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Report to Congressional Requesters

September 2019

ANIMAL USE IN RESEARCH

Federal Agencies Should Assess and Report on Their Efforts to Develop and Promote Alternatives

GAO-19-629

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GAO Highlights

Highlights of GAO-19-629, a report to congressional requesters

September 2019

ANIMAL USE IN RESEARCH

Federal Agencies Should Assess and Report on Their Efforts to Develop and Promote Alternatives

Why GAO Did This Study

U.S. research facilities use a wide range of animal species in research, and some procedures used during such research cause animals pain or distress. Federal laws and principles require that researchers consider alternatives to animal use, such as *in vitro* methods and computer modeling. HHS, USDA, and EPA conduct and fund animal research and regulate products tested on animals. HHS and USDA also oversee federal and nonfederal research facilities including researchers' consideration of alternatives to animal use.

GAO was asked to review issues related to alternatives to animal research. This report (1) describes how HHS, USDA, and EPA ensure researchers consider the use of alternatives to animals and (2) examines the steps the agencies have taken to facilitate the use of alternative research methods and to assess the effect of their efforts on animal use. GAO reviewed documents, such as agency policies and practices relevant to the consideration of alternatives and interviewed agency officials. GAO also interviewed representatives of a nongeneralizable sample of 12 federal and nonfederal research facilities randomly selected across agencies and facilities.

What GAO Recommends

GAO recommends that HHS's National Institute of Environmental Health Sciences facilitate the establishment of an interagency workgroup to develop metrics for assessing progress on the development and promotion of alternatives to animal use and incorporate those metrics into public reports. HHS agreed with our recommendation.

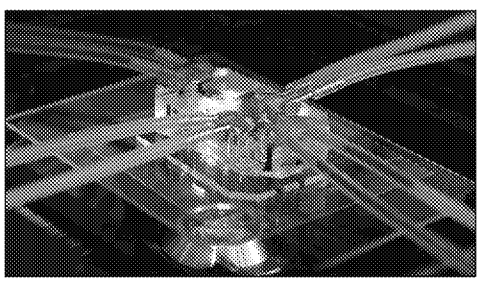
View GAO-19-629. For more information, contact Steve Morris at 202-512-3841 or morriss@gao.gov

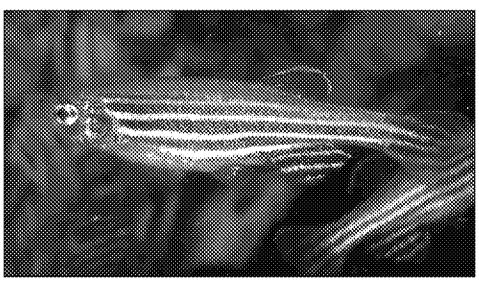
What GAO Found

The Department of Health and Human Services (HHS), U.S. Department of Agriculture (USDA), and Environmental Protection Agency (EPA) use a variety of methods to ensure researchers consider alternatives to animal use in research (see figure). Two of these methods are (1) requiring researchers to obtain approval of their research protocols, including their consideration of alternatives, from their institutions, and (2) calling for or recommending researchers to use database searches to identify alternatives. HHS and USDA also help ensure that researchers consider alternatives through the agencies' oversight of research facilities. For example, USDA is to conduct annual inspections of nonfederal research facilities. Futhermore, the agencies have provided training to researchers on the consideration of alternatives.

HHS, USDA, and EPA have facilitated the development and use of alternatives to animal use in research through individual and collaborative efforts. These efforts include agency strategies and policies for promoting the use of alternative methods and the development of testing methods that rely on non-animal models. Additionally, the agencies are members of the Interagency Coordinating Committee on the Validation of Alternative Methods, which is managed by HHS's National Institute of Environmental Health Sciences. The committee promotes testing methods that protect human health and the environment while reducing animal use. The interagency committee's 2018 strategic roadmap calls for it to identify appropriate metrics for monitoring progress and measuring success in adopting alternatives. However, the committee and its member agencies have not routinely developed or reported metrics that demonstrate how their efforts to encourage the use of alternative methods affect animal use. They have also not designated an interagency workgroup to address the challenges related to developing and reporting such metrics. Facilitating the establishment of such a workgroup would help the committee and its member agencies better monitor their progress across the range of their efforts to reduce animal use and report members' progress to the public.

Examples of Methods to Replace, Reduce, or Refine Animal Use in Research





Alternatives that replace, reduce, or refine animal use include tissue chips (left) that are lined with living cells and contain features designed to replicate the complex biological functions of specific organs, and zebrafish (right), which are inexpensive to house, reproduce quickly, and have transparent embryos in which biological functions are easily observed.

Sources: Wyss Institute for Biologically Inspired Engineering, Harvard University (left photo); https://www.goodfreephotos.com (right photo). | GAO-19-629

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Abbreviations

APHIS	Animal and Plant Health Inspection Service
ARS	Agricultural Research Service
CDC	Centers for Disease Control and Prevention
EPA	Environmental Protection Agency
FDA	Food and Drug Administration
HHS	Department of Health and Human Services
ICCVAM	Interagency Coordinating Committee on the Validation of Alternative Methods
NIH	National Institutes of Health
PETA	People for the Ethical Treatment of Animals
Tox21	Toxicology in the 21st Century Program
USDA	U.S. Department of Agriculture

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U.S. GOVERNMENT ACCOUNTABILITY OFFICE
441 G St. N.W.
Washington, DC 20548

September 24, 2019

Congressional Requesters

U.S. research facilities use a wide range of animal species in research, testing, teaching, and experimentation, and some procedures used in such research produce pain or distress in the animals.[1] These procedures may include surgery, inhalation toxicity studies, studies involving tumor growth, and food or water deprivation or restriction. However, a growing number of alternatives are available that enable researchers to replace, reduce, or refine their use of animals.[2] Researchers and agencies may seek to develop and use alternatives for several reasons, including the desire to promote animal welfare, the potential to provide more accurate information about human diseases or health than animal research can provide, and the potential to conduct research at a lower cost and in a shorter time frame than with research using animals. Alternatives that may replace animals or reduce their use in research include *in vitro* methods (i.e., testing cells and tissues in test tubes or other chambers) and computer modeling in biomedical research or drug safety testing. Alternatives that may refine animal use include surgical methods that minimize or eliminate pain and distress and adjustments that improve animals' psychological and behavioral welfare such as enhancements to housing conditions.

Federal agencies are involved in animal research in several ways. Agencies such as the National Institutes of Health (NIH) within the Department of Health and Human Services (HHS) and the Agricultural Research Service (ARS) within the U.S. Department of Agriculture (USDA) conduct or fund research using animals to answer important questions about human or animal health. Other agencies, such as the Environmental Protection Agency (EPA) and HHS's Food and Drug

[1]Our report focuses on federal and nonfederal research facilities and does not generally distinguish between research, testing, teaching, and experimentation activities; we use the term "research" to encompass all these activities. In addition, we use the term "facilities" to encompass all entities that conduct research, including entities that others refer to as institutions in certain contexts.

[2]In this report, we use the term "researcher" to refer generally to individuals who work with animals in research, testing, teaching, or experimentation. The work conducted by these individuals may be governed by different laws and policies, depending on the type of activity in which the individuals are engaged.

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Administration (FDA), regulate products that are tested for safety or efficacy using animals and conduct research to support regulatory activities. In addition, USDA's Animal and Plant Health Inspection Service (APHIS) and NIH are responsible for overseeing the welfare of certain species of animals used for certain types of research.

Federal laws, regulations, and policies that govern how animals are to be used and cared for call for the consideration of alternatives to animal research. In particular, the Animal Welfare Act, administered by APHIS, calls for the Secretary of Agriculture to establish standards for animal care, treatment, and practice that minimize pain and distress of animals in research facilities and directs that such standards require researchers to consider alternatives to any procedure likely to produce pain or distress in an experimental animal.[3] The act's implementing regulations also require that research facilities provide annual reports to APHIS containing assurances that each of their researchers considered alternatives to painful procedures. Similarly, under the Health Research Extension Act of 1985, applicants for funding from NIH and other HHS agencies covered by the act must provide certain assurances to NIH for research on animals. These assurances include that researchers involved with animal care, treatment, and use have available to them instruction or training in the concept, availability, and use of research or testing methods that limit the use of animals or limit animal distress.[4]

Furthermore, in 1985, federal agencies that use or require the use of experimental animals adopted certain principles that apply when agencies develop requirements for testing, research, or training procedures involving the use of vertebrate animals and whenever these agencies actually perform or sponsor such procedures.[5] Among other things, these

[3]7 U.S.C. §2143(a)(3)(B). The act applies this requirement to principal investigators, which the implementing regulations define as an employee of a research facility or other person associated with a research facility who is responsible for a proposal to conduct research and for the design and implementation of research involving animals. We refer to principal investigators as researchers in this report.

[4]The Health Research Extension Act applies this requirement to scientists, animal technicians, and other personnel; we refer to these individuals as researchers in this report.

[5]The U.S. Government Principles for the Utilization and Care of Vertebrate Animals Used in Testing, Research, and Training were developed in 1985 by the Interagency Research Animal Committee. Vertebrate species are distinguished by the possession of a backbone or spinal column and include mammals, birds, reptiles, amphibians, and fishes.

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principles call for researchers to use the minimum number of animals required to obtain valid results and to consider alternative methods such as mathematical models, computer simulation, and *in vitro* biological systems. The principles call for researchers to consider alternatives regardless of whether the procedures cause pain or distress to the animals.

Federal agencies also have undertaken various efforts to further develop and promote alternatives to animal research. For example, in June 2018, EPA issued a strategic plan for the reduction of testing in vertebrates for chemicals that the agency regulates under the Toxic Substances Control Act. In addition, the National Institute of Environmental Health Sciences within NIH manages the Interagency Coordinating Committee on the Validation of Alternative Methods (ICCVAM), which is composed of officials from U.S. federal regulatory and research agencies that require, use, generate, or disseminate toxicological and safety testing information.[6] One of the committee's purposes is to reduce, refine, or replace the use of animals in testing where feasible.

We have previously reported on the use of animals in federal research. In May 2018 we issued a report on selected agencies' reporting and sharing of information on their animal use programs.[7] You also asked us to review federal agencies' efforts related to the use of alternatives to animals in federal research. This report (1) describes how HHS, USDA, and EPA ensure that researchers consider the use of alternatives to animals and (2) examines the three agencies' efforts to facilitate the use of alternative research methods and assess the effect of their efforts on animal use.

To conduct our work, we selected agencies and offices within HHS, USDA, and EPA that conduct or fund research using animals, regulate products that may be tested using animals, or have an oversight role in relation to the Animal Welfare Act or Health Research Extension Act.

