

US: It's Not Easy Being Green: Are weed-killers turning frogs into hermaphrodites?

by William Souder, **Harpers**
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In the summer of 1997, Tyrone Hayes, a biologist at the University of California, Berkeley, accepted what seemed a harmless offer to join a panel of eight other scientists investigating the safety of the common weed-killer atrazine. The panel had been commissioned by atrazine's inventor and primary manufacturer, the Swiss-based chemical giant then called Novartis and since renamed Syngenta. The company wanted to know if its product threatened "non-target" organisms, including fish, reptiles, and amphibians—creatures whose fate had remained largely unexplored through the half century in which atrazine had become the most heavily used herbicide in the United States as well as one of its most widespread environmental contaminants.

Hayes himself was acutely interested in discovering the causes of a global decline in frog populations that had worried scientists since the early 1990s. Many of the hormones and genes that regulate reproduction and development and metabolism in frogs perform similar functions in people, making frogs important proxies for humans—nature's test animals in a changing world. Syngenta's concern was different. The Environmental Protection Agency had been ordered by Congress to "reregister" atrazine as part of a program to subject a large number of older pesticides to current safety testing, a process that required considerable new data.

Initially, Hayes was asked only to review the scientific literature for studies involving atrazine and frogs. The review turned up nothing, so Hayes designed an experiment to test atrazine directly on the animals. "I honestly thought that the compound wouldn't do anything," Hayes says. "There was no basis that I knew of for a hypothesis that it would. My concern was how it would look to my colleagues. Would it look like I had prostituted myself to a company to do studies that weren't going to produce anything?" Hayes took a vote among his students in the Department of Integrative Biology, some of whom were so anticorporate, he says, that they wouldn't go to Starbucks. But they agreed to do the experiment. Over the course of the next two and a half years, Syngenta paid Hayes's lab \$250,000.

The experiment was similar to ones Hayes had performed many times before. Newly hatched tadpoles were reared in water containing atrazine in amounts ranging from .01 to 25 parts per billion (ppb) until the animals completed metamorphosis. The test animal was the African clawed frog, a species known as the "lab rat of amphibians" and typically referred to by its generic name, *Xenopus*. Once used in human pregnancy testing, *Xenopus* is easier to rear than native North American species, largely because it is entirely aquatic, can be readily force-bred, grows quickly through well-defined stages, and will eat almost any commercial animal feed. Hayes gives his tadpoles Purina Rabbit Chow.

In March 1999, Hayes and his students divided 900 *Xenopus* tadpoles among thirty small aquariums. Half of the tanks contained atrazine; the rest—the control tanks—did not. All the tanks were coded, so neither Hayes nor his students knew which animals were

swimming in what dose. Every three days, the tanks were cleaned and the solutions replaced. After forty days, the tadpoles had become frogs. When Hayes examined the frogs, all the control animals were normal. So were all the females. But among the males that had been exposed to atrazine at concentrations of 1 ppb or more, about 80 percent had smaller than expected laryngeal dilator muscles—puny voice boxes.

Laryngeal muscle size is an important secondary sexual characteristic in frogs; male frogs rely on the strength and pitch of their mating calls to attract females. Male bullfrogs sometimes sit near a spring at the edge of a pond where the inflow of colder water constricts the larynx and lowers the tone of their call.

Examining the frogs more closely, Hayes was surprised to discover that about a third of the male frogs exposed to atrazine also had abnormal reproductive organs. Some had malformed or multiple sets of testes. Others had both testes and ovaries, sometimes in odd numbers. The cooccurrence of testes and ovaries is rare in vertebrates and rarer still in *Xenopus*. Yet in Hayes's experiment this morphology had been elicited at concentrations as low as .1 ppb, a tenth of the amount that altered their voice boxes. Such a dose is equivalent to a grain of salt dissolved in a ten-gallon aquarium. To put it another way, the federally established "safe" limit for atrazine in human drinking water is 3 ppb, thirty times the dose that turned some of Hayes's frogs into hermaphrodites.

