Appendices for the Report of the Peer Review Meeting on Acrylonitrile

September 22 and 23, 2003
University of Cincinnati
Cincinnati, Ohio

Peer Review Organized by:
Toxicology Excellence for Risk Assessment
April 16, 2004

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APPENDIX A

Panel Member Biographical Sketches
And
Conflict of Interest Statements

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Peer Review of Acrylonitrile Risk Assessment
Panel Membership and Conflict of Interest and Bias Disclosures
September 22-23, 2003

An essential part of panel selection is the identification and disclosure of potential conflicts of interest and biases to ensure credible results and confidence in the panel's recommendations. The policy of Toxicology Excellence for Risk Assessment (*TERA*) is that any conflict of interest (COI) would prevent a person from consideration for a peer review panel. Conflicts of interest include authorship or previous review of the subject document, current employment by the Sponsor or Author organizations, current personal financial support from the Sponsor (i.e., contracts or grants directly from the company to the individual), and direct personal financial interests in the outcome of the review. *TERA*'s procedures also seek to identify and disclose situations of potential partiality or bias. *TERA*'s COI policy and procedures for peer review meetings is found at http://www.tera.org/peer/COI.html .

For this peer review of acrylonitrile, all panel members were asked to complete a questionnaire to determine whether their involvement in certain activities could pose a conflict of interest or could create the appearance that the peer reviewer lacked impartiality. An answer of "yes" to any of the questions generated follow up by *TERA* staff for additional information. *TERA* staff carefully reviewed these forms and discussed the answers with the panel members to ascertain whether conflicts of interest might exist and to identify potential sources of bias. *TERA* determined that none of the panel members has a conflict of interest as defined above. Involvement of some panel members or their companies with acrylonitrile research or other than acrylonitrile work for the sponsors, while not conflicts of interest, might be considered to create situations of potential bias. After discussing these situations with individual reviewers, *TERA*'s judgment is that these situations will not hinder the panel members' ability to provide impartial judgments. Information from each panel member relevant to these situations is summarized below to make sure the other panel members and the public are fully aware of these activities.

The panel members are asked to objectively evaluate the assessment, and use the provided information, along with their personal knowledge and expertise, to independently reach conclusions on this document. The disclosures below will be discussed by the panel at the beginning of the meeting and any panel member is free to ask questions or raise concerns. If the panel as a group has significant concerns they may ask that a fellow panel member not be allowed to vote for consensus. In addition, if any panel member feels at any time that another member is trying to influence the outcome of the review in an inappropriate way, he or she should immediately bring this to the attention of the Chair and/or *TERA* meeting coordinator so that it may be addressed.

The peer reviewers are donating their time and talents to this effort. They have been selected based upon their expertise and qualifications and are employed by many types of organizations. *TERA* strives to create a balance of expertise and affiliations for each meeting. However, individual peer reviewers represent themselves and the views they express are their own, and should not be construed to be the opinions of their employers, of any group who may have nominated them, or any group with which they may be associated. This peer review panel is a distinguished group, with many years experience in a wide range of disciplines.

Toxicology Excellence for Risk Assessment (*TERA*) has been asked by the Acrylonitrile Group to organize and conduct this peer review meeting. The Acrylonitrile Group is paying *TERA* time and expenses to conduct the review, including the travel expenses of panel members. Dr. Dourson of *TERA* is donating his time as a reviewer as are all other panel members. *TERA* is responsible for independently selecting panel members, evaluating conflict of interest, preparing the charge to the peer reviewers, conducting the meeting, and drafting the meeting report. The panel will review the draft meeting report for accuracy and completeness. The final report will be posted on the *TERA* website (http://www.tera.org/peer).

DISCLOSURES: *TERA* has evaluated the carcinogenicity of acrylonitrile while under contract with the Acrylonitrile Group in 1996 and published a paper on that assessment (Felter SP and JS Dollarhide. 1997. Acrylonitrile: a re-evaluation of the inhalation database to support a cancer risk assessment. *Reg. Tox. Pharmacol*., 26(3):281-287.). *TERA* conducted a peer review of this assessment in 1996. *TERA* also organized a peer review of an acrylonitrile assessment for Health Canada in 1998. *TERA* is not currently working on any projects for the Acrylonitrile Group beyond this peer review for which Dr. Dourson's time as a reviewer is being donated. Several individual Acrylonitrile Group companies are sponsors of recent and current *TERA* projects, but these do not involve acrylonitrile. Some of these efforts (peer consultations of Acrylonitrile Group member companies) are being conducted using EPA cooperative agreement funding, rather than company funds.

Peer Review Panel for the Acrylonitrile Toxicological Review

John C. Christopher, Ph.D., DABT. Dr. Christopher is a staff toxicologist with the Department of Toxic Substances Control, California Environmental Protection Agency where he reviews, critiques, and approves assessments of risk to human health and ecological risk assessments at military facilities and other hazardous waste sites and permitted facilities in California. Prior to his current position with the State of California, he conducted risk assessments for ICF Kaiser Engineers and IT Corporation. He has also worked for research laboratories where he conducted and managed animal studies. Dr. Christopher is a Diplomate of the American Board of Toxicology and has served as President of the Risk Assessment Specialty Section of the Society of Toxicology. He is a peer reviewer for *Toxicological Sciences, Risk Analysis*, *Human and Ecological Risk Assessment,* and *CRC Critical Reviews in Toxicology*. Dr. Christopher was selected for this panel due to his expertise in toxicology, risk assessment, and exposure assessment.

DISCLOSURES: Dr. Christopher is employed by the California EPA, which is a regulatory agency. Dr. Christopher noted: "The opinions I express as a member of this panel are my own and not necessarily those of my employer, the California Department of Toxic Substances Control, which is part of the California Environmental Protection Agency. Cal/EPA regulates various aspects of thousands of chemicals in commerce. This includes acrylonitrile, at least insofar as it is transported, stored, or disposed as a hazardous waste in California, or as this chemical might be involved in cleanup of hazardous waste sites. However, I am not now, nor have I ever been, engaged directly in regulatory decisions about acrylonitrile. I know of no reason why my employment as a government regulator would interfere with my rendering an

unbiased scientific opinion as a member of this panel." Dr. Christopher served on the *TERA* organized peer review of the Acrylonitrile Group assessment in 1996. *TERA* does not consider Dr. Christopher's employment or other activities to pose a conflict of interest or create a potential for bias.

Michael L. Dourson, Ph.D., **DABT**, **Chair.** Dr. Dourson is the Director of *TERA*; his research interests include investigating methods to extrapolate toxicity data garnered on experimental animals or healthy adults to the appropriate sensitive human population. Topics such as adversity of effect, and characterization of risk are also of interest. Dr. Dourson is a Diplomate of the American Board of Toxicology and served on its Board as President, Vice President and Treasurer. Dr. Dourson has served on numerous expert panels, such as EPA's peer review panels for IRIS assessments and its Risk Assessment Forum, *TERA*'s International Toxicity Estimates for Risk (*ITER*) independent peer reviews and consultations, and the National Sanitation Foundation's Health Advisory Board. Dr. Dourson was selected for this panel due to his extensive experience in quantitative risk assessment and chairing peer review panels.

DISCLOSURES: Dr. Dourson is employed by *TERA,* which has evaluated the carcinogenicity of acrylonitrile while under contract with the Acrylonitrile Group in 1996 and published a paper on that assessment (Felter and Dollarhide, 1997). That assessment underwent a *TERA*-organized peer review in 1996 and Dr. Dourson served on that panel as well as the 1998 panel reviewing the Health Canada acrylonitrile assessment in 1998. In 1991, Dr. Dourson co-chaired EPA's RfD/RfC Work Group where an acrylonitrile RfC was reviewed and he supervised its placement on EPA's Integrated Risk information System (IRIS). *TERA* is not currently working on any projects for the Acrylonitrile Group (beyond this peer review for which Dr. Dourson's time as a reviewer is being donated). Several individual Acrylonitrile Group companies are sponsors of recent and current *TERA* projects, but these do not involve acrylonitrile. After discussing these projects with Dr. Dourson, *TERA* does not think the precious acrylonitrile work will create a bias as the work was completed over five years ago and much new science has emerged since that time that needs to be considered in forming opinions and conclusions. Recent and current *TERA* efforts for Acrylonitrile Group member companies do not involve acrylonitrile, and in some cases involve use of EPA funds.

