ically declined to answer questions about the boards. As for the contention of the families of Law's patients, we deeply sympathize with their plight. The Food and Drug Administration (FDA) told Thompson that it had received complaints about Law's foundation both from physician-scientists and from parents of children with the disease. The FDA has clarified its statement and has indicated that the families who complained had considered Law's treatment and rejected it. *Science* regrets the error.—***The Editors***

■

Carcinogenicity of Butadiene

Philip H. Abelson's editorial (19 June, p. 1609) "Exaggerated carcinogenicity of chemicals" is more a legal brief than an editorial. Any and all evidence that suggests 1,3-butadiene is not likely to be carcinogenic in humans is emphasized, while a large body of evidence that it is indeed carcinogenic for humans is ignored. Butadiene is carcinogenic to Swiss mice without the murine leukemia virus and to Sprague-Dawley rats in spite of metabolic and pharmacokinetic differences. Butadiene-induced mouse neoplasms contain K-ras oncogenes and inactivated tumor suppressor genes, similar to those in humans. The preliminary study by B. J. Divine (*1*) showed a clear increase in lymphopoietic cancers and leukemia. The finding of overall lower cancer mortality is consistent with the healthy worker effect. Other studies also show that butadiene is a human carcinogen. If trillions of dollars and loss of competitiveness and jobs are really at stake, the readers of *Science* deserve a more careful review of the literature.

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Abelson's editorial contains an unbalanced and cursory review of 1,3-butadiene toxicity and of the recent National Institute for Occupational Safety and Health (NIOSH) risk assessment of butadiene (*1*). A thorough review of the metabolic, toxicologic, and epidemiologic data for butadiene is available (*2*). The NIOSH risk assessment was based on a recent National Toxicology Program study (*3*), in which $B6C3F_1$ mice were exposed to butadiene concentrations of 6.25 to 625 parts per million (ppm), a range which overlaps that of actual occupational exposures (*2*). In order to evaluate the sensitivity of our risk estimates to modeling assumptions, we applied time-to-tumor models under several assumptions. None of these models led to the 100% predicted response at 2 ppm that was implied in the editorial.

Abelson's statement that, after exposure to 10 ppm butadiene, mice retain 10 times more of it than rats, and 33 times more than monkeys, is not an accurate summary of the data in (*4*). Of greater importance is the requirement for metabolic activation to observe genotoxicity (*2*), which suggests that butadiene metabolism is a more meaningful measure of dose than ^{14}C retention. Percent metabolism in rats and mice is similar and is independent of exposure concentration in the range of linear kinetics (*4*). We assumed that this would also hold for humans. Although cryogenic trapping data suggest that primates produce smaller quantities of genotoxic metabolites than do rodents (*4*), the validity of this comparison is questionable because of protocol differences between mouse and monkey experiments and the nonspecificity of the cryogenic trapping (*2*).

Abelson's interpretation of interspecies differences in epoxide hydrolase activities and in urinary metabolites is misleading. A recent analysis concluded that epoxide hydrolase is not the major enzyme involved in the elimination of butadiene monoepoxide in mice, rats, and humans (*5*). Urinary metabolites measured at high concentrations (8000 ppm) (*6*) are not relevant to estimating risks at low concentrations.

The epidemiological evidence for the carcinogenicity of butadiene is stronger than was suggested in the editorial. A study by B. J. Divine (*7*), cited as negative evidence, actually reported a 2.3-fold statistically significant excess of lymphosarcoma. Abelson did not point out studies (*8*) which found evidence of excess lymphatic and hematopoietic neoplasms.

Both toxicologic and epidemiologic data support our concern that butadiene may produce cancer in occupationally exposed humans and that the current Occupational Safety and Health Administration's Permissible Exposure Limit of 1000 ppm may not be protective.

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Abelson argues that "a searching review of the risk assessment methodology of the regulatory agencies is overdue." To support his thesis, he chose the case of 1,3-butadiene, a monomer used extensively in the production of synthetic rubber. On the basis of an epidemiologic study of a population of butadiene workers employed by Texaco that found no overall increase in cancer mortality (*1*), Abelson states that butadiene is not a potent human carcinogen. He argues that the results of positive animal bioassays of the carcinogenicity of butadiene (*2*) should be discounted.