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Tyrone Hayes is five feet three and sturdy from years of predawn cycling and running. He has shoulder-length black hair, which he wears braided or in a ponytail, or, sometimes, swept back from his face in a stiff mane. Around the lab he's usually in shorts and a T-shirt, but for speaking engagements and faculty meetings, he favors a black suit, an iridescent tie, and dangly earrings. Hayes was born in 1967, in Columbia, South Carolina, where his father is a carpet layer. He attended Harvard, where he earned a summa cum laude for a thesis on how temperature influences development in wood frogs. In graduate school, at Berkeley, Hayes studied endocrinology, investigating the impact of environmental factors on frog hormones. At thirty-two, he became the youngest tenured professor in the department's history and was named a full professor three years later.

Hayes says that he was naive about how his findings would be received. After reporting his discovery to the other panelists studying atrazine, Hayes argued with them and with Syngenta for months about what to do next. There were protracted discussions about the statistical relevance of the voice-box data and disagreements over the pace of follow-up studies. Hayes was asked for repeated revisions of the "final" report on his results. He saw all of this as an effort to discourage him from publishing his findings. In November 2000 he quit the panel. In his letter of resignation he complained that were he to remain on the team, "recent history suggests that I will spend a great deal of effort preparing reports that will not be finalized in a timely manner, let alone published." He added, "It will appear to my colleagues that I have been part of a plan to bury important data."

In fact, Hayes's contract with Syngenta's atrazine panel did not prevent him from publishing his research. There was, however, an implicit understanding that panel members—in addition to scientists at Syngenta—would review one another's work. Hayes

worried that such consultation, which had already slowed him, would eventually paralyze his research. Hayes's colleagues, meanwhile, wondered at his impatience. "Tyrone is an interesting person," says Keith Solomon, a professor of environmental biology at the University of Guelph, in Ontario, who continues to serve on Syngenta's panel. "But he's in a hurry."

In January 2001 staff scientists from Syngenta visited Hayes at Berkeley in an attempt to get him to rejoin the team. The meeting, which included discussions of a direct arrangement with Syngenta in which Hayes would continue his work, did not go well. "I'm certain they would have had control," Hayes says. Hayes instead went forward with money he had obtained from Berkeley and the National Science Foundation. He repeated the *Xenopus* experiment two times, and in April 2002 he published his findings in the Proceedings of the National Academy of Sciences.

He also performed a series of similar experiments using a common native species, the northern leopard frog. Hayes found that doses of atrazine as low as .1 ppb again caused various degrees of "sex reversal" in about a third of the males, and that some of the animals also displayed a freakish abnormality that Hayes had not seen in *Xenopus*: eggs forming in their testes. In the summer of 2001, Hayes and his students conducted field surveys of wild leopard frogs at eight locations in the United States and found the same deformities they had seen in the lab. At a site on the North Platte River in eastern Wyoming, far from the nearest farmland, Hayes discovered high levels of atrazine in the water and gonad problems in 92 percent of the male leopard frogs. In October 2002 he published these findings in *Nature*. The following summer he returned to the North Platte and found the atrazine contamination much reduced and only 8 percent of the frogs abnormal. A year later he measured no atrazine in the water at the site, and all the frogs were normal. (Hayes believes that the river had been temporarily contaminated somewhere upstream.)

In his published articles, Hayes argued that atrazine activates a gene that produces an enzyme called aromatase, which converts testosterone to estradiol, the strongest of the naturally occurring estrogens. Elevated levels of aromatase, he proposed, could explain the males' stunted voice boxes and multiple, mismatched sex organs—as well as the fact that atrazine appeared to have no effect on the females.

Hayes called the process "chemical castration and feminization." He was not surprised that the abnormalities he found were associated with extremely weak doses of atrazine; hormones, including testosterone and estradiol, typically function at very low concentrations. "If you're a toxicologist, this is a low-dose effect," Hayes says. "If you're an endocrinologist, it's a reasonable effect." Chemical poisons tend to be more toxic as the dose increases—the classic "linear" dose-response association. But chemicals that affect hormonal systems sometimes operate in nonlinear ways: In women, for example, estradiol is necessary to stimulate ovulation, but a large dose of estradiol—the amount contained in the birth control pill—cancels this effect.

