

2000 Annual Report

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

Cincinnati, Ohio

February 2001

Dear Trustees:

Calendar year 2000 was good for our corporation. We hired Ms. Sheri Lawson to replace Caitlin McArleton, who moved to San Francisco. We also hired Ms. Andrea Wullenweber as the leader of our International Toxicity Estimates for Risk (*ITER*). Biographical sketches for both of these folks can be viewed at www.tera.org. We also:

- developed assessments for quite a few chemicals,
- significantly improved the existing *ITER* database (and won an award in the process!) through the use of a modest amount of grant money and collaboration with Concurrent Technologies Corporation,
- conducted several independent peer review meetings,
- published several papers, and
- donated ~1200 hours (~7% of all time) to pro bono activities, including the State Hazard Evaluation Lending Program (StateHELP) and scientific organizations.

The attached agenda includes a number of important items for discussion, including approval of short and long-term goals and election of new trustees. 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

2/13/01

Annual Meeting Board of Trustees

Toxicology Excellence for Risk Assessment

Time: 9:00 am, February 28th, 2001

Draft Agenda

Call to Order and Approval of Agenda (M. Dourson)

Introduction of New Staff (M. Dourson)

Old Business

- *VERA* - Verifiable Estimates for Risk (L. Haber)
- *ITER* - International Toxicity Estimates for Risk (A. Wullenweber)
- Peer Review (J. Patterson)
- Education and Outreach (J. Dollarhide)
- Research (K. Poirier and L. Haber)
- Financial Report of 2000 (M. Dourson)
- Other?

New Business

- *TERA* Plans for the Future (*TERA* staff and Trustees)
- Election of new Trustees (Trustees)
- Development of Officers with the Board (Trustees)
- Other?

Good and Welfare (*TERA* staff and Trustees)

Adjourn at 11:00 a.m.

An Open House will be held on Tuesday (2/27/01) from 5:00 – 8:00 p.m. with invitations to risk assessment folks from Cincinnati and surrounding areas

VERA **(Verifiable Estimates for Risk Assessment)**

Status of Goals for *VERA* - 2000

Long-term Goals

- Be known for developing partnerships and fostering cooperation between industry and government.
- Be known for expertise in developing noncancer and cancer toxicity values using the best science.
- Develop new market areas (e.g., mechanistic focus using tie-in with the University of Cincinnati; international, food supplements)

Selected *VERA* 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. The year 2000 marked the first full year that *TERA* held an EPA support contract, as a subcontractor with EPA's Office of Water. In 2000 we did a considerable amount of work for EPA's Office of Water under this contract, primarily in the development of Criteria Documents. In 2000, several assessments were undertaken as a part of the *VERA* project. Highlights of these projects include:

- **Perchlorate.** *TERA* has continued its involvement in the perchlorate assessment, in association with the U.S. Air Force, U.S. EPA, and the Perchlorate Study Group (a group of 9 aerospace companies), acting as a study monitor for a number of studies and providing technical support on perchlorate risk assessment issues.
 - Completed immunotoxicity studies of perchlorate – Sheep Red Blood Cell assay and Local Lymph Node (delayed type hypersensitivity assay) in mice following 14 and 90 days of exposure to ammonium perchlorate in drinking water. These studies were conducted following comments made at the Peer Review meeting regarding the need for these studies. Gary Burleson, Burleson Research Labs, RTP, NC conducted the study. Activities included reviewing an approving study reports and conducting a site visit.
 - Acted as study monitor for a study being designed to address questions raised by peer review regarding the potential for perchlorate to have effects during the late fetal and

early neonatal periods. The study, conducted in four parts, includes a guideline Segment II study in rats (a second species, in addition to rabbits) and examines thyroid hormones, thyroid histopathology, and neurohistopathology in both dams and pups at the following time points: Gestation Day 21, Postnatal Days 5, 10, 22. Primedia Argus is conducting the study; the in-life phase was completed in 2000 when preliminary drafts of the results were submitted to U.S. EPA. Work on the neurohistopathology and preparation of the final report will continue in 2001. Activities included finalizing the protocol and approving protocol amendments, reviewing and approving drafts of subcontractor (pathology and hormone analysis) reports, responding to EPA questions, and identifying neuroanatomy experts to consult on interpretation of brain results.

