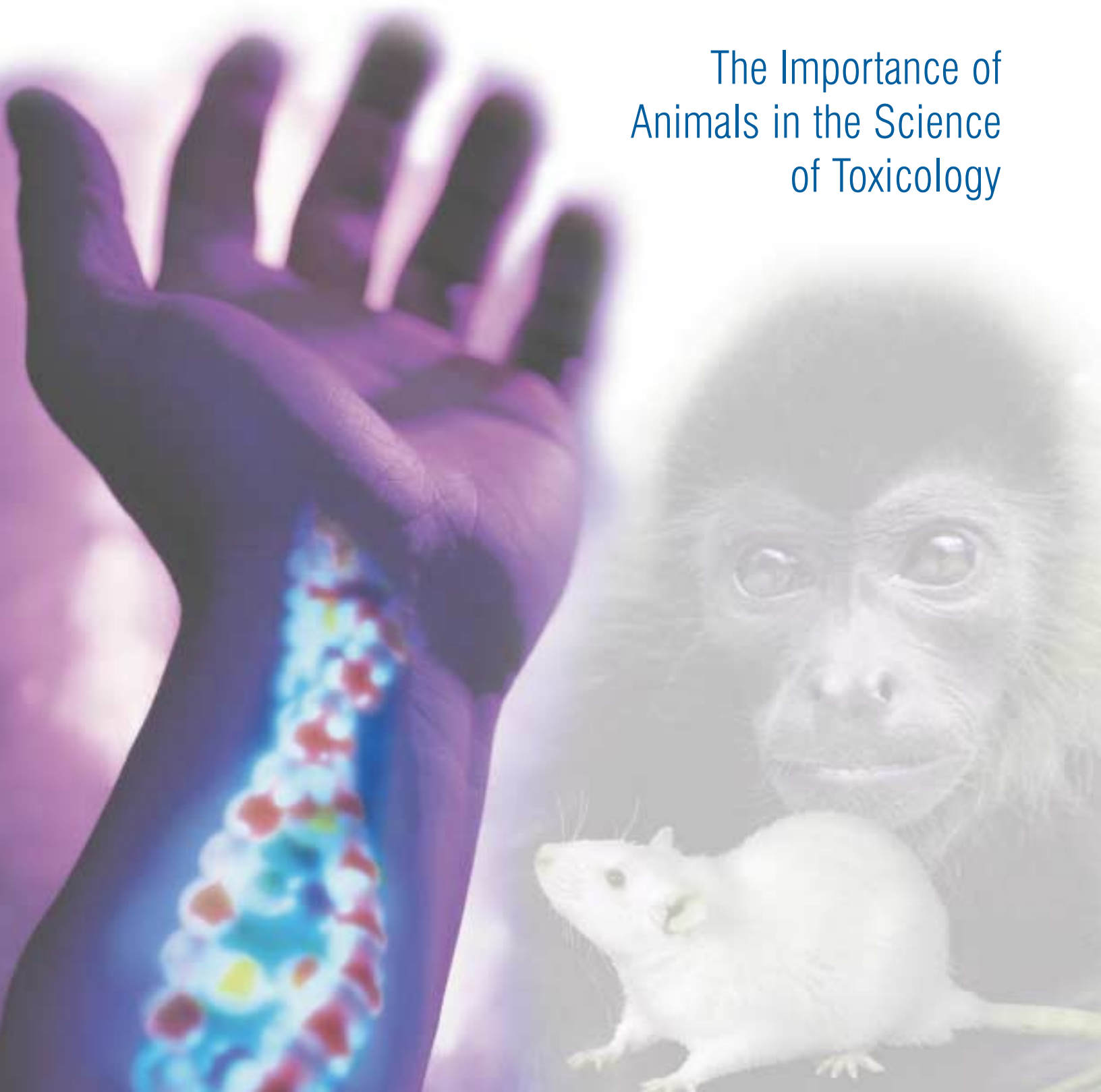


Animals in Research

The Importance of
Animals in the Science
of Toxicology



The Importance of Animals in Research • Society of Toxicology

- Research involving laboratory animals is necessary to ensure and enhance human and animal health and protection of the environment.
- In the absence of human data, research with experimental animals is the most reliable means of detecting important toxic properties of chemical substances and for estimating risks to human and environmental health.
- Research animals must be used in a responsible manner.
- Scientifically-valid research designed to reduce, refine or replace the need for laboratory animals is encouraged.