The science of endocrine disruption, as chemical interference with hormones has been dubbed, is new and complex. Unlike acute toxins, which can kill an organism outright, endocrine disrupters cause subtle damage, such as reproductive-system abnormalities or

conditions that can lead to cancer. Effects seen at very low doses but that do not occur at higher doses confound traditional toxicological assay techniques. In 1996, Congress directed the EPA to include endocrine-disruption studies as part of its safety screening of licensed chemicals, but a decade later the agency is still trying to develop standards for laboratory tests.

According to Bruce Blumberg, an associate professor of developmental and cell biology at the University of California, Irvine, scientists who study endocrine disruption often see dramatic biological effects when they expose cell cultures to weak chemical concentrations. Curiously, Blumberg says, research sponsored by chemical companies rarely detects such effects.

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Atrazine is among the world's oldest and most effective herbicides—the aspirin of weed-killers. It was developed during a period of intense innovation in the chemical industry that began with the Second World War and the invention of 2,4-D, the first “selective” herbicide: it could kill weeds without killing the crops. (It was later mixed with 2,4,5-T by the military to make the decidedly nonselective defoliant Agent Orange.) Syngenta, a company with roots dating back a couple of centuries that also gave the world DDT and LSD, introduced atrazine to the market in 1959. The new chemical was far more selective than 2,4-D—it is nearly impossible to kill corn with the stuff—and it was an immediate hit with farmers.

Syngenta does not divulge sales figures for individual products, but atrazine continues to contribute a significant portion of the company's U.S. revenues from selective herbicides, which last year totaled \$1.9 billion worldwide.

Atrazine residues are not found in significant amounts in food. Nor is it especially poisonous to vertebrates; it's unlikely that you could dissolve enough atrazine in water to kill a frog. A handful of studies have linked atrazine exposure to increased incidences of cancer in humans, but many more studies have found no evidence of such a correlation. Hayes, for his part, believes that atrazine, because it may cause endocrine problems in people, could play an indirect role in cancer. Estrogen, he points out, is known to promote tumor growth; a current treatment for breast cancer involves a drug that inhibits the production of aromatase. “How can we take the risk of exposing people to something that does the opposite?” he asks. In 2000 the EPA—in a move that downgraded the agency's earlier concerns about atrazine and cancer—declared that the compound is “not likely to be carcinogenic to humans.”

Nevertheless, a fraction of the nearly 80 million pounds of atrazine applied to crops in the United States every year ends up contaminating surface water, groundwater, rain, and even fog. In the spring, concentrations in rivers and streams in the Midwest frequently exceed 10 ppb, and Syngenta has twice voluntarily reduced the suggested application rate for atrazine on corn, from four pounds per acre to three in 1990, and to two and a half in 1992. Although atrazine breaks down fairly quickly in soil and shallow surface water, it is more stable in larger bodies of water and in underground aquifers. In 1999 and 2000 the EPA and the United States Geological Survey, measuring reservoirs in agricultural areas of

a dozen states, found atrazine in posttreatment drinking-water samples collected from community water systems, in some cases at concentrations of more than 2 ppb. In 2003 the EPA reported that a survey of more than 14,000 water utilities, drawing water from wells in twenty-one states, had found that atrazine, where it previously had been detected, averaged about .55 ppb—more than five times the amount that caused abnormalities in Hayes's initial experiment. Because water can take years to percolate down into aquifers, atrazine would still be found in well water for decades even if use of the pesticide were halted today. That very concern led the European Union to ban atrazine in the fall of 2003.

People, unlike frogs, don't undergo critical developmental stages exposed to the elements, and frogs may be particularly sensitive to water-borne chemicals. Still, in the same year atrazine was banned in the European Union, an American epidemiologist named Shanna Swan, then at the University of Missouri School of Medicine, published research showing reduced semen quality in men exposed to pesticides. Swan compared men in Columbia, Missouri, with men living in Minneapolis. The Columbia group had about half as many moving sperm in their semen as their Minneapolis counterparts. Urine samples from the Columbia group showed significantly higher herbicide residues. Swan says few of the men in Columbia were farmers and that she suspects their exposure to pesticides was through drinking water contamination. Reduced semen quality is correlated not only with reduced fertility but also with testicular cancer. One of the pesticides Swan detected in the Missouri group was atrazine.

