Undercover investigation reveals animal suffering in toxicology laboratory

April 2022

Undercover in a toxicology laboratory

An investigator for the Humane Society of the United States spent seven months inside Inotiv, a CRO (contract research organization) laboratory in Indiana that conducts toxicology tests on dogs, primates, minipigs, mice and rats for pharmaceutical companies. Our investigator witnessed thousands of animals being used in more than 70 studies, many of whom endured prolonged, unalleviated pain and were killed at the end of the study.

Toxicology tests do not show whether a drug effectively treats a particular disease or condition. Instead, they crudely measure the amount of a substance that the animal can tolerate before suffering from toxic (adverse) effects.

Inotiv, and other commercial labs hired by drug and chemical companies, force dogs, primates and other animals to ingest substances again and again, often daily or even multiple times a day for some tests. Workers force the substances into animals either through feeding tube (gavage) or by injection.

Animals used for toxicology tests are only let out of their cages when they are being tested on or during periodic cage cleaning. At the end of the tests, animals are euthanized and necropsied to examine any toxic effects on the animals' bodies.

Toxicology testing on animals is still routine for many industries even though alternative, more effective methods exist (and are continually being developed) and animal and human bodies often react quite differently to substances.

Background on Inotiv

Inotiv was founded in 1974 and is headquartered in West Lafayette, Indiana. Until March 2021, its name was Bioanalytical Systems, Inc. From recent acquisitions of other smaller toxicology companies as well as dog, rabbit and primate breeding/holding facilities, Inotiv appears intent on growing its animal toxicology business at a time when there is ever-increasing evidence that toxicity testing results in animals are inaccurate and misleading. Science is instead taking toxicology into high-tech realms such as organ-on-a-chip technologies, organoids, 3D printing of human tissues and powerful computer modeling.

Inotiv and its recently acquired and combined companies have facilities in Maryland, Colorado, Missouri, Virginia, Texas, North Carolina and elsewhere, including several locations in Indiana. The Texas location is a primate quarantine facility where approximately 7,800 monkeys are held for future use in toxicity tests and other experiments.

Inotiv's subsidiary in Cumberland, Virginia, is a dog breeding facility that amassed a litany of appalling Animal Welfare Act violations in several recent inspections by the U.S. Department of Agriculture. Unbelievably, the facility was killing fully conscious puppies by injecting euthanasia solution directly into their hearts, according to a USDA inspection report of the Virginia facility (which is designated as site 005 on the report). This method has long been considered too cruel to use and unacceptable according to American Veterinary Medical Association's euthanasia guidelines. Dogs were suffering from serious

untreated wounds and dental disease. The mistreatment of dogs at Inotiv's dog breeding subsidiary was so immense that Virginia lawmakers recently passed four laws to place restrictions on the facility as well as other facilities in the state that breed dogs and cats for research.

Inotiv played down this disturbing revelation in communications with its Indiana laboratory staff and, instead of improving its standards, arranged for an outside contractor to provide a webinar on how to recognize an undercover investigator on the job because it appeared the dog breeding facility had been exposed by one. The HSUS undercover investigator was required to sign a paper confirming that they had watched the webinar on how to identify an undercover investigator.

Inotiv's laboratories in Indiana, Missouri, Maryland and Colorado are accredited by the Association for the Assessment and Accreditation of Laboratory Animal Care International and, because of that accreditation, they are only partially inspected by the USDA during yearly "focused" inspections. Focused inspections are less in-depth than full inspections. An inspector may not view all of the conditions of a facility, or even the animals themselves. The policy that essentially allows a non-regulatory body such as AAALAC to stand in for an agency with the power to enforce the Animal Welfare Act leaves animals vulnerable and the public in the dark, since AAALAC documents are not publicly available. The last USDA inspection of Inotiv was done in May 2021 and found no Animal Welfare Act violations.

