



*promoting responsible environmental,
health, and safety decision-making*

The Annapolis Accords

on

The Use of Toxicology in Risk Assessment and Decision-Making

An Annapolis Center Workshop Report

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Introduction

Toxicology is the study of adverse responses in biological systems that are caused by exposure to biological, chemical, or physical agents. Toxicologic research (typically performed in laboratory animals) is important for understanding the nature and mechanisms of adverse effects and their dependence on defined dose levels. Toxicologic research also provides information to assess the likelihood of adverse effects in exposed human populations.

Because toxicologic information plays a central role in the identification, characterization, and management of risks, the methods of interpretation and application of toxicologic findings have a significant influence on the process of how risks are assessed. Of particular concern are the assumptions about risks that are made by default in the face of scientific uncertainty. For example, the relevance for a given substance of rodent-carcinogenicity data obtained at high dose levels to humans exposed at much lower levels may be interpreted using the assumption that the dose-response relationship has no threshold (*i.e.*, there is some risk at any dose). In some cases this assumption may be appropriate, while in others it may overestimate the potential for adverse effects at environmental exposure levels. Many in the scientific community, including panels organized by the Society of Toxicology and the National Research Council, have criticized unconditional reliance on default assumptions, particularly when they conflict with the apparent implications of a substantial body of scientific data. These critics are concerned that reliance on the use of invalid assumptions can lead to spurious conclusions, which may result in inadequate protection of human health or may waste

resources by focusing attention on substances that do not pose a substantial risk. Furthermore, the use of inappropriate assumptions undermines the credibility of the science that is used in the risk assessment process. Ultimately, the credibility and appropriateness of the resulting risk management actions may suffer.

The use of default assumptions in risk assessment stems from the fact that information is often needed for the purpose of making risk management decisions before adequate toxicologic information is available. Postponing action in the absence of definitive information is often not possible because even taking “no action” has consequences. For example, postponing a decision as to whether a substance currently used in the workplace should have lower permitted exposure limits may put exposed individuals at unacceptable risk in the interim. Delaying a decision as to whether a new substance should be approved (*e.g.*, for pharmaceutical use) because of “precautionary” concerns will prevent accrual of the benefits of use. Because decisions about managing risks will be made, uncertainty must be addressed.

The Annapolis Center, in partnership with the Society of Toxicology and the American College of Clinical Pharmacology, convened a workshop to draft a series of Accords (or principles) to help guide the interpretation and use of data from toxicology studies in human health risk assessment and risk management. Workshop participants included 12 toxicologists from the fields of environmental health assessment, food safety, and pharmaceutical development. The participants hope that the Accords set forth here will serve as guideposts for the purposes of evaluating the strengths and weaknesses of past risk analyses, and of improving the quality of future analyses. The Accords are the product of the workshop participants' consensus and do not necessarily represent the opinions of the participants' employers.

Annapolis Accords for the Use of Toxicology in Decision-Making

- 1. Toxicology provides reliable, relevant, and objective scientific information that should be used in efforts to assess and compare health and environmental risks, to identify risk reduction opportunities, and to reduce uncertainty.**

Toxicology is a discipline applying the methods of science that is used to protect human and environmental health. The science of toxicology has demonstrated that all agents are not alike; substances vary markedly among one another in the amount of exposure necessary to cause biological effects, in the nature and severity of the effects generated, and in the specific circumstances of exposure under which they may constitute hazards. Such information is directly useful in risk assessment, risk management, and basic toxicologic research. Through risk assessment, toxicologic information enhances understanding of the source, magnitude, and likelihood of risks.

There is concern in the public health community that personal and social decisions often focus on risks of minor biological significance while ignoring risks of greater, biologic significance. For example, small risks that may possibly be posed by pesticide residues in foods have produced considerable consumer concern, while more substantial and more certain risk to ill health caused by poor nutrition and unbalanced diets have received less attention. The scientific information developed by toxicologists has important uses in social decisions about risks from physical, chemical, or biological agents. If used properly and systematically, toxicologic information can help decision-makers, legislators, journalists, and the public understand the relative magnitude of different risks. Toxicologic research also can help identify methods of risk reduction, thereby decreasing the uncertainties associated with risk assessment.

