2006 Annual Report

Toxicology Excellence for Risk Assessment (*TERA*)

Cincinnati, Ohio

March 30, 2007

Table of Contents

TERA: Providing Public Service Through Excellence in Risk Assessment

In 1995, Dr. Michael Dourson developed a non-profit and independent corporation for improving the science of risk assessment through a focus on partnerships among *all* members of the risk assessment community. His vision of toxicology excellence for risk assessment to support the protection of public health would be accomplished by developing and communicating risk assessment information, sponsoring peer reviews and consultations, improving risk methods through research, and educating interested parties on risk assessment issues. *TERA* focuses on providing high quality science and building bridges among diverse stakeholder groups.

As a nonprofit, *TERA* is committed to serving the needs of the risk assessment community. For example, *TERA* developed the *ITER* database to assist risk assessors in identifying available risk values (see www.tera.org). *TERA* donates a percentage of staff time to serve the risk assessment community, professional societies, and the public. In addition, our State HELP program assists states and local governments. Although we have expanded our capabilities over the years, our mission to support the protection of public health and our vision to provide toxicology excellence for risk assessment remain unchanged. See highlights below and visit www.tera.org to see more of what *TERA* has accomplished with its sponsors.

The Alliance for Risk Assessment Continues to Grow

An open and transparent multi-stakeholder approach for addressing the technical support needs of state and local risk assessors, environmental organizations, and the regulated community is needed. Since its inception, *TERA* has provided technical assistance to many states under our State HELP Program. Recognizing growing needs in this area, an ***Alliance for Risk Assessment*** was launched in 2006 to expand significantly resources available to the risk assessment community. This effort has been led by *TERA*, the National Library Medicine (NLM) and other non-profit collaborators. A new website has been launched to provide information updates. Visit the website at www.allianceforrisk.org to learn more about current *ARA* activities such as the recent naming of the *ARA* Steering Committee and a list of outreach efforts and presentations, as well as to find information resources including, project and technical report updates, project request submission information, and links to free resource databases such as *ITER*. For more information on how to participate in this effort, contact Dr. Andrew Maier (Maier@tera.org or 513-542-7475 ext. 16).

Dose Response Assessment Boot Camp

TERA is proud to announce its ***Dose-Response Assessment Boot Camp***, a new initiative providing intensive, in-depth hands-on training in hazard characterization and dose-response assessment for developing human health risk assessments. The first offering of this comprehensive course is slated for the fall of 2007. The week-long course with emphasis on dose response assessment will be based on our popular chemical risk assessment training sessions developed and presented to various audiences in the past decade. It is designed to provide systematic training in current assessment practices as well as in the latest methods in human health chemical risk assessments. The students will learn all aspects of hazard characterization and dose response assessment, and practice the skills learned in the classroom.

Upon completing the course, the participants will be able to derive or evaluate risk values for noncancer and cancer risk assessments and will receive a certificate documenting their successful completion of the course. Contact Patricia Nance at nance@tera.org or 513-542-7475 x25 for more information.

TERA Announces CRADA to Improve Cancer Risk Assessment

TERA, the Food and Drug Administration's National Center for Toxicological Research (NCTR), and ENVIRON have established a collaborative relationship (Cooperative Research and Development Agreement) for informing mode of action (MOA) analysis for cancer risk assessment. This collaboration seeks to investigate a new approach to evaluate whether tumors induced by mutagenic chemicals with multiple plausible MOAs are due to the chemical's mutagenicity or another MOA. The essence of the approach focuses on using transgenic *in vivo* shuttle vector models to directly evaluate mutations in the tumor target tissue in the same rodent strain. The analysis compares the time to mutation with time to tumors, as well as comparing *in vivo* mutagenicity dose-response with the tumor dose response. Supplemental evaluations may include markers for other potential MOAs. The analytical approaches being developed also have implications for quantitative evaluation of other potential MOAs. We invite companies and government agencies to join us by participating in and/or sponsoring studies under this CRADA. For more information or a copy of a related manuscript contact Dr. Lynne Haber (Haber@tera.org or 513-542-7475 x17).