Linda S. Erdreich, Ph.D. Dr. Erdreich is senior managing scientist with Exponent. She is an epidemiologist with 25 years of experience in environmental epidemiology and health risk assessment. Dr. Erdreich has extensive experience assessing epidemiological research and integrating this information with that from other disciplines for qualitative and quantitative risk assessments. She has directed or contributed to assessments for chemicals, physical agents, and radiofrequency. Prior to joining Exponent, Dr. Erdreich was with Bailey Research Associates, Clement Associates, and before that with the U.S. Environmental Protection Agency. Dr. Erdreich has served on advisory committees to government, regulatory organizations, and industry regarding health risk assessments of chemicals and electromagnetic fields. Dr. Erdreich is a Fellow of the American College of Epidemiology. She is also an adjunct associate professor at the Robert Wood Johnson Medical School in New Jersey. Dr. Erdreich served on the *TERA* organized peer review of the Acrylonitrile Group assessment in 1996. Dr. Erdreich was selected

for this panel for her expertise in epidemiology, interpreting and using epidemiology data in risk assessment, and evaluating brain tumors.

DISCLOSURES. Dr. Erdreich is employed by Exponent, a large and diverse engineering and consulting firm with many clients, which may include some of the sponsor companies. Dr. Erdreich is not currently working on any projects for the sponsoring companies and is not aware of any work her company is doing on acrylonitrile for the sponsors or any other group. She did recently consult on a matter unrelated to acrylonitrile with attorneys who represented one of the sponsor companies. *TERA* does not think this is a conflict or that it would render Dr. Erdreich unable to render impartial judgments and assistance for this acrylonitrile peer review.

Susan P. Felter, Ph.D. Dr. Felter is a Senior Toxicologist with the Central Product Safety group of the Procter & Gamble Company where she conducts science-based cancer risk assessments. She previously worked for *TERA* where she prepared qualitative and quantitative human health risk assessments. Prior to that she worked for the U.S. Environmental Protection Agency, Environmental Criteria and Assessment Office where she served on the Carcinogen Risk Assessment Verification Endeavor Work Group and the Phase VI-B Drinking Water Work Group. As the Drinking Water Program Coordinator, she developed scientific documentation of cancer and non-cancer risk assessments of drinking water contaminants. Dr. Felter served on a peer review panel that reviewed Health Canada's acrylonitrile assessment in 1998. Dr. Felter was selected for the panel for her expertise in toxicology and cancer and non-cancer risk assessment.

DISCLOSURES: As an employee of *TERA*, Dr. Felter was co-author of an inhalation cancer assessment for acrylonitrile, which was sponsored by the Acrylonitrile Group in 1996. This assessment is found on *TERA's ITER* database and a summary was published (Felter and Dollarhide, 1997). After discussing these past activities with Dr. Felter, *TERA* does not consider these as sources of conflict or bias because it has been more than five years since Dr. Felter worked for *TERA* and she has had no further involvement with the Acrylonitrile Group since that time. In addition, much new science has emerged since that time that needs to be considered in forming opinions and conclusions.

Timothy R. Fennell, Ph.D. Dr. Fennell is a Senior Research Biochemist with RTI International. He was previously with the CIIT Centers for Health Research from 1988-2002, where he conducted research on the metabolism and pharmacokinetics of a variety of industrial chemicals including acrylonitrile. CIIT is funded by member companies, some of which are members of the Acrylonitrile Group. Dr. Fennell has published a number of peer-reviewed papers on acrylonitrile metabolism, protein adducts, and DNA adducts. He was a co-author on a 1995 publication with Dr. Gargas, who is a primary author of the document being reviewed, (Gargas, M.L., et al., 1995. A physiologically-based dosimetry description of acrylonitrile and cyanoethylene oxide in the rat. *Toxicol Appl. Pharmacol., 134*: 185-194.). Dr. Fennell is currently working on a National Cancer Institute grant studying hemoglobin adducts, one of which is from acrylonitrile (among a long list). Dr. Fennell was selected for the panel because of his expertise in metabolism, pharmacokinetics, biomarkers, and cancer mode of action, as well as his research on acrylonitrile.

DISCLOSURES. Dr. Fennell is employed by RTI International, a large research organization with many clients, which may include some of the sponsoring companies, but does not include the Acrylonitrile Group. Dr. Fennell is not currently working on any projects for the Acrylonitrile Group or the individual sponsoring companies. He is not aware of any work his company is doing on acrylonitrile for the sponsors or any other group. He recently completed a project for one of the sponsoring companies on a chemical other than acrylonitrile, but has no current project with them (although RTI may be proposing work in the future on chemicals other than acrylonitrile to one or more sponsoring companies). Dr. Fennell worked on studies and projects involving acrylonitrile while with CIIT. Some of those studies were funded by the Acrylonitrile Group. *TERA* does not consider these situations to constitute a conflict of interest, because Dr. Fennell is not personally involved in ongoing work for the sponsoring organizations. Based on discussions with Dr. Fennell, *TERA* does not consider that his previous work at CIIT suggests any potential partiality.

Jeffrey Fisher, Ph.D. Dr. Fisher is a Professor and head of the Department of Environmental Health Sciences at the University of Georgia. He has 17 years of experience in physiological modeling and has trained 20 graduate students and postdoctoral fellows on the concepts and application of physiological models. He spent most of his career at the Toxicology Laboratory, Wright Patterson AFB (included stints as a visiting scientist at Chemical Industry Institute of Toxicology and NIOSH) and accepted an academic position at the University of Georgia in July 2000. Dr Fisher's modeling and research activities with solvents (e.g., trichloroethylene and its p450 mediated metabolites, trichloroacetic acid and dichloroacetic acid; perchloroethylene, methanol and carbon tetrachloride) have focused on the development and validation of mathematical models for cancer risk assessment, estimating lactational transfer of solvents, understanding *in utero* and neonatal dosimetry, and quantifying metabolism of solvent introduced as mixtures. Recently Dr. Fisher has worked on pharmacokinetic and pharmacodynamic models for hypothyroidism in rats using perchlorate to induce hypothyroidism. He has served on several federal panels and advisory boards and has participated in DoD toxicology issues with North Atlantic Treaty Organization countries. He served on the International Life Sciences Institute (ILSI) Steering Committee which evaluated chloroform and dichloroacetic acid using EPA proposed Carcinogen Risk Guidelines. Dr. Fisher is currently president of the Biological Modeling Specialty Section of the Society of Toxicology, reviewer for several toxicology journals and is Co-Principal Investigator on a National Institutes of Health (NIH) supported workshop on Mathematical Modeling at University of Georgia in the fall of 2003. Dr. Fisher was selected for this panel because of his expertise in toxicology and physiologically based pharmacokinetic (PBPK) modeling.

DICLOSURES: Dr. Fisher has no conflicts of interest.

David W. Gaylor, Ph.D. Dr. Gaylor, whose expertise is in the fields of biometry, statistics, and health risk assessment, retired from the National Center for Toxicological Research (NCTR), FDA, where he served as the principal advisor to the NCTR Director/FDA Associate Commissioner for Science. In a prior position with the NCTR, he was Director of the Biometry

and Risk Assessment Division where he developed experimental protocols and provided statistical analyses of experiments in carcinogenesis, teratogenesis, mutagenesis, and neurotoxicity, and developed techniques to advance the science of quantitative health risk assessment. Dr. Gaylor also serves as an Adjunct Professor of Statistics at the University of Arkansas for Medical Sciences and the University of Arkansas, Little Rock. He is a Fellow of the American Statistical Association and the Society for Risk Analysis. Dr. Gaylor has served on more than 70 national and international work groups and committees on many aspects of biometry, toxicology, and risk assessment. He currently serves on numerous advisory committees, including those for the Centers for Disease Control, the U.S. Food and Drug Administration, the U.S. Army, and others. He is currently a member of the editorial board of *Risk Analysis*, *Human and Ecological Risk Assessment, Toxicology and Industrial Health*, and *Regulatory Toxicology and Pharmacology*. Dr. Gaylor was selected for this panel for his expertise in biostatistics and quantitative risk assessment.

DISCLOSURES Dr. Gaylor is retired and does private consulting. He is listed as an Affiliate on the Sapphire Group website and as such has occasionally subcontracted to work on projects with that company. He is not currently working on any projects for the Sapphire Group and has not worked on any acrylonitrile project with them. Dr. Gaylor had a project with the one of the company sponsors over a year ago, but this project did not involve acrylonitrile. He has no current work with this company or any of the sponsoring companies. *TERA* discussed these situations with Dr. Gaaylor and does not think this creates a COI or bias that would cause Dr. Gaylor to be unable to render impartial judgments and assistance for this acrylonitrile peer review.

