

Job-related cancer likely to increase, expert says

BY JOHN ONODA
Chronicle Staff

Exposure to cancer-causing substances is killing tens of thousands of workers, and the situation will probably worsen, a researcher who has spent decades studying job-related cancer said here.

Dr. Irving J. Selikoff of Mt. Sinai Hospital in New York said Friday that intense exposure to carcinogens such as asbestos can produce cancer rates as much as 1,000 times greater than occur naturally in humans.

Speaking at a conference on job-related cancer, Selikoff said cancer rates are highest among workers who expose themselves to carcinogens (cancer-causing substances) on the job and who also smoke.

Most of Selikoff's audience were workers and government officials. He talked mainly about asbestos, although he referred to other carcinogens such as benzene and vinyl chloride.

Selikoff reported a government estimate that about 10 percent of all cancer deaths in the United States may be related to asbestos exposure. Then he noted that a local cancer expert, Dr. R.A. Slatone, has concluded that this carcinogen may cause even more deaths, as many as 14 percent of all cancer fatalities in the nation.

Selikoff said one of five asbestos workers dies of cancer, although the disease often appears 15 or 20 years after first exposure to the carcinogen.

Congressman Bob Eckhardt spoke to the conference about the effects and costs of chemical dumping grounds. He said dumping at Love Canal dump near Niagara Falls was followed by miscarriages in several women and by rates of sickness and cancer far higher than the national average.

These phenomena were reportedly caused by chemicals, buried during the 1950's, that reached the surface and contaminated the surrounding area.

Eckhardt said the federal government has spent \$23 million trying to "clear up the area," in contrast, he said, to an estimated cost of \$4 million to properly dispose of the chemicals.

Eckhardt said the proper handling of carcinogens may be much cheaper than industry opponents argue. He said that when regulations for the carcinogen vinyl chloride were imposed in 1974, the government estimated that industrial changes would cost \$1.85 billion, but the industry estimate was close to \$3 billion.

Eckhardt said a recent study found that the change had cost industry only \$127 million, about one-fifteenth of the government estimate and one-forty-fifth of the industry estimate.

Eckhardt said the lower cost could be attributed to innovations in disposal and control of the chemical.

Another speaker at the

conference was Dr. Eula Bingham, head of the U.S. Occupational Safety and Health Administration (OSHA), who said that one third of all cancer deaths may be job-related.

"I am now convinced that many factories have a carcinogen-rich environment," she said. "And if there are carcinogens in the work place, there are carcinogens outside of the work place."

Dr. Bingham said some industries that use carcinogens are moving to Mexico and South America to escape OSHA restrictions. She said her department communicated with its counterparts south of the border to urge the adoption of American fair labor standards, "which include the protection from chemicals."

The conference began

with a panel of area workers voicing their grievances against local industry, reporting incidents in which, they said, their employers refused to take steps to protect them from industrial carcinogens.

"What scares workers more than anything else is the latent period of cancer," said Rod Morgan of Texas City. "They may have something today and not find out for 20 years."

Fred Mabry, representing the United Steelworkers of America, criticized companies that refuse to take action to protect workers from carcinogens until after statistics have proven a danger exists.

"You've got to count the dead bodies before anything gets done. You've got to find the bodies before anybody cares," he said.

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LETTERS

Chemical Carcinogens

Thomas H. Maugh II's recent articles on chemical carcinogens (Research News, 29 Sept. 1978, p. 1200; 6 Oct. 1978, p. 37) were both provocative and timely, although we were disturbed by several errors of fact and interpretation. Our concern stems in part from preliminary results of our 2-year study (1) investigating quantitatively the carcinogenic potencies of more than 500 chemicals adequately tested and reported in the literature. We have also quantified the sensitivity of negative cancer tests, expressing how potent a carcinogen would have to be to be detected by these tests.

A dispute of long standing in regulatory circles is whether chemical carcinogens exhibit "thresholds," or doses below which there is either no effect or an effect considerably less than that predicted by linear extrapolation from responses at higher doses. Two investigators are cited by Maugh in support of the "threshold theory," Gehring on vinyl chloride and Stokinger on chloroform. Their arguments are either misleading or inaccurate and do not support the contention that the risk to society from these chemicals is negligible because of thresholds.