Summary of investigation findings

We have submitted a complaint to the USDA detailing alleged violations of the Animal Welfare Act that we believe occurred during our investigation and after the agency's last inspection of the lab. Our complaint covers a wide range of issues, including but not limited to the following.

Failure to provide prompt and necessary veterinary care, including euthanasia, to severely sick and injured dogs, pigs and primates

- Some dogs and primates were made so sick by test substances that they could not eat.
- Dogs and primates lost significant body weight in studies due to a lack of appetite or the toxic effects of test substances.
- Puppies in a two-week toxicity study were dosed despite serious adverse effects such as shaking, high fevers, vomiting, rapid heart rates and labored breathing.
- A primate suffering serious adverse effects from a test substance was dosed despite her dire condition. A technician called the veterinarian who, without even coming to look at the animal, pronounced that she should be dosed again with the test substance regardless of her condition. While he was dosing the primate, the technician who had spoken to the vet said "I'm so sorry, lady, maybe this will be your last dose. I kind of hope it is because it's torture at this point."
- A minipig used in a dermal toxicity test was thought to have had her leg broken by an impatient worker trying to get her out of the cage she was housed in; she was not X-rayed because she was scheduled to be necropsied in six days. Another minipig in the same study sustained a possible fracture of his mid-tibia after a supervisor restrained him by sitting on his back during a blood draw. He did not receive veterinary care because he was "scheduled for necropsy soon after evaluation."

Failure to provide availability of emergency, weekend and holiday care, as required by the Animal Welfare Act

- After an employee contacted the laboratory's only veterinarian to request assistance to alleviate the pain being experienced by moribund dogs in a toxicity study, the veterinarian said the dogs would have to wait to receive treatment and alleviation of their suffering until the following day because he was watching his children while his wife was out of town. The dogs could not rise to their feet but lay on the cement floors of their kennels shaking, salivating, vomiting and moaning in an unearthly way.
- A technician told our investigator that another lab worker was holding a dying dog, but the veterinarian refused to come in because his children were opening Christmas presents.

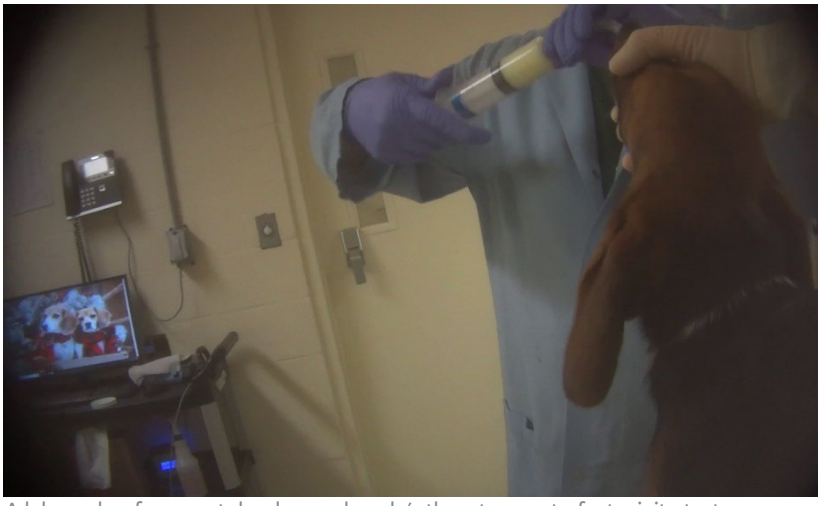
Failure to provide enough staff to properly care for animals

- Primates died in restraint chairs by accidental hanging when no one was monitoring them.
- So many toxicology projects were taken on at Inotiv that there was not enough staff to attend to even the most mundane of husbandry tasks, such as trimming dogs' toenails so they wouldn't get caught and torn in chain-link kennels.

Note: The suffering and inadequate veterinary care of the rodents wasn't included in the complaint to USDA because those animals are not covered by the Animal Welfare Act.

