

**Report of the Peer Consultation of the
Potential Risk of Health Effects from
Exposure to Tertiary-Butyl Acetate**

Volume II

January 7-8, 2009

**Northern Kentucky University METS Center
Erlanger, Kentucky**

**Peer Consultation Organized by:
Toxicology Excellence for Risk Assessment
(<http://www.tera.org/peer/>)**

April 15, 2009

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Appendix A
Peer Consultation Meeting on the Potential Risk of Health Effects
from Exposure to Tertiary-Butyl Acetate

January 7-8, 2009

Panel Biographical Sketches and Conflict of Interest

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Panel Biographical Sketches and Conflict of Interest

This document discusses the measures taken by Toxicology Excellence for Risk Assessment (*TERA*) to evaluate potential conflict of interest and provides brief biographical sketches for each of the panel members. As part of their voluntary agreement with EPA, LyondellBasell selected and contracted with *TERA* to independently organize and conduct this peer consultation. *TERA* is being paid for labor and the direct expenses related to this consultation under a contract with LyondellBasell.

TERA has no current financial relationship or other work supported by the LyondellBasell Corporation (beyond this peer consultation) or any current financial relationships with any of the competing VOC-exempt solvent producers, or companies intending to produce TBAC. *TERA* is not doing any other work on TBAC for any sponsor. In the past decade, *TERA* has provided technical review on projects to various government agencies on several of the competing VOC-exempt solvents and has worked on projects for several of the producers of competing VOC-exempt solvents. However, none of this work was related to evaluating solvent exemptions, or on TBAC or competing VOC-exempt solvents.

In selecting panel members, *TERA* carefully screens candidates for potential conflicts of interest and biases that might interfere with an expert's objectivity in evaluating the subject materials. *TERA* follows the U.S. National Academy of Sciences (NAS) guidance on selection of panel members to create panels that have a balance of scientific viewpoints on the issues to be discussed. As a result, the expert panels have a broad and diverse range of knowledge, experience, and perspective, including diversity of scientific expertise and affiliation. Panel members serve as *individuals*, representing their own personal scientific opinions. They do not serve as representatives of their companies, agencies, funding organizations, or other entities with which they are associated. Their opinions should not be construed to represent the opinions of their employers or those with whom they are affiliated.

The selected panel members have a variety of relevant expertise and affiliations to provide a range of opinions and perspectives on the subject document. The major areas of expertise for this peer consultation include renal toxicity and tumors, pathology, study design, neurotoxicity, genotoxicity, carcinogenicity, mechanisms of toxicity, metabolism and toxicokinetics, inhalation toxicology, risk assessment, endocrine effects, reproductive and developmental toxicology, and mode of action.

An essential part of panel selection is the identification of potential conflicts of interest and biases or the appearance of conflicts or biases. Prior to selecting the panelists, each candidate completed a questionnaire to identify their activities, financial holdings or relationships, or affiliations that could pose a real or perceived conflict of interest or bias. The completed questionnaires were reviewed by *TERA* staff and discussed further with panel candidates as needed. *TERA* used the information collected to identify potential conflicts and/or biases and evaluate whether these situations would hinder the candidate

from objectively participating in the peer consultation discussions. (See www.tera.org/peer/COI.html for *TERA*'s conflict of interest and bias policy and procedures for panelist selection).

TERA considered the provisions for panel independence outlined in the voluntary agreement in evaluating potential conflict of interest. To facilitate the evaluation of potential conflict of interest and bias situations for the part of peer consultation candidates, *TERA* identified a list of potentially affected or interested parties for this peer consultation and asked the candidates to consider these parties and information when completing their forms. These parties included LyondellBasell Industries, Lyondell Chemical Company (the sponsor of this peer consultation), and Equistar Chemical, LP (a wholly owned subsidiary of Lyondell); producers of TBAC (currently Lyondell is the only producer); producers of competing VOC-exempt solvents; organizations that have taken public positions against the use of TBAC; the Environmental Protection Agency offices that are signatories to the voluntary agreement with Lyondell-- the Office of Air Quality Planning and Standards and the Office of Science Policy; and companies that intend to produce TBAC.

The key question when evaluating candidates for conflict of interest is whether a candidate's participation can have a direct and predictable effect on his or her finances or financial relationships with the parties affected or involved in the matter. Direct means close causal link between any decision or action taken in the course of the peer consultation and a predictable effect on the financial interests of the candidate. There must be an actual, as opposed to speculative, possibility that the matter will affect the financial interest to be a real conflict of interest.

TERA has selected members for the panel that are free from conflict of interest and are able to objectively participate and contribute to this peer consultation. None of the panel members works for, or is doing work for, Lyondell or the other identified parties. None of the panel members has a financial interest that can be affected by the work of the panel or the outcome of this peer consultation. In addition, none of the panel members was an author of or contributor to the report under review.

Every scientist and expert has biases resulting from his or her education, training, and experience. *TERA* sought to identify sources of biases and evaluated these to determine if the biases would interfere with the peer consultant's ability to objectively participate in the discussions and peer consultation. Evaluation of bias included consideration of candidates' relationships with affected parties and public positions on the chemical or key issues.

A brief biographical sketch of each panel member is provided below. In the interests of transparency, as appropriate, a short disclosure statement is provided.

Marni Y. (Vaningam) Bekkedal
Ph.D., Experimental Psychology, Bowling Green State University
Research Scientist, Wisconsin Department of Health Services
Neurotoxicologist, Two Steps Forward, LLC

Dr. Marni Bekkedal is a neuroscientist with expertise in neural chemistry and function related to neurobehavioral toxicology and brain development. Dr. Bekkedal was the deputy director of the neurobehavioral toxicology laboratory at the Navy's Environmental Health Effects Laboratory for five years. She supervised activities and collaborated with partners in neurobehavioral assessments for a number of compounds including jet fuel, depleted uranium and ammonium perchlorate. Projects have ranged from neural microelectrode array recordings, rodent neurobehavioral tests and human assessments. Currently she has a half-time position with the State of Wisconsin where she serves as Program Manager in the Bureau of Environmental and Occupational Health, overseeing the Environmental Public Health Tracking Network program. Additionally, she leads the program's partnerships with a number of agencies to develop unique protocols that can be implemented as routine surveillance tools for the proactive identification of environmental health concerns. The position is funded by a cooperative agreement with the Centers for Disease Control. She was an assistant professor at Rollins College and an adjunct professor at Wright State University in their psychology departments, and currently holds an adjunct faculty position at the University of Wisconsin School of Medicine, Department of Population Health. She has published a number of peer-reviewed publications and has provided numerous platform presentations related to neurobehavioral and environmental health research. As vice president of Two Steps Forward, LLC, she provides consultation with science-based solutions for improving human interactions and supporting optimal neurobehavioral performance. She is currently providing neurobehavioral research support to the U.S. Navy as a subcontractor to SAIC). Dr. Bekkedal was selected for the panel for her expertise in neurotoxicity and neurobehavioral toxicology.

Disclosures: none.

Ronald P. Brown, M.S., DABT
M.S., Physiology, University of Maryland, Baltimore
U.S. Food and Drug Administration

Mr. Ronald P. Brown is a board-certified toxicologist and leader of the Laboratory of Biological Risk Assessment in the U.S. Food and Drug Administration (FDA/CDRH) Office of Science and Engineering Laboratories. At FDA, his research efforts focus on developing new and more clinically relevant approaches for assessing the risk posed by exposure of patients to compounds released from medical device materials. He receives no outside sources of funding. Mr. Brown represents the United States on several working groups involved with developing international consensus standards for the safety assessment of medical devices and serves as the convener of the ISO TC 194 working group with the responsibility for developing toxicological risk assessment methods for medical devices. Mr. Brown is a Diplomate of the American Board of Toxicology, he is a councilor of the Association of Government Toxicologists and has served as President of the Dose-Response Specialty Group of the Society for Risk Analysis. Mr. Brown has served on numerous committees including several for ILSI, ICCVAM, and the U.S. EPA. He is currently a member of the FDA Bisphenol A/Phthalates Task Force and Committee on FDA Science. Prior to joining FDA in 1994, Mr. Brown held positions at the ILSI Risk Science Institute, and Technical Resources Inc. Mr. Brown was selected for the panel for his expertise in metabolism and toxicokinetics, renal tumors and quantitative risk assessment.

Disclosure: None.

**Michael L. Dourson, DABT, FATS
Ph.D., Toxicology, University of Cincinnati
Toxicology Excellence for Risk Assessment (TERA)**

Dr. Dourson is the President of Toxicology Excellence for Risk Assessment (TERA), a nonprofit corporation dedicated to the best use of toxicity data in risk assessment. Before founding TERA in 1995, Dr. Dourson held leadership roles in the U.S. Environmental Protection Agency as chair of EPA's Reference Dose (RfD) Work Group, charter member of the EPA's Risk Assessment Forum and chief of the group that helped create the Integrated Risk Information System (IRIS). Dr. Dourson received his Ph.D. in Toxicology from the University of Cincinnati. Dr. Dourson has served on or chaired numerous expert panels, including peer review panels for EPA IRIS assessments, EPA's Risk Assessment Forum, TERA's International Toxicity Estimates for Risk (ITER) independent peer reviews and consultations, FDA's Science Board Subcommittee on Toxicology, the NSF International's Health Advisory Board, and SOT's harmonization of cancer and non-cancer risk assessment. Dr. Dourson is a Diplomate of the American Board of Toxicology and a Fellow of the Academy of Toxicological Sciences. He served as Secretary for the Society for Risk Analysis (SRA) and has held leadership roles in specialty sections of SRA and SOT. He is currently on the editorial board of three journals. Dr. Dourson has published more than 100 papers on risk assessment methods, has co-authored over 100 government risk assessment documents, and has made over 90 invited presentations. Dr. Dourson was selected for the panel for his expertise in toxicology and risk assessment, as well as his experience in chairing expert panels.

Disclosure: Dr. Dourson is the President of Toxicology Excellence for Risk Assessment (TERA). Please see the disclosure statement for TERA above. Dr. Dourson personally reviewed a toxicity assessment on tertiary-butyl alcohol (TBA) in a volunteer capacity for NSF International in 2002. The resulting NSF International conclusions and risk values are on the ITER database. TERA does not believe Dr. Dourson's previous review of a TBA assessment will interfere with his objectivity as a panel member or chair for this peer consultation.

Susan Emeigh Hart, DACVP, DABT, ERT
V.M.D., University of Pennsylvania School of Veterinary Medicine
Ph.D., Pathobiology, University of Connecticut
Auxillium Pharmaceuticals, Inc.

Dr. Emeigh Hart is a board certified veterinary pathologist/toxicologist with expertise in renal pathology, physiology and toxicity, including mechanisms of renal carcinogenesis, and methods of assessment of renal injury and function. Her additional areas of expertise include ocular and hematologic pathology and toxicology, and drug development in metabolic diseases, oncology and ocular diseases. She has extensive experience as Study Director and study pathologist/peer review pathologist for all phases of compound development (discovery, acute, subchronic, chronic, carcinogenicity, reproductive toxicology, neurotoxicity, and special/mechanistic toxicity studies). Dr. Emeigh Hart is currently Senior Director, Non-clinical Development, at Auxillium Pharmaceuticals, and previously worked for Genaera Corporation, AstraZeneca Pharmaceuticals, the DuPont Pharmaceutical Company, Pfizer Central Research, and Ciba Crop Protection. Dr. Emeigh Hart has dual board certification (anatomic and clinical pathology) through the American College of Veterinary Pathologists (ACVP) and has dual certification in toxicology through the American Board of Toxicology (ABT) and the UK Register of Toxicologists (Eurotox Registered Toxicologist (ERT)). Dr. Emeigh Hart is a member of numerous scientific professional societies and currently serves as Secretary on the ABT Board of Directors. She has served as Secretary-Treasurer for the SOT Toxicologic and Exploratory Pathology Specialty Section and served on numerous committees of the Society of Toxicologic Pathology. She served on the editorial board of *Toxicologic Pathology* and is a peer reviewer for several other journals. She has served on several ILSI committees on pathology techniques and nephrotoxicity. Dr. Emeigh Hart has dozens of peer review publications and has written four book chapters on methods of assessment of renal injury and function. Dr. Emeigh Hart was selected for the panel for her expertise in renal physiology and toxicity, mechanisms of renal carcinogenesis, and pathology.

Disclosure: Dr. Emeigh Hart was employed about seven years ago by a pharmaceutical firm that is a part of a larger company that produces a competing VOC-exempt solvent; however, she has no current interest, financial or otherwise in her former employer. *TERA* has concluded that Dr. Emeigh Hart does not have a conflict of interest because she has no current financial interest in any of the interested/affected parties. *TERA* does not believe that Dr. Emeigh Hart's previous employment by a company that is part of one of the competing solvent companies will interfere with her objectivity as a panel member for this peer consultation.

**A. Wallace Hayes, DABT, FATS, ERT, FIBiol, FACFE, ERT
Ph.D., Biochemistry, Auburn University
A.W. Hayes & Associates, Inc.
Visiting Professor, Harvard School of Public Health**

Dr. Hayes is a toxicologist with over 35 years of experience in industry and academy. He has written more than 200 peer reviewed publications and is the editor of the textbook, *Principles and Methods of Toxicology, 5th Edition*. Dr. Hayes also is the editor of *Cutaneous and Ocular Toxicology*, the international journal of Human and Experimental Toxicology and a co-editor of the Target Organ Toxicity Series. He has edited the Proceedings of the International Congress of Toxicology III (Developments in the Science and Practice of Toxicology) and the Proceedings of the 5th Congress of Toxicology in Developing Countries (Toxicology in the New Century—Opportunity and Challenge). Before joining Harvard School of Public Health, Dr. Hayes was Vice-President of Corporate Product Integrity at the Gillette Company, where he had management responsibility for the safety evaluation of a variety of consumer products, plant safety, environmental stewardship, and quality control. Dr. Hayes was an NSF predoctoral fellow at Auburn University, a NIH postdoctoral fellow at the Vanderbilt University School of Medicine, a Research Development Award of the NIH, and a NATO Senior Scientist at the Central Veterinary Laboratory, Weybridge, England. Dr. Hayes has served the American College of Toxicology as a member of the Education/Continuing Education Committee and is currently the President of the College. Dr. Hayes is a past member of the council of the Society of Toxicology and received the 2006 Merit Award from the Society of Toxicology. He has served as a delegate to IUTOX and on several IUTOX commissions. Dr. Hayes is in his second term as the Secretary-General of IUTOX. Dr. Hayes has served on committees and expert panels for the National Academy of Sciences, the National Institutes of Health, the Environmental Protection Agency and the Department of Defense as well as on several international expert panels. Dr. Hayes has served two terms as a member of the Advisory Committee on Alternative Toxicological Methods, NIEHS. Dr. Hayes is a Research Professor, University of Massachusetts; an Adjunct Professor, University of Louisville School of Medicine; and a Visiting Professor, Harvard School of Public Health. He serves as a Principal Advisor to Spherix, Incorporated and is a member of the scientific advisory board of CeeTox and Neways. He serves a member of the scientific expert panel for environmental biomonitoring for water, U.S. Army. Dr. Hayes is a diplomat of the American Board of Toxicology, the Academy of Toxicological Sciences, and the American Board of Forensic Medicine and the American Board of Forensic Examiners. He is a Fellow of the Academy of Toxicological Sciences, the Institute of Biology (UK) and the American College of Forensic Examiners. Dr. Hayes is a registered toxicologist in the European Union (ERT) and a certified nutrition specialist. Dr. Hayes was selected for the panel for his expertise in reproductive and developmental toxicity, study design, and genotoxicity.

Disclosure: None.

M.E. (Bette) Meek
M.Sc., Toxicology, University of Surrey
University of Ottawa

Ms. Meek is currently the Associate Director of Chemical Risk Assessment with the McLaughlin Institute of the University of Ottawa on interchange from Health Canada, where she managed the Existing Substances Division in the Safe Environments Programme. Her responsibilities in this capacity are related to development and implementation of process and methodology for the assessment of the effects on human health of Existing Substances under the Canadian Environmental Protection Act, including setting priorities for assessment from among all 23,000 commercial chemicals used in Canada by September, 2006 (i.e., categorization). Ms. Meek has considerable experience in the development of methodology for evaluation of health-related data on environmental contaminants, having also managed previously programmes within Health Canada on contaminants of drinking water and air. She has served as a technical advisor and/or reviewer to several international organizations, including the NAS, ILSI, OECD, WHO, IPCS, TERA, and U.S. EPA. Ms. Meek has a M.Sc. in Toxicology from the University of Surrey and is a Ph.D. candidate at the University of Utrecht. She has authored over 150 scientific publications in human health risk assessment and toxicology evaluation. Her specific areas of experience include development of frameworks to increase transparency in the assessment of human relevance of animal modes of action, increasing incorporation of biological data in dose-response as a replacement for default, development of predictive exposure and hazard modelling and increasing efficiency in assessment through effective problem formulation and early and continuing peer engagement. Ms. Meek was selected for the panel for her expertise in mode of action and cancer guidelines, quantitative risk assessment, and has experience in applying toxicokinetic information to risk assessment.