SOT Animals in Research Public Policy Statement 1999

6 Research involving laboratory animals is necessary to ensure and enhance human and animal health and protection of the environment. 9

SOT Animals in Research Public Policy Statement

Research involving laboratory animals is important to people and to our quality of life. In the past century, most inhabitants of this planet have experienced an unprecedented rise in living standards, life expectancy and personal opportunity, in large part due to the many ways chemicals have been put to work for us. For example, drugs whose effects range from curing previously fatal bacterial infections, reducing the impact of AIDS, minimizing heart disease, decreasing age-related wrinkles, to reducing hair loss are widely available today. The many benefits of the diverse uses of our natural resources are an outcome of careful scientific research and of using chemicals in an appropriate and safe manner. Toxicologists, the scientists who help determine the limits for safe use of materials, use modern technological research methods, including tests on animals, to protect human and animal health and the environment.

What is toxicology?

Toxicology is the study of how chemical substances interact with living systems and affect normal processes, and the use of this information to predict safe exposure levels. Toxicological research and testing helps us to live safely and to derive benefit from natural and synthetic substances while avoiding harm. Toxicologists are involved in the evaluation of household products, medicines and the effects of incidental and occupational exposure to natural and manufactured substances. Toxicology also helps us develop the best treatments in the event that accidental overexposure does occur.

What is safe?

Toxicologists know that no substance is risk-free. One fundamental tenet of the science of toxicology is that all

chemicals can cause harm at some level of exposure, summed up in the phrase "the dose makes the poison." This means that exposure to a specific small amount of any substance will have no detectable impact on normal biological processes and is considered safe. Some doses actually have beneficial effects, as we all know from use of medicines. But increasing exposure to most substances will, at some point, cause harmful effects. Substances are considered toxic at that level. For example, digitalis is a plant product that has been used with great benefit to treat heart irregularities, but too large a dose will cause death. Oxygen provides another example of how increasing the dose can turn a safe compound into a toxic one. Oxygen is essential to life and part of the air we breathe, but when given at high concentrations it can cause lung and eye damage in infants.

Sometimes the possible negative effects of a substance are outweighed by the positive benefits at that dose. Dogs are treated with heartworm medication because the risk of death from heartworms is much greater than the risk of toxicity of the medication. Similarly, chemotherapeutic agents are used to destroy cancerous cells even though they may damage healthy cells in the process.

Prior to the use of new substances, toxicologists and policy makers are responsible for determining the range of exposure that is safe and the level of exposure that may be harmful to human health or to the environment. The effect of the level of exposure is also important when toxicologists assess the risk caused by a substance already present in the environment. The benefits of using a new substance, or the costs of removing an environmental contaminant, are viewed relative to the perception of what is safe.

How do toxicologists determine which exposures may harm?

Toxicologists conduct basic research, using both whole animals and *in vitro* methods, to learn how various chemicals and dosages interact with living systems. Basic research is necessary to understand mechanisms that maintain living organisms and to determine baselines for physiological processes. For many chemicals that enhance the quality of our lives, the mechanism that produces the beneficial effect is the same mechanism that makes the chemical toxic. For example, aspirin reduces pain and fever by reducing the activity of enzymes in the body that normally increase production of compounds associated with pain and distress. However, acute toxicity can occur when the aspirin dose is so high that inhibition of similar enzymes in the heart interferes with normal function. Animal studies help determine the ratio between the beneficial dose and the toxic dose of medications.

Toxicologists determine which levels of a substance cause harm by conducting safety studies which progress from the test tube to animal studies and, in some cases, to human trials. Safety testing is needed to identify the crossover points between no impact, beneficial effects and harmful effects. For example, alcohol, when ingested, is taken directly into the bloodstream and blood levels rise in direct proportion to consumption. Many people enjoy the feeling produced by one alcoholic beverage and may consider that a beneficial effect. However, one drink, such as 12 ounces of beer, will impact motor skills and judgment. Two such drinks in a short interval result in a blood alcohol content of .08% in a 120-pound woman. Persons with levels above 0.08% ethanol in the bloodstream are considered too impaired to drive an automobile in many states. Further increases (above 0.4%) can lead to loss of consciousness and death.