Principles of Peer Review Extended to Peer Input and Consultation

TERA has organized independent reviews since 1996 and our program and procedures for selection of reviewers and conduct of meetings are consistent with the guidance provided by the U.S. OMB, U.S. EPA and the National Academies of Science. In recent years, we have extended the principles and practices of peer review into earlier stages of work product development to use peer input and peer consultation to strengthen draft or intended final work products. *TERA* works with each sponsor to design an approach that is most effective for the type of work product, stage of development, and purpose for engaging experts. Peer input, peer consultation and peer review are three approaches we use, all of which follow the principles that are the cornerstone of our program – selection of appropriate expertise, scientific robustness, and transparency. A fourth principle, independence, is essential for all peer reviews and an important consideration for peer input and consultation efforts. More details about the program can be found later in this report. For information or a copy of a related manuscript contact Ms. Jacqueline Patterson (Patterson@tera.org or 513-521-7426).

Development and Application of State-of-the-Art Methods

TERA has a number of projects on the cutting-edge of risk assessment. We continue to work on novel methods for incorporating biomarker data into dose-response analysis, such as using Bayesian analysis. We have developed a generic PBPK model for developmental toxicity that incorporates parameters for the time-varying changes in fetal weight and in several maternal parameters. *TERA* scientists are also working on in-depth evaluations of the mode of action of several high-visibility chemicals, *TERA* scientists also worked with US EPA to develop a series of online training presentations on BMD modeling and categorical regression in dose response assessment.

PROGRAM UPDATES

International Toxicity Estimates for Risk (ITER) Database

The purpose of *ITER* is to develop and maintain a comprehensive database that provides risk assessors tools to help protect public health through the use of the best toxicity information. *TERA* has provided this service to the risk assessment community since 1996, having developed and expanded *ITER* to add more organizations and, recently, to offer a more searchable version of *ITER* to users via the National Library of Medicine's (NLM) TOXNET compilation of databases.

Our *ITER* web statistics for 2006 shows more than 30% growth to an average of over 330 users per day. The average time spent on ITER has also increased. Additional web statistics are listed in the table for multiple years.

ITER WEB STATISTICS - AVERAGES

Year	Avg. Daily Hits	Avg. Daily Users	Avg. Length in Minutes
2006	2404	333	42
2005	2906	240	34
2004	2407	185	31
2003	1812	116	36
2002	1375	103	10
2001	1318	97	8

We have continued to coordinate with sponsors, state governments, and other parties to further the concept of the Alliance for Risk Assessment as related to *ITER*. We are also collaborating with sponsors on the development of a hazard notification system called the Risk Information Exchange (RiskIE), which will be linked to and/or integrated with *ITER*. We have identified the need for an additional column on *ITER*, the Independent Peer Review (IPRV) column, which

will house data that has been peer reviewed by groups other than *TERA*. We are also continuing to update and expand *ITER* with additional data from ATSDR, EPA, NSF International, RIVM, and IARC.

Peer Consultation and Review Program

The Peer Consultation and Review Program provides scientists and others with the opportunity for expert independent peer consultation and peer review of risk assessment related documentation through panel meetings or other venues. Since 1996 we have organized and conducted over 50 panel reviews and numerous paper reviews. Our meetings are conducted in a transparent fashion and are usually open to the public. *TERA* manages all aspects of the peer consultation or review including selection of the panel, identification of conflict of interest and bias, development of issues to focus panel discussions, conducting meeting, all logistical and facility arrangements, and preparation of a meeting report.

In 2006, the Peer Consultation and Review program continued to organize and conduct peer reviews and consultations for both private and public organizations. *TERA* also continued to organize and conduct peer consultation meetings for Voluntary Children's Chemical Evaluation Program (VCCEP) submissions in 2006. A benzene VCCEP submission was the subject of a meeting in June 2006 and a toluene submission underwent peer consultation in November of 2006. *TERA* scientists worked with Dr. Pamela Williams, a *TERA* Visiting Scientist, to prepare and submit a manuscript on peer consultation and results from the first half of the VCCEP pilot, which was published in the June 2006 issue of *Risk Analysis*. In a project for Health Canada, *TERA* scientists prepared a manuscript on uses and benefits of peer involvement of risk assessment work products.

Also in 2006, *TERA* had the opportunity to assist the multi-stakeholder group in Sudbury Ontario with independent expert peer reviews of their community and area-wide human health and ecological risk assessments. For the State of Michigan and Dow Chemical, *TERA* continues to provide peer consultation services for issues regarding bioavailability of dioxins in soil.

