

# **1998 Annual Report**

**Toxicology Excellence for  
Risk Assessment  
(*TERA*)**

**Cincinnati, Ohio**

**May 31, 1999**

## Introduction to the Annual Report

Dear Trustees:

Calendar year 1998 was good for our corporation. We hired 5 individuals (Dr. Lynne Haber, Mr. Andy Maier, Ms. Meg Poehlmann, Dr. Ken Poirier, and Mr. Jason Unrine. Biographical sketches for these folks are enclosed at the back of this report and can be viewed at [www.tera.org](http://www.tera.org). We lost one of our scientists, Dr. Susan Felter, to P&G. We developed assessments for several chemicals, significantly improved the existing *ITER* database through the use of a limited amount of grant money and collaboration with Concurrent Technologies Corporation, conducted several independent peer review meetings, published several papers, and donated ~650 hours of time to State Hazard Evaluation Lending Program (StateHELP) and scientific organizations. We also posted a modest gain of ~\$35,936. Our % balance of profit/nonprofit work was 34/66.

The attached agenda includes a number of important items for discussion, including approval of the 1999 budget and expansion of the Board of Trustees. We seek input on suggestions for appropriate individuals to replace the folks that are retiring this year (Eula Bingham, Jim Wilson and Bob Roberts). We would like our Board to be made up of a diverse group of individuals with experiences in either fundraising, marketing or business planning, in addition to technical skills and public participation from which our risk assessment group can draw.

We look forward to a productive meeting and value your contributions of time and talent!

Sincerely,

Michael L. Dourson, Ph.D., DABT  
President

5/31/99

## **Annual Meeting Board of Trustees Toxicology Excellence for Risk Assessment**

**June 13th, 1999, 3:00 to 5:00 p.m.**

### **Agenda**

1. Call to Order and Approval of Agenda (Michael Dourson)
2. Introduction of New Staff (All)
3. Old Business
  - *VERA* - Verifiable Estimates for Risk (Lynne Haber)
  - *ITER* - International Toxicity Estimates for Risk (Jacqueline Patterson)
  - Peer Review Meetings and Other Reviews (Jacqueline Patterson)
  - Education and Pro Bono (Joan Dollarhide)
  - Research (Ken Poirier)
  - Financial Report of 1998 and Proposed 1999 Budget (Michael Dourson)
  - Other?
4. New Business
  - *TERA* Plans for the Future (All)
  - Expansion of the Board of Trustees (Board of Trustees)
  - Other?
5. Good and Welfare

6:30 p.m. Dinner

**June 14th** Monday: *ITER* peer review meeting on arsenic teratogenicity

Monday evening Social: An open house social will be held at the new offices of *TERA*. Risk assessment scientists and managers from around Cincinnati will be invited. Scientists from the peer review meeting will also be in attendance.

**June 15** Tuesday: *ITER* peer review meeting on a Barium RfD

## **Selected *VERA* (Verifiable Estimates for Risk Assessment) Projects**

Under the *VERA* project, *TERA* scientists develop hazard characterizations and/or risk estimates for interested parties. Generally, these assessments are developed for chemicals that either have not been evaluated by other agencies (e.g., U.S. EPA), or for which the available assessments are not up-to-date. The product of an assessment under *VERA* may take many forms, depending on the need of the sponsoring party. The assessment may be in the form of a report, a manuscript suitable for publication, or in the format used by U.S. EPA for their risk assessment files. Upon completion of a *VERA* assessment, the sponsor may opt to submit the new or updated assessment to a government agency (e.g., U.S. EPA) for their consideration, or may opt to bring the assessment to a *TERA*-sponsored peer review meeting for consideration of inclusion on our *ITER* database. Reflecting *TERA*'s maturing as an organization, the assessments conducted in 1998 continued a trend of progressively more complex and detailed assessments. A first in 1998 was the preparation of Toxicological Support Documents for EPA's IRIS database.