Vitamins also illustrate the variation in effect depending upon the dose. Vitamins are essential elements that are not manufactured by the body and must be furnished from the outside, typically in the diet. In general, either vitamin deficiency or vitamins in excess can affect health and even cause birth defects. Birth defects such as spinal bifida are less likely to occur if the mother has a daily vitamin A intake of 5000 IU in advance of the pregnancy. However, women using one prescription treatment for acne that involves high doses (50,000 IU) of a form of this vitamin (isotretinoin) must take precautions to avoid pregnancy due to the risk of birth defects.

Safety evaluations establish a margin of safety to compensate for differences in response among individuals. For example, women in general are affected more by the same dose of alcohol than men are, not only because of smaller body size but also because alcohol is processed at different rates by men and women. Persons of differing ethnic heritages also metabolize ethanol at different rates.

Toxicologists use *in vitro* methods and animal models that have been accepted by the scientific community and recognized by regulatory bodies so that people who use and are exposed to a variety of chemicals can enjoy the benefits with a minimum of risk. Similarly, use of accepted tests protects other organisms, including pets and farm animals, as well as the environment.



- 6 In the absence of human data, research with experimental animals is the most reliable means of detecting important toxic properties of chemical substances and for estimating risks to human and environmental health. 9

SOT Animals in Research Public Policy Statement

What is necessary for basic research and safety testing?

Scientists need to study natural situations to understand life processes and to investigate how introducing a particular substance can change living systems. It is often helpful to break a process into steps and then investigate how introduction of the substance affects each step. This first stage in toxicity assessment takes place *in vitro*. The investigator can pinpoint the various changes that could occur when a compound encounters a living cell and then make safety recommendations. Only a few substances successfully pass these initial trials. Those substances must then be tested further. Humans and other living things—plants, animals, and even molds and bacteria—are complex systems. The processes in any organism are far more complicated than just the sum of the individual parts. It is difficult to replicate at the lab bench the complex interactions. When safety is not assured, ethical research procedures restrict testing on humans. Additional experiments must be performed using other animals first.

Why is there a need to use animals?

All organisms are composed of chemicals, and chemical reactions power all life processes. When a substance is introduced into an animal, it can interact in many places throughout the whole body, and effects upon one process can cause unexpected

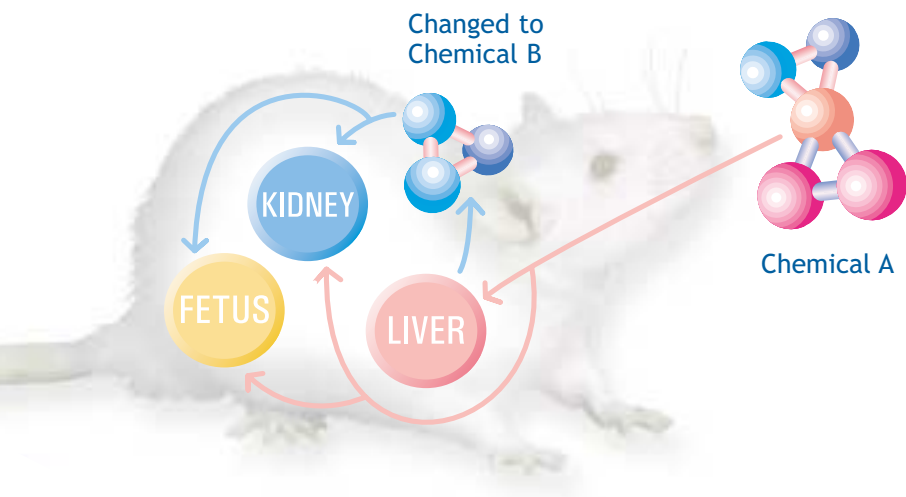
consequences in others (see diagram). Using animals in experiments is critical because such complexity cannot be duplicated in cell culture or in nonliving systems. For example, toxicity can be influenced by the speed with which the substance enters the system, how the liver and other organs change it and how it is taken up by and interacts with various body tissues. Some of the response is influenced by the tissue characteristics (e.g., liver is different than kidney tissue). Because "the dose makes the poison" at the level of the individual organ, we need to be able to analyze not only how a chemical acts, but the relationship between the dose given to the animal and the dose delivered to the different organs and tissues in the body. Studies in whole animals are required to ensure the proper use of beneficial chemicals such as medicines, because the tissue or organ receiving the beneficial effect might be harmed if exposures are greater than needed. In many cases, laboratory tools simply cannot duplicate these complicated phenomena. Ultimately, animal testing is the best method to detect effects such as cancer and birth defects.