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On April 16, 2002, the day Hayes's *Xenopus* study appeared in print, *The Wall Street Journal* published a brief article about it, in which Tim Pastoor, Syngenta's North American head of research for human safety health issues, described Hayes's findings as "inconclusive." Syngenta, the *Journal* reported, "considers the Hayes study to be 'preliminary work' that might have to be retracted as the result of more detailed testing." Two months later, Hayes's former colleagues on Syngenta's atrazine research panel issued a press release stating that two teams of scientists, working independently, had tried to replicate Hayes's results and failed. Both studies had been funded by Syngenta and were led by members of the atrazine research panel. One was overseen by James Carr, a biologist at Texas Tech University; the other by John Giesy, a zoologist at Michigan State University. Hayes was furious. "Saying they couldn't replicate my work is different from saying they didn't replicate it," he says.

Reproducibility is a hallmark of good science, and the charge that a researcher's work cannot be duplicated is serious. An experiment that can't be repeated implies either incompetence or fraud on the part of the original author. A perfectly replicated experiment should always yield the same result, in the same way that two identical columns of numbers will add up to the same total. In practice, many variables come into play and experiments are never exactly the same. But as became clear from the data and descriptions of their experiments later submitted to the EPA, both Carr and Giesy departed from Hayes's methods—and neither proved as skillful at the difficult task of rearing frogs. Giesy performed two key experiments loosely modeled on Hayes's. In one of the experiments, more than three quarters of the frogs died. In both, the control tanks

were accidentally contaminated with atrazine at concentrations averaging at least .1 ppb, rendering the results inconclusive. (Giesy says his experiments were no more contaminated than anyone else's and that he merely had reported the control levels more precisely.)

Carr had problems, too. His frogs had been overcrowded and underfed, and many of his tadpoles failed to achieve metamorphosis. Some that did took longer than usual to reach that stage. Carr did not test atrazine at concentrations of less than 1 ppb. Even so, his experiment did produce frogs with abnormal gonads, though he found the effect statistically significant only at 25 ppb—250 times the amount that caused abnormalities in Hayes's experiment. Ordinarily, the detection of a similar effect in an experiment that only approximates the original is considered evidence that the effect is "robust." (Carr did not respond to my requests for comment.)

In any case, Hayes's research had already caught the attention of the EPA. In April of 2002, Hayes had been contacted by Tom Steeger, a scientist in the agency's Office of Pesticide Programs, in Washington, who said in an email that it would be "imprudent" of the agency to ignore the "disturbing results" of Hayes's investigation. The following July, Steeger visited Hayes's lab, where the experiments on *Xenopus* and leopard frogs were under way. After Steeger returned to Washington, he exchanged dozens of emails with Hayes and other scientists on the atrazine panel and at Syngenta in an effort to determine who had gotten what right about frogs and atrazine.

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The Environmental Protection Agency regulates pesticides under a law called the Federal Insecticide, Fungicide, and Rodenticide Act. Adopted by Congress in 1947 and extensively amended since, FIFRA is now a book-length set of rules, the most important of which is this: the EPA is supposed to weigh a pesticide's economic benefits against any "unreasonable adverse effects" it may have on the environment or on human health. In 1988, Congress adopted the provision to reregister pesticides that had been licensed before 1984.

The EPA does not actually investigate the economic benefits of any pesticide, nor does it usually conduct its own research on the safety of such compounds. When confronted with evidence that a pesticide has adverse effects, the EPA usually responds with a recommendation that the matter be studied further, and under the peculiar logic of pesticide regulation, it is the manufacturer and not the agency that is responsible for testing chemical products. (The EPA stipulates what kinds of studies are necessary and requires companies to submit raw data in addition to safety conclusions.)

One way to maintain the perception that a pesticide is safe is to take a very long time reviewing information suggesting it is not. The EPA routinely reframes questions about the safety of pesticides in such a way that they remain questions, and evidence of adverse effects usually results in a demand for more study.

Pesticide makers are allowed extravagant amounts of time for such follow-up work. And because the companies know the EPA must carefully review every study they submit, pesticide makers can game the system by submitting flawed and inconclusive research.

