



Position and Policy Statements:

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Council Procedures for Developing Position papers on Major Issues

Animals in Research Public Policy Statement Guiding Principles in the Use of Animals in Toxicology, adopted March 1999

Appointment and Participation of Scientists on Peer Review Panels and Scientific Advisory Boards, adopted April 2003—Amended December 2008

Commentary: Toxicology Principles Do Not Support the Banning of Chlorine, adopted October 1994

Guiding Principles in the Use of Animals in Toxicology, adopted July 1989—Amended December 2008

Journal Policy on Manuscripts Reporting on the Use of Human Subjects, adopted November 2004

Principles for Research Priorities in Toxicology, adopted January 1998—Amended December 2008

Role of Government in Science Regulation, adopted January 1998

The Safety of Genetically Modified Foods Produced Through Biotechnology, adopted September 2002

Toxicological Sciences Public Access Policy, adopted May 2005

Use of Animals in Toxicology, adopted January 1986

Questions?

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Council Procedures for Developing Position Papers on Major Issues

1. Any member who has identified an issue that appears to warrant the SOT's comment should notify either the president of an appropriate specialty section or a member of the SOT Council.
2. If the person contacted deems the issue appropriate for SOT comment, he or she should inform the SOT Council's Specialty Section Liaison or the SOT President.
3. The SOT President, with the Council's concurrence (i.e., a two-thirds vote), will decide whether or not to proceed with soliciting member comment and, if there is a decision to go forward, will identify which specialty section(s) will play the key role. The SOT Council's Specialty Section Liaison will inform the key specialty section(s) President(s) of the assignment, deadline and form of the response. The Council Specialty Section Liaison will also inform the other specialty sections of the task.
4. The Specialty Section Liaison will organize and chair an *ad hoc* Working Group to develop a draft Position Paper to be presented to Council. The working group will be comprised of at least 4 individuals, in addition to the Chair. Pursuant to a request made by the Specialty Section Liaison, presidents of particular Specialty Sections will be asked to nominate approximately 1-3 members of their specialty sections to serve as members of the working group (the President may nominate himself/herself as a member). The goal is to provide Council with a list of at least 10 (e.g., 10-12) nominees.
5. Council will review the list of nominees and select those who will serve on the Working Group. Depending upon Council's initial review of the list, it may request that the President(s) of a particular Specialty Section(s) nominate an additional member(s) of his/her Specialty Section in order to achieve a reasonable degree of "balance" on the Working Group.
6. Council will identify the potential target audience(s) and methods of dissemination of the Statement.
7. An article will be placed on our Web site, and in the *Communiqué*, announcing that the Society is developing a position paper. This article will include:
 - (1) the issue under consideration;
 - (2) the names of the members serving on the ad hoc committee working on the paper;
 - (3) an estimated time-line for the project, including the date that a draft (bearing the notation "Limited Distribution-Draft Only" on each page) is expected to be available on the Web site so that members may provide their comments.
8. The Working Group members are expected to solicit input from their respective Specialty Section membership, working through their Section's President, as they participate in drafting the position statement.
9. To gain a broad-based perspective on the issue, the working group will solicit comments from other groups/individuals (e.g., additional SOT Specialty Sections, SOT Committees, SOT Regional Chapters) and take into consideration comments received from the membership pursuant to No. 7, above, before presenting their draft to the Council.
10. The SOT Council will review the draft and may seek additional input before finalizing the document and issuing it as a SOT Position Paper (requiring the approval of at least eight (8) of the eleven (11) Council members). The Council will consider submitting position papers for publication in a scientific journal as a method of disseminating the information.

Animals in Research Public Policy Statement

(Adopted by the Society of Toxicology in March 1999)

- 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.

Appointment and Participation of Scientists on Peer Review Panels and Scientific Advisory Boards

(Adopted by the Society of Toxicology in April 2003—Amended December 2008)

Toxicologists and other scientists provide a critical role in the implementation of science in regulatory and public policy decision-making. Scientists not only create new ideas and test hypotheses that address the health and well-being of humans and the environment through research, but also play critical roles as advisors/reviewers for scientific journals, federal and state regulatory agencies and other governmental agencies, non-profit foundations, non-governmental organizations (e.g., the National Academy of Sciences), and industry. Of paramount importance in any of these scientific review activities is the objectivity and lack of significant bias of the individual reviewers, which are designed to ensure fair representation of different scientific perspectives. Policies and procedures for full disclosure of potential bias and/or conflict of interest¹, as described in the Federal Advisory Committee Act (FACA)², should be clearly defined and implemented by the appointing body. However, equally important to the full disclosure of potential biases or conflicts of interest of the appointees is the assurance, through policies and actions, that the selection of the appointees is free from political influence or other forms of discrimination. The Society of Toxicology holds to the following principles regarding the selection and appointment of scientists to peer review panels and scientific advisory boards, which are in accord with FACA:

- 1. Criteria for Appointments:** Appointments to scientific advisory bodies should be based principally on the scientific credentials, demonstrated accomplishments, and professional credibility of the nominee. His/her source of employment and funding (past or present), religious beliefs, political persuasion, sexual orientation, gender, or race/ethnicity should not be used as (a) determinant(s) of exclusion to such a scientific advisory body. However, we recognize that membership diversity is an important consideration to ensure balance of scientific perspectives, as long as scientific credentials and professional credibility are considered as the primary criteria for inclusion or exclusion of an individual member.
- 2. Responsibilities of the Appointees:** Scientists appointed to peer review panels or advisory boards / committees must openly and honestly divulge any real or perceived conflicts of interest or potential biases that might be construed by others to interfere with the scientific credibility of the report, panel recommendations, or other product of the advisory group. If a significant conflict of interest, perceived or real, arises during the course of review activities, the individual should notify the chair and recuse him/herself from further discussion. Procedures should be established to permit the formal disclosure of such conflicts at the outset, along with an affirmative statement from each panel member that there are no conflicts if that is the case.