In 1998, several assessments were undertaken as a part of the *VERA* project. Highlights of these projects include:

- **Soluble Nickel Salts.** In a project jointly sponsored by U.S. EPA's Office of Water, Health Canada, and the Metal Finishing Association of Southern California (MFASC, an industry group), *TERA* prepared the IRIS Toxicological Support Document for soluble nickel salts. Cancer and noncancer assessments via the oral and inhalation routes were conducted. The Toxicological Support Document underwent external peer review through *TERA*'s *ITER* peer review program (with the reviewers chosen by a subset of the trustees to avoid conflict of interest), and the document has been revised in response to the peer review comments. More concise reports are also being prepared in a format appropriate for loading onto EPA's IRIS database. An objective of obtaining funding for this project from multiple sources was to foster cooperation between industry and regulatory agencies, as well as to leverage scarce government dollars by supplementing them with industry funding. Results of the assessment have been presented at scientific meetings. In order to reach a wider scientific audience, the results of the assessment are also being prepared for publication in a peer-reviewed journal.

- **Chloroform.** *TERA* developed a risk assessment/characterization document for chloroform, based in part on existing EPA and other texts. This document included one of the first margin of exposure (MOE) analyses conducted for EPA under the 1996 cancer assessment guidelines. *TERA* played a key role in discussions with EPA as to how to apply in practice the rather broad areas that the 1996 guidelines recommends be considered for a MOE analysis. *TERA* also responded to technical issues associated with public comments, and finalized the text at EPA's direction.
- **Disinfection Byproduct Bromate.** *TERA* developed a risk assessment and characterization document for the drinking water disinfection byproduct bromate, under EPA's 1996 proposed cancer guidelines. Both genotoxicity and oxidative stress were considered as potential cancer modes of action. Based on the weight of evidence, a linear dose-response was recommended. In follow-up work under a separate contract, *TERA* wrote the IRIS Toxicological Review of bromate, which presented the toxicokinetics and toxicity data in animals and humans, in support of the development of oral and inhalation cancer and noncancer assessments for bromate.
- **Acrylamide Tumorigenicity.** *TERA* conducted an evaluation of acrylamide tumorigenicity, with particular attention to the mode of action. Acrylamide is unusual in that multiple modes of action for both cancer and noncancer effects may be occurring at similar doses. The scientific basis and support for these modes of action were evaluated in light of the framework presented in the 1999 SAB draft of EPA's cancer guidelines. An interim report of this work was prepared, and the draft was discussed at a peer input meeting.
- **Perchlorate.** *TERA*, in association with the U.S. Air Force, U.S. EPA, and the Perchlorate Study Group, has acted as study monitor for several studies on perchlorate that will fill in data gaps that currently exist in the database. Prior to submission of the studies to EPA, *TERA* reviewed the studies for accurate presentation of the data and compliance of the reports to EPA guidelines. The following studies were conducted and have been incorporated by EPA into a reassessment of the perchlorate RfD.

**Segment II study (and dose range-finding study) in rabbits.** Conducted by Argus Research Laboratory, Inc. in Horsham, Pennsylvania. Funded by the Perchlorate Study Group. This study evaluated the potential for perchlorate to cause developmental effects and was designed to meet U.S. EPA testing guidelines and reduce uncertainty associated with an incomplete database.

**Two-generation reproduction study in rats.** Conducted by Argus Research Laboratory, Inc. in Horsham, Pennsylvania. Funded by the Perchlorate Study Group. This study evaluated the potential for perchlorate to cause reproductive effects and was designed to meet U.S. EPA testing guidelines and reduce uncertainty associated with an incomplete database.

**Genetic Toxicity Battery.** Funded by the Perchlorate Study Group. The battery included a *Salmonella typhimurium* mammalian microsome mutation assay, a mouse lymphoma cell mutation assay, and an *in vivo* mouse bone marrow micronucleus test, and was conducted by Mantech Environmental Technology, Inc. Because the mouse lymphoma mutation assay did not meet EPA criteria for acceptance, *TERA* arranged for a repeat of that assay to be conducted by a different laboratory. The repeat assay was conducted by BioReliance, and was accepted by EPA.

