimates an upper bound on low-dose risk of 10^{-7} per femtogram of exposure per kilogram of body weight per day over a lifetime. A single molecule of TCDD weighs approximately 5.35×10^{-7} femtograms. If one assumes a human weighs 70 kilograms, the upper bound on risk from exposure to one molecule of TCDD per kilogram of body weight per day would be 5.35×10^{-14}; in other words, if every one of the 5×10^9 people on Earth were exposed to one molecule of TCDD per kilogram of body weight per day for their entire lifetime, it would be approximately 4000 global human generations before we could expect to observe a single additional tumor (roughly 200,000 years). So, "one molecule can cause cancer," but it is highly unlikely. Levels of current human exposure to TCDD far exceed a single molecule and in industrialized nations have been estimated as between 300 and 600 femtograms per kilogram per day. This amounts to 5×10^8 to 5×10^9 molecules per kilogram per day and an estimated upper bound on risk of three to six additional cancer cases per 100,000 exposed humans.

Abelson's arguments concerning TCDD and breast cancer seem to imply that one should allow chemicals that are potentially harmful into the environment if they are also potentially beneficial. It is well documented (for test animals and for humans) that numerous agents are both carcinogenic and chemotherapeutic for cancer.

Finally, "linear extrapolation" is not and never has been the "current mode of extrapolating high-dose to low-dose effects"; it is the default method when additional information is unavailable.

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Abelson addresses a critical problem in toxicological evaluation. The problem in animal cancer studies is not the way we obtain the data (destructive testing is perfectly valid), but rather what we do with it when cancer occurs at the high dose. Biologically, linear extrapolation from high doses to zero dose is never valid. Numerous protective mechanisms ensure that life survives even under the steady and constant rain of chemical insults to our DNA. In the average rat or mouse oncogenicity study, the majority of the treated animals do not show chemically related tumors. The issue is not whether to continue investigating, but why the no-threshold model was advanced, why it was taken up by the EPA, and why it continues to be used despite a complete lack of scientific evidence to support it.

The supporters of the no-threshold model say that one must "prove" the existence of a threshold in each case. Rather, they should produce evidence of "no-threshold carcinogenicity." Every biological stimulus-response that has been tested shows a threshold. Foreign chemicals, drugs, vitamins, essential elements, nerve transmission, touch, taste, hormonal action, mating—you name it, and there is an example. The "no-threshold" faithful cannot produce one single process, including radiation, that stands up to critical scientific evaluation as having no threshold for oncogenic or other toxic effects.

The origin of all this seems to be a paper by Mantal and Bryon (*1*). It deserves careful reading by all concerned with cancer risk assessment. The authors present their model, not because it appears to fit the facts, but because it is the most conservative way of treating the data from the animal oncogenicity tests. To advance the conservative approach, they did not extrapolate from an effect dose to zero dose, but presented the upper 99% confidence limit of that extrapolation. This kind of mathematics leads to a strange result. We are certain of one thing about every foreign chemical; at zero exposure it cannot produce cancer. At zero dose, the cancer expectation should be zero (±zero). The extrapolation used, in fact, all extrapolations (including our own upper 95% confidence limit), gives a positive cancer-producing potential at zero dose.

Why is the model used? There is no record that was ever presented to the Office of Pesticide Programs' Science Advisory Panel for comment. Nor is there a record that it was presented to the agency's Science Advisory Board. There is no record of why it has come to be acceptable in various cancer risk assessment processes followed by EPA. These processes state roughly that if certain studies produce positive results, the chemical is classified in a particular category and a Q_1^* is calculated (the Q_1^* is the upper 95% confidence limit of the linear low-dose extrapolation). This value is used with the estimated daily lifetime exposure to determine the individual increased cancer risk. The daily lifetime exposure is based on the assumption that 365 milligrams per kilogram in one shot is toxicologically equal to 1 milligram per kilogram per day for 365 days. The background risk of cancer is 0.33. . . . . (one out of three of us will get cancer), and an increased individual risk of more than 0.000,001 is considered unacceptable.

I believe there are two reasons why this invalid procedure continues to be used by the EPA. The first is simple ignorance: Those in charge do not have the technical knowledge to recognize the fundamental error of the process and the conclusions that it leads to. The second reason is self-serving: There are too many people (thousands) whose livelihood depends on risk assessment, using it, buying it, and selling it. They consult, they contract, they write books, they publish journals, they give symposia, and they teach courses. If the linear extrapolation model is abandoned, these people will have to look for new jobs.

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Abelson writes that linear extrapolation from large doses of a DNA-damaging substance to zero dose in order to calculate effects of small doses "implies that mammals have no defense against effects that injure DNA." This is not correct. There is no necessary incompatibility between the operation of defense mechanisms and a linear dose-response relation. What linearity implies is that the efficiency of defense (the increment of damage per increment of dose) is independent of dose. Linear extrapolation from doses that have no large effect on the efficiency of relevant defense mechanisms can be a valid procedure. If the efficiency of defense decreases with increasing dose, as could occur if defense mechanisms become saturated, linear extrapolation overestimates the damage. If efficiency increases with dose, as could happen if defense mechanisms are induced by exposure, linear extrapolation can underestimate the damage. Clearly, it is important to know what the defense systems are and how they operate.