- 3. Responsibilities of the Appointers:** Leaders/organizers of peer review panels or advisory boards, and Editors and/or Editorial Boards of journals, should ensure that their appointment procedures are free from political bias and other forms of discrimination. They should strive for a balance of scientific perspectives and interests as well as scientific credibility, and should clearly establish the expectation for full disclosure of conflict of interest or bias among the panel members prior to the convening of important activities.

The Society of Toxicology endorses the policies and procedures that address bias and conflict of interest for committee service, as required by law under FACA, and as outlined by the National Research Council and approved by the Councils of the National Academies of Science and Engineering, the Institute of Medicine and NRC Governing Board³.

References

1. The Society of Toxicology has adopted a Conflict of Interest policy for our publications and meeting presentations that provides specific examples of what may constitute a conflict of interest. This policy is posted on the SOT Web site at www.toxicology.org
2. The Federal Advisory Committee Act (FACA) pertains to federal advisory committees established by U.S. House and/or Senate legislative action (see http://www.epa.gov/ocem/faca/fed_adv_comm_act.htm for a complete description). Essential elements of FACA relevant to this position paper include the following: "In considering legislation establishing, or authorizing the establishment of any advisory committee such legislation shall—
 - (1) contain a clearly defined purpose for the advisory committee;
 - (2) require the membership of the advisory committee to be fairly balanced in terms of the points of view represented and the functions to be performed by the advisory committee;
 - (3) contain appropriate provisions to assure that the advice and recommendations of the advisory committee will not be inappropriately influenced by the appointing authority or by any special interest, but will instead be the result of the advisory committee's independent judgment."
3. "The National Research Council Policy on Disclosure of Personal Involvements and Other Matters Potentially Affecting Committee Service", November 1, 1992.

Commentary

Toxicologic Principles Do Not Support the Banning of Chlorine^{1,2}

A Society of Toxicology Position Paper

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Received October 12, 1994

“Toxicologic Principles Do Not Support the Banning of Chlorine: A Society of Toxicology Position Paper.”
Fundamental and Applied Toxicology. Karol, M. H. (1995). 24, 1–2.

1. This document was prepared in consultation with the SOT *ad hoc* Chlorine Working Group. Members of the group were J. P. Kehrler (SOT Mechanisms Specialty Section), J. C. Lamb (SOT Regulatory Affairs and Legislative Assistance Committee), J. A. Moore (SOT Risk Assessment Specialty Section), J. Zurlo (SOT Committee on Public Communications) and J. I. Goodman, Chair (SOT Council Liaison to the Specialty Sections).
2. Affiliations: J. P. K., Division of Pharmacology and Toxicology, University of Texas at Austin, TX; J. C. L., Jellinek, Schwartz & Connolly, Inc., Washington, DC; J. A. M., Institute for Evaluation Health Risks, Washington, DC; J. Z., Department of Environmental Sciences, Johns Hopkins University, Baltimore, MD; J. I. G., Department of Pharmacology and Toxicology, Michigan State University, East Lansing, MI; M. H. K., Department of Environmental and Occupational Health, University of Pittsburgh, Pittsburgh, PA.
3. President, Society of Toxicology.

Proposals have been made to develop a national strategy for substituting, reducing, or prohibiting the use of chlorine and chlorine-containing compounds based on the premise that such action would improve protection of human health and the environment (International Joint Commission, 1994; U. S. Environmental Protection Agency, 1994). The Council of the Society of Toxicology (SOT), the governing body of the Society, views these proposals as being contradictory to the principles on which the science of toxicology is based.

The SOT is a professional organization composed of scientists (almost 5,000) from academia, government, non-governmental organizations and industry who are engaged in various areas of toxicology. The toxicologist is specially trained to examine the nature of the adverse effects of chemical and physical agents on living organisms and the chemical and physical agents on living organisms and the environment. Toxicologists investigate the mechanism of action on the agent under consideration and assess its potential to cause adverse effects.

The literal definition of toxicology the study of poisons is somewhat simplistic in that it implies that we know which substances are toxic and which are not. In fact, a truism that has endured for about 500 years is that essentially every chemical, either alone or in combination with other chemicals—in sufficient doses—is capable of producing an adverse effect. In more familiar terms, the dose makes the poison. Chemicals may have beneficial effects at some doses and adverse effects at others. A responsibility of the toxicologist is to define the potential toxic effects that chemicals can induce and to determine the conditions of use that minimize or prevent these effects so that the beneficial attributes of chemicals can be realized safely.

Some chlorinated compounds may present a justifiable health concern and indeed, some (e.g., DDT) have been banned. However, a comprehensive strategy to eliminate a class of chemicals containing a common element (e.g., chlorine) is simplistic and ignores the basic principles of toxicology that govern risk assessment. In addition, it is important to note that elimination of chlorine from the environment would be impossible because there are many naturally occurring chlorine-containing chemicals (including sodium chloride). The number of such that have been identified that has expanded markedly in the past decade, e.g., 30 naturally occurring chlorinated chemicals had been identified in 1968 compared with 1500 in 1992 (Willes et al., 1993).

We should continue to conduct research to identify the potential for chemicals to damage the environment and / or endanger human health, ideally before they are released. The risk from a chemical exposure can be predicted realistically only if there is adequate information about the intrinsic toxicity of the chemical (including dose-response data), the potential for exposure and the capacity for the chemical to bioaccumulate and persist in the environment. Chlorinated chemicals not only differ substantially in their toxic potencies, but they also differ in their propensities to bioaccumulate and persist in the environment. Thus, the mere presence of an element, e.g., chlorine, does not automatically impart harmful properties to a chemical.

All chlorine-containing compounds are not equally hazardous. Therefore, SOT takes the position that a broad-based ban of the class of chemicals containing chlorine, or any other element for that matter, would be both irresponsible and unscientific. Such a prohibition would unnecessarily eliminate many beneficial chemicals from common use. For example, the chlorination of drinking water in the vast majority of U. S. water systems has prevented untold numbers of illnesses and deaths by killing pathogenic organisms found in the water supply. The formation of low levels of potentially toxic chlorinate compounds as a result of this process is certainly of concern and must be minimized.