[6]ICCVAM members are the Agency for Toxic Substances and Disease Registry and the National Institute for Occupational Safety and Health within the Centers for Disease Control and Prevention; the Consumer Product Safety Commission; the Departments of Agriculture, Defense, Energy, Interior, and Transportation; EPA; FDA; NIH and several of its components: the National Cancer Institute, National Institute of Environmental Health Sciences, and National Library of Medicine; the National Institute of Standards and Technology; and the Occupational Safety and Health Administration.

[7]GAO, *Animal Use in Federal Research: Agencies Share Information, but Reporting and Data Quality Could Be Strengthened*, GAO-18-459 (Washington, D.C.: May 31, 2018).

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Based on our review of documents from and interviews with agency officials, we selected the following agencies and offices that have a role in animal research and are relevant to our review:

- HHS's Centers for Disease Control and Prevention (CDC), FDA, and NIH;
- USDA's ARS, APHIS, and National Institute for Food and Agriculture; and
- EPA's Office of Research and Development, Office of Science Coordination and Policy, and Office of Chemical Safety and Pollution Prevention. The latter includes the Office of Pesticide Programs and Office of Pollution Prevention and Toxics.

To describe how EPA, HHS, and USDA ensure researchers consider the use of alternatives to animals, we reviewed federal statutes, regulations, policies, principles, and guidance governing animal research funded or overseen by federal agencies, including:

- the Animal Welfare Act and USDA's regulations and guidance for implementing the act;
- the section of the Health Research Extension Act that pertains to animal care, NIH's policy for implementing that section of the act—the Public Health Service Policy on Humane Care and Use of Laboratory Animals (Public Health Service Policy)[8]—and related NIH guidance;
- U.S. Government Principles for the Utilization and Care of Vertebrate Animals Used in Testing, Research, and Training, developed by the Interagency Animal Research Committee; and
- the *Guide for the Care and Use of Laboratory Animals* published by the National Academies of Sciences, Engineering, and Medicine (National Academies).

We reviewed documentation from APHIS and NIH on their implementation of requirements and guidance for researchers to consider

[8]HHS's Public Health Service has a policy requiring institutions to establish and maintain proper measures to ensure the appropriate care and use of all animals involved in research, research training, and biological testing activities conducted or supported by the service. The Public Health Service endorses the U.S. Government Principles for the Utilization and Care of Vertebrate Animals Used in Testing, Research, and Training, developed by the Interagency Research Animal Committee. The Public Health Service Policy is intended to implement and supplement those principles.

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alternatives. In particular, we reviewed APHIS's inspection guide and obtained copies of citations agency inspectors issued to research facilities for noncompliance with the Animal Welfare Act requirement to consider alternatives. We also reviewed NIH's template for site visit questions. In addition, for each of the selected agencies and offices within HHS, USDA, and EPA, we reviewed documentation on their oversight of research, in particular researchers' consideration of alternatives.

We interviewed APHIS and NIH officials directly responsible for overseeing compliance with the Animal Welfare Act or the Health Research Extension Act regarding the agencies' oversight of animal research. In particular, we discussed researchers' consideration of alternatives to animal research and the agencies' procedures for and results from conducting inspections or site visits at research facilities in fiscal years 2015 through 2018.

To learn more about researchers' consideration of alternatives to animal research, we reviewed documents from and interviewed members of animal care and use committees and other representatives from a nongeneralizable sample of 12 research facilities—six federal facilities and six nonfederal facilities—that conduct animal research.[9] To select the six federal facilities, we randomly selected one facility each from APHIS, ARS, CDC, EPA, FDA, and NIH. We selected these facilities from among the agency components that agency officials identified as performing the most animal research. To select the six nonfederal facilities, we obtained a list of research facilities that were registered with APHIS as of September 26, 2018. We randomly selected from this list facilities that (1) had an assurance under the Health Research Extension Act approved by NIH as of September 26, 2018, and (2) were shown in publicly available federal databases as having received federal funding from EPA, HHS, or USDA at some point from 2015 through 2018. We used these criteria to select facilities that interacted with at least one of the federal agencies in our scope. We then interviewed the chair and other members of each facility's animal care and use committee about the process each committee uses to determine that researchers adequately consider

[9]Under the Animal Welfare Act and its implementing regulations, research facilities are to appoint an animal care and use committee to, among other things, review research proposals to determine whether the proposed activities are in accordance with the act. In particular, the committees are to determine whether researchers have considered alternatives to procedures that may cause more than momentary or slight pain or distress to animals and have provided a written narrative description of the methods and sources used to determine that alternatives were not available.

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alternatives to animal use. We then performed a content analysis of the officials' responses to our questions. The views of these representatives are not generalizable to all research facilities that perform animal research but provide examples of how federal and nonfederal research facilities have addressed requirements to consider alternatives. We also obtained copies of the protocol forms that the 12 facilities require their researchers to use to describe their planned use of animals and consideration of alternatives, and we compared the ways in which the forms require researchers to document how they identified and considered alternatives.[10]

To examine the efforts of HHS, USDA, and EPA to facilitate the use of alternative research methods and assess the effect of their efforts on animal use, we identified and reviewed statutes directing agencies to develop alternatives to animal research or plans for increasing the use of alternatives. In addition, we reviewed agency documentation related to each agency's efforts to facilitate the use of alternatives, including strategic plans, regulations and guidance regarding the review of the safety and efficacy of products, and information published on agency websites and in agency reports on alternatives the agencies have developed. We interviewed officials from HHS, USDA, and EPA and their component agencies and offices to identify illustrative examples of efforts to develop new alternative methods or promote the use of alternative methods by others. During our interviews with representatives from the 12 selected research facilities, we asked for their views on agencies' efforts to facilitate the use of alternative research methods, challenges the agencies face in developing or promoting alternatives, and how researchers at the institutions obtain information on alternatives. To describe interagency collaboration to facilitate the use of alternative research methods, we reviewed documents from ICCVAM, such as its website and 2018 strategic roadmap, and documents on the Toxicology in the 21st Century Program.[11] We also interviewed agency officials about their efforts to collaborate with other agencies and nongovernmental organizations.

[10]The animal use protocol is a detailed description of the proposed use of laboratory animals; researchers prepare these protocols for review and approval by animal care and use committees.

[11]The program is a collaborative effort among NIH, FDA, and EPA to characterize the potential toxicity of chemicals by using cells and isolated molecular targets instead of laboratory animals.

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For additional context on both objectives, we interviewed officials from organizations that we identified through our document reviews and interviews and that represent researchers, advocate for animal welfare or the use of alternatives to animal research, provide training or guidance on animal research, or have a role in ensuring the humane treatment of animals used for research.[12] In addition, we attended meetings related to animal research or the development of alternatives, including the 2018 national meeting of the American Association for Laboratory Animal Science, a one-day series of presentations in November 2018 sponsored by the Center for Alternatives to Animal Testing at the Johns Hopkins University Bloomberg School of Public Health, and a May 2019 ICCVAM public forum with presentations by member agencies.

We conducted this performance audit from June 2018 to September 2019 in accordance with generally accepted government auditing standards. Those standards require that we plan and perform the audit to obtain sufficient, appropriate evidence to provide a reasonable basis for our findings and conclusions based on our audit objectives. We believe that the evidence obtained provides a reasonable basis for our findings and conclusions based on our audit objectives.

Background

Federal agencies conduct a variety of activities related to animal research. These activities include:

- funding intramural research conducted by agency personnel at federal facilities;
- funding extramural research conducted by universities, industrial firms, and other nonfederal entities through contracts, grants, or cooperative agreements;
- establishing guidelines for regulating products that may have been tested for safety or efficacy using animals; and
- overseeing the welfare of animals used for research.

[12]These organizations were AAALAC International, the Alternatives Research and Development Foundation, the American Anti-Vivisection Society, the American Association for Laboratory Animal Science, the Collaborative Institutional Training Initiative, the Federation of American Societies for Experimental Biology, the Humane Society of the United States, the International Foundation for Ethical Research, the Johns Hopkins University Center for Alternatives to Animal Testing, the National Association of Biomedical Research, the National Academy of Sciences Institute for Laboratory Animal Research, and the Physicians Committee for Responsible Medicine.

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Table 1 shows key activities related to animal research or use that HHS, USDA and EPA and their component agencies and offices are involved in through their funding of intramural and extramural research and regulation of products.

Table 1: Key Activities of HHS, USDA, and EPA Related to Animal Research or Use

Agency/office	Key activities related to animal research or use
Department of Health and Human Services (HHS)	
Centers for Disease Control and Prevention (CDC)	Conducts research using animals at five CDC centers and institutes. Funds extramural research that may use animals.
Food and Drug Administration (FDA)	Conducts research using animals at seven FDA centers. Funds extramural research that may use animals. Uses animal testing data to regulate products, including food, drugs, biological products, medical devices, and tobacco products under the Federal Food, Drug, and Cosmetic Act and the Public Health Service Act.
National Institutes of Health (NIH)	Conducts research using animals at 23 NIH institutes and centers. Funds extramural research that may use animals. *Office of Laboratory Animal Welfare.* Provides guidance and interpretation of the Public Health Service Policy on Humane Care and Use of Laboratory Animals, supports educational programs, and monitors compliance with the policy by research institutions that receive funding from agencies covered by the policy.
U.S. Department of Agriculture (USDA)	
Animal and Plant Health Inspection Service (APHIS)	*Animal Care*. Ensures humane treatment of animals covered by the Animal Welfare Act. *Wildlife Services.* Conducts research using animals at nine APHIS facilities. Funds extramural research that may use animals. *Veterinary Services*. Conducts research using animals at two APHIS laboratories. Uses animal testing data to regulate veterinary products such as vaccines.
Agricultural Research Service (ARS)	Conducts research using animals at 38 ARS facilities. *Animal Welfare Information Center.* Helps facilities regulated under the Animal Welfare Act with employee training and promotes the humane care and use of animals by providing information on alternatives that can reduce or replace animal use or minimize pain and distress to animals.
National Institute of Food and Agriculture	Funds extramural research that may use animals.
Environmental Protection Agency (EPA)	
Office of Research and Development	Conducts research using animals at three EPA laboratories. Funds extramural research that may use animals.
Office of Science Coordination and Policy	Coordinates the development and validation of animal and non-animal methods used to screen pesticides and other chemicals for endocrine disruption under the Federal Food, Drug, and Cosmetic Act.
Office of Chemical Safety and Pollution Prevention	*Office of Pesticide Programs*. Uses animal testing data submitted by pesticide registrants to regulate pesticides under the Federal Insecticide, Fungicide, and Rodenticide Act. *Office of Pollution Prevention and Toxics*. Uses animal testing data submitted by chemical manufacturers or found in public sources to evaluate and regulate, if necessary, chemicals under the Toxic Substances Control Act.