- On behalf of the PSG, *TERA* offered to coordinate the Quality Assurance audit for all of the human studies conducted by either PSG or the Air Force in support of developing a pharmacokinetic model for perchlorate. *TERA* sought bids and reviewed the qualifications of several QA companies and awarded a contract to Toxicology/Regulatory Services (TRS). Most of one study audit was completed in 2000, and the remaining two will be completed in early 2001.
 - Manuscripts on the rabbit developmental study, the rat 2-generation study, and the neurodevelopmental studies were submitted to peer-reviewed journals.
- **Drinking Water Disinfectant Byproducts (DBPs).** *TERA* has prepared a number of Drinking Water Criteria Documents on disinfectant byproducts for EPA. Toxicity and toxicokinetics in animals and humans via the oral, inhalation, and dermal routes are considered, and multiple exposure durations are included. Exposure via all three routes is also considered in the documents, although the prime's staff typically writes this section. The documents also include an evaluation of potential mechanisms of toxicity, interactions, and sensitive populations. Finally, the quantification section includes the derivation of health advisories, RfDs, and cancer assessments, based on all available data, including mode of action considerations. Draft criteria documents prepared include the following:
 - Cyanogen chloride and its metabolites. Due to the lack of data on cyanogen chloride, data on its known metabolites (cyanide, thiocyanate) and potential metabolites (e.g., cyanamide, were also considered.
 - Haloacetonitriles. (Bromochloroacetonitrile, dibromoacetonitrile, dichloroacetonitrile, and trichloroacetonitrile)
 - Brominated acetic acids (monobromoacetic acid, bromochloroacetic acid, dibromoacetic acid)
 - Chlorinated acetic acids (monochloroacetic acid, dichloroacetic acid, trichloroacetic acid)
 - Chloropicrin. (Short summary.) Chloropicrin is both a disinfectant byproduct and a pesticide.
 - Together with colleagues on the prime contractor's staff, *TERA* also updated the Office of Water report "Health Risks to Fetuses, Infants, and Children," to include updated data on Stage 1 disinfectants and DBPs, and information on Stage 2 DBPs, using existing Criteria Documents and IRIS documents. Chemicals addressed included the brominated trihalomethanes, haloacetic acids, chlorine dioxide/chlorite, bromate, and MX. Reproductive and developmental toxicity data, based on animal studies and epidemiology studies, were considered. Toxicokinetic on age-related differences in enzyme activities were discussed,

together with the toxicologic implications of such differences. The toxicity data were also evaluated to determine whether there are age-related differences in toxicodynamics.

- **Drinking Water Criteria Documents for Pesticides.** Also for EPA's Office of Water, *TERA* developed modules for the Drinking Water Criteria Document for the pesticide aldicarb, in collaboration with GRAM staff, and assisted in the development of the Criteria Document for the pesticide atrazine and its chlorodegrade metabolites. These documents addressed the same issues as noted above for the DBPs, with particular consideration to mode of action. Consistent with agreements between EPA's Office of Water (OW) and Office of Pesticide Programs (OPP), documents developed by OPP constituted major sources for these documents.
- **Determining the Reference Dose For Methylmercury (methyl Hg): How Can We Further Reduce Uncertainties?** This work, funded by EPRI, *TERA*'s State Hazard Evaluation Lending Program (State HELP), and *TERA* Developmental Reserve, began as a review of the well-done NAS report on methyl Hg, and has evolved into ongoing work in 2001. Conclusions of the review include the following. The determination of the critical effect for methyl Hg is important. Investigating potential critical effects in addition to the neurodevelopmental endpoint will either change the basis of the RfD or reduce the need for uncertainty factors. The Faroe Islands data are from exposures to a mixture of chemicals, while the Seychelles Island data are from exposures to primarily one chemical. These different exposures may allow us to use studies from both areas to derived RfDs for a mixture and a single chemical exposure, respectively. Another issue that would merit investigation is the implication of the differences in methyl Hg bolus dose resulting from fish and pilot whale consumption in the Faroe Islands (approximately a 15-fold difference), and similarly the implications of bolus dose differences between the methyl Hg exposure in the Faroe Islands and the Seychelles Islands. Application of the current EPA RfD guidelines can be enhanced with new approaches to uncertainty factors and using data unique to methyl Hg. In brief, the excellent analysis of the NAS panel may be considered directly as the factor for human variability in toxicokinetics, in lieu of a default uncertainty factor recommended by the NAS panel.
- **Phenol.** *TERA* continued work on the IRIS Toxicological Review for phenol, under contract to EPA's Office of Solid Waste. The document was revised in response to EPA comments, and a number of issues raised by EPA comments were researched. It is expected that the document will undergo external review in the early part of 2001, and *TERA* will prepare any additional revisions needed in response to external peer reviewer comments.