- 2. Toxicologic research seeks to define the conditions of exposure to physical, chemical, or microbial agents that do not produce adverse effects. Attainment of this goal requires the best available characterization of intensity (dose), duration, frequency, and route of exposure.**

A fundamental tenet of toxicology is that the dose makes the poison. Consequently, sound assessment of safety requires knowledge of the conditions of exposure, especially the intensity, duration and frequency of exposure. Numerous toxicologic studies have demonstrated that similar intensities (doses) of exposure to an environmental¹ agent can have widely different effects depending on duration and frequency. Proper use of toxicologic information in risk assessment should, insofar as possible, match exposure information to the known toxicologic determinants of response.

¹ “Environmental” in this context refers to physical, chemical, or microbial agents

- 3. Differences in factors potentially influencing toxicologic susceptibility among people should be considered relevant to a risk assessment if those factors have been demonstrated to influence target organ toxicity, clinical disease, or objectively verifiable biochemical abnormalities.**

Advances in understanding of genetic differences among people have occurred amidst public interest in potential variation in human susceptibility to various health hazards. This Accord addresses the concern that identifiable genetic differences among people might be inappropriately interpreted as differences in risk. Importantly, potential sources of variation are not always toxicologically relevant at expected conditions of exposure.

As more information about genetic variability and susceptibility becomes available, it is critical that data about intensity, duration, and frequency of exposure be considered in any quantitative assessment of risk. Differences among people can be irrelevant at some doses but may be relevant at others. The relationship will rarely be proportional to measurable differences in biomarkers such as enzymatic rates or protein function. The differences will be chemical- and effect-specific. Use of this type of toxicologic information in risk assessment should occur only when the differences have been demonstrated to be relevant for toxic effects at expected exposure levels.

- 4. In order to be useful for assessing health outcomes, biomarker determinations must accurately predict target organ toxicity, clinical disease, or biological abnormalities. Biomarkers of exposure should not be used as predictors of adverse effects if no such relationship has been or can be shown.**

The development of biomarkers as indicators of exposure to a toxic agent or of induction of adverse effects in individuals or populations enhances a closer collaboration between exposure assessment and toxicology. Biomarkers have promise for increasing knowledge of dose-response relationships for risk assessment; however, unvalidated biomarkers can potentially be misused.

The relationship between a biomarker and an endpoint of concern must be established. Biomarkers of exposure (*e.g.*, protein adducts) should not be used as markers of toxicity unless specific data have been developed that quantitatively link the marker to disease or toxicity. Biomarkers of toxicity also must be validated for their predictive power and quantitative relationship to a specific adverse effect. Biomarkers are potentially powerful toxicologic tools for risk assessment, but appropriate application requires an understanding of the nature of a marker and validation of its association with toxicity or illness.

- 5. Plausible alternative interpretations of exposure and toxicologic information underlying a risk assessment should be articulated. The extent of scientific consensus associated with those interpretations should be characterized.**

Risk assessment necessarily requires assumptions and choices when using toxicologic information. The need to make decisions before scientific certainty can be established, if indeed it can be established, means there will be uncertainty in the use of toxicology information for risk assessment. Alternative choices and assumptions can have very different implications for judgments about risk. To provide decision-makers with an accurate characterization of a situation, all scientifically plausible estimates of risk should be articulated and the scientific differences among them identified. The judgment of toxicologists should be used to guide identification of the most scientifically valid interpretations.

6. Toxicologic research in animals can improve understanding of potential hazards to human health. Characterization of animal evidence in assessment of human health risk should consider the weight of the evidence for a particular effect and its relevance to humans.

Toxicologic research often relies upon studies of animals to characterize and extrapolate the potential effect of substances on humans and other species. The need to generalize effects across species and to extrapolate to different exposure conditions requires judgment in evaluating toxic effects and their relevance to other species. Confidence in judgments about the interspecies relevance and reliability of animal toxicity data is enhanced when the following issues are explicitly addressed.

- Rigor – Studies should be evaluated for their proper conduct and analysis. Greater weight should be given to more rigorous studies. Some studies may have been performed so poorly that their results should be discounted.
- Power – The statistical power of an experimental design should be examined for its ability to detect effects of a given magnitude. For example, in some "negative" studies, a low level of response could be misinterpreted as a lack of response.
- Corroboration – When specific effects are replicated in similar studies, or similar effects are seen under varied conditions, decision-makers can be confident that effects would be seen under conditions of human exposure as well. Conversely, lack of corroboration provides a basis for doubting either the validity of single experimental results or their applicability to other species or conditions of exposure.
- Universality – When valid testing reproduces an effect in multiple species by various routes of exposure, decision-makers can be more confident that the effect may apply to humans. By contrast, if an effect is restricted to a certain species, strain, or route of administration, there is less confidence in the ability to generalize the response to other species or routes.
- Proximity – When effects have been shown in a species taxonomically related to humans or at doses similar to those expected in humans, such

results weigh more heavily than effects found in taxonomically less related species by less relevant routes, or at markedly different dosages.²