The EPA then judiciously pores over the new data, finds it wanting, and asks for something more definitive. The oversight the agency thus exercises can be thought of as a kind of business service. The EPA helps chemical companies understand safety concerns in terms of overhead. The agency refers to pesticide makers as “registrants,” a term that makes them sound like guests in a luxury hotel, which in some ways does not seem far from accurate.

The Bush Administration has a deserved reputation for hostility to environmental regulation, but the EPA's process for licensing pesticides has become less stringent over the course of many years, under both Republican and Democratic leaders.

According to a knowledgeable former EPA official, the agency was more aggressive in restricting and banning pesticides in its early years. It remained more independent and “professional” under the first President Bush than it has since become. During the Clinton years, the former official said, the agency adopted a conciliatory attitude toward pesticide manufacturers in an effort to counter the perception that it was staffed by environmental zealots. At the same time, chemical companies were becoming more adept at forging alliances with farm advocacy groups, which have enormous clout in Washington and have learned how to turn the EPA's “data addiction” to their advantage. “Scientists culturally cannot say no to data,” the former official said of the staff in the agency's pesticide program. “It's hard for them to make a decision about what's in front of them when there is a promise of more information in the future.” Delay, of course, has decided economic benefits for pesticide makers.

Syngenta's crop-protection division, where Tim Pastoor works, is located in Greensboro, North Carolina, in a leafy, campus-like complex just off Interstate 40. Pastoor, a pleasant, sandy-haired toxicologist, says the regulatory onus on his company is immense—a research program without end. Hearing that work disparaged because it's funded by the company “drives me crazy,” Pastoor says.

“It's as if they”—the company's safety studies—“are tainted when they're not.” In an effort to anticipate the kinds of studies the EPA is likely to request of them, companies like Syngenta often undertake expensive research independent of the regulatory review process. When the company decided to look at atrazine's effects on frogs, it was under no obligation to do so. Pastoor says that since the reregistration process began, in 1994, Syngenta has spent \$30 million on atrazine research and submitted close to 200 studies to the EPA. “I can assure you that I'm not concerned about the safety of atrazine use,” Pastoor says.

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Atrazine is one of nearly 900 pesticides that the EPA identified for reregistration eighteen years ago. In 1994, when the compound was still considered a cancer risk, it was placed under “special review.” Twelve years later, with the August deadline for a final decision on reregistration approaching and the special review set to be completed within a year, the EPA's file on atrazine has swollen to more than a million pages of documents. The pace of reevaluation might have been even slower had it not been for a series of deadlines

imposed on the EPA by a court order stemming from a case brought against the agency in 1999 by the Natural Resources Defense Council.

The NRDC, a well-funded environmental advocacy group based in Washington, D.C., is frequently in court against the EPA. With respect to atrazine, the group has sued the EPA for violating provisions of FIFRA, the Endangered Species Act, the Food Quality Protection Act, and the Federal Advisory Committee Act. These are not tort cases: the NRDC has sued not for damages on its own behalf or anyone else's but instead solely in an attempt to make the EPA follow the federal laws that govern its regulation of pesticides. Like the reregistration process itself, these court cases tend to drag on for years.

Aaron Colangelo, a slight and plainspoken thirty-one-year-old graduate of Harvard Law School and a principal litigator for the NRDC, says that the agency should have suspended atrazine in the spring of 2002, after Hayes published his first article. "There was certainly enough justification to do it," Colangelo says. In atrazine cases, he says, he has often found himself alone at the plaintiff's table across the aisle from attorneys for the EPA and Syngenta—despite the fact that the NRDC has never named the company as a defendant in any of its actions. The EPA apparently is not embarrassed to be joined in court by lawyers for a company that it is supposed to be regulating.

The NRDC has not been alone in urging the EPA to act against atrazine. In 2002 the attorneys general of New York and Connecticut asked the agency to ban atrazine. Judith Schreiber, chief scientist at the Environmental Protection Bureau in the New York Attorney General's Office, wrote a pointed letter to the EPA arguing that the agency's own review of atrazine risks for human health and the environment warranted cancellation of the pesticide. And she scolded the agency for ignoring Hayes's findings. The EPA had failed "to adequately consider the endocrine disruption and reproductive effects of atrazine," Schreiber wrote, adding that Hayes's aromatase theory suggested that atrazine could act through a "common mechanism among frogs, reptiles and mammals, including humans."