In his review of the Texaco study, Abelson does not mention that, despite the overall deficit in cancer mortality [observed in relatively fit populations of industrial workers (*3*)], there was a striking and statistically significant excess in mortality from cancer of the lymphatic and hematopoietic system. This excess was most strongly evident in production and maintenance workers (who are regularly exposed to butadiene) and in black workers. Also, Abelson does not mention a study of 12,113 rubber workers in the United States and Canada (*4*) that also found excess mortality from lymphatic and hematopoietic malignancies despite an overall deficit in cancer mortality. The excess was most strongly evident in production and black workers, for whom the standardized mortality ratio (SMR) for these malignancies was 507 (five times greater than background). That increase reflected an SMR of 532 for lymphosarcoma, 656 for leukemia, and 482 for other lymphatic cancers.

It would be fitting if Abelson withdrew his ill-conceived and selectively researched editorial.

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Response: Studies performed exposing $B6C3F_1$ mice and Sprague-Dawley rats to different amounts of butadiene show that it is weakly tumorigenic at a few sites in the rats, but is a potent carcinogen in the mice, with abundant tumors in many sites, including liver and lung carcinomas. If studies that use these mice cannot predict morbidity in rats, can they reliably predict cancer in humans? Moreover, studies that use $B6C3F_1$ mice could not even predict the numbers of lymphomas in Swiss mice (*1*).

Rall, Dankovic *et al.*, and Landrigan have emphasized lymphohematopoietic cancer findings for *selected* short-term employee subgroups. These data do not represent a comprehensive picture of the butadiene-lymphopoietic cancer epidemiologic literature. In fact, there are no elevations of lymphopoietic cancer mortality rates in long-term workers in any of the available studies. Also, these scientists give no weight to the major finding that overall incidence of cancer mortality among butadiene workers was substantially below that of standard populations.

I cited the study by B. J. Divine (*2*) because it was one of the few in which the principal substance present was butadiene. I did not mention studies by Matanoski and others (*3*) because of the complexity of exposures received by the cohorts. Even the data in (*2*) were probably not free of confounders because of the cohorts' earlier exposure to other chemicals in other plants. Elevations in mortality associated with lymphohematopoietic cancer were principally limited to short-term workers and usually occurred after short latency periods, which implies previous exposure to other chemicals that were carcinogens. In workers who were employed for 10 years or more, there were 6 deaths from lymphohematopoietic cancer, as opposed to 8.6 expected. In contrast to the large incidence in $B6C3F_1$ mice, not one liver cancer death occurred in the cohort (*2*) employed for more than 5 years, and the observed cancer incidences of the respiratory system, including the lung, were substantially less than expected. A forthcoming publication (*4*) provides a further discussion of the limitations of the studies by Matanoski and others (*3*).

The current approach to toxic substances preserves the hysteria of the 1970s, when the public was repeatedly frightened by assertions that 90% of human cancer would be caused by synthetic chemicals (*5*). We now know that almost all excess cancer is caused by cigarette smoking, diet, and factors other than industrial chemicals (*6*). Agencies have been slow to respond to new science and to give appropriate weight to data from the epidemiological monitoring of more than a million industrial workers. Regulators still rely on procedures for, and interpretations of, animal experiments that were formulated during the cancer scare of the 1970s. Estimates of human cancer risk are still based on

- the assumption that the metabolism of "the most sensitive species" is representative of that of humans;
- the direct one-for-one extrapolation to humans of cancer incidence in such species;
- the pooling of benign and malignant tumor counts to determine risk;
- experiments using maximum tolerated dose (cell death and mitogenesis for 2 years);
- unproved models for extrapolating (for example, the no threshold model);
- the use of a 95% confidence limit; and
- scenarios that assume extremely high exposure (for example, that of a man who stands for 70 years at a plant gate or a child who eats dirt at a Superfund site).

These procedures lead to estimates that overstate risks by orders of magnitude and have led to unrealistically low regulatory limits and high costs for Superfund remediation.

—Philip H. Abelson

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