- Relevance – From knowledge of the underlying biologic basis for a toxic response in animals, experts and decision-makers can assess whether similar metabolism, mechanisms of damage and repair, and molecular targets of toxic action should be expected to operate in humans. Accordingly, confidence in applicability to humans can increase or decrease.
- Cohesion – The extent to which all of the data are consistent and are subject to a single biologically plausible explanation increases weight of evidence when compared to situations where inconsistencies require *ad hoc* explanations and exceptions to general patterns.

These themes, while not entirely distinct, identify key elements of information and judgment that contribute to valid assessment of the weight of evidence used to decide if an effect seen in animal studies should be regarded as a potential risk in exposed humans. If a more operational scheme is needed, it may be necessary to codify the judgments into rules about what elements of evidence will lead to acceptance of an effect as sufficiently established to pose a risk to human health. Rigid rules for interpretation of scientific evidence however, can work against the exercise of good judgment. Consequently, consensus criteria should not be followed blindly if evaluation of the considerations listed above suggests that doing so would be misleading.

Summary

The science of toxicology plays an important role in identifying safe conditions of use or exposure for many different kinds of environmental³ agents. The use of toxicologic information in risk assessment requires careful analysis, evaluation of data, and scientific judgment. These Annapolis Accords are intended to guide appropriate use in risk assessment of the scientific information from toxicology. We believe that application of these principles will improve the scientific credibility of risk assessment and the quality of decisions aimed at reducing and eliminating risks to human health and the environment.

² The index of similarity to humans is genetics and taxonomy, not size of species. Also, some experimental models are historically known to give good or bad predictions of human toxicity in spite of taxonomic relations, and such accumulated experience should make a substantial contribution to reasonable interpretations.

³ “Environmental” in this context refers to physical, chemical, or microbial agents

Biographies of Toxicology Workshop Participants

George M. Gray, Ph.D., Project Chair

George M. Gray is a Lecturer in Risk Analysis at the Harvard School of Public Health and Director of the Program on Food Safety and Agriculture at the Harvard Center for Risk Analysis. As a scientist, George is a strong proponent of the use of more and better scientific information in the risk assessment process and risk-based frameworks to guide social efforts to manage health and environmental hazards. His primary research interests are risk characterization and risk communication applied to food safety and agriculture and to chemicals in the environment. Dr. Gray's current work focuses on the potential for bovine spongiform encephalopathy in the United States, interpretation of rodent cancer bioassays for risk assessment, risk/risk tradeoffs in pesticide regulation, methods for evaluation of the benefits of changes in drinking water quality standards, and right-to-know policies for environmental management. Dr. Gray teaches toxicology and risk assessment at the Harvard School of Public Health and directs the Center's continuing education short course "Analyzing Risk: Science, Assessment and Management." He has worked with many companies and trade organizations as well as Federal and State government groups to increase understanding of the size and sources of health and environmental risks. George holds a B.S. degree in Biology from the University of Michigan, and M.S. and Ph.D. degrees in Toxicology from the University of Rochester. Dr. Gray is a member of The Annapolis Center's Board of Directors.

Steven I. Baskin, Pharm.D., Ph.D., DABT, FATS

Steven I. Baskin received a doctors of pharmacy with honors from the University of Southern California where he was elected to Rho Chi honorary and received the Lundsford Richardson International Research award in pharmacy and the Merck award. While there, he studies the roles of sugars in the Orchidaceae. He studied pharmacognosy under Dr. Jack Beal and Pharmacology under Dr. Bernard Marks and others at Ohio State University, receiving a Ph.D. in Pharmacology and Toxicology. He went on to serve as a postdoctoral fellow with Dr. Theodore Brody, Chair of the Pharmacology Department of Michigan State University where he continued his studies on digitalis glycosides and their inaction with sodium/potassium stimulated ATPase.

He joined the Pharmacology Department of the Medical College of Pennsylvania where he became an associate Professor. There he conducted studies on mimosa, catecholamines, and in the field of aging. He also studies mechanisms of phenytoin. He went on to MRCID and is an adj. Professor of Pathology at the Medical School of Maryland. He currently is looking at mechanisms of cyanide, sulfur mustard, and organophosphorus compounds. He is the CSO at Citadel Capital Corp.