Disclosure: Ms. Meek is a Health Canada employee on an interchange appointment to the University of Ottawa. Lyondell has made a Schedule 5 notification regarding TBAC listing on Canada's Domestic Substances List (DSL) to Health Canada/Environment Canada. Lyondell has also requested a VOC exemption from the Environment Canada. Ms. Meek notes that in her previous position at Health Canada she was not directly involved in the administration of entries and listing/delisting decisions on the DSL or on VOC exemptions. In her current position, Ms. Meek does not carry responsibility for decision-making relating to assessment and/or management of substances under the Canadian Environmental Protection Act, including the DSL. Therefore, TERA concluded this is not a conflict of interest, nor would the situation cause Ms. Meek to be biased in the peer consultation.

Martha M. Moore

Ph.D., Genetics, University of North Carolina, Chapel Hill

National Center for Toxicological Research (NCTR), U.S. Food and Drug Administration

Dr. Martha M. Moore is the Director of the Division of Genetic and Reproductive Toxicology, National Center for Toxicological Research (NCTR), Food and Drug Administration (FDA) in Jefferson, Arkansas. Prior to her appointment at NCTR in 2000, Dr. Moore was the Chief of the Genetic and Cellular Toxicology Branch, Environmental Carcinogenesis Division, National Health and Environmental Effects Research Laboratory, U.S. Environmental Protection Agency (EPA). Dr. Moore has been a federal employee for 32 years. Her current research funding is primarily from FDA, and her research Division also receives funds from CDC, National Institute of Children's Health and Development, NTP, Teijin Pharmaceuticals (Japan) and The Hamner Institute. Dr. Moore has served on numerous EPA, FDA and other Government Agency advisory groups and committees. She is the chair of an international effort for protocol harmonization for the *in vitro* gene mutation mouse lymphoma assay. She is a member of numerous professional societies and has served as the President of the Genotoxicity and Environmental Mutagen Society; on the council of the Environmental Mutagen Society; and as a councilor or officer of several Society of Toxicology specialty sections. She has served as an expert reviewer to NIEHS, ASTM, ATSDR, TERA, and the U.S. EPA. She is currently a member of several FDA committees, including the FDA CDER Genetic Toxicology Committee and the NCTR/FDA Genetic Toxicology Working Group subgroup of the ICCVAM. Her research interests include: (1) the development and utilization of mechanistically based *in vitro* and *in vivo* gene mutation assays (2) the interpretation and use of genetic toxicology data in cancer risk assessment and (3) the integration of rodent and human mutagenicity data in regulatory decision making. She has dozens of peer reviewed journal articles, several book chapters, and has written many technical reports. Dr. Moore has published articles and made presentations concerning mutagenic mode of action for cancer; a recent publication in Regulatory Toxicology and Pharmacology concerns an approach to informing cancer mode of action (Moore et. al., 2008). Dr. Moore was selected for the panel for her expertise in genetics and risk assessment.

Disclosure: none.

Richard C. Pleus
Ph.D., Environmental Toxicology, University of Minnesota
Intertox, Inc.

Dr. Richard C. Pleus has been Managing Director of Intertox since 1995, and is an expert in neurological and reproductive toxicology with over 25 years experience assessing the risk to humans exposed to chemical and biological agents via food, consumer products, therapeutic agents, and the environment. His clients include companies from the nanotechnology, pulp and paper, utility, cement manufacturing, mining, building material, water, and chemical industries; law firms; citizen groups; and governmental agencies both national and international. Dr. Pleus' research focuses on human health risk, including mode-of-action studies aimed at quantifying exposure to critical organ systems, with particular interest in human and laboratory animal nervous system development. His recent work has been focused primarily on emerging contaminants, especially in water, such as endocrine disruptors, pharmaceuticals, and personal care products. Dr. Pleus earned his Ph.D. in Environmental Toxicology from the University of Minnesota, and conducted postdoctoral research in neuropharmacology at the University of Nebraska Medical Center. Dr. Pleus has served on expert panels for the U.S. EPA and TERA. Dr. Pleus has written several book chapters and published numerous articles. Dr. Pleus has taught at the University of Minnesota and Metropolitan State University. He is an adjunct Associate Professor in the Department of Pharmacology at the University of Nebraska Medical Center, as well as a faculty member of the Center for Environmental Toxicology at the University of Nebraska. He is an elected member of the Delta Omega Honorary Society in Public Health. He has recently served on the board of directors of Frontier Geosciences, Inc. and Urban Environmental Institute in Seattle Washington and on the board of advisors for Good Company in Eugene Oregon. He serves as a stakeholder advisory committee member for the WasteReuse Foundation, to review the development of indicators and surrogates for chemical contaminant removal during wastewater treatment and reclamation. Dr. Pleus also currently serves as counselor to a regional chapter of SOT, U.S. delegate to ANSI and ISO committees on nanotechnology. Dr. Pleus was selected for the panel for his expertise in neurotoxicity, human health risk assessment, thyroid toxicity, and developmental/reproductive toxicity.

Disclosure: Dr. Pleus noted that Intertox has not provided consulting services on TBAC nor done work in the past for any of the affected/interested parties. Intertox has been involved in past work on several of the competing VOC-exempt solvents; however, Intertox has no pending engagements or future plans on these substances. TERA concluded that Dr. Pleus does not have a conflict of interest because his previous work on several VOC-exempt solvents is complete, was not for any of the affected/interested parties and he has no direct and predictable financial interest in the outcome of review. TERA does not believe that Dr. Pleus previous work on several solvents will interfere with his objectivity as a panel member for this peer consultation.

Michael G. Wade
Ph.D., Zoology, University of Guelph
Health Canada

Dr. Wade is a Research Scientist in the Environmental Health Science and Research Bureau, Healthy Environments and Consumer Safety Branch, Health Canada, where he serves as the Leader of the Reproductive Toxicology Laboratory. He conducts toxicological research to assist in the evaluation of possible human health hazards from commercial substances in Canada. Dr. Wade earned his Ph.D. in zoology from the University of Guelph, Ontario. His dissertation research involved the regulation of testicular androgen production. He serves as Canada's representative and Assistant Chair to the Task Force for Endocrine Disruptor Testing and Assessment, Test Guidelines Program of the OECD. He also serves as the Chair of the Validation Management Committee Mammalian, Sub-committee of the Task Force. He has over two dozen publications on reproductive and thyroid toxicity and endpoints for a number of chemicals and substances. Dr. Wade was selected for the panel for his expertise in thyroid and endocrine disruptors, and reproductive toxicity.

Disclosure: Dr. Wade works for Health Canada. Lyondell has made a Schedule 5 notification regarding TBAC listing on Canada's Domestic Substances List (DSL) to Health Canada/Environment Canada. Lyondell has also requested a VOC exemption from the Environment Canada. Dr. Wade notes that the DSL activity is in another division of the Directorate he works in, and that he is not involved in the DSL decisions. He is sometimes asked by other offices of the Directorate to review studies and provide his opinion on interpretation of data, but has not been asked to do so for TBAC. *TERA* concluded this is not a conflict of interest because Dr. Wade does not have any current involvement with TBAC. This situation would not cause Dr. Wade to be biased in the peer consultation because Dr. Wade's position does not involve DSL listing/delisting decisions, nor is he involved in VOC exemption activities.

**Raymond G. York, Ph.D., DABT, FATS, ERT
Ph.D., Toxicology, University of Cincinnati
R.G. York and Associates**

Dr. York is a formally trained developmental toxicologist with over 24 years of research experience. He is a board-certified Diplomate of the American Board of Toxicology and currently serves on its Board of Directors. He recently was certified as a European Registered Toxicologist and a Fellow of the Academy of Toxicological Sciences. He has served as a study director on over 700 safety evaluation studies, and published over a 100 manuscripts, review articles, book chapters and abstracts, and has been an invited speaker at international conferences. Dr. York earned his Ph.D. in Toxicology at the University of Cincinnati Medical Center and completed a two-year postdoctoral fellowship at the Children's Hospital Research Foundation in Cincinnati, in the area of developmental toxicology. Dr. York was the Program Manager for Reproductive Toxicology Services at Charles River Laboratories until November, 2008. Currently, Dr. York is a toxicology consultant. Dr. York has been a member of the Teratology Society since 1984, and has been a member and served as the President for both Midwest Teratology Association (MTA; 1989) and the Middle Atlantic Reproduction and Teratology Association (MARTA; 2004). He has also been a member of the Society of Toxicology since 1985, and the American College of Toxicology since 1998. As a member of the Reproductive and Developmental Toxicology Specialty Section of SOT, he served on its Nominating Committee in 2006 and currently is on the Program Committee for the Middle-Atlantic Regional Section (MASOT). Dr. York has served as a reviewer for *Toxicology and Applied Pharmacology* and as a member of the Editorial Board of *Fundamental and Applied Toxicology*. He was the reproductive toxicologist reviewer for the USEPA Biodiesel Program. Dr. York was selected for the panel for his extensive expertise in developmental and reproductive toxicity and study design, as well as considerable experience in neurotoxicity and thyroid toxicity.

Disclosure: Dr. York recently left Charles River Laboratories and is now a toxicology consultant. To the best of his knowledge, Charles River is not currently providing, nor anticipating providing services in the near future to the affected or interested parties. Dr. York notes that Charles River conducted some minor studies for Lyondell several years ago, but he was not aware of the details or test substance and did not work on the projects. Over the years Charles River has also conducted studies for two companies that produce competing VOC-exempt solvents, but Dr. York was not the Study Director and does not know the test substances or type of studies conducted. Dr. York also disclosed that his wife, Dr. Patricia McGinnis, is the Vice President of the Environmental Science group at Syracuse Research Corporation. Dr. McGinnis has not worked on TBAC, nor with any of the interested/affected parties. *TERA* concluded that Dr. York has no conflict of interest. While his previous employer has done work for Lyondell, the work is complete and he was not involved; Dr York has no current or ongoing financial relationship with Lyondell or any of the other affected/interested parties. *TERA* does not believe that Dr. York's previous employer's activities will interfere with his objectivity as a panel member for this peer consultation.

Errol Zeiger
Ph.D., Microbiology, George Washington University
J.D., North Carolina Central University
Errol Zeiger Consulting

Dr. Zeiger has nearly 40 years experience in biology and toxicology as a laboratory researcher, project director, and scientific program manager, concentrating on the design and direction of laboratory validation studies to determine the effectiveness of short-term genetic toxicity tests and develop standardized test protocols; the evaluation, interpretation, and integration of toxicological test data; the use of short-term, genetic toxicity tests to predict chronic effects; structure-activity relationships in mutagenicity and carcinogenicity; and the study of mechanisms of chemical mutagenesis and carcinogenesis. Much of this work was performed under the auspices of the U.S. National Toxicology Program where he was responsible for developing and managing its genetic toxicology testing program and evaluating the test data. From April 1999 through June 2000, he was assigned as a consultant to the Environmental Directorate of the Organisation for Economic Co-operation and Development (OECD), where he wrote and edited health effects Test Guidelines and Guidance Documents, and helped manage the OECD's *in vivo* endocrine disruptor assay validation program. Since January 2001, Dr. Zeiger has served as a consultant to organizations in the U.S., Canada, and Europe, including Air Force Research Laboratory, OECD, NTP, and Interagency Center for the Evaluation of Alternative Toxicological Methods. Dr. Zeiger earned an M.S. and Ph.D. in microbiology from George Washington University, and a J.D. from North Carolina Central University. Dr. Zeiger is a member of a number of scientific societies and has approximately 200 publications in the scientific literature. He serves or has served on a number of editorial boards (including *Mutation Research*, *Environmental and Molecular Mutagenesis*, and *Environmental Health Perspectives*), was Editor-in-Chief of the scientific journal, *Environmental and Molecular Mutagenesis*, and was co-editor and contributor to the 1997 *Handbook of Carcinogenic Potency and Genotoxicity Databases*. Dr. Zeiger was selected for the panel for his expertise in genetic toxicology.

Disclosure: Dr. Zeiger consulted in the past with one of the companies that produces a competing VOC-exempt solvent; however, that work was on gluteraldehyde and not related to the competing solvent or TBAC. He also served as a member of that company's Toxicology Advisory Board (2001-2005), which was tasked with reviewing the lab's toxicology testing and development program; individual chemicals were never discussed. Dr. Zeiger has a small number of shares (value < \$4000) of one of the companies that produces a competing VOC-exempt solvent in his IRA. *TERA* concluded that Dr. Zeiger does not have a conflict of interest as his work for the VOC-exempt solvent producer was not related to this review (was completed in 2005), and he has no direct and predictable financial interest in the outcome of this review. *TERA* does not believe that Dr. Zeiger's previous work for a company that produces a competing VOC-exempt solvent, nor his small stock holdings in an interested party company, will interfere with his objectivity as a panel member for this peer consultation.

Meeting Co-Chair**Andrew Maier, CIH, DABT****Ph.D., Toxicology, University of Cincinnati****Toxicology Excellence for Risk Assessment (*TERA*)**

Dr. Maier has 13 years of professional work experience in the areas of environmental health, occupational hygiene, and toxicology. He currently serves as the Director for the non-profit organization Toxicology Excellence for Risk Assessment (*TERA*). He leads *TERA* efforts related to occupational toxicology and industrial hygiene, and provides oversight for numerous risk and safety assessment projects and spearheads new initiatives. Dr. Maier completed his Ph.D. in toxicology from the University of Cincinnati with research interests in the molecular mechanisms of toxicity. He is well-versed in the areas of occupational exposure assessment, development and implementation of control strategies, hazard communication and training, and health and safety management systems. Recently his research efforts have focused on methods and approaches for using biological exposure and effect markers to reduce uncertainties in risk assessment and methodologies for deriving occupational exposure limits. He is a Diplomate of the American Board of Toxicology and is certified in comprehensive industrial hygiene practice by the American Board of Industrial Hygiene. He has served in several capacities in support of scientific peer reviews and workshops, including as a panel chairperson, meeting organizer, and external peer reviewer. Dr. Maier remains active in communicating his findings to the broader scientific community through active participation and leadership in professional societies, routine publication of his work (on over 150 individual substances), development of training courses, and invited presentation lectures.

Dr. Maier will serve as a co-chair and assist Dr. Dourson in running the meeting. He is not a panel member and will not participate in panel discussions.

Appendix B

Peer Consultation Meeting on the Potential Risk of Health Effects from Exposure to Tertiary-Butyl Acetate

January 7-8, 2009

Overview of TBAC Peer Consultation Process, List of Attendees, Agenda, and Presenter Biographical Sketches

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Overview of the TBAC Peer Consultation Process

Background

This peer consultation meeting has been organized by Toxicology Excellence for Risk Assessment (*TERA*). *TERA* is an independent non-profit organization with a mission to protect public health through the best use of toxicity and exposure information in the development of risk assessments. *TERA* has organized and conducted peer review and consultation meetings for private and public sponsors since 1996 (see www.tera.org/peer for information about the program and reports from meetings).

The subject of this public peer consultation is a risk assessment document that evaluates the underlying toxicity data on tertiary-butyl acetate (TBAC) and draws conclusions regarding hazard and risk characterization. This document was prepared by LyondellBasell Industries (the primary manufacturer of TBAC) under a voluntary agreement between Lyondell and the U.S. Environmental Protection Agency (EPA). Lyondell had petitioned EPA to exempt TBAC from regulation as a volatile organic compound (VOC) based on studies demonstrating its low photochemical reactivity. Given the potential for increased use of TBAC upon exemption from regulation as a VOC, EPA requested Lyondell conduct additional testing, assessment and review of TBAC. Lyondell has conducted additional toxicity tests and has prepared an assessment for chronic exposures. Lyondell and EPA are working cooperatively to assure that this assessment adequately addresses potential public health concerns.

The voluntary agreement between EPA and Lyondell calls for:

“A third party (organization or individual) shall be selected by Lyondell Chemical Company (Lyondell), and approved by EPA, to manage, summarize and report a peer consultation on the TIER I data on TBAC, including genotoxicity and acute toxicity studies previously conducted, data on similar compounds, and the subchronic studies included in this agreement. The third party shall have no financial interest in Lyondell, or Equistar Chemicals, LP, any other producer of TBAC, any producer of a competing product, or any organization opposing the use of TBAC as a solvent.

