Nitrites: FDA Beats a Surprising Retreat

In 1978 the FDA said nitrites posed a risk to health; the basis for this major conclusion has now crumbled

Consumers may have been surprised last month when the Food and Drug Administration (FDA) abruptly told them to forget its warning of 2 years ago that nitrites, the widely used preservative in meats, posed a risk of cancer to humans. They would be even more surprised if they looked behind the scenes at the decision-making within the FDA on the nitrites issue.

Nitrites have long been a target of the consumer movement, which has argued that the preservative's role in preventing botulism is marginal and does not outweigh its possible risks. Nitrite is known to be mutagenic in test animals, for example.

Consumers' efforts to have nitrites removed from food have been unsuccessful because of opposition by the meat industry, and because the scientific case against it was not overwhelming.

All that seemed to change, however, when the FDA learned the results of a nitrite feeding study undertaken by Paul Newberne of the Massachusetts Institute of Technology. Newberne's results were apparently conclusive: nearly twice as many rats fed nitrite developed lymphomas as did the controls.

Armed with this evidence, the then-FDA Commissioner Donald Kennedy decided to move decisively against nitrites in August 1978. In a joint announcement with USDA Assistant Secretary Carol Foreman, he stated that nitrites had been found to pose a risk of human cancer, and that the agency would take steps to phase out their use.

Almost immediately after the initial announcement, doubts about the study surfaced among toxicologists. Half of the scientists to whom the FDA sent the report for comment declared that it lacked enough data to permit proper review; others said it had a number of flaws, including improper statistical calculations and a failure to check for exposure to nitrosamines, a known carcinogen that might have formed inside the rats by a combination of nitrites and amines in the diet. An FDA inspection of Newberne's laboratory while the experiment was in progress raised questions about his procedures for animal handling. And even before the 1978 announcement, pathologists at the National Cancer Institute and within FDA had raised questions about Newberne's diagnoses of rat lymphomas.

None of these doubts were revealed to the public when FDA and USDA released their proposal for a nitrite phaseout on 11 August 1978, even though an internal FDA group had been formed just 3 days earlier to look into them. The reason is that Commissioner Kennedy and a special task force of a dozen FDA lawyers and scientists were confident that Newberne's study would hold up under attack.

Kennedy voiced this confidence in a memo to then-Secretary of Health, Education, and Welfare Joseph Califano on 11 September 1978. "We know more than enough about the Newberne study to be convinced that it is well done and strongly supports the hypothesis that nitrites are carcinogenic *per se*."

Kennedy went on to discuss how the public might react to criticism of the Newberne study: "Even in the unlikely event of a successful challenge of the study, the outcome would not be clear: it would appear to the public as such things inevitably appear—as rather arcane, confusing debates among the cognoscenti. Thus the possibility for real embarrassment even given the worst possible outcome of our evaluation is very slight, simply because outcomes are never that clear in a matter so complex." He even put his job on the line. "You have a politically expendable regulator who is prepared to take the blame," Kennedy told Califano, "if the outcome proves more disastrous than this argument predicts."

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It almost did prove more disastrous. Califano found Kennedy's argument resistible for a combination of political and legal reasons, and FDA was never given the go-ahead to officially propose a nitrite phaseout. Califano's reluctance to do so was a lasting source of friction between Kennedy and himself. That reluctance has been vindicated: the FDA's intensive review of Newberne's study has now shown that in fact the rats fed nitrite had the same incidence of lymphomas as those not fed nitrite. Newberne, in the reviewers' opinion, had misdiagnosed as lymphomas a rare cancer that cannot be related to nitrites. The reviewers also disagree with his diagnosis of certain lesions as precursors of cancer. The review was conducted by FDA's working group on nitrites, which included scientists from three other federal agencies and a committee of pathologists from a

NAS and Sakharov

On 12 August the council of the National Academy of Sciences extended its suspension of interacademy exchanges with the Soviet Academy of Sciences, citing continuing "deep concern" for Soviet academician Andrei D. Sakharov. The council had voted initially, last February, to suspend group activities for 6 months in protest at Sakharov's internal exile.

Some scientists have voiced concern about such restrictions, saying that science should be above political turmoil and world tensions, and that exchange agreements benefit both sides. They predict that suspension of relations probably will have little or no effect on Soviet policy-makers and that American scientists may be penalized as well as their Soviet counterparts.

There is no restriction on exchanges on an individual basis, however. On both occasions, the academy council exempted from restriction exchanges between individual scientists and joint discussions on arms control and disarmament.—SCHERRAINE MACK

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dozen members of Universities Associated for Research and Education in Pathology. In response to earlier criticisms of his study Newberne has said that "I have no apologies and no doubt that the implications my diagnoses delineated are indeed correct." In a statement prepared last week Newberne describes the differences in diagnosis as subjective but says that "In principle, I agree that [the FDA working group] did an excellent job with a difficult task."

