

62

J O S E P H D . R O S E N

Much Ado About Alar

*Review of a
confusing and
misguided episode
offers important
lessons for regulating
agricultural
chemicals.*

In the spring of 1989, millions of consumers stopped buying apples and apple products. The sudden action was prompted by fears that Alar (a chemical widely used by apple growers to prevent pre-harvest fruit drop, promote color development, and increase storage life) causes cancer. Children were thought to be at especially high risk. In response to the widespread public concern, Uniroyal Chemical Company canceled all sales of Alar on June 2, 1989.

Almost overnight, the image of apples had been transformed, seriously disrupting the apple-growing industry. And many viewed the incident as a victory for the public good. But is Alar truly a significant hazard, and were consumers' best interests served?

The Alar episode provides a window on the forces influencing agricultural chemical regulation in the United States. On one side are agricultural and chemical interests that believe the products they use and sell are safe and essential to the continued success of U.S.

agriculture. On the other side are consumer activist groups who believe that many chemicals in current use harm public health and the environment. These groups have long been frustrated by what they perceive as excessive corporate influence on government policies and do not hesitate to manipulate the

media and exploit the public's fear of cancer to get their point across. In the middle are government agencies that, while under considerable political pressure, must make decisions based on incomplete scientific information and sometimes-contradictory laws. Meanwhile, many Americans have lost faith in their government's ability to protect the food supply and have turned for advice to people unqualified to give it.

Thus the significance of the Alar case clearly goes beyond Alar. But by exploring the history of the Alar incident and drawing appropriate lessons, it may be possible to deal with agricultural chemicals in a more intelligent and reasonable manner in the future.

Conservative assumptions

To understand the story behind the dire warnings about Alar, it is first necessary to review briefly how chemicals are tested for cancer and how the results are used

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to assess cancer risk in humans. The standard protocol for testing a chemical for carcinogenicity is to administer very high doses of the test substance to animals. Such doses are typically thousands of times higher than those to which humans will be exposed, but the procedure is intended to prevent weak carcinogens from escaping detection.

Many toxicologists are critical of performing cancer assays at such high levels because the observed tumors may arise from toxicity-related mechanisms, rather than any inherent tumor-causing potential of the test chemical. Extremely high doses of a chemical can kill cells, and the animal responds by rapidly producing new cells. This time of rapid cell growth is precisely the point at which cells are at greatest risk for cancer-initiating events. Bruce Ames, a prominent biochemist at the University of California at Berkeley, suggests that reliance on extremely high doses in cancer testing may in fact be one reason why about half of the synthetic and naturally-occurring chemicals tested to date have been branded as mutagens and possible carcinogens.

Nevertheless, the data obtained in such studies are used to calculate the risk that the substance poses for humans. And those calculations, too, are laden with assumptions and uncertainties that further compound the problem of obtaining useful risk assessments. It is important to keep in mind that Environmental Protection Agency (EPA) guidelines mandate the use of extremely conservative mathematical models and exposure assumptions in order to err on the side of Safety: Thus the agency takes into account only the total number of benign and malignant tumors at the target site in the most sensitive species at very high doses. Data that indicate no danger are ignored. Furthermore, all chemicals that appear to induce tumors are treated as genotoxins—materials that can be carcinogenic at extremely low doses because they cause generic damage that leads to the formation of tumors—even if there is no evidence that the chemical is genotoxic.

As a result of its numerous conservative assumptions, this approach yields a risk assessment that is a worst-case scenario. Actual risk is much less and possibly nonexistent.

Hefty doses

The firestorm about Alar began in 1973 with studies in which Bela Toth of the Eppley Institute for Research in

Cancer in Omaha found that 1,1-dimethylhydrazine (unsymmetrical dimethylhydrazine or UDMH) was responsible for the appearance of blood vessel, lung, kidney, and liver tumors in mice. (Commercially available Alar contains about 1 percent UDMH. In addition, EPA estimates that humans convert approximately 1 percent of ingested Alar to UDMH. Heat accelerates the hydrolysis of Alar to UDMH so that approximately 5 percent of the Alar residue on apples is converted to UDMH in the production of applesauce and apple juice.) In a subsequent study completed in 1977, Toth reported a high tumor incidence in mice who were given Alar instead of UDMH.

