2004 Annual Report

Toxicology Excellence for Risk Assessment *(TERA)*

2300 Montana Avenue, Suite 409
Cincinnati, OH 45211
513-542-7475
TERA@TERA.org

March 2005
CHAIRPERSON’S MESSAGE

Steven C. Lewis, Ph.D., DABT
President & Principal Scientist
Integrative Policy & Science, Inc.
Chair, Board of Trustees
Toxicology Excellence for Risk Assessment

March 30, 2005

Michael L. Dourson, Ph.D., DABT, President
Toxicology Excellence for Risk Assessment
2300 Montana Avenue
Suite 409
Cincinnati, OH 45211

Dear Dr. Dourson:

I have enjoyed the first year of my term as Chair of TERA’s Board of Trustees. It’s both an honor and pleasure to work with you and the extraordinary folks at TERA. I have watched with delight and wonder at the progress that you and your colleagues have made.

It’s especially gratifying to note the visibility that TERA – and you, personally – enjoy. I’m sure it’s very satisfying to you to see the growth – in both professional and business dimensions - which TERA has achieved in its relatively brief history.

This past year was marked by significant challenges. You and your staff have responded with creativity and confidence. Your commitment to scientific excellence remains TERA’s critical distinguishing characteristic.

On behalf of the entire Board of Trustees, I want to congratulate you on exceptional performance.

Very truly yours,

/s/

Steven C. Lewis, Ph.D., DABT
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Introduction

Toxicology Excellence for Risk Assessment (TERA) is a nonprofit organization with a mission to protect public health by developing and communicating risk assessment values, sponsoring peer reviews and consultations, improving risk methods through research, and educating the public on risk assessment issues. 2005 marks the end of our first decade of public service.

In 1995, Michael Dourson developed this independent non-profit 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 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's focus on high quality science and building bridges between government, industry, and environmental groups has led, now ten years later, to 15 employees conducting work with a diverse group of partners, ranging from state and federal agencies, environmental groups, private companies, and trade associations.

By actively seeking partners from all sectors of the risk assessment community TERA gains a broad perspective and understanding of the scientific issues of risk assessment. Because we are not dependent on any single sector for our funding, we are able to conduct independent, high-quality science and prepare work products that reflect TERA’s best scientific judgment, rather than the biases of any particular partner. The value of this approach is recognized by diverse sponsors who individually and jointly approach TERA to play a key role in their projects.

As a nonprofit corporation, 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. The ITER database was developed with donations and grants from numerous government and industry sponsors, as well as internal TERA funds, and has now grown to include over 600 chemicals, six organizations, and independent values, and is part of the National Library of Medicines’ TOXNET database. TERA donates 5% of staff time to serve the risk assessment community, professional societies, and the public. Individual staff members donate even more personal time. Publication of our work in the peer-reviewed literature and on TERA’s website are other ways in which we ensure that our work is available to benefit the public.

Although in ten years we have expanded our capabilities, our mission to protect public health and our vision to provide toxicology excellence for risk assessment remains unchanged. We have expanded our core focus of detailed, mechanistic evaluations of chemicals to include screening and ranking methods. Our independent peer review program is now exploring the concept of peer consultation, a mechanism for obtaining expert input at an earlier stage. We are expanding the application of physiologically-based pharmacokinetic (PBPK) modeling and quantitative risk assessment methods in both our assessment and research programs. In addition, we continue to develop new training courses on basic and advanced noncancer and cancer risk assessment methods.
Highlighted below are just a few of TERA’s projects. These projects cover a broad range of topics and illustrate the scope of TERA’s work.

**Highlights of 2004**

**Development of a Biomarker Decision Support System**

TERA is conducting a study with the National Institute for Occupational Safety and Health (NIOSH) to develop and demonstrate a system for integrating complex data from emerging technologies (e.g., gene expression assays) with traditional toxicity data, validating biomarkers using Bayesian networks and other graphical modeling techniques, and incorporating the biomarkers in risk assessment. Biomarkers spanning the exposure-disease continuum are validated or rejected by analyzing the strength of the dependencies among exposure, the potential biomarkers, and disease. Regression analysis is used to analyze dose-biomarker-response relationships to define an effective dose using the biomarkers indicated by the Bayesian network analysis. The approach will reduce the need to extrapolate from high doses that induce severe effects to more meaningful changes that occur at early time points and low doses. Linking early effects with clearly adverse effects can also enhance our understanding of interspecies and human variability.

