A Is for Apple, Alar, and... Alarmist?

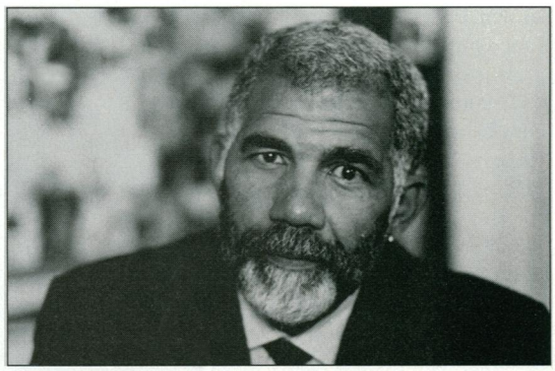
Two years ago environmentalists branded Alar the most dangerous chemical residue in children's food; since then, the official risk estimates have fallen

ALAR, THE CHEMICAL SPRAYED ON ORCHARDS during the 1980s to slow the ripening of apples, is once again at the center of a scientific controversy. U.S. environmentalists, led by the Natural Resources Defense Council (NRDC), won a stunning victory 2 years ago when their media blitz on the chemical yielded fruit. CBS's "60 Minutes" ran a frightening exposé against the backdrop of a giant apple marked with a skull and crossbones. Actress Meryl Streep began speaking out against the substance at press conferences. Schools stopped buying apples. Growers, in a desperate attempt to quell the public panic, pleaded with Congress and Alar's manufacturer, the Uniroyal Co., to take the chemical off the market. Then, in a coup de grace, the U.S. Environmental Protection Agency (EPA) announced that interim results of an ongoing review suggested that Alar is a probable carcinogen and ought to be banned from food. Beleaguered, Uniroyal voluntarily withdrew the chemical for use on food. But Alar did not go quietly into the history books. Toxicologists have continued to battle over the basic toxicology on Alar, and in recent weeks the fight has taken a surprising turn.

Science has learned that EPA, in a just-completed toxicology analysis, finds that Alar and its byproduct UDMH*—while still regarded as carcinogens—are half as potent as the agency estimated at the peak of the Alar crisis in 1989. This reduction, while not a big change for a risk-setting exercise, continues a downward trend: The 1989 estimate was itself a factor of 10 lower than a potency estimate made by EPA in 1987, which was cited by environmentalists during their campaign to ban Alar.

This backpedaling on risks isn't limited to the United States, either. A panel of international experts meeting in Geneva last week—including three participants from EPA—went further. After examining the most recent data, a United Nations advisory committee composed of experts from most of the industrialized nations disagreed with EPA's conclusion that Alar per se is a carcinogen, and reaffirmed an earlier judgment that it is safe to eat as a trace residue in food.

These new, more benign assessments won't resurrect Alar as an agricultural chemical, but they will breathe new life into the dispute over the compound. And the dispute will move into two new forums: the courts and Congress. In the next few months, a $200-million lawsuit filed by apple growers in Washington state will begin working its way through the courts (see box, p. 21). The growers charge that CBS, NRDC, and its media advisers knowingly hyped the risks of the chemical to get attention. (The defendants deny the charge.) High on the list of evidence for that suit will be EPA's final toxicology assessment. And Congress is expected soon to take up a variety of bills that would overthrow the infamous Delaney amendment, which forbids the marketing of any product that—like Alar—is judged carcinogenic and shows up in processed food. The legislation would permit products to be kept in use if the health risks are deemed negligible—which is exactly what some toxicologists claim for Alar.



Maggie O'Bryan

Bettmann

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1989 media blitz. *CBS's Ed Bradley* (top) *delivered an exposé on "60 Minutes" and Meryl Streep spoke out, but Senator Steve Symms was not convinced.*

The roots of the controversy

Alar's dubious distinction as the lightning rod for disagreement over the regulation of toxic chemicals can be traced directly to the events of 1989, which burned into the public consciousness the image of Alar as a deadly toxin. Skirmishing over the compound began more than a decade before it hit the headlines, however. NRDC targeted Alar as a dangerous chemical and pushed EPA to cancel its registration after a set of limited toxicology studies in the 1970s showed UDMH to be carcinogenic. EPA took a step toward banning Alar on food crops in 1985, but the agency's Scientific Advisory Panel ruled that the technical basis for doing so was flimsy. EPA retreated, ordering up new studies. Yet in 1987 the agency adopted a carcinogenic potency factor for UDMH based on the same data. Not long afterward, the publicity hit.

