Letters

Significance of Nitrosamines in Animal Diets

A recent News and Comment briefing (13 Oct. 1978, p. 192) concerned our report (*1*) that laboratory animal feeds may be contaminated with up to 50 parts per billion (micrograms per kilogram) of the carcinogen *N*-nitrosodimethylamine (NDMA).

A subsequent letter (8 Dec. 1978, p. 1034) from William Lijinsky challenges the significance of this finding. He takes issue with our concern that the NDMA might have synergistic action with other (test) carcinogens. He states, "There is little evidence of a detectable synergistic effect of nitrosamines in carcinogenesis, even when much higher doses are given . . . "; and, in the next sentence, he says, "I suggest that a study of chemical carcinogenesis and its literature would enable the scientists who made this report to place their findings in perspective."

We have indeed examined the literature and find several reports which describe positive synergistic effects of nitrosamines (*2*), including a 1977 review by Lijinsky himself (*3*). In this article he concludes a brief discussion of synergism between carcinogens by stating "Several experiments with nitrosamines have also shown this type of synergism in carcinogenesis."

Lijinsky further challenges the significance of our results by stating that " . . . its [NDMA] presence at this concentration in the diets of rats or mice could have no bearing on the outcome of any test." We agree that 50 parts per billion of NDMA in feed is unlikely *by itself* to cause significant tumor response in small numbers of rodents exposed from the time of weaning, as in the studies cited by Lijinsky. However, this may not be the case if larger groups or younger animals, or both, are used. For instance, Lijinsky has stated (*3*), "Fetuses are often much more sensitive to carcinogens than are children or adults." A soon-to-be-published article from the Sloan-Kettering Institute (*4*) demonstrates that as little as 10 parts per billion of NDMA included in the water supply of strain A/J mice during the whole fetal, weaning, and postweaning period up to 22 weeks of age causes a tripling in the lung tumor incidence from 8 percent to 23 percent. Whether or not one accepts this rather tumor-prone strain as an appropriate model (*5*), these studies clearly refute Lijinsky's claim that up to five times more NDMA "presents no measurable risk to experimental animals that live only 2 to 3 years."

GORDON S. EDWARDS
Cancer Research Division,
Thermo Electron Corporation,
Waltham, Massachusetts 02154
JAMES G. FOX
Division of Laboratory Animal
Medicine, Massachusetts Institute of
Technology, Cambridge 02139

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Phenacetin Studies

Thomas H. Maugh II, in his article "Chemical carcinogens: The scientific basis for regulation" (Research News, 29 Sept. 1978, p. 1200), treats a topic of increasing importance to drug safety evaluation and exposure to toxic substances. Maugh appropriately states that there is a difficulty with epidemiological data, namely, " . . . most of the people involved have generally been exposed to a number of other potentially hazardous agents. It is thus difficult to develop evidence of carcinogenicity from epidemiology alone." Yet, he presents a tabulation of "chemicals known to be carcinogens in man" based, in some cases only on case reports or epidemiological *associations* with exposure without confirmatory data from animal studies.

The source material for this list is apparently the summary report of the Monograph Program of the International Agency for Research on Cancer by Tomatis *et al.*, published in *Cancer Research* (*1*). The article listed chemicals and industrial processes associated with cancer induction in humans based on two criteria: "(a) that there is evidence of human exposure and (b) that there is some evidence of carcinogenicity in experimental animals and/or some evidence or suspicion of human risk." Tomatis *et al.* indicated that two of the drugs listed, oxymetholone and chloramphenicol, were included on the basis of epidemiological data, and that no adequate test results for carcinogenicity in experimental animals were available. A third drug, phenacetin, was included because of clinical case reports, not on the basis of any extensive epidemiological evidence. The article further indicated that adequate test results in animals were not available for phenacetin. Adequate tests, however, have been conducted and the results are available.

In 1970, Bengtsson and Angervall reported (*2*) on 14 clinical cases in which tumors of the renal pelvis were observed in patients who reputedly had a history of prolonged analgesic abuse. After this report was published, the Wellcome Research Laboratories undertook a long-term carcinogenicity study in mice. Phenacetin alone and aspirin-phenacetin-caffeine analgesic mixtures were administered to mice at maximum tolerated doses. This study, in which two known carcinogens were used as controls, is on file with the Food and Drug Administration. Neoplasms of the urinary tract were not observed in any analgesic-treated animal, whereas they were observed in the controls.

Also, a summary has been published (*3*) of the "NCI [National Cancer Institute] report on the bioassay of a mixture of aspirin, phenacetin and caffeine (APC) for possible carcinogenicity" covering two additional studies. The report summary states, "After a 78-week period of compound administration, observation of the rats continued for up to an additional 35 weeks and observation of the mice continued for an additional 16 weeks. For both species the survival in all groups was adequate for statistical analysis of tumor incidence. Under the conditions of this bioassay there was insufficient evidence to indicate that APC was carcinogenic in Fischer 344 rats or in B6C3F1 mice."