Given the above, what is the responsibility of the toxicologist?

Scientists use whole living systems—animal models—in experiments to understand the relationships between exposure and effect, and to use them appropriately, responsibly and humanely. Data from these studies provide the essential foundation to distinguish and recommend which level of exposure is safe and which is harmful to people, animals and the environment.

What are the specific benefits of using animals in toxicology research?

Safe Products and Safe Medicines—Toxicology studies are crucial to the discovery and development of safe products such as new drugs, cleaning products, plastic food containers, flame-retardant infant clothing and food additives, to name a few. Toxicologists perform research in whole animals to ensure the short-term and long-term safety of such products before they are brought to market. If research on a new substance predicts significant risks to human or animal health, or to the environment, then that substance may never reach



Many complex interactions with a chemical can occur that can only be detected in a living organism.



the marketplace. Alternatively, animal safety studies in combination with relevant information in humans can demonstrate that lower doses of some medicines may produce the same beneficial effects with a reduction in side effects. Products previously available only by prescription can then be released. Recent examples include medicines used to treat inflammation and stomach ulcers. We all benefit from their increased availability and lower price as well as their pharmacologic properties. Animals also benefit from medicines originally developed for human use. In addition, research leads to useful safety and first aid label statements. These labels provide consumers with information to make wise choices about appropriate use. Toxicologists, using animal studies to validate results, provide a critical level of protection while enabling the use of products for an enhanced quality of life.

Avoiding Too Much of a Good Thing—All chemicals may cause harm, depending on the dose of the exposure. Toxicologists help determine the appropriate level of exposure, develop the understanding of how chemicals cause injury and, in addition, their studies provide treatment alternatives in the event of poisoning. Information

gained from research with animals is used by Poison Centers worldwide, where the majority of calls concern children under the age of five. How does a caregiver know what to do when a child drinks a household cleaner? The caregiver can call the Poison Center to learn the best action to take, based upon information from scientific studies conducted by toxicologists.

Safe Environment—Both animal and non-animal research is used to study the potential health problems associated with the world around us, including exposures to industrial processes, air pollution, soil and water contamination, hazardous waste and natural toxins. Toxicologists use these studies to determine how much of a substance is safe and how much might be hazardous. Use of lead in paints and gasoline resulted in high exposure to lead in homes and along highways. Studies with mice, for example, have demonstrated that even small amounts of lead can affect the nervous system and behavior. These effects were only evident in humans by subsequently conducting long-term studies that measured exposure in very large numbers of people. Then the importance of reducing lead exposure was clear.

Position Statement Regarding the Use of Animals in Toxicology

The Society of Toxicology is dedicated to the acquisition and dissemination of knowledge that improves the health and safety of humans and animals and the protection of their environment.

To fulfill this objective, the Society is committed to:

- the design and conduct of the best possible scientific research;
- the responsible use of laboratory animals in toxicological research and testing as necessary and vital to ensure and enhance the quality of human and animal health and the environment;
- the development and use of alternatives to the use of animals;
- the use of research designs that employ less painful or stressful procedures and improve animal care; and
- a reduction in the number of animals used for research and testing when this is scientifically appropriate and valid.

The Code of Ethics of the Society of Toxicology states that each member shall observe the spirit as well as the letter of the laws, regulations and ethical standards with regard to the welfare of humans and animals involved in any experimental procedures.