He has co-edited five scientific books, over 100 papers and monographs and approximately 40 chapters. He has been elected as a Fellow of the American College of

Clinical Pharmacology, a Fellow of the American College of Cardiology, a Fellow of the American Board of Toxicology, and a Fellow of the Academy of Toxicology Sciences. He has served as president of the Chesapeake chapter of Sigma Xi, the Scientific honorary and is current past president of the Association of Government Toxicologists. He is a member of the American Chemical Society, the American Society of Pharmacology and Experimental Therapeutics, and the Society of Toxicology where he has served as councilor of the NACSOT chapter, the European Society of Toxicology, and the Israeli Society of Physiology and Pharmacology. He is considered an international authority on the pharmacology and toxicology of sulfur containing amino acids including taurine and nitriles (Cyanide). He has also published in cardiovascular fields.

Dr. Baskin participated as a representative of the American College of Clinical Pharmacology.

Gail Charnley, Ph.D.

Dr. Gail Charnley is an internationally recognized expert in environmental health risk assessment and risk management science and policy. During its tenure, she was executive director of the Presidential/Congressional Commission on Risk Assessment and Risk Management, mandated by Congress to evaluate the role that risk assessment and risk management play in federal regulatory programs, establishing her as a leader in health risk-related public policy. Before her appointment to the Commission, she served as acting director of the Toxicology and Risk Assessment Program at the National Academy of Sciences/National Research Council. She has been the project director for several National Academy of Sciences' committees, including the Committee on Risk Assessment Methodology and the Complex Mixtures Committee, and served as the chair of several U.S. Army Science Advisory Board committees that evaluated health risk assessment practices in the service. Currently, she develops scientific, regulatory, and risk communication strategies to help clients respond to legal, regulatory, and public perception challenges in the United States and Europe. She holds an adjunct faculty position at the Harvard Center for Risk Analysis and is immediate past-president of the international Society for Risk Analysis. She received her Ph.D. in Toxicology from M.I.T. and her A.B. in biochemistry from Wellesley College.

Joshua T. Cohen, Ph.D.

Dr. Cohen is a Senior Research Associate at the Harvard School of Public Health Center for Risk Analysis. Dr. Cohen's research focuses on the application of decision analytic techniques to environmental risk management problems with a special emphasis on the proper characterization and analysis of uncertainty. He is the author of a case study conducted for the U.S. EPA demonstrating the application of decision analytic techniques to the evaluation of alternative drinking water treatment technologies. Dr. Cohen directed a project to develop a population risk assessment for styrene, and also worked on the Center's risk/benefit evaluation of letting people use cell phones while driving. Currently, he is working with other Center for Risk Analysis staff members on a risk

assessment of bovine spongiform encephalopathy (mad cow disease) in the United States. He is also directing a Center project to compare alternative propulsion systems for heavy-duty urban vehicles (*e.g.*, buses and trash hauling trucks). He received his Ph.D. in Decision Sciences from Harvard University.

Lois Swirsky Gold, Ph.D.

Lois Swirsky Gold is Director of the Carcinogenic Potency Project at the National Institute of Environmental Health Sciences Center at the University of California, Berkeley, and a Senior Scientist at the Ernest O. Lawrence Berkeley National Laboratory. Dr. Gold has published 115 papers on the methodology of risk assessment, analyses of animal cancer tests, and the implications for cancer prevention and regulatory policy. Her Carcinogenic Potency Database (CPDB), published as a CRC handbook, analyzes the results of 5,500 chronic, long-term cancer tests on 1,400 chemicals. Dr. Gold's work has addressed many issues in the field of risk assessment: methodological issues such as validity problems associated with the use of limited data from animal cancer tests to estimate low-dose human cancer risks; reproducibility of results in near-replicate animal cancer tests; misconceptions about the causes of cancer, which underlie current regulatory policy; qualitative and quantitative extrapolation between species; target organs of carcinogenesis; ranking possible carcinogenic hazards of naturally-occurring and synthetic chemicals; and statistical issues in risk estimation. Dr. Gold has served on the Panel of Expert Reviewers for the National Toxicology Program, the Board of the Harvard Center for Risk Analysis, and the Harvard Risk Management Group. She is currently on the Editorial Board of Regulatory Toxicology and Pharmacology. Dr. Gold is the recipient of the 1999 Annapolis Center Award for Risk Communication.

Nancy Kerkvliet, Ph.D.