All the animals with whom our investigator worked—with the exception of the minipigs—were subjected to oral gavage, subcutaneous injection and IV infusion methods of delivering test drugs. The gavage method can kill animals if the tube is accidentally placed in the animals' lungs instead of their stomachs. The pigs had a substance smeared on their skin. A room within the lab contains the unfortunate "practice" animals whom new staff members use to learn how to gavage.

The dogs at Inotiv


A lab worker forces a tube down a beagle's throat as part of a toxicity test.

Friendly, docile beagles wagged their tails as workers picked them up from their cages to gavage them. Despite knowing what was going to happen to them, the dogs could not resist human attention. Many dogs, especially the puppies, fought against the gavage tube but always lost the battle.

An average of 62,000 dogs per year are used in U.S. laboratories, according to USDA annual facility reports from 2008 to 2020, with an additional 38,000 bred or held at 350 laboratories owned by the government, universities or private companies, such as Inotiv.

Beagles are the dog of choice for use in laboratory testing because they are friendly and submissive. Inotiv bought beagles from Marshall Farms, a facility in upstate New York that has more than 20,000 dogs at any one time. Inotiv's subsidiary in Virginia breeds dogs for use in toxicity testing, but one Inotiv employee said the beagles from that facility "suck" because they are frightened and unsocialized.

During our investigation at Inotiv, beagles were killed for a new painkiller that was supposed to be non-addictive, a new medication for Cushing's disease, a cancer drug that reportedly caused diabetes, a drug for hepatitis B and other drugs that remain unknown. In all cases, the tests done were to determine whether, or at what point, these drugs caused toxic effects and did not determine whether the drugs worked to address those diseases or conditions. Most of the Inotiv workers administering the test substances to the dogs did not know the nature of the drug they were working with or its possible side effects.

A beagle in a range-finding toxicity study is dying on his kennel floor as the HSUS investigator tries to comfort him. Inotiv's veterinarian finally arrived the following day to put the beagle out of his misery.

In a study near the end of our investigation, 16 beagles, 5 months to 7 months old, were gavaged with an unknown substance that caused the highest-dose dogs to develop fevers, tremors, rapid heart rates, labored breathing and unsteadiness. Our investigator and their coworker summoned the veterinarian and the study director, who ruled that the affected dogs must be gavaged again despite the dramatic harmful effects of the test substance.

Two of the dogs had to be euthanized over the next two days and a coworker reported to our investigator what was happening to those dogs internally: "So, it's [messing] with their muscles and making them super big and spongy and discolored. And it's forming lesions on their stomachs. The one dog had a golf ball-sized clot in his heart. It's messing with the thymus gland . . . it pretty much wiped out their white blood cell count."

The dogs at this facility should not have had to endure pain and egregious suffering as long as they did. The Animal Welfare Act calls for minimization of pain and distress, and it is well known that establishing "humane endpoints" for every experiment conducted on animals is important both ethically and scientifically. In other words, a researcher or toxicologist must state at what point they will provide animals with either euthanasia or treatment to alleviate their suffering. An AAALAC inspection report that our investigator had access to during our investigation cited Inotiv for failure to establish humane endpoints.

An undercover investigator comforts one of the 80 puppies at Inotiv to be used in a toxicity test. The Humane Society of the United States is calling for the puppies' release.

As our investigator was preparing to leave Inotiv, two toxicity studies using 80 beagle puppies began. The fate of these dogs is of great concern due to the duration of the studies (one will last four months, the other nine months) and the number of puppies (32 and 48 respectively) who will endure daily oral gavage dosing and possible toxicity from the substance.

The HSUS is calling for the urgent release of these puppies, as the group of 32 puppies is scheduled to be euthanized in mid-May 2022. We are also calling on the lab to seek out alternatives and stop testing on all animals in this lab and find appropriate homes for them.