- **NIOSH Profiles.** *TERA* developed 10 chemical-specific Hazard Profile Documents for the National Institute for Occupational Safety and Health (NIOSH), on gasoline, ethylene glycol, bentonite, morpholine, boric acid, aluminum, chlorobenzene, methacrylic acid methyl ester, methyl ethyl ketone, and mercury. These documents provide a summary of human and animal toxicity studies for each substance, and are intended to provide a resource to support the chemical-specific information presented in the “NIOSH Pocket Guide to Chemical Hazards”. Work on additional hazard profile documents is expected to continue in 1999.
- **NIOSH IDLH.** Immediately Dangerous to Life or Health Concentrations (IDLH) are airborne concentrations that upon exposure are likely to result in death or immediate or delayed permanent adverse health effects or prevent escape from the exposure environment. These values are frequently used in an occupational setting to define respiratory equipment requirements and in the evaluation of procedures for entering exposure environments. In a project sponsored by NIOSH, *TERA* provided critical review and analysis of the human health and animal toxicity data upon which 15 of the IDLH concentrations were derived. A second level of the analysis included an evaluation of the consistency of the approach used in establishing the IDLH concentrations across a series of substances.

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

*TERA*'s International Toxicity Estimates for Risk (*ITER*) database is a compilation of risk values for several hundred environmental pollutants. *TERA* initiated and created this database to serve the needs of risk assessors and managers worldwide for current and reliable risk value information. *TERA* has solicited and obtained funds from several sources to conduct this work and partially funds the development of *ITER* from *TERA* developmental reserve. Data have been extracted from risk assessment documents from EPA's IRIS, ATSDR Toxicological Profiles and Health Canada Priority Substances Supporting Documentation. These data are compiled in comparative tables and explanations for differences between values are included. It is available on the Internet at <http://www.tera.org/iter>.

During 1998 *TERA* worked with Concurrent Technologies Corporation (*CTC*) to further develop and expand the *ITER* database. *CTC* reformatted the database for housing on its computers and developed a data entry module with design assistance from *TERA*. *CTC* compiled information on 70+ new chemicals for the system, extracting data from risk assessment documents from EPA's IRIS and ATSDR Toxicological Profiles. *CTC* compiled these data into comparative tables where were then reviewed by *TERA* for accuracy and approval for loading. *TERA* developed explanations for differences between values that are included for each chemical section. *ITER* grew to 129 chemicals during 1998 with this support from *CTC*.

*TERA* applied for and was awarded a \$10,000 grant from the Cinergy Corporation during 1998. These funds were used for ongoing support of the *ITER* database and 80 additional chemicals were added to *ITER* by the end of 1998.

This is an ongoing *TERA* project, with plans to add additional information and organizations (e.g., WHO and RIVM) in the near future as funding is secured.

During 1998 *TERA* received \$34,161 from *CTC*, and \$10,000 from Cinergy. In addition, \$10,000 of *TERA* Developmental Reserve funds were used in the preparation of data for *ITER*.

## **Selected Peer Review Meetings and Other Reviews**

### ***ITER* Peer Review Meetings**

*TERA* organizes and conducts independent peer review meetings for both public and private sponsors. Since 1996, *TERA* has coordinated more than 20 external peer reviews involving more than 50 different reviewers. *TERA* is responsible for all administrative and technical support for these peer reviews of single chemical assessments, protocols, and research efforts. During 1998 four meetings were held in Cincinnati and 2 additional conference calls took place. Discussions and sponsors were:

Acrolein Supporting Documentation, Health and Risk Assessment Sections  
(Health Canada)

Acrylamide Cancer and Mode of Action Issues  
(Acrylamide Monomer Producers Association)

Acrylonitrile Supporting Documentation, Health and Risk Sections  
(Health Canada)

Butyl benzyl phthalate Supporting Documentation, Health and Risk Assessment Sections  
(Health Canada)

Chromium RfC  
(ChemRisk Division of McLaren/Hart)

Protocol for an acute study in humans of copper ingestion  
(International Copper Association)

Research Plan to validate an *in vitro* method to measure bioavailability of lead and arsenic (U.S. EPA, Region 8)

Methylmercury RfD (fish ingestion)  
(ICF Kaiser International and Alcoa)