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

Overall Goal

- To develop the world's most comprehensive risk value database, so that risk assessment scientists everywhere will start their day with *ITER*.

Summary of accomplishments in 2000

International Toxicity Estimates for Risk (*ITER*) is a free Internet database (www.tera.org/iter) that contains risk values for 540+ chemicals from: U.S. Environmental Protection Agency (U.S. EPA); Agency for Toxic Substances & Disease Registry (ATSDR), Health Canada (HC), and independent parties whose risk values have undergone peer review. The *ITER* database is the only Internet database that provides international risk assessment information in a side-by-side format and explains differences in risk values derived by different organizations. It is also the only database that includes risk information from independent parties whose risk values have undergone peer review through *TERA's* *ITER* Peer Review Program.

The *ITER* Database has become a valuable international resource. During 2000, *ITER* grew dramatically to include all of EPA's IRIS data for a total of over 540 chemicals. This completion plus an article in the Risk Policy Report entitled, "Expanded Risk Database to Allow Comparisons of Toxicity Values" (February 21, 2000), was followed by a major increase in visits to *ITER*. The number of daily users of *ITER* doubled during the course of the year, as compared with the number of daily users in 1999. During 2000, *ITER* won a Links2Go "Key Resource" Award from an independent, web based company for being the 7th most frequently visited website in the environmental studies topic. This award is based on an analysis of millions of web pages, and only the most heavily cited web pages can qualify for an award.

In addition to expanding *ITER* to include all of EPA's data, we have solidified a partnership with RIVM, the Netherlands, to add its data to *ITER* during Spring 2001. We have also made several additions and updates to *ITER*. Some improvements to *ITER* include the addition of a "What's New" page to highlight any additions or updates we have made, and a "Support *ITER*" page to encourage users to contribute money, resources, or ideas to help grow *ITER*. We also completed well over a dozen updates to chemical entries on *ITER* based on ATSDR and EPA updates, and we added data from Health Canada for 7 chemicals.

In September 2000, we hired Ms. Andrea Wullenweber to manage the *ITER* database and assist with the peer review program. Before joining *TERA*, Ms. Wullenweber worked for three years at U.S. EPA, Region 10, as the Air Toxics Program Coordinator. While at EPA, she received an award for Outstanding Public Service from the Seattle Federal Executive Board, and received Special Act and Special Accomplishment Awards from U.S. EPA. Previous to EPA, Ms. Wullenweber was an Environmental Manager at Wright-Patterson Air Force Base responsible for NEPA and Natural & Cultural Resources projects. Ms. Wullenweber has been a positive addition to our team.

Peer Review Program

TERA conducts expert peer review through the International Toxicity Estimates for Risk (*ITER*) Peer Review Program and under individual contracts with sponsors. In addition, *TERA* scientists serve on peer review panels and perform expert reviews of others' work.

***ITER* Peer Review**

Overall Goal

To provide risk assessors and managers worldwide the opportunity for independent peer review of risk assessment documentation and positions.