The primates at Inotiv

On a cold February day, our investigator helped unload approximately 80 young cynomolgus macaque monkeys shipped to Inotiv in a trailer that appeared to lack temperature control. The trailer in which the primates were stacked in wooden crates belonged to Quebedeaux Transport, LLC, the same company involved in a crash in Pennsylvania a month prior in which primates, also in wooden crates, were thrown out of a trailer pulled by a pickup and onto the highway. After the crash, three primates who had escaped their crates were shot and killed.

Primates used in studies at the lab will wear the collars for the rest of their lives.

Lab workers unload primates confined in wooden crates from a trailer after they were shipped to Inotiv.

At Inotiv after unloading, the terrified primates were sedated and fitted with restraining collars in what was, in all likelihood, a new and unwelcome experience for them. The collars are hard plastic or nylon, affixed around the animals' necks to enable workers to put the primates into "chairs" where the animals will be forcibly dosed. The collars stay on until the day the primates die in the lab.

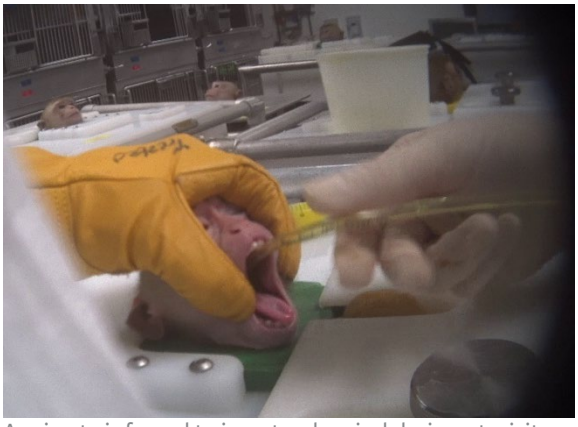
During our investigator's time at Inotiv, at least two primates died by hanging in the restraint chairs while they were reportedly left unattended.

Two newly arrived primates to Inotiv clutch each other for comfort after collars have been affixed to them.

These primates at Inotiv are locked into restraint chairs where they will be forcibly dosed for toxicity tests.

Like the dogs at Inotiv, most toxicity tests done on primates were via oral gavage. Other methods include intramuscular and intravenous administration.

In one primate toxicity study during the investigation, two females and one male in the high-dose group died within the first few days. Their body temperatures dropped dangerously low. Animal technicians at the lab said that mixing this drug with a sedative could have been the reason for the precipitous temperature drops and that this response happened in a previous study for the same drug. The investigator did not have access to post-study documents to confirm the technicians' accounts.



A primate is forced to ingest a chemical during a toxicity test at Inotiv.

A primate in a toxicity test at Inotiv is strapped down for an IV infusion of a substance.

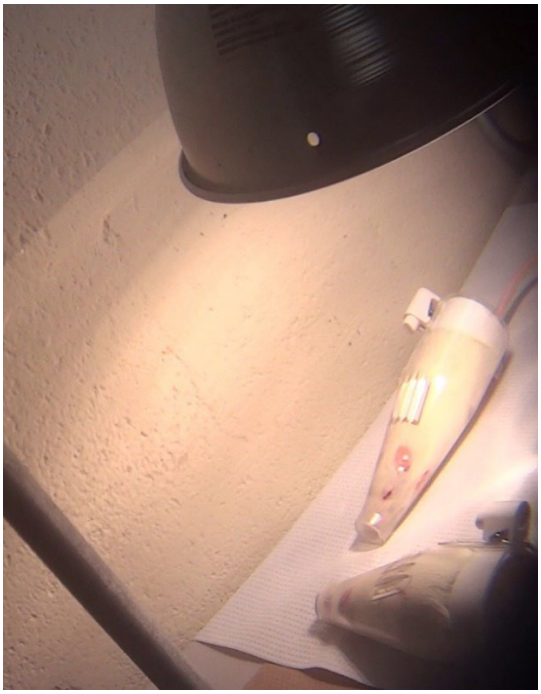
Overall, an average of 67,000 primates per year were used in laboratories, according to USDA annual facility reports from 2008 to 2020, with an additional 40,000 bred or held at approximately 200 laboratories owned by the government, universities, hospitals or private companies such as Inotiv.