In the summer of 2002, Everett Wilson, chief of the U.S. Fish and Wildlife Service's Division of Environmental Quality, also complained to the EPA about atrazine. In a letter to the agency's chemical review manager, Wilson contended that atrazine could harm endangered species, especially amphibians, by interfering with their hormonal processes or by killing the aquatic plants and invertebrates that amphibians eat. Wilson cited the Barton Springs salamander, an endangered amphibian that is known to live only in a spring-fed pool in a park in downtown Austin, Texas. Water samples collected in Austin by the U.S. Geological Survey show that when it rains, atrazine from grass treatment contaminates the salamander's habitat in concentrations that are sometimes greater than .5 ppb.

Unlike FIFRA, the Endangered Species Act, which was adopted by Congress in 1973, contains no provision for balancing adverse environmental outcomes against economic considerations; it simply prohibits harm to any of the more than 1,000 species on the endangered list.

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In November 2002, Hayes proposed an experiment he believed could end debate over his findings: he offered to provide *Xenopus* specimens to three labs in order to run concurrent studies, one by him at Berkeley, one at a lab chosen by Syngenta, and the third at a lab selected by the EPA. Hayes said that he would train lab workers at all locations in protocols—including how to feed and care for the animals—at his own expense. At the experiments' conclusion, each lab would exchange a third of its animals with each of the other labs, allowing all three parties to examine one another's frogs for abnormalities.

The EPA and Syngenta declined Hayes's invitation to collaborate. Jim Carr said in an email that he was “in principle” not opposed to the idea, but complained that Hayes was insensitive to the fact that there were features of his experiment that “we do not wish to repeat.” Keith Solomon agreed, reminding his colleagues by email of their previous inability to raise frogs using Hayes's methods.

Hayes says that, even allowing for start-up time, these new experiments could have been completed in a matter of months. Instead, the EPA asked for further analysis of the extant data, in the form of white paper that would consider seventeen recent studies—published and unpublished—involving atrazine and amphibians, including research by Hayes, Carr, and Giesy. (Twelve of the projects had been sponsored by Syngenta.) This white paper would, in turn, be submitted to the EPA's Scientific Advisory Panel, a group of seven scientists whose job is to provide the agency with “independent, external, expert scientific peer review.” In this case, the panel was to be expanded to fifteen scientists, and a public hearing—a standard feature of such reviews—was scheduled for June 2003.

The white paper—written by Tom Steeger with help from Joe Tietge, a biologist at the EPA's Mid-Continent Ecology Division, in Duluth, Minnesota, who had led the agency's investigation of deformed-frog incidents several years earlier—was never conceived as a means of deciding the safety of atrazine. It was, according to the EPA, an effort to determine “whether there is a need for additional data to characterize more fully atrazine's potential risk to amphibian species, and, if so, what data should be developed.” In other words, the white paper was intended from the outset primarily to help the agency decide what further research should be done on atrazine. Hayes deduced as much, and complained to Steeger that the white paper would merely lead to a routine call for more study—and that inclusion of Syngenta's dubious research was an effort to “dilute” his own legitimate findings with “garbage.”

Extraordinary attention was paid to the white paper's wording. In May 2003 it was reviewed by two departments at the White House, the Council on Environmental Quality and the Office of Management and Budget, both of which advise the president on environmental policy. According to the NRDC's Aaron Colangelo, this degree of executive-branch involvement in the oversight of a single pesticide registration was unprecedented.

On June 17, 2003, the Scientific Advisory Panel convened for a four-day public hearing at the Crowne Plaza Hotel in the shimmery Crystal City suburb of Washington, D.C. Unlike peer reviewers for scholarly journals, who are unpaid and free to make whatever comments they like about the research they are asked to evaluate, the advisory panel members worked within narrow guidelines in assessing the white paper. They were paid \$400 a day, and, although panelists sign detailed financial-disclosure forms crafted to

expose conflicts of interest, there is no prohibition against scientists serving on the panel who receive research funding from the EPA in other areas and who thus might be reluctant to criticize its findings.