Summary of Accomplishments in 2000

The purpose of the *ITER* peer review program is to provide both the public and private sectors with independent peer review of risk assessment values and documentation. Panels of volunteer experts are convened up to four times a year to review documentation authored by government agencies, consultants, universities, or industry. Meetings are open to the public and summaries of discussions are made available on *TERA*'s home page (www.tera.org/peer). If the expert panel concurs with an assessment, it may be made available to the public on the *ITER* database.

During 2000, two *ITER* peer review meetings were held, with two additional meetings convened by conference call. For Health Canada's Priority Substances Program we conducted a peer review of two chemicals - ethylene glycol and dimethylformamide. This meeting was held in Ottawa. Subsequent to the meeting, a conference call meeting on ethylene glycol was held to provide further discussion on questions regarding the pathology findings in a key study. The panel approved the Health Canada assessments, which will be loaded on the *ITER* database in early 2001.

For American Home Products (Whitehall-Robbins) and the Neutrogena Company, *TERA* conducted an expert peer review of the lifetime skin cancer risk from use of coal tar containing shampoos as part of a California Proposition. ICF Consulting authored this complex assessment. They evaluated the toxicity and epidemiology literature and established a No Significant Risk Level (NSRL) for California's Proposition 65. A Monte Carlo analysis was used to estimate dose from the critical study. An exposure assessment also utilized Monte Carlo analyses to estimate the Lifetime Average Daily Dose (LADD) that was compared to the NSRL to characterize risk. The expert peer review panel identified a number of issues and asked the authors to conduct additional research and analyses to address these. A conference call was then held to discuss the revised documentation. The panel approved the conclusions of the revised document and a summary of the assessment is now available on the *ITER* database.

During 2000 we improved our descriptive materials on the program to provide a better description for potential sponsors. In addition, we developed a policy addressing situations when *TERA* authors documents and the sponsor would also like to use our independent review

program. This short document highlights the advantages and disadvantages of this approach so that the sponsor may make a fully informed decision.

While we conducted fewer reviews than we had planned in 2000, we have discussed the program and possible reviews with numerous potential sponsors. A number of these are preparing documentation and plan on reviews in 2001. During 2000, *TERA* has explored expanding the *ITER* peer review program to specifically address occupational exposure levels and related issues. We began discussions for the need for this type of expansion with potential sponsors as well as others developing and reviewing occupational risk values. This effort will continue in 2001.

Additional Peer Review

In addition to the *ITER* Peer Review Program, *TERA* organizes private peer reviews to meet specific needs of sponsors. For example, in 2000 *TERA* organized an expert panel to review the public health implications of a new water treatment technology being developed by a private chemical company.

TERA scientists also serve as expert peer reviewers for a variety of government and industry work products, ranging from chemical-specific assessments to risk methods and research plans. Because of our scientists' knowledge and experience in risk assessment, we are frequently called upon to serve as expert reviewers of documentation prepared by others. During 2000, individual staff provided several dozen written reviews of risk assessment related documentation for EPA, other government agencies, as well as private and non-profit organizations. These included IRIS Toxicological Reviews, chemical-specific assessments, studies and methods, and review of proposals. In addition, *TERA* scientists chaired, or were members of, expert panels convened by EPA, FOSIE (Food Safety in Europe), the U.S. Army, and others to evaluate assessments and reports, or write chapters of assessments. For example, Dr. Lynne Haber was a session chair of the peer review of EPA's Benchmark Dose methodology. Dr. Michael Dourson participated in a TNO sponsored meeting on acute occupational exposure levels.

These private reviews and expert review provided by *TERA* staff are a small, but significant portion of *TERA*'s efforts. They provide *TERA* with visibility and recognition for our knowledge and expertise and provide individual staff with opportunities for career enhancement.