The first argument is that mechanisms detoxifying carcinogens are overwhelmed at the high dose levels often used in rodent bioassays, and a disproportionately large carcinogenic effect occurs at these doses. As an example, Gehring implies that at dose levels of vinyl chloride above 50 to 150 parts per million, where detoxification mechanisms may be saturated, a disproportionate increase in carcinogenic effect in rodents would occur. Yet the animal bioassay results of Maltoni (2), Lee *et al.* (3), and Viola *et al.* (4) on vinyl chloride suggest, if anything, just the opposite: as inhalation exposures increase beyond 150 ppm, the increase in carcinogenic response is *less* than that predicted from a linear extrapolation of the responses in the dose range 0 to 150 ppm (Fig. 1). Thus, the risk from exposure to low levels of vinyl chloride might be more than a millionfold higher than Gehring's estimate (5). Based on recent pharmacokinetic studies on vinyl chloride (6), the explanation for this proportionately greater activity at low doses may be that the mechanisms that activate vinyl chloride to the proximate carcinogen are saturated at high doses.

A second argument cited in support of the threshold theory is that high doses of

chemicals cause pathological damage to tissues and increase their susceptibility to cancer. At low doses few tumors should appear. However, the evaluation of chloroform bioassay data attributed to Stokinger in support of this argument is incorrect. Stokinger is cited as saying that rodents in the National Cancer Institute (NCI) test had "severely distended abdomens, markedly shortened life-spans, and extensive liver damage. . . . Tumors were observed in only the most debilitated animals." In fact, however, in the bioassay on mice, (i) abdominal distension was caused by the liver tumors induced by chloroform treatment; (ii) the life-span of three of the four dose/sex groups did *not* differ from the controls, although each group *did* develop a high incidence of liver tumors; and (iii) neither extensive liver damage (for example, necrosis), reduced weight gain, nor any other pathological sign of nonneoplastic debilitation was associated with chloroform treatment (7). Furthermore, in the NCI rat bioassay, chloroform treatment increased kidney and thyroid tumors significantly without any increase in nonneoplastic damage to these tissues.

The assertion that Roe "fed chloroform to mice, rats, and dogs at doses that did not produce pathological damage, and these animals show no evidence of malignant tumors," is incorrect in two respects: Roe's doses in rodents (i) *did* produce pathological damage and (ii) *did* produce malignant tumors, although Roe found no relationship between pathological damage and tumor incidence in a tissue (8). Roe's test on dogs was not as

sensitive as his test on rodents: chloroform would have to be more than 5 times as potent (on a milligram per kilogram per day basis) in dogs as in rodents to be positive in his tests. Thus, Roe's experiments on the carcinogenicity of chloroform are consistent with those from NCI and support the conclusion that chloroform is a renal and hepatic carcinogen in rodents.

Thresholds, or a disproportionately small effect at low doses, may someday be demonstrated for certain carcinogens, but there is no evidence that they are the general case or that they have been demonstrated for vinyl chloride or chloroform.

In addition to the possibility of thresholds, Maugh also suggests that predicting human risk from animal cancer tests is extremely difficult because of large variations in carcinogenic response between sexes and species. Whether this is a difficulty, however, can only be decided by a systematic, quantitative analysis of the data, including an analysis of the power of negative cancer tests. Our preliminary results using this type of analysis suggest that there is generally good agreement between species, sexes, and strains. Considering the more than millionfold range in carcinogenic potency observed among chemical carcinogens, even an order-of-magnitude agreement between sexes and species would be quite useful, especially in supporting priorities for regulation.

With respect to the relationship between carcinogenic potency and mutagenic potency from short-term assays, Maugh refers to the reservations expressed by Ashby and Styles that such a relationship is tenuous, at best. Yet Maugh fails to mention, as we observed elsewhere (9), that their reservations were based on experiments with serious conceptual and technical errors. While we would not expect that the correlation would be precise, preliminary evidence (10) suggests that a battery of short-term tests may be quite useful in approximately estimating carcinogenic potency and thus in helping to set priorities among large numbers of new mutagens that have not been tested in animals.

Maugh also quotes Lijinsky as saying the *Salmonella* (Ames) test is not a useful qualitative predictor of carcinogenicity on the basis that it has only a 55 percent correlation for a group of polycyclic hydrocarbons that he tested for both mutagenicity and carcinogenicity (11). However, the Ames test has been extensively validated in three independent studies (12, 13), all of which agreed that approximately 90 percent of the carcino-

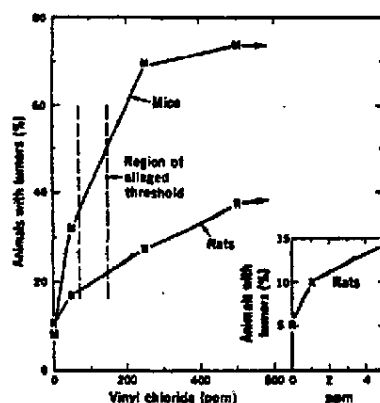


Fig. 1. Tumors from inhaled doses of vinyl chloride (2). The percent of Sprague-Dawley rats or Swiss mice with tumors is plotted against the vinyl chloride concentration in air (4 hours daily) over two dose ranges, 0 to 500 ppm (lifetime observation) and 0 to 5 ppm (87-week observation). There is no evidence for a threshold.

gens from a wide variety of classes were mutagens in the test. Furthermore, Lijinsky's study does show that the *Salmonella* mutagenicity assay is an excellent test for the detection of carcinogenic polycyclic hydrocarbons: 88 percent of the carcinogenic hydrocarbons analyzed (14 out of 16) were mutagenic in *Salmonella*. This agrees with a larger study on polycyclics by Coombs *et al.* (14), in which 38 out of 38 carcinogenic polycyclics were mutagenic in the test.