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Research is also necessary to reduce risk for workers who might be exposed to hazardous levels of a material in the workplace day in and day out. Animal studies can test for risk before humans are exposed to dangerous situations, or help establish which mechanisms result in damage when consequences in humans are suspected. The results of these toxicity screens can be used to restrict or eliminate occupational contact with chemicals and thus protect the health of workers. For example, research in the fast-moving semiconductor industry identifies many novel chemicals, including unusual metal compounds created for their reactive properties. Animal studies are necessary in order to make informed decisions about worker protection on the production line where these compounds would be used.

In the regulatory world, the results of whole animal testing are often used to disallow or tightly regulate the amount of chemical released from facilities that treat, store or dispose of hazardous waste. Decisions must also be made about environmental remediation of possible contaminants. Human risk and hazard criteria for what constitutes a safe level of exposure to a possible environmental hazard are derived from *in vitro* and animal studies. Toxicologists establish the relationship between exposures received by animals and those received by humans in order to interpret test results and predict risk. This in turn helps regulatory agencies to prioritize funding for environmental clean up.

Accurate assessment of risk from environmental exposure is difficult from laboratory models alone. Such experiments control and simplify variables. For example, in the laboratory a known dose of chemical may be administered to test animals in a liquid solution. This favors maximal absorption of the chemical. However, data from an experiment conducted in this manner may not accurately reflect how the chemical is absorbed into the body from contaminated soil. The impact of soil on the rate of absorption might be predicted from models that mimic conditions in the digestive system, but these models must be based on results obtained from living organisms. The matter is further complicated because some chemicals (such as arsenic) exist in multiple forms in the environment. Testing absorption rates independently for each form of arsenic would only produce part of the picture. Mathematical and computer models based on the predicted relationship must be validated by tests in animals and humans.

The whole animal model, using species such as rats and miniature swine, is essential to equitably allocate limited resources to environmental remediation, just as in other decisions about human health and environmental protection.

Basic Research—Toxicology research often leads to breakthroughs in our understanding of disease and its treatment as well as in the development of new therapeutics. By studying how chemicals interact with living systems, toxicologists and other scientists unravel some of the fascinating mysteries of how living organisms normally function. For example, in the study of cancer-causing products created by ordinary combustion, such as barbecuing meat or burning plastics, toxicology research has shown that some of these (certain polynuclear aromatic hydrocarbons and chlorinated dioxins) will combine with proteins called aryl hydrocarbon receptors that are found inside our cells. This combination can move into the cell nucleus, attach to DNA and influence the behavior of DNA and expression of genes. Further basic research in this area has shown that these protein receptors play an essential role in the normal development of mammalian cells. Therefore, research in toxicology has led to a better understanding of normal gene function.

The relationship of plants, animals and humans to the environment is a dynamic one, with normal physiological processes that allow living systems to process chemicals in constant balance with the world. Too little is known about many of these fundamental processes. The effects of disturbing this balance, for example by increasing levels of one substance, go largely unknown until some nonspecific, visible measure of toxicity becomes apparent. When predatory bird populations began decreasing in the early 1970's, the source of the problem was not obvious. Ultimately scientists discovered that hatching failure was due to thinning of eggshells, which turned out to be a consequence of concentration of DDT in organisms high on the food chain. DDT interfered with eggshell production.

The use of animal models allows toxicologists to develop fundamental knowledge necessary to the understanding of chemical toxicity. This understanding can be translated into protection of humans, animals, and the environment from toxic levels of natural—as well as man-made—exposures.