However, the estimate hazard posed by the trace amounts of these materials that are produced is insignificant compared with that from untreated water. Accordingly, the benefit of a chlorinated water supply vastly outweighs its estimated risks. Other essential uses for chlorinated compounds include hospital disinfection, plant protection and the production of countless consumer products, including pharmaceuticals and plastics. Therefore, before a ban of chlorinated compounds (or a marked reduction of their use) can be considered in realistic context, the feasibility of producing effective and less toxic substitutes must be demonstrated. The concern surrounding the use of chlorine and chlorine-containing compounds is related at least in part to the large amount of information that has been generated by research on the toxicities of some of the compounds in this class. However, a similar body of evidence does not exist (i.e., the studies have not been performed) for most alternative compounds. Thus, before changes are made, the consequences of elimination of a compound or the hazard of using another chemical to achieve the same end must be considered.

The Society of Toxicology supports a comprehensive objective approach to understanding the potential hazards of chlorine and chlorine-containing compounds. It recognizes that there is a substantial body of evidence that implicates some of these compounds as potential human and environmental hazards. It is also aware that other, non-chlorinated, chemicals have a similar or greater potential to cause harm. Consequently, the SOT takes the position that the most responsible and scientifically sound approach is to assess the toxicity of agents on a chemical by chemical basis, rather than target one class of chemicals (e.g., chlorine-containing compounds) for study and elimination. The determination of unacceptability should be based on scientific data that document the adverse effects of exposure and a weighing of the risks vs. benefits of using the chemical in question. Indeed, based upon sound principles of toxicology, rational and effective assessments of the potential toxicity of chemicals, including chlorinated chemicals, are currently taking place and rigid standards exist for registration of new products to which people will be exposed.

References

International Joint Commission on the Great Lakes, Durnil, G. K., Lanthirt, C., Cleveland, H. P., Goodwin, R. F., Macaulay, J. A. and Walker, G.W. (Commissioners) (1994). Seventh Biennial Report on Great Lakes Water Quality, Windsor, Ontario, Canada, February 1994.

U.S. Environmental Protection Agency's 1994 Recommendations in the Pollution Discharge Prohibitions of the Clean Water Act Reauthorization, as Transmitted to the Congress by the Executive Office, p.22, February 1994, EPA 800-R-94-001. [A copy of this may be obtained from the Society of Toxicology, 1767 Business Center Drive, Suite 302, Reston, VA 20190.]

Willes, R. F., Nestmann, E. R., Miller, P. A., Orr, J. C. and Munro, I. C. (1993). Scientific principles for evaluation the potential for adverse effects from chlorinated organic chemicals in the environment. *Regul. Toxicol. Pharmacol.* 18, 313-356.

Guiding Principles in the Use of Animals in Toxicology

(Adopted by the Society of Toxicology in July 1989, revised March 1999—Amended December 2008)

1. The use, care and transportation of animals for toxicological research, training, 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.

*U.S. Government Principles for the Utilization and Care of Vertebrate Animals Used in Testing, Research and Training.

Selected References

1. *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].
2. The Animal Welfare Act of 1966 (P.L. 89–544) as amended by the Animal Welfare Act of 1970 (P.L. 91–579); 1976 Amendments to the Animal Welfare Act (P.L. 94–279); the Food Security Act of 1985 (P.L. 99–198), Subtitle F (Animal Welfare File Name: PL99198); and the Food and Agriculture Conservation and Trade Act of 1990 (P.L. 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.
3. *Guide for the Care and Use of Laboratory Animals*. Institute of Laboratory Animal Resources, Commission on Life Sciences, National Research Council, National Academy Press, Washington, D.C., 1996 or succeeding revised editions. www.nap.edu/readingroom/books/labrats.
4. *International Guiding Principles for Biomedical Research involving Animals*. Council for International Organizations of Medical Sciences (CIOMS), Geneva, 1985.
5. *Interdisciplinary Principles and Guidelines for the Use of Animals in Research, Testing and Education*. Ad Hoc Animal Research Committee, New York Academy of Sciences, 1988.
6. *Recognition and Alleviation of Pain and Distress in Laboratory Animals*. A report of the Institute of Laboratory Animal Resources Committee on Pain and Distress in Laboratory Animals. NCR (National Research Council). Washington, D.C.: National Academy Press, 1992.
7. *Education and Training in the Care and Use of Laboratory Animals: A Guide for Developing Institutional Programs*. AVMA (American Veterinary Medical Association). Report of the AVMA panel on euthanasia. *J. Am. Vet. Med. Assoc.* 202(2):229–249, 1993.
8. *Guide to the Care and Use of Experimental Animals*. CCAC (Canadian Council on Animal Care) Vol. 1, 2nd ed. Edited by E. D. Olfert, B. M. Cross and A. A. McWilliam. Ontario, Canada: Canadian Council on Animal Care, 1993. 211 pp.

Journal Policy on Manuscripts Dealing with Human Subjects

Adopted by the Society of Toxicology in November 2004

Toxicological Sciences Information for Authors

Toxicological Sciences will consider manuscripts presenting data obtained from research involving human subjects (<http://www.cdc.gov/OD/ads/hsrdocs.htm>). Research on human subjects must be approved by an appropriate Institutional Review Board (IRB) and comply with all relevant federal, state and local regulations. For research conducted outside federal regulations, authors must provide documentation that the research was conducted according to the principles of the Declaration of Helsinki. A statement describing IRB approval, consent procedures and that all human participants gave written informed consent must appear at the beginning of the Methods section; the editor may request to see such documentation. In addition, authors will be asked to indicate and certify that they have complied with all appropriate government regulations when the manuscript is submitted for review and confirm their understanding that the editor will rely on all of the disclosures called for under this policy in determining whether to accept the manuscript. No paper will be considered for review and publication without this certification from the authors. If accepted, the published paper will include a footnote stating that the authors certified that the work in human subjects was compliant with all relevant regulations or the Declaration of Helsinki, as appropriate.