The third party shall have demonstrated competence in toxicity, in management of review panels, and weight of the evidence summaries from a variety of positions.

The panel shall consist of at least five persons with expertise in at least one of the following: exposure assessment, genotoxicity, inhalation toxicity, mechanisms of toxicity, endocrine effects, carcinogenicity or risk assessment. Peer consultation participants shall have no financial interest in Lyondell, or Equistar Chemicals, LP, any other producer of TBAC, any producer of a competing product, or any organization opposing the use of TBAC as a solvent. Participants will complete a background/conflict of interest form similar to that used by the National Research Council, or EPA VCCEP for review panel participation. It will include listing employer, remunerated and volunteer non-business relationships (professional organizations, trade associations, public interest or civic groups), government service history, research support history, and public

statements or positions that may be relevant. Persons with a conflict of interest will not be panel participants.” (TBAC Voluntary Agreement)

As part of their voluntary agreement with EPA, LyondellBasell selected and contracted with Toxicology Excellence for Risk Assessment (*TERA*) to independently organize and conduct this peer consultation according to the guidance outlined in the voluntary agreement. *TERA* is being paid for labor and the direct expenses related to this consultation under a contract with LyondellBasell.

This peer consultation is organized for the purpose of providing expert input and advice regarding the TBAC risk assessment. The objective of this peer consultation is for a diverse group of appropriate experts to review the TBAC assessment document and the underlying toxicity data on TBAC to reach conclusions regarding hazard and risk characterization and the need for further testing. The exposure assessment section of the assessment will not be reviewed in detail by this panel. The peer consultation seeks to gain the opinions of technical experts with a variety of perspectives and backgrounds.

Independent Expert Review Panel

The peer consultation panel is made up of scientists with expertise in the key disciplines necessary to evaluate the proposed approach. Dr. Michael Dourson of *TERA* will chair the panel. Each panelist is a well-respected scientist in his or her field. The panel members have training and experience in renal toxicity and tumors, pathology, study design, neurotoxicity, genotoxicity, carcinogenicity, mechanisms of toxicity, metabolism and toxicokinetics, inhalation toxicology, risk assessment, endocrine effects, reproductive and developmental toxicology, and mode of action.

TERA asked the sponsors and the U.S. Environmental Protection Agency (EPA) for suggestions of expert candidates for *TERA* to consider in selecting the panel. *TERA* carefully considered their suggestions and independently identified other candidates. It was from this larger list of candidates that the final panel members were selected. *TERA* was solely responsible for the selection of the panel members. *TERA* offered to cover travel expenses and offered an honorarium to partially compensate panel members for their time to review the materials and participate in the meeting.

Each panel member has disclosed information regarding potential conflicts of interest and biases related to the proposed approach and its sponsors. *TERA* carefully evaluated these disclosures when selecting panel members as discussed below. Short biographical sketches and disclosure statements for panel members are provided to all meeting participants and will be part of the final meeting report.

Review Materials and Charge to Peer Reviewers

The panel received the review package six weeks prior to the meeting to ensure adequate time to carefully review the documentation and prepare for the meeting discussions. The review package included the assessment document, an appendix of robust study summaries, and copies

of key references. *TERA* reviewed an earlier draft of the document to determine if it was ready for the peer consultation and identified several sections of the document text that *TERA* thought could be clarified or enhanced to increase reader understanding. Based on the draft document, *TERA* prepared a “charge” document derived from key questions that EPA and Lyondell agreed should be asked of the panel. The resulting charge document outlines the key questions and scientific issues that will focus the panel’s discussions.

Meeting Procedures

The meeting has been organized to make the best use of the time available to hear and discuss the opinions of the panelists regarding the assessment and answers to charge questions. The meeting will begin with brief panel introductions and a disclosure of conflict of interest and bias issues. The authors will then present background information and describe the studies sponsored by Lyondell. The panel discussion will address the three broad areas of the assessment: carcinogenicity and mode of action, noncancer endpoints and mode of action, and derivation of reference values. To start each discussion section, the authors of the assessment document will make a short presentation. These presentations will highlight the salient points and focus on important issues. There will be a brief period for panel member clarifying questions and then the panel will discuss the relevant charge questions.

Observers

This meeting is open to the public; interested persons were invited to attend the meeting either in person or observe via a real-time Internet webcast. Observers were provided the opportunity to provide written technical comments or present brief oral comments at the meeting. No written comments were submitted.

Meeting Report

***TERA* will draft a meeting report that summarizes the panelists’ discussions and suggestions. The meeting report will serve as a record of the peer consultation and will assist the authors in making revisions and improvements to the risk assessment. The report will be reviewed by the panel members for accuracy before it is finalized.**

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List of Attendees

Dr. Marcy Banton
LyondellBasell Industries

*Mr. Marc Cooley
Sacramento Metropolitan Air Quality Management District

Dr. Willem D. Faber
WFTC, LLC

*Dr. Jianli Jiao
New Chemical Substances Section
Health Canada

Dr. Terry J. Keating
Office of Air & Radiation
U.S. Environmental Protection Agency

*Dr. Dongmin Luo
California Air Resources Board

Dr. Andrew Maier
Toxicology Excellence for Risk Assessment (*TERA*)

Dr. Douglas McGregor
FRCPath, Toxicity Evaluation Consultants

Ms. Ann Parker
Toxicology Excellence for Risk Assessment (*TERA*)

Ms. Jacqueline Patterson
Toxicology Excellence for Risk Assessment (*TERA*)

Dr. Daniel B. Pourreau
LyondellBasell Industries

*Mr. Ralph Propper
California Air Resources Board

Dr. Douglas C. Wolf
Office of Research and Development
U.S. Environmental Protection Agency

*Participating via WebCast

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Agenda

Wednesday, January 7, 2009

8:00 Continental Breakfast and Registration

8:30 Meeting Convenes¹

Welcome and Logistics: Ms. Jacqueline Patterson, *TERA*
Introductions and Conflict of Interest and Bias Disclosures: Panel
Meeting Process, Dr. Michael Dourson, chair and Dr. Andrew Maier, co-chair

8:45 Presentation on Lyondell Sponsored Studies

Dr. Daniel Pourreau, LyondellBasell
Dr. Willem Faber, Willem Faber Toxicology Consulting, LLC

Clarifying Questions from Panel
Observer Comments
Panel Discussion (Question 1)

10:30 Presentation on Metabolism/Kinetics, Noncancer Endpoints and Mode of Action

Dr. Willem Faber, Willem Faber Toxicology Consulting, LLC

Clarifying Questions from Panel
Observer Comments
Panel Discussion (Questions 7-8)

12:00 Lunch

1:00 Continue Panel Discussion on Noncancer Endpoints

3:00 Presentation on Genotoxicity, Carcinogenicity and Mode of Action

Dr. Douglas B. McGregor, Independent Consultant

Clarifying Questions from Panel
Observer Comments
Panel Discussion (Questions 2-6)

5:00 Adjourn

¹ The chair will call for mid-morning and mid-afternoon breaks at appropriate times.
Report of the Peer Consultation of the Potential Risk of Health Effects
from Exposure to Tertiary-Butyl Acetate

Thursday, January 8, 2009

- 7:30** **Breakfast and Registration**
- 8:00** **Continue Panel Discussion on Cancer Endpoints and Mode of Action**
- 12:00** **Lunch**
- 1:00** **Presentation on Derivation of Reference Values**
Dr. Willem Faber, Willem Faber Toxicology Consulting, LLC
- Clarifying Questions from Panel
Observer Comments
Panel Discussion (Questions 9-12)
- 4:00** **Summary of Panelists' Conclusions and Suggestions**
- 4:45** **Evaluation of Meeting**
- 5:00** **Adjourn**

Biographical Sketches of Presenters

Willem D. Faber, Ph.D.

Willem Faber Toxicology Consulting, LLC (WFTC, LLC)

Dr. Faber received a Ph.D. in toxicology from the Environmental Sciences Center at the University of Rochester in 1989. He worked as a reproductive and developmental and general toxicologist at the Health and Environment Laboratories at the Eastman Kodak Company from 1989 thru April, 2000. Since that time, Dr. Faber has been the principal toxicologist for Willem Faber Toxicology Consulting, LLC (WFTC, LLC) providing toxicology consulting services with emphasis on reproductive and developmental toxicology issues. He has been involved in toxicity issues throughout product development, toxicity screening, testing for product registration and labeling, risk assessment procedures, and basic research studies. Throughout his career, Dr. Faber has worked with toxicity issues for industrial chemicals with a focus on chemicals produced in very high volumes. In this respect, Dr. Faber has experience with materials that have very little exposure potential (e.g. site-restricted industrial intermediates) as well as materials that are found in considerable quantities in consumer goods (e.g. solvents, biocides) and therefore have very widespread exposures. Dr. Faber has served on two review panels for the Center for Evaluating Risks to Human Reproduction (CERHR). He is a member of the Teratology Society since 1987 and has prepared numerous study reports and publications during his career. Dr. Faber has been a Diplomat of the American Board of Toxicology since 1993.

Douglas B. McGregor, BSc., PhD., FIBiol., FRCPath **Independent Consultant**

Dr. McGregor received a Ph.D. in Zoology from King's College at the University of London in 1966. He has approximately 25 years of laboratory experience, 20 of which were in toxicology using a wide variety of *in vitro* and *in vivo* techniques, either directly or as a study supervisor including testing for mutagenicity, carcinogenicity and teratogenicity. This was followed by 11 years of carcinogen hazard and risk evaluation experience at the World Health Organization's (WHO) International Agency for Research on Cancer (IARC) where he participated in the *IARC Monographs Programme on the Evaluation of Carcinogenic Risks to Humans*. Dr. McGregor is currently an independent consultant in toxicology with continued involvement in hazard and risk evaluation for non-commercial, national and international organizations, including but not limited to: International Programme on Chemical Safety (IPCS); European Food Safety Authority (EFSA); L'Institut National de Recherche et de Sécurité (INRS), France; L'Institut de Recherche Robert-Sauvé et en Sécurité du Travail (IRSST), Québec, Canada; Republic of Ireland, at the Committee for Veterinary Products (CVMP) of the European Medicines Authority (EMA). He has also provided toxicology consulting to

several commercial enterprises in the petrochemical, metallurgic, pesticide, food and medicinal product areas. He serves on the editorial board for Mutation Research (Reviews section), Food and Chemical Toxicology, and GreenFacts (President of Scientific Board – www.greenfacts.org). Dr. McGregor has been a Fellow of the Royal College of Pathology since 1986 and a Fellow of the Institute of Biology since 1989. He is a member of the British Toxicology Society (Registered Toxicologist, re-registered May 2001 and 2006), Society of Toxicology, and the Environmental Mutagen Society, and has over 100 publications in journals, book chapters and on the web.

Additional Authors and Contributors

Drs. David Morgott and Abby Li contributed to the toxicology review portion of the risk assessment, Dr. Michael Gargas and Mr. Chris Kirman contributed the benchmark dose analysis, Dr. Daniel Pourreau wrote the exposure portion of the assessment, and Dr. Marcy Banton reviewed the risk assessment.

Appendix C

Peer Consultation Meeting on the Potential Risk of Health Effects from Exposure to Tertiary-Butyl Acetate

January 7-8, 2009

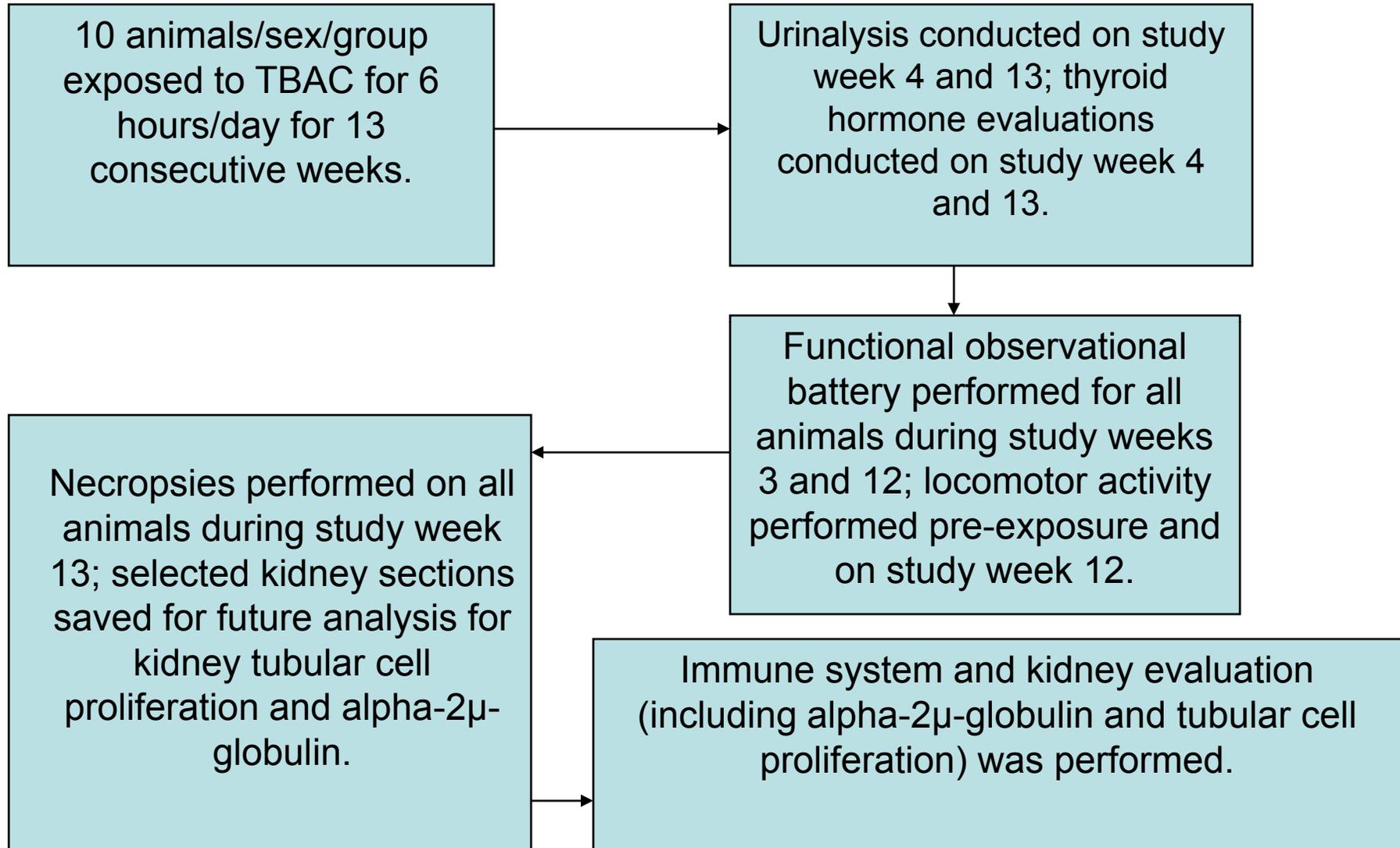
Presenter Slides

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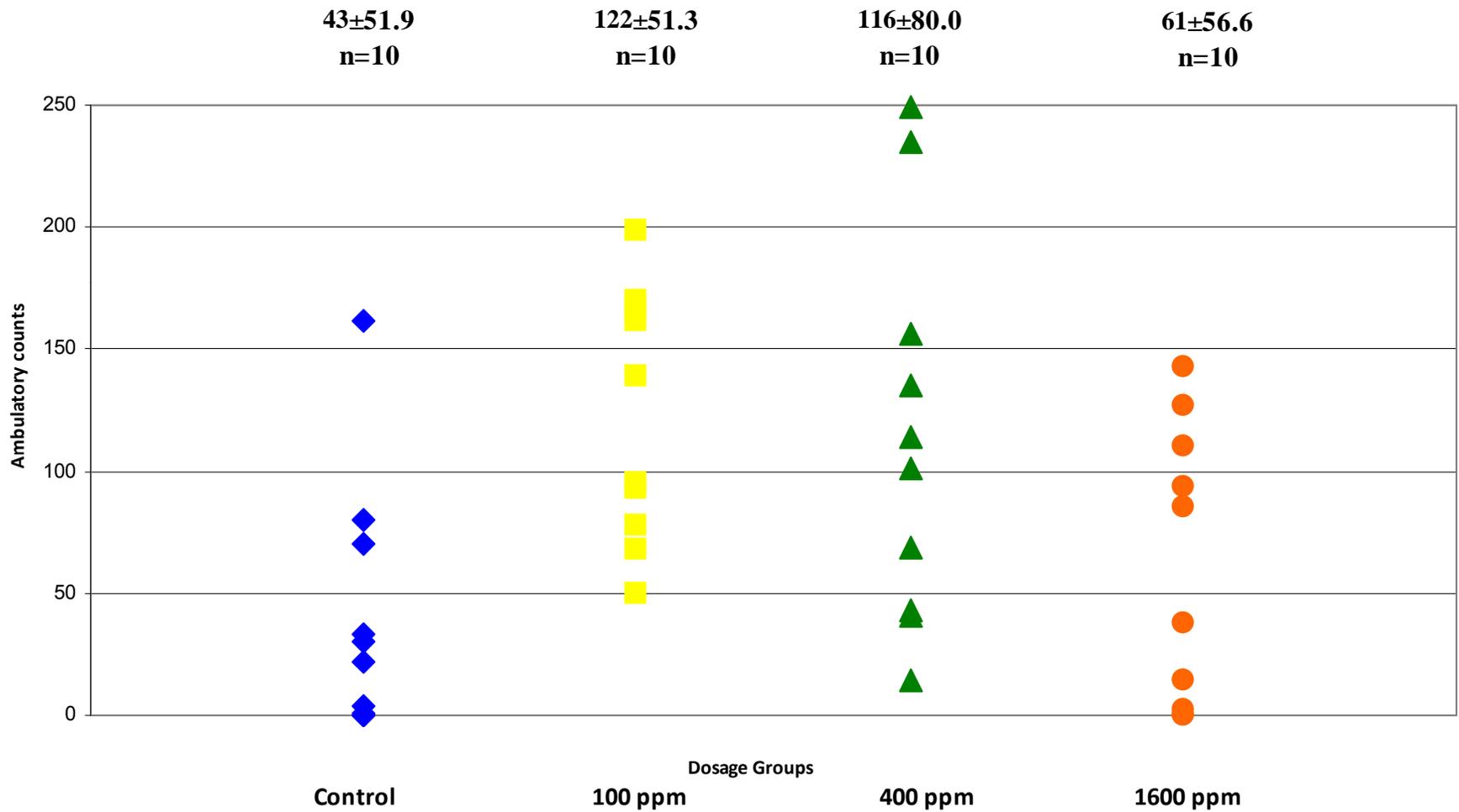
Study Information