Source: GAO analysis of information from EPA, HHS, and USDA. | GAO-19-629

Note: Extramural research is conducted by an institution other than the funding agency, for example, a university or industrial firm.

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Some agencies within USDA and HHS have roles in overseeing animal welfare at federal and nonfederal research facilities. Under the Animal Welfare Act and its implementing regulations, USDA's APHIS oversees federal and nonfederal research facilities to ensure the humane treatment of covered species of warm-blooded animals when they are used in research, teaching, testing, or experimentation. These species include dogs, cats, nonhuman primates, guinea pigs, hamsters, rabbits, horses used for research purposes, and (with certain exceptions) other warm-blooded animals.[13] Requirements under the act related to consideration of alternatives to animal research include the following:

- Under the act, research facilities are to appoint an animal care and use committee to, at least semiannually, review the facility's program for humane care and use of covered animals, inspect all facilities, and prepare reports of its evaluation.[14] The committee is responsible for reviewing research proposals to determine whether the proposed activities are in accordance with the act. This includes a review of research proposals to determine whether researchers have (1) considered alternatives to procedures that may cause more than momentary or slight pain or distress to covered animals and (2) have provided a written narrative description of the methods and sources they used to determine that alternatives were not available. The committee can ask a researcher to explain why any alternatives found are not used in the researcher's proposal or withhold approval of the proposal.
- Facilities that used or intended to use live covered animals in research are to submit a retrospective annual report about those animals to APHIS on or before December 1 of each calendar year. In particular, the annual

[13]The Animal Welfare Act's definition of "animal" excludes birds, rats of the genus *Rattus*, and mice of the genus *Mus* when those animals are bred for use in research. The act also excludes horses not used for research purposes; other farm animals used or intended for use as food or fiber or in certain types of research; cold-blooded animals such as fish, reptiles, or amphibians; and invertebrates.

[14]Under the Animal Welfare Act and its implementing regulations, an animal care and use committee shall be composed of a chair and at least two additional members. Of the three or more committee members, at least one shall be a doctor of veterinary medicine, with training or experience in laboratory animal science and medicine, and this person shall have direct or delegated program responsibility for activities involving animals at the research facility. Additionally, at least one member shall not be affiliated in any way with the facility other than as a member of the committee and shall not be a member of the immediate family of a person who is affiliated with the facility.

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reports are to include an assurance that each researcher considered alternatives to painful procedures.

HHS's NIH is responsible for establishing guidelines implementing certain provisions of the Health Research Extension Act of 1985. NIH's responsibilities under the act include reviewing federal and nonfederal research facilities' vertebrate animal care and use programs to determine whether they meet relevant standards and are thereby eligible to receive funding from HHS agencies covered by the act, including NIH.[15] NIH implements the animal care provisions of the act through its Public Health Service Policy.[16] The policy's requirements related to research facilities' consideration of alternatives include the following:

- Consistent with the act, NIH's Public Health Service Policy directs facilities to provide for NIH's approval a document that describes their vertebrate animal care and use program and that provides assurances that the research institution meets applicable standards. Such assurances must include a synopsis of training or instruction in research or testing methods that minimize the number of vertebrate animals required to obtain valid results and minimize animal distress and that the facility offers to scientists, animal technicians, and other personnel involved in animal care, treatment, or use.
- As a condition of receiving funding for animal research from HHS agencies, facilities must, for the most part, adhere to the eighth edition of

[15]The Public Health Service Policy defines animals as any live, vertebrate animal used or intended for use in research, research training, experimentation, or biological testing or for related purposes.

[16]In addition to NIH, the agencies covered by the Public Health Service Policy include the Agency for Healthcare Research and Quality, Agency for Toxic Substances and Disease Registry, Centers for Disease Control and Prevention, Food and Drug Administration, Health Resources and Services Administration, Indian Health Service, and Substance Abuse and Mental Health Services Administration. The requirement to provide assurances to NIH also covers activities conducted or supported by the Department of Veterans Affairs, the National Aeronautics and Space Administration, and the National Science Foundation under memoranda of understanding or interagency agreements between these agencies and NIH. USDA's National Institute for Food and Agriculture directs that its grantees, including other federal agencies, have an approved animal welfare assurance on file with NIH.

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the *Guide for the Care and Use of Laboratory Animals (Guide)*.[17] The Guide states that in preparing and reviewing research protocols, researchers and animal care and use committees should consider the availability or appropriateness of using less invasive procedures, other species, isolated organ preparation, cell or tissue culture, or computer simulation. The Guide does not limit this to research that is painful or distressful.

NIH conducts site visits at selected research facilities to assess compliance with the act. Whereas the Animal Welfare Act applies to certain warm-blooded animals, the definition of animals used for the purposes of the Health Research Extension Act covers all vertebrates, including the mice, rats, and fish species commonly used in laboratory research.

Other Relevant Legislation

Other laws relevant to the consideration of alternatives include the following:

- The National Institutes of Health Revitalization Act of 1993 directs the Director of NIH to prepare a plan to conduct or support research into methods of biomedical research and experimentation that do not require the use of animals, that reduce the number of animals used in such research, and that produce less pain and distress in such animals. The act also directs NIH to prepare a plan for establishing the validity and reliability of the new methods it develops, encouraging the scientific community's acceptance of these methods, and training scientists in using such methods. The act further directs NIH to periodically review this plan and, as appropriate, make revisions and include those revisions in a biennial report. In response to the act, in September 1994 NIH established ICCVAM as an ad hoc committee.
- The ICCVAM Authorization Act of 2000 directed NIH to establish the ICCVAM as a permanent interagency committee under NIH's National Toxicology Program Interagency Center for the Evaluation of Alternative

[17]National Academy of Sciences, National Research Council, *Guide for the Care and Use of Laboratory Animals: Eighth Edition* (Washington, D.C.: The National Academies Press, 2011). The stated purpose of the *Guide* is to assist institutions in caring for and using animals in ways judged to be scientifically, technically, and humanely appropriate. The *Guide* is also intended to assist researchers in fulfilling their obligation to plan and conduct animal experiments in accordance with the highest scientific, humane, and ethical principles.

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Toxicological Methods.[18] ICCVAM is administered by the National Institute of Environmental Health Sciences. The act specifies that ICCVAM be composed of the heads (or their designees) of 15 agencies or subagencies, including EPA, agencies within HHS, and USDA. The National Institutes of Standards and Technology joined voluntarily in 2016. The act directed ICCVAM to, among other things, review and evaluate alternative test methods that may be acceptable for specific regulatory uses and to prepare biennial progress reports. Under the act, an alternative test method is one that reduces the number of animals required; refines procedures to lessen or eliminate pain or distress to animals or enhances animal well-being; or replaces animals with non-animal systems or one animal species with a species presumed to have less ability to feel pain, such as replacing a mammal with an invertebrate. In January 2018, ICCVAM published a strategic roadmap articulating its vision to meet its purpose.

- The Frank R. Lautenberg Chemical Safety for the 21st Century Act amended the Toxic Substance Control Act in 2016 to include language on the use of alternative methods. The act directs the Administrator of EPA to reduce and replace, to the extent practicable, scientifically justified, and consistent with the policies of the Toxic Substances Control Act, the use of vertebrate animals in the testing of chemical substances or mixtures under the Toxic Substances Control Act. The act also directs the Administrator to develop a strategic plan to promote the development and implementation of alternative test methods and strategies to reduce, refine, or replace vertebrate animal testing.

[18]The Interagency Center for the Evaluation of Alternative Toxicological Methods is an office of the National Toxicology Program that focuses on the development and evaluation of alternatives to animal use for chemical safety testing.

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Table 2: Selected Federal Laws and Principles Related to Alternatives to Animal Research

Selected laws and principles	Relevance to alternatives to animal research
Animal Welfare Act (1966; last amended in 2014)	For covered species of warm-blooded animals, the act requires that (1) researchers consider alternatives to procedures that may produce pain or distress to an animal covered by the act and (2) institutions conducting experiments on animals establish animal care and use committees to, among other things, ensure researchers consider alternatives.
Health Research Extension Act (1985)	Under the act, applicants for funding from the National Institutes of Health (NIH) must provide an assurance that researchers involved with vertebrate animal care, treatment, and use have available to them instruction or training in the concept, availability, and use of research or testing methods that limit the use of animals or limit animal distress.[a]
National Institutes of Health Revitalization Act of 1993	The act directed NIH to prepare a plan to conduct or support research into methods of biomedical research that do not require the use of animals, that reduce the number of animals used, or that reduce pain and distress in animals; establish the validity and reliability of those methods; encourage the scientific community to accept such methods; and train scientists in their use.
ICCVAM Authorization Act of 2000	The act directed NIH to designate the Interagency Coordinating Committee on the Validation of Alternative Methods (ICCVAM) as a permanent committee with the purpose of, among other things, reducing, refining, or replacing the use of animals in testing, where feasible. ICCVAM is to prepare and make publicly available biennial reports on its progress under the act.
Frank R. Lautenberg Chemical Safety for the 21st Century Act (2016)	The act directed EPA to (1) reduce and replace, to the extent practicable and scientifically justified, the use of vertebrate animals in the testing of chemical substances or mixtures under the Toxic Substances Control Act; (2) develop a strategic plan to promote the development and implementation of alternative test methods and strategies to reduce, refine, or replace vertebrate animal testing; and (3) include a list in the strategic plan of scientifically reliable, relevant, and capable alternative test methods or strategies that do not require the use of vertebrate animal testing.
U.S. Government Principles for the Utilization and Care of Vertebrate Animals Used in Testing, Research, and Training (1985)	The principles were developed in 1985 and adopted by federal agencies that either develop requirements for or sponsor procedures involving the use of vertebrate animals. The principles call for researchers to use the minimum number of animals necessary and to consider alternative methods such as computer models.

Source: GAO analysis of laws, policies, and guidelines. | GAO-19-629

[a]NIH implements the animal care provisions of the Health Research Extension Act through its Public Health Service Policy. Under the policy, the requirement to provide an assurance to NIH also covers activities conducted or supported by the Department of Veterans Affairs, the National Aeronautics and Space Administration, and the National Science Foundation under memorandums of understanding or interagency agreements between these agencies and NIH. The U.S. Department of Agriculture's National Institute for Food and Agriculture requires that its grantees, including other federal agencies, have an approved animal welfare assurance on file with NIH.