DISCLAIMER for front of *ToxSci*:

The author(s) of each article appearing in this journal is/are solely responsible for the content thereof and for compliance with the journals policy with respect to research involving human subjects, the publication of an article shall not constitute or be deemed to constitute any representation by the Editors, the Society of Toxicology or its Boards that the data presented therein is correct or is sufficient to support the conclusions reached or that the experimental design or methodology is adequate. General notes for how this would work in Manuscript Central (would be similar to conflict of interest query):

1. A field asking whether the paper includes research involving human subjects will be added
2. If no, move on through submission.
3. If yes, two additional fields will be required (paper cannot be submitted without being completed)

First field requires authors to copy and paste from the methods section describing IRB review and consent procedures (this will be verified by Ed. Office)

Second field will state: The authors certify that all research involving human subjects was done in compliance with relevant government regulations (yes/no toggle).

Principles for Research Priorities in Toxicology

(Adopted by the Society of Toxicology in January 1998—Amended December 2008)

Support and advancement of basic and applied research in toxicology and incorporation of sound science into risk assessment are the first two items addressed in our Long-Range Plan, adopted in June 1997.

Accordingly, the Council has approved the following principles for research priorities in toxicology to highlight the SOT's commitment to research in the context of our concern for human health, animal health and the environment. Classic toxicity testing, involving the use of animal models, has served us well and will continue to do so in the future.

However, we must continue to strive for improvement in accordance with the following principles:

1. A focus on basic research aimed at discerning the mechanism/mode of action of the chemical or physical agent of interest is of fundamental importance. Toxicology is a basic science because the study of mechanisms of toxicity will increase our understanding of essential aspects of biology.
2. Knowledge of mechanisms underlying the toxicity of the agent of interest is required to help incorporate sound science into risk assessment, a critical aspect of our Strategic Plan. The overall goal is to enhance our ability to estimate whether or not people or the environment could be harmed under realistic conditions of exposure. This entails hypothesis-driven research and is consistent with the notion that "it is the dose which makes the poison."
3. The scientific basis of risk assessment can be enhanced by the development of improved test systems (not simply adding to the number of existing "tests") and means for results interpretation. Key aspects of any risk assessment include an emphasis on:
 - (1) dose selection;
 - (2) dose-response relationships, including extrapolation from high to low doses;
 - (3) species-to-species extrapolation issues; and (4) exposure assessment.
4. Research should be judged on the basis of scientific merit, without regard for the funding source or where the studies are conducted (e.g., academia, government, or industry).

Role of Government in Science Regulation

(Adopted by the Society of Toxicology in January 1998)

Several scientific issues have emerged in which Congress has mandated specific approaches to examine the role of environmental chemicals/environmental factors on human health. In one case, Congress mandated the method (i.e., developmental validation of specific screening and testing procedures) to address the issue of endocrine disruption. This ignores the scientific process. In contrast, in the case of particulate air pollution, Congress required development of an integrated research strategy to address this issue in the absence of mandating specific scientific approaches. This second example is more in keeping with the scientific process.

The position of the SOT on the mandating of specific approaches to examine potential problems of environmental chemicals/environmental factors on human health is provided below:

The Society of Toxicology is supportive of congressional initiatives to pursue hypothesis-driven research aimed at understanding how chemical and/or physical agents in the environment may adversely affect human health and/or the environment. We believe that a strong emphasis on a mechanism of action approach is required in order to facilitate the rational identification, remediation and prevention of releases into the environment of levels of agents which may produce adverse effects. The position of the Society of Toxicology is that Congress should use scientific experts to assist in the development of legislation and should refrain from mandating specific approaches with respect to pursuit or accomplishment of research objectives.

The Safety of Genetically Modified Foods Produced Through Biotechnology

(Adopted by the Society of Toxicology in September 2002)

This document was prepared in consultation with the SOT ad hoc Working Group. Members of the group were Robert M. Hollingworth, Steve L. Taylor, Barbara Jean Meade, Ian Kimber, Michael Bolger, Leonard F. Bjeldanes, and Ken Wallace (Council Liaison).

Executive Summary

The Society of Toxicology (SOT) is committed to protecting and enhancing human, animal and environmental health through the sound application of the fundamental principles of the science of toxicology. It is with this goal in mind that the SOT defines here its current consensus position on the safety of foods produced through biotechnology (genetic engineering). These products are commonly termed genetically-modified foods, but this is misleading since conventional methods of microbial, crop and animal improvement also produce genetic modifications and these are not addressed here.

1. The available scientific evidence indicates that the potential adverse health effects arising from biotechnology-derived foods are not different in nature from those created by conventional breeding practices for plant, animal, or microbial enhancement, and are already familiar to toxicologists. It is therefore important to recognize that it is the food product itself, rather than the process through which it is made, that should be the focus of attention in assessing safety.
2. We support the use of the substantial equivalence concept as part of the safety assessment of biotechnology-derived foods. This process establishes whether the new plant or animal is significantly different from comparable nonengineered plants or animals used to produce food that is generally considered to be safe for consumers. It provides critical guidance as to the nature of any increased health hazards in the new food. To establish substantial equivalence, extensive comparative studies of the chemical composition, nutritional quality, and levels of potentially toxic components in both the engineered and conventional crop or animal are conducted. Notable differences between the existing and new organism would require further evaluation to determine whether the engineered form presents a higher level of risk. Through this approach, the safety of current biotechnology-derived foods can be compared with that of their conventional counterparts using established and accepted methods of analytical, nutritional and toxicological research.
3. Studies of this type have established that the level of safety to consumers of current genetically engineered foods is likely to be equivalent to that of traditional foods. At present, no verifiable evidence of adverse health effects of BD foods has been reported, although the current passive reporting system probably would not detect minor or rare adverse effects or a moderate increase in effects with a high background incidence such as diarrhea.
4. The changes in the composition of existing foods produced through biotechnology are quite limited. Assessing safety may be more difficult in the future if genetic engineering projects cause more substantial and complex changes in a foodstuff. Methods have not yet been developed with which whole foods (in contrast to single chemical components) can be fully evaluated for safety. Progress also needs to be made in developing definitive methods for the identification

and characterization of proteins that are potential allergens and this is currently a major focus of research. Improved methods of profiling plant and microbial metabolites, proteins and gene expression may be helpful in detecting unexpected changes in BD organisms and in establishing substantial equivalence. A continuing evolution of toxicological methodologies and regulatory strategies will be necessary to ensure that the present level of safety of biotechnology-derived foods is maintained in the future.