Nancy Kerkvliet, Ph.D., is a Professor in the Department of Environmental and Molecular Toxicology (formerly Agricultural Chemistry) at Oregon State University, Corvallis, OR. Dr. Kerkvliet also serves as the Director of Community Outreach and Education and the Co-director of the Cell and Tissue Analysis Core of the Environmental Health Sciences Center at OSU. Dr. Kerkvliet currently serves on the National Research Council's Committee on Toxicology and is a past Councilor of the Society of Toxicology. Dr. Kerkvliet has published over 75 papers in the field of immunotoxicology, highlighting her research interests in understanding the mechanisms of actions of dioxins (TCDD) and other Ah receptor ligands on the immune system. She is also active in public outreach education programs in toxicology and risk communication.

VADM Harold M. Koenig, Medical Corps, U.S. Navy (Retired)

VADM Koenig became the thirty-second Surgeon General of the Navy and Chief, Bureau of Medicine and Surgery, on June 29, 1995. He retired from that position on June 30, 1998 after completing 32 years of active duty service. He currently serves as Chair and President of The Annapolis Center.

A native of Salinas, California, he attended the U.S. Naval Academy and received his Bachelor of Science Degree from Brigham Young University. He received his Medical Degree from Baylor University College of Medicine. He is certified by the American Board of Pediatrics in general pediatrics and pediatric hematology-oncology.

VADM Koenig is a Diplomate of the American College of Healthcare Executives. In 1994 the American Hospital Association named him "The Federal Health Care Executive of the Year".

VADM Koenig served in a variety of clinical roles in the Navy, including general medical officer, residency training program director, department chairman, hospital executive officer and commanding officer. His staff assignments before becoming the Navy Surgeon General included: command of the Naval Health Sciences Education and Training Command, Director of Health Care Operations in the Office of the Chief of Naval Operations, Deputy Assistant Secretary of Defense (Health Affairs) for Health Services Operations and Deputy Surgeon General and Chief of the Medical Corps.

VADM Koenig's personal awards include the Navy Distinguished Service Medal, Defense Superior Service Medal, Legion of Merit with Gold Star, Meritorious Service Medal with Gold Star, Navy Commendation Medal, and the Navy Achievement Medal.

Steven C. Lewis, Ph.D., DABT

Dr. Lewis holds a B.A. in Chemistry from Indiana University at Indianapolis (1970) and a Ph.D. in Toxicology (minor in Biomedical Sciences) from Indiana University School of Medicine (1975).

Dr. Lewis joined Exxon Corporation in 1975 and has held various technical, consulting and management positions, including Manager of the Petroleum and Synthetic Fuels Group. His research and safety assessment activities have focused on the assessment of potential health risks from exposure to chemical carcinogens, toxicants to the nervous system, and chemical hazards to reproductive health. Presently, Dr. Lewis acts as a corporate advisor on scientific and science-policy issues in the areas of occupational and environmental health. Dr. Lewis received Exxon Biomedical Sciences' Exceptional Achievement Award in 1993.

Dr. Lewis has been a Diplomate of the American Board of Toxicology since the Board's inception in 1980 (recertified in 1985, 1990 and 1995). He has served on the editorial boards of five scientific journals (four are current), and is active in a variety of

professional societies, including the Society for Risk Analysis (elected to Society Council in 2000), the International Society for Regulatory Toxicology and Pharmacology, and the Society of Toxicology.

Dr. Lewis serves as a consultant to the U.S. EPA in various capacities, and is a frequent commentator on scientific and regulatory issues before U.S., state, and international agencies. Dr. Lewis also holds the title of Senior Fellow at the Cecil and Ida Green Center for the Study of Science and Society (University of Texas at Dallas), where he was a visiting scholar in 1995. Dr. Lewis also holds the position of Adjunct Professor of Environmental and Community Medicine at the University of Medicine and Dentistry of New Jersey, Robert Wood Johnson Medical School.

Dr. Lewis has published and presented the results of his work widely, and has delivered numerous invited seminars and other presentations.

