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Animals in Testing: How the CPI is Handling a Hot Issue

Anonymous

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In the classic LD50 (lethal dose 50%) test, a dose of a test substance is gradually increased in the diets of 40-100 animals until half of them die. It's that kind of treatment of animals in laboratories that has the American Anti-Vivisection Society looking for a chemical company to sue. "We're doing a legal search with our lawyer in New York," says Michael Ware, assistant to the organization's president. "It may be over the LD50 or maybe one of the other animal tests. We haven't yet made a public determination of which company it'll be."

Although a lawsuit will be a new tactic for groups that support animal rights and welfare, the company it is directed at is likely to face rough sledding. Animal rights activists have steadily grown more sophisticated and effective in challenging the animal testing practices of cosmetic, pharmaceutical and chemical companies. Since 1980, such groups, through a number of demonstrations, write-in campaigns and newspaper advertisements, have scored a series of important victories:

- Cosmetics companies have given more than $3 million to support research aimed at developing *in vitro* nonanimal alternatives to the Draize test, in which substances ranging from shampoo to lye are put into rabbits' eyes to test for inflammation or injury.
- The drug industry—followed by the Food and Drug Administration, the Consumer Product Safety Commission and the Environmental Protection Agency—has declared the 10**50** acute toxicity test obsolescent, if not yet obsolete.
- Major drug and chemical companies have developed guidelines emphasizing humane treatment and minimum use of animals. It is "your obligation to assure that pain is not inflicted in any kind of unnecessary manner," says Dr. G. Gilbert Cloyd, Human and Environmental Safety Div. director at Procter & Gamble's Miami Valley, Ohio, lab.

But despite this heightened awareness of animal welfare issues, activist groups are not resting, because the number of animals used in testing and experimentation continues to grow. In all, 13.7 million mammals were used in U.S. laboratories in fiscal 1982, according to estimates by Health Designs (Rochester, N. Y.), which has prepared figures for the congressional Office of Technology Assessment. In fiscal 1983, Health Designs says, the number rose to 14 million.

Universities and medical schools use most of the animals--28.3%--and drug, health device and diagnostic firms follow with 26.4%. Tests done by chemical companies use a scant 2.4%, although toxicology testing labs—which chemical firms often employ—account for 5.8% of the total, Health Designs estimates.

Pressure

Being a small factor in the field does not mean that chemical process companies can stay out of the line of fire. In fact, those firms that have changed their testing practices have generally done so as a direct response to pressure from animal welfare and animal rights organizations. For instance, the current policy on animal testing at Smith Kline & French Laboratories, a subsidiary of SmithKline Beckman, grew out of a threat by the Pennsylvania Animal Rights Coalition (PARC) to conduct a demonstration at the firm's facility in Philadelphia. In its policy statement, dated May 5, 1983, the company notes: "Historically, scientists and animal welfare groups have often treated each other's views with skepticism and, on occasion, with overt hostility. Such attitudes are not constructive." Instead, Smith Kline says, "We are

dedicated to the development of new methods to conserve animals and to seek alternative test procedures."

Such pressure groups have had a "significant" impact on the chemical industry, too, says Philip G. Watanabe, director of mammalian and environmental toxicology at Dow Chemical. "They've influenced everyone," he says.

Dow's statement of "guiding principles for the use of experimental animals" was written last year as a direct result of Smith Kline's memo, Watanabe says. "It was pretty obvious the whole issue was coming on," he notes. Dow has tried to reconcile two conflicting demands: the need to ensure the most beneficial use of drugs and other chemicals and a "strong ethical responsibility to use experimental animals as sparingly and as humanely as possible."

However, James G. Aftosmis, associate director of DuPont's Haskell Laboratory for Toxicology, refuses to link DuPont's animal welfare policies with any animal rights activities, though the firm's policies are similar to Smith Kline's and Dow's. Healthy, well-treated animals are "very critical for the validity of the research," Aftosmis says.

But he is alarmed by the "rather violent" tactics of animal rights groups in Great Britain and the recent spread of this violence to France, Germany and even the U.S., where some activists have raided labs to set animals free. "There have been about 30 break-ins across the U. S.," Aftosmis says.

