TOXICOLOGY

Academy Panel Mulls Ethics of Human Pesticide Experiments

Over the past 6 years, a number of companies have been deliberately exposing human volunteers to pesticides to see how much is needed to trigger a metabolic response or even make subjects sick. Such “dosing” experiments offer the best safety data, industry officials assert. Yet despite their admitted utility, these tests have posed a quandary for the U.S. Environmental Projection Agency (EPA). If it accepts these data in its safety reviews, is the agency condoning practices that many consider unethical?

Such information “is valuable,” says EPA office of risk assessment director William Farland, and the agency “would like to find a way to bring human data into the process.” But, he adds, “whether it’s ethical is the question we’re all struggling with.”

In late 2001, the agency turned to the National Academy of Sciences (NAS) for advice. Last week, the new NAS panel heard from both advocates and opponents of dosing experiments. Their vehement debate underlines the difficulty the panel faces in trying to untangle the scientific and ethical questions.

The panel’s recommendation, due in December, could be far reaching. In addition to pesticides, EPA has recently received data on humans deliberately exposed to groundwater contaminants, and the agency hopes to continue to use outside human studies testing the toxicity of air pollutants.

The trigger for this recent spate of testing was the 1996 Food Quality Protection Act, which mandated that EPA reduce acceptable levels of pesticides in foods to protect children. Up to that point, EPA had set a limit several orders of magnitude smaller than the minimum dose that causes effects in animals. Faced with the new law, pesticide companies began supplementing animal studies with human data in an effort to avoid a 10-fold safety factor built in to account for possible higher sensitivity in people; this could offset the tighter limits for children.

Since the new law was enacted, companies have submitted about two dozen human toxicity studies to EPA (see table). In 1998, the Environmental Working Group (EWG) in Washington, D.C., questioned the ethics of these studies, in which volunteers (mostly in the United Kingdom) were paid $600 or more. EPA officials had shelved the studies until an advisory committee weighed in (Science, 1 January 1999, p. 18). That committee issued a report in 2000 saying that some human tests, such as metabolism studies, were acceptable under strict conditions—but most dosing experiments were not. Switching gears, EPA under the Bush Administration indicated that it would consider the tests but, facing heavy criticism, it held off and requested the academy study.

Much of the ethics debate hinges on what are perceived to be industry’s motives. Pesticide-dosing tests are unethical because they are done expressly for the benefit of

Selected Human Pesticide Dose-Response Studies

<table>
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<tr>
<th>Pesticide</th>
<th>Exposure</th>
<th>Company</th>
<th>Date</th>
</tr>
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<tbody>
<tr>
<td>Dichlorvos</td>
<td>oral</td>
<td>Zeneca Central Tox. Lab</td>
<td>1997</td>
</tr>
<tr>
<td>Cyfluthrin</td>
<td>inhalation</td>
<td>Inveresk Clinical Research</td>
<td>1997</td>
</tr>
<tr>
<td>Chlorpyrifos</td>
<td>oral</td>
<td>Dow Chemical Co.</td>
<td>2000</td>
</tr>
<tr>
<td>Phosmet</td>
<td>oral</td>
<td>Inveresk Clinical Research</td>
<td>1999</td>
</tr>
<tr>
<td>Malathion</td>
<td>oral</td>
<td>Inveresk Clinical Research</td>
<td>2000</td>
</tr>
<tr>
<td>Diazinon</td>
<td>oral</td>
<td>Novartis Crop Protection</td>
<td>1998</td>
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industry and offer no conceivable advantage to society, asserted EWG’s Richard Wiles. But Ray McAllister of CropLife America, an industry group, argued that dosing tests of pesticides are in fact no different from phase I clinical trials of drugs, which test toxicity and don’t directly benefit the subject.

Some of the toxicologists on the panel suggested that if the tests were well designed ethically and scientifically, the public might benefit from the data. John Doull of the University of Kansas Medical Center in Kansas City pointed out that some human studies have shown that people are more sensitive than animals to certain substances, such as lead, so human dosing experiments might sometimes result in more protective standards. But Jennifer Sass, a toxicologist at the Natural Resources Defense Council, argued that the dosing studies are often too small to be scientifically meaningful.