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Abelson argues that "the current mode of extrapolating high-dose to low-dose effects is erroneous. . . . Safe levels of exposure exist," but the report by A. Chaudhary *et al.* in the same issue (p. 1580) provides a contrary argument. Dose-effect measurements are typically carried out on young rodents in controlled environments. The genetic material of such animals has not had the opportunity to acquire significant amounts of metabolic and environmental damage. Chaudhary *et al.* show that adult human liver DNA has accumulated substantial amounts of damage resulting from endogenous lipid peroxidation. The presence of altered bases in DNA suggests that either the damage has escaped the repair mechanisms or that they have been saturated. What will be the effect of additional damage resulting from an exogenous source? Will the organism view this as a completely novel insult? Alternatively, is there some cumulative effect of different damages such that the exogenous damage interacts with the accumulated endogenous changes? If the latter is the case, older individuals would be at greater risk from a given exogenous insult, as they would have accumulated greater amounts of endogenous damage. The data are not available to answer the question. Very likely, different types of damage will produce different results. This uncertainty suggests that

conservative, linear-dose assumptions continue to be the prudent way of protecting the public health.

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Those who carry out research on antimutagenesis, anticarcinogenesis, and DNA repair generally support Abelson's editorial, saying that low levels of genomic damage induced by environmental sources do not constitute a hazard to humankind. Indeed, low levels of ionizing or ultraviolet radiation induce latent DNA repair mechanisms that appear to repair both radiation-induced and spontaneous lesions in the DNA. A new compilation and analysis of human mortality data derived from victims who survived nuclear detonations, nuclear exposures, radioactive fallout, and other exposures, such as those received by radium dial painters or from just plain living with a high radiation background, confirms induction of DNA repair: In every case, life expectancy is higher and cancer mortality is lower for exposed populations than for control and general populations (*1*). The overwhelming amounts of these data demonstrate that back-extrapolation from high doses of radiation provides expectations not in accord with reality. In fact, the expectations of ill-health effects seem to be the reverse of what really happens.

Lest one be led to believe that public panic might not be justified for radiation, but might be justified for toxic chemicals, a few examples should suffice to underline the irrationality of the latter belief. At the 4th International Conference on Mechanisms of Antimutagenesis and Anticarcinogenesis (held in Banff, Canada, 4 through 9 September 1994), investigators from Japan, Europe, and North America made it clear that hundreds of antimutagens are known to be present in natural products, many of which are consumed in food. Commonly known examples are vitamins C and E, which are powerful antioxidants, and dietary fiber and constituents of dairy products, which are not antioxidants. Four different laboratories working with four different carcinogens have discovered independently that caffeine is a powerful antimutagen against the action of the carcinogens. Many of the modes of anticarcinogenesis can be separated from antimutagenesis because some carcinogens can function at cellular levels (for example, retinoids), whereas antimutagenesis mechanisms are more strictly molecular phenomena. That is, the antimutagens either protect DNA, reverse molecular lesions, induce DNA repair, or lower the spontaneous mutation rate, and the anticarcinogens do that and more. It is reasonable to suppose that exogenous and endogenous antimutagens, anticarcinogens, and DNA repair processes would neutralize biologically many of the environmental compounds existing in low concentrations that now are posed as hazards.

Further, a reexamination of animal test data of carcinogens and their analogs by Frank M. Johnson and Joseph K. Haseman of the National Institute of Environmental Health Sciences tested the effects of known human carcinogens on mice, the control being analogs of these carcinogens that were not human carcinogens. The goal was to determine which chemical radicals and their placements on molecules caused carcinogenic action. The chemicals after testing were classified as either "carcinogens" or "noncarcinogens." Unexpectedly, when Johnson and Haseman reexamined the original data, they found that most of the chemicals tested for carcinogenicity exhibited anticarcinogenic responses, actually reducing the spontaneous cancer incidence from that found in the untreated controls.

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Abelson reports that the current mode of extrapolating high-dose to low-dose effects is erroneous for both chemicals and radiation, and he predicts safe levels of exposure. This conclusion is based on a study where the extent of damage to linear DNA caused by different dose levels of chemical test substances was measured. In some cases, the exposure to low doses had apparently beneficial effects. Safe levels of exposure are then also postulated for ionizing radiation. Do safe levels of exposure to ionizing radiation really exist? Some results of an epidemiological study carried out by a study group of the International Agency for Research on Cancer (IARC) give answers. Seven cohorts of nuclear industry workers in three countries were combined to estimate the excess relative risk (ERR) of cancer associated with increasing cumulative doses of ionizing radiation (*1*). The data, obtained from nearly 96,000 workers in the nuclear industry, are probably the most comprehensive available. The workers had been exposed to low-level x- and γ-radiation. Close to 60% of the subjects had received cumulative doses below 10 millisieverts (mSv), 80% received doses below 50 mSv, and fewer than 1% received doses greater than 500 mSv. The ERR for mortality from all cancers (excluding leukemia) was −0.07 per sievert (90% confidence interval: −0.39, 0.30), and for mortality from leukemia, excluding chronic lymphocytic leukemia (CLL), 2.2 per sievert (90% confidence interval: 0.1, 5.7). In both cases, the 90% confidence intervals around the ERR estimates for nuclear workers included values on the order of twice the linear estimates obtained from atomic bomb survivors. There is no evidence that the estimates which form the basis for current radiation protection recommendations are appreciably in error. If the safe levels of exposure to ionizing radiation postulated by Abelson really exist, then for leukemia (excluding CLL) the level must be set to such a low value that it would not have any consequences regarding radiation protection. The linear dose response model may be conservative, but it prevents underestimation of possible risks.

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