**ITER Database Joins the National Library of Medicine**

TERA’s Internet database of human health risk values, the International Toxicity Estimates for Risk (ITER) Database ([www.tera.org/iter](http://www.tera.org/iter)) is now part of the National Library of Medicine's TOXNET compilation of databases, located at [http://toxnet.nlm.nih.gov/](http://toxnet.nlm.nih.gov/). As part of TOXNET, ITER can now be searched by chemical synonym and via free text. Additionally, multi-file searching allows a single query to be run against multiple toxicological databases, including ITER, and links to TOXLINE allow users to obtain current literature references and abstracts on ITER chemicals. ITER continues to expand with the addition of risk data from NSF International ([www.nsf.org](http://www.nsf.org)) and cancer classifications from the International Agency for Research on Cancer (IARC) ([http://monographs.iarc.fr/](http://monographs.iarc.fr/)). Risk information from NSF International and IARC joins the existing data in ITER from the Agency for Toxic Substances and Disease Registry (ATSDR), Health Canada, the National Institute of Public Health & the Environment (RIVM) - The Netherlands, the U.S. Environmental Protection Agency (US EPA), and independent parties whose risk values have undergone peer review.

**Trichloroethylene PBPK Model Harmonization and Peer Consultation**

At the request of the U.S. Air Force (USAF) and the US EPA, TERA facilitated and provided support to a USAF-US EPA workgroup developing a harmonized physiologically-based pharmacokinetic (PBPK) model for trichloroethylene (TCE) and its metabolites. The project used the best science and updated data to derive a comprehensive TCE PBPK model as an input for ongoing TCE risk assessment activities. TERA provided technical support to the USAF-US EPA workgroup, and gathered input from scientists from academia and private consulting with experience in developing TCE PBPK models, toxicokinetics of TCE and its metabolites,
biostatistics, and TCE risk assessment. The resulting harmonized model was the subject of a public peer consultation meeting organized by TERA in June 2004.

Summary of TERA Program Activities

Peer Consultations and Peer Reviews

TERA’s Peer Consultation and Review Program provides sponsors with high quality, independent, expert scientific review of risk assessment related documentation through panel meetings or other venues. TERA uses a transparent and public process for peer reviews and consultations to facilitate maximum sharing of information and credibility of conclusions. TERA’s role is to manage all aspects of the peer consultation or review, including independent selection of the panel, identification of conflict of interest and bias issues, development of the panel charge, conduct of meetings, all logistical and facility arrangements, and preparation of meeting reports.

2004 Highlights

- 2004 was the second year TERA conducted peer consultations for the Voluntary Children’s Chemical Evaluation Program (VCCEP) pilot. Industry submissions on n-alkanes and methyl ethyl ketone were reviewed by panels with diverse expertise in children’s health, exposure assessment, risk assessment and other pertinent disciplines. The submissions included hazard, dose-response, and exposure assessments, culminating in judgments regarding the need for additional data, studies, and analyses to evaluate the risk to children from potential exposure to these chemicals.

- Utilizing funding from a 5-year cooperative agreement with the U.S. Environmental Protection Agency (US EPA), TERA is conducting a variety of peer consultations. These efforts allow TERA to explore and further develop the concept of peer consultation as a distinct process from peer review. During 2004, TERA explored issues related to selection of peer consultants and what constitutes a conflict of interest or unacceptable bias, how best to structure meetings to meet the different needs of a peer consultation, and how best to communicate results to the public.

2004 Peer Consultation Meetings

- VCCEP Methyl Ethyl Ketone
  ACC Ketones Panel
- VCCEP n-alkanes
  ACC n-Alkanes VCCEP Consortium
- Evaluation of Contribution to IARC
  NIEHS
- Complex Exposure Tool (ComET)
  Health Canada
- Trichloroethylene PBPK Model
  Department of Defense
- Non Lethal Weapon Systems
  Department of Defense

2004 Peer Review Meetings

- Reference dose (RfD) for Resorcinol (second meeting)
  Beazer East, Inc
• **TERA** uses its considerable expertise to assist community groups and others who have developed assessments or must evaluate them. For example, **TERA** staff reviewed a memorandum for the development of a Remedial Action Criteria (RAC) for a soil contaminant, prepared by a consulting group as part of an overall cleanup assessment for a mining site.” **TERA**’s work contributed to support for a community group representing residents affected by the site and was funded by the responsible party through a fund set up for the community group.