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HHS, USDA, and EPA Have Used a Variety of Methods to Ensure Researchers Consider Alternatives to Animals

Methods HHS, USDA, and EPA have used to ensure that researchers consider alternatives to animal research include requiring researchers to describe and document their consideration of alternatives. In addition, USDA's APIHS and HHS's NIH help ensure that researchers consider alternatives by overseeing research facilities and these facilities' animal care and use committees, including the committees' review of animal research protocols. USDA and NIH also provide training to researchers and animal care and use committees to help ensure researchers have considered alternatives.

HHS, USDA, and EPA Call for Written Descriptions of the Consideration of Alternatives and Recommend a Method for Identifying Alternatives

For research that they conduct or fund, component agencies and offices within HHS, USDA, and EPA call for individual researchers to describe their consideration of alternatives to animal research. USDA's APHIS and HHS's NIH require research facilities to consider alternatives through the agencies' implementation of the Animal Welfare Act regulations and Public Health Service Policy, respectively. EPA research is covered by the two laws to the extent that it uses animals covered by the Animal Welfare Act or Health Research Extension Act. Table 3 summarizes the factors that determine whether researchers are required under the acts to consider alternatives.

Table 3: Factors Affecting Whether Researchers Are Required to Consider Alternatives to Animal Research

Factors	Consideration of alternatives under the Animal Welfare Act and implementing regulations[a]	Consideration of alternatives under the Health Research Extension Act and relevant policy[a]
Species of animal used	Required for warm-blooded species covered by the act, but not for mice, rats, and birds bred for research; cold-blooded vertebrates such as fish; and invertebrates.	Required for all vertebrate animals.
Nature of procedures used	Required for procedures that cause more than slight or momentary pain or distress.	Required for all procedures, regardless of pain or distress.
Funding source	Required regardless of funding source.	Required for research facilities seeking funding from agencies covered by the policy
Type of research facility	Required for both federal and nonfederal research facilities.	Required for both federal and nonfederal research facilities.

Sources: GAO analysis of the Animal Welfare Act and the Public Health Service Policy on Humane Care and Use of Laboratory Animals. | GAO-19-629.

[a]In certain situations, researchers are not required to consider alternatives to animal use. For example, a private research facility would be exempt from the Animal Welfare Act by using animals not covered by the act and would be exempt from the Health Research Extension Act by not requesting funding from agencies covered by the Public Health Service Policy on Humane Care and Use of Laboratory Animals.

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The steps HHS, USDA, and EPA take to help ensure that agency researchers and the researchers that they fund or oversee meet the requirement to consider alternatives include (1) calling for written descriptions of researchers' consideration of alternatives and (2) prescribing or recommending that researchers use searches, such as of databases of published scientific literature, to identify alternatives.

- **Call for written descriptions.** As specified in the Animal Welfare Act regulations and Public Health Service Policy, HHS, USDA, and EPA call for researchers to send written descriptions of research projects involving animals to animal care and use committees for their review and approval. In particular, the Animal Welfare Act regulations require these committees to determine that researchers have provided a written narrative description of the methods and sources they used to determine that alternatives were not available. The Public Health Service Policy requires that researchers' institutions submit written descriptions of research projects to the committees and for the committees to determine that researchers' procedures avoid or minimize discomfort, distress, and pain to animals, consistent with sound research design, among other things, and that researchers follow the U.S. Government Principles for the Utilization and Care of Vertebrate Animals Used in Testing, Research, and Training. The principles require the consideration of alternatives. In our review of protocol forms from our sample of 12 research facilities (including HHS, USDA, and EPA facilities), we found that all of the forms requested information on researchers' consideration of alternatives, though the forms varied in the particular information they requested. The types of information requested included a rationale for involving animals and for the number of animals to be used, assurance that research activities do not unnecessarily duplicate previous experiments, and a description of the methods and sources used to determine that alternatives were not available. Several of the protocol forms required researchers to identify alternatives considered but not adopted.
- **Recommended method for identifying alternatives.** In their implementation of the Animal Welfare Act and Health Research Extension Act, respectively, USDA and NIH consider database searches as a best practice for researchers using animals covered by the acts to identify and consider alternatives to animal testing. A database search involves a researcher using keywords related to the planned use of animals to query citations in databases of published scientific literature. From April 1997 through July 2018, USDA maintained a policy, known as Animal Care Policy #12, in its animal care policy manual. In Policy #12, the agency recommended a database search as the most effective and

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efficient method for demonstrating compliance with the requirement to consider alternatives to painful or distressful procedures.[19] According to USDA's Deputy Administrator responsible for implementation of the Animal Welfare Act regulations, in July 2018, USDA placed the policy in inoperative status after determining that some research facilities and agency inspectors had misinterpreted the policy as a requirement. Moreover, in response to the 21st Century Cures Act, USDA is reviewing its animal care policy manual, including Policy #12, to ensure the policies in the manual conform with the Animal Welfare Act and its implementing regulations, harmonize with NIH guidance, and reduce researcher burden where possible.[20]

According to the Deputy Administrator, as of June 2019, USDA had not decided what, if anything, it would do to revise or replace Policy #12. According to a draft interagency report in response to the 21st Century Cures Act, USDA will make any revised and future policies involving the use of animals available for public comment using regulations.gov or a similar service.[21] However, according to the Deputy Administrator, even though Policy #12 is inoperative, USDA continues to advocate for database searches, particularly through the USDA Animal Welfare Information Center's provision of information to the scientific community about how to search for alternatives.[22] According to a senior NIH official, NIH requires that agency researchers conduct database searches. Also, in a sample animal study proposal form NIH has provided to animal care and use committees, NIH recommends that researchers at other facilities conduct database searches. Furthermore, 11 of the 12 research facilities

[19]According to the inoperative policy, a search of one database is seldom adequate, and in some circumstances (as in highly specialized fields of study) conferences, subject expert consultants, or other sources may provide information on alternatives in lieu of or in addition to a database search.

[20]The 21st Century Cures Act directs NIH, in collaboration with USDA and FDA, to review applicable regulations and policies for the care and use of laboratory animals and make revisions, as appropriate, to reduce administrative burden on researchers while maintaining the integrity and credibility of research findings and protection of research animals. The act also requires NIH to identify ways to ensure regulations and policies are not inconsistent, overlapping, or duplicative.

[21]21st Century Cures Act Sec. 2034(d) Working Group, *Reducing Administrative Burden for Researchers: Animal Care and Use in Research*, Draft Report (November 2018). The agencies requested public comments on the draft report and received comments both in support of and critical of database searches as a method to identify alternatives.

[22]The information center trains researchers on how to conduct database searches and conducts searches at their request.

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we reviewed (including HHS, USDA, and EPA facilities) used research protocol forms that required or recommended that their researchers conduct a database search for alternatives to animal research.[23]

Agencies may apply additional requirements to individual researchers at their own facilities or through grants they fund, in addition to applying the requirements of the Animal Welfare Act and Health Research Extension Act. For example, CDC's Fort Collins, Colorado, facility requires researchers to provide assurance on their protocol forms that the facility's animal care and use committee's statistician reviewed the form to determine whether the research would use an appropriate number of animals or explain why a review of the number of animals did not occur. Similarly, the Chairman of APHIS's National Wildlife Research Center committee told us that its animal care and use committee includes a biostatistician who conducts an analysis to ensure that the numbers of animals to be used will produce statistically significant results. USDA's National Institute for Food and Agriculture requires applicants for funding from the agency's Agriculture and Food Research Initiative Competitive Grants Program to use statistical power analysis, when appropriate, to determine the sample sizes of animals to be used in research. USDA officials told us that this type of analysis provides a justification for the number of animals needed to provide valid results and helps prevent the unnecessary use of animals.

Agencies may also require information on animal use in proposals submitted by extramural researchers. For example, NIH instructs researchers to describe the use of animals in their work in a section of grant applications, contract proposals, and cooperative agreements. Specifically, when submitting a proposal, researchers must justify to agency officials and other reviewers that the species used is appropriate for the proposed research and explain why research goals cannot be accomplished using an alternative model, such as computational, human, invertebrate, or *in vitro* models.

[23]The results of our sample of 12 research facilities are not generalizable to all research facilities.

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APHIS and NIH Oversee the Review and Approval of Animal Research Protocols by Animal Care and Use Committees

APHIS and NIH help ensure that researchers consider alternatives through the agencies' oversight of research facilities and these facilities' animal care and use committees, including the committees' review of animal research protocols. In particular, APHIS collects and reviews annual reports from federal and nonfederal research facilities in which the facilities are required to provide an assurance that researchers considered alternatives. The Animal Welfare Act requires APHIS to annually inspect nonfederal research facilities to determine whether the facilities are in compliance with the act.[24] As part of a facility inspection, APHIS inspectors are to examine whether researchers have met the requirement to consider alternatives to any procedure likely to produce pain in or distress to species of animals covered by the act.

According to APHIS officials, inspectors examine a sample of approved animal research protocols to check whether the protocol forms include a written narrative on the consideration of alternatives and to ensure that the facility's animal care and use committee approved the protocol forms. The inspectors may issue citations of noncompliance if they find inadequate documentation that researchers associated with one or more protocols considered alternatives to procedures that may cause more than momentary or slight pain or distress to animals. APHIS provided us with inspection reports for fiscal years 2015 through 2018 in which inspectors issued 57 citations to research facilities for noncompliance with the Animal Welfare Act regulations that require researchers to consider alternatives to animals or issued "teachable moments."[25] The inspection reports included some citations that, according to APHIS officials, were incorrectly issued because inspectors interpreted the Policy #12 recommendations on database searches as requirements.

[24]APHIS officials have the authority to inspect nonfederal research facilities, records, and animals to enforce the provisions of the act. The Animal Welfare Act does not expressly provide APHIS the authority to inspect federal research facilities, and APHIS will not do so unless invited. In February 2016, APHIS and ARS signed a memorandum of understanding through which ARS agreed to register its research facilities with APHIS and APHIS agreed to inspect ARS facilities.

[25]According to APHIS officials, APHIS inspectors began to issue teachable moments in fiscal year 2016 for issues that do not adversely impact animal welfare and that meet certain other criteria. According to APHIS's Animal Welfare Inspection Guide, teachable moments are minor noncompliance items identified during an inspection that meet certain criteria, and these items are not cited on the inspection report that APHIS posts on its website. At the next inspection, however, an APHIS inspector will confirm if corrective action was taken. In contrast, a citation of noncompliance is documented on the inspection report along with a date by which the institution must take appropriate corrective action.