Most executives distinguish between "legitimate" animal welfare issues and what they see as "unreasonable" goals—such as a total ban on animal testing. Charles Cleveland, a staffer with the Pharmaceutical Manufacturers Assn., says he tells pro-animal activists he will gladly cooperate on animal welfare, but that "we part company when you start talking about animal rights."

The roots of the animal welfare movement go back at least as far as mid-19th century Britain, where animal lovers decried wanton cruelty to farm animals and pets. The movement's early victories came with the passage of the British Cruelty to Animals Act of 1876 and, in the U. S., of the "28-hour law" protecting livestock shipped by rail.

Not for rats

The U.S. Animal Welfare Act—passed in 1966 and amended in 1970 and in 1976—charges the U.S. Dept. of Agriculture (USDA) with overseeing the humane handling and housing of animals in experimental laboratories, wholesale pet dealerships and exhibitions. But while the law covers lab animals, experiments as such are specifically excluded. And USDA's regulations offer no protection to the most common lab animals, mice and rats.

In contrast with animal welfare, the animal rights—or animal liberation—movement derives from 18th century humanism, 19th century abolitionism and the equal rights movements of the 1960s and '70s. The modern theoretician of this movement is Peter Singer, chairman *of* the philosophy department at Australia's Monash University, whose 1975 manifesto, *Animal Liberation,* attacks "speciesism," defined as a "bias toward the interests of members of one's own species and against those of members of ·other species."

Singer believes that regardless of their differences, people should have an equal right to protect their own interests; in the case of animals, those rights must be protected by people. He quotes the 17th century philosopher Jeremy Bentham: "The question is not, Can they reason? nor Can they talk? but Can they suffer?"

Interestingly, Singer's attitude toward killing—as opposed to hurting—animals is based on somewhat different criteria. He believes that intelligence and the capacity for a meaningful life are relevant measures of the relative worth of nonhuman and human animals in weighing, for example, which should live and which should die if there is not enough food for both. The lower down the biological chain he goes, the less he objects to killing animals for sound reasons.

In recent years, the "establishment" animal welfare organizations—such as the Humane Society of the United States (HSUS) and the American Society for the Prevention of Cruelty to Animals (ASPCA)—have themselves become more militant. Whether they have actually adopted the more radical views of the animal rights groups or simply fear losing members to them, the old-line organizations are joining the activists in narrowly focused actions.

In 1980, coalitions against the Draize test and the LD50—sponsored initially by Pegeen Fitzgerald, a New York City radio personality and president of the Millenium Guild, an animal rights group—soon included both HSUS and ASPCA. Last year, HSUS was a major sponsor of Mobilization for Animals rallies held throughout the world on behalf of laboratory animals.

More recently, HSUS has filed suit along with Jeremy Rifkin, a critic of gene splicing, to stop the transfer of human growth genes into the hereditary makeup of animals, charging USDA with "disregard for the nature or telos of each animal species" (*CW, Oct. 10, p. 58*). ASPCA is challenging the Pentagon's use of goats and pigs in gunshot wound experiments.

Meanwhile, the animal rights movement has become more violent, particularly in Europe (Box 1). A British group recently announced that it had injected Mars candy bars with rat poison to protest the manufacturer's support of tooth-decay experiments on monkeys. The "poisoning" turned out to be a hoax, but other deeds have not. British activists have smashed windows and sprayed paint in the shops of butchers and furriers, cancer research centers and lab officials' homes—and have broken into various places to "liberate" meat, fur and laboratory animals.

U.S. activists

So far, violence by animal rights activists in the U.S. has been limited to laboratory break-ins, mostly at university research labs, which are often less secure than industrial labs. Usually, the invaders just set animals free, although in a few cases research records have been stolen.

Most of the break-ins have been attributed to a loose-knit international group called the Animal Liberation Front (ALF), which was formed in England in 1976. ALF claimed responsibility for taking 12 dogs from the Harbor-UCLA Medical Center last Christmas. More recently, individuals claiming to be ALF members broke into a University of Pennsylvania laboratory and stole videotapes of primate experiments aimed at determining how much of a physical blow will cause brain damage.