Research Program

The Research Program seeks to move the science of risk assessment forward globally by improving the application of current methods, developing and defining new methods, and obtaining the data to support such applications, as well as educating the scientific community and the general public about advances in risk assessment research.

The Research Program works closely with the *TERA* assessment *(VERA)* program in identifying and addressing key issues related to risk assessment methods. Research projects were conducted for a variety of government sponsors, including EPA, NIOSH, and DOD, as well as some industry sponsors.

We are developing and demonstrating a decision support system for validating and using biomarkers in risk assessment. A case study analysis was conducted with benzene, using a variety of methods (including a Bayesian network, other graphical modeling techniques, and

regression analysis) for validating biomarkers of exposure and effect. Work is now underway on applying the decision support system to titanium dioxide (including inhalable particles and nanoparticles), with additional chemicals to follow.

In work supporting the University of Cincinnati, *TERA* is enhancing a process for reviewing research protocols regarding handling of potentially toxic materials in the laboratory. The work includes enhancements to a decision logic developed in previous work on this project, and development of a database to improve data handling. The final software product will be shared with other research institutions, which showed considerable interest in earlier presentations of the methodology.

TERA is providing support to U.S. EPA's Office of Water on writing the guidance document for the development Health Advisories. This work includes consideration of some basic methods issues related to development of these risk values.

TERA teamed with another consulting company on a winning proposal to U.S. EPA for developing an approach for categorizing biomarkers and other endpoints along a pathophysiological progression. The work is intended to assist in developing a consistent approach to assist in evaluating mode of action, interpreting the implications and severity of biomarker changes, consideration of interspecies differences, and aid in the standardization and uniformity of chemical health assessments.

Verifiable Estimates for Risk Assessment (VERA) Program

The *VERA* Program seeks to provide high quality risk assessment service by developing unbiased and science-based risk assessments for all sponsors, including government agencies, industry groups, and environmental groups. *TERA* is viewed as a source of high quality technical expertise as evidenced by ongoing projects, requests for new work by existing and former sponsors, recent referrals, and requests for training.

In 2006, *TERA* staff worked on 23 significant projects, as well as a variety of other smaller projects. The program has maintained a diverse portfolio of work (number of projects shown in parenthesis), including: projects sponsored by industry (8), U.S. EPA or NIOSH (9), state and Non-U.S. governments (4), and the U.S. Department of Defense (2); projects covering diverse scopes, such as comprehensive toxicity reviews (6), hazard screening (6), occupational toxicology (3), risk assessment training courses (4), and application of new assessment methods.

In 2006, *TERA* staff continued to be active in support of U.S. EPA and NIOSH. *TERA* reviewed the basis of assessments by U.S. EPA and other agencies for noncancer and cancer endpoints, considered the availability of new studies, and conducted screening-level evaluations of RfDs for developmental and reproductive toxicity endpoints for over 40 chemicals. We also developed a database of dose-response information for over 400 studies to support the development of new QSAR models. We provided significant technical support to U.S. EPA's National Homeland Security Research Center via Argonne National Laboratory in developing provisional advisory levels (PALs) for contaminants that might be released to a public drinking water supply or urban air by a catastrophic event, such as a terrorist attack.

We were awarded a contract to provide technical assistance to EPA National Center for Environmental Assessment (NCEA) in conducting beta testing for the new benchmark dose modeling software (BMDS) modules. *TERA* also received a contract to support NCEA in updating the Air Quality Science Assessment Document for Oxides of Nitrogen, continuing into 2007. For NIOSH, *TERA* is developing documentation in support of a new skin notation methodology for 48 chemicals and is providing support of the Immediately Dangerous to Life or Health (IDLH) Program, building from a research project developed in 2005.

TERA's has demonstrated technical leadership in various areas of risk assessment has led to multiple requests for risk assessment training. For the U.S. EPA, we developed a series of U.S. EPA online training presentations on dose-response methods, including: BMD introduction, dichotomous models, continuous models, cancer model, nested models, and categorical regression. In collaboration with U.S. EPA and Health Canada developed and presented a training course on the IPCS approach for chemical-specific adjustment factors (CSAF). *TERA* provided a series of risk assessment training workshops to a number of organizations, including the Texas Commission on Environmental Quality (TCEQ), including training on cancer and noncancer risk assessment, dosimetric adjustment, and BMD modeling in risk assessment.