Lynn Goldman, a pediatrician at Johns Hopkins University who headed the EPA pesticides office from 1993 to 1998, argued that EPA should ban dosing tests with well-studied organophosphate pesticides because they don’t add much new information. But EPA should permit human-dosing studies of environmental pollutants such as ozone to which people are “exposed daily anyway,” she suggested. Goldman added that mechanistic studies involving human subjects might sometimes be justified, for example, with new pesticides.

The overarching problem with all human data used by EPA, said Goldman, is that unlike the Food and Drug Administration, EPA has no protocols for human studies and lacks a stringent policy for ethics reviews of human data. The agency “needs strong and enforceable standards,” she says, an issue the panel will likely consider.

—JOCELYN KAISER

EVOLUTIONARY BIOLOGY

Uphill Dash May Have Led to Flight

A century-long flap among evolutionary biologists concerns how the ability to fly evolved in birds. Some propose that avian ancestors took wing by gliding from trees; others say early birds got a running start and lifted off the ground as they beat their feath ered forelimbs. A new study suggests that neither idea is quite right.

Instead, flight may have evolved in proto-birds that used their wings to scale inclined objects and trees, says Kenneth Dial, an experimental functional morphologist and behav ioral ecologist at the University of Montana, Missoula. Dial’s 15-year-old son clued him in to this new possibility. He claimed that he saw half-kilogram chukar partridges, whose flight development Dial studies, running straight up bales of hay. On page 402, Dial reports that the birds indeed flap their way up steep inclines—although not the way he and his colleagues would have thought—and suggests that avian ancestors may have done the same. Dial hypothesizes that in evolving the ability to climb ever steeper slopes, these animals came to move their forelimbs as modern birds do—up and down—instead of just back and forth like reptiles. This switch set the stage for flight, he explains. His finding “has blown the field wide open,” says Kevin Padian, an evolution ary biologist at the University of California, Berkeley.

Chukars are related to chickens, quails, and turkeys. These galliform birds’ flight and running dynamics might reflect those of their great, great ancestors—the birdlike dinosaurs. Like them, the modern descendants have wings but don’t fly well, and their legs are strong.

Working with his son Terry and another high school student, Ross Randall, Dial monitored chukars’ movements and found that newly hatched birds could walk up slopes of 45 degrees and could master steeper inclines by flapping their baby wings. They tackled ever steeper slopes as they matured. Even more remarkable, adults could sprint up overhangs of 105 degrees, sometimes climbing 5 meters. These skills declined when the researchers clipped or removed the birds’ feathers.

Using high-speed video recordings and devices that monitor acceleration, Dial analyzed wing strokes and the effects of flapping on the bird’s body. As the birds run up an incline, the films reveal, they flap their wings at a different angle than when they are flying. The net effect pushes the bird into the incline so that its feet don’t slip—akin to spoilers on a race car. On a vertical surface, they hold their wings as if flying. “The films are amazing,” says Padian. “[They] tell us something about living birds that we didn’t know.”

Researchers interested in the evolution of bird flight are taking note, and some interpret the results as bolstering their own ideas. For those who think flight evolved from birds parachuting from trees, this behavior could solve the problem of how the birds got into the trees in the first place. In contrast, Luis Chiappe, a paleontologist at the Natural History Museum of Los Angeles County, sees the findings as supporting his theory that flapping wings led to ever faster running speeds that eventually made it possible to lift off. “Although [Dial’s] view falls between the strict application of the ground-up and trees-down theories, I would place it closer to the realm of ground-up theories,” he notes.

But Dial thinks his findings add a new scenario to the debate. “These animals are doing something that none have proposed,” he says. The key innovation that allowed avian ancestors to fly, he claims, came as they evolved a new way of moving their forearms. Being able to flap wings up and down as well as back and forth was advantageous because it got the animals up steep surfaces. Once thus equipped, they could flap away as nature’s first flyers, Dial says.

It might be impossible to determine when this new ability developed, but analyses of some fossils indicate that protobirds—much like chukars—were able to flap their wings either back and forth or up and down. Dial is now studying other, more primitive birds, such as South America’s tinamous, to rule out the possibility that this locomotor skill evolved late in bird history. However, neither Dial nor his colleagues think the issue is settled. Indeed, Chiappe points out, “I imagine people will continue to argue about the origin of bird flight for a long time.”

—ELIZABETH PENNISI

Take to the sky. Studies of modern birds suggest that flight may have evolved via climbing.