- Protocols designed by George Cruzan and Doug Wolf
- Exposures started October 13, 2005 and ended January 15, 2006
- George Cruzan – study monitor until August 2006, Willem Faber – study monitor thereafter
- Additional contributors external to the testing laboratory – Abby Li and Susan Borghoff

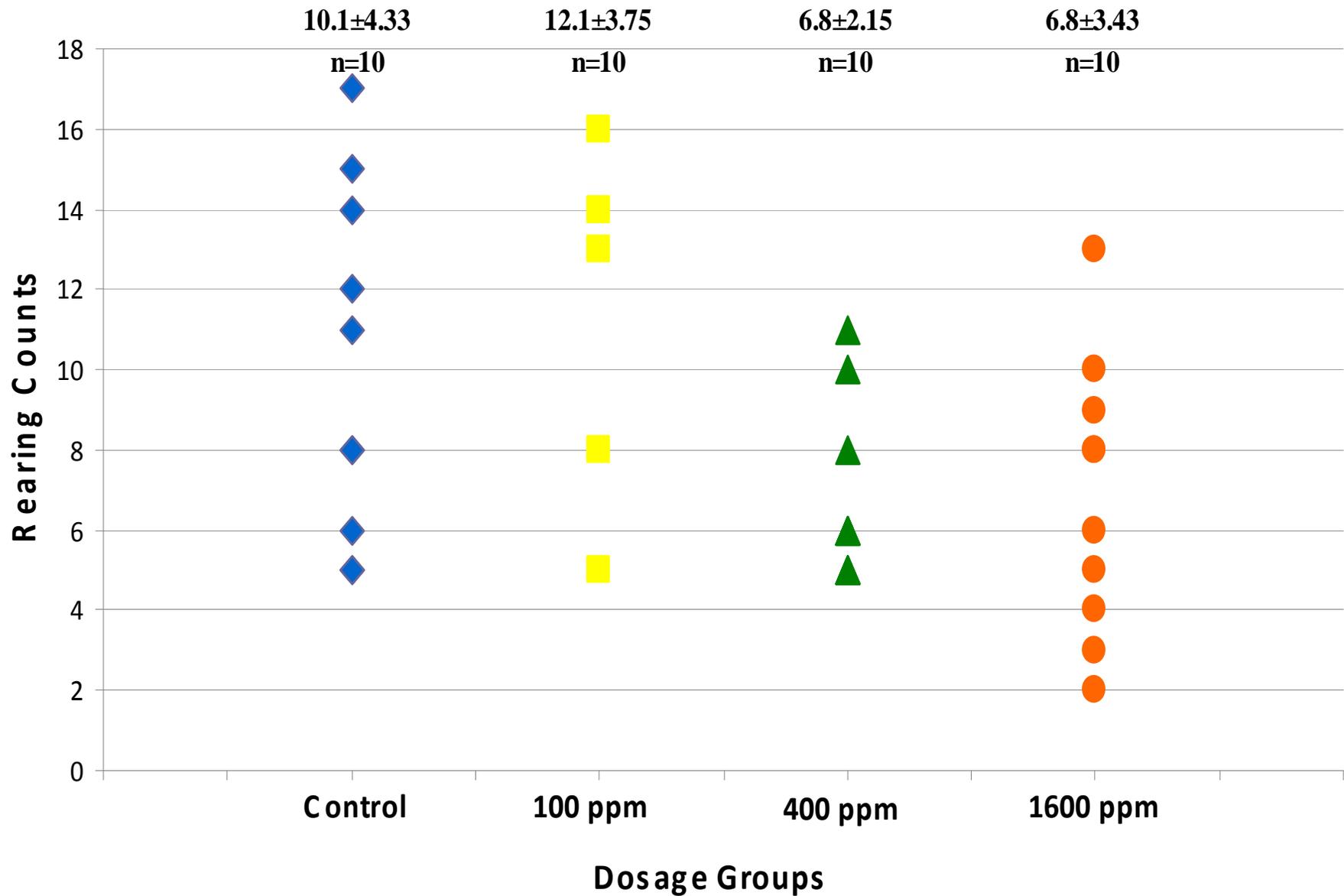
Rat Subchronic Toxicity Phase



Individual Ambulatory Motor Activity Counts from Minutes 45-60 During Week 12 in Female Rats Exposed to t-Butyl Acetate for 13 weeks.



Individual Rearing Counts During Week 12 Functional Observational Battery Testing in Male Rats Exposed to t-Butyl Acetate for 13 weeks.



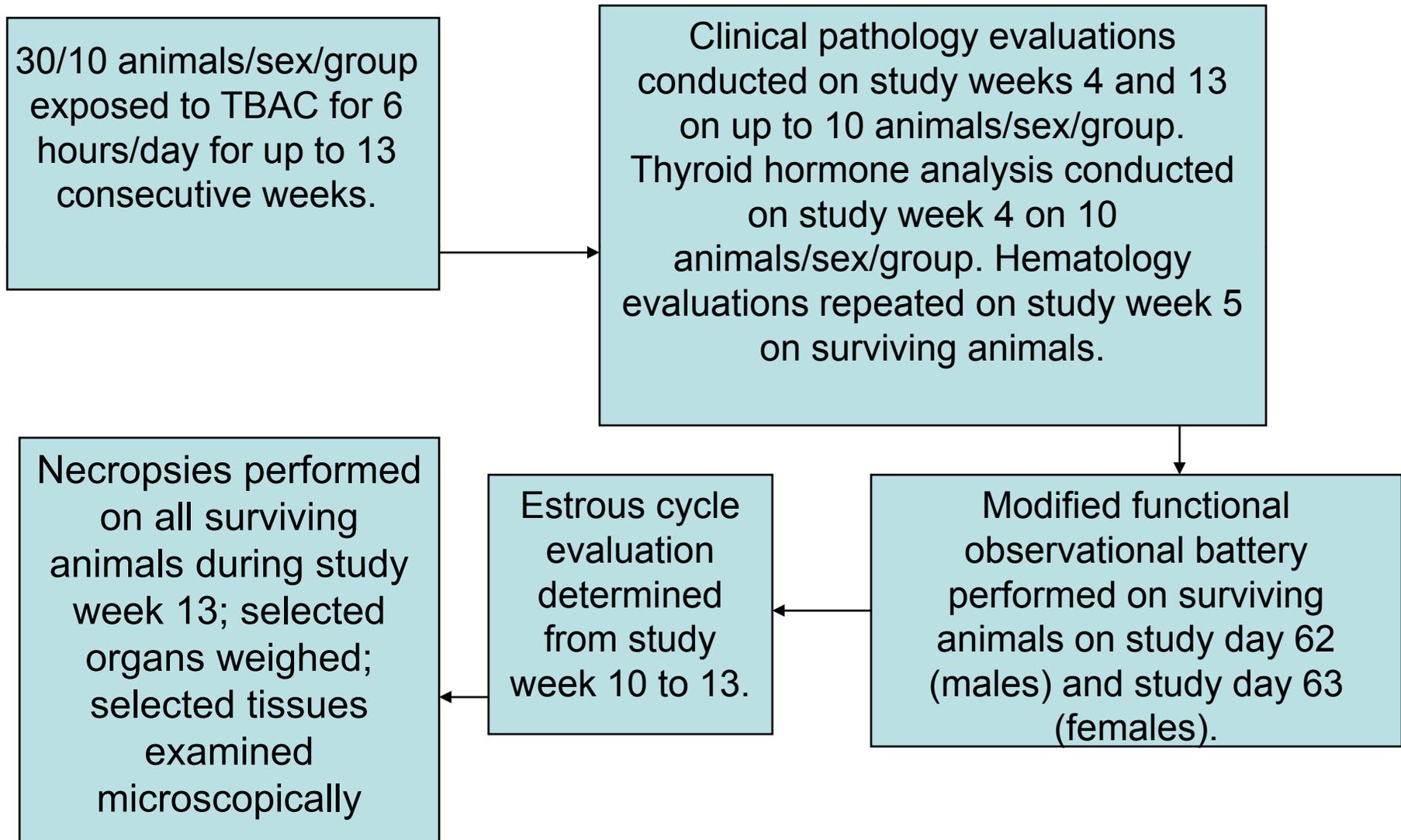
Rat Subchronic Toxicity Phase Additional Parameters Evaluated

- Study conducted according to OPPTS guidelines.
- Thyroid Hormone analysis including TSH, T3 and T4 were evaluated on study week 4 and 13
- Kidneys of each male rat was evaluated for alpha-2 μ -globulin by immunohistochemical staining and ELISA.
- Kidney tubular cell proliferation was assessed by immunohistochemical staining for proliferating cell nuclear antigen (PCNA).
- Immunotoxicity evaluation based on an extended microscopic examination of the spleen, thymus, Peyer's patches, bone marrow and mandibular, mesenteric, bronchial and mediastinal lymph nodes was performed.

Endpoints of Interest

- Motor Activity – male 1600 ppm group
- Organ weight changes
- Alpha – 2u-globulin
- Liver – metabolic induction

Mouse Subchronic Toxicity Phase



Mouse Subchronic Toxicity Phase Additional Parameters Evaluated

- Study conducted according to OPPTS guidelines.
- Thyroid Hormone analysis including TSH, T3 and T4 were evaluated on study week 4.
- Liver cell proliferation was assessed using immunohistochemical staining for proliferating cell nuclear antigen (PCNA).

Functional Observational Battery Measures in Mice

- Chambers opened as soon as TBAC stopped – Controls first, low, mid and high.
- Control group removed from inhalation area to test room.
- Exposed groups then moved to test room.
- Animals randomized within groups for FOB testing and acclimated for 15 minutes.
- 1 minute refers to open arena time only.
- Table 11 within report gives sequence of data collection.

Endpoints of Interest

- During and post-exposure clinical signs
- Liver effects
- Thyroid effects

Noncancer Endpoints

Developmental Toxicity

Metabolism

Mode of Action

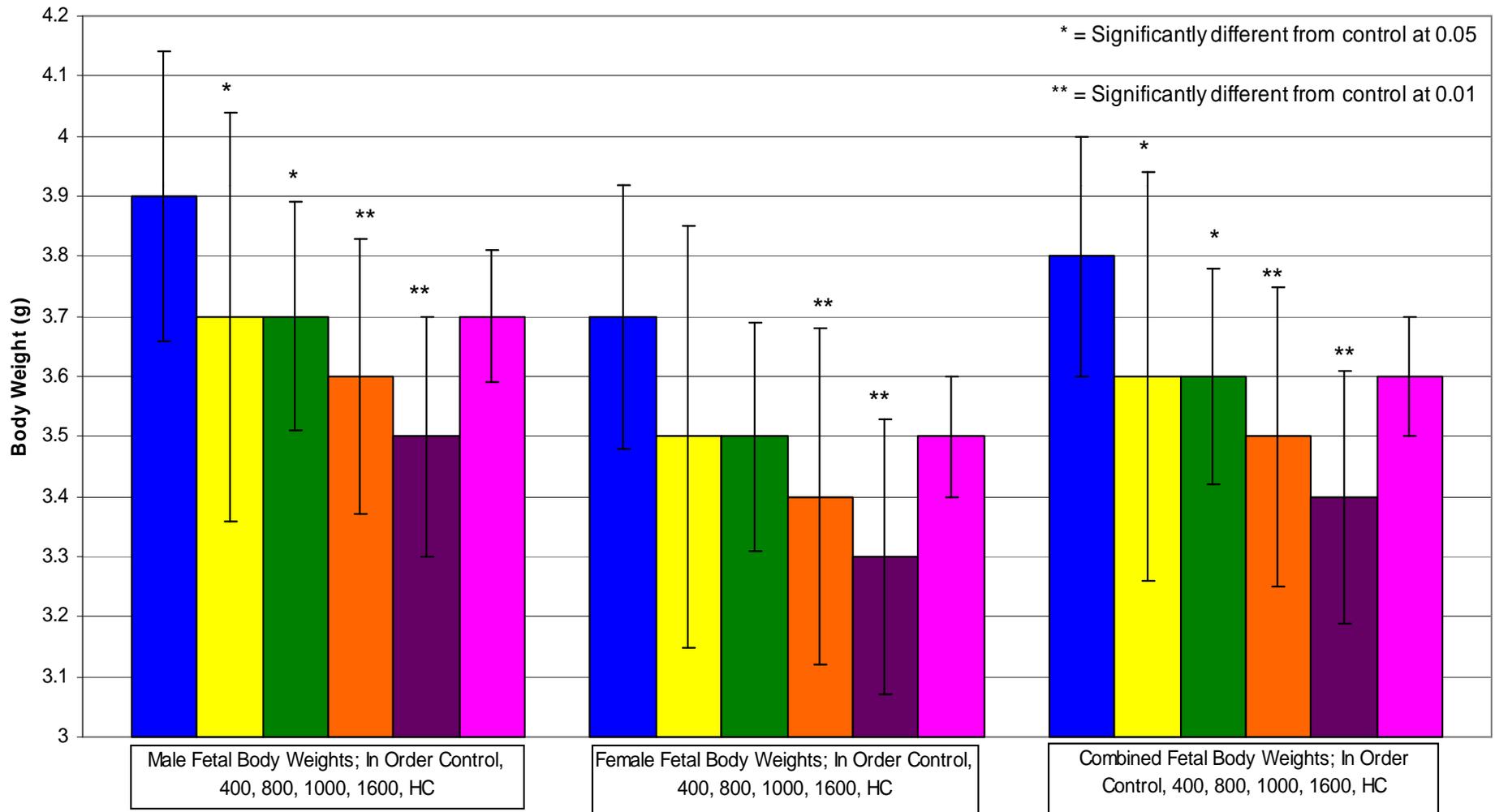
Developmental Toxicity

- Yang, et al., published between 1st and 2nd version of the RA
- Confusion on unit of statistical analysis – Fetus or Litter?
- Authors contacted and data reviewed, corrected and analyzed
- Maternal toxicity – minimal investigation
- Endpoints affected in Yang et al., are closely associated with maternal toxicity
- Oral toxicity – little known
- Study conducted examining maternal toxicity to replicate dosing regimen of Yang, et al
- Not enough time for fetal evaluations to be done within the timeframe for the RA