TERA scientists continued to build work of interest to industry partners. Ongoing support has been provided for several biotechnology and pharmaceutical companies, including continued support calculating cleaning criteria for shared manufacturing equipment, and identifying health-protective screening-level Occupational Exposure Levels for the workers. Other industry projects in the *VERA* program have focused on product safety support, including developing and applying hazard screening approaches for product ingredients and preparing material safety data sheets (MSDS).

TERA continues to look for opportunities to pursue collaborations outside of North America. Recently *TERA* collaborated with a Japanese consultancy to provide a risk assessment document on nickel compounds for submission to the Japanese Ministry of Health. Our scientists actively participated in Regional SOT sections for scientists from Africa and China.

TERA Public Service Activities

TERA staff continued to dedicate significant effort supporting scientific development through *pro bono* activities and our *TERA* Corporate Development funds. Staffers have served as peer reviewers of submitted manuscripts for journals: *Regulatory Toxicology* and *Pharmacology*, *Human* and *Experimental Toxicology*, *Critical Reviews* in *Toxicology, and the Journal* of *Toxicology* and *Environmental Health*. Staff also served on editorial boards for several of these journals. Our staff made multiple presentations at national meetings such as the Society of Toxicology Annual Meeting, Society for Risk Analysis, and the Toxicology and Risk Assessment Conference, the Annual Meeting of the International Hormesis Society, and the American Industrial Hygiene Conference and Exposition.

TERA staffers were active on numerous scientific committees and advisory boards in 2006, for example, the AIHA WEEL, NSF International, Underwriters Lab. *TERA* staff members are

officers in professional societies, holding several leadership positions: the Society for Risk Analysis Ohio Chapter (Past President - Zhao and Secretary Gadagbui), Risk Assessment Specialty Section (RASS) of SOT (Secretary/Treasurer - Haber).

TERA staff also provided courses or lectures to Universities or Society Local Sections: risk assessment lectures for several graduate courses at the University of Cincinnati, Miami University of Ohio and the Northland SOT Section. Staff also provided lectures to several Chinese universities and government agency groups.

In our local communities *TERA* employees participated in environmental efforts, including local Earth Day events and the Alliance for Chemical Safety, provided guidance to local groups on water quality and air quality issues, and served as newsletter editors for Oxbow Inc.'s *Wetland Matters* and *EchoBats Inc.*

TERA's Board of Trustees

TERA's Board of Trustees members serve 3-year rotating terms. Listed below are *TERA's* Board members for 2006.

TERA's Board of Trustees plays an important role in the organization. We seek nominations for a diverse membership. We have members who are involved with government agencies, universities, industry and nonprofit organizations. By having a diverse membership, our board is better able to advise *TERA* on issues and growth in the field of toxicology and risk assessment.

Board of Trustees - 2006

Michael Dourson, Toxicology Excellence for Risk Assessment
Michael Fremont, Rivers Unlimited (emeritus)
Sam Kacew, University of Ottawa
Steven Lewis - BOARD CHAIR, Integrated Policy & Sciences Inc.
Randall Manning, State of Georgia
Roger O. McClellan - PAST CHAIR, CIIT (emeritus)
Jennifer Orme-Zavaleta, U.S. Environmental Protection Agency
Jerry Rice, University of Georgetown
Sue Ross, University of Cincinnati
Chad B. Sandusky - BOARD TREASURER, Physicians Committee for Responsible Medicine
James D. Wilson, Resources for the Future (emeritus)

TERA Staff and Contacts

TERA is pleased to announce that Mr. Oliver Kroner has joined us as a Research Associate in 2006. Dr. Richard Hertzberg has joined *TERA*'s group of external risk assessment collaborators through our Visiting Scientist Program. Dr. Hertzberg has expertise and international recognition in biomathematics and mixtures risk assessment.

Director: Michael Dourson, Ph.D., DABT, ATS
Dourson@tera.org or 513-542-7475 ext. 14

Associate Director: Andrew Maier, Ph.D., CIH, DABT
Maier@tera.org or 513-542-7475 ext. 16

Research Program: Lynne Haber, Ph.D., DABT
Haber@tera.org or 513-542-7475 ext. 17

VERA Program: Andrew Maier, Ph.D., CIH, DABT
Maier@tera.org or 513-542-7475 ext. 16
AND
Lynne Haber, Ph.D., DABT
Haber@tera.org or 513-542-7475 ext. 17

Peer Review and Consultation Program: Jacqueline Patterson, M.En. Patterson@tera.org or 513-521-7426

***ITER* Database**: Andrea Wullenweber, M.S.
Wullenweber@tera.org or 512-863-5441

Financial Statement

TERA's 2006 income was $1,826,183 and actual expenses totaled $1,807,665. This resulted in net income of $18,518.