SOT Guiding Principles in the Use of Animals in Toxicology

1. The use, care and transportation of animals for training and for toxicological research and testing for the purpose of protecting human and animal health and the environment must comply with all applicable animal welfare laws.
2. When scientifically appropriate, alternative procedures that reduce the number of animals used, refine the use of whole animals or replace whole animals (e.g., *in vitro* models, invertebrate organisms) should be considered.
3. For research requiring the use of animals, the species should be carefully selected and the number of animals kept to the minimum required to achieve scientifically valid results.
4. All reasonable steps should be taken to avoid or minimize discomfort, distress or pain of animals.
5. Appropriate aseptic technique, anesthesia and postoperative analgesia should be provided if a surgical procedure is required. Muscle relaxants or paralytics are not to be used in place of anesthetics.
6. Care and handling of all animals used for research purposes must be directed by veterinarians or other individuals trained and experienced in the proper care, handling and use of the species being maintained or studied. Veterinary care is to be provided in a timely manner when needed.
7. Investigators and other personnel shall be qualified and trained appropriately for conducting procedures on living animals, including training in the proper and humane care and use of laboratory animals.
8. Protocols involving the use of animals are to be reviewed and approved by an institutional animal care and use committee before being initiated. The composition and function of the committee shall be in compliance with applicable animal welfare laws, regulations, guidelines and policies.
9. Euthanasia shall be conducted according to the most current guidelines of the American Veterinary Medical Association (AVMA) Panel on Euthanasia or similar bodies in different countries.

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Research animals must be used in a responsible manner.

SOT Animals in Research Public Policy Statement

How does SOT promote responsible use of animals?

Position on Use of Animals—The Society of Toxicology (SOT) is a professional and scholarly organization of 5,000 scientists from academic institutions, government and industry representing the great variety of scientists practicing toxicology in the U.S. and around the world. The Society is dedicated to supporting the creation of sound scientific information that reduces uncertainty in assessing risks to human health and the environment. Reducing uncertainty in risk assessment benefits everyone through improved decision-making that protects the health of people, animals and their environment. The SOT believes that animal research is necessary for the protection of humans and other organisms (see "Position Statement Regarding the Use of Animals in Toxicology"), and that the welfare of research animals is of paramount importance.

All applicants for membership in the Society must indicate that they will abide by the SOT Code of Ethics, which states that members will "observe the spirit as well as the letter of law, regulations and ethical standards with regard to the welfare of humans and animals involved in my experimental procedures." In addition, those who submit an abstract for presentation at the Society's meetings must conduct their research in accordance with the "Guiding Principles in the Use of Animals in Toxicology" (see guidelines on previous page).

Good science requires that animals used in research are healthy and well cared for, and that pain and distress to the animals is minimized. In addition to ethical concerns, there are scientific reasons for this position. It is well known that altering an animal's state of health (e.g., inducing stress or pain) can alter the physiology of the animal and the outcome of an experiment.

Recognition of accomplishments in promoting animal welfare

The Society of Toxicology recognizes toxicologists whose research innovations promote the welfare of animals, as well as individuals whose efforts increase the public understanding of the use of animals in toxicology research.

The Society of Toxicology Enhancement of Animal

Welfare Award is presented annually to a member of the Society in recognition of the contribution made to the advancement of toxicological science through the development and application of methods that replace, refine or reduce the need for experimental animals. This award recognizes outstanding and significant contributions made by members of the Society of Toxicology to the scientifically sound and responsible use of animals in research. The achievement recognized may be either a seminal piece of work or a long-term contribution to toxicological science and animal welfare.

The Society of Toxicology Award for Contributions to Public Awareness of the Importance of Animals in Toxicology Research

is presented annually to an individual or organization in recognition of the contributions made to the public understanding of the role and importance of experimental animals in toxicological science. This award is important because it encourages and recognizes activities enhancing public understanding of, and appreciation for, the crucial benefits to humans, animals and the environment that result from the use of animals in toxicological research. This award may be for either a single activity or a longer-term contribution to public understanding of the necessity of the use of animals in toxicological research.

Guidelines for both awards are found on the Society's Web site (www.toxicology.org), and the application deadline is in October of the year preceding the award.



What standards regulate animal welfare?

Around the world, animal welfare legislation sets the standards for the proper care and treatment of research animals. For example, in the European Union the European Animal Welfare Directive (Council Directive 86/609/EEC) guides animal welfare. In the United States, the federal Animal Welfare Act (AWA) (P.L. 89-544) and the Health Research Extension Act (P.L. 99-158) define standards for the proper care and treatment of laboratory animals.