R. Michael McClain, Ph.D.

Dr. R. Michael McClain is currently a part-time faculty member in the Department of Community and Environmental Medicine at the UMDNJ Robert Wood Johnson Medical School. He was formerly a Distinguished Research Leader and Director of Toxicology, Hoffmann-La Roche Inc and now works primarily as a consultant in toxicology. Dr. McClain received his Ph.D. from the Department of Pharmacology at the University of Iowa and B.S. and M.S. degrees from Duquesne University. Dr. McClain is a Diplomate of the American Board of Toxicology and a Fellow of the Academy of Toxicological Sciences. He has worked in the pharmaceutical industry for over 30 years in the areas of teratology and reproductive toxicology, general toxicology and carcinogenicity testing. His research activities are involved primarily in mechanisms of chemical carcinogenesis for thyroid, liver and adrenal and regulatory aspects for cancer risk assessment. He has been active in the Pharmaceutical Research and Manufactures Association and PhRMAs efforts on harmonizing international guidelines for drug development (ICH). He has been involved with the ILSI organization and served as President of the ILSI's Health and Environmental Science Institute (HESI) and as a member of ILSI's Board of Trustees. Dr McClain is a member of the National Advisory Environmental Health Sciences Council for NIEHS. Dr. McClain is also active in the Society of Toxicology having served a term as Treasurer and as President of the Society in 1998.

Dr. McClain participated as a representative of the Society of Toxicology.

Lorenz R. Rhomberg, Ph.D.

Dr. Rhomberg is a Principal at Gradient Corporation, a Cambridge, MA environmental consulting firm. Before joining Gradient he was an Assistant Professor at the Harvard School of Public Health, where he maintains an adjunct appointment. From 1984-1994 he was a risk assessor at the U.S. Environmental Protection Agency in Washington, D.C. Dr. Rhomberg earned his Ph.D. in population biology from the State University of New York at Stony Brook and his B.Sc. in biology from Queen's University in Ontario. His interests

lie in methodology and science policy for quantitative risk analysis, including pharmacokinetic modeling and probabilistic methods with special emphasis on cross-species extrapolation, chlorinated solvents and endocrine active agents. Dr. Rhomberg is a member of the Office of Pesticide Programs' FQPA Science Review Board, has served on several FIFRA Scientific Advisory Panels, on NAS Committees, and other panels. He is a past President of the New England Chapter of the Society for Risk Analysis. He has published two books and over 50 articles and book chapters on risk analysis topics.

JACK W. SNYDER, M.D., J.D., Ph.D., DABT

Dr. Jack Snyder is a physician-attorney with training and experience in pharmacology, toxicology, pathology, and occupational medicine. Prior to assuming his new role, Dr. Snyder was a member of the full-time faculty in the departments of medicine, emergency medicine, and laboratory medicine at the Thomas Jefferson University in Philadelphia, Pennsylvania. He is a frequent lecturer, advisor, and consultant to corporate, academic, legal, and governmental organizations in matters involving legal medicine, forensic, sciences laboratory medicine, toxic torts, workers' compensation, hazardous waste, occupational disease, disaster planning, and adverse drug reactions. Dr. Snyder received a B.S. in Chemistry and an M.D. from Northwestern University, a J.D. from Georgetown University, a Master of Public Health from Johns Hopkins University, a Master of Forensic Science from George Washington University, and a Ph.D. in Pharmacology & Toxicology from the Medical College of Virginia. He is the president of the American College of Legal Medicine, a member of the Board of Directors of The Annapolis Center, and serves as treasurer of the American Board of Legal Medicine. He is a member of the Florida, Virginia, and Pennsylvania bars, and is licensed to practice medicine in Pennsylvania, Virginia, Louisiana, and the District of Columbia. Dr. Snyder has been certified by the American Boards of Preventive (Occupational) Medicine, Toxicology, Medical Toxicology, Toxicological Chemistry, Clinical Chemistry, Legal Medicine, Quality Assurance & Utilization Review, and Anatomic, Clinical, and Chemical Pathology. He has published widely in medical, scientific, and legal literature, and is recently the co-editor of the ninth edition of Conn's Current Diagnosis.

L. Bruce Weekley, D.V.M., M.S., Ph.D.

Bruce Weekley is a Veterinarian-Scientist with training and experience in Pharmacology, Toxicology, Pathology and Comparative Veterinary Medicine. Dr. Weekley earned his D.V.M. from Colorado State University, Ph.D from The University of Wyoming, M.S. from the Medical College of Virginia and B.S from Virginia Commonwealth University. Dr. Weekley is a Senior Research Veterinarian with Merck Research Laboratories. Dr. Weekley's research interests include defining appropriate animal models for *in vivo* pharmacologic and toxicologic evaluations. Dr. Weekley has published and presented the results of his work at numerous invited seminars and in other forums. He is a member of the American College of Clinical Pharmacology and a Diplomate of the American College of Laboratory Animal Medicine.

Dr. Weekley participated as a representative of the American College of Clinical Pharmacology.

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