• **TERA** also assisted government and private sponsors by reviewing the technical basis for chemical assessments and methodologies they have developed.

These requests recognize the considerable expertise **TERA** has in toxicology and risk assessment. Some of the reviews in 2004 included risk methods for the Consumer Product Safety Commission; Draft Air Toxics Risk Assessment Guidance Documents, IRIS Toxicological Reviews, and Provisional Toxicity Values Developed for the Hazardous Waste Identification Rule for US EPA; chemical assessments for Health Canada, and review of an occupational exposure limit for n-Propyl Bromide for a private company.

**International Toxicity Estimates for Risk (ITER) Database**

**TERA** has revolutionized the delivery of human health risk values with its International Toxicity Estimates for Risk (ITER) Database ([http://www.tera.org/ITER](http://www.tera.org/ITER)), which is a free Internet database of human health risk values and cancer classifications for over 600 chemicals of environmental concern from organizations worldwide. In 2004, **TERA** expanded the delivery of **ITER** by becoming part of the National Library of Medicine's (NLM) TOXNET system ([http://toxnet.nlm.nih.gov](http://toxnet.nlm.nih.gov)). As part of TOXNET, **ITER** can now be searched by chemical synonym and via free text. In addition, a multi-file searching function allows a single query to be run against multiple toxicological databases, including **ITER**. Links to TOXLINNE allow users to obtain current literature references and abstracts on **ITER** chemicals. **ITER** has strengthened and broadened TOXNET’s data in support of risk assessment by its incorporation of sound risk values from highly regarded national and international organizations.

In addition to users now having the choice of accessing **ITER** directly from the **TERA** website or through the TOXNET system, two new organizations are being added to **ITER**. During 2004, **TERA** began adding oral risk data and cancer classifications from NSF International and the International Agency for Research on Cancer (IARC), respectively. These organizations join the Agency for Toxic Substances and Disease Registry, Health Canada, Independent parties (listed under the **ITER** column), the National Institute of Public Health & Environmental Protection (RIVM) (the Netherlands) and the U.S. Environmental Protection Agency (U.S. US EPA). Thus, we now have seven organizations on **ITER**, and several more are under consideration.
Research in Risk Assessment Methods

The purpose of TERA’s Research Program is to move the science of risk assessment forward by improving the application of current methods, developing and defining new methods, obtaining the data to support such applications, and educating the scientific community and the general public about advances in risk assessment research. TERA scientists bring together a practitioner’s knowledge of the issues and pitfalls involved in the day-to-day application of methods for developing risk values, along with expertise in cutting-edge risk assessment methods. Our staff has led efforts in the development of the reference dose (RfD), categorical regression, and use of mechanistic data in risk assessment. We continue to research and publish in these areas, as well as on other methods for improving the practice of risk assessment. Training courses are available in many of these areas. A significant part of the research program has continued to be the risk characterizations of nonlethal weapons (including the development and application of new risk assessment approaches to complex problems, and bringing the NAS risk assessment paradigm to nonchemical agents); and evaluation of issues related to the trichloroethylene (TCE) risk assessment.

2004 Research Projects

- Evaluation of methods for development of NIOSH IDLH values
- Nonlethal weapons risk characterizations
- Support for Health Canada’s Domestic Substances List (DSL)
- Screening and ranking methods
- Consideration of persistence and bioaccumulation
- Use of biomarker data in risk assessment – using Bayesian analysis
- Integrating excess and deficiency in evaluation of copper exposures
- White paper on issues related to trichloroethylene risk assessment
2004 Highlights

- Evaluation of approaches for development of Immediately Dangerous to Life and Health (IDLH) values – Current approaches for extrapolating from experimental animal data to develop an IDLH are being evaluated. This includes evaluation of how well a factor of 0.1 applied to the $L_{C50}$ estimates the $L_{C05}$, $L_{C01}$, or $L_{C00}$, and determining whether other factors would be better for estimating the IDLH. Separate analyses are being conducted for different modes of action.