Kannan Krishnan, Ph.D. Dr. Krishnan is Professor of Occupational and Environmental Health at the University of Montreal where he is also the Director of the Human Toxicology research group (TOXHUM). He has been the leader of the risk assessment methodologies theme team of the Canadian Network of Toxicology Centres (1994 – 2001), and Vice President of the Biological Modeling Specialty Section of the Society of Toxicology (2001-2002). Dr. Krishnan is a member of the U.S. National Academy of Sciences (NAS) Sub-committee on Acute Exposure Guideline Levels (2001-2004). He is currently a temporary advisor for the World Health Organization for developing a document on the scientific principles for the health risk assessment for children. His primary expertise is in the areas of pharmacokinetics, PBPK modeling, risk assessment methods, Quantitative Structure Activity Relationship (QSAR) modeling and mixture toxicology. He has been a peer reviewer of several IRIS updates, risk assessments, mixture risk assessment supplemental guidance and efforts on interactions for US EPA and on toxicological profiles of chemicals, interaction profiles involving environmental contaminants and mixture risk assessment guidelines for ATSDR. He is currently on the editorial boards of *Toxicological Sciences*, *International Journal of Toxicology*, *Journal of Applied Toxicology*, and the *Journal of Children's Health*. Dr. Krishnan was selected for this panel because of his expertise in toxicology and PBPK modeling.

DISCLOSURES: Dr. Krishnan is employed by the University of Montreal. He is part of a group of scientists who received a 3-year unrestricted research grant for work on risk assessment methods from the Dow Chemical Company Foundation (under the hands-free award program of

SHERE) *TERA* does not think this funding creates a conflict of interest or potential for bias, as these are unrestricted grants made to academic researchers who are studying important health and environmental questions and are used to fund post-doctoral fellows who are conducting research into areas of general interest to the industry.

R. Jeffrey Lewis, Ph.D. Dr. Lewis has been a Scientific Associate with ExxonMobil Biomedical Sciences, Inc. since 1990. He is responsible for designing and conducting epidemiological studies of ExxonMobil employees, and advising the Corporation regarding environmental health issues. Dr. Lewis is also an Adjunct Assistant Professor of Occupational Health at the University of Texas, School of Public Health. Dr. Lewis has over 15 years experience in designing, conducting, analyzing, and publishing epidemiology studies and has served on several committees, work groups, and task forces associated with the American Chemistry Council, the International Institute of Synthetic Rubber Producers, and the European Center for Ecotoxicology and Toxicology of Chemicals. None of these committees has been involved with acrylonitrile research. Dr. Lewis is a current member of the American College of Epidemiology and the Society for Epidemiological Research. Dr. Lewis was selected for the panel for his expertise in epidemiology and interpreting epidemiology data for use in risk assessment.

DISCLOSURES: Dr. Lewis has no conflicts of interest.

Alan R. Parrish, Ph.D. Dr. Parrish is an Assistant Professor in the Department of Medical Pharmacology and Toxicology, College of Medicine, Texas A&M University. His research in the laboratory is focused on the molecular mechanism(s) of renal failure, specifically focusing on the selective loss of N- and Ksp-cadherin during acute renal failure, and the loss of renal N-cadherin during end-stage renal disease due to aging. He serves on the editorial board of *Cell Biology and Toxicology* and is an *ad hoc* reviewer for numerous other journals. He was selected for this panel for his expertise in cellular oxidative stress and signal transduction.

DISCLOSURES: Dr. Parrish has no conflicts of interest.

Jerry M. Rice, Ph.D. Dr. Rice served as the Chief of the IARC Monographs Programme on the Evaluation of Carcinogenic Risks to Humans at the World Health Organization's International Agency for Research on Cancer (IARC) in Lyon, France. He previously served in the U.S. Public Health Service Commissioned Corps at the National Cancer Institute (NCI)in a variety of positions, most recently as Chief of the Laboratory of Comparative Carcinogenesis. At NCI Dr. Rice's research focused on mechanisms of chemical carcinogenesis (including the roles of transforming and tumor suppressor genes in human and experimental tumors); transplacental and perinatal carcinogenesis in rodents and non-human primates; tumor promotion; and molecular and comparative pathology of tumors, especially tumors of the nervous system. He has organized and participated in numerous national and international committees and advisory boards and is the Carcinogenesis Field Editor of the journal, *Teratogenesis, Carcinogenesis and Mutagenesis*. Dr. Rice was selected for this panel because of his general expertise in

carcinogenesis, risk assessment, pathology, and brain tumors; as well as familiarity with the acrylonitrile data and issues. He was responsible for oversight of the NCI epidemiology review of occupational exposures to acrylonitrile; and helped organize the most recent IARC evaluation of the carcinogenic hazard of acrylonitrile, published in IARC Monographs Volume 71 (1999); and was a member of the pathology review panel for brain tumors induced by acrylonitrile in rats, sponsored by the (industrial) Acrylonitrile Group and coordinated by Experimental Pathology Laboratories, Inc. (2002). Dr Rice retired from the U.S. Public Health Service in 1996, and from the World Health Organization in 2002.

DISCLOSURES: Dr. Rice has no conflicts of interest.

James E. Trosko, Ph.D. Dr. Trosko has been a Professor in the Department of Pediatrics/Human Development at Michigan State University since 1968. He has conducted research in radiation genetics, mutagenesis, carcinogenesis, gap junction-based intercellular communication, epigenetic toxicology and, more recently, stem cell research in toxicology, resulting in over 300 publications. Dr. Trosko has received numerous awards and honors, including the Society of Toxicology's Scientific Achievement Award (2000). While on a 2-year leave of absence from Michigan State, he served as Chief or Research for the Radiation Effects Research Foundation in Hiroshima Japan. Dr. Trosko was selected for the panel for his extensive expertise in mechanisms of carcinogenicity and mode of action. He has published several papers on the effects of acrylonitrile on gap junctional intercellular communication in rat astrocytes, rat liver epithelial, and rat glial cells (Kamendulis, et al., 1999 and Rupp and Trosko, 1995). Dr. Trosko is a reviewer for several journals and an Editorial Advisor for *Environmental Carcinogenesis and Mutagenesis*.

DISCLOSURES: Dr. Trosko received funding from the Acrylonitrile Group during 1993-4 for research on the effect of acrylonitrile on the ability to block cell-to-cell communication *in vitro* (results published in Kamendulis, et al., 1999). *TERA* does not believe this constitutes a conflict of interest as the funding and work were ten years in the past. Dr. Trosko has received no funding from the Acrylonitrile Group or its member companies since that time. After discussing the situation with Dr. Trosko *TERA* also does not think this prior funding will interfere with his ability to objectively evaluate the current body of knowledge on acrylonitrile.

Vernon E. Walker, D.V.M., Ph.D. Dr. Walker is a research scientist at Lovelace Respiratory Research Institute, and a Clinical Associate Professor at the University of New Mexico, College of Pharmacy. Previously he was with the New York State Department of Health's Wadsworth Center and was an Assistant Professor at the State University of New York at Albany. Dr. Walker's primary research interests are mechanisms of chemical carcinogenesis and mutagenesis. His research has included characterization of the genotoxic risks and low-dose effects from exposures to epoxide/epoxide-forming compounds (*e.g.*, acrylonitrile, 1,3-butadiene, and ethylene oxide) known to induce lung cancers in rodent models. From 1985-1991 Dr. Walker was a Postdoctoral Trainee at the Chemical Industry Institute of Toxicology (CIIT) where he conducted research on the formation of DNA and hemoglobin adducts of industrial chemicals including acrylonitrile and ethylene oxide. CIIT is funded by member companies,

some of which are members of the Acrylonitrile Group. Dr. Walker served on a peer review panel that reviewed Health Canada's acrylonitrile assessment in 1998.

DISCLOSURES. Dr. Walker worked on studies and projects involving acrylonitrile while with CIIT. Some of those studies were funded by members companies of the Acrylonitrile Group. *TERA* does not consider this to constitute a conflict of interest, because Dr. Walker is not personally involved in ongoing work for the sponsoring organizations. Based on discussions with Dr. Walker, *TERA* does not consider that his previous work at CIIT suggests any potential partiality.

Other Participants

Dr. Cohen was asked to serve on the panel but due to conflicts were not able to make the meeting.

Samuel M. Cohen, M.D., Ph.D. Dr. Cohen is Professor and Chair of the Department of Pathology and Microbiology at the University of Nebraska Medical Center. Dr. Cohen's research involves several aspects of carcinogenesis, with an emphasis on the urinary bladder as a model system in rodents and extrapolation between rodent models and the human disease. His interests are in chemical carcinogenesis and mechanism, toxicology and risk assessment, surgical pathology and urologic pathology. He has served as the President, Carcinogenesis Specialty Section of the Society of Toxicology and is on the editorial Board or associate editor for *Lab. Invest., Fd. Chem. Toxicol., Toxicol Sciences, Int. J. Oncology, Urologic Oncology, Toxicol. Pathol., and Intl. Pathol*. Dr. Cohen has served on many panels, boards, and advisory committees, including CIIT, ILSI Risk Sciences Institute, and the National Toxicology Program Board of Scientific Counselors, National Research Council, U.S. EPA, and IPCS. He recently served as Vice-Chair of the ILSI committee on mechanisms and risk assessment.