In the U.S., the animal rights movement is more confrontational than violent, and the companies or institutions challenged are chosen more for their vulnerability than for the gravity of their offenses. This was true when members of PARC approached Smith Kline early in 1982. "We thought Smith Kline was a good target," says Roxanne Curran, one of PARC's organizers. "It was close by, it used a lot of animals, and it was using the LD50."

As a first step in its campaign PARC wrote to Smith Kline executives, asking to discuss its objections. "They declined," Curran says, so the group planned' the demonstration at Smith Kline's Philadelphia facility. "We could have had 50 or 75 people," she says.

How animal testing is faring abroad

In Britain, the number of animal experiments has dropped since 1977; according to the Home Office, which issues animal-testing licenses. In 1983 there were 3.6 million experiments, 600,000 fewer than in 1982, and 1.7 million less than in 1977. "This most welcome reduction in live animal experiments indicates a real desire on the part of the scientific community to reduce the number of experiments and to seek alternatives wherever possible," says David Mellor, Home Office parliamentary undersecretary of state.

In May 1983, a government White Paper proposed tightening the stiff controls of experiments under Britain's Cruelty to Animals Act of 1876. The proposals, not effective before 1986, would continue to recognize the Draize rabbit eye test if it is "stopped at the first sign of irritancy so that needless suffering is not caused to the animal." The new policy would require the LD50 acute toxicity test "where there is still a requirement" for it through either European Community (EC) directives or international law.

Pressure from member nations has led to a preliminary agreement to change the EC directive that governs drug testing. One change would lower the level of precision required in determining a medicine's dose effects, heralding at least a modified LD50.

Taking the lead on regulation of animal testing in Europe, however, is the Council of Europe, an older body than EC with 21 member countries, including Turkey and the Vatican. In late 1982, a Council of Europe committee of experts agreed to two texts that may someday form the basis of new Europe-wide rules for animal testing.

The draft convention, which must be approved by the council's supreme Committee of Ministers and by member governments, sets out guidelines for tests, depending on their purposes. Both the LD50 and Draize tests would be allowed; but the convention states that an animal test should not be done if an alternative scientific test is available that does not harm animals.

Each country that eventually signs the convention must collect and make public statistical data on animals used in testing. The convention also provides for mutual recognition of test results to minimize test duplication.

In Switzerland, which is not an EC member, the number of animals used by the chemical industry and at affiliated institutes was 1.5 million this year; down from 1.64 million last year; Swiss industry has pledged to use the minimum number, for humane and economic reasons, so the downward trend is expected to continue.

Too mild

But there is growing pressure from Swiss antivivisectionists to prohibit all animal experiments. The 1981 National Animal Protection Law established the first nationwide standards for animal experiments, but antivivisectionists consider it too mild. Their national referendum against the proposed law was overwhelmingly defeated in 1978, but another referendum—to be held within the next two years—would prohibit all live experiments on vertebrates and all "tortuous" experiments on other species.

If this new referendum passes, "the pharmaceutical industry might well be paralyzed," says Yves Dunant, chairman of drug maker Sandoz. Passage, he says, would lead to the "wholesale" relocation of the Swiss pharmaceutical industry (*CW, June 22, 1983, p. 37*).

The Swiss drug firms might prefer to conduct their research in Japan, where the Ministry of Health and Welfare views the LD50 test as "scientifically valid and meaningful," according to a ministry official. In fact, the ministry says it is trying to convince other nations' test authorities to "discuss the issue from a scientific rather than a social [animal welfare] standpoint."

Not delighted

A Smith Kline executive recalls the situation. "We'd just built a new hotel next to our headquarters, so we weren't delighted with the idea of pickets marching back and forth," he says. "Also, they threatened a boycott against Contac," a major Smith Kline consumer product.

Giant steps for test reform

The animal rights movement can claim two major accomplishments in the last few years: the virtual elimination of the LD50 (lethal dose 50%) test as a regulatory requirement and steady scientific progress—with funding from the cosmetics industry—in developing alternatives to the Draize rabbit eye irritation test.

When the, test first came under attack in 1981, "People were saying it'd take 10 to 12 years to get that changed—if we ever got it changed," recalls Alan M. Goldberg, director of the Johns Hopkins Center for Alternatives to Animal Testing. But scientists at the center's second symposium in October 1983 reported that alternative tests already developed by industry will supply more and better data than the LD50—and with fewer animals.