Soluble Nickel Salts  
(Metal Finishing Association of Southern California; U.S. EPA, Office of Water; and Health Canada)

Telone II Assessment  
(Dow AgroSciences)

*TERA* initiated this program in 1996 to provide government, industry, consulting firms, and others with high quality, independent review of risk values and risk assessment documentation. Notes of all discussions are taken and summaries of the discussions and conclusions are written by *TERA* scientists. The peer reviewers review these summaries and their comments are incorporated into the final meeting record, which is made available on *TERA*'s home page. To insure high quality reviews, *TERA* staff provide an initial quality assurance of risk assessment documents to identify scientific and content issues which may hinder a high quality peer review. *TERA* scientists then work with the authors to resolve issues of concern and help them identify issues and questions to focus the peer review (i.e., Charge to Peer Reviewers). For peer review, conflict of interest is addressed and documented.

*TERA* has created the peer review program as a service to the risk assessment community. The goal is to break even on costs and expenses. At the suggestion from last year's Trustee meeting, we tracked the *ITER* Peer Review meeting income and expenses separately from the rest of *TERA*'s budget. During 1998 expenses totaled \$148,781 of which \$127,229 was *TERA* labor. Income during 1998 was \$121,050. During 1998 several changes were made to the program. These included *TERA* covering all reviewers expenses (prior to this we only paid for government employees) and *TERA* labor charged at a rate halfway between our nonprofit and regular hourly rates to reflect that the sponsors are half government and half private. Fees charged to sponsors during 1998 were \$12,000 for private and \$8000 for government for 1/2 day discussion (approximately the time needed for the discussion of one risk value). Fees have been increased to \$15,000 and \$10,000, respectively, for 1999.



### **Other Peer Reviews**

- Member of the external peer review panel for EPA's proposed mixtures guidelines
- Member and chair of the external peer review panel for EPA's IRIS assessment of vinyl chloride
- Member of the external peer review panel for EPA's noncancer assessment of benzene for IRIS
- Members of expert elicitation panel for an Air Force evaluation of acute toxicity of rocket emission toxicants
- Peer reviewer of a number of research proposals submitted under Strategic Research and Development Program

### **Selected Education/*Pro bono***

**Cancer Risk Assessment Course.** *TERA* developed course materials for a 2-hour module on cancer mode of action, for an internal multi-day EPA training course on Cancer Risk Assessment Guidelines. The course began with basic biology concepts, such as the production of DNA adducts, DNA repair, and cell cycle regulation. Several common modes of action were discussed, including genotoxicity, cell proliferation related to mitogenicity, cell proliferation related to cytotoxicity, receptor binding, and hormone disruption. For each mode of action, the course presented the basic biology, studies that demonstrate that mode of action, relevance to humans, and implications for risk assessment.

**Basic Principles Of Toxicology.** *TERA* also developed a poster explaining the basic principles of toxicology and human health for a regional town meeting and symposium entitled "Environmental Health in Our Neighborhoods: Speaking Out about Pollution and Health". The meeting was co-sponsored by the University of Cincinnati, Department of Environmental Health, and the National Institute of Environmental Health Sciences (NIEHS). Two *TERA* scientists attended the meeting and interacted with environmental activists other environmental professionals, and members of the community. Several notable speakers participated in the environmental town meeting including: Cincinnati's mayor Ms. Roxanne Qualls, NIEHS director Dr. Kenneth Olden, environmental lawyer Mr. David Altman, and Cincinnati community leader and activist Ms. Linda Briscoe. There was a positive response from both scientists and activists to our poster.

**Pro Bono Articles Written.** *TERA* scientists have authored a peer review article, and have begun a book chapter.

- *TERA* scientists are writing the chapter on noncancer risk assessment for Patty's Industrial Hygiene.

- In addition, three *TERA* scientists wrote the paper "Replacing the Default Values of 10 With Data-Derived Values: A Comparison of Two Different Data Derived Uncertainty Factors for Boron" for publication in The Proceedings of the 10x Uncertainty Factor in Human and Ecological Risk Assessment.
- Wrote article for Biological Effects of Low Level Exposure (BELLE) newsletter.