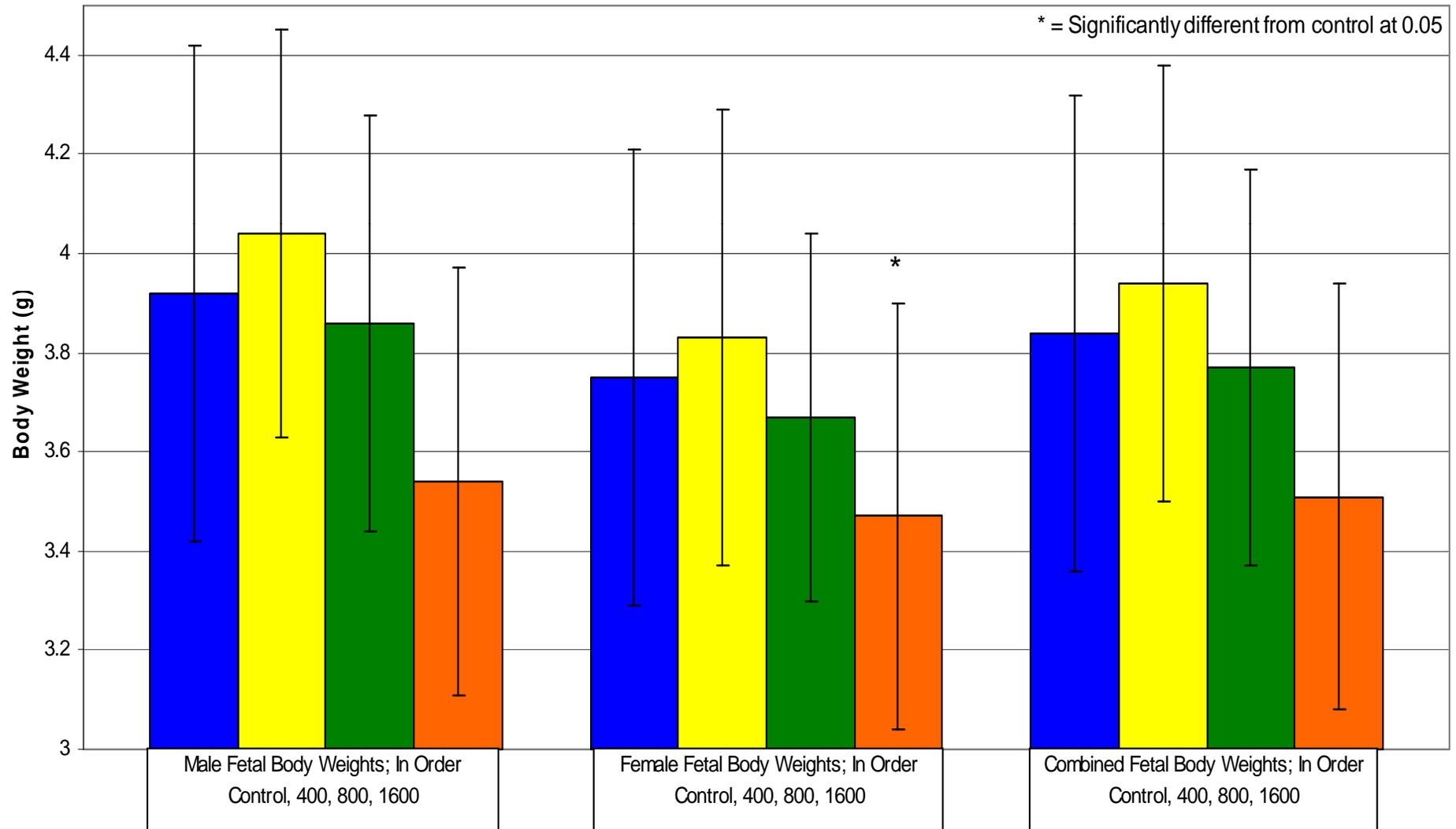
Litter Size in the Maternal Toxicity Study with Historical Control Data

	Control	400 mg/kg/day	800 mg/kg/day	1000 mg/kg/day	1600 mg/kg/day	WIL Historical Control
Mean	14.4	15.4	15.3	15.4	15.9	15.2
SD	2.21	2.11	1.98	1.82	2.01	0.57
SEM	0.14	0.45	0.42	0.39	0.44	0.05
N	22	22	22	22	21	2829

Fetal Body Weights from Maternal Toxicity Study with Historical Control Data



Fetal Body Weights From Yang et al.



Metabolism and Kinetics

- Dose dependency
- Cytochrome P450-mediated pathway
- Esterase pathway
- Kinetics from inhalation exposures

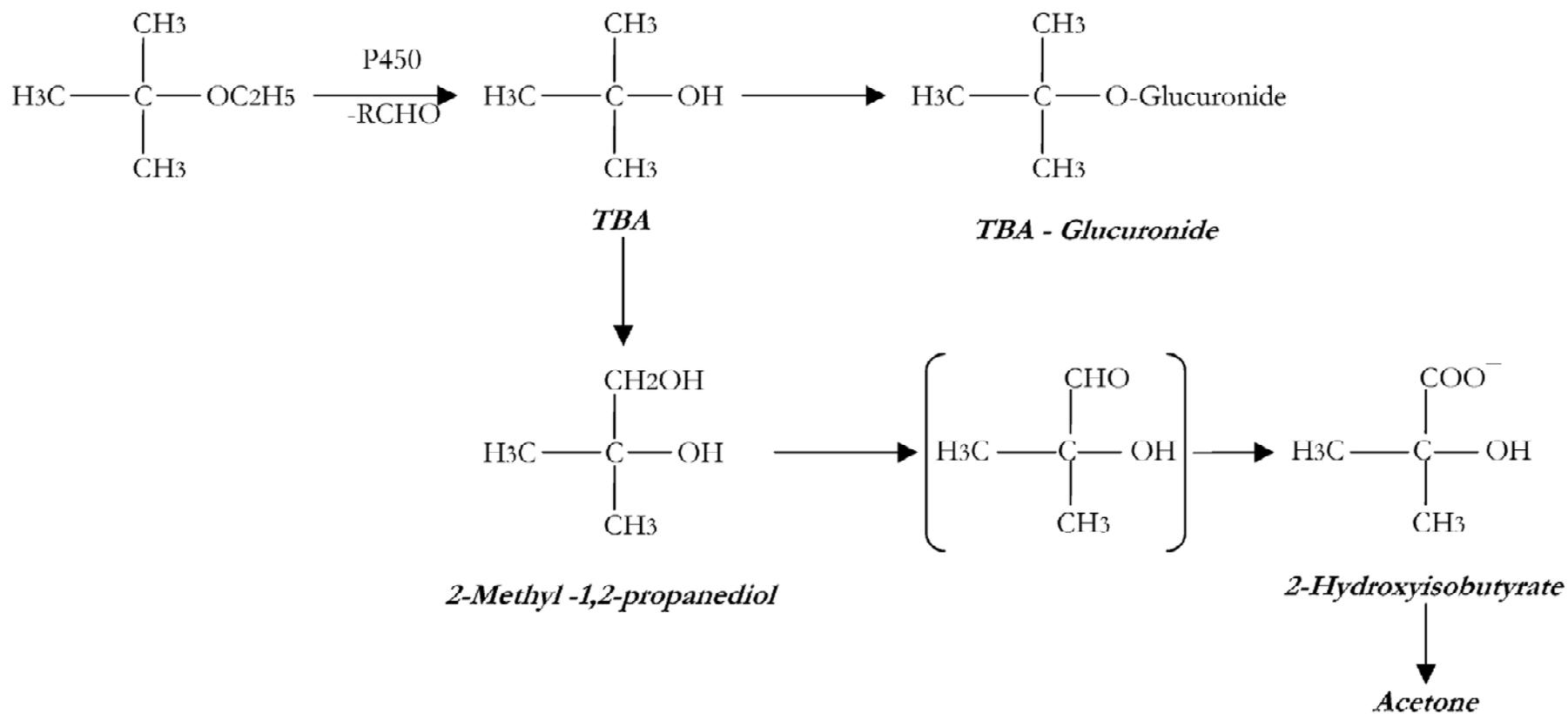
MOA Alpha-2u-globulin

- Kidney weights
- Histopathology
- Immunohistochemistry
- ELISA
- Data from metabolite (TBA)

MOA Thyroid Effects

- Thyroid hormone values
- Organ weights (post fixation)
- Histopathology
- Liver weights
- TBA data

Metabolism of MTBE/ETBE in mammals



Genetic Toxicity: TBAC

Non-significant responses in single studies for:

- Bacterial mutations
- Human lymphocyte chromosomal aberrations
- Rat bone–marrow cell micronuclei

McGregor et al. (2005), Cruzan et al. (2006)

Genetic Toxicity: the TBAC metabolite TBA (*non-contentious data*)

Gene mutation in L5178Y cells (<i>tk</i>): (5000 µg/ml)	—
Sister-chromatid exchange in CHO cells: (5000 µg/ml)	—
Chromosomal aberrations in CHO cells: (5000 µg/ml)	—
Micronuclei in peripheral blood of mice: (40 mg/ml drinking water for 13 weeks)	—

McGregor et al. (1988), NTP (1995)

Genetic Toxicity: the TBAC metabolite TBA (*contentious data*)

- Bacterial mutation tests (3)

Zeiger et al. (1987) Williams-Hill et al. (1999) McGregor et al. (2005)

- Comet assay in HL-60 leukaemia cells (1)

Tang et al. (1999) McGregor (2006) Cruzan et al. (2006)

Carcinogenicity: the TBAC metabolite TBA

Rats, NTP (1995) [1]

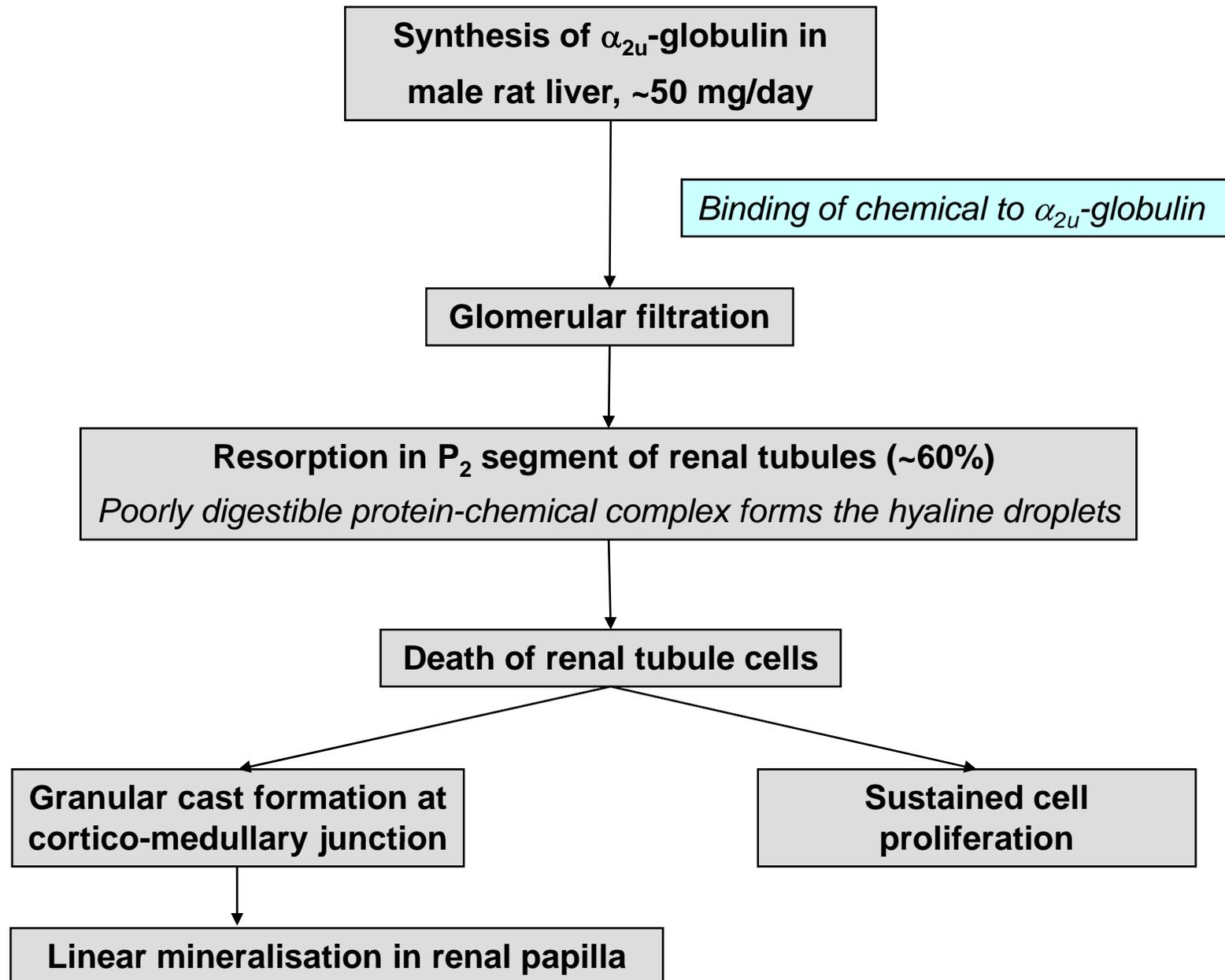
Proliferative lesion	Sex	Dose (mg/ml)				
		0	1.25	2.50	5.0	10.0
Renal tubule cell adenoma	F	0/50	0/50	0/50	-	0/50
RTC adenoma	M	1/50	3/50	4/50	3/50	-
RTC adenoma + carcinoma <i>(step sectioning)</i>	M	8/50	13/50	19/50	13/50	-

Carcinogenicity: the TBAC metabolite TBA

Rats, NTP (1995) [2]

Proliferative lesion	Sex	Dose (mg/ml)				
		0	1.25	2.50	5.0	10.0
Mononuclear cell leukaemia	F	22/50	20/50	18/50	-	13/50
	M	30/50	28/50	24/50	23/50	-
Mammary Ad, fib-ad, or Ca	F	17/50	16/50	12/50	-	10/50
Pancreatic islet Ad or Ca	F	2/50	1/50	4/48	-	1/50
	M	17/50	15/50	9/49	6/49	-

α_{2u} -globulin-associated nephropathy MoA



Chronic progressive nephropathy (CPN)

Chemical interaction

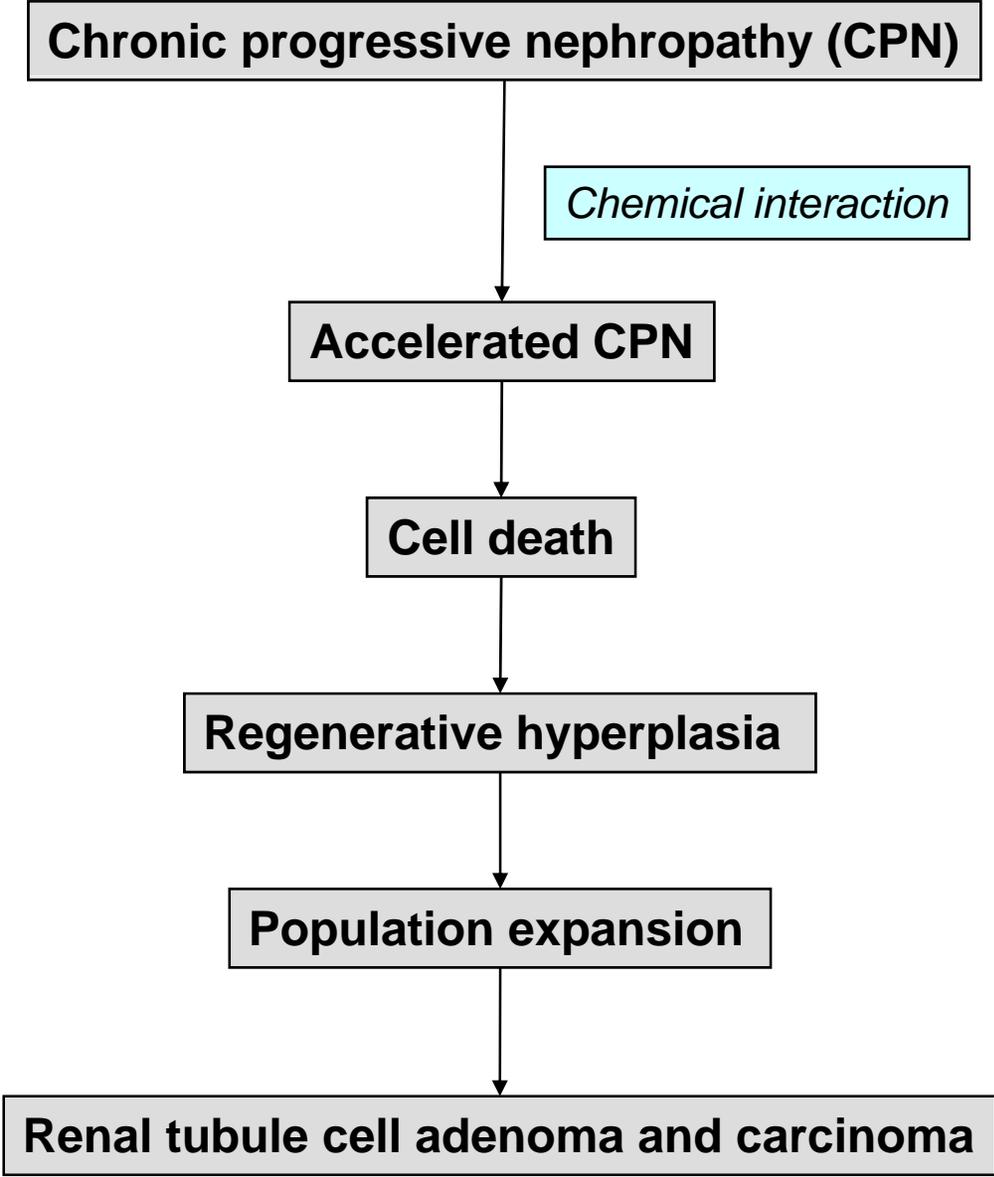
Accelerated CPN

Cell death

Regenerative hyperplasia

Population expansion

Renal tubule cell adenoma and carcinoma



Carcinogenicity: the TBAC metabolite TBA

Thyroid Follicular Cell Adenomas in Mice

TBA in drinking water

Males

Dose (mg/kg bw/day)	0	535	1035	2065
Incidence	1/60	0/59	4/59	1/57

Females

Dose (mg/kg bw/day)	0	510	1015	2105
Incidence	2/58	3/60	2/59	9/59

Carcinogenicity: the TBAC metabolite TBA Thyroid Follicular Cell Adenomas in Mice