In February 1989, while the new animal tests were still under way, NRDC released a report, "Intolerable Risk: Pesticides in Our Children's Food." It branded Alar a "potent carcinogen," by far the biggest threat to children's health among 23 chemicals in food that the organization studied. The NRDC concluded that children were at greater risk than adults of getting cancer from UDMH because they consume proportionally more apple products by body weight, and are more vulnerable because their cells are dividing rapidly. The bottom line, according to NRDC, was that one out of every 4000 preschoolers exposed to UDMH was likely to get cancer. NRDC's risk assessment was prepared by William Nicholson of the Mt. Sinai School of Medicine and reviewed by a panel of scientists including toxicologists Marvin Schneiderman, then at the National Academy of Sciences, and Bailus Walker, then at the State University of New York at Albany.

NRDC zeroed in on Alar, says the organ-

*UDMH stands for unsymmetrical dimethyl hydrazine, a trace contaminant in Alar and a byproduct that appears when Alar is heated or hydrolized in the body, said to occur at concentrations of up to 1%. However, there are no reliable data on the rate at which Alar is converted to UDMH in the body.

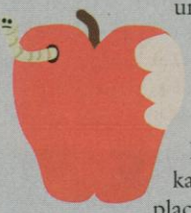
ization's expert on the chemical, staff scientist Lawrie Mott, in part because it is not essential: The apple crop this year may hit record levels, she points out, and growers seem to be doing fine without it. That makes virtually any risk associated with the chemical unacceptable, Mott says. In addition, she points out that risk studies on Alar examine only one chemical, not the additive and synergistic effects of multiple residues that actually occur in food. "You have to view these risk assessments as understatements."

Because Uniroyal threw in the towel in the face of the panic that followed publication of NRDC's report, EPA's official action on Alar as a food residue came to an end. Staffers decided not to submit the 1989 "interim" risk estimate they had been working on to the Scientific Advisory Panel—the group that had rejected the proposal to ban Alar several years earlier. Instead, EPA decided to wait for the final data from the mouse study.

Illustrations: D. DeFrancesco

A Bite Out of the Market

Apple growers in Washington state, gunning for revenge as well as cash, are suing for losses they say they incurred after the Natural Resources Defense Council (NRDC) and CBS News publicized an NRDC report on the dangers of Alar and other farm chemicals. Eleven families filed suit in Yakima County, Washington, last November, claiming to represent all growers in the state. They accuse NRDC, its press agent Fenton Communications, and CBS News of spreading "false, misleading, and scientifically unreliable statements about red apples." Wiley Brooks, the growers' spokesman, says they're outraged about the "junk science" that NRDC put forward and want to collect "more than $200 million" in compensation for lost sales.



The first arguments in the case will begin on 10 October in the U.S. District Court in Spokane, dealing with whether the trial should take place under state jurisdiction, as the growers want, or in federal court, as the defendants want. Brooks estimates the trial will cost $1.5 to $2 million, of which the growers have raised only $200,000 so far.

One tricky point the growers will have to explain is why the apple business has done so well since Alar was taken off the market in 1989. Even Brooks concedes that business has never been better "for those who survived" the Alar scare. Harvests in the past 2 years have been approaching a 20-year record level, and apple prices are also high. The value of the total crop is on the rise, and, as Brooks notes, orchard owners who invested in "specialty" apples such as the multicolored gala apple are now reaping nice profits, for they have tapped a big demand for these apples even at premium prices overseas. So who lost money?

Doug Wilson/The New York Times

Plaintiffs. *Orchard owners Robert and Cathy Bernath joined other growers in a lawsuit.*

Economist Boyd Buxton at the U.S. Department of Agriculture says the apple crop did stumble momentarily in the spring of 1989 after NRDC released its report. For about 4 months—from March, after the report was released, until June—shipments fell off. Then they resumed their normal pace, and have been climbing ever since. Buxton says when the mid-1989 pause ended, a temporary glut appeared in an already oversupplied market, causing prices to drop to half their normal level until the end of summer. Buxton figures growers made about $120 million less that year than they otherwise would have.

Brooks says those who were hit hardest were small West Coast orchard owners and East Coast owners who raised Macintosh apples—which apparently were more dependent on Alar. ■ E.M.