These three independent toxicity studies involving lifetime exposure of large numbers of animals to maximum tolerated doses did not yield any positive evi-

dence of cancer induction by phenacetin-containing analgesic mixtures. As Maugh states, "Virtually all investigators thus agree that chemicals which are carcinogenic in humans are also carcinogenic in animals." Therefore, the change in classification from "associated" with reports of carcinogenicity, as in Tomatis *et al.*, to "chemicals *known* to be carcinogens in man" [emphasis added] introduces an error and gives wide circulation to misinformation.

At a time when serious continuing effort to evaluate risk in drug safety requires effective communication between clinicians, epidemiologists, and laboratory scientists, it is a disservice when assumptions are circulated as fact. The classification of any chemical or drug as a carcinogen is of vital importance and must be related to sound evidence.

PEDRO CUATRECASAS
Wellcome Research Laboratories, Burroughs Wellcome Company, Research Triangle Park, North Carolina 27709

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Science and Regulatory Policy

As a health policy consultant to federal regulatory agencies, I agree with Comar (Editorial, 16 June 1978, p. 1225) that bad science is to be deplored. He raises the specter of "bad science" being used to justify unnecessary regulatory policies. Bad science can take another form, that of rejecting findings merely because they challenge accepted beliefs.

It should also be noted that doing science and setting policies are distinct activities. The National Academy of Sciences' committee on decision making for regulating chemicals reported (*1*) in 1975 that there is no absolutely objective way to set many regulatory policies. "All difficult decisions are characterized by inadequate information. . . . Problems of regulating chemicals in the environment are particularly beset with information characterized by a high degree of uncertainty" (*1*, p. 12).

During the past decade, protests about scientific quality and industry costs have been frequently used when regulatory policy is contested, as though regulatory decisions rested exclusively on science and market economics. Every known human carcinogen except arsenic has been demonstrated to be an animal carcinogen. Some suggestive animal and human epidemiological studies have preceded the discovery of serious health problems in humans. It is a policy decision to interpret these kinds of data as grounds for regulation. In the cases of dibromochloropropane (*2*), asbestos (*3*), and anesthetic gases (*4*), we have learned at considerable economic and human cost that reports of their potential hazards for humans should have been followed up earlier.

No one can precisely calculate the total economic costs of bad science leading to the delay of sound environmental and occupational regulation. Surely, however, this accounts for some part of our annual cost of $17.4 billion for cancer and $57 billion for heart, lung, and blood diseases (*5*). Other human costs are greater; for example, those of lives being shortened and diminished by exposure to controllable hazards.

The difficulty with so many preliminary reports of health hazards in animals is that current scientific theory holds that their implications for humans can only be confirmed through human epidemiological studies; hence, the "quick evaluation" that Comar proposes of such reports may not be possible. Even where such evaluation may be made, the regulatory process is often slow (*6*).

In this situation lie fundamental scientific, social, and economic contradictions. Much data relevant for epidemiological analysis were never intended to be so used; problems of noncomparability, disaggregation, and insufficient information abound. Obtaining good epidemiological data that can resolve certain issues will require 20 years or so. To wait for such resolution may expose humans to potential hazards that can lead to even greater burdens and health care costs.

In many instances, current data are sufficiently strong to warrant policies for regulatory intervention. In these cases, the economic and social costs of waiting for more definitive scientific answers outweigh the costs of preventive policies that limit exposure to suspected health hazards. To wait would make the human population mere fodder for epidemiological studies, subjecting the health of this and future generations to potentially grave and irreversible risks. If we are wrong, we can change our regulatory policies. If we are right, we will have saved lives.

DEVRA LEE DAVIS
Environmental Protection Agency, Washington, D.C. 20460

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4. V. R. Hunt, *Work and Women's Health* (CRC Press, West Palm Beach, Fla., in press); A. I. Vaisman [*Eksp. Khir. Anesteziol.* **3**, 44 (1967)] reported on increased rates of miscarriage.
5. B. S. Cooper and D. P. Rice, *Soc. Sec. Bull.* **39**, 21 (February 1976).
6. Several billion pounds of the carcinogen vinyl chloride is produced each year. Final regulations for the safer manufacture of vinyl chloride were not in effect until some 3 years after the process of declaring it an "imminent hazard" had begun.

Davis makes several points with which in principle there can be no disagreement, namely: setting regulatory policy is not science; policy is made with inadequate information; bad science and especially inadequate epidemiology should not be used to delay needed regulation; needed regulatory processes should be speeded up.

Obviously, policy-makers will never have enough data; however, "bad science" severely compounds the problem, and premature regulation can have many disbenefits, including the foreclosure of research. But most important is the misconception conveyed that somehow regulatory policy exclusive of science and of market economics could (i) reduce a significant part of the annual $231-billion health bill, (ii) avoid making the human population "mere fodder for epidemiological studies, subjecting the health of this and future generations to potentially grave and irreversible risks," and (iii) save lives.

Matters are just not that simple. Increased industrial costs and inefficiencies mean increased poverty and decreased health which has to be balanced against the health effects avoided in the first place. One example—New York City has spent $200 million a year since 1970 to reduce the average annual concentration of sulfur dioxide in air from 0.06 to 0.03 part per million. Worthwhile? See (*1*). We need less bad science and more regulatory policy based on good science and economics in the interests of individuals and society.

CYRIL L. COMAR
Electric Power Research Institute, Palo Alto, California 94303

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