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In addition, NIH's Office of Laboratory Animal Welfare is responsible for the general administration and coordination of the Public Health Service Policy and provides specific guidance, instruction, and materials to research facilities that receive funding from agencies covered by the act. For all such facilities, NIH is to review the facilities' assurance documents describing their animal care and use programs. In particular, the Animal Welfare Assurance document is to describe the procedures—including review of animal research protocols—that the animal care and use committees follow to fulfill the directives of the NIH Public Health Service Policy. Further, NIH conducts site visits at a small number of facilities. The Public Health Service Policy states that each awardee institution is subject to review at any time by agency staff and advisors to assess the adequacy and accuracy of the institution's compliance or expressed compliance with the policy, and this review may include a site visit. According to NIH officials, when agency staff conduct site visits, they examine the facility's protocol form to confirm that its animal care and use committee requests information from researchers about their consideration of alternatives. NIH officials may also examine a sample of approved protocol forms during a site visit. According to NIH officials, the Office of Laboratory Animal Welfare conducted 38 site visits in fiscal years 2015 through 2018 and found one deficiency related to the consideration of alternatives.

USDA and NIH Provide Training to Researchers and Facilities' Animal Care and Use Committees to Help Ensure Alternatives Are Considered

USDA and NIH have provided training to researchers and animal care and use committee members on the requirements of the Animal Welfare Act and the Health Research Extension Act. The training has addressed, among other things, the requirement to consider alternatives and has included advice on how to search for alternatives.

Through its Animal Welfare Information Center, USDA provides training on how to conduct database searches for alternatives to animal research and assists individual researchers with their literature searches.[26] According to USDA staff, the information center provides three workshops per year on meeting the requirements of the Animal Welfare Act, each

[26]The Animal Welfare Act directs the Secretary of Agriculture to establish an information service at the National Agricultural Library to work in cooperation with the National Library of Medicine to provide information that is pertinent to employee training, that could prevent unintended duplication of animal experimentation, and on improved methods of animal experimentation, including methods that could reduce or replace animal use and minimize pain and distress to animals. In response, USDA established the Animal Welfare Information Center in ARS.

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lasting a day and a half. The workshops are open to anyone working with animals in research, including scientists, veterinarians, librarians, and animal care and use committee members. The center also gives workshops upon request at specific facilities. Additionally, the center's website contains resources for conducting literature searches, and, according to a senior information center official, the center plans to put workshops into an online format that will be available upon demand. According to the official, the center conducted 137 database searches upon request in fiscal years 2014 through 2018.

NIH has also provided training on the consideration of alternatives to help researchers meet their requirements under the Health Research Extension Act.[27] For example, in 2014 NIH presented a webinar on searches for alternatives. The webinar, titled *Meeting Requirements for Alternatives Searches* and available on NIH's website, provides advice on how to conduct database searches. For example, the webinar provided advice on the timing of the search, the search strategy, and particular databases to use. In September 2015, NIH presented a webinar demonstrating how to use NIH's database of research projects to find researchers, projects, and publications that may help replace, reduce, and refine the use of animals in research.

The NIH Office of Laboratory Animal Welfare provides on its website a sample animal study protocol form that emphasizes database searches for any procedures that cause more than momentary or slight pain or distress to the animals. In addition, according to a senior official from the NIH office overseeing the agencies' intramural research using animals, researchers at NIH must complete an online course regarding animal use every 3 years. The course includes a section on replacing, reducing, and refining animal use and outlines how researchers are to report literature searches in order to show they considered alternatives.

[27]The Health Research Extension Act states that the Director of NIH shall require each applicant for a grant, contract, or cooperative agreement involving research on animals that is administered by NIH or any national research institute to include in its application or contract proposal assurances, satisfactory to the Director of NIH, that scientists, animal technicians, and other personnel involved with animal care, treatment, and use by the applicant have available to them instruction or training in the humane practice of animal maintenance and experimentation and the concept, availability, and use of research or testing methods that limit the use of animals or limit animal distress.

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HHS, USDA, and EPA Have Facilitated the Development and Use of Alternatives to Animals in Research but Have Not Consistently Assessed the Effect of Their Efforts

EPA, HHS, and USDA have facilitated the development, use, and promotion of alternative research methods through individual and collaborative efforts, including strategies for promoting the use of alternative methods and development of policies and guidance on alternative methods. The three agencies have also developed alternative research methods that rely on non-animal models and procedures to test how various products would affect humans. Additionally, the agencies have worked collaboratively with each other and with nonfederal stakeholders to promote alternative methods, in particular through ICCVAM, which is required to report to the public on its progress. However, ICCVAM and its member agencies have not routinely developed or reported metrics for assessing the effect that their efforts are having on animal use.

EPA and Agencies within HHS and USDA Have Issued Strategies, Policies, and Guidance on Alternative Research Methods

EPA has issued a strategic plan and FDA has issued a roadmap for the use of methods that may reduce animal use in assessments of the safety and efficacy of various products. Both agencies and others within HHS and USDA have also issued guidance on using alternatives to animal research in particular contexts, such as vaccine testing.[28]

Strategic Plan and Guidance for Reducing Animal Testing for EPA-Regulated Toxic Chemicals and Pesticides

In June 2018, EPA's Office of Chemical Safety and Pollution Prevention issued a strategic plan for the reduction of vertebrate animal testing for toxic chemicals regulated under the Toxic Substances Control Act.[29] The office developed and issued this strategic plan to implement a provision in the Frank R. Lautenberg Chemical Safety for the 21st Century Act (Lautenberg Act) calling for such a plan.[30] The strategic plan describes a multi-year process with incremental steps for adopting and integrating methods that do not use vertebrate animals in evaluating chemicals regulated by the Toxic Substances Control Act for their effect on human

[28]Our report does not contain an exhaustive list of agencies' actions to promote the use of alternative research methods.

[29]Environmental Protection Agency, Office of Chemical Safety and Pollution Prevention, *Strategic Plan to Promote the Development and Implementation of Alternative Test Methods Within the TSCA Program* (Washington, D.C.: June 22, 2018). EPA's Office of Research and Development collaborated with the Office of Chemical Safety and Pollution Prevention to develop the plan.

[30]Frank R. Lautenberg Chemical Safety for the 21st Century Act, Pub. L. No. 114-182, § 130 Stat. 448 (2016).

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health and the environment.[31] The strategic plan states that the agency's long-term goal is to reduce and eventually eliminate vertebrate animal testing for chemicals regulated under the act.[32] Pursuant to the strategic plan, in June 2018 EPA published a list of methods the agency had identified that require no vertebrate testing and that are capable of providing information of equivalent or better scientific reliability and quality than that which would be obtained from vertebrate animal testing. According to EPA, the agency plans to update the list at least once a year. EPA's strategic plan calls for other near-term activities such as retrospectively identifying and evaluating the studies that it has requested and received for both new and existing chemicals. The plan states that EPA will complete this analysis in 2019 and use the results to support the future development of alternative methods to fit the agency's needs.

In May 2011, EPA's Office of Chemical Safety and Pollution Prevention issued a strategic plan in response to a 2007 National Academies report calling for a more efficient and informative risk assessment process to predict and characterize potential human health and environmental hazards from exposures to pesticides.[33] The office's strategic plan envisions using a combination of computational and predictive modeling approaches, *in vitro* techniques, and targeted in vivo testing to supplement or replace the existing toxicity tests required in federal regulations for pesticide registration under the Federal Insecticide, Fungicide, and Rodenticide Act.

Pursuant to this strategic plan, EPA's Office of Chemical Safety and Pollution Prevention has issued guidance on data requirements for assessing pesticide safety that may reduce animal use. For example, EPA issued guidance in May 2013 on the data that the agency needs in

[31]The plan refers to these methods as "new approach methodologies" and defines them as any non-animal technology, methodology, approach, or combination thereof that can be used to provide information on chemical hazard and risk assessment.

[32]EPA also stated that the use of the methodologies must be practicable, scientifically justified, and consistent with the policies of the Toxic Substances Control Act. EPA listed eight criteria in the plan for consideration of scientific reliability and relevance of new approach methodologies.

[33]Environmental Protection Agency, Office of Pesticide Programs, *Strategic Vision for Adopting 21st Century Science Methodologies* (Washington, D.C.: May 2011). National Research Council of the National Academies, *Toxicity Testing in the 21st Century: A Vision and a Strategy* (Washington, D.C.: National Academies Press, 2007).

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order to adequately assess pesticide risks.[34] The guidance also provided information to manufacturers on how to request waivers from the data requirements, which would enable the manufacturers to reduce animal use. EPA also issued guidance in November 2016 that allows pesticide manufacturers to request a waiver from the requirement to provide data on acute toxicity tests and that contains a policy statement waiving all acute lethality dermal studies for formulated pesticide products; such waivers can reduce the need for pesticide manufacturers to conduct tests using animals.[35] For example, EPA reported granting a total of 223 waivers in fiscal years 2016 and 2017, pursuant to the agency's May 2013 guidance for toxicity studies, which the agency estimated avoided the use of 85,000 animals and saved pesticide manufacturers $26.4 million in conducting toxicity studies.[36]

In February 2016, EPA announced an effort to evaluate and implement alternative methods for tests involving acute oral, dermal, and inhalation toxicity; skin and eye irritation; and skin sensitization.[37] As part of this effort, in April 2018, EPA issued a draft policy to reduce the use of animals in testing chemicals to evaluate whether they cause an allergic reaction, inflammation, or sensitization of the skin. EPA's policy describes conditions under which the Office of Chemical Safety and Pollution Prevention will accept alternative approaches to laboratory animal studies for identifying skin sensitization hazards.

[34]Environmental Protection Agency, Office of Pesticide Programs, *Guiding Principles for Data Requirements* (Washington, D.C: May 31, 2013).

[35]Environmental Protection Agency, *Guidance for Waiving Acute Dermal Toxicity Tests for Pesticide Formulations and Supporting Retrospective Analysis* (Washington, D.C.: Nov. 9, 2016).

[36]EPA reported these numbers to Congress in 2017 and 2018. See Environmental Protection Agency, *Implementing the Pesticide Registration Improvement Act–Fiscal Year 2017* (Washington, D.C.: Mar. 1, 2018) and *Implementing the Pesticide Registration Improvement Act–Fiscal Year 2016* (Washington, D.C.: Mar. 1, 2017).

[37]Environmental Protection Agency, Office of Pesticide Programs, *Process for Evaluating and Implementing Alternative Approaches to Traditional In Vivo Acute Toxicity Studies for FIFRA Regulatory Use* (Washington, D.C.: Feb. 4, 2016). This collection of six tests is often collectively referred to as the "six pack studies."