- Screening and Ranking Methods – provided input to methods being used by Health Canada for ranking the Domestic Substances List (DSL) of 23,000 chemicals based on toxicity considerations. In collaboration with Exponent, prepared a white paper on issues related to incorporation of persistence and bioaccumulation (P and B) criteria in evaluating human exposure and health effects. Issues related to blanket use of P and B criteria were noted, and a decision logic process was proposed that enables the use of expert judgment in considering P and B criteria in light of the potential for indirect human exposure.

Verifiable Estimates For Risk Assessment (VERA) Program

TERA’s Verifiable Estimates for Risk Assessment (VERA) program is designed to develop independent, neutral, science-based risk assessment values and characterizations of risks. Because risk assessment methodologies are constantly evolving and improving, and new epidemiology, toxicology, and mechanistic data are frequently published new or updated risk estimates are needed for many chemicals. TERA scientists develop chemical risk assessments through a detailed understanding of current risk assessment methods (including quantitative dose-response and pharmacokinetic modeling), expertise in toxicology and environmental health, and by actively interacting with and building partnerships among interested parties. Figure 2 below shows a breakdown of the program, based on percentage of effort in different areas.

Figure 2. Percentage of VERA Program effort by type of assessment.
2004 Highlights

- **TERA** Develops Several New IRIS Assessments for US EPA. **TERA** recently completed several Toxicology Reviews for the US EPA’s Integrated Risk Information System (IRIS) that are currently undergoing various stages of review by the Agency. We developed a draft Toxicology Review for the brominated flame retardant, Decabromodiphenyl Ether for the Office of Water, along with a Toxicology Review on Cyanide.

An initial draft Toxicology Review for Benzo[a]pyrene is undergoing further revision by US EPA’s IRIS Staff. **TERA** has also provided recent support for revision of ongoing assessments, including for Soluble Nickel Salts and Tetrahydrofuran. **TERA** prepares these comprehensive chemical assessments for both government and private sponsors and utilizes our detailed understanding of cutting-edge science and how it is applied practically in risk assessment.

- The Science of Perchlorate. Since 1995, **TERA** has been working to improve the science and risk assessment of perchlorate. At **TERA**’s suggestion, an industry group has worked cooperatively with US EPA to generate an extensive collection of animal, human clinical, and epidemiology studies needed to complete the database for perchlorate risk assessment. We recently published a scientific paper on perchlorate using **TERA** internal funds (Strawson et al., 2004) that describes our best scientific judgment about the most appropriate risk assessment approaches for perchlorate. Key scientific conclusions from this paper were confirmed by the National Academy of Science in its recent report on perchlorate: human studies are the most relevant to perchlorate risk assessment; iodide uptake would have to be reduced by at least 75% for several months or longer to cause declines in thyroid hormone production that would have adverse health effects; and the data from populations in Chile exposed naturally to perchlorate are relevant for evaluating the U.S. experience with perchlorate in drinking water. Efforts to evaluate how the newest data from sensitive populations in Chile will affect the perchlorate risk assessment will continue.

Public Service

**TERA** staff continues to dedicate significant effort supporting scientific development through *pro bono* activities and our **TERA** Developmental Reserve “funds.” In 2004, we used over 2000 hours, or approximately 5% of overall hours, to support these activities. Staff donated additional personal time. Examples of *pro bono* efforts of the staff included, but were not limited to:

- Peer reviewed manuscripts for the journals Regulatory Toxicology and Pharmacology, Human and Experimental Toxicology, Critical Reviews in Toxicology, Journal of Toxicology and Environmental Health, Human and Ecological Risk Assessment, and the Journal of Children’s Health

- Served on editorial boards for four of these journals

- Submitted numerous invited articles to the Encyclopedia of Toxicology
• Presented posters and presentations at meetings of the Society of Toxicology Annual Meeting, the Toxicology and Risk Assessment Conference, the Society for Risk Analysis, and the Midwest States Risk Assessment Symposium