Introduction

The Society of Toxicology (SOT) is committed to protecting and enhancing human, animal and environmental health through the sound application of the fundamental principles of the science of toxicology. It is with this goal in mind that the SOT defines here its current consensus position on the safety of foods produced through biotechnology. In this context, biotechnology is taken to mean those processes whereby genes that are not endogenous to the organism (transgenes) are transferred to microorganisms, plants or animals employed in food production, or where the expression of existing genes is permanently modified, using the techniques of genetic engineering. We intentionally avoid using the term genetically modified organisms (GMOs) or foods in this context since conventional techniques of plant and animal breeding, which are not considered here, also involve genetic modification. The extent of the genetic changes resulting from such conventional breeding techniques, which is generally undefined, far exceeds that typically produced by transgenic methods. Consequently, it is important to recognize that it is the product, and not the process of modification, that is the focus of concern regarding the human or environmental safety of biotechnology-derived (BD) foods.

The principal responsibilities of toxicologists are to define and characterize the potential for natural and manufactured materials to cause adverse health effects and to assess, as accurately as possible, the plausibility and level of risk for human or animal health or for environmental damage under a defined set of circumstances. It is not the task of the Society of Toxicology to determine the overall value of a product or process by balancing health or environmental risks with potential benefits, or to choose between different strategies to manage risk, although toxicological considerations are important in both processes. Our purpose here is rather to identify and consider the primary toxicological issues associated with BD foods. Major areas of concern in the development and application of such foods in agriculture relate to the possibility of deleterious effects on both human health and the environment. We do not consider here some aspects of the possible environmental impact of GM organisms such as gene transfer to non-engineered plants.

Types of Toxicological Hazards to Consumers and Producers Associated with BD Foods

Current techniques of developing organisms used in the production of BD foods typically involve the transfer to the host of the desired gene or genes in combination with a promoter and a gene for a selectable marker trait that allows the efficient isolation of cells or organisms that have been transformed from those that have not. Common selectable markers in plants have included resistance to antibiotics (kanamycin/neomycin or ampicillin) or herbicides.

Several key issues have been raised with respect to the potential toxicity associated with BD foods, including the inherent toxicity of the transgenes and their products, and unintended (pleiotropic or mutagenic) effects resulting from the insertion of the new genetic material into the host genome. Unintended effects of gene insertion might include an over-expression by the host of inherently toxic or pharmacologically-active substances, silencing of normal host genes, or alterations in host metabolic pathways. It is important to recognize that, with the exception of the introduction of marker genes, the process of genetic engineering does not, in itself, create new types of risk. Most of the hazards listed above are also inherent in conventional breeding methods.

The Concept of Substantial Equivalence

The guiding principle in the evaluation of BD foods by regulatory agencies in Europe and the USA is that their human and environmental safety is most effectively considered relative to comparable products and processes currently in use. From this arises the concept of "substantial equivalence." If a new food is found to be substantially equivalent in composition and nutritional characteristics to an existing food, it can be regarded as being as safe as the conventional food (FDA, 1992; OECD, 1993; Maryanski, 1995; Kuiper et al., 2001) and does not require extensive safety testing. Evaluation of substantial equivalence includes consideration of the characteristics of the transgene and its likely effects within the host, and measurements of protein, fat and starch content, amino acid composition and vitamin and mineral equivalency together with levels of known allergens and other potentially toxic components. BD foods can either be substantially equivalent to an existing counterpart, substantially equivalent except for certain defined differences (on which further safety assessments would then focus), or be non-equivalent, which would mean that more extensive safety testing might be necessary. The examination of substantial equivalence therefore may only be the starting point of the safety assessment. It provides a valuable guide to the definition of potential hazards from BD foods and illuminates necessary areas for further study (FAO/WHO, 2000). While there is some concern relative to the meaning of "substantial" and how equivalency should be established, and debate over its use continues (e.g. see Millstone et al., 1999 and following correspondence; Royal Society of Canada, 2001; Kuiper et al., 2001), the concept appears to be logical and robust in assessing the safety of foods derived from both genetically-modified plants and microorganisms (FAO/WHO, 2000; 2001a). If it can be established with reasonable certainty that a BD food is no less safe than its conventional counterpart, it provides a standard likely to be satisfactorily protective of public health. It is also an approach that has the flexibility to evolve in concert with the field of transgenic technology. A recent study of FDA procedures for assessing the safety of BD foods by the US General Accounting Office reviews these procedures and concludes that the current regimen of safety tests are adequate to assess existing BD foods (US General Accounting Office, 2002).

Key issues with respect to human health effects of BD Foods

1. Is the transgene itself toxic? Can it be transferred to the genome of a consumer?

Humans typically consume a minimum of 0.1 to 1 gram of DNA in their diet each day (Doerfler, 2000). Therefore, the transgene in a genetically engineered plant is not a new type of material to our digestive systems and it is present in extremely small amounts. In transgenic corn, the transgenes represent about 0.0001% of the total DNA (Lemaux and Frey, 2002). Decades of research indicate that dietary DNA has no direct toxicity itself. On the contrary, exogenous nucleotides have been shown to play important beneficial roles in gut function and the immune system (Carver, 1999). Likewise, there is no compelling evidence for the incorporation and expression of plant-derived DNA, whether a transgene or not, into the genomes of consuming organisms. Defense processes have evolved, including extensive hydrolytic breakdown of the DNA during digestion, excision of integrated foreign DNA from the host genome, and silencing of foreign gene expression by targeted DNA methylation that prevent the incorporation or expression of foreign DNA (Doerfler, 1991; 2000). Although much remains to be learned about the fate of dietary DNA in mammalian systems (Doerfler, 2000), the possibility of adverse effects arising from the presence of transgenic DNA in foods either by direct toxicity or gene transfer is minimal (FAO/WHO, 2000; Royal Society, 2002).