Disclosures: Dr. Cohen has received research support from Bayer and DuPont several years ago. He has also received consulting fees from Bayer and BP in the past. None of this was for work on acrylonitrile and he does not currently have any funding from the Acrylonitrile Group or its member companies. *TERA* does not consider this past funding to be a conflict or interest or bias.

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APPENDIX B

Written Comments

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University of Nebraska Medical Center

PATHOLOGY AND MICROBIOLOGY

NEBRASKA'S HEALTH SCIENCE CENTER
A Partner with Nebraska Health System

September 19, 2003

Jacqueline Patterson
Toxicology Excellence for Risk Assessment
1757 Chase Avenue
Cincinnati, Ohio 45223

Dear Jacqueline,

I have reviewed the toxicological review of acrylonitrile (ACN), as well as supporting references and appendices, and to be perfectly honest, have difficulty coming to any definitive conclusion. Clearly, the emphasis in the animal studies has been on brain tumors, whereas in humans there has been a broad approach to epidemiology, but with some suggestion of effects on lung tumors. I believe that overall, the epidemiologic data does not support a carcinogenic risk in humans, leading the IARC classification of the chemical as a possible human carcinogen, rather than probable. It is my impression that the details of the epidemiologic data need to be reviewed carefully by the epidemiologists on the review committee, as it is a fairly strong data base, and should provide the most definitive evidence with regard to the carcinogenicity of ACN in humans.

There is no question that ACN is a multi-site, multi-species carcinogen by various routes of administration. The focus of mode of action research seems to have been primarily on the brain.

The summary by Dr. Klaunig provides reasonable support for the idea that the brain lesions in the rat are secondary to oxidative damage. However, as indicated in the review by Dr. Whysner, the possibility that increased cell proliferation, most likely in response to cytotoxicity, still needs to be better evaluated. Dr. Whysner refers to some documents that I did not have available for review that address this issue. In actuality, a concurrent mode of action involving oxidative damage and cytotoxicity with regenerative cell proliferation would make considerable sense.

With respect to the genotoxicity issue, to say that it is bewildering is to understate the obvious. Clearly, ACN is an in vitro genotoxicant in a variety of assays. The question is whether it is a genotoxicant in vivo, particularly in the brain, and I believe that is still not resolved. I would like to see considerably more detail regarding the in vivo DNA adduct studies following ACN administration, to come to more definitive conclusions. What were the specific procedures of the assays, what was the sensitivity of the assays, and what tissues were specifically evaluated (what portion of the brain, versus whole brain)?

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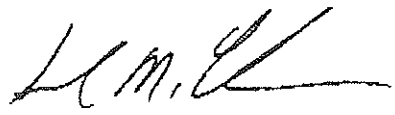
The most disconcerting aspect of the review to me is the fact that little to no attention was paid to the modes of action involved with the tumors produced in other tissues, not only in the rat, but in the mouse. Are we to assume that oxidative damage is also the mode of action in these tissues? If so, there are no data to support this. Based on the review, it appears that little research has been done on the modes of action of these other tumors, and to assume that they are the same as for the brain is an unreasonable premise for an evaluation.

Whether direct genotoxicity or indirect genotoxicity secondary to oxidative damage is the mode of action in the rat, I saw nothing in the documents that explains definitively why the human could not develop these exact same lesions. Although there are quantitative differences in metabolism, the critical metabolites appear to occur in humans, so that given a sufficiently high exposure, one could reasonably anticipate the same process to occur in humans. That is why I believe it so important to carefully evaluate the details of the epidemiology study, particularly reviewing the implications for brain tumors. I did not see anything in the document that would exclude the possibility of similar modes of action in humans compared to the rat. If it is not occurring in humans, there should be some qualitative or quantitative explanation.

In summary, ACN is a multi-site, multi-species carcinogen, but the epidemiologic data strongly suggest that there is not a significant cancer risk in humans. The major mode of action suggested for brain tumors in rats is oxidative damage, an indirect genotoxic effect. However, I do not believe the data adequately exclude the possibility of direct genotoxicity because of DNA adduct formation, nor is there adequate information to evaluate mode of action in the other tissues involved.

I am sorry that I cannot attend the meeting, but I look forward to the summary of your deliberations.

Sincerely yours,



Samuel M. Cohen, M.D., Ph.D.
Professor and Chair, Pathology and Microbiology
Havlik-Wall Professor of Oncology

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APPENDIX C

Acrylonitrile Charge Questions and Cross-Reference to Sections of the Meeting Report

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Charge Questions and Cross-Reference

Acrylonitrile Charge to Peer Reviewers

1. LITERATURE SEARCH – Section III.d.1, p. 17

Was the literature search approach appropriate and adequate? Are there additional published studies or published data that you think should be considered for this risk assessment of acrylonitrile?

2. CANCER HAZARD CHARACTERIZATION – Section III.d.2, pp. 17-32

Have the appropriate mode(s) of action been identified? Have the appropriate data been adequately considered in the discussion of the mode(s) of action? Is the proposed mode of action defensible?

- Specifically, can oxidative stress be accepted as the mode of action for brain cancer in rats? If so, using EPA's current (1999 and 2003) guidelines for carcinogen risk assessment; does the assessment make an adequate case that this mechanism is not relevant in humans?

- More generally, are the tumors observed in animals biologically significant and relevant to human health? Points relevant to this determination include whether or not the choice follows from the dose-response assessment, and if the effect (including tumors observed in the cancer assessment) and the species in which it is observed is a valid model for humans.

- Can acrylonitrile be considered to not demonstrate mutagenic or other activity consistent with linearity at low doses, so that a nonlinear extrapolation should be conducted under the EPA cancer guidelines? Does the evidence for a non-linear mode of action meet the standard for nonlinearity set in, for example, the IRIS assessment for chloroform?

How do you interpret the overall occupational database? Is the proposed WOE that epidemiological studies "do not support identifying acrylonitrile as a human carcinogen" supportable under the EPA cancer guidelines? Is the estimated carcinogenic potency from the results of the epidemiology studies, even though they failed to reach significance, consistent with the available animal data?

Is the weight of evidence for cancer from both oral and inhalation exposure assigned at the appropriate level and does it follow the EPA guidelines? Does the weight-of-evidence statement present a clear rationale and accurately reflect the utility of the principal studies, the relevancy of the critical effects to humans, and the comprehensiveness of the data base?

3. PBPK MODEL – Section IV.c., pp. 35-41

Was the PBPK model appropriately developed and validated? What are the limitations to the model, if any, and are there any relevant conditions for which it should not be applied?

- Was the correct dose metric chosen?
- What are the implications of using a model validated in rats but not humans?

4. CANCER DOSE-RESPONSE – Sections VI and VII, pp. 45-55

In light of the hazard characterization for cancer, should cancer risk be calculated? If so, what is the appropriate data set (i.e., experimental animal or human) to use as the basis of the cancer dose-response?

What is the appropriate point of departure?

- If experimental animal data are used, is the use of the gamma model, which was determined to provide an acceptable visual, but not statistical, fit to the dose response assessment, reasonable? Does the suggestion that the lack of a statistically acceptable fit is due to scatter in the data appear correct? If so, should this scatter in preclude the use of a pooled dose response data in the assessment?
- If experimental animal data are used, what is the proper choice of LED for brain tumors in rats? How model dependent is this estimate?

What is the appropriate low dose extrapolation procedure?

- If nonlinear, what is the best approach for estimating cancer risk at low doses?
- If the judgment is that a linear extrapolation is appropriate, is the choice of dose response model and rationale reasonable?

If a cancer risk is calculated, are the calculated oral and inhalation unit risks appropriate?

5. INHALATION NONCANCER HAZARD AND DOSE-RESPONSE, Section V, pp. 41-45

- What do the data on acrylonitrile absorption, distribution, metabolism, elimination, and mode-of-action tell us about identifying the critical effects and dose response assessments in humans and animals?
- Are the choice of the critical effects for RfC and the rationale for those choices appropriate? (The critical effects are those adverse effects appearing first in a exposure-response continuum)?

- Is the choice and rationale of the principal study for RfC appropriate? (The principal study should present the critical effects in the clearest exposure-response relationship.)
- Are there other issues to consider in determining noncancer hazard?
- What is the appropriate point-of-departure (POD) for an acrylonitrile RfC? (appropriate calculation of HEC?) If a BMC based on the animal data is used as the point of departure (POD), was the benchmark dose modeling appropriately conducted in determining this POD?
- Are the uncertainty factors applied to derive the RfC for acrylonitrile appropriate and the rationale for the selections adequate? Do they follow EPA practice? Is the RfC derived appropriately?