As a result of the Toth findings, in 1980 EPA announced plans to conduct a “special review” of Alar: such intensified risk reviews are triggered by new data that were not available at the time a product was approved for use. The review was subsequently canceled (following private discussions between EPA and Uniroyal-Alar’s sole manufacturer—according to a chronology prepared by the Congressional Research Service) but then reinstated in 1984 after litigation by the Natural Resources Defense Council (NRDC), a public interest group.

As part of the review, EPA’s Federal Insecticide, Fungicide, and Rodenticide Act Scientific Advisory Panel—composed of academic experts—was asked to review Toth’s results and methods. In September 1985, the panel, noting several errors in scientific procedure, concluded that Toth’s data were inadequate to serve as a basis for quantitative risk assessment and failed to provide the EPA with sufficient justification for banning Alar. A 1989 British review reached similar conclusions about the unreliability of the Toth studies. The major problem cited by the reviewers was that in both studies Toth treated the animals with such high doses—29 milligrams per kilogram of body weight per day (**mg/kg/day**), higher even than the highest dose EPA subsequently considered worth studying—that it was possible that the toxicity, and attendant biochemical changes, produced the observed tumors.

Given the inadequacy of the Toth data, the EPA announced in January 1986 that it would permit continued use of Alar but would require Uniroyal to provide residue and chronic toxicity data. None of the company’s subsequent studies showed an increased incidence of cancer when Alar, even at very high doses, was administered to mice and rats. The UDMH

studies also were negative at all doses in rats. And mice showed no tumors when they received UDMH at the level that previous studies found was the maximum dose they could tolerate without experiencing high levels of toxicity—2.9 mg/kg/day (males) or 5.8 mg/kg/day (females). The dose for males is more than 35,000 times the highest estimate of daily intake of UDMH by preschoolers—the most exposed population.

It was only when mice were given doses of UDMH above the accepted toxicity threshold that tumors appeared. In one of the company's studies, one mouse out of a group of 45 receiving UDMH for one year at 11.5 mg/kg/day had a lung tumor. Blood vessel (both benign and malignant) and lung (benign only) tumors also were observed in 11 of 52 mice that had received a hefty 23 mg/kg/day dose of UDMH. In fact, the dose was so high that 80 percent of the male mice died prematurely because of extreme toxicity.

The risk assessment that EPA offered to the public was based on data from the study in which mice received 23 mg/kg/day and the assumption that mice receiving 11.5 mg/kg/day would exhibit statistically significant tumor incidence by the end of the study. Extrapolating those results, the EPA concluded that the *continued use of Alar would result in an increased lifetime risk of 45 cancers per 1,000,000 exposed individuals. EPA policy forbids the use of any agricultural chemical that causes more than one cancer per million exposed individuals, so EPA was forced to take regulatory action. On February 1, 1989, the agency announced that it would permit the use of Alar until July 31, 1990, because less than one case per million people would occur by then, but would ban its use after that.

In a press release announcing the action, the EPA stated that the mice dosed with the 23 mg/kg/day UDMH in their drinking water were dying early from tumors. The EPA press release noted, however, that “it may be argued that the deaths are the result of excessive toxicity, which may compromise the outcome of the study,” but in spite of this caveat, the message that reached the public was that Alar presented a serious

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cancer risk. Few realized that this conclusion was based essentially on a questionable interpretation of one study, and that the doses involved were almost as great as those of the discredited Toth studies.

Even greater risk?

Although EPA seemed to have done everything possible to come up with a worst-case scenario, the Natural Resources Defense Council demonstrated that the potential

risk could be made to appear even more alarming. “Intolerable Risk: Pesticides in our Children's Food” (NRDC's analysis of the risk of Alar and several pesticides) estimated 240 cancer cases per 1,000,000 population among children who are average consumers of Alar-treated food, and a whopping 910 per 1,000,000 (“an additional cancer case for every 1,100 children exposed”) for heavy consumers.