2. Does the product encoded by the transgene present a risk to consumers or handlers?

The potential toxicity of the transgene product must be considered on a case-by-case basis. Particular attention must be paid if the transgene produces a known toxin (such as the *Bacillus thuringiensis* (Bt) endotoxins) or a protein with allergenic properties.

2a. Production of toxins

The level of risk of these gene products to consumers and those involved in food production can be and is evaluated by standard toxicological methods. The toxicology testing for the Bt endotoxins typifies this approach and has been described in detail by USEPA (USEPA, 1998; 2001). The safety of most Bt toxins is assured by their easy digestibility as well as by their lack of intrinsic activity in mammalian systems (Betz et al., 2000; Siegel, 2001; Kuiper et al., 2001). In this case, the good understanding of the mechanism of action of Bt toxins, and the selective nature of their biochemical effects on insect systems, increases the degree of certainty of the safety evaluations. However, each new transgenic product must be considered individually based on exposure levels and its potency in causing any toxic effects, as is typical of current risk assessment paradigms for chemical agents.

2b. Production of allergens

Allergenicity is one of the major concerns about food derived from transgenic crops. However, it is important to keep in mind that eating conventional food is not risk-free; allergies occur with many known and even new conventional foods. For example, the kiwi fruit was introduced into the U.S. and the European market in the 1960's with no known human allergies; however, today there are people allergic to this fruit (Pastorello et al., 1998).

The issues that have to be addressed regarding the potential allergenicity of BD foods are:

- do the products of novel genes have the ability to elicit allergic reactions in individuals who are already sensitized to the same, or a structurally similar, protein?
- will transgenic techniques alter the level of expression of existing protein allergens in the host crop plant?
- do the products of novel genes engineered into food plants have the ability to induce de novo sensitization among susceptible individuals?

Considerable scientific resources are being committed to determine the most appropriate and accurate approaches for identifying and characterizing potentially allergenic proteins. The first systematic approach to allergenicity assessment was developed by the International Life Sciences Institute (ILSI) in collaboration with the International Food Biotechnology Council and published in 1996 (Metcalf et al., 1996). The hierarchical approach described therein has been reviewed and revised by the World Health Organization (WHO) and the Food and Agriculture Organization of the United Nations (FAO) (FAO/WHO, 2001b). The main approaches currently used in the evaluation of allergenicity are:

(i) Determinations of structural similarity, sequence homology and serological identity: The objective is to determine whether, and to what extent, the novel protein of interest resembles other proteins that are known to cause allergy among human populations. There are essentially three generic approaches. The first is to examine the overall structural similarity between the protein of interest and known allergens. The second is to determine, using appropriate databases, whether the novel protein is similar to known allergens with respect to either overall amino acid homology, or with respect to discrete areas of the molecule where complete sequence identity with a known allergen may indicate the presence of shared epitopes. The third approach is to determine whether specific IgE antibodies in serum drawn from sensitized subjects are able to recognize the protein of interest.

(ii) Assessment of proteolytic stability: There exists a good, but incomplete, correlation between the resistance of proteins to proteolytic digestion and their allergenic potential, the theory being that relative resistance to digestion will facilitate induction of allergic responses provided the protein possesses allergenic properties (Astwood et al., 1996). One approach therefore is to characterize the susceptibility of the protein of interest to digestion by pepsin or in a simulated gastric fluid. However, this approach alone may not be sufficient to identify cross-reactive proteins with the potential to elicit allergic responses in food- or latex-sensitized individuals as in the case of oral allergy syndrome or latex-fruit syndrome (Yagami et al., 2000). Nor are considerations of stability to digestion necessarily relevant for allergens that act through dermal or inhalation exposure and that may have significance for worker health. In these cases, other approaches such as structural homology searches and the use of animal models may be effective in identifying potential new allergens.

(iii) Use of animal models: Currently there are available no widely accepted or thoroughly evaluated animal models for the identification of protein allergens. Nevertheless, progress is being made and methods based on the characterization of allergic responses or allergic reactions in rodents and other species have been described (Kimber and Dearman, 2001).

Although testing strategies for allergens are still evolving and no single test is fully predictive of human responses, the approaches outlined above, when used in combination, allow scientists to address questions of potential allergenicity and these will increase in precision and certainty with time. Considerations of this type led the US federal agencies to deny approval of StarLink corn for human consumption because of the possibility that its Bt protein, Cry9C, may be a human allergen. This protein had been modified to slow its digestion and prolong its effect in the insect gut and this change rendered the protein less digestible in the human gut as well. After the accidental introduction of StarLink corn into the human food chain, a limited number of illnesses among consumers were reported. These were investigated by the Centers for Disease Control who found no evidence that the corn products were responsible (CDC, 2001). However, although this study is reassuring, methodological limitations make it less than conclusive (Kuiper et al., 2001), and it cannot eliminate the possibility that some adverse effects may have occurred that were not reported. Because of this incident, StarLink corn is no longer marketed. With the exception of Cry9C, none of the engineered proteins in foods so far evaluated through the FDA consultation process has had the characteristics of an allergen.

The only documented case where a human allergen was introduced into a food component by genetic engineering occurred when attempts were made to improve the nutritional quality of soybeans using a Brazil nut protein, the methioninerich 2S albumin. Allergies to the Brazil nut have been documented (Arshad et al., 1991), and while still in pre-commercial development, testing of these new soybeans for allergenicity was conducted in university and industrial laboratories. It was found that serum from people allergic to Brazil nuts also reacted to the new soybean (Nordlee et al., 1996). Once this was discovered, further development of the new soybean variety was halted and it was never marketed. This work led to the identification of the major protein associated with Brazil nut allergy which was previously unknown (Nordlee et al., 1996).

