NAS Study Highlights Chemical Mutagens

Heritable genetic defects caused by exposure to chemicals might be a big medical problem. A premarketing screen for such chemicals is proposed

Although an estimated 10 percent of human disease is caused by heritable genetic mutations, there are currently no regulations that require chemicals to be tested for these types of mutagenic effects. A report just issued by the National Academy of Sciences* (NAS) could, however, provide the basis for much more systematic premarket testing to identify potential human mutagens. But the Environmental Protection Agency (EPA), to whom the report was addressed, has so far shown little urgency to ensure more widespread screening for germ line mutagens.

With some 70,000 synthetic chemicals currently in commercial use, and another 1000 new ones synthesized each year, the need for such testing is clear. A major problem until recently, however, has been the lack of rapid, reliable, inexpensive tests that can detect chemicals capable of inflicting heritable genetic damage. But the NAS report, which was produced under the leadership of James Crow of the University of Wisconsin at Madison, concludes that, while not ideal, there is now available a series of tests that can fulfill this important function.

Such tests include the famous Ames test and employ, variously, bacterial, fungal, and mammalian cell cultures that under the correct experimental conditions can mimic certain important metabolic modifications relevant to mutagenesis. Typically, these tests cost a few hundred dollars and can be completed in a matter of a few days or weeks.

These short-term tests, even in combination with more elaborate procedures using fruit flies or mice, do not provide a perfect screen because, as the NAS report makes clear, there is still a tremendous amount of ignorance surrounding heritable mutation in humans. For instance, there has so far been no documented case of human exposure to chemicals or other known mutagenic agents that has resulted in increased genetic defects, and this includes the aftermath of Hiroshima (see, however, *Science*, 11 March, page 1196). "There are known chemical mutagens in animals," comments Crow, "and there is no reason to expect that the situation will be different in humans. There is a great need for some thorough epidemiology."

A second important region of ignorance is in the link between the genetic defect and the resultant health effects. "Even if the *damage* to human germ cells could be measured precisely, we lack the knowledge to translate the measurements into a total *impact* on the health and welfare of future generations," concludes the report. "Nor is this situation likely to change in the near future."

A third problem is that an increase in heritable human mutations is likely to be difficult to detect because it might be manifested in a very wide range of rather unconnected conditions. Moreover, several generations might pass before effects on health become obvious.

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Partly for these reasons, a great deal more public and regulatory attention has been devoted to a related health effect of mutagenesis, that of cancer. With cancer, the consequence of exposure to a mutagen is clear: it is a readily identifiable disease that develops in the relatively short term—under 20 years. No one denies the great social impact of environmentally caused cancer, but the NAS report gives a sense of a health problem that might be as big or even bigger. And the fact that heritable genetic defects will be cumulative through the generations adds an important dimension to the potential magnitude of this problem.

Although the NAS report concentrates on genetic disease in relation to mutagenesis, it recognizes the close ties with carcinogenesis. It cites sources, for instance, that suggest that 88 percent of all carcinogens are mutagens. Although this figure is challenged as being too high by some authorities, the upshot has been that short-term tests designed to screen for potential carcinogens in fact identify mutagens. More than 100 such tests have been devised during the past decade, though the sensitivity and reliability varies between them considerably.

Crow and his colleagues also note that epidemiological data collected in relation to chemical carcinogenesis are likely to be useful in assessing heritable genetic defects too. "Inasmuch as carcinogenicity is highly correlated with mutagenicity, it may be possible to monitor human populations through the extensive existing registries of cancer incidence and mortality." The same population that is at risk of increased incidence of cancer following exposure to a chemical mutagen is also at risk of a higher rate of heritable defects.

A recurrent uncertainty with short-term tests, some of which are exquisitely sensitive to chemical mutagens, is that in the absence of human data it is simply not possible to validate them as predictors of heritable genetic defects in the way that has been possible with carcinogenesis. At best, a chemical that shows positive in these tests can be labeled a putative mammalian mutagen. The same can be said of results from a very sensitive and reliable test that employs the fruit fly.

The animal most suitable for testing mutagenesis in mammals is, of course, the laboratory mouse. Although the mouse is genetically closer to humans than, say, the *Salmonella* bacterium, a standard mutagenicity test might use 100,000 animals, take many months to complete, and cost half a million dollars. In addition, many of the procedures for detecting heritable mutations in these animals are relatively insensitive, so that the only sure result is a positive one. A chemical that produces a positive result in the mouse tests can be termed a demonstrated mammalian mutagen and a presumptive human mutagen.

There are cases of chemicals that give positive results in some of the short-term tests but are negative in the mouse. There are several sound biological reasons why this might occur. For instance, the chemical might have been prevented access to the germ cells, or perhaps it was inactivated; DNA damage might have been repaired, or damaged cells removed. These possibilities are of uncertain relevance to humans.

But there are other possibilities too. For instance, a small mutagenic effect might have gone undetected because the number of mice used was too small. In any case, disconcerting uncertainties hover over a negative result, so much so that the NAS report states the following:

**Identifying and Estimating the Genetic Impact of Chemical Mutagens* (National Academy Press, 2101 Constitution Avenue, NW, Washington, D.C. 20418).