**Pro Bono Articles Reviewed.** *TERA* scientists have conducted a number of pro bono peer reviews of submitted articles, and of assessments by EPA and other organizations. These reviews include:

- More than 10 articles submitted for publication in scientific journals, including such articles as "Modeling of Deposition and Clearance of Inhaled Ni Compounds in the Human Lung" by T. H. Hsieh et al. for Regulatory Toxicology and Pharmacology (RTP), and "A study of Matched Area and Personal Airborne Asbestos Samples: Evaluation for Relationship and Distribution" by John H. Lange et al. For RTP;
- "Draft Region 4 Guidance Bulletin on Statistical Comparison to Background" for US EPA;
- Review of two RIVM risk assessment documents.

#### ***TERA* Scientists Contributed To Professional Societies**

- Jacqueline Patterson served as President Elect for the Ohio Chapter of the Society for Risk Analysis. She organized programs on children's risk and every day risks;
- Michael Dourson served as President of the American Board of Toxicology. He ran all board meetings and assisted in the preparation of exams.

#### **State Hazard Evaluation Lending Program (State HELP)**

- *TERA* scientists made a presentation (by phone) to California EPA scientists on the science behind the uncertainty factor for inter-individual variability in humans, and the relationship to children's risk issues.
- *TERA* scientists made a presentation at a public meeting on the results and process of the peer review of the assessment for soluble nickel salts.
- General consultation in risk assessment for a number of states on small issues, including consulting on risk assessment methods for the State of Montana.

## Selected Research Projects

*TERA* scientists, through sponsored projects and *TERA* efforts, investigate new risk methods and improvements on existing methods. *TERA* has worked on projects such as data-derived uncertainty factors, comparative dietary risk for fish advisories, and acute exposure to soluble copper in human volunteers. Each of these projects has (or will) result in the publication of peer-review manuscripts, a listing of which can be viewed at [www.tera.org/research](http://www.tera.org/research). Specific activities for 1998 follow.

- **Derived-Derived Uncertainty Factors (ongoing task).** *TERA* was asked by U.S. Environmental Protection Agency and Health Canada to develop a workshop on establishing criteria for the use of data derive uncertainty factors in noncancer risk assessment. The AIHC also contributed monies towards this effort. As risk assessors move from application of uncertainty factors that are protective to ones that are more predictive (i.e., data-derived), there is a unique opportunity for increased communication among international agencies. While this cooperation may not lead to full harmonization, cooperation at the early stages of these developments can lead to a better common understanding of issues related to the quantity and quality of data, which may serve as the basis for replace of default factors with data-derived values.

This workshop originated in 1998, based on the IPCS (1994) data-derived approach initially proposed by Renwick (1993). A key aspect of this approach is that the risk assessor considers *whether data exist* to move away from default values. If data do exist, they may be used in place of defaults. The determination of sufficiency of data for moving away from defaults is an active area of research. If sufficient data do not exist, the default values for each sub-area may be used. For interspecies extrapolation, these default values consist of a factor of 2.5 for toxicodynamics and a factor of 4.0 for toxicokinetics. For inter-individual variability, the default values consist of a factor of 3.16 for toxicodynamics and a factor of 3.16 for toxicokinetics. Health Canada also uses an adaptation of the data-derived scheme in its noncancer health assessments (Meek et al., 1994).

This workshop was attended by several principal investigators of the data-derived uncertainty factor approach. This meeting was designed to move beyond the default uncertainty factors of the IPCS (1994) scheme, by providing an initial description of criteria for the sufficiency of data for use as the basis of data-derived uncertainty factors.

The results of this brief meeting will be published as a *TERA* report in 1999, and are intended to be reviewed and enhanced by other interested scientists and governing bodies. *TERA* staff also published one paper on data-derived uncertainty factors during this time: Dourson, M., A. Maier, B. Meek, A. Renwick, E. Ohanian and K. Poirier. 1998, Re-evaluation of toxicokinetics for data-derived uncertainty factors. *Biological Trace Element Research* 66:453-463. *TERA* staff have also had another paper on a similar topic accepted for publication: Zhao, Q., J. Unrine and M.