6. ORAL NONCANCER HAZARD AND DOSE-RESPONSE – Section VIII, pp. 55-58

- What do the data on acrylonitrile absorption, distribution, metabolism, elimination, and mode-of-action tell us about identifying the critical effects and dose response assessments in humans and animals?
- Are the choice of the critical effects for the RfD and the rationale for those choices appropriate? (The critical effects are those adverse effects appearing first in a dose-response continuum.)
- Is the choice and rationale of the principal study for the RfD appropriate? (The principal study should present the critical effects in the clearest dose-response relationship.)
- Has the benchmark dose modeling been used appropriately in the choice of the critical effects?
- Are there other issues to consider in determining noncancer hazard?
- What is the appropriate point-of-departure for an acrylonitrile RfD? If a BMD is reasonable, was the benchmark dose modeling appropriately conducted in determining this POD?
- Are the uncertainty factors applied to derive the RfD for acrylonitrile appropriate and the rationale for the selections adequate? Do they follow EPA practice? Is the RfD derived appropriately?

7. OVERALL SUMMARY AND PANEL CONCLUSIONS – Sections IX, pp. 58-64

- Panel conclusions and recommendations to the sponsors/authors
- Outstanding issues

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APPENDIX D

Sponsor Presentations

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Acrylonitrile Toxicological Assessment TERA Peer Review

The Acrylonitrile Group, Inc.
Washington, DC
www.angroup.org

September 22, 2003

Members of the AN Group

- Bayer Corporation
- BP Chemicals, Inc.
- Cytec Industries Inc.
- The Dow Chemical Company
- DuPont Company
- GE Plastics
- Solutia, Inc.
- Sterling Chemicals, Inc.

Mission of the AN Group

- To facilitate the protection of human health and the environment through all stages of the AN product life-cycle
- To support studies necessary to expand the data base relating to AN
- To monitor and address regulatory activities affecting AN

What is AN used for?

- **Adiponitrile (ADN)**
  - production of hexamethylenediamine (HMDA)
  - nylon 66 resins and fibers
- **Acrylonitrile-butadiene-styrene (ABS)**
  - thermoplastic resin
  - bridge between commodity plastics (*e.g.*, polystyrene) and higher-performing engineering resins (*e.g.*, polycarbonate)
- **Acrylic Fibers**
  - Acrylic fibers for apparel and home furnishings
- **Acrylamide**
- **Nitrile Rubbers (NBR)**
  - Copolymer of butadiene and acrylonitrile

Other Uses of Acrylonitrile

- Acrylonitrile copolymers
  - Polymer Polyols
  - Barrier Resins
  - Weatherable Polymers
- DMAPA
- Carbon Fibers
- AMPS
- Fatty Alkyl Diamines
- 3,3'-Thiodipropionate Esters
- Miscellaneous

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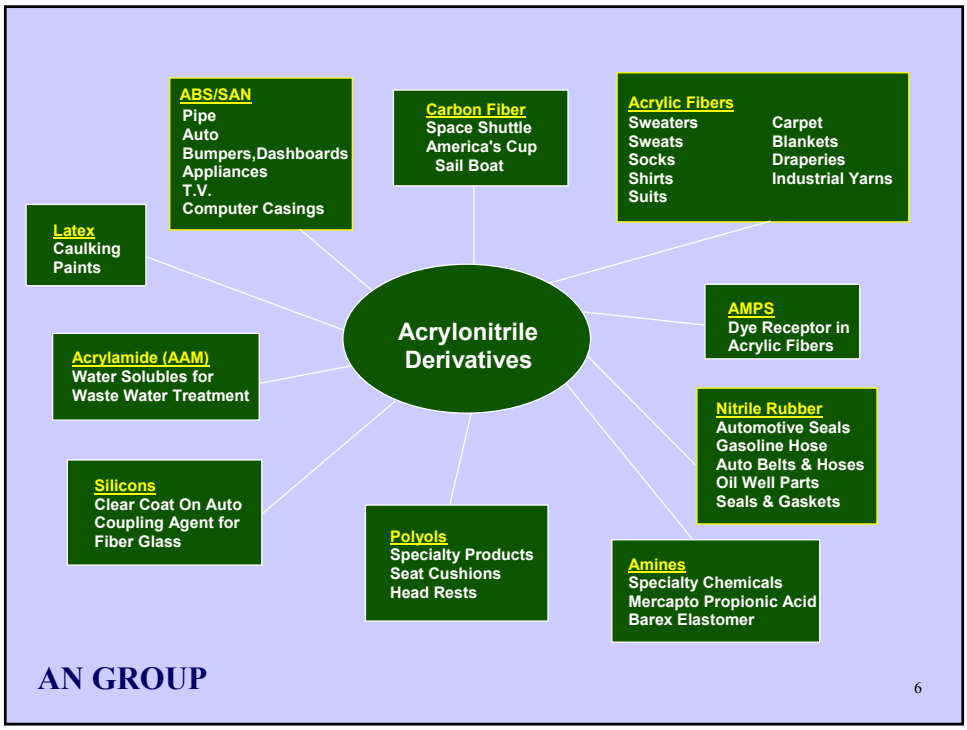

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6

AN Group Activities

- Sponsorship of Research on AN
  - Mode of Action
  - PBPK Modeling
  - Epidemiology
- Sponsorship of Dialogue on AN
  - Toxicology Forum
  - Oxford Conference
- Sponsorship of New Health Assessment and Peer Review
- Regulatory Agency Interaction

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7

Purpose of Assessment

GOAL: Develop updated risk values (cancer and non-cancer) using all relevant information and best available scientific understanding of toxicological properties

- Existing assessments are based on old data and obsolete methodologies
- A considerable amount of data has been published over the past 20 years, particularly with respect to the epidemiology, kinetics, and mechanism of action for AN

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8

Potential Uses of Risk Assessment

- Publish in peer reviewed scientific journal
- Use in industry assessments
- Share with other who have an interest in health risk assessments of AN
  - US EPA Air Office
  - National Sanitation Foundation International
  - US FDA
  - US OSHA
  - EU Risk Assessors

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9

Using Human Data for Acrylonitrile Risk Assessment

Thomas B. Starr, Ph.D.
TBS Associates
Raleigh NC

21 September 2003

US EPA's 1983 Assessment

- Reviewed 10 epidemiology studies
  - 6 showed no evidence of carcinogenicity
  - 4 showed significantly increased lung cancer risk
- Only O'Berg (1980) deemed adequate for potency evaluation
  - 1345 DuPont textile fiber plant workers
  - SMR = 357 (5 cases vs 1.4 expected) among "at least moderately exposed workers (~ 15 ppm)
  - Cumulative exposure ~ 15*9 = 135 ppm-working yrs
- Linear relative risk model => central (MLE) estimate of 70 yr lifetime risk = 28 per 1,000 for 50 ppm-working years

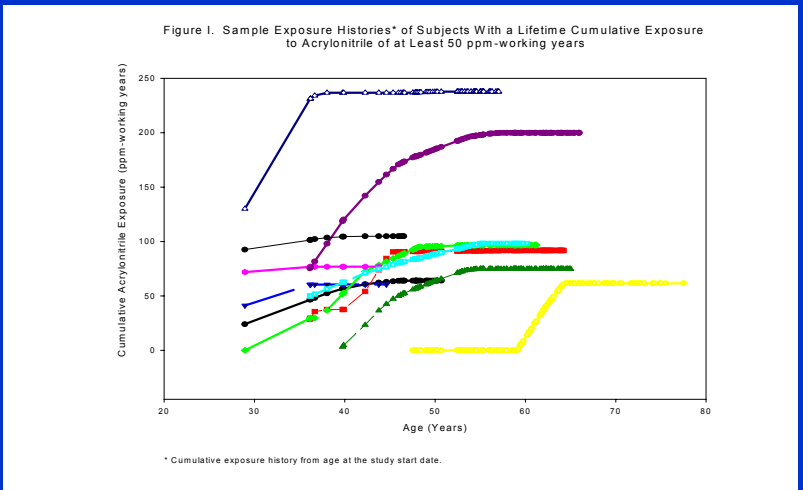
2

Starr et al. (2003) Assessment

- Analyzed Blair et al. (1998) NCI/NIOSH study data
  - 25,460 workers in 8 plants, 163 lung cancer deaths
  - Detailed individual exposure histories reconstructed from job/process descriptions and monitoring data
  - Used semi-parametric Cox proportional hazards model vs age-specific cumulative exposure
  - Evaluated 3 plausible exposure scenarios leading to 50 ppm-working yrs total exposure
  - Central and upper bound estimates of added risk

3

Some High End Exposure Histories



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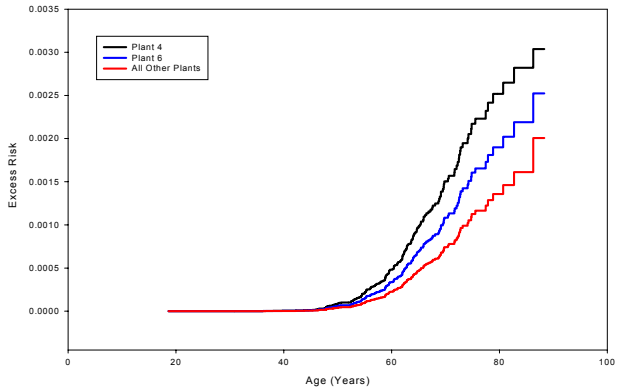
Added Risk (MLE): 2 ppm, ages 30-54