The AWA regulates the use of dogs, cats, primates, guinea pigs, hamsters, rabbits and farm animals (and other animals, as the Secretary of Agriculture may determine) for use in for research, testing and teaching. Originally passed in 1966 and amended several times since, the AWA is administered by the U.S. Department of Agriculture (USDA) and requires that all proposals to use animals be reviewed and approved by an Institutional Animal Care and Use Committee (IACUC). In addition, the AWA requires that animals be provided with adequate food, living space and veterinary attention. Facilities using any of the regulated animals submit annual reports and are inspected periodically and unannounced by the USDA.

The role of the IACUC, as defined by the AWA, is to review every research proposal involving animals and consider the design of each project as it affects the animal. The IACUC also oversees an institution's animal program, facilities and procedures. The IACUC must include a Doctor of Veterinary Medicine with training or experience in laboratory animal science and medicine, an individual who is not affiliated with the institution in any other way and at least one additional member. Prior to receiving the approval of the IACUC, researchers must demonstrate that the most appropriate species has been selected and that the minimum number of animals needed to produce scientifically valid results will be used. For procedures having the potential to cause discomfort or pain, the researcher must justify the use of such methods and take all necessary steps to minimize the discomfort or pain. Such committees ensure that animals will be used humanely and responsibly to achieve valid scientific goals.

The Public Health Service (PHS) Policy on Humane Care and Use of Laboratory Animals, issued in 1985, requires the IACUC to review and approve all research using vertebrate animals that is funded by Public Health Service Agencies, including the National Institutes of Health. Furthermore, this policy sets forth the requirements that are applicable to all research, research training, biological testing and related activities involving animals that are supported or conducted by agencies of the PHS according to the standards set forth in the AWA and the PHS *Guide for the Care and Use of Laboratory Animals*.

To insure the highest standards of animal care, many laboratories in the U.S. are voluntarily evaluated and accredited by the American Association for the Accreditation of Laboratory Animal Care International (AAALAC), an organization that has been accrediting programs for institutions since 1965. AAALAC accreditation signifies that the research facilities are not only meeting the standards required by law, but are going the extra step to achieve excellence in animal well-being.



Scientifically-valid research designed to reduce, refine or replace the need for laboratory animals is encouraged.

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Can't testing be limited to techniques that don't use whole animals?

The Society of Toxicology joins other researchers and organizations that seek to obtain validated scientific information while minimizing the number of animals used in research. One way is by using *in vitro* tests, laboratory tests using cell or organ cultures rather than whole organisms. In other cases, organisms such as worms or bacteria are used instead of mammals. Computer models can also be developed to predict outcomes of testing. However, each of these methods provides limited information that applies to a very specific test situation and may not fully anticipate the results in a complicated organism (such as humans) with many interacting organ systems. It also takes time to develop methods and prove that they are suitable replacements for other accepted methods. Fifteen U.S. agencies are working together as the Interagency Coordinating Committee for Validation of Alternate Methods (ICCVAM) to establish criteria for scientific validity and regulatory acceptance of new tests. So far, two such tests, the murine local lymph node assay and the dermal corrosivity test, have been recognized as alternatives to replace some whole animal tests. Internationally, similar reviews of proposed methods are in progress.

Will we need animals in the future?

Yes, animals will continue to be important agents in toxicology studies as new chemicals, combinations and concerns are studied. At a minimum, whole animal testing will still be needed to validate the results of methods that do not use whole animals and as a last protective step before exposure of humans and animals to potentially dangerous substances. However, the vast majority of animals now used in studies are rats and mice.

The future promises many exciting ways to predict and quantify human susceptibility to agents causing specific molecular alterations. With the entire sequence of the human genome now available for study, in the coming years specific human gene mutations may be induced and quantified in cell culture, thus implying that these same genes may be susceptible after, say, environmental exposures of a person to a particular chemical. Using organisms into which human genes have been incorporated (transgenic systems), exposure and consequent change in expression of these specific genes may be analyzed. Information about the dose-response in the whole animal may then be compared to actual incidence of genetic variation in exposed human populations. Such methods will enable the scientist to use hard experimental evidence to predict human diseases caused by genes mutated by environmental exposures to chemicals and their metabolic products. These methods will also enable better treatment of diseases by targeting medicines for the best response with lowest toxicity based on the patient's genetic makeup.