Selected Education/Pro Bono

Support to Cinergy Corporation on Toxic Release Inventory Reporting. *TERA* continues to provide support to Cinergy Corporation on assessing risk from power plant emissions and communicating risk to the public. *TERA* conducted a screening level assessment of the emissions from a proposed gas turbine generating station in Indiana and also evaluated the risks from inhalation of aerosols containing *E. coli* released from the cooling tower of this proposed station. In support of this assessment, *TERA* staff gave testimony to the Indiana Utility Rate Commission, attended several meetings of Indiana environmental organizations, and worked with the Cinergy public affairs office to respond to reporters' questions.

In addition, *TERA* started work on updating our earlier risk assessment of emissions from Cinergy's 10 coal-fired power plants in Indiana, Ohio, and Kentucky by evaluating risks posed by their 1999 emissions. The purpose of this assessment was to explain the health effects of hazardous air pollutants that are reported to the U.S. EPA's Toxics Release Inventory (TRI) and to identify for power plant neighbors the potential health risks associated with living near a plant. Cinergy requested that *TERA* expand the scope of the risk assessment by including all chemicals for which they estimate emissions, not just the chemicals reported to the TRI. In addition, the updated assessment will include multiple exposure scenarios in order to better describe the range of potential risks. Work on this project with Cinergy continues during the year 2001.

Legal. For the law firm Orrick, Herrington & Sutcliffe, *TERA* conducted a peer review (see peer review section) of an assessment of lifetime skin cancer risk of coal tar shampoos that was conducted to address issues under California's Proposition 65. Dr. Dourson chaired the meeting and agreed to act as an expert witness in order to introduce the Peer Review report into evidence and to explain the peer review process and results to the court. *TERA* staff responded to discovery requests relating to the peer review and Dr. Dourson gave a deposition in preparation for trial. There is no date set for the trial at this time.

Support to PSG on Perchlorate Toxicity. In addition to our scientific work on the perchlorate issue, *TERA* has provided communication support to the PSG. *TERA* staff gave two invited presentations on perchlorate toxicity and risk assessment issues at the Department of Defense Remedial Technology Conference in San Antonio, Texas and to the ITRC (Interstate Technology Regulatory Cooperation) can't remember what this stands for) Annual Conference in San Antonio, Texas. In addition, *TERA* maintains a Perchlorate page on its website which offers up to date information on the status of perchlorate toxicity studies and responds to questions from the general public, reporters, and state environmental agencies on perchlorate toxicity.

Lecture at General Electric. Developed and presented a 4-hour course to GE health and safety staff on advanced topics in occupational toxicology that highlighted new mechanistic toxicity concepts and their use in deriving occupational exposure limits.

Education Summer Intern. During the summer, *TERA* hosted and provided an internship opportunity for Russell E. Savage Jr., Ph.D., a medical writing degree candidate from Miami University's Master's Degree Program in Technical and Scientific Communication (MTSC). The internship is intended to provide students with supervised, first-hand experience at applying what

they have learned in their classes to the kinds of professional situations they will encounter in their careers.

Aside from routine editing and writing tasks for a number of *TERA* documents produced during his tenure, Dr. Savage made important contributions to a number of significant projects. A few of particular note included:

- Served as co-editor for a Special Issue of the journal *Comments on Toxicology* on Noncancer Health Risk Assessment in the 21st Century
- Contributed as a co-author, the manuscript entitled “Incorporating Biomarkers into 21st Century Risk Assessments” for the Special Issue.
- Conducted literature research and developed a document in support of Cinergy’s Toxic Release Inventory Reporting.