The rats and mice at Inotiv

Birds, mice and rats bred for research purposes have no protection under the federal Animal Welfare Act, despite the fact that many lawmakers intended for their inclusion when the AWA went into effect in 1966. Laboratory mice, rats and birds were explicitly excluded from the act in 2002.

It is estimated that tens of millions of mice and rats are used for research and testing in the U.S. every year. Labs such as Inotiv give mice and rats a minimum of care. They are considered disposable even though their suffering is equal to that of a dog or primate. Our investigator saw mice and rats in clear distress, some with extremely large tumors, and no action taken to relieve their suffering.

At least one staff member confided in our investigator that these species at Inotiv got the short end of the stick when it came to veterinary care during toxicity studies.



Two rats in plastic restraint tubes wait to have blood drawn.

A "practice" rat at Inotiv suffers from a large tumor.

A better way forward for humans and animals

The Humane Society of the United States and Humane Society Legislative Fund are working hard to make testing on animals a thing of the past. Animal testing is a complicated issue that requires more than an investigation: Changes require a scientific paradigm shift and funding—all of which need the public's voice to accelerate.

Extensive evidence demonstrates that results from toxicity tests in animals, which are slow and expensive, don't accurately predict toxicity in humans and never will. Available technologies are superior to animal tests in terms of predicting toxic effects in humans. These approaches are often faster and less expensive than animal tests, and they are becoming increasingly sophisticated.

According to various external sources, including the Food and Drug Administration and the National Institutes of Health, approximately 90% of drugs first tested in animals ultimately fail in human trials, an estimated half of which are due to unexpected toxicity in humans following animal tests where toxicity wasn't observed.

We encountered a clear example of harm to humans after animal tests during our investigation. While tests for a drug were underway on primates and rodents at Inotiv, the pharmaceutical company that commissioned the tests announced it was ending development of the drug, which was intended for potential treatment of chronic hepatitis B, after it caused drug-induced liver toxicity in a human clinical trial, hospitalizing one patient. The drug had cleared previous animal tests with no such result. What if the company had used human liver chips instead? Could this suffering have been avoided?

Another drug used to treat hepatitis B, known as fialuridine, led to human harm after reliance on animal tests. Human clinical trials were discontinued when five of the 15 people in the trial died due to liver

failure and two people needed liver transplants. Animal testing data did not indicate liver toxicity. The drug was later tested using liver chips and shown to cause damage to the human liver chips even though it did not affect rat liver chips. If liver chips had existed at the time and been used, testing the drug in human liver chips instead of animals would have likely revealed the toxicity issues.

Every day that we continue to use animals for toxicity tests, we're causing needless animal suffering, potential harm to people from drugs that have been evaluated with unreliable methods and delays in bringing effective drugs to market.

Drug manufacturers and the FDA must act now. Without industries, regulators, NGOs and the public working together to demand more predictive and relevant non-animal testing methods, new drugs entering human trials will continue to reflect the current failure rate of 90%—a miserable track record that proves the current system of testing on animals isn't working.

We were pleased to see that President Biden's budget for fiscal year 2023 demonstrates movement away from animal use and toward human-relevant technologies, but all parties need to act with more urgency. We are calling on the FDA to:

- Make it clear that animal tests aren't required and that non-animal (new approach) methods will be considered as part of the decision-making process to approve new drugs for human use.
- Incentivize companies to use non-animal methods.
- Invest in continued development of non-animal methods to ultimately end animal testing.

Our goal in conducting investigations into what goes on behind the closed doors of contract laboratories is to make the public, private companies and regulators aware that testing on animals is cruel and ineffective. We must do better for humans and animals by moving away from animal testing and embracing 21st century technologies.