Toxicology is part of the solution!

Toxicology helps sustain the high-quality of life attributable directly to the appropriate use of chemicals. Toxicologists will continue to play an important role in defining the conditions of use that permit us to enjoy a high standard of living. For humane, ethical, scientific and economic reasons research animals will be used only when necessary and in the lowest numbers scientifically possible. However, the responsible use of animals in research will continue to be required to protect human and animal health and to safeguard the environment.



For Further Information

Selected Other Research Societies and Groups

American Association for Laboratory Animal Science (AALAS) — www.aalas.org
American Association of Poison Control Centers — www.aapcc.org/findyour.htm
American Physiological Society (APS) — www.the-aps.org/index.htm
Americans for Medical Progress (AMP) — www.amprogress.org
American Veterinary Medical Association (AVMA) — www.avma.org
Association for Assessment and Accreditation of Laboratory Animal Care International (AAALAC) — www.aaalac.org
California Biomedical Research Association (CBRA) — www.ca-biomed.org
Canadian Council on Animal Care (CCAC) — www.ccac.ca/english/welcome.htm
Canadian Network of Toxicology Centres (CNTC) — www.uoguelph.ca/cntc
Foundation for Biomedical Research (FBR) — www.fbresearch.org
Institute for Laboratory Animal Research (ILAR), National Research Council, National Academy of Sciences — www4.nas.edu/cls/ilarhome.nsf
Johns Hopkins Center for Alternatives to Animal Testing (CAAT) — altweb.jhsph.edu/index.html
Join Hands Educational Foundation — www.joinhand.org
Massachusetts Society for Medical Research, Inc. (MSMR) — www.msmr.org
National Association for Biomedical Research (NABR) — www.nabr.org
North Carolina Association for Biomedical Research (NCABR) — www.ncabr.org
Public Responsibility in Medicine and Research (PRIM&R) — www.primr.org
Scientist Center for Animal Welfare (SCAW) — www.scaw.com

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Public Health Service Policy on Humane Care and Use of Laboratory Animals. PHS (Public Health Service), 1996, U.S. Department of Health and Human Services, Washington, D.C., 28 pp. (PL 99-158. Health Research Extension Act, 1985). The policy is available from NIH Office of Protection from Research Risks, 6100 Executive Blvd., MSC 7507, Suite 3801, Rockville, MD 20892-7507. www.books.nap.edu/books/0309042755/html/R1.html and www.grants.nih.gov/grants/olaw/references/phspol.htm

The Importance of Animals in Biomedical and Behavioral Research is a PHS statement available from the Public Health Service, 5600 Fishers Lane, Rockville, MD 20852. www.the-aps.org/pub_affairs/humane/pa_phspolicy.htm

The Animal Welfare Act of 1966 (PL. 89-544) as amended by the Animal Welfare Act of 1970 (PL. 91-579); 1976 Amendments to the Animal Welfare Act (PL. 94-279); the Food Security Act of 1985 (PL. 99-198), Subtitle F (Animal Welfare File Name: PL99198); and the Food and Agriculture Conservation and Trade Act of 1990 (PL. 101-624), Section 2503, Protection of Pets (File Name: PL101624). Rules and regulations pertaining to implementation are published in the Code of Federal Regulations, Title 9 (Animals and Animal Products), Chapter 1, Subchapter A (Animal Welfare). Available from Regulatory Enforcement and Animal Care, APHIS, USDA, Unit 85, 4700 River Road, Riverdale, MD 20737-1234, File Name 9CFR93. www.nal.usda.gov/awic/legislat/awicregs.html and www.aphis.usda.gov/ac

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International Guiding Principles for Biomedical Research Involving Animals. Council for International Organizations of Medical Sciences (CIOMS), Geneva, 1985.

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Interagency Coordinating Committee on the Validation of Alternative Methods (ICCVAM) — iccvam.niehs.nih.gov

European Centre for Validation of Alternative Methods (ECVAM) — altweb.jhsph.edu/science/pubs/ECVAM/ecvam.htm

Be sure to check the Society of Toxicology Web Site at www.toxicology.org for additional relevant links.

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