Figure IIIA. Estimated Plant Group- and Age-Specific Additional Risk of Lung Cancer Mortality Associated With Hypothetical Exposure Scenario 1: 2 ppm AN from age 30-54 in standard working years



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The Bottom Line

- Our central 70 year lifetime risk estimates are 18- to 41-fold lower than the US EPA 1983 value of 28 per 1,000
- Our upper 95% confidence bound estimates are 2- to 4-fold lower
- The newer, more complete, and more extensive epidemiology data are statistically inconsistent with the 1983 potency factor when analyzed with a conservative, low-dose linear dose-response model

6

Advantages of Our Approach

- Utilizes complete detail of invidividual exposure histories
- Accounts for competing risks of death from other causes
- Baseline hazard rates estimated within the cohort
- Accommodates age-dependent exposure patterns
- Predicts entire pattern of age-specific risks, not just 70-yr lifetime risks
- Extremely flexible, limited only by input data base

7

Concluding Remarks

- Starr et al. (2003) now *in press* at *Risk Analysis*
- Completed similar analysis of Wood et al. (1998) DuPont cohort
  (2,559 workers, 2 plants, 46 lung cancer deaths)
  - Results consistent with those from Blair et al. study
  - Slightly negative central estimate of potency despite markedly higher cumulative exposures
  - Upper bound potency estimates virtually identical
- Collaborators:
  Jim Collins (Dow), Gary Marsh, Christine Gause, Ada Youk, Roslyn Stone (University of Pittsburgh)

8

PBPK Modeling and Cancer Dose-Response Assessment for Acrylonitrile

Presented By:
Michael L. Gargas, Ph.D.
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on behalf of
The AN Group, Washington, D.C.

Presented To:
TERA Peer Review Panel
University of Cincinnati,
Kingsgate Conference Center
September 22, 2003

Inhalation Unit Risk Based Upon Human Data

Step 1: Data Set: Blair et al. (1998) as analyzed by Starr et al. (2003)
Step 2: Dose Measure = External dose (ppm-years)
Step 3: Response Measure = Relative risk
Step 4: Dose-Response Model = Cox proportional hazard model
Step 5: Point of Departure = ~ED001 (1/1000)
Step 6: Low-Dose Extrapolation = Linear
Step 7: Unit Risk = 2.9×10^{-6} $(ug/m^3)^{-1}$ (range: 1.3×10^{-6} – 2.9×10^{-6})

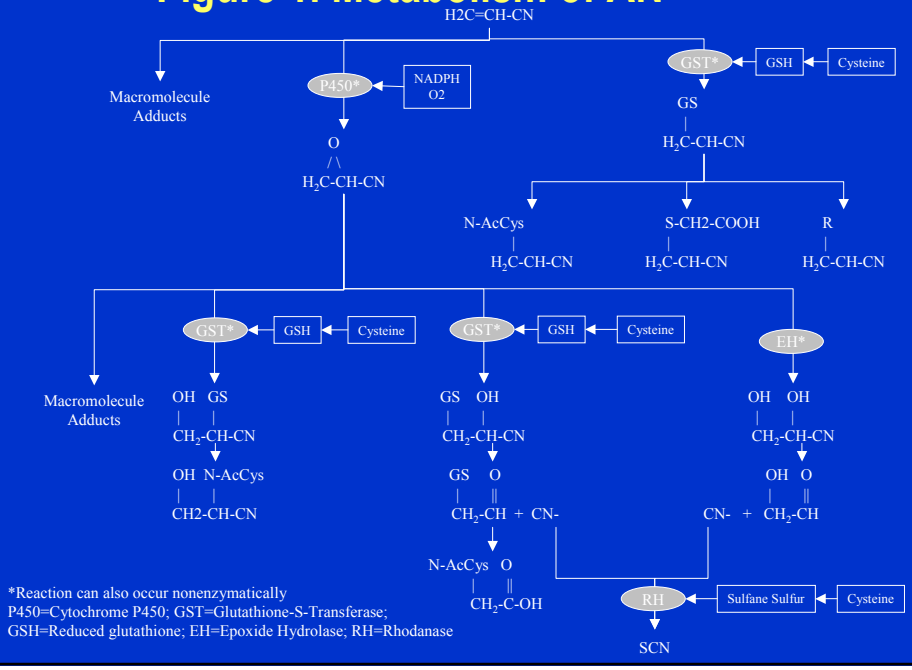
10

AN Kinetics

- Understanding of AN kinetics has greatly improved over the past 20 years
- Quantitative differences between rodents and humans with respect to metabolism (EH and GST pathways)
- Nonlinear kinetics at high doses (saturation of metabolism, co-factor depletion)
- Metabolism pathways (Figure 1)

11

Figure 1. Metabolism of AN

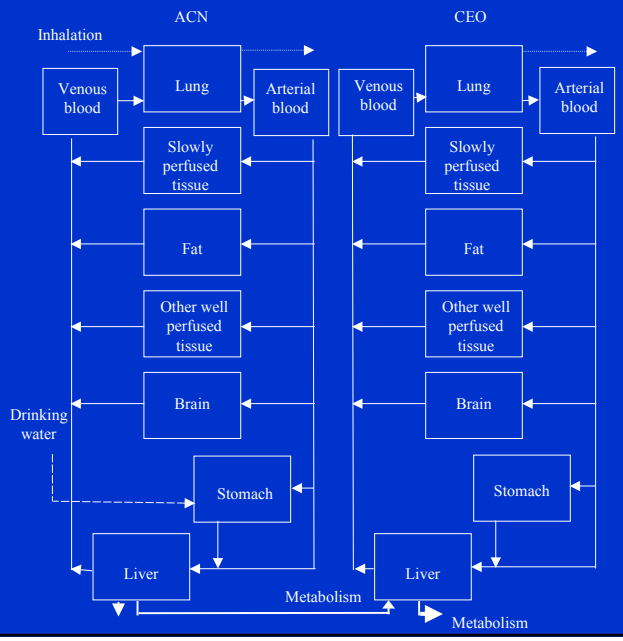


PBPK Model for AN

- A PBPK model is available for AN and its epoxide metabolite, cyanoethylene oxide (CEO), in rodents and in humans
- Rat Model
  - Gargas et al. (1995)
  - Kedderis et al. (1996)
  - Validated
- Model Structure (Figure 2)

13

Figure 2. PBPK Model Structure for AN and CEO



Human PBPK Model for AN

- Same structure as rat models (Gargas et al.,1995; Kedderis et al., 1996)
- Human physiological parameter values from literature
- Human AN blood:air partition coefficient, rat AN tissue:air and CEO partition coefficients, human GSH concentrations
- Human metabolic rates estimated by parallelogram method
  - Validated human PBPK models developed by parallelogram approach: carbon tetrachloride, chloroform, perc, vinyl chloride and MTBE
- Human model for AN not validated, but variability analysis conducted

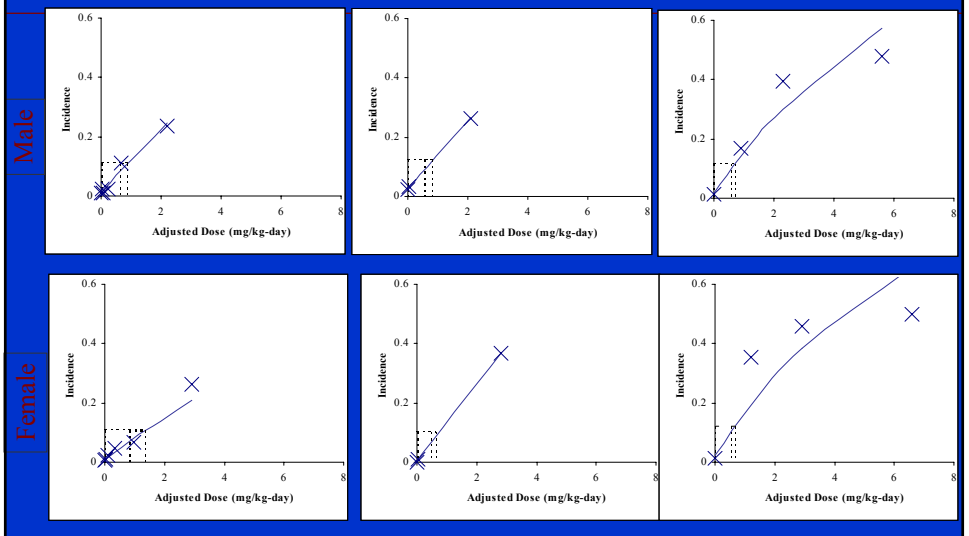
15

Cancer Dose-Response Assessment Based Upon Animal Data

- Step 1: Data Set - Rat Brain Tumors (Johannsen and Levinskas, 2002a,b; Maltoni, 1977, 1988; Quast, 1980) (Figures 3 & 4)
  - Oral and inhalation data assessed independently and pooled
- Step 2: Dose Measure - External dose (ug/m^3, mg/kg-day) and Internal dose (Peak CEO in brain, mg/L)