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Roadmap for Developing and Evaluating Tools for Assessing FDA-Regulated Products and Guidance for Industry

In December 2017, in response to direction from the FDA Commissioner, FDA developed a roadmap to foster the development and evaluation of emerging tools and methods that can improve toxicology methods for assessing the safety of FDA-regulated products.[38] The roadmap does not have an explicit goal to replace, reduce, or refine animal testing but states that new methods may have the potential to do so. In that regard, the roadmap states that FDA will encourage medical product sponsors to submit a scientifically valid approach for using a new method early in the regulatory process and to engage in frequent communication with the agency about the suitability of that method.[39] In addition, the roadmap recommended that FDA establish an organizing committee; conduct training; foster communication and collaboration with stakeholders, such as industry and academia; engage in research; and track and report annually on its progress. In June 2019, FDA posted its first annual report on its progress in implementing the roadmap.[40]

Previously, FDA had taken steps to reduce animal use by issuing guidance to members of industry seeking approval for FDA-regulated products. In general, FDA guidance states that industry may choose to use an approach—such as a non-animal testing method—other than one set forth in guidance as long as it complies with relevant statutes and regulations.[41] FDA has also taken more specific steps to modify guidance to promote the use of alternative methods. For example, in 2012, FDA issued guidance to industry that states that firms may use non-animal alternative methods to test the toxicological safety of pharmaceutical drugs if the methods are appropriate or scientifically justified.[42] In 2013, FDA issued guidance that, among other things, allowed industry to use *in*

[38]Food and Drug Administration, *FDA's Predictive Toxicology Roadmap* (Washington, D.C.: December 2017). FDA-regulated products include human and animal drugs, medical devices, food and food ingredients, and biological and tobacco products.

[39]Medical product sponsors include drug, biological product, and medical device sponsors.

[40]Food and Drug Administration, Toxicology Working Group, *FDA's Predictive Toxicology Roadmap: 2018 Annual Report*, accessed September 9, 2019, https://www.fda.gov/science-research/about-science-research-fda/fdas-predictive-toxicology-roadmap.

[41]21 C.F.R. § 10.115(d)(1), (2).

[42]Food and Drug Administration, *Guidance for Industry: S6 Addendum to Preclinical Safety Evaluation of Biotechnology-Derived Pharmaceuticals* (Washington, D.C.: May 2012).

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vitro assays[43] rather than mice to detect toxins in shellfish meant for human consumption; this guidance subsequently played a role in the adoption of additional methods that do not employ animal use.[44]

Other HHS and USDA Agencies' Guidance on the Use of Alternatives to Animal Research

Other HHS and USDA agencies within our scope do not have strategic plans or roadmaps that promote a comprehensive strategy for alternative research methods, but some of the agencies have issued guidance to their own researchers or to regulated entities that may reduce animal use. For example, in 2017, APHIS updated its guidance to allow manufacturers of animal vaccines, inactivated bacterial products, and antibody products to request an exemption to animal safety testing if the products have a documented history of acceptable safety results and controlled manufacturing processes that ensure batch consistency and sterility.[45] APHIS also issued a notice in 2017 of a testing option that can reduce by up to 50 percent the number of hamsters required for potency testing of vaccines for the bacterial disease leptospirosis, according to the notice.[46] In addition, APHIS issued memorandums in 2013 and 2015 that provide guidance on *in vitro* techniques that researchers may use instead of animals to test the potency of vaccines.[47]

Some agencies have also adopted alternative methods for their researchers without issuing specific guidance to do so. For example, in September 2018, CDC began routine use of an *in vitro* procedure developed by the agency that allows its laboratories to test for botulism in

[43]An assay is a quantitative or qualitative procedure for detecting the presence, estimating the concentration, or determining the biological activity of a macromolecule, such as an antibody or antigen, molecule, or pathogen.

[44]Food and Drug Administration, *National Shellfish Sanitation Program (NSSP): Guide for the Control of Molluscan Shellfish 2013 Revision* (Washington, D.C.: 2013). The NSSP is a cooperative program between FDA and the Interstate Shellfish Sanitation Conference. According to FDA officials, the agency was involved in the adoption of other alternative methods that have been approved for use in detecting shellfish toxins and listed in subsequent versions of the NSSP.

[45]U.S. Department of Agriculture, Veterinary Services, *Target Animal Safety Testing Exemption*, Memorandum No. 800.116 (Washington, D.C.: Aug. 14, 2017).

[46]U.S. Department of Agriculture, Animal and Plant Health Inspection Service, *Option to Remove Back-titration Hamsters from In Vivo Potency Tests for Leptospira Serogroups Pomona and Grippotyphosa*. CVB Notice 17-06 (Washington, D.C.: Apr. 21, 2017).

[47]U.S. Department of Agriculture, Veterinary Services, *Exemption from Leptospira Bacterin Testing Under 9 CFR 113.101-104 and the Associated References and Studies*, Memorandum 800.102 (Washington, D.C.: Dec. 12, 2013) and *Guidelines for Validation of In Vitro Potency Assays*, Memorandum 800.112 (Washington, D.C.: Apr. 10, 2015).

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human serum specimens without using mice. CDC officials stated that this method is fast and inexpensive and would reduce the need for hundreds of mice. CDC officials told us that their researchers plan to expand use of the *in vitro* procedure to test other types of specimens, further reducing the use of animals.

HHS, USDA and EPA Have Developed Alternative Research Methods

HHS, USDA, and EPA have made multiple efforts to develop alternative research methods that, according to the agencies, have reduced animal use or have the potential to do so. Some of these efforts target reducing the use of animals in a particular research context while others have broader applications in toxicology and computer modeling. In some cases, agency officials provided estimates of how their targeted efforts have reduced or may reduce animal use. Examples of targeted efforts include the following:

- CDC researchers told us they have evaluated a method that reduces the number of animals and time needed to produce kits that are distributed worldwide to identify influenza virus subtypes and thereby aid in strain selection for the influenza vaccine each season. Under the original method, antibodies for the kits were generated from blood samples in sheep that were later euthanized. The CDC researchers concluded that an alternative automated method that draws antibody-rich plasma from goats instead of blood from sheep could reduce the time needed to produce the kits and require fewer animals.
- According to FDA officials, FDA is collaborating with others on the development of an *in vitro* assay that will be used to test the potency of human rabies vaccines that manufacturers submit to FDA for approval. This new method will replace the animal-based assay that is part of the current license to manufacture rabies vaccine. The officials said that the animal-based assay uses 600 mice, on average, for each batch of vaccine submitted by a manufacturer.
- According to an ARS research paper, ARS worked with academic researchers to develop an *in vitro* method for feeding blood to ticks.[48] According to ARS officials, the method allows researchers to reduce the number of animals used when studying disease transmission in animals via tick-borne pathogens.

[48]Massaro W. Ueti et al., *Pathogen Isolation and Purification Using the In Vitro Tick Feeding System* (forthcoming).

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- APHIS currently holds federal pesticide registrations with EPA for active ingredients formulated into end-use products, such as rodenticides, that APHIS uses to prevent damage to agriculture, endangered species, or critical habitats. According to APHIS officials, the agency uses an EPA-approved method for testing the risks to human health from new pesticide products that substantially reduces animal use. The method generally involves progressively increasing the pesticide dose on a relatively small number of animals compared to the previous method and waiting to observe whether the dose causes mortality before deciding whether to increase the dose in further testing. APHIS officials said the new method reduces animal use by 50 percent or more per test.

EPA's Endocrine Disruptor Screening Program Uses Alternatives to Animals

Led by its Office of Science Coordination and Policy, EPA established the Endocrine Disruptor Screening Program in 1998 to fulfill a congressional mandate in the 1996 Food Quality Protection Act to develop a program to screen for certain chemicals (e.g., pesticides) that affect human hormones. EPA expanded the scope of the program to include screening the effects of chemicals on the human thyroid system and wildlife. The program began using automated, large-scale screening methods and computational models to evaluate and screen chemicals and, according to EPA, allows EPA to screen more chemicals in less time, use fewer animals, and reduce cost.

Source: Environmental Protection Agency (EPA). | GAO-19-629

Agencies' broader efforts include the integration of advances in biology, chemistry, and computer science into areas of research, such as toxicology, that currently rely heavily on animal use. For example, EPA launched the Toxicity Forecaster in 2007 as an effort to use automated technologies to expose living cells or isolated proteins to chemicals and screen the cells or proteins when exposed to chemicals for changes in biological activity that suggest potential toxic effects. According to EPA documents, these methods could limit the number of required laboratory animal-based toxicity tests while quickly and efficiently screening large numbers of chemicals.[49] According to EPA documents, in the first phase of this effort, which the agency completed in 2009, EPA evaluated more than 300 well-studied chemicals (primarily pesticides) that had extensive data from traditional animal-based toxicity testing; the agency then compared results from automated screening technologies with the results from the traditional animal tests. As of 2018, EPA had developed and made publicly available a library of toxicity data on more than 4,500 chemicals. The availability of the Toxicity Forecaster data has enabled EPA to reduce the need for animal testing in its Endocrine Disruptor Screening Program for identifying chemicals that may affect human hormone systems (see sidebar).

Similarly, FDA has initiated a broad effort to incorporate greater use of computer modeling and simulation into its decision-making on FDA-regulated products. For example, FDA formed an agency working group on modeling and simulation in 2017. According to the Chair of the working

[49]Environmental Protection Agency, Office of Research and Development, *Science in Action: Toxicity Forecaster (ToxCast)*, accessed September 6, 2019, https://www.epa.gov/sites/production/files/2019-01/documents/toxcast_factsheet_dec2018.pdf.

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group, it does not have an explicit objective to reduce animal testing, but such reduction is a potential benefit of the testing approaches the group is advancing. For example, the Chair said that modeling and simulation can help refine questions about products submitted for FDA approval and therefore could reduce the number of animal studies needed before clinical trials.

EPA and NIH have provided funding to extramural researchers to develop alternative research methods. For example, from 2013 through 2018, EPA provided $24 million in funding for research on 3-D models containing human cells (these devices are also known as tissue chips) that can be used for tests that otherwise might be conducted using animals. In 2018, EPA also announced $4.25 million in funding for research to promote the development and use of alternative methods that reduce, refine, or replace vertebrate animal use for toxicity testing. Similarly, in 2017, NIH awarded a $962,000 grant to a research facility to conduct studies of an *in vitro* human bronchial tissue model for predicting the toxicity of inhaled chemicals. Additionally, while USDA's National Institute for Food and Agriculture did not set aside a specific amount of funding, in May 2019 the agency made clear to applicants for its Welfare and Well-being of Agricultural Animals grant program that proposals that study ways to reduce the need for animals in research are eligible for funding in fiscal years 2019 and 2020.