Lijinsky obtained the "55 percent correlation" estimate by combining his results on the 16 carcinogens with the 8 "noncarcinogens," of which 8 out of 8 were mutagens. Unfortunately, Lijinsky accepts the results of limited or inadequate cancer tests as definitive evidence that a chemical is a "noncarcinogen." But the word "noncarcinogen" has meaning only in the context of an analysis of the power of the test. We have discussed elsewhere (15) the problems with using Lijinsky's insensitive cancer tests for determining whether or not a chemical is a "noncarcinogen." His analysis of carcinogenicity was based entirely on skin painting studies, which are considerably less sensitive than the standard NCI feeding studies and do not meet NCI criteria for an adequate test. It remains problematical whether his skin painting studies would have detected very many of the known human carcinogens at the doses used, although the *Salmonella* test detects almost all of these (13).

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References and Notes

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15. B. N. Ames and L. Haroun, in preparation. For example, Lijinsky (17) lists benz[a]pyrene as one of the eight "noncarcinogens." The *Salmonella* test shows that benz[a]pyrene is a mutagen, but it is only 1/360 as potent as benz[a]pyrene. Other short-term tests using animal cells also show that benz[a]pyrene is a mutagen. Before Lijinsky can conclude that these tests are unreliable because benz[a]pyrene is not a carcinogen, he should show that the power of the cancer test is such that it could detect a chemical 1/360 as potent as benz[a]pyrene.

In his review (Research News, 6 Oct. 1978, p. 40) of some of the arguments concerning the existence of threshold doses in carcinogenesis, Thomas Maugh reproduces a graph [from David B. Clayson (1, p. 164)] as the basis for some people's argument that high dose-low dose extrapolation of animal data (and hence extrapolation from animal to man) is a nearly impossible task. The graph reproduced is incomplete in that the dose scale—log dose—that was in the original article is left out.

That graph implies a biological model—the logarithm of the percent of animals developing a tumor is linearly related to the logarithm of the dose. Not one of the extrapolation techniques that I know (Mantel-Bryan, Crump *et al.*, Albert-Altschuler, one-hit, multi-hit, log-logistic, and others) uses this model. I know no theory of carcinogenesis that is consistent with such a model. Gently put, the model is inappropriate. Finally, the confidence intervals as drawn can come only from an experiment without a low response at some low dose, that is, an experiment without a control group.

If the point is that an inappropriate biological model combined with a defective experiment is likely to give nonuse-

ful answers, I agree wholeheartedly. If the point is that that graph provides a serious argument against extrapolation using a reasonable biological model from data gathered in a well-conducted experiment, then serious questions arise in my mind about its pertinence and their logic.

By way of analogy, I find that a picture of a centipede is not proof (or even evidence) that a horse is not a quadruped.

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There is a continuing national debate over determining the risks of small amounts of toxic substances by extrapolations of massive exposure studies. The legend of figure 1 of Maugh's 6 October 1978 article on chemical carcinogens states "Most scientists, however, now think that the actual response is indicated by the smooth curve passing through zero dose and zero response." Dose is plotted on a logarithmic scale. In figure 2 response is plotted on a logarithmic scale. How do "most" scientists plan to extrapolate these logarithmic scales to zero?

All models of dose versus response in which the curve increases monotonically must include the points (0,0) and (∞ , 100 percent), but this does not help to distinguish among them. In probit theory the relationship between log dose and susceptibility is a normal curve. Response is the integral of this normal curve which is "S shaped" but can give the impression of a straight line over narrow dose ranges. Probit analysis requires at least two real points to independently evaluate potency and the standard deviation of a diverse population to this effect.

It is ironic that so much energy is wasted on a debate over what amounts to the proper choice of coordinate axes.

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Mexican Oil Reserves

All of us owe a debt to William D. Metz for his commentary "Mexico: The premier oil discovery in the Western Hemisphere" (News and Comment, 22 Dec. 1978, p. 1261). Recognition in the United States of the Mexican accomplishment is long overdue, and Metz makes his point in a most effective man-