Last year at an Acute Studies Workshop sponsored by the Food and Drug Administration, FDA representatives announced that the agency would not specifically require LD50 data for approval of virtually all cosmetic and drug products. The test, an FDA official .said, is "often credited with greater quantitative and scientific accuracy than it merits."

As it turns out, the LD50 is still required for three antitumor antibiotics, but FDA has proposed ending these requirements. And Environmental Protection Agency (EPA) officials say that they have "gone out of [our] way" to discourage use of the LD50. Weeks before the third Hopkins symposium in October, EPA announced new acute toxicity testing guidelines. The agency says that it wants a rough estimate of acute toxicity, not a precise measurement

'Limit test'

Many companies—including Du Pont, Dow Chemical, Avon and Colgate-Palmolive—have already replaced the LD50 with a "limit test," which substitutes a judiciously selected single dose for a series of incremental doses, reducing the number of animals used from 50-60 to about 20. Procter & Gamble has developed an "up-and-down" test using "only six to eight rats." A selected dosage is used on one animal. If it lives, the dosage is raised on the next animal; if the first animal dies, the dose is lowered. But regulatory agencies would "like to see a little more validation" for the test, says Dr. G. Gilbert Cloyd, director of the Human and Environmental Safety Div. at P&G's Miami Valley lab.

Union Carbide is working on an acute toxicity test substituting earthworms for mammals. And Kurt Enslein of Health Designs (Rochester, N. Y.) has come up with a computer-generated mathematical model that he says estimates a compound's LD50 value with 80% accuracy.

At the Hopkins center's most recent symposium, which focused on the Draize test, some of the more promising in vitro tests were picked out at a press conference by Dr. James P. McCulley, ophthalmology chairman at the University of Texas Health Sciences Center (Dallas), to show how far researchers had come in just the past three years. Most involve several generations of cultured cells:

- At the University of Washington in Seattle, assistant ophthalmology professor Kwan Y. Chan is checking how much plasminogen activator enzyme is released from rabbit cornea epithelial cells when exposed to a test chemical and to a nonirritating saline solution.
- At Rockefeller University's Animal Research Laboratory in New York City, researcher Charles Shopsis is measuring the rate at which uridine—a nucleotide that cells use to make ribonucleic acid—is incorporated into cultured mouse fibroblast cells. Any irritant interferes with this process.
- Also at Rockefeller, Ellen Borenfreund is looking at cell lines to see how chemicals change the cell shapes. Both Rockefeller tests, Dr. McCulley "would be more sensitive than waiting to find cell death."
- Dennis M. Stark, head of the Rockefeller University team, is trying to get an inflammation index by measuring the migration of macrophages to mouse cells exposed to test chemicals. "You might be able to kill cells and not get inflammation of particular nodes, or we might be able to cause a lot of inflammation as we have in allergic conditions when . . . our eyes fill up and get red," Dr. McCulley says. "So one has to look at both."
- At the Eye Research Institute in Boston, tissue culture specialist Marcia M. Jumblatt and ophthalmic pharmacologist Arthur H. Neufeld are trying to "go for the gold," Dr. McCulley says; by running tests with human epithelial cells. But the project has hit some snags because the human cells are difficult to grow in culture.
- At the Medical College of Pennsylvania in Philadelphia, Dr. Joseph Leighton, an experimental pathologist, is using the membranes that surround chick embryos. Unlike cell cultures, which are bloodless, the membranes are rich in arteries, veins and capillaries but contain no nerves.
- At Rockefeller, veterinary pathologist James Walberg has developed a modified Draize test that uses living rabbits, but with two advantages. The test substance is greatly diluted, so the rabbit suffers no pain. And, unlike the Draize, Walberg's test offers an objective measurement: It counts the cells that come loose in the distilled water used to wash a rabbit's eye an hour after exposure.

Goldberg says that scientific consensus is needed before any of these tests can replace the Draize test. First, the tests must be validated with "lots of known compounds," a process that is still going on, he explains. "If the tests don't work, we're going to know that very quickly. If they work, it's going to feed on itself."