TBA from inhaled MTBE

Males

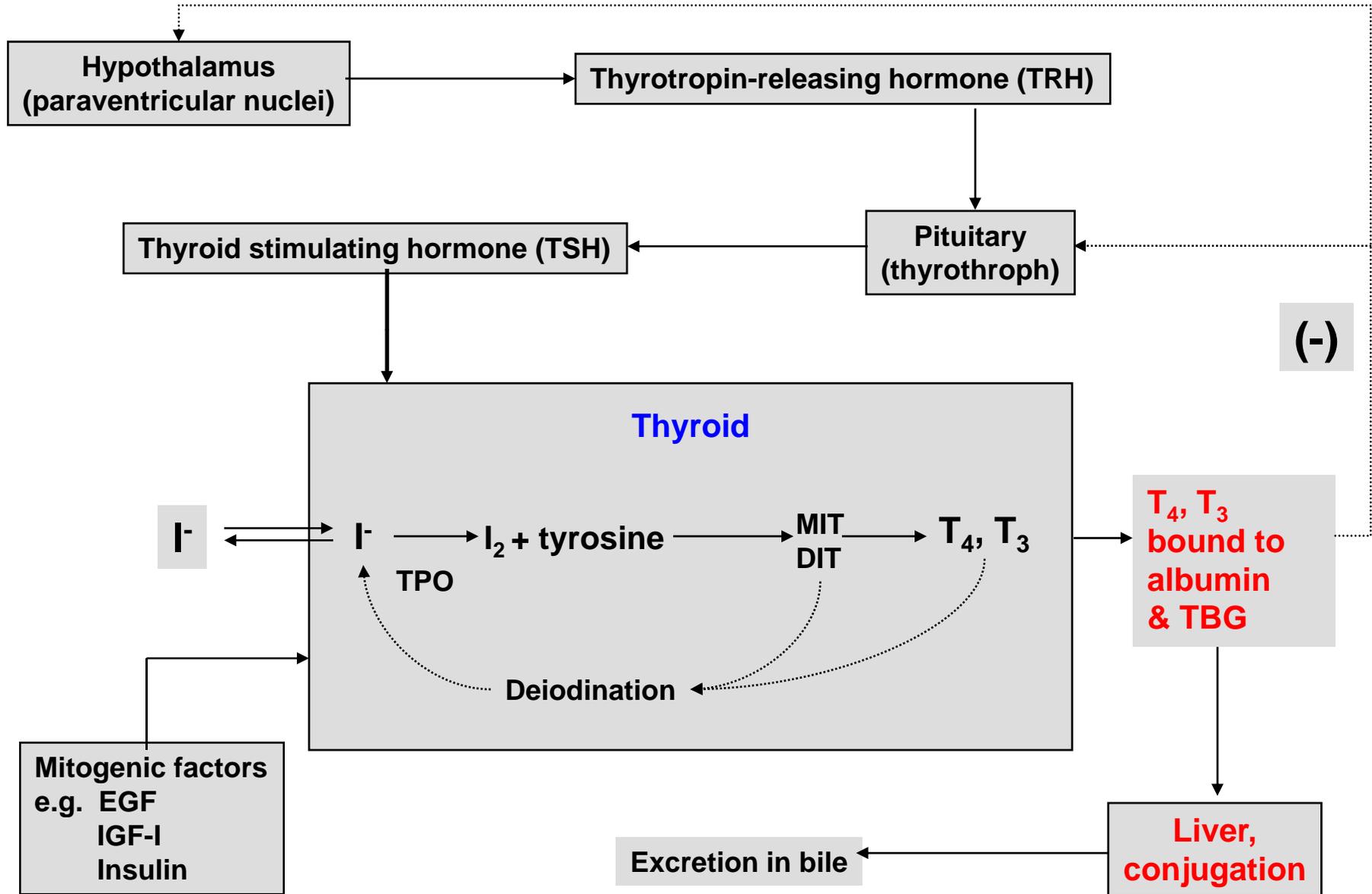
Dose (mg/kg bw/day)	0	153	1127	3017
Incidence	0/49	0/11	0/19	0/48

Females

Dose (mg/kg bw/day)	0	182	1345	3620
Incidence	0/50	0/11	0/14	0/49

Burleigh-Flayer et al.(1992) Bird et al (1997)

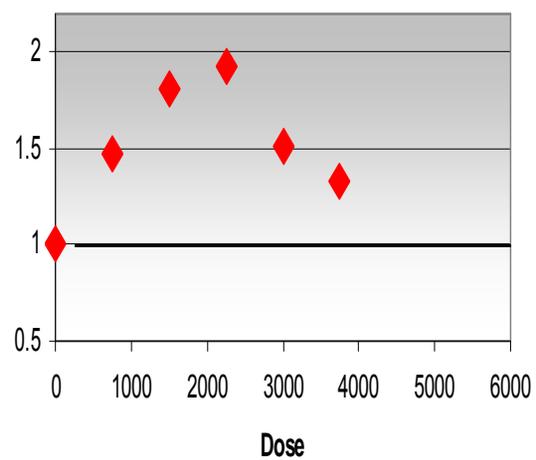
Thyroid feedback control



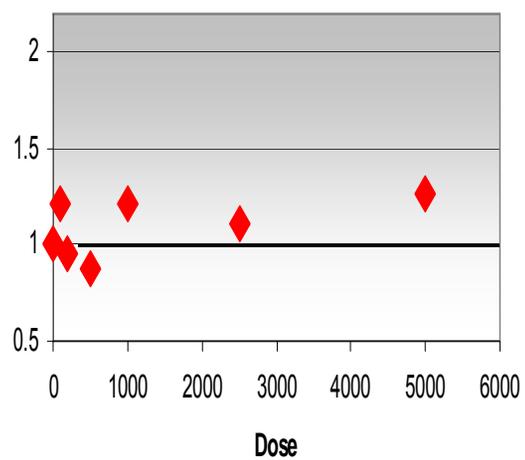


S. typhimurium TA102: TBA, Water solvent [1]

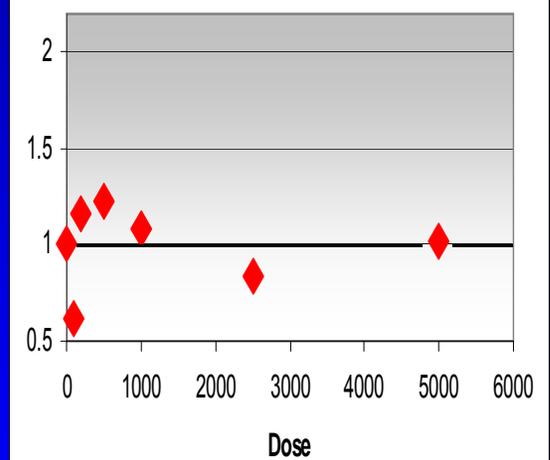
Williams Hill et al. +S9



McGregor et al. +S9 [1]

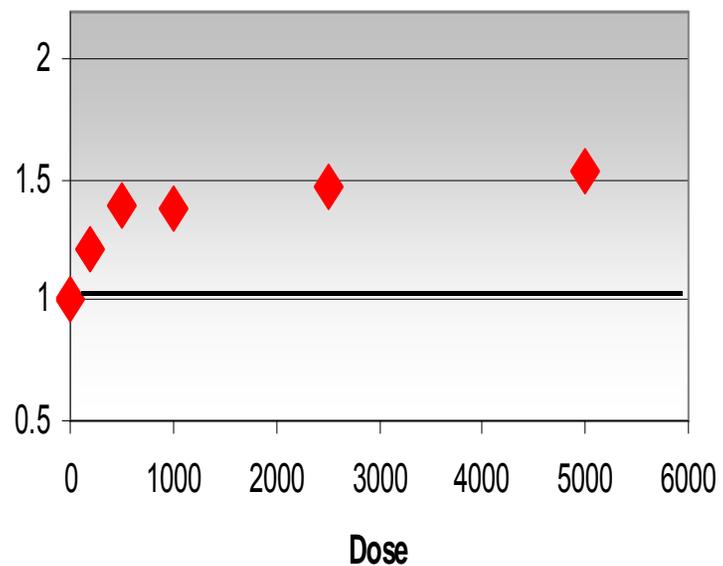


McGregor et al. +S9 [2]

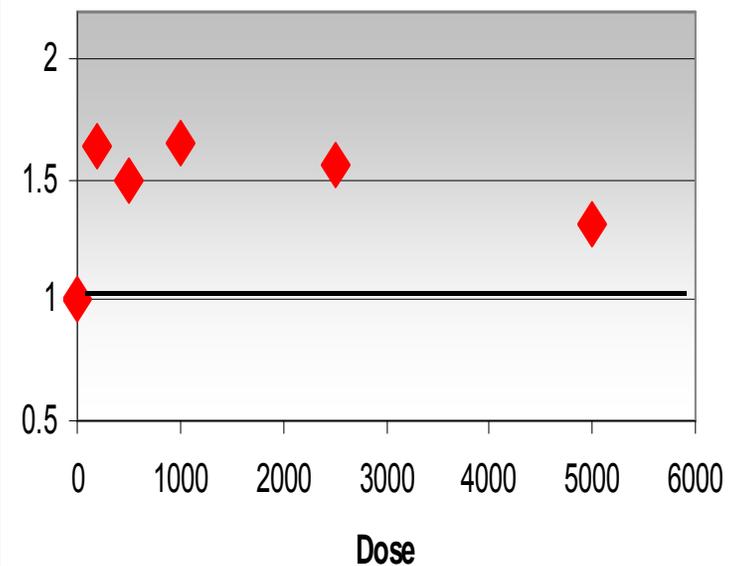


S. typhimurium TA102: TBA, Water solvent [2]

McGregor et al. w/o S9 [1]

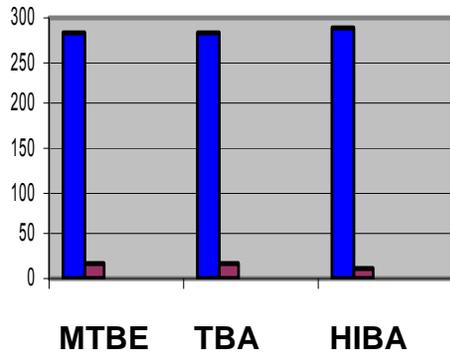


McGregor et al. w/o S9 [2]

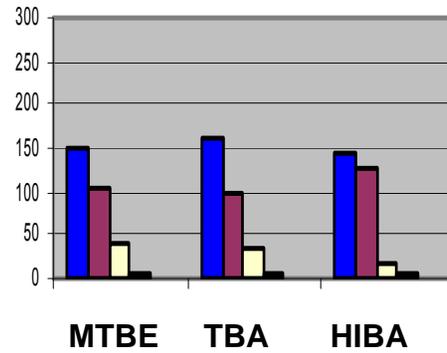


Comet assay, MTBE, TBA, HIBA (*Tang et al. 1997*)

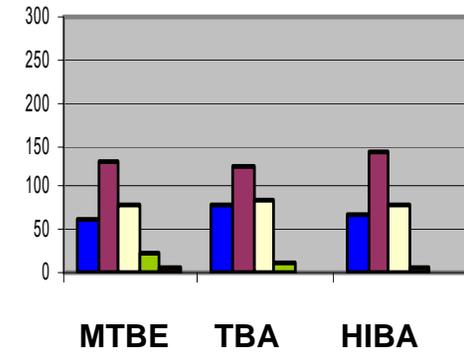
Exposure = 0 mmol/L



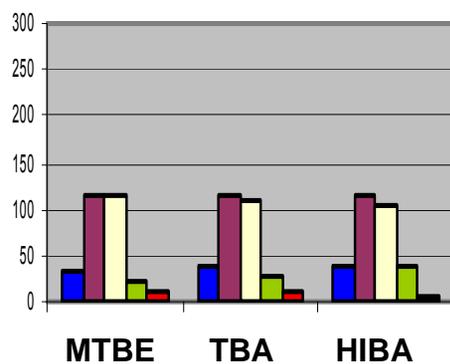
Exposure = 1 mmol/L



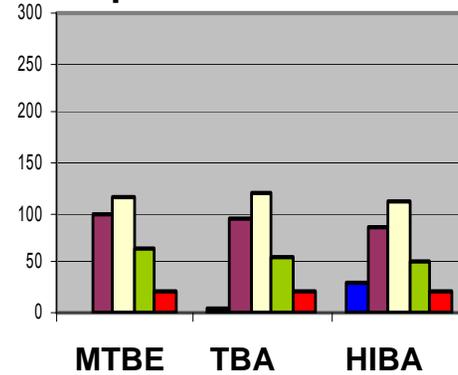
Exposure = 5 mmol/L



Exposure = 10 mmol/L



Exposure = 30 mmol/L

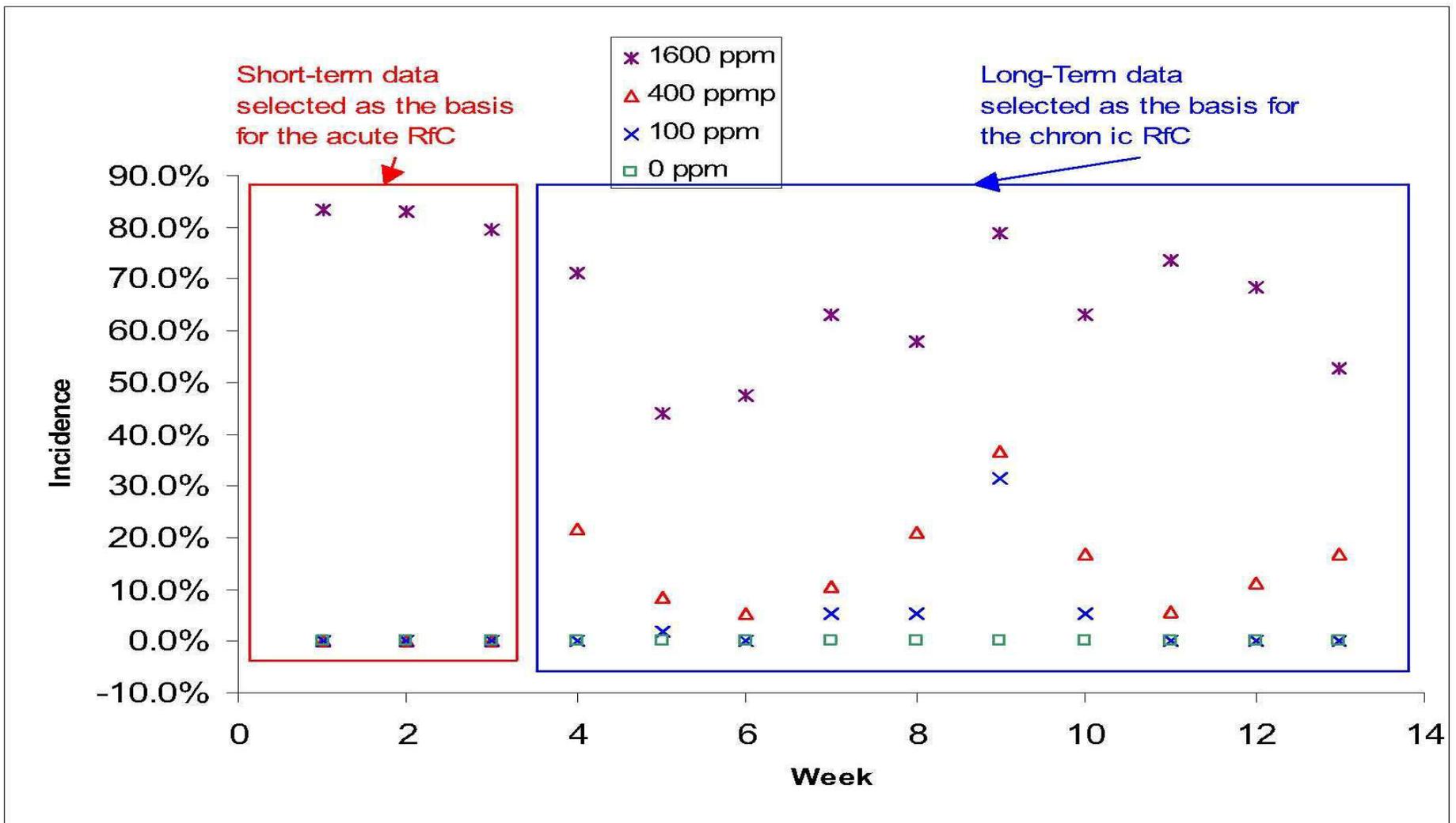


Bench Mark Dose (BMD) Analysis

Selection of Critical Study

- Studies compared for critical effects
- Endpoints not relevant to human health or not replicated – removed from consideration
- Key Study/Endpoint – acute neurotoxicity endpoints collected in mouse 13-week study
- Hyperactivity endpoint (post-exposure) modeled for acute and chronic exposures