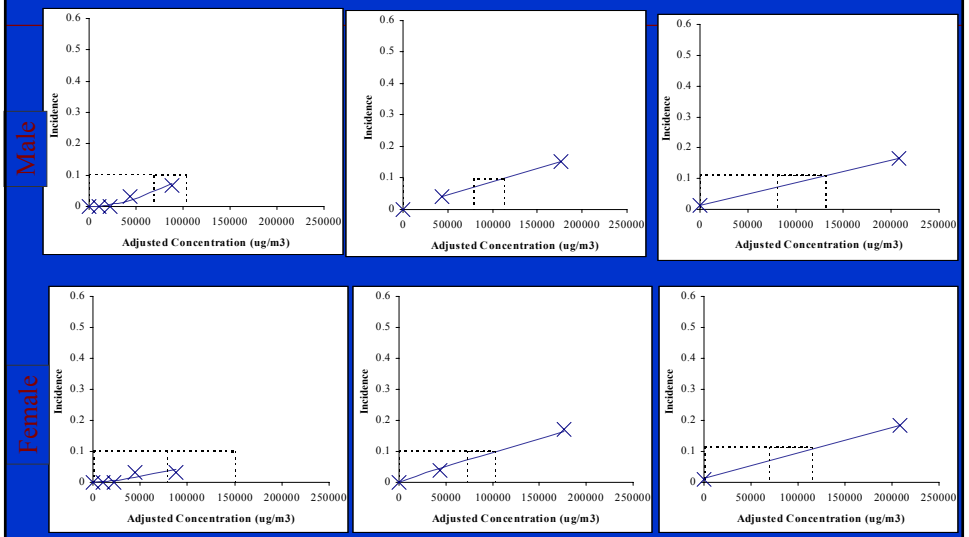
16

Figure 3. Oral Data Sets for Brain Tumors in Rats



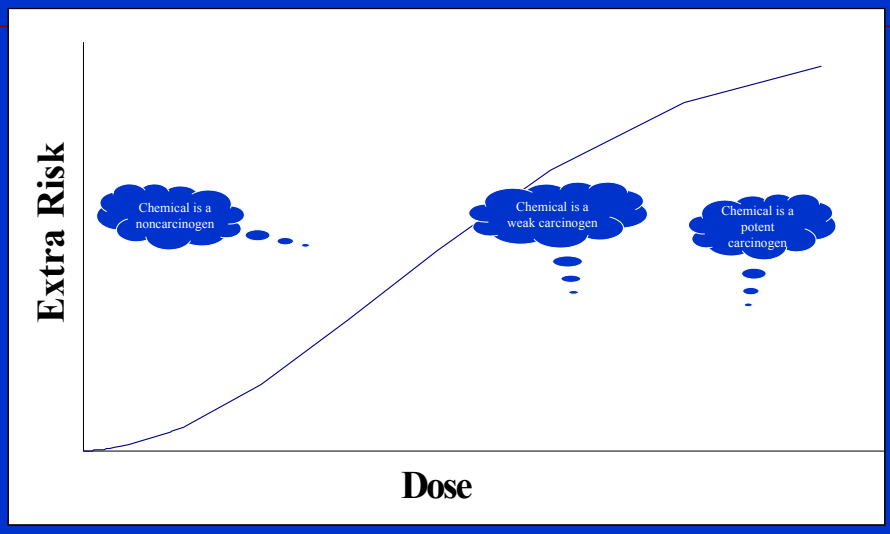
17

Figure 4. Inhalation Data Sets for Brain Tumors in Rats



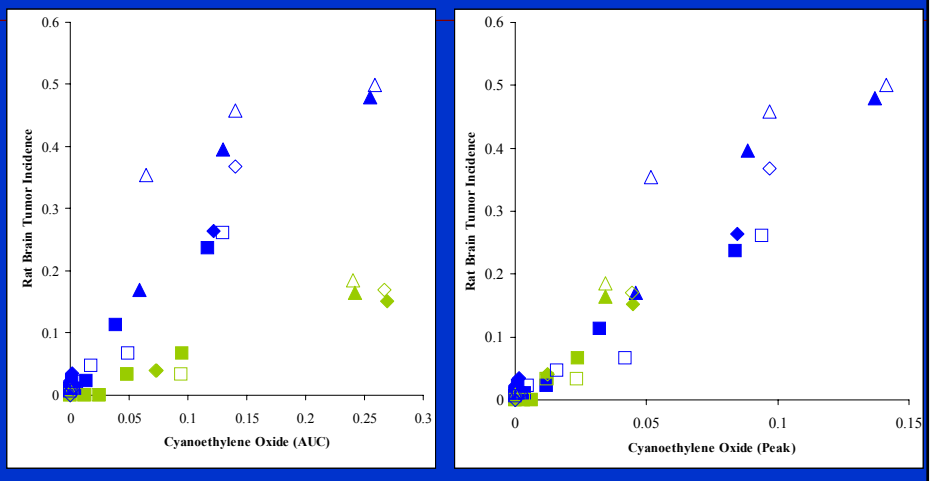
18

Limitations/Problems with Data Set Selection



19

Figure 5. Pooling Data Using Different Internal Dose Measures (Kirman et al. 2000)



20

Dose-Response Assessment Based Upon Animal Data

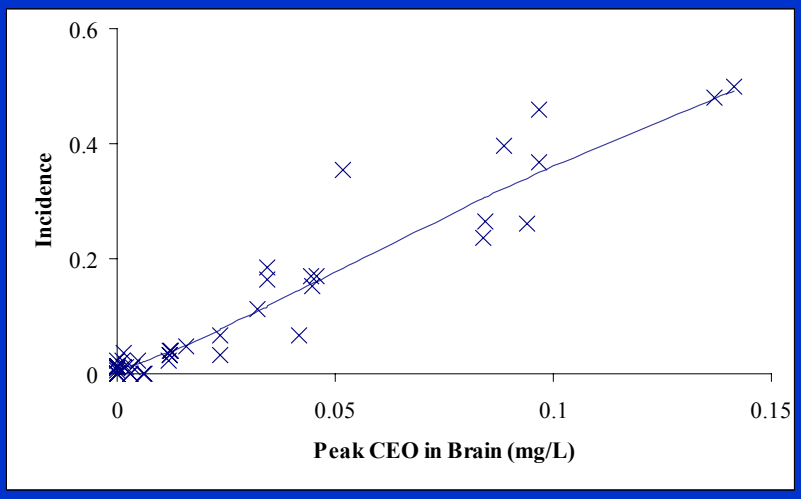
Step 3: Response Measure = Extra risk (default)

Step 4: Dose-Response Model = Gamma (pooled data, Figure 6), Multistage (individual data sets)

Step 5: Point of Departure = LED001 (Figure 7)

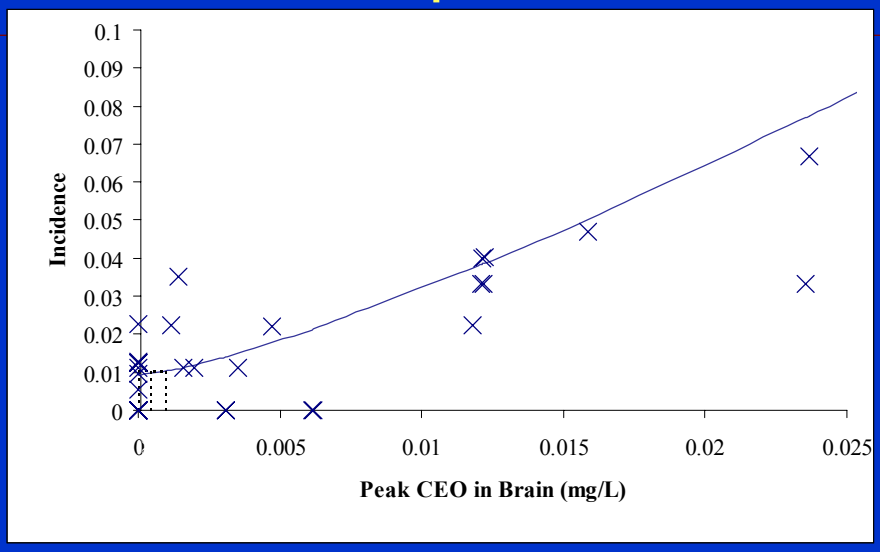
21

Figure 6. Gamma Model Fit to Pooled Data for Brain Tumors in Rats



22

Figure 7. Dose-Response Relationship at Low Doses



23

Step 6. Select a Method for Low-Dose Extrapolation

- Animal data
  - Evidence supporting an MOE approach
    - Lack of DNA-adducts in rat brain
    - Nonlinearity in dose-response relationship due to kinetic factors
    - Peak CEO better than AUC
  - Evidence supporting linear
    - Uncertainty in mode of action
    - Unclear as to the shape of the dose-response relationship at low doses for oxidative stress in rat brain
  - Therefore, both linear and MOE assessments are conducted