The NRDC assessments far exceeded the EPA levels for several reasons. First, NRDC used the Toth data, which indicated cancer potency ten times greater than that found in the more recent studies used by EPA. Second, NRDC used a time-dependent mathematical model that builds in an increased risk on the assumption that exposure to a genotoxin early in life is much more serious than subsequent exposures because the cells affected by the genotoxin have much more time to multiply (probably true) and that children are more sensitive than adults (sometimes true, depending on the chemistry and the metabolism of the genotoxin). EPA, on the other hand, used a time-independent model that did not specifically account for age at exposure. Although it is reasonable to assume that genotoxins ingested early in life are more dangerous, this assumption is irrelevant to Alar and UDMH, because neither is a genotoxin. (Indeed, Britain's Advisory Committee on Pesticides concluded that non-genotoxicity coupled with extremely low human exposure was reason enough to declare Alar safe for all consumers.)

Third, the EPA and NRDC differed on their estimates of consumer intake of apples and apple products. The EPA used data from a 1977-78 consumption survey of about 30,000 people by the US.

Department of Agriculture (USDA); NRDC relied on a 1985-86 USDA study of only 2,000 people that suggested a 30 percent increase in fruit and vegetable consumption since the earlier study. EPA and NRDC agreed that children consume more fruit than adults, and both claimed they used average residue figures from Uniroyal.

A third study, by the California Department of Food and Agriculture (CDFA), illustrates how much risk estimates can change with seemingly minor changes in methodology. Like EPA, CDFA used the 1977-78 USDA consumption survey and the more recent cancer assays, but it parted ways with the agency in that it factored in the results of studies that found no cancer risk. Like NRDC, it built in an extra safety factor for children, although not as large as the one NRDC used. The CDFA arrived at a worst-case risk estimate of 2.6 excess cancers per million population, a risk that could easily be reduced below one per million by banning the use of Alar-treated apples in the production of apple juice and apple sauce. More important, CDFA calculated *probable* lifetime risk, which it estimated at 3.5 cancer cases per trillion population.

Science vs. public relations

Scientists and regulators recognize that at every stage calculations are intended to err on the side of safety. As a result, a substance such as Alar (or UDMH) that produces no increased cancer incidence in animals even at doses tens of thousands times higher than humans ingest can still be deemed unsafe. Unfortunately, the average consumer is unaware that the figures reported are worst-case scenarios, not actual risk. And in the Alar episode, thanks to a well-orchestrated media campaign by NRDC and a credulous press, many consumers knew only of the worst of the worst cases. NRDC hired Fenton Communications (a public-relations firm) to publicize its report; Fenton offered the television program *60 Minutes* an exclusive opportunity to break the story, and *60 Minutes* produced an NRDC-guided story that is a classic case of slipshod journalism.

The opening shot of the February 26, 1989, telecast set the scene. Correspondent Ed Bradley was seated in front of a backdrop featuring a skull and crossbones superimposed on an apple. A top EPA official then tells Bradley that a new tolerance application for Alar would be denied under current regulations, but

that the law prevents him from immediately canceling the existing tolerances because Uniroyal could sue. "Let them sue," says the next interviewee, Congressman Jerry Sikorski (D-Minn.). "Go to a cancer ward in any children's hospital in this country and see the bald, wasting-away kids and then make a decision whether the risks balance over the benefits." (Never mind that Alar has not been identified as the cause of a single childhood cancer.)

Next, viewers watch young children drinking apple juice while Bradley explains that kids are at increased risk because they drink 18 times as much apple juice as their mothers. The NRDC's Janet Hathaway states that Alar is "a cancer-causing agent used on food that the EPA knows will cause cancer in thousands of children over their lifetime." A representative of Consumers Union reveals that 23 of 31 apple juice samples from New York City supermarkets contained Alar, but he fails to mention that the average amount of Alar was only 0.23 parts per million and that the UDMH concentration would be only about 5 percent of that.

With utter disregard for objective reporting, there is not one hint of another side to the story. There is no mention of the fact that a panel of experts discredited the Toth studies or that an EPA study produced results very different from those of NRDC. All other information was ignored in favor of the NRDC spin.

The NRDC report was released the next day, and press conferences were held in 13 cities. In addition to the *60 Minutes* program, Fenton also arranged advance interviews with the major women's magazines and set appearance dates with the Donahue show and other television programs. To heighten media attention, it also arranged with actress Meryl Streep to announce formation of "Mothers and Others for Pesticide Limits" at a March 7 news conference. The message throughout was that chemical residues on food are a major hazard.