The backlash

Some private toxicologists, offended by the heavy-handed public relations the environmentalists used to crush their adversaries, weren't prepared to wait, however. Instead, they responded with a harsh counterattack of their own. Gary Flamm, a former Food and Drug Administration staffer, now a consultant, sums up their feelings this way: "One has to conclude the publicity [Alar] got really had nothing to do with the science," says Flamm, adding that some of his colleagues are still angry about it. Apple growers were "severely injured," Flamm claims, and "we are not talking about truth, justice, and mercy prevailing." "My own feeling is that scientists who sit by and watch [such] things happen" without protesting are "no different from scientists who fudge data."

Leading the charge was Joseph Rosen, a food scientist at Rutgers University. In an article in *Issues in Science and Technology*, a journal published by the National Academy of Sciences, he blasted NRDC for using arguable math, unreliable food consumption data, and a dubious cancer potency figure. Rosen pointed out, for example, that NRDC had taken its potency estimate from UDMH studies done in the 1970s by Bela Toth of the Eppley Institute for Research on Cancer in Omaha, Nebraska. Toth's research had been judged "inadequate" for quantitative risk estimation by EPA's scientific advisory panel in 1985.

Albert Meyerhoff, who runs NRDC's pesticide litigation, responds that while the food data used in the risk estimate may have been flawed, they were at least more up-to-date than those used by the government, and that fruit consumption has been increasing. As for Toth's research, Meyerhoff says it was the best available in 1989. In fact, it had served as the basis for EPA's own potency calculations on UDMH, issued in 1987.

Part of the backlash that followed publication of the NRDC report came from the chemicals industry, according to a California official who wishes to remain anonymous. "There's been a lot of organizing among industry people to hammer down" and dismantle the current methods of cancer risk assessment—the very methods that got Alar thrown off the market—this official says. Indeed, Meyerhoff says he expects increasing flak from industry as chemicals that have been used for many years undergo rodent carcinogenicity tests mandated by a 1988 change in federal law. Already, Meyerhoff says, "about half" of the in-use compounds tested under the new rules have come up positive. They may get caught in EPA's screen, like Alar.

How much is too much?

How can well-informed experts and good scientists differ so sharply for so long on so important a subject? At the heart of the debate over Alar is a question that underlies virtually all regulation of suspect carcinogens: How reliable are animal studies that use very high doses of a test compound?

Bruce Ames, the microbiologist at the University of California, Berkeley, who invented the widely used *Salmonella* test for chemical mutagens, was among the first to complain about the Alar tests on these grounds. Ames and his Berkeley colleague Lois Gold argued that feeding chemicals at high doses to rodents—as was done with UDMH—is not a good way to find out whether they trigger cancer at low doses in humans. Chemicals fed at high doses have a direct cell-killing effect, they think, causing

cells to proliferate and additional mutated cells to form tumors. Ordinarily the body repairs mutations before cancer develops. But this cannot happen if the animal's metabolism is swamped by exogenous chemicals. It is a mistake, according to Ames and Gold, to assume that the cell-killing effect at high doses is the same as the carcinogenic effect that produces tumors at low doses (see *Science,* 31 August 1990, p. 970).

As a rule, toxicologists try to limit the highest dose in a cancer bioassay to a "Maximum Tolerated Dose" (MTD) that causes no more than a 10% weight loss in test animals, scant toxic effects, and few early deaths. In his rodent studies during the 1970s, Toth had set the top dose of UDMH fed at 29 milligrams per kilogram of body weight (mg/kg) per day. Many animals died early, and by today's standards, the study is not valid for risk estimation. In later studies that EPA required Uniroyal to conduct in the mid-1980s, rats and mice were given up to 20 ppm of UDMH in water (3 mg/kg). These animals developed no significant increase in tumors. EPA then insisted that the dose of UDMH be quadrupled. Uniroyal scientists demurred, saying the high doses would destroy the animals' livers. EPA responded in 1986 that there was no evidence that the MTD would be exceeded and required that doses be set at 40 and 80 ppm (or 7 and 13 mg/kg) to elicit hard to detect cancers. (For comparison, EPA estimated that in the 1980s, the average U.S. citizen's exposure to UDMH was 0.000047 mg/kg.)