Dourson, Replacing the default values of 10 with data-derived values: A comparison of two different data derived uncertainty factors for boron. Human and Ecological Risk Assessment, (in press).

- **Comparative Dietary Risks: Balancing The Risks And Benefits Of Fish Consumption (ongoing task).** *TERA* was asked by U.S. Environmental Protection Agency to develop a workshop on establishing a framework for comparing the potential risks and benefits from fish consumption using a diverse team of scientists: P Anderson of Ogden Environmental and Energy; D Cartledge of Prescott College, Prescott, AZ; M Daviglus of Northwestern University, Chicago, IL; M Dourson, J Patterson and J Unrine of *TERA*; B Knuth of Cornell University, Ithaca, NY; E Murkin and J Sheeshka of University of Guelph, Guelph, ON; and J Stober of U.S. EPA, Athens, GA.

A framework for comparing the risks from chemical contamination of sport-caught fish to the reduction in the relative risk of several adverse health endpoints from eating fish was developed. The framework includes a simple method based on a four-category severity scale and a novel approach to determine the risks from chemical exposures above the RfD in order to combine the health risks from cancer and non-cancer toxicity. A similar severity construct is used to compare these risks with the benefits of eating fish. The framework accommodates scales for perceived severity and cultural benefits, if desired. The framework is able to compare the risks and benefits of fish consumption over a wide range of fish consumption rates, illustrated with two case studies. People using the framework should be able to apply it to many contaminants at various concentrations. Data limitations, and assumptions used to develop the framework, are highlighted.

The results of this research will be published as a *TERA* report in 1999, and are intended to be reviewed and enhanced by other interested scientists and governing bodies. A presentation of this work at the SOT 1999 annual meeting won an award.

- **Human Copper Research.** *TERA* conducted a peer review of a protocol for the International Copper Association for a research project to determine the acute toxicity threshold (nausea) for soluble copper in human volunteers. This review was conducted as part of the *ITER* process in June 1998. *TERA* also took the lead on organizing and coordinating the approved research protocol at the three international sites where the study will be conducted (Grand Forks, North Dakota; Coleraine, Northern Ireland; and Santiago, Chile). The study is expected to be completed by mid-1999 and will result in a peer-reviewed publication.

- *TERA* published a paper with scientists from ChemRisk and the U.S. EPA [Price, P.S., R.E. Keenan, J.C. Swartout, C.A. Gillis, H. Carlson-Lynch, and M.L. Dourson. 1997. An approach for modeling noncancer dose responses with an emphasis on uncertainty. Risk Analysis. 17(4):427-438] that gives another approach to estimating risks above the RfD. This paper won the risk assessment paper of the year award at the annual SOT meeting in 1998. *TERA*'s efforts on this paper were sponsored by *TERA*.

### **Financial Report for 1998**

*TERA* earned ~\$739,921 reflecting an ~\$230,279 shortfall in projected income. This shortfall in projected income was offset by actual expenses that were ~\$197,586 less than budgeted. The net income for *TERA* was ~\$35,907.

## ***TERA* Plans for the Future**

Several years ago, TERA staff put together the following goals for the future. Several of these goals have been met or are being pursued. We list them again here for your comment and enhancement.

### Technical Goals

- *TERA* To Be Known For...

Moving The Science Of Risk Assessment Forward

High Quality, Unbiased And Neutral Work

Customer Orientation

(As) Leading The Field Of Risk Assessment In Resolving Major Issues

(As) The Employer Of Choice

- Success For *TERA* Would Be...

Viewed As Equal Value By Government And Industry Clients

The First Name In The Minds Of Clients

One Million \$ To Give Away

To Be Able To Pick And Choose Clients

Recognition By Outside Folks As Individuals And The Group

### Financial Goals

- Establish A Base Of Work With...

*ITER* Peer Review

*VERA* Projects

Clients As "On Call" Risk Assessors

Grants For *ITER* Development

Grants For Risk Assessment Research

- Develop A Six Month Operating Reserve Over A Six Year Period

- Grow To A Modest Size That Allows For...

In-House Expertise

No Cumbersome Bureaucracy

### Links With Other Groups That Share A Common Mission