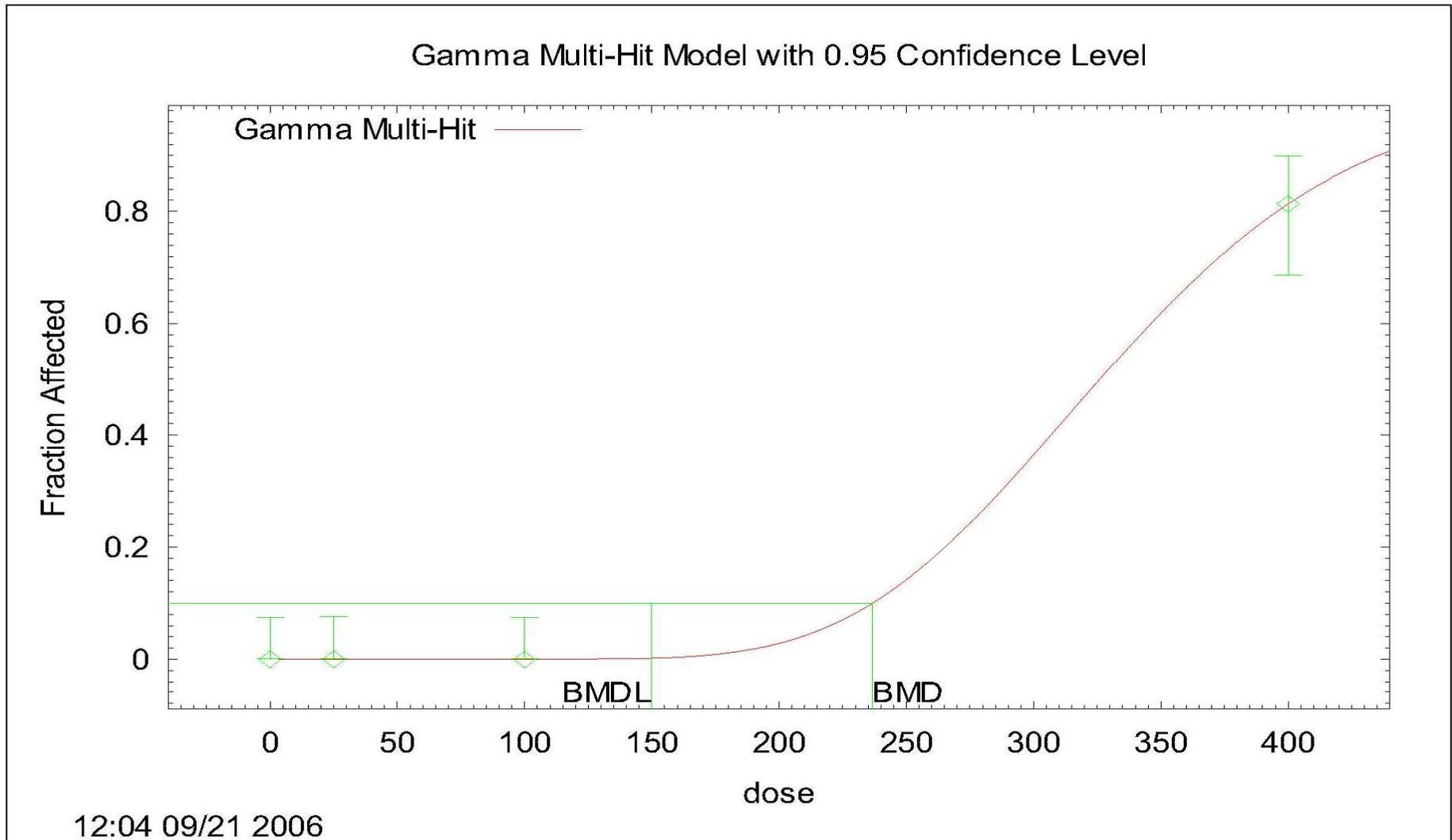
Incidence of Hyperactivity in the Mice Exposed to TBAC (Post-Exposure Observations)



Comparison of Dose-Response Models for Short-Term Exposure to TBAC (*Model was selected for use in deriving the RfC value based upon visual inspection and goodness of fit)

Model	Point of Departure (ppm, continuous)			Model Fit	
	ED10	LED10	ED10/LED10	AIC	p-Value
gamma*	236.6	149.8	1.6	58.8	1.000
logistic	346.9	203.4	1.7	60.8	1.000
log logistic	312.6	151.6	2.1	60.8	1.000
probit	302.3	180.1	1.7	60.8	1.000
log probit	254.7	141.2	1.8	60.8	1.000
Weibull	329.4	164.4	2.0	60.8	1.000
multistage	161.1	139.05	1.2	61.9	0.656
quantal quadratic	108.3	95.6	1.1	71.0	0.0776
quantal linear	43.8	34.5	1.3	105.3	0.000

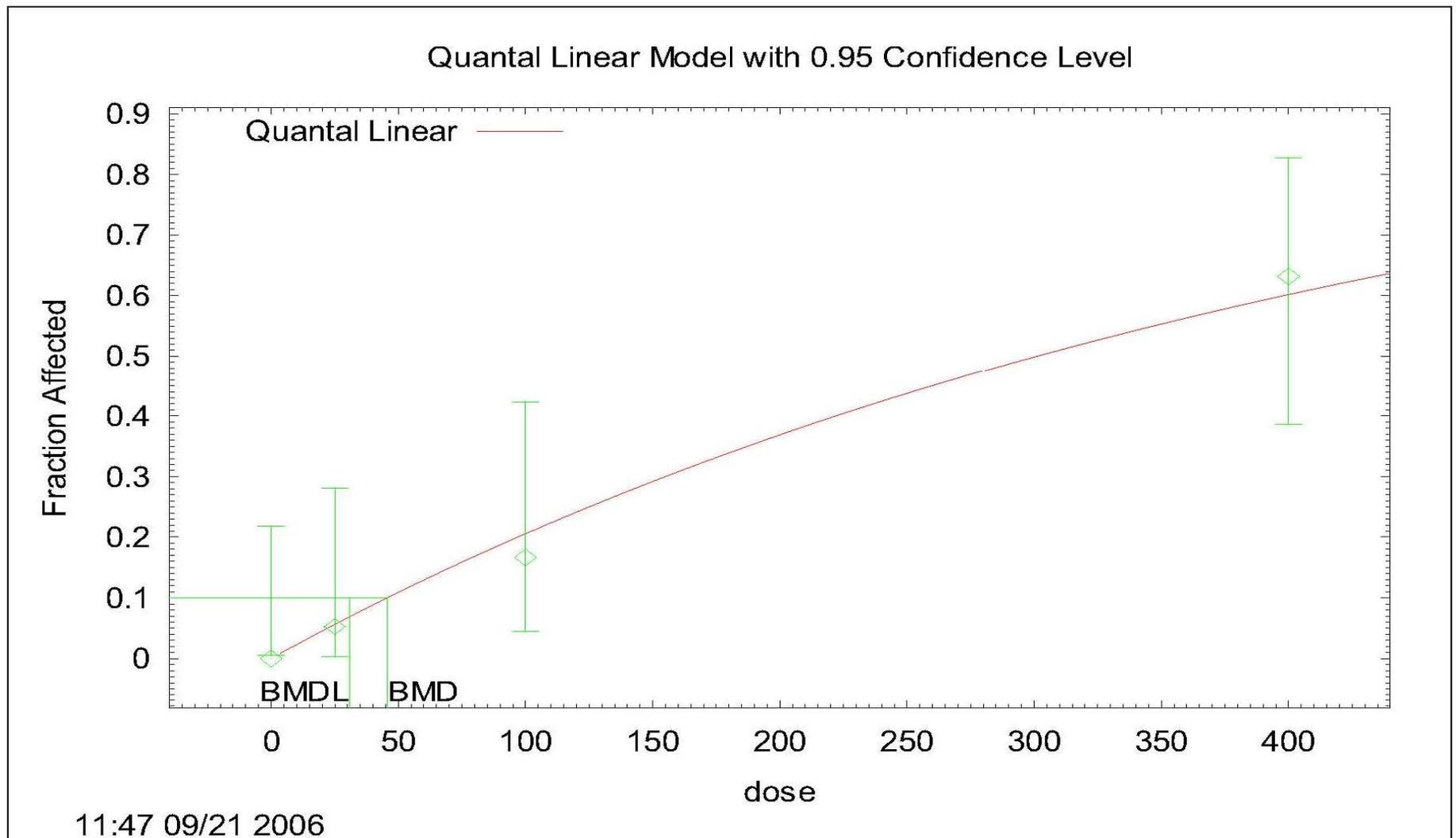
Fit of the Gamma Dose-Response Model to Hyperactivity Data in Mice Following Short-Term Exposure to TBAC



Comparison of Dose-Response Models for Long-Term Exposure to TBAC (*Model was selected for use in deriving the RfC value based upon visual inspection and goodness of fit)

Model	Point of Departure (ppm, continuous)			Model Fit	
	ED10	LED10	ED10/LED10	AIC	p-Value
quantal linear*	45.7	30.7	1.5	51.3	0.971
multistage	55.9	31.2	1.8	53.1	0.987
Weibull	55.0	17.5	3.1	53.2	0.952
gamma	54.4	16.2	3.4	53.2	0.944
log logistic	54.9	19.5	2.8	53.3	0.875
log probit	51.2	19.9	2.6	53.6	0.766
probit	123.7	89.6	1.4	55.0	0.507
quantal quadratic	127.1	100.6	1.3	55.4	0.403
logistic	136.6	97.2	1.4	55.4	0.447

Fit of the Gamma Dose-Response Model to Hyperactivity Data in Mice Following Long-Term Exposure to TBAC



Appendix D

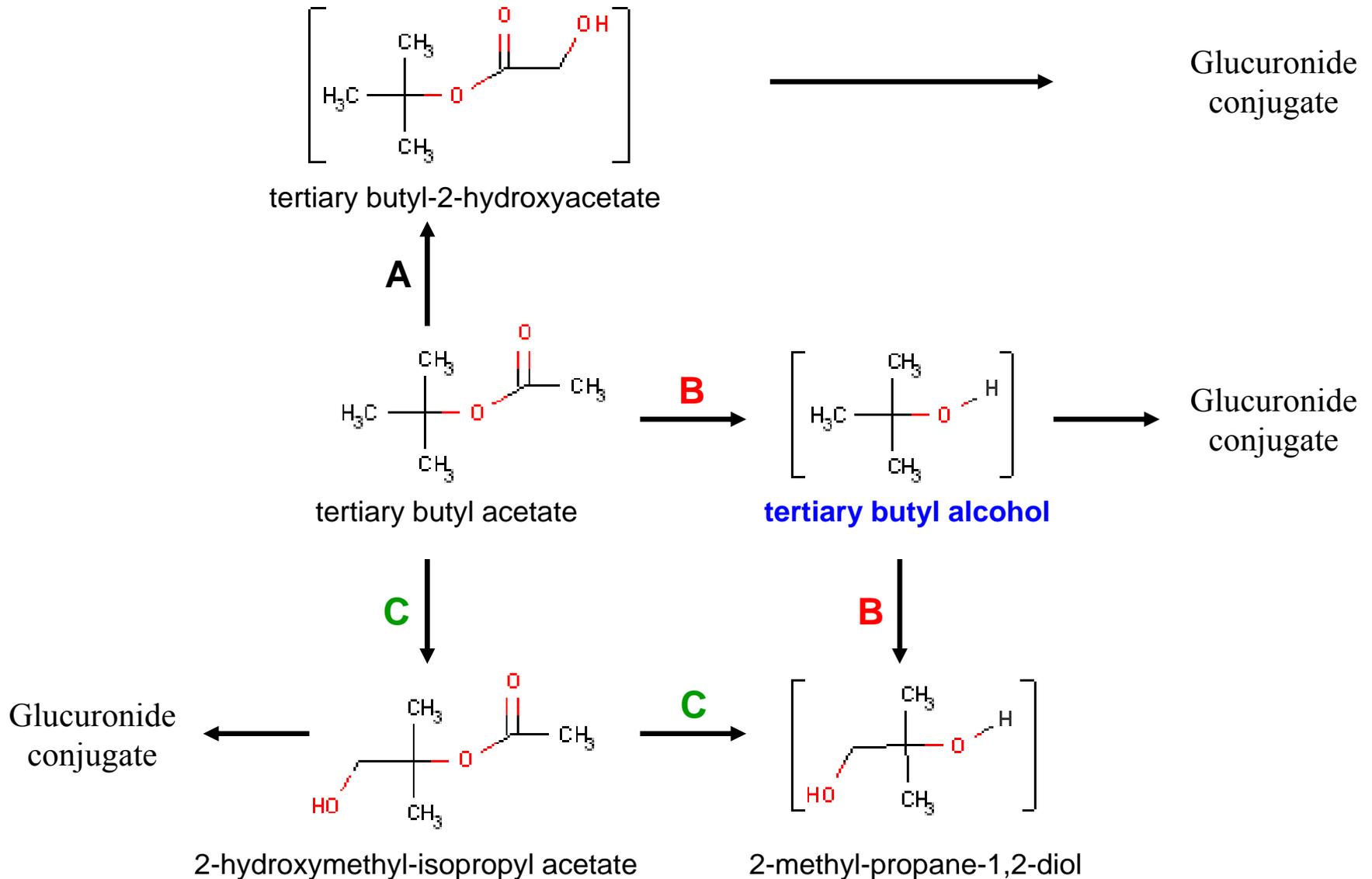
Peer Consultation Meeting on the Potential Risk of Health Effects from Exposure to Tertiary-Butyl Acetate