Throughout the extensive media coverage of the issue, a few important facts were conspicuously absent: Cancer epidemiologists do not consider chemical residues to be a significant food safety problem. After 40 years of widespread pesticide use, there is no evidence of increased cancer linked to pesticide residues on food. Many naturally occurring chemicals in food are carcinogenic and are found at levels 100 to 1,000 times higher than even the most heavily-applied synthetic chemicals. Organic produce, recommended

by NRDC and its allies, is not treated with fungicides and may therefore contain high levels of carcinogenic mycotoxins. And most significant, the daily dose of UDMH administered in the studies on which the risk estimates were based is about 280,000 times the amount that is ingested daily by preschool children, according to NRDC's own calculations.

Given the unbalanced information conveyed to the public, the results were not surprising. In late February and early March of 1989 many school systems removed apples and apple products from their lunches, and supermarkets were inundated by customer demand for organic produce. Many consumers responded by not buying apples and apple products at all. By May, apple growers reported losses of \$ 100 million and demanded that the EPA stop the economic bleeding by cancelling Alar registrations immediately. Legislation was introduced in Congress to that effect. Finally, besieged on all sides, Uniroyal announced immediate suspension of all U.S. sales of Alar.

Doing things right

Having recognized the problems with the current system, we can develop some important lessons that could help prevent similar incidents from occurring in the future. The first of these is that the review process for pesticides now in use is too long—the UDMH data were first published in 1973—and these delays understandably provoke public outrage. Three or four years is sufficient time to gather and evaluate data on a product, and such a time limit should be put into law. And when a preliminary risk assessment on a pesticide presents serious safety concerns (one cancer per 10,000 to 100,000 population), its use should be temporarily suspended at once while further study and analysis are undertaken. In taking such an action, the EPA must make very clear that this is precautionary only and that further review may result in reinstatement. The agrochemical industry is aware that approximately 20 other agricultural chemicals in use today have caused cancer in animals after being administered in massive doses, and any of these could

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become another Alar. The industry should be conducting the appropriate residue and exposure studies on those substances now.

The second lesson is that the public becomes unduly alarmed by EPA's worst-case estimates. Moreover, the agency does not compare agricultural chemical risk to other, more familiar, risks. The agency should be required to specify clearly that its risk assessment values are worst-case, and it should also supply probable lifetime-risk estimates.

In the case of Alar, the worst-case risk estimate issued by the EPA and picked up by the media was 45 lifetime cases of cancer per million population—justifiable cause for concern, if true. But probable risk is more meaningful than maximum possible risk. For perspective, CDFR's estimate that probable risk is about 3.5 lifetime cancer cases per trillion population means that the population of the United States would have to increase 1,000 times before we would expect to find one tumor caused by Alar. In addition, if EPA compared the risks of agricultural chemicals with other risks, consumers would be in a better position to decide whether they should be concerned. Reaction to Alar would probably have been much different if the public had been told that a person whose diet consisted of nothing but four and a half pounds of applesauce—the food with the highest UDMH concentration—every day would ingest in one year an amount of UDMH equal in weight to the tar inhaled by smoking two filtered cigarettes.

Third, the Alar episode again vividly demonstrates that too few reporters understand the scientific issues involved in their stories, and that they consequently disseminate incorrect information. This should be addressed by educating journalists about the complexities of cancer testing and risk assessment. For example, educational seminars could be sponsored by the agrochemical and farming industries, government regulatory agencies, and scientific societies.

The fourth lesson is that current cancer assay protocols may fail to adequately evaluate a chemical's cancer potential. More research is needed on the hormonal and physiological effects of using extremely

high doses of test substances on test animals and on ways to take into account the effect of such doses on cell proliferation. Such knowledge could improve the scientific basis of regulatory actions and enable regulators to concentrate their efforts on chemicals that pose an actual threat to the public rather than wasting money on materials such as Alar that pose trivial risks.

The fifth-and probably most important lesson for the regulated industries-is that producers of agricultural chemicals must stop being defensive and secretive about their products. Instead, they must initiate dialogues with consumers and discuss issues of concern honestly and openly before the concerns become media events. The public must be made to understand why it should accept any risk at all-reasons such as cost, out-of-season availability, and ridding fruits and vegetables of fungi and insects. At the same time, industry must underscore its concern for human health and be ready to cut back voluntarily on some chemical use. This is not an easy lesson for industry. But ignoring consumer concerns and failing to be responsive to them are incompatible with running a prosperous business.

Recommended reading

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