Letters

Toxicological Testing Dilemma

The controversy over the priorities of research conducted at the National Cancer Institute to reduce the time required to perform bioassay tests and the high cost ($47 million) of the Institute's carcinogenesis program (News and Comment, 7 May, p. 529) underscore the problems currently associated with testing procedure for carcinogens and other toxic substances. Before new chemicals manufactured for human consumption can be registered, federal regulatory agencies require a long (3 to 10 years) series of toxicological tests: the acute, a single dose with a range of concentrations; the subchronic, repeated doses or exposures administered for up to 90 days; and the chronic, lasting 2 to 10 years, depending on the species being tested. Routes of administration are selected on the basis of the most likely mode of human contact (such as ingestion, inhalation, or skin contact) (*1*). Several species and large numbers of animals are required for statistical reliability and to assess interspecific variation in the reactions to toxic substances. Human health evaluation according to the standard, accepted protocols currently costs more than $500,000 per compound. Wildlife, aquatic, plant, and domestic animal toxicity evaluation (*2*) costs are additional. Twelve government agencies conduct toxicological testing and research and spend probably more than $100 million annually; private industry probably spends much more. If the $100 million the federal agencies now spend were devoted to human health effects research alone, testing of only about 200 compounds could be started each year. However, many thousands of chemicals are in need of toxicological evaluation (*3*). Obviously, the current federal allocation is insufficient to test the majority of these chemicals.

Many toxicologists agree that faster and less costly testing procedures are urgently needed (*4*) and that research should be devoted to evaluating in vitro testing methodologies (*5*). Moreover, the acute test is being challenged, since a single exposure is much less likely to occur in an environmental or an occupational situation than repeated low level exposures. The chronic test is often conducted using the lowest effective concentration determined in the subchronic test and a one or half log dilution below that. Since two dilutions provide sufficient empirical data in approximately 95 percent of the cases, why conduct the chronic test, which is six to ten times more expensive than the subchronic? The answer is because lifetime studies are the accepted procedure for assessing carcinogenic and other possible toxic effects, including reproductive malfunctions (*6*). However, less expensive batteries of mutagenic screening tests (*4*) could be employed that would estimate the potential for carcinogenicity.

Furthermore, in vivo tests are subject to interspecific variation in test animals. Species have different strategies to deal with toxicity. Measurable toxic effects often represent exposure levels higher than concentrations of pollutants actually found in the environment. More sensitive tests, such as those based on behavioral toxicology, are being developed (*7*), but few are widely accepted. The National Center for Toxicological Research and other agencies are developing such new and rapid tests, and the National Institute of Environmental Health Sciences is evaluating the possible substitution of the traditional, long-term, in vivo tests with rapid screening methods. The Committee for In Vitro Toxicity Testing of the Tissue Culture Association is defining and validating the presently available in vitro tests. Although faster and cheaper tests are being developed, we wonder whether we can afford to wait? The Toxic Substances Control Act will soon be implemented (*8*). Many potentially useful chemicals remain unevaluated.

We propose that a more decisive step be taken: a team of expert toxicologists and scientists from related fields should be assembled to evaluate existing technology and identify a battery of the most predictive screening tests, including in vitro systems, animal models, and chemical behavior (*5*). A combination of quick tests could replace the conventional protocols, whereas any single test might not. This team could also perform cost-benefit analyses and estimate how much, if any, sacrifice of confidence would result from using a battery of screening tests at this time. Use of a combination of screening tests might allow a tenfold reduction in cost and a fivefold reduction in time for toxicological testing. We would expect little or no sacrifice of safety, since most of the tests tend to err on the side of false positives. Standard methods could still be employed if indicated by the screening results.

The findings of the "blue ribbon" team should be presented to a national referendum symposium of decision-making toxicologists representing all the federal agencies, academic institutions, and private industries involved in toxicological testing. The prevailing opinion could then be presented to the regulatory agencies for their consideration and the current requirements modified.

If a battery of screening tests were to be accepted, we would find the process of testing many thousands of chemicals a more manageable task. At present it looks pretty hopeless.

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Recombinant DNA: Unknown Risks

Bernard D. Davis's letter (6 Aug., p. 442) makes interesting reading in a week in which 25 Legionnaires have died and more than 100 are still ill—some critically—of a disease of unknown ori-