Seeking another route, Smith Kline called Frankie Trull, executive director of the Assn. for Biomedical Research. Trull suggested talking with animal rights activist Henry Spira. "Rather than standing outside and pointing a finger and saying everyone's terrible, he [Spira] tries to understand the others' point of view," Trull says.

Spira, 57, is a former merchant sailor, union and civil rights activist, crusading journalist and high school English teacher who has devoted the past 10 years of his life to "reducing pain" in animals. His accomplishments for animal rights have been impressive.

In 1976, with funding from the Millenium Guild, Spira persuaded New York City's American Museum of Natural History to stop scientific research on cats that had gone on for 15 years. Three years later, he led a successful effort to repeal New York State's Metcalf-Hatch Act, which had forced state-funded animal shelters to give their unwanted cats and dogs to research labs.

With Millenium Guild backing, Spira launched the 1980 campaign that led Revlon and other cosmetics companies to spend about $3 million for research to find alternatives to the Draize test. That research has turned up promising in vitro tests. Spira's most recent crusade, against the LD50, has in just two years virtually ended the use of the 56-year-old test (Box 2).

When Spira met with representatives from Smith Kline, "It became clear to Henry that his interest, and the interest of animal rights activists, are generally consistent with our interests," says Stanley Crooke, Smith Kline & French's president of research and development. "He was impressed with our policies."

As a result of their meeting, Spira and Smith Kline agreed that the firm would give Spira, as an animal rights leader, documents showing what Smith Kline was doing and an analysis of its animal usage … Both parties agreed, Crooke says, to "put together a policy statement that could serve as a model for ourselves and other companies." When this agreement was reached, the threat of a demonstration ended.

Spira is unusual in convincing companies and, in this case, an animal rights group looking for a fight that their interests are best served by cooperation. In a confrontational era, Spira carefully defines his targets and goals to ensure that an adversary's self-interest is clearly served by going along with him.

In an interview in the January/February 1981 issue of the industry journal Lab Animal, Spira explained why he chose the Draize test and Revlon as his first targets. "It's the type of test that people can identify with," he said. "People know what it feels like to get a little bit of soap in their eyes."

He also chose the test because "rabbits are seen as symbols of innocence." One more reason for focusing on the Draize was that scientists also were saying that nonanimal alternatives were possible and, perhaps, superior.

Perceptions

Spira decided to focus on the cosmetics industry—even though manufacturers of chemicals, soap and detergents probably use more rabbits in testing their products. "An important part of any struggle is what people's perceptions are," he said. "Most people perceive that it's not beautiful to harm others, especially when the end goal is trivial and frivolous. I think that there are very few people on the street who'll say, 'Yeah, go around and blind rabbits to produce another mascara.' "

The choice of one firm—Revlon—was a way of maximizing the campaign's impact. "We had to target one company and make it worth their while to research alternatives—in a way, to make it cost-effective for them," Spira said.

Before launching his public campaign, Spira said that he dealt with the firm privately. "We suggested that they put 0.01% of their gross revenues—which would be around $240,000 now out of $2.4 billion—into alternatives research," Spira said. "We weren't after a public relations victory—we were looking for expertise and funds for research." But after a year and a half, "They said they were going to push [our position paper] onto another committee, and that all they could guarantee was that somebody would look at the paper."

At that point, Spira organized the Coalition to Stop Draize Rabbit Blinding Tests, supported by 407 organizations claiming "a combined membership in the millions." In April 1980, the coalition ran a series of full-page ads in New York City newspapers that cost about $78,000, most of it coming from the Millenium Guild. The ad featured a white rabbit, tape across both eyes, under the headline: "How many rabbits does Revlon blind for beauty's sake?" Readers were asked to write to Revlon President Michel Bergerac "that you and your friends will not use Revlon products until Revlon funds a crash program to develop nonanimal eye irritancy tests."

A month later, about 300 people, some dressed in rabbit costumes, demonstrated outside Revlon's offices on New York City's Fifth Avenue. A march followed in June, and in September, there were demonstrations in Britain, Canada and Australia.