HHS, USDA, and EPA Have Collaborated with Each Other and with Other Federal and Nonfederal Stakeholders to Promote Alternative Methods

HHS, USDA, and EPA have joined partnerships to develop, use, and promote alternative testing methods.[50] For example, the agencies participate in ICCVAM, which states that its mission is to facilitate the development, validation, and regulatory acceptance of test methods that replace, reduce, or refine the use of animals. ICCVAM itself does not conduct research or validation studies on alternative methods. Instead, it relies on stakeholders including federal agencies that generate, require, or use toxicological data; companies that develop toxicological tests; and animal welfare organizations. According to committee guidelines, stakeholders can submit the results of their research to ICCVAM, and the committee then conducts evaluations and makes recommendations on

[50]These efforts include collaborations with international organizations and foreign governments to promote alternative methods. However, this report focuses on agencies' domestic efforts to promote alternative methods.

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submissions for regulatory uses that align with the needs and priorities of member agencies.[51]

Zebrafish Are Used as Alternatives to Other Animals in Research

A zebrafish is a freshwater, tropical vertebrate fish that is widely used in pharmaceutical development and medical and scientific research due to certain qualities of its morphology and development as well as its inexpensive cost to use and maintain. Some of these qualities include genetic and structural similarities to other vertebrates that mimic human responses to certain genes involved in human diseases and its transparent embryonic development that enables researchers to use it as an alternative model for toxicity screening of drugs and chemicals. These qualities have led to the use of zebrafish embryonic models for automated, large-scale screening programs by the National Toxicology Program and the Environmental Protection Agency, among others.

Sources: National Institutes of Health; https://www.goodfreephotos.com (photo). | GAO-19-629

ICCVAM's website contains information on current ICCVAM-recommended protocols for specific test methods, such as methods to test for eye corrosion and irritation and skin sensitization, and on events organized by NIH and others that are relevant to the replacement, reduction, or refinement of animal use in research. For example, the website has a link to a page on NIH's website that has the slide presentations given at six webinars from 2017 through 2018 on the use of zebrafish in toxicology testing. Researchers may use zebrafish and their embryos in particular as a replacement for other animals, such as mice (see sidebar).

ICCVAM maintains on its website a list of 108 alternative methods that, as of June 2019, had been accepted by one or more federal agencies. These include methods that ICCVAM and its member agencies contributed to developing or validating.[52] However, according to ICCVAM's strategic roadmap issued in January 2018, the committee concluded that its evaluations of new methods during its first 15 years were lengthy, inefficient, and resource intensive. ICCVAM concluded that researchers and test method developers often initiated the development of alternative methods with little input from federal agencies or regulated industries and, therefore, these methods did not always meet the needs of federal agencies. Consequently, these methods were either not accepted by federal agencies or were accepted by the agencies but not used by the regulated community. Recognizing these limitations, ICCVAM initiated a strategic shift in 2013 aimed at adjusting the validation of new test methods to be more responsive to the needs of federal agencies and other stakeholders. Accordingly, ICCVAM's 2018 strategic roadmap set new objectives for reducing animal use, including the following:

- Connect the developers of alternative methods with the regulatory agencies and the regulated industries that would ultimately use the new

[51]National Institutes of Health, National Institute of Environmental Health Sciences, *ICCVAM Guidelines for the Nomination and Submission of New, Revised, and Alternative Test Methods* (Research Triangle Park, NC: September 2003).

[52]According to ICCVAM, the list contains methods for chemical safety testing that are accepted by U.S. and international regulatory authorities as replacement, reduction, or refinement alternatives to required animal tests. The list also includes guidance to support replacement, reduction, or refinement alternatives to animal use for required testing.

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technologies to increase the likelihood of the methods being successfully developed and implemented.

- Foster the use of efficient and flexible practices, such as public-private partnerships to promote communication and cooperation, to establish confidence in new methods.
- Encourage the adoption and use of new methods and approaches by federal agencies and regulated industries, such as through training programs on the use of new methods.[53]

ICCVAM has established workgroups to develop detailed implementation plans to address roadmap goals. According to the strategic roadmap, the implementation plans will include four key elements: (1) definition of testing needs; (2) identification of any available alternative tests and computer models; (3) a plan to develop integrated approaches to testing and assessment and defined approaches for interpreting data; and (4) a plan to address both scientific and nonscientific challenges, including regulatory challenges, such as international harmonization. As of June 2019, workgroups on acute systemic toxicity, eye and skin irritation, and skin sensitization had posted information concerning these elements on ICCVAM's website. For example, each workgroup authored an article published in a peer-reviewed journal and posted on the ICCVAM website about the testing needs of regulatory agencies and information about available alternatives.

Another interagency effort that has a goal of promoting the use of alternative methods is the Toxicology in the 21st Century (Tox21) Program. Formed in 2008, the program is a collaborative effort among NIH, FDA, and EPA to characterize the potential toxicity of chemicals by using cells and isolated molecular targets instead of laboratory animals. A central component of the program is its focus on developing and evaluating automated *in vitro* screening methods to assess the hazards of chemical substances. As of February 2018, the program had used this method to assess approximately 10,000 chemicals for their potential impacts on biological systems. According to NIH's Tox21 website, these automated methods have yielded high-quality toxicity data on environmental substances in a fraction of the time that would have been required with traditional animal testing. To address key challenges in toxicology testing, the program's federal partners developed a strategic

[53]Interagency Coordinating Committee on the Validation of Alternative Methods, *Strategic Roadmap for Establishing New Approaches to Evaluate the Safety of Chemicals and Medical Products in the United States,* January 2018.

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and operational plan in March 2018 that expanded the focus of Tox21's research activities to include developing alternative test systems that predict chemical toxicity in humans and addressing the technical limitations of and strengthening scientific confidence in current *in vitro* test systems.[54] According to NIH, activities under the plan will lead to better predicting chemical toxicity to humans through using non-animal alternatives such as stem cells and computational models.

Since 2011, federal agencies have also collaborated to develop devices containing human cells that can be used for tests that otherwise might be conducted using animals. See figure 1 for an example of such devices, known as tissue chips or human microphysiological systems. According to NIH officials, this evolving technology may reduce animal testing and produce results more relevant to human health. The interagency effort was initiated in September 2011 when the President announced the formation of a collaborative project between NIH, the Defense Advanced Research Projects Agency, and FDA to develop tissue chips loaded with living human cells to screen the efficacy, safety, and toxicity of drugs, vaccines, or biological products for humans. Subsequently, in July 2012, NIH launched the Tissue Chip for Drug Screening program, which provided 19 grants to research facilities to develop tissue chips that accurately model the structure and function of the human lung, liver, heart, and more. In September 2014, NIH announced a second phase of the program in which researchers would refine existing tissue chips and combine them into an integrated system that can mimic the complex functions of the human body. In one example of this collaboration, two project teams funded by the Defense Advanced Research Projects Agency—the Massachusetts Institute of Technology and the Wyss Institute at Harvard University—are working with NIH-funded researchers to develop platforms that integrate 10 tissue chips that each represent a separate human organ.

[54]Russell S. Thomas et al., *The US Federal Tox21 Program: A Strategic and Operational Plan for Continued Leadership,* ALTEX 35(2) (Mar. 8, 2018). doi: 10.14573/altex.1803011.

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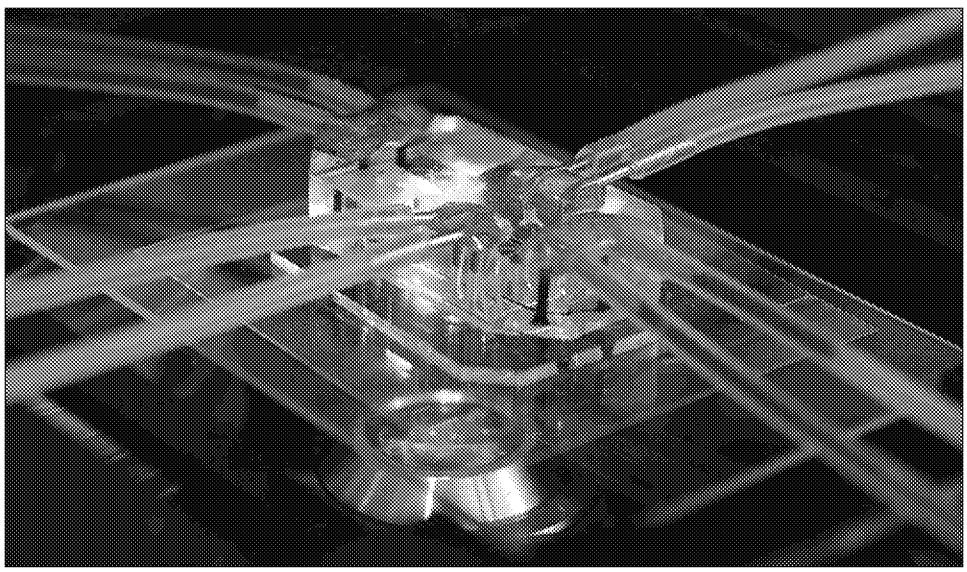
Figure 1: Example of a Tissue Chip



Tissue chips contain features designed to replicate the complex biological functions of specific organs.

Source: Wyss Institute for Biologically Inspired Engineering, Harvard University. | GAO-19-629

Federal agencies have also collaborated with nongovernmental organizations on training to promote the use of alternative methods. For example, NIH and the People for the Ethical Treatment of Animals (PETA) International Science Consortium offered a webinar series from March through September 2016 on alternative approaches for assessing acute inhalation toxicity.[55] Webinar presenters described alternative approaches for identifying substances likely to cause acute systemic toxicity through inhalation. Similarly, EPA collaborated with the PETA International Science Consortium and the Physicians Committee for Responsible Medicine on webinars in November 2018, February 2019, and April 2019 that addressed alternative methods for testing the effect of chemicals on skin, for predicting the effect of inhaled substances, and for identifying substances that cause irritation or inflammation in human respiratory systems.

[55]The PETA International Science Consortium is a conglomeration of PETA U.S., PETA U.K., and their affiliates.

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ICCVAM and Its Member Agencies Have Not Established a Workgroup to Develop Metrics on the Effect of Their Efforts on Animal Use

ICCVAM's strategic roadmap calls for its members to identify appropriate metrics for prioritizing activities, monitoring progress, and measuring success toward the goals described in the roadmap. However, ICCVAM and its member agencies have not routinely developed metrics that they could report to the public to demonstrate how their individual or collective efforts to encourage the use of alternative methods have affected or will affect animal use.