***Pro bono* Articles Written.** *TERA* scientists completed several *pro bono* articles in 2000, including:

- *TERA* scientists played a significant role in the completion of a *Comments on Toxicology* Special Issue on Noncancer Health Risk Assessments in the 21st Century. *Comments on Toxicology* is a vehicle for concisely and authoritatively written critical discussions of recent important developments in toxicology. This Special Issue was prepared to coincide with the beginning of the new century and to focus on a number of risk assessment tools which would be emerging as critical to the discipline in the 21st Century. Noteworthy accomplishments included:
 - Along with Ms. Annie Jarabek, USEPA, this issue was co-edited by *TERA*’s Michael Dourson and Russell E. Savage Jr.
 - *TERA* staff contributed as participating authors on four of the nine manuscripts comprising the Special Issue.
 - Forum (Toxicological Sciences) article on use of mechanistic data in risk assessment
 - A chapter written for health care personnel on “*Persistent Environmental Contaminants*” in Environmental Health Secrets.
- **Human risk paper**
The value of using human data in the assessment and management of risk is evaluated. Although the use of such data has a long and successful history with environmental contaminants and the development of drugs and commercial chemicals, recent deliberations within the Environmental Protection Agency (EPA) have questioned this practice in part. Specifically, we evaluated the degree to which Reference Doses (RfDs) and Reference Concentrations (RfCs) derived from human data on EPA’s Integrated Risk Information System differ with RfDs and RfCs estimated from experimental animal data. Human-based RfDs are more than 3-fold lower than the corresponding animal-based RfDs for 23% of the comparisons. Human-based RfDs or RfCs are lower than corresponding animal-based RfDs or RfCs for 36% of the comparisons. Furthermore, for 10 out of 43 possible comparisons, insufficient experimental animal data are readily available or data are inappropriate to estimate either RfDs or RfCs.

- **Compound Specific Assessment Factors**

TERA staff participated as co-authors of a report describing research to move beyond the default uncertainty factors of the IPCS (1994) scheme. This report provided an initial description of criteria for the sufficiency of data for use as the basis of data-derived uncertainty factors. The results of this effort were reviewed at an international meeting of scientists in Berlin during May of 2000. Comments were incorporated into draft methods for review during the fall of 2000. These methods are intended to be reviewed and enhanced by other interested scientists and governing bodies.

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

- Mike Dourson is on the editorial review board of Human and Ecological Health, Regulatory Toxicology and Pharmacology, and Human and Experimental Toxicology. As a result, several *TERA* staff members reviewed several manuscripts submitted to these journals.

Invited Presentations and Lectures. *TERA* scientists were invited to give presentations on a variety of risk assessment topics in several different forums. These presentations include:

- *TERA* had been invited by ILSI-Europe to participate in an initiative to define Food Safety Issues in Europe (FOSIE). This effort involves meeting regularly with a subgroup of this panel to write a chapter on New Mathematical Methods in Risk Assessment. This chapter will be one of six that will be compiled for publication in a peer-review journal.
- Presentation to U.S. EPA's Risk Assessment Forum on risk above RfD in a colloquium titled Approaches to Quantifying Health Risks for Threshold or Nonlinear Effects at Low Dose.
- Under the auspices of the IPCS, Mike Dourson was asked to present 5 lectures to a diverse international audience of risk assessment scientists and managers in Thailand. Lectures included topics such as dose response assessment, benchmark dose, categorical regression, risk characterization, and uncertainty analysis.
- Invited presentation at the 6th International Symposium on Metal Ions in Biology and Medicine
- Invited participant in meeting sponsored by NIOSH: Future Research for Improving Risk Assessment Models: Of Mice, Men, and Models
- Lectures on noncancer and cancer risk assessment were given to graduate student interns at the University of Cincinnati.

Participation in Professional Societies. *TERA* scientists are members of several professional societies including the Society of Toxicology, the Society for Risk Analysis, and the Society of Environmental Toxicology and Chemistry. As members, *TERA* participated in local chapter meetings and attended the national annual meetings of these societies. Several *TERA* staff has also held leadership roles in these societies:

- Mike Dourson is the current vice president of the risk assessment specialty section of the SOT and coordinated several aspects of program for the SOT 2001 Annual Meeting

- Jacqueline Patterson is the immediate past president and councilor to the Ohio chapter of SRA. She organized a comparative risk symposium for the national SRA meeting.
- Lynne Haber served as the Vice President for Education of the Dose-Response Specialty Group of the Society for Risk Analysis.
- Ken Poirier served as the Treasurer for the Ohio chapter of SRA.

Other Pro Bono Activities.