In December, Revlon threw in the towel. The company's public relations director—who had recommended stonewalling the issue--resigned, and the new director began "serious discussions" with Spira's coalition. Within a few weeks, the company offered to establish a center for alternatives to animal tests at Rockefeller University with a $750,000, three-year grant.

The Revlon grant was "crucial," Spira says, because it "legitimized" the search for test alternatives—and not so incidentally Spira himself—in the eyes of industry and the scientific community. Today, he says, toxicologists address animal welfare as part of their work, and toxicology journals routinely carry articles on the subject. "People don't laugh if you talk about reducing the numbers, the pain" of animals, he says, and the issue is no longer cast as "humaniacs vs the scientific community."

Once Revlon had agreed to fund an academic center, Spira says, "It was a simple thing to go to Avon" and "tell them that they couldn't do any less." Avon, in fact, matched Revlon, donating $750,000 in March 1981 to support the Cosmetics, Toiletry & Fragrance Assn., which had established a $1 million fund to set up a center for the study of alternatives to animal testing at Johns Hopkins University in Baltimore. "This set the pattern," says Spira. "Estee Lauder [which gave $250,000 to the Hopkins center] and a number of other companies soon came into line."

Sharper focus

Initially, Avon's decision was a response to pressure from Spira's coalition, says Dr. Yale Gressel, the firm's director of product safety and integrity. "There's no question in my mind that that was industry's response to a great deal of pressure." Although Gressel claims that Avon had altered much of its testing on its own initiative, he adds, "It is conceivable that there was a sharper focus in recent years" because of "issues being raised by the animal welfare people."

Spira's next campaign, against the LD50, at first was focused on another consumer products company. But his strategy was different "We went to Procter & Gamble, and we told them we weren't interested in

bucks," he says. "We wanted an internal plan and program to reduce and replace the use of animals, and we wanted the plan publicized so that it could be used as a model for other companies to follow." P&G says that it had already developed alternatives to the LD50 and the Draize and had set up an Animal Sciences Task Force to make recommendations on minimizing animal use and suffering in safety assessment: After meeting with Spira, the firm says, it agreed to publicize its policies and new discoveries so that they could be used by other firms.

"Our initial relation with Henry Spira was an adversarial one," says P&G spokesman William Dobson; Spira says he went to a shareholders meeting and refused to give up the microphone. But P&G decided that "the best approach was to invite him in" to talk with company scientists, Dobson says. '"We have developed a good, solid working relationship with Henry Spira," says Dobson, who adds that he now often tells other groups to get in touch with Spira.

Spira himself says he is perfectly willing to give the company all the credit, once it turns to other methods or donates to research. He stresses that "industry really doesn't lose" by addressing animal welfare issues. Since using fewer animals doesn't hurt anyone—except, perhaps, the breeding facilities that sell them—it's "one of the rare issues where everybody can come out a winner," Spira says. On the other hand, he adds, industry is well aware that, if more conciliatory efforts fail, he will try something similar to the Revlon ad.

'The lubricant'

Some of the scientists who have supported the development of in vitro replacements for animal tests, however, say that the easy victories may have already been won. In the future, they suggest, the interests of animal rights activists and of industry will diverge. Alan M. Goldberg, director of the Johns Hopkins Center for Alternatives to Animal Testing, says that Spira was "clearly the lubricant" for the establishment of both the Hopkins and Rockefeller centers. But the work of the centers has so far focused exclusively on finding nonanimal substitutes for routine toxicity tests rather than on long-term chronic toxicity tests.

The short-term tests—most of them required by government regulatory agencies—use only about 25% of the animals killed each year in U. S. labs, the great majority of them rodents. But Goldberg says he doubts that animals would ever be replaced "in the area of fundamental research, in the area of trying to understand disease states." That's about 75% of the animals that the activists are determined to save.

Robert A. Neal, president of the Chemical Industry Institute of Toxicology, agrees that "bacteria are not really going to replace whole animals" –at least not "for the forseeable future." But Neal thinks it may be possible to use fewer animals by targeting the species that will be most predictive of human reaction to a given substance. Rats and mice are both used in many studies of suspected carcinogens, but Neal explains that rats may be far more reliable indicators for human exposure to many of these substances. Although basic toxicology work will continue to use whole, living animals, Neal says, "We'll be using fewer of them."

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