"The committee is unwilling to assume that negative mouse data necessarily outweigh the consensus of a variety of short-term tests. . . . All the evidence needs to be taken into account, and the decision based on the weight of evidence in each case."

Because there is no simple single test that provides a yes/no answer, the committee recommends at two-tiered approach. The first tier consists of a series of microbial and cell culture tests, a positive in two or more of which labels a chemical as a presumed mammalian mutagen. A single positive sends the chemical to the second tier, which involves fruit flies.

This screening through a two-tiered battery of short-term tests constitutes the first of five levels in a proposed mutagen assessment program. "In most cases, the outcomes of such tests wll be sufficient to support industrial or governmental control." If a simple mutagen/nonmutagen answer is insufficient, assessment moves onto a second level, that of hazard characterization. This depends on being able to measure the degree of mutagenic potency expressed.

Level three looks to data from carcinogenicity tests that might aid in judging mutagenic hazard. And if uncertainty still exists, one of several possible mouse tests can be undertaken, which constitutes level four. Information from these tests, together with other data, should be enough to estimate the risk associated with the chemical. The NAS committee took risk assessment no further than this, but pointed out that calculations involving probable exposures and weighing of benefits could eventually yield a risk/benefit analysis. Parenthetically, the committee also observes that those bearing the risks often are not those who accrue the benefits.

Although the report has only just been published, its findings have been in the hands of the Environmental Protection Agency, which was the contracting agency, since mid-December. EPA, however, sees no apparent urgency for its perusal. The agency's first public foray into mutagenicity risk assessment was at the end of 1980, with the publication in the *Federal Register* of proposed guidelines on the topic. Following public review and comment, the guidelines went to the agency's scientific advisory board for further review and revision.

The NAS report, which confirms and extends much of what was contained in the original proposal, will be an important source of information for the final revision of the guidelines. In the unlikely event that the delays that have hampered progress to date do not continue, new guidelines are due by the end of 1983.

—ROGER LEWIN

Waxman Bill Seen as Threat to NIH

Is NIH panel chairman just trying to tidy up statutory authority, or would changes undermine agency's traditional status?

Representative Henry A. Waxman (D–Calif.), chairman of the House authorizing subcommittee for the National Institutes of Health (NIH), is pushing ahead with legislative changes that would substantially increase the direct influence of Congress—particularly of Waxman—in NIH affairs.

Waxman heads the health and environment subcommittee of the House Energy and Commerce Committee. The panel is expected to act favorably on Waxman's bill, H.R. 1555, which would extensively revise the authority under which NIH operates. Critics in the biomedical research community believe that the changes proposed threaten the flexible authority under which NIH has traditionally operated and which agency advocates see as the key to its research excellence. Waxman and his associates say this is not the case and that the bill is designed to bring needed order to an administrative tangle caused by the rapid growth of NIH programs

In 1980, Waxman sought successfully to legislate time and dollar limits for NIH. This time, his proposals stop well short of that, but some critics say the changes would make it easier later to require periodic reauthorization of NIH.

Waxman consolidated his control of the subcommittee in the 4 years since he won the chairmanship after a bruising contest (*Science*, 30 March 1979, p. 1319). In the same period he has become a major force in House handling of environmental and health issues.

Waxman served a three-term political apprenticeship in the rough-and-tumble California state legislature before coming to Congress in 1974, and in Washington has proved himself an effective practitioner of quid pro quo politics. An unabashed liberal, Waxman represents a Los Angeles district which includes Hollywood and Beverly Hills, and his skill in tapping his politically and financially liberal constituents and directing their contributions to the campaigns of like-minded colleagues in Congress has bolstered his influence in the House.

The long-term concern of NIH partisans centers on Section 301 of the venerable Public Health Service Act that sets forth the research status of NIH. It is unique in giving NIH "open-ended" authority. This means that most NIH institutes do not come before Congress periodically to have their statutory authority renewed and escape the full force of special interest pressures.

Reasonable or not, underlying the resistance to recodification is a conviction that the special protection of its open-ended authority is crucial to NIH. NIH is seen as particularly vulnerable to the powerful "disease constituencies" and other special interest groups that abound in the health field. NIH advocates recognize the power of appeals in behalf of suffering patients. They see the consequences of opening NIH to standard authorization politics as the fragmentation of NIH into an incoherent collection of special interest enclaves. An old NIH nightmare is the vision of recodified NIH institutes facing periodic reauthorization bouts that would turn into legislative free-for-alls in committee and on the floor. Pessimists see the signs of trouble already in the reported glut of amendments being readied for H.R. 1115.

After taking over the subcommittee chairmanship, Waxman in 1980 sought to end NIH's open-ended authorization. This met the strong opposition from the Carter Administration, NIH officials, and biomedical researchers and the organizations that represent them, notably the Association of American Medical Colleges. Waxman dropped the provi-