- Mike Dourson a member of the Health Advisory Board of the National Sanitation Foundation, a member of the Oversight Group for the EPA Cooperative Agreement at George Washington University, and a temporary Advisor to the World Health Organization for Consultation on Uncertainty and Variability: BGVV, Berlin Germany. 9-11 May (and continuing)
- Several *TERA* staff members have responded to requests for information by way of phone and our feedback forms.

State Hazard Evaluation Lending Program (StateHELP). *TERA* scientists provide risk assessment support in 2000 to several states under the StateHELP program.

- Provide technical support to a Citizens Group in New Mexico on issues related to risk assessment of copper for a copper mine Superfund risk assessment. *TERA* staff reviewed the baseline risk assessment that was prepared for this site and provided comments on the appropriateness of the overall risk assessment. Specific focus was given to the discussion of copper toxicity and the choice for copper RfD. *TERA* staff made recommendations on sources of new data on copper toxicity and responded to additional questions from the group on the development of a new RfD based on the new data.
- Provide guidance to the Minnesota Department of Health on procedures for estimating relative source contribution in the development of drinking water action levels.
- Provide information to the Texas Natural Resources Conservation Commission on guidelines for the application of data-derived uncertainty factors in risk assessment.
- Provide general consultation in risk assessment for a number of states on small issues.

Research

Status of Goals for Research - 2000

Long-term Goals

- Be known for doing cutting edge work using the best science in the development of risk assessment methods.
- Be known for the design and implementation of well-conducted studies targeted to develop key data for risk values.

Selected Research Projects

TERA's research program includes two major components: chemical-specific research, and methods development. Research on the acute nausea threshold for copper has continued to constitute a major component of our research program, and will be continuing into 2001. A new development in 2000 was our winning a risk assessment methods research grant from the Risk Assessment Methods Technical Implementation Panel (RAM-TIP) of the American Chemistry Council (ACC, formerly the Chemical Manufacturer's Association), under its new competitive grants program.

Copper Studies in Humans. In this ongoing project, *TERA* is helping the International Copper Association in the coordination and oversight of two human studies to identify an acute nausea threshold for copper in drinking water. In 2000, the data analysis for Phase I (conducted in Grand Forks, ND; Coleraine, Northern Ireland; and Santiago, Chile) was completed, and a journal article summarizing the results from the Phase I was written and submitted to *Regulatory Toxicology and Pharmacology*. Phase 2 of the study will be looking at other factors, such as concentration and volume effects of copper ingestion, as well as reconfirming the dose response data determined from phase 1. This Phase is ongoing at four international sites (the above three plus Shanghai, China). The protocol was completed at Shanghai and Santiago, with the Grand Forks and the Coleraine sites expected to finish their legs in early 2001.

Using Data on Human Polymorphisms and Variability in Risk Assessment. This work is being done in collaboration with the K.S. Crump group of ICF Consulting, and is sponsored by ACC. Objectives of this project include (1) collecting data on known polymorphisms in genes that encode enzymes responsible for the metabolism of environmentally-relevant chemicals, focusing on the resulting variability in enzyme activity, and the population frequency of the polymorphisms, and (2) developing an approach for using PBPK modeling to incorporate these data into standard risk assessment methods (e.g., incorporating these data into the toxicokinetic portion of the intraspecies uncertainty factor [UF] for noncancer risk assessment), taking into account other aspects of interindividual variability. This work will be done in three phases. Phase 1 serves to integrate data on the relative activities of key metabolic enzymes encoded by polymorphic alleles, the frequency of the altered phenotypes in the general population, and information on the metabolic pathway for representative chemicals. Phase 2 involves the development of case studies using these data, together with PBPK models and Monte Carlo

analyses, to determine the resulting variability in tissue dose. Phase 3 is the most speculative, and involves an attempt to develop a framework for the extension of this approach to consider chemicals for which PBPK models are not available. This project was begun late in 2000. *TERA* is also working with other investigators investigating similar issues, to facilitate collaboration.