24

Step 7: Calculate Slope Factor and Unit Risk Values

- Inhalation Unit Risk
  - Using an MOE of 174 (3 for interspecies, 5.8 for intraspecies, 3 for nature of response, and 3 for human exposure) and a point of departure of 635 ug/m^3, concentrations below 4 ug/m^3 are not expected to result in an appreciable risk of cancer in exposed populations
  - Using linear extrapolation from the point of departure, an inhalation unit risk of $1.6x10^{-6}$ $(ug/m^3)^{-1}$ was derived
  - Confidence: Medium to High
- Oral Slope Factor
  - Using an MOE of 174 and a point of departure of 0.051 mg/kg-day, doses below 0.0003 mg/kg-day are not expected to result in an appreciable risk of cancer in exposed populations
  - Using linear extrapolation from the point of departure, an oral slope factor of $(mg/kg\text{-}day)^{-1}$ was derived
  - Confidence: Medium to High

25

Key Issues/Questions for Cancer Dose-Response Assessment

- PBPK Model
  - Appropriateness of internal dose measure (peak CEO)?
  - Confidence in PBPK modeling (high, medium,low)?
  - Data needs
- Cancer Dose-Response
  - Which data set (epi or animal) serves as a more appropriate basis for risk assessment?
  - Given the information available for mode of action for brain tumors, which extrapolation method (linear or nonlinear) is more appropriate for the rat data?
  - Data Needs

26

Noncancer Assessments for Acrylonitrile

Presented By:
Michael L. Gargas, Ph.D.
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on behalf of
The AN Group, Washington, D.C.

Presented To:
TERA Peer Review Panel
University of Cincinnati,
Kingsgate Conference Center
September 23, 2003

Existing RfC/RfD for AN

- RfC = 0.002 mg/m^3
  - Based upon a LOAEL of 20 ppm (43 mg/m^3) for nasal lesions in rats (Quast et al., 1980).
  - LOAEL value adjusted for discontinuous exposure (6 hours/day, 5 days/week) to yield 7.7 mg/m^3
  - RGDR adjustment for respiratory effects in extrathoracic region to yield HEC of 1.9 mg/m^3
  - An uncertainty factor of 1,000: UFh = 10 (default value); UFa = 3 (RGDR adjustment considered); UFl = 3 (minimally adverse endpoint); UFd = 10 (lack of inhalation bioassay in second species; lack of reproduction study by inhalation route)
- RfD: None

2

Dose-Response Assessments

General Approach

1. Identification of a Critical Effect/Data Set
2. Identification of a Dose Measure
3. Identification of a Response Measure
4. Selection of a Dose-Response Model (using BMDS package)
5. Selection of Response Level (BMD)
6. Selection of a Method for Extrapolating to Low Doses (Uncertainty Factors)
7. Calculation of RfC

3

Step 1: Identification of a Critical Effect/Data Set

- Hazard ID section concluded that irritation and neurological endpoints are the major effects of AN
- Inhalation RfC
  - Human data: Irritation (Sakurai *et al.*, 1978)
  - Animal data: Nasal lesions (Quast, 1980)
- Oral RfD
  - Animal data: Neurological (Gagnaire et al. 1998)

4

Step 2: Identification of Dose Measure

- Inhalation RfC
  - Human data: External concentration (mg/m^3)
  - Animal data: External concentration (mg/m^3), adjusted using RGDR methods
- Oral RfD
  - Internal dose (AUC AN and AUC CEO)

5

Steps 3-5 for RfC/RfD Derivation

- Step 3: Response Measure
  - RfC: Human data - Not applicable (NOAEL used); Animal data: Extra risk (default)
  - RfD: Arithmetic mean for AMAP, post-recovery (continuous data used)
- Step 4: Dose-Response Model
  - RfC: Human data - Not applicable (NOAEL used); Animal data - Logistic model selected based upon goodness-of-fit and visual inspection
  - RfD: Linear model selected for AUC AN as dose measure; Power model selected for AUC CEO as dose measure
- Step 5: Point of Departure
  - RfC: Human data - NOAEL value; Animal data - LED10
  - RfD: 1 SD

6

Figure 1. Nasal Lesions in Rats Exposed to AN (Quast et al., 1980)

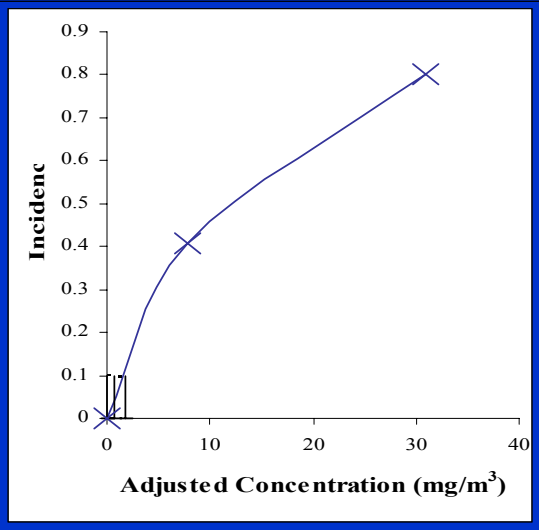

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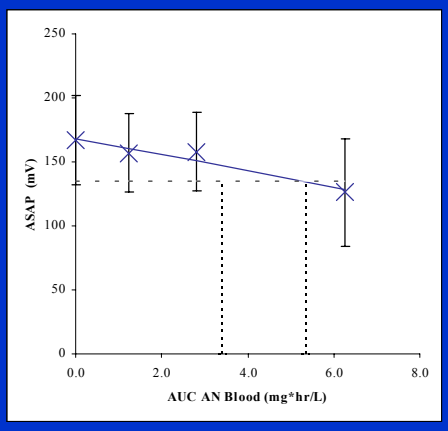
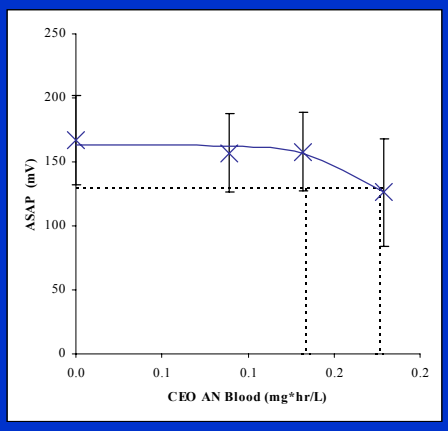
Figure 2. Dose-Response Models Fit to Gagnaire et al. (1998) Data Using Different Internal Dose Measures





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Step 6. Select a Method for Low-Dose Extrapolation

- RfC
  - Human data: Net UF = 58
    - UFh = 5.8 based upon uncertainty analysis for human model (Sweeney et al., 2003)
    - UFs = 10 (default)
  - Animal data: Net UF = 17.4
    - UFa = 3 (considering RGDR adjustment)
    - UFh = 5.8 (same as above);
- RfD
  - Net UF = 174
    - UFa = 3 (for potential dynamic differences between rats and humans)
    - UFh = 5.8 (based upon uncertainty analysis for human PBPK model in Sweeney et al., 2003)
    - UFs = 10 (default)

9

Step 7: Calculate Reference Values

- RfC
  - Human data: 0.1 mg/m^3
    - Confidence in this RfC value is considered medium to high (Confidence in the critical study is medium; Confidence in the database is high)
  - Animal data: 0.02 mg/m^3
    - Confidence in this RfC value is considered medium (Confidence in the critical study is high; Confidence in the database is high; Confidence in the kinetic adjustments (RGDR) used to support this RfC value is low)
- RfD
  - Based on AUC AN as the internal dose measure: 0.2 mg/kg-day
  - Based on AUC CEO as the internal dose measure: 0.005 mg/kg-day
  - Confidence in the oral RfD: medium-to-high (Confidence in key study is medium; Confidence in database is high; Confidence in the PBPK modeling is medium)

10

Key Issues/Questions for Noncancer Dose-Response Assessments

- Appropriateness of endpoints/studies selected?
- Appropriateness of uncertainty factor values?
- Confidence in RfD and RfC values (low, medium, high)?

11