January 7-8, 2009

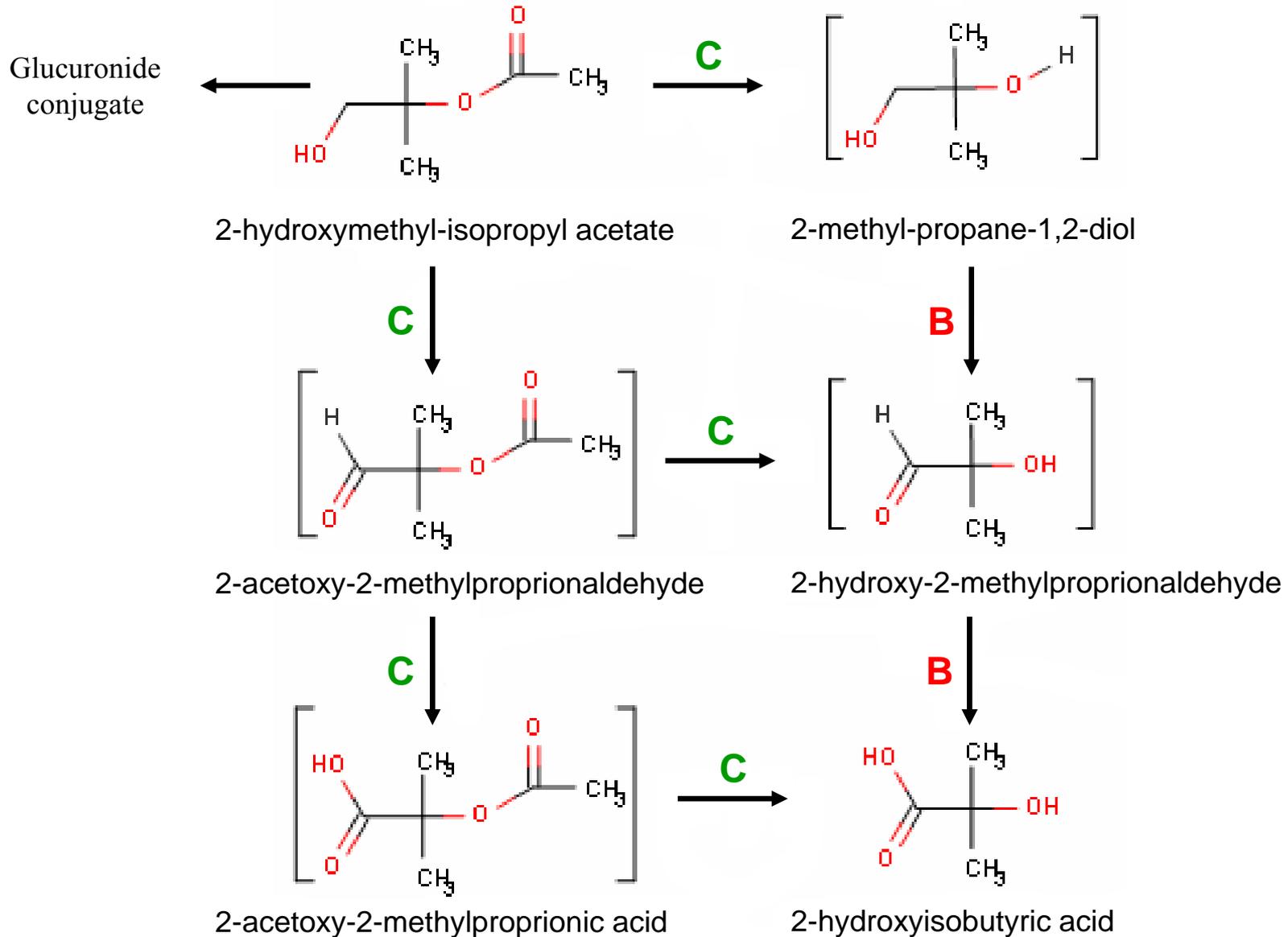
Additional Handouts

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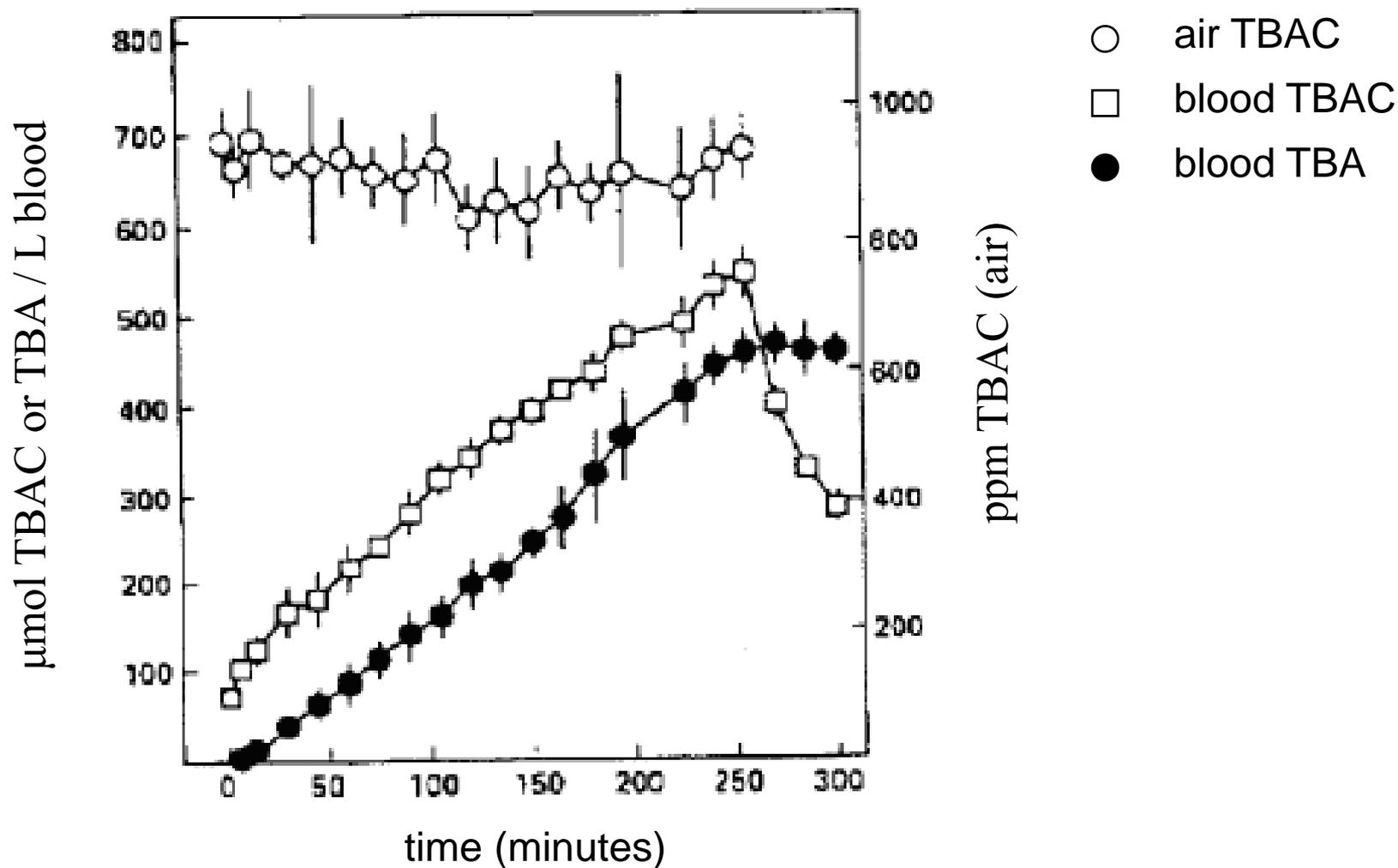
Metabolic pathways of TBAC in rats (I)



Metabolic pathways of TBAC in rats (II)

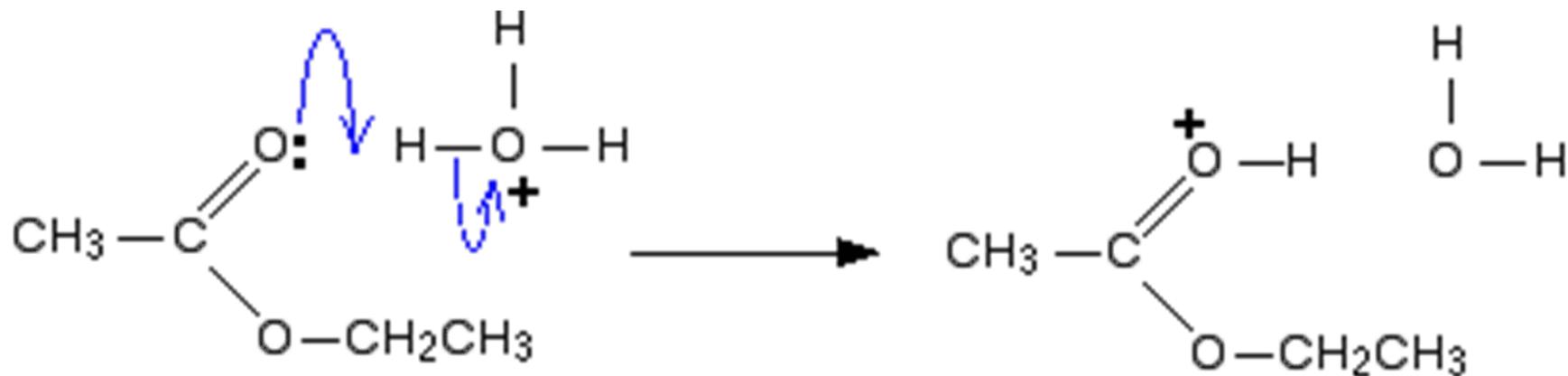


Concentrations of TBAC and TBA in blood of rats exposed to TBAC by inhalation

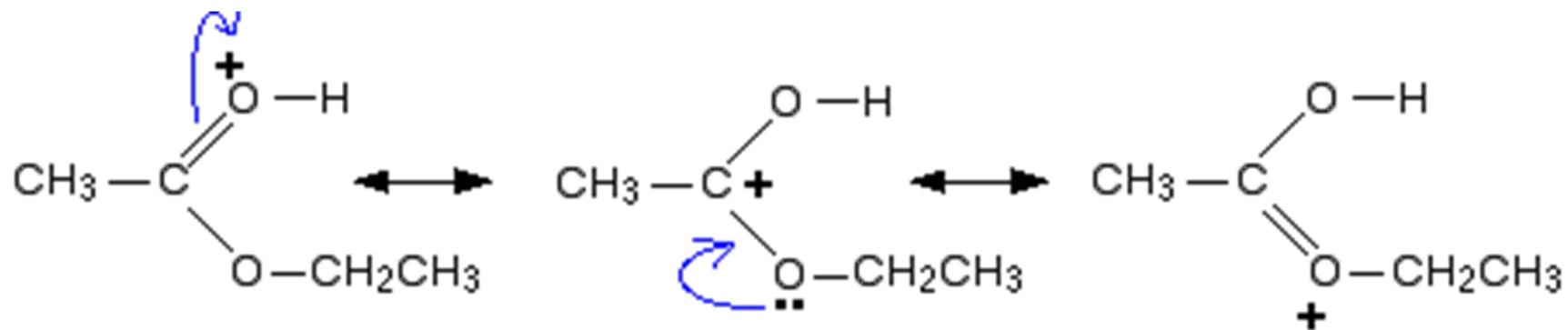


Ester hydrolysis I

Step 1

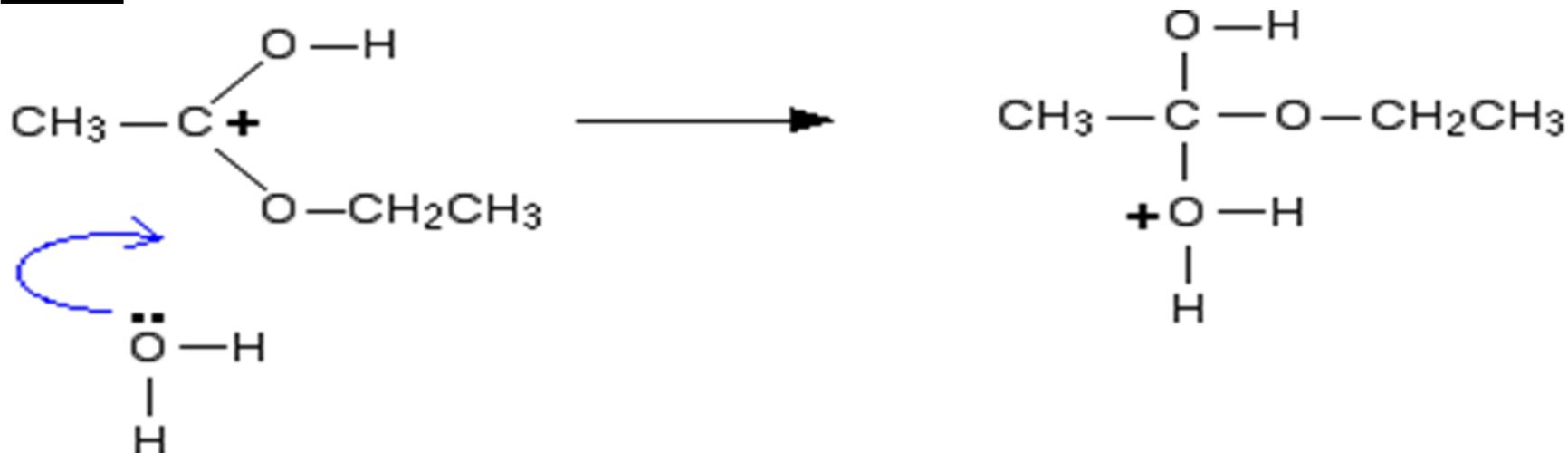


Step 2

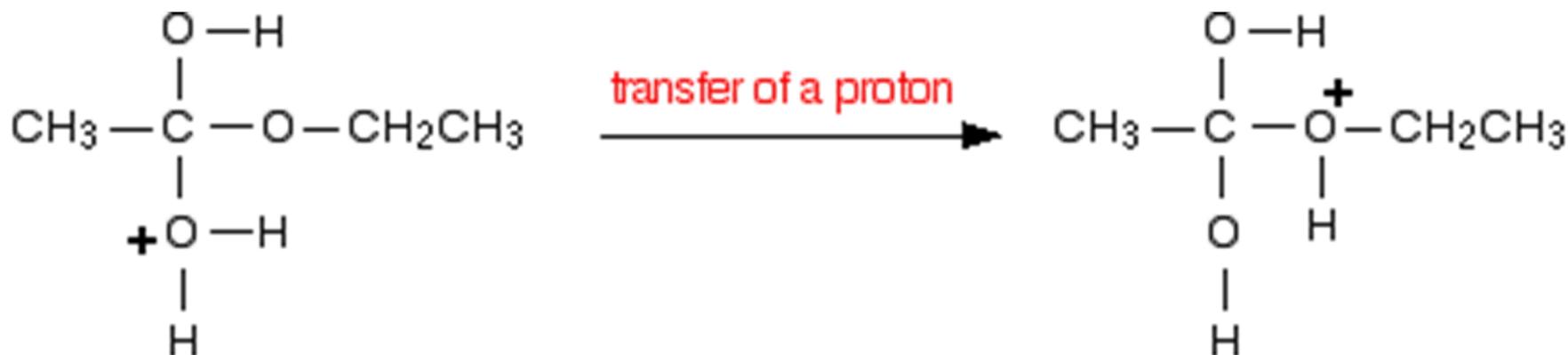


Ester hydrolysis II

Step 3

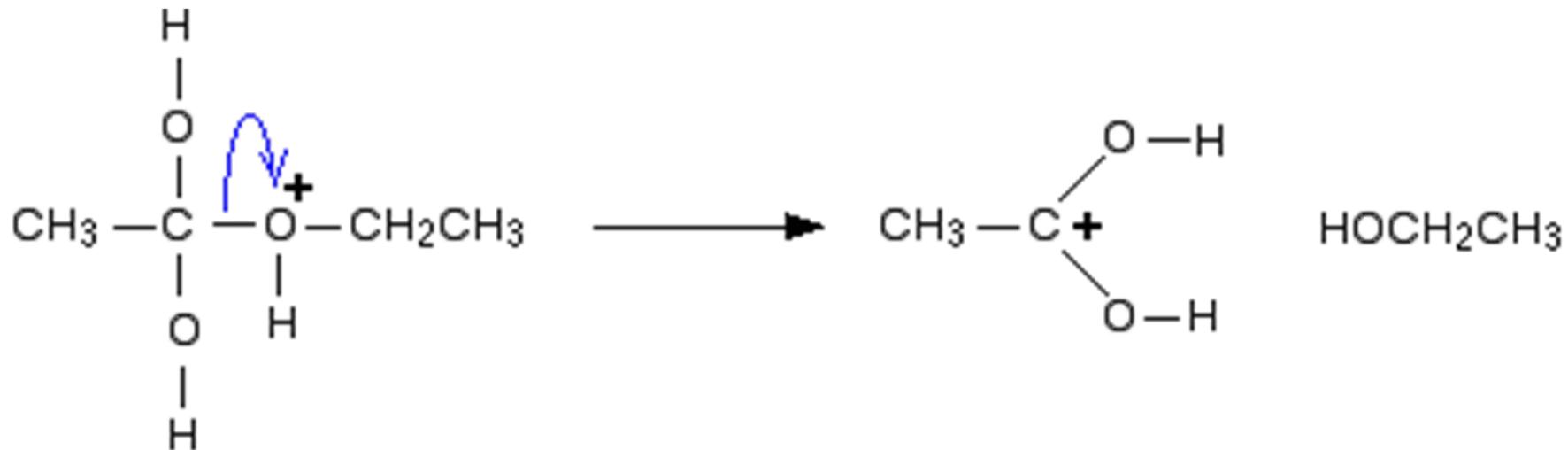


Step 4



Ester hydrolysis III

Step 5



Step 6