The effect of FDA's reversal is to vindicate the congressional and scientific critics of its phaseout proposal and to validate the argument of the meat and poultry industry, that no regulation of nitrite should proceed unless the results of an animal test have been duplicated. C. Manly Molpus, president of the American Meat Institute, says that "certainly the government's attempt . . . to halt the use of nitrite was ill-advised, and the need for peer review of studies of this type should be an essential element of the process."

Several FDA scientists claim that if Kennedy had followed ordinary procedures for the in-house review of a study such as Newberne's that the flaws would have been caught before the agency stuck its neck out. Albert Kolbye, associate director for toxicology in the Bureau of Foods, has complained to the General Accounting Office and the Congressional Research Service that he and other employees in the bureau were excluded from decision-making before the first public announcement.

Kennedy, now president of Stanford University, insists that "the procedure for review we followed was correct. In the first place, there is no *ordinary* procedure, and I was perfectly satisfied that the people on that task force were competent." Asked if it would have been better to withhold a regulatory proposal until after a more lengthy scientific review had been completed, Kennedy replied, "You can't simply analyze the results and then say no option suggests itself when in fact one does."

Top officials at FDA say they are inclined to act more deliberately and seek more review in light of the nitrite reversal. "You can't handle an issue like this privately," says one official, "even though you pay a price for handling it publicly."

Where does this leave the consumer of hams, hot dogs, and bacon? The FDA says it has asked the National Academy of Sciences to search the literature on nitrite and investigate alternative ways of preserving meats. Privately, FDA officials see the study as a device for getting both Congress and consumer activist groups off the backs of both FDA and USDA.

William Lijinsky, an expert in cancer-causing nitrosamines at the Frederick (Md.) Cancer Research Center, says that nitrites still pose a risk of cancer because they might combine with amines after consumption to form nitrosamines. "Even though we've been given the impression that nitrites are now safe, this risk remains." Jere Goyan, current FDA Commissioner, agrees that "nitrites are not home-free by any means. There are still questions, and I'm sure they will eventually be phased out of the food supply because of the nitrosamine problem."—R. JEFFREY SMITH

DNA: Chapter of Accidents at San Diego

Not sabotage, but cross-contamination, was the most likely cause of the wrong virus being cloned

Events have conspired to cast an air of drama around the case of the miscloned virus at the University of California, San Diego.

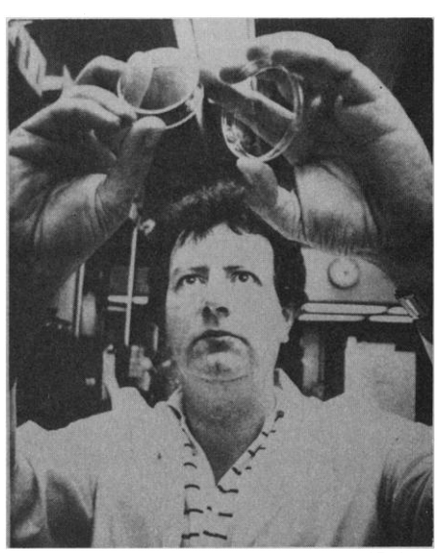
The first such event was a sudden announcement from the University's Institutional Biosafety Committee. There had been a violation of the recombinant DNA safety rules in the laboratory of Ian T. Kennedy, the committee reported in a letter of 31 July to the National Institutes of Health.

Students in Kennedy's laboratory had informed the chairman of their department of ambiguities in Kennedy's results. Tests by the California State Department of Health confirmed that cloned material meant to contain the mosquito-borne Sindbis virus seemed to be instead the closely related Semliki forest virus, which was also under study in Kennedy's laboratory.

Semliki forest virus is classified, along with smallpox and yellow fever, as a class 3 agent. Class 3 agents, according to the January 1980 version of the NIH safety rules, may not be cloned. Concluding it had a violation on its hands, the Institutional Biosafety Committee confiscated all Kennedy's cloning materials and rescinded permission for further cloning. Kennedy was himself a member of the committee.

Kennedy's sudden disbarment from the cloning fraternity was followed by the theft of a bottle of rabies vaccine from the laboratory Kennedy works in. Kennedy then revealed that over the past 6 months he has received several anonymous calls from a person objecting to recombinant DNA research. Sabotage, he suggested in press interviews, might have been the cause of his cloning the wrong virus, although before the rabies incident he had suggested contamination of virus stocks in transit as the cause.

This mountainous drama has not yet been resolved, but the outlines of several molehills are already discernible. The University of California, San Diego, has some $1.8 million worth of recombinant DNA research grants at stake, so that the biosafety committee's quick reaction to a possible violation is understandable. But the committee may have acted al-



AP photo

Ian Kennedy

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