• Served on numerous scientific committees, including the NAS subcommittees on Review of the Department of Defense Research Program on Low-Level Exposures to Chemical Warfare agents (Haber) and Ethical Issues In Housing-Related Health Hazards Research Involving Children, Youth And Families (Patterson), and AIHA’s Workplace Environmental Exposure Levels Committee (Maier)

• Served as officers in the Society for Risk Analysis (Secretary/Dourson) and in its Ohio Chapter (President/Maier and Treasurer/Nance), and as the vice-president of the Chinese section of the Society of Toxicology (Zhao)

• Taught in risk assessment courses at the University of Cincinnati, University of Kentucky, and Ball State University

• Reviewed a thesis on risk assessment for New Zealand Public Health Directorate employee

• Supported several states through the State Hazard Evaluation Lending Program (State HELP), for example, the State of Indiana on a TCE issue and the State of Minnesota with a pesticide degradate issue

• TERA hosted booth at Cincinnati’s celebration of Earth Day, presenting general ideas on thresholds and toxicology

• Published a manuscript on a Reference Dose (RfD) for perchlorate


**TERA Publications and Reports**

As a non-profit organization, TERA is dedicated to making its work available for public use. To that end, we publish our reports on our website (www.tera.org/pubs) and in peer reviewed journals and other publication venues. The following is a list of 2004 reports and publications available on our website.


Reports of Peer Reviews and Peer Consultations


Financial Report

TERA’s 2004 income was $1,742,738 and actual expenses totaled $1,729,944. This resulted in net income of $12,794.

TERA conducts work for both public and private sector sponsors. In 2004 TERA conducted a large percentage of work for government agencies and other non-profits (82%). Eighteen percent of our work was for private sector sponsors. While 2004 was heavy on government, this
ratio varies from year to year dependent upon the needs of sponsors and other conditions. Over the nine years of TERA’s operations, we have devoted 62.8% percentage to government work and 37.2% to private sector (see Figure 3 below for details).

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<tr>
<th>Nonprofit Billable</th>
<th>Profit Billable</th>
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<tr>
<td>67%</td>
<td>37%</td>
<td>55%</td>
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<tr>
<td>33%</td>
<td>63%</td>
<td>45%</td>
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<td>7%</td>
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<td>7%</td>
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Figure 3. Percentage of Profit and Nonprofit Work for Billed hours and Percent of Probono Effort for Total Hours

TERA’s efforts are broken down into five areas: Research, VERA, ITER, Peer Review and Peer Consultation and Developmental Reserve. Figure 4 below shows what percentage of total TERA effort was devoted to each program during 2004. This distribution among programs also fluctuates based upon sponsor needs in any given year.

Figure 4. Percentage of TERA effort by program area for 2004.

TERA’s Board of Trustees and Officers

TERA’s Board of Trustees consists of 10 members who serve 3-year rotating terms. Listed below are TERA’s Board members for 2004. The date in parenthesis indicates the year of election (or reelection).
Board of Trustees - 2004

Daniel Acosta (resigned in 2004)
Gail Charnley (resigned in 2004)
Michael Dourson (non-expiring member)
Steven Lewis (2004), Chair
Roger O. McClellan (2003), Past Chair
Joyce Martin (2003)
Jerry Rice (2004)
Chad B. Sandusky (2003), Treasurer

On March 29, 2004, the Board of Trustees met for a retreat with TERA staff, followed by its annual meeting on March 30, 2004, to discuss the 2003 Annual Report and the plans and budget for 2004. Both the retreat and the annual meeting were held in Cincinnati, Ohio, and the annual meeting convened at 9:00 a.m. Eastern. The Board held its midyear conference call meeting on October 8, 2004. This meeting was held in Cincinnati, Ohio, and began at 10:00 a.m. Eastern.

The Nominating Committee of the Board moved that the following slate of candidates for officers of the Board and Corporation be accepted at the mid-year meeting. Nominations were unanimously approved as follows:

Steve Lewis, Chair (two-year term)
Dan Acosta, Vice Chair (two-year term)
Chad Sandusky, Chair of Finance Committee (two-year term)
Michael Dourson, President (one-year term)
Jacqueline Patterson, Vice President and Secretary (one-year term)
Lynne Haber, Treasurer (one-year term)