The new high-dose study was still in progress in 1989 when the apple panic erupted; in the midst of it, EPA issued its interim toxicology review based on pathology of animals sacrificed midway through the test. EPA's conclusion: UDMH was clearly carcinogenic, with a potency factor of 0.88. This was far less than the value based on Toth's data (around 9). *Science* has obtained the toxicology section of EPA's final analysis of the high-dose study, and the director of EPA's special review on Alar, Janet Auerbach, confirms that it will lead to a factor of 2 reduction in the potency estimate for UDMH—to 0.46.

While the increased rate of cancer in the test mice persuaded EPA that Alar was clearly carcinogenic, other experts have not found it so. For example, Colin Berry, a well-known British pathologist at the London Hospital Medical College and president of the European Society of Pathology, agrees with Uniroyal that in this study, the mice were given too much UDMH to yield results that can be sensibly applied to human experience. One reason for uncertainty is that Alar itself does not test positive as a mutagen, and UDMH produces mixed results. Yet at high doses, UDMH is clearly toxic.

Uniroyal argued, of course, that the results of the high-dose study should be set aside because the mice had lethally overdosed on UDMH. EPA's toxicologists concede there were many signs of liver toxicity in the UDMH mouse study, but they judged them irrelevant because these toxic effects showed up in a different type of cell from the type that became cancerous.

AP/Wide World

Less cause for alarm. *Testing for Alar in the midst of the panic.*

On this point, again, experts disagree. "A good scientist can argue the case either way," says Charles Aldous, a former EPA toxicologist now at the California State Department of Food and Agriculture. While experts agree in principle on how to determine an MTD, they often disagree in practice. The Alar mouse studies illustrate that point, but Aldous maintains that "a majority" of his peers would consider that the UDMH doses of 40 and 80 ppm were unreasonably high. Lois Gold, after reading EPA's final toxicology report, said she thought the 80 ppm dose exceeded the MTD, while the 40 ppm dose may not have—and that at this lower dose there appeared to be some significant tumors.

Europe goes its own way

The British government reviewed the interim high-dose mouse studies and concluded in 1989, in the words of an expert panel appointed by Parliament, that there was "no risk to health," considering the small quantities of Alar and UDMH detected in food. Colin Berry, who chaired that group, says the British view may differ from EPA's because "we tend to be a bit more cautious" about the science: "We don't always make the assumption that the animal data are transferable to man, particularly in the absence of pharmacokinetics that make it clear that the compound is handled in the same way at massive doses as it is at low doses."

For similar reasons, a United Nations panel concluded in 1989 that Alar was "not oncogenic in mice" and that UDMH raised no special concern because it is always present in Alar feeding studies as a contaminant or breakdown product. This group, which includes seven members from the World Health Organization (WHO) and seven from the Food and Agriculture Organization (FAO), was so confident of its opinion that in late 1989 it set a high tolerance for Alar residues in food—recommending that governments permit an "acceptable daily intake" of up to 0.5 mg/kg of body weight.

Last week, these experts met again, reviewed the final UDMH data, and again endorsed their decision. Said John Herrman, secretary for the joint panel: "If you take the results of these [new UDMH] studies, you actually have an increased margin of safety compared to what the committee concluded at the previous meeting" in 1989. At that session, the panel found that Alar produced no cancer in mice at doses below 3000 ppm (396 mg/kg of body weight), and UDMH produced no increase in tumors below 30 ppm (3.9 mg/kg of body weight). So they decided that public health officials need not be alarmed about Alar residues in human food of less than 0.5 mg/kg.

The WHO-FAO panel may be the closest the UDMH toxicology analysis will come to getting an independent peer review. Normally, EPA's Scientific Advisory Panel would review a study like this if it were being used for a regulatory decision. But in this case it may not, says EPA official Janet Auerbach. Why not? Alar has already been withdrawn from use on food crops, says Auerbach, so there was no need to double-check EPA's 1989 interim risk analysis or its 1991 final version. Besides, getting outside scientists involved slows down the process, she says.

Under the U.S. system, no chemical that's judged to be a carcinogen is considered safe as a food additive. This means—now that EPA has officially labeled Alar a carcinogen—that it will continue to be banned from processed food, regardless of what future risk estimates may show. And particularly, now that the apple industry has demonstrated that it can get along quite well without Alar, it's clear that this chemical's salad days are over. But as a symbol of the scientific controversies swirling around the regulation of environmental chemicals, it will clearly live on. ■ ELIOT MARSHALL