As a neutral, non-profit corporation, TERA strives for work on both public and private projects in a roughly equal amount. In 2006 *TERA* conducted a larger percentage of work for government agencies and other non-profits (77%), while twenty-three percent of work was for private sector sponsors. The table below shows the percentage of government and private work for each year since our inception. This balance of sponsors varies from year-to-year reflecting the needs of sponsors and our goal of providing scientifically credible and neutral guidance.

FUNDING SOURCES

Year/Source	Government and other Nonprofit	Industry and Industry Related
1995	67%	33%
1996	37%	63%
1997	55%	45%
1998	63%	37%
1999	66%	34%
2000	59%	41%
2001	48%	52%
2002	72%	28%
2003	66%	34%
2004	82%	18%
2005	82%	18%
2006	79%	21%

2006 Publications

DOURSON, M and D. DRINAN. 2006. **Sensitive Populations and Risk Assessment**. In: *Toxicokinetics in Risk Assessment.* Taylor and Francis Publishers. J.C. Lipscomb and E.V. Ohanian, Eds. Informa health care, New York. Pp. 251-210.

GADAGBUI, B.K., L.T. HABER, and M.L. DOURSON. 2006. "**Chemical Risk Assessment as Used in Setting Regulatory Levels or Standards**." Chap. 3.3.1 in *Transforming Sustainability Strategy into Action: The Chemical Industry*, edited by Beth Beloff, Marianne Lines, and Dicksen Tanzil. Hoboken , NJ : John Wiley & Sons, Inc. pp. 35-41.

HABER, L.T. 2006. **Overview of Approach to Noncancer Risk Assessment**. In: *Toxicokinetics in Risk Assessment*, Taylor and Francis publishers, J.C. Lipscomb and E.V. Ohanian, eds. Informa health care, New York. Pp. 1-26.

HABER, L.T., A. MAIER and M.L. DOURSON. 2006. **Using Best Science in Cancer Risk Assessment.** Editorial. Human and Ecological Risk Assessment. 12: 1-8.

HACK, C.E., W.A. CHIU, Q.ZHAO, and H.J. CLEWELL. 2006. **Bayesian Population Analysis of a Harmonized Physiologically-based Pharmacokinetic Model of Trichloroethylene and its Metabolites.** Reg. Tox. Pharm. 46:63-83.

SCHOENY, R., L. HABER and M. DOURSON. 2006. **Data Considerations for Regulation of Water Contaminants**. Toxicology. 221 (2-3): 217-224.

WILLIAMS, P., D. BRIGGS, and J. PATTERSON. 2006. **VCCEP Pilot: Progress on Evaluating Children's Risks and Data Needs.** Risk Anal. 26(3): 781-802.

ZHAO, Q., M. DOURSON, and B. GADAGBUI. 2006. **A Review of the Reference Dose for Chlorpyrifos.** Reg. Toxicol. Pharmacol. 44(2): 111-124.

Manuscripts In Preparation

HACK, C.E., HABER, L.T., MAIER, A., SCHULTE, P., FOWLER, B., LOTZ, W.G., and SAVAGE. R.E. 2006. **A Method for Biomarker Validation and Biomarker-based Dose Response: A Case Study with Benzene and a Bayesian Network**.

MAIER, A., B. GADAGBUI, E. HACK, Q. ZHAO, A. PARKER, A. WEINRICH, and C. GERACI. 2006. **Use of Animal Acute Toxicity Data to Derive Immediately Dangerous to Life or Health Concentrations: Extrapolating to Human Effect Thresholds.**

MAIER, A., E. HACK, Q. ZHAO, L.T.HABER and M.L. DOURSON. 2006. **Derivation of an Occupational Exposure Limit for Inorganic Borates using a Weight of Evidence Approach.**

MAIER, A. and L.T. HABER. 2006. **Toward the Goal of Harmonizing Occupational Exposure Limits: Approaches for Enhancing Derivation Methods.**