3. Will insertion of the transgene increase the potential hazard from toxins or pharmacologically active substances present in the host?

Concern has been expressed about the randomness with which genes are inserted into the host by current genetic engineering processes. This could, and does, result in pleiotropic and insertional mutagenic effects. The former term refers to the situation where a single gene causes multiple changes in the host phenotype and the latter to the situation where the insertion of the new gene induces changes in the expression of other genes. Such changes due to random insertion might cause the silencing of genes, changes in their level of expression or, potentially, the turning on of existing genes that were not previously being expressed. Pleiotropic effects could be manifested as unexpected new metabolic reactions arising from the activity of the inserted gene product on existing substrates or as changes in flow rates through normal metabolic pathways (Conner and Jacobs, 1999).

Unexpected and potentially undesirable pleiotropic or mutagenic changes in the genome of the host do occur (e.g. see a recent listing by Kuiper et al., 2001), but these would likely be revealed by their effects on the development, growth or fertility of the host, or by the extensive testing of its chemical composition compared with isogenic untransformed plants which is a necessary part of any safety evaluation of transgenic crops.

In the US, since 1987, the USDA Animal and Plant Health Inspection Service has completed over 5000 field trials with more than 70 different transgenic plant species. The only unexpected result was a mutation in a color gene and gene silencing through changes in the methylation status of these genes that led to unexpected color patterns in petunia flowers. Both of these effects are also seen in conventional plant breeding (Meyer et al., 1992). While the possibility of an undetected increase in a toxic component in a new food cannot be entirely eliminated, the current safeguards make this unlikely and no toxicologically or nutritionally significant changes of this type are evident in the transgenic plants so far marketed for food production.

Substantial public concern about the safety of BD products was raised in 1989 when a number of cases of eosinophilic myalgia syndrome (EMS) were reported among users of the amino acid tryptophan as a dietary supplement. By mid- 1993, 37 deaths had been attributed to this outbreak (Mayeno and Gleich, 1994). The development of the syndrome appeared among users of some batches of the supplement after a change in the manufacturing process that included the use of a new genetically modified microorganism in the fermentation. However, concomitant with this change were additional alterations in certain filtration and purification steps used previously in the manufacturing process. The exact cause of the outbreak and the nature of the toxic impurity have not been established with certainty. Thus, it is not possible to determine whether the change in purification, the genetic engineering of the organism, or some other factor or factors were to blame (Mayeno and Gleich, 1994). A subsequent investigation revealed that cases of EMS occurred among consumers of tryptophan before the GM organism was introduced into the manufacturing process, although at a lower incidence. Thus, the genetic modifications might have caused an increase in the level of the agent which was responsible for tryptophan-associated EMS, but it did not create a novel toxicant (Sullivan et al., 1996). This event is troubling in that the tryptophan would be regarded as highly purified (99.6% or higher) and no adequate animal model has been found to replicate EMS, a probable autoimmune disease. This illustrates that toxicology has limits in its ability to explain and predict adverse effects in humans.

These examples indicate that careful analysis of the changes in BD organisms is necessary to ensure against unexpected alterations in the levels of toxins, allergens and essential nutrients. This will be particularly critical if, as seems likely, engineering of the synthetic pathways of secondary metabolites is undertaken in plants e.g. to increase their resistance to insects and pathogens or produce compounds of pharmaceutical value. Such changes might create new and unanticipated secondary compounds with unknown toxic properties. New approaches to profiling changes in metabolites, proteins, and gene expression (Kuiper et al., 2001) may be helpful in such cases.

4. Does the possible transfer of antibiotic resistance marker genes from the ingested BD food to gut microbes present a significant human hazard?

The development of antibiotic resistance among pathogenic bacteria is a significant human health issue. However, no contribution to antibiotic resistance in gut bacteria arising from antibiotic resistance markers in BD foods has been documented. For several reasons, including the efficient destruction of the resistance gene in the human gut and the very low intrinsic rate of plant-microbe gene transfer, any contribution from this source is expected to be extremely small (Royal Society, 1998). Genes for resistance to kanamycin and related antibiotics already occur quite commonly in the environment including the flora of the human gut which naturally contains about 1 trillion (10¹²) kanamycin- or neomycin-resistant bacteria (Flavell et al., 1992). Even if the occasional transfer of resistance from plant to bacterium did occur, the practical impact would be negligible. However, since any increase in antibiotic resistance is recognized as undesirable, and the technology is now available to omit the use of such marker genes, future genetically-modified organisms are unlikely to contain them (e.g. see Goldsbrough et al., 1996; Koprek et al., 2000). Thus concerns related to their use are likely to diminish.

5. Will genetic transformation adversely affect the nutritional value of the host?

In the USA, the FDA is entrusted with assuring that the nutritional composition of BD foods is substantially equivalent to that of the non-modified food. Studies are performed to determine whether nutrients, vitamins and minerals in the new food occur at the same level as in the conventionally bred food sources (e.g. see Berberich et al., 1996; Sidhu et al., 2000). A typical example is the case of Roundup Ready soybeans. In this case, the protein, oil, fiber, ash, carbohydrates and moisture content and the amino acid and fatty acid composition in seeds and toasted soybean meal were compared with conventional soybeans. Fatty acid compositions and protein or amino acid levels of soybean oil were compared and special attention was given to checking the levels of antinutrients typically found in soybeans, e.g., trypsin inhibitors, lectins and isoflavones (Padgett et al., 1996). One difference between the conventional and nonconventional soybeans was detected in defatted, non-toasted soybean meal, the starting material for commercially utilized soybean protein which is not itself consumed. In this material, trypsin inhibitor levels were 11-26% higher in the transgenic soybeans. The levels of the trypsin inhibitors were similar in all lines in the seeds and in defatted, toasted soybean meal, the form used in foods. Except for this difference in trypsin inhibitor levels, all other nutritional aspects were equivalent between the transgenic line and the conventional soybean cultivars. Feeding studies demonstrated that there were no evident differences in nutritional value between the conventional and transgenic soybeans in rats, chickens, catfish and dairy cattle (Hammond et al., 1996). Domestic animal feeding studies with a number of other transgenic crops (e.g. see Kuiper et al., 2001) have similarly shown no significant adverse changes in nutritional value.