In their assessment, Steeger and Tietge wrote that there was enough evidence to “establish the plausibility of a hypothesis that atrazine could affect amphibian development,” but, because of flaws in all of the existing studies, the EPA could neither accept nor reject such a theory. They proposed that Syngenta conduct further research. In its report to the EPA, submitted in August 2003, the Scientific Advisory Panel agreed that more research was needed in order to understand the effects of atrazine on frog development. The panel added that the existing data was sufficient to “warrant concern”—a conclusion only marginally more forceful than the white paper’s ambiguous finding.

“I would never go on an EPA panel again,” says Darcy Kelley, a biology professor at Columbia University who participated in the panel’s deliberation, and who is a leading authority on sexual differentiation in *Xenopus*. “It’s a curious process, which is run within a set of guidelines that guarantee nothing will be done.” Kelley, who has visited the EPA’s lab in Duluth, said she was puzzled that the agency hadn’t tried to replicate Hayes’s experiment and surprised that each of the seventeen studies was given equal weight in the EPA’s evaluation. She found Hayes’s research worrisome because hermaphroditism does not normally occur in *Xenopus*. “He had the most striking results I’ve seen in a long time,” she said. “I’d have said if you want to err on the side of caution, then you should not re-license atrazine.” But, as David Skelly, an ecologist at Yale University who was also on the panel, put it, the group was not permitted to reach such a “novel conclusion.”

Still, in its report, the panel noted that, with the exception of the two experiments by John Giesy at Michigan State, the laboratory studies all suggested that atrazine disrupts normal reproductive development in frogs. “The inability to detect gonadal abnormalities with atrazine exposure in [Giesy’s experiments] should not detract from the positive results noted in the majority of the studies,” the panel members wrote.

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In the fall of 2003, the EPA concluded an interim reregistration of atrazine. In compliance with the recommendation of the advisory panel, the agency also ordered Syngenta to conduct additional experiments on frogs and atrazine. Two years later, in the summer of 2005, scientists at Syngenta began their initial testing of atrazine on *Xenopus*. They expect to have results by the end of this year, more than four years after Tyrone Hayes proposed the joint experiment that could have resolved the issue in a few months. Meanwhile, in all likelihood, the reregistration of atrazine will be finalized this August.

In January, Hayes published two new papers in *Environmental Health Perspectives*. In one paper, he showed that when frogs are exposed to atrazine in combination with other pesticides—as they are in the environment—the damage to the animals’ hormonal systems is more severe than from exposure to atrazine alone. In the other, he reported that when male tadpoles are exposed to estradiol (or to a synthetic compound that suppresses testosterone) they develop the same kinds of gonadal abnormalities that are

associated with atrazine—a finding, he argues, that provides further support for his theory of “chemical castration and feminization.”

Hayes has also been trying to figure out why some male frogs in his experiments fail to exhibit elevated levels of aromatase or gonadal abnormalities after being exposed to atrazine. (The reason, he thinks, may have something to do with natural differences in the rates at which the frogs develop.)

Although Syngenta's current research is not, strictly speaking, an attempt to replicate Hayes's work—the experiments involve alternative methods—Hayes says he has full confidence that they will find the same adverse effect. Different methods and different strains of *Xenopus* could result in somewhat different frequencies and patterns of abnormal gonadal development or even no deformities at all. But, Hayes says, he can think of no reason why the essential result would not be the same. He also knows of no reason why the EPA will not continue to do nothing as the testing moves on to another phase. “My view is that the EPA is never going to take action on atrazine,” Hayes says.

Legally, the EPA needn't find a threat to human health to ban atrazine. Adverse effects in the environment are sufficient for the agency to take action, and in the view of many biologists it makes little sense to see humans in isolation from the environment. The question of what direct effects, if any, atrazine has on human health will be hard to answer, and will likely depend on inferences drawn from studies of surrogate species. Such inferences are never certain. Vertebrate toxicology is a kind of Russian roulette: Some species get lucky when they're exposed to chemicals; some don't. Thalidomide—the sedative that caused horrific birth defects in human infants in forty-six countries half a century ago—was believed safe because tests showed it had no effect on rats. In the very same ecosystems where Tyrone Hayes has found abnormal northern leopard frogs, he has also discovered that a close relative of that species—the plains leopard frog—appears to be unaffected by atrazine. As is usually the case with environmental contaminants, the real-world experiment is already up and running.

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