HHS, USDA, and EPA officials, as well as ICCVAM's roadmap, have cited challenges to measuring the results of ICCVAM and its member agencies' efforts. For example, according to agency officials, differences in the regulatory contexts in which agencies use data generated through animal research—for example, in regulation of pesticides versus human or animal drugs—limit agencies' ability to develop metrics that can be applied across multiple agencies. Furthermore, the ICCVAM roadmap states that measuring the actual impact of encouraging the adoption and use of new methods is difficult in the United States due to the limited ability to quantify animals used for toxicity testing. In particular, the Animal Welfare Act does not cover several species commonly used in research, including mice, rats, and birds bred for research and cold-blooded species such as fish. Therefore, research facilities are not required under the act to report their use of those species to APHIS, and the data APHIS receives from research facilities can only be used to track a subset of the total number of animals used for research in the United States.[56]

Although ICCVAM and its member agencies face challenges in developing metrics, the roadmap also states that agency-specific mechanisms to measure progress may exist, such as tracking the number of waivers granted for a particular animal test. For example, as discussed above, EPA has estimated the extent to which its granting of data waivers to pesticide manufacturers has reduced animal use and research costs. Additionally, some agencies have estimated the effect that a new alternative method could have on animal use. Moreover, officials from FDA and EPA said that their agencies are able to accept non-animal test data in lieu of animal test data if the data meet their regulatory needs. Measuring the frequency with which the agencies receive non-animal test data instead of animal data could be another mechanism for estimating changes in animal use.

[56]For more about the reporting requirements of the Animal Welfare Act, see GAO, *Animal Use in Federal Research: Agencies Share Information, but Reporting and Data Quality Could Be Strengthened*, GAO-18-459 (Washington, D.C.: May 31, 2018).

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In addition, the ICCVAM Authorization Act of 2000 requires ICCVAM to prepare biennial public reports on its progress under the act—including its efforts to ensure that new and revised test methods are validated to meet the needs of federal agencies and to reduce, refine, or replace the use of animals in testing, among other things. ICCVAM, with support from NIH's National Institute of Environmental Health Sciences, has issued the required biennial progress reports since 2001, including the most recent report issued in July 2018 that covers 2016 and 2017. However, the committee's biennial progress reports, including the July 2018 report, provide few quantitative or qualitative assessments of the progress the member agencies have made, individually or collectively, toward reducing, refining, or replacing animal use in testing.

ICCVAM's strategic roadmap states that it envisions that workgroups will play a key role in implementing the goals of the strategic roadmap, but ICCVAM has not designated a workgroup to address the challenges related to metrics, similar to other workgroups that the committee has established to address the roadmap's goals. According to officials from NIH's National Institute of Environmental Health Sciences, which manages the committee, the strategic roadmap is a work in progress and developing metrics is the third of three roadmap goals. The ICCVAM Authorization Act of 2000 does not provide the National Institute of Environmental Health Sciences with authority to direct agencies to develop and report metrics. However, agency officials agreed that ICCVAM could facilitate the establishment or designation of a workgroup of member agencies to identify a range of potential quantitative and qualitative metrics that member agencies could use to assess their progress toward reducing, refining, or replacing animal use. By establishing or designating such a workgroup to develop metrics that the agencies could use to assess their individual or collective progress toward reducing, refining, or replacing animal use in testing and by incorporating those metrics in ICCVAM's biennial progress reports, ICCVAM and its member agencies could better monitor progress across the range of the committee's efforts and report the members' progress to the public.

Conclusions

HHS, USDA, and EPA use a variety of methods to ensure that researchers—whether employed by or receiving research funding from these agencies—consider alternative methods to animal research. The agencies also have engaged in multiple efforts to expand the range of available alternatives. Under one of these efforts, ICCVAM's strategic roadmap calls for its members to identify appropriate metrics for prioritizing activities, monitoring progress, and measuring success. The

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roadmap envisions that workgroups will play a key role in implementing the goals of the strategic roadmap. However, ICCVAM has not designated a workgroup to address the challenges related to developing and reporting metrics. In addition, ICCVAM has issued the required biennial progress reports since 2001, but the reports provide few quantitative or qualitative assessments of the progress member agencies have made, individually or collectively, toward reducing, refining, or replacing animal use in testing. By establishing or designating a workgroup to develop metrics to assess the progress member agencies have made, individually or collectively, toward reducing, refining, or replacing animal use in testing and by incorporating those metrics in ICCVAM's biennial progress reports, ICCVAM and its member agencies could better monitor progress across the range of the committee's efforts and report the members' progress to the public.

Recommendation for Executive Action

The Director of the NIH's National Institute of Environmental Health Sciences should (1) facilitate the establishment or designation of a workgroup of representatives of ICCVAM member agencies to develop metrics that the agencies could use to assess the progress they have individually or collectively made toward reducing, refining, or replacing animal use in testing and (2) incorporate those metrics into the committee's biennial progress reports. (Recommendation 1)

Agency Comments and Our Evaluation

We provided a draft of this report to HHS, USDA, and EPA. HHS provided written comments on the draft, which are presented in appendix I. In its written comments, HHS stated that NIH concurred with our recommendation. NIH further commented that ICCVAM's activities in support of promoting alternatives for animal use in testing do not extend to animal use in any other context, such as research or training. NIH explained that our use of the terms research and researcher to refer more generally to research, testing, teaching, or experimentation could cause misunderstanding. We understand that ICCVAM's activities are focused on animal use in product testing. In addition, we intended our recommendation that the Director of the National Institute of Environmental Health Sciences facilitate the establishment or designation of an ICCVAM workgroup to be focused on product testing rather than on other types of animal research. However, for editorial reasons, we did not modify our report's use of the terms research or researcher.

HHS and EPA also provided technical comments, which we incorporated as appropriate. Among those comments, HHS's FDA officials stated that

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the agency encourages the use of alternatives to animal testing and supports the principles of replacement, reduction, and refinement, but if no alternative exists, animal testing may be the most appropriate way to meet certain regulatory requirements to ensure the safety and efficacy of medical products.

In its technical comments, EPA cited a September 2019, memorandum EPA's Administrator issued after we sent our draft report to the agencies for comment. The memorandum commits the agency to take several steps to reduce, replace, and refine animal testing requirements. For example, the Administrator committed EPA to reducing its requests for, and funding of, whole and live mammal studies by 30 percent by 2025 and eliminating all mammal study requests by 2035. We acknowledge EPA's announcement but did not assess it in our review of federal efforts to facilitate the use of alternative research methods.

We are sending copies of this report to the appropriate congressional committees, the Secretary of Agriculture, the Secretary of Health and Human Services, the Administrator of the Environmental Protection Agency, and other interested parties. In addition, the report will be available at no charge on the GAO website at http://www.gao.gov.

If you or your staff members have any questions about this report, please contact us at (202) 512-3841 or morriss@gao.gov or neumannj@gao.gov. Contact points for our Offices of Congressional Relations and Public Affairs may be found on the last page of this report. GAO staff who made key contributions to this report are listed in appendix II.

Steve D. Morris
Director, Natural Resources and Environment

John Neumann
Managing Director, Science, Technology Assessment, and Analytics

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List of Requesters

The Honorable Jeanne Shaheen
Ranking Member
Subcommittee on Commerce, Justice, Science, and Related Agencies
Committee on Appropriations
United States Senate

The Honorable Cory Booker
United States Senate

The Honorable Elizabeth Warren
United States Senate

The Honorable Betty McCollum
Chairwoman
Subcommittee on Interior, Environment, and Related Agencies
Committee on Appropriations
United States House of Representatives

The Honorable Ken Calvert
United States House of Representatives

The Honorable Raul Grijalva
United States House of Representatives

The Honorable Lucille Roybal-Allard
United States House of Representatives

The Honorable Dina Titus
United States House of Representatives

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Appendix I: Comments from the Department of Health and Human Services

DEPARTMENT OF HEALTH & HUMAN SERVICES

OFFICE OF THE SECRETARY

Assistant Secretary for Legislation
Washington, DC 20201

SEP 03 2019

Steven Morris
Director, Natural Resources and Environment
U.S. Government Accountability Office
441 G Street NW
Washington, DC 20548

Dear Mr. Morris:

Attached are comments on the U.S. Government Accountability Office's (GAO) report entitled, "*Animal Use in Research: Federal Agencies Should Assess and Report on Their Efforts for Developing and Promoting Alternatives*" (GAO-19-629).

The Department appreciates the opportunity to review this report prior to publication.

Sincerely,

Sarah Arbes
Acting Assistant Secretary for Legislation

Attachment

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GENERAL COMMENTS OF THE NATIONAL INSTITUTES OF HEALTH (NIH) ON THE GOVERNMENT ACCOUNTABILITY OFFICE (GAO) DRAFT REPORT ENTITLED: "ANIMAL RESEARCH: FEDERAL AGENCIES SHOULD ASSESS AND REPORT ON THEIR EFFORTS FOR DEVELOPING AND PROMOTING ALTERNATIVES" (GAO-19-629)

The National Institutes of Health (NIH) appreciates the review conducted by GAO and the opportunity to provide clarifications on this draft report. NIH respectfully submits the following general comments.

GAO Recommendation 1:
The Director of the National Institute of Environmental Health Sciences (NIEHS) should:

a. facilitate the establishment or designation of a workgroup of representatives of ICCVAM member agencies to develop metrics that the agencies could use to assess the progress they have individually or collectively made toward reducing, refining, or replacing animal use in testing and
b. incorporate those metrics into the committee's biennial progress reports.

NIH Response:
NIH concurs with GAO's finding and corresponding recommendation as stated above. NIEHS is reviewing the recommendation carefully and will provide an action plan to address the recommendation.

GAO Footnote 2, page 1:
In this report, we use the term "researcher" to refer generally to individuals who work with animals in research, testing, teaching, or experimentation.

NIH Response:
The editorial decision to conflate the wider range of animal use activities under the terms "researcher" and "research" in this draft may give rise to misunderstanding. For example, the second paragraph on page 1 that refers in its opening paragraph to "animal research" goes on to mention safety and efficacy testing as well as research. See also the first paragraph on page 3, which similarly mentions "alternatives to animal research" in the first sentence and then immediately points to the EPA strategic plan for reduction of animals in testing and the existence and mission of ICCVAM – which is focused solely on alternatives to animals in testing – as examples. While the difference may not seem material to the average reader, these different types of activities are undertaken for different reasons and have different policy governance issues.

NIEHS and NTP would like to make sure that there is no expectation that the activities of ICCVAM and NICEATM in support of the promotion of alternatives for animal use in **testing** would be expected to extend to responsibility for animal use in any other context, such as **research** or **training**.

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Appendix II: GAO Contact and Staff Acknowledgments

GAO Contacts

Steve D. Morris, (202) 512-3841 or Morriss@gao.gov

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Staff acknowledgments

In addition to the individuals named above, Joseph Cook (Assistant Director), Rodney Bacigalupo, Kevin Bray, Ross Campbell (Analyst-in-Charge), Tara Congdon, Hayden Huang, Amber Sinclair, and Kari Terrio made key contributions to this report.

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