6. Will the transgene product adversely affect non-target organisms?

In addition to the general concerns addressed that relate to food safety, additional attention is needed when the gene product is pesticidal or otherwise may be toxic to non-target organisms that consume it. The effects of each transgene product that is designed for pesticidal effects must be evaluated on a case-by-case basis against target and nontarget organisms under specific field growth conditions for each transgenic crop. The foremost current example of this is the incorporation of Bt genes into crop plants for insect control. The toxic properties of Bt endotoxins to both target and nontarget species of many kinds are well known (Betz et al., 2000). They show a narrow range of toxicity limited to specific groups of insects, primarily Lepidoptera, Coleoptera or Diptera, depending on the Bt strain. Nevertheless, Bt-producing plants have been tested broadly to determine whether any alteration in this limited spectrum of toxicity has occurred, without the discovery of any unexpected results (see Orr and Landis, 1997; Pilcher et al., 1997; Lozzia et al., 1998; Gatehouse et al., 2002 for examples of such studies). Exotoxins and enterotoxins, which are much more broadly toxic than the endotoxins, are also produced by some Bt strains, but these are not present in the transformed plant because their genes are not transferred into the crop.

In plants transformed with Bt genes to control lepidopterans, toxicity to non-target lepidopterans would be expected if exposure occurs by feeding on the transformed crop. Particular concern has been expressed over the potential toxicity of the Bt toxin in corn pollen to the Monarch butterfly after initial laboratory studies showed increased mortality in larvae fed on leaves dusted with transgenic pollen (Losey et al., 1999). However, most transgenic corn pollen contains much lower, non-lethal levels of Bt toxins than the strain used in this study and there is only a limited synchrony between the feeding period of the most sensitive younger larvae and the period when corn pollen is shed. Also, corn pollen does not typically move far beyond the borders of the field, leaving significant amounts of milkweed uncontaminated in many locations. For these reasons, a detailed risk assessment concluded that it is unlikely that a substantial risk to these butterflies exists in the field since only a negligible portion of the population is exposed to toxic levels of Bt (Sears et al., 2001; Gatehouse et al., 2002). Beyond the question of the potential toxicity of Bt corn to such valued insects, it is also important to recollect that the common alternative is to spray corn with synthetic insecticides, which are not as selective as the Bt toxin. In a sweet corn field containing milkweed plants and treated with a synthetic pyrethroid for insect control, 91-100% of the monarch butterfly larvae placed on the milkweed leaves after spraying were killed. In plots where Bt sweet corn was planted and the pollen fell naturally on the milkweed leaves, larval death rates were much lower (7-20%) and indistinguishable from those in untreated non-Bt corn plots (Stanley-Horn et al., 2001).

Future Challenges in the Assessment of the Safety of BD Foods

Current safety assessment methodologies are focused primarily on the evaluation of the toxicity of single chemicals. Food is a complex mixture of many chemicals. Using animal models, the evaluation of most aspects of the safety of single components of the diet, such as a Bt toxin, is possible using widely accepted protocols. Future projects may involve more complicated manipulations of plant chemistry. In this case, safety testing will be more challenging. Whole foods cannot be tested with the high dose strategy currently used for single chemicals to increase the sensitivity in detecting toxic endpoints (MacKenzie, 1999; Royal Society of Canada, 2001). Also, the question of potential deleterious interactions between new, or enhanced levels of known, toxic agents in BD foods will undoubtedly be raised. The safety testing of multiple combinations of chemicals remains a difficult proposition for toxicologists. In view of these challenges, there is a clear need for the development of effective protocols to allow the assessment of the safety of whole foods (NRC, 2000; Royal Society of Canada, 2001).

Conclusions

1. The responsibility of toxicologists is to assess whether foods derived through biotechnology are at least as safe as their conventional counterparts and to ascertain that any levels of additional risk are clearly defined. In achieving this goal, it is important to recognize that it is the food product itself, rather than the process through which it is made that should be the focus of attention. In assessing safety, the use of the substantial equivalency concept provides guidance as to the nature of any new hazards.
2. Scientific analysis indicates that the process of BD food production is unlikely to lead to hazards of a different nature than those already familiar to toxicologists. The safety of current BD foods, compared with their conventional counterparts, can be assessed with reasonable certainty using established and accepted methods of analytical, nutritional and toxicological research.
3. A significant limitation may occur in the future if transgenic technology results in more substantial and complex changes in a foodstuff. Methods have not yet been developing definitive methods for the identification and characterization of protein allergens and this is currently a major focus of research. Improved methods of profiling plant and microbial metabolites, proteins and gene expression may be helpful in detecting unexpected changes in BD organisms and in establishing substantial equivalence.
4. The level of safety of current BD foods to consumers appears to be equivalent to that of traditional foods. Verified records of adverse health effects are absent although the current passive reporting system would probably not detect minor or rare adverse effects, nor can it detect a moderate increase in common effects such as diarrhea. However, this is no guarantee that all future genetic modifications will have such apparently benign and predictable results. A continuing evolution of toxicological methodologies and regulatory strategies will be necessary to ensure that this level of safety is maintained.

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Toxicological Sciences is pursuing the feasibility of offering to automatically transmit papers directly to NIH as a service to authors in the future. However, it is not yet clear that NIH can accommodate automated third party submissions. We are motivated to provide this service to our authors, and we will continue to monitor developments concerning this and other issues relating to the PubMed Central Repository.

Use of Animals in Toxicology

(Adopted by the Society of Toxicology in January 1986, revised March 1999)

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 continued 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;
- 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.