Children's Cancer Risk Assessment. *TERA* has begun work on this project of assisting the Pest Management Regulatory Agency of Health Canada in developing an optimum approach for the assessment of cancer risk to the general population and specifically for children. In the first phase of the work, *TERA* will be summarizing the methods used by Health Canada, USEPA, and IPCS for hazard identification, dose-response assessment, and exposure assessment, and building relationships with other groups doing similar work. This phase also includes a focussed literature search on issues related to cancer and children's risk, and developing working relationships with other groups working on this issue.

Dose-Response Assumptions. *TERA* received an investigator-initiated grant from NIEHS and U.S. EPA/Office of Research and Development to write a white paper on research that has impacted the default assumptions used in dose-response assessment, particularly those used in extrapolation to environmentally-relevant exposures. The project Director is Hugh Spitzer, a visiting scientist with *TERA*, and the Co-Director is Dr. James Wilson, of Resources for the Future. In 2000, Drs. Spitzer and Wilson completed interviewing scientists and risk assessment practitioners on their opinions of the use of default assumptions, and ongoing research that will affect the assumptions. A preliminary report was prepared on the history of assumptions used and summarizing the results of the interviews and presented to the advisory committee. The preliminary report will be revised in the beginning of 2000, and follow-up workshops are planned for 2001 and 2002.

Financial and Managerial Report for Fiscal Year 2000

Financial and Managerial Goals for 2000 and Specific Accomplishments

- Goal: Make budget, including 50K increase in net worth & 60K to developmental reserve

Accomplishment: Our income over expenses was 51K. This increased our net worth from a -\$105K* to -\$55K. Developmental reserve funds were 47K, all of which were used during the year. (*This net worth was a result of the auditors review of our 1999 books, which added 80K in accrued expenses. These expenses were unpaid vacation and sick leave at the end of 1999. TERA is investigating the purchase of short-term disability insurance to reduce this accrued expense.)

- Goal: Allow *TERA* to develop its own character including size, style and work, in a manner that allows maximum operational flexibility. (This may mean new hires for *VERA* and *ITER* to free up some of leaders to build their areas, or contract work out as we did in 1999.)

Accomplishment: We hired a new leader for *ITER*, Andrea Wullenweber, and refocused Jacqueline Patterson's efforts on the whole peer review program of *TERA*. We moved Lynne Haber to the lead of the research program and Ken Poirier to senior regulatory toxicologist. Several quick turn around jobs were partially subcontracted out. This allowed the flexibility to accomplish the work, and the oversight to maintain excellence in our products.

- Goal: Obtain 50/50 balance of government/private sector work

Accomplishment: We achieved a 59/41 balance.

- Goal: Maintain *TERA*'s reputation as an independent party and arbiter of the science

Accomplishment: Reputation appears to be maintained in that an approximately equal number of unsolicited requests for help are coming from industry and government sectors.

- Goal: Assist Program Leaders in reaching their program goals

Accomplishment: Many of the individual program goals were reached, due in part to better adherence to billable time goals and focus on accomplishments. More effort is still needed in this area.

- Goal: Develop the careers of all staff

Accomplishment: Several international trips, first-authored publications, and presentations were done by staff other than the director. We anticipate that this trend will continue.

Adopted Resolutions of the Board of Trustees in 2000

1. The Board of Trustees accepts the budget recommended by the *TERA* staff for 2001 with an emphasis on *TERA* management achieving revenues in excess of expenses and staffing of *TERA* projects appropriately.
2. *TERA* management is to continue to strengthen internal financial controls by hiring an outside financial group to conduct a formal review of the FY1999 and FY2000 with a long-term goal of a formal audit for FY2001.

Recommendations of the Board of Trustees in 2000

3. The Board of Trustees also recommended that *TERA* management consider the development of several long-term funding proposals to decrease emphasis on short-term special-project-oriented work. Such long-term projects would enable *TERA* to further secure its financial resources by providing a stable base of funding.
4. *TERA* Trustees further recommended that the *TERA* management recommend a special outside financial group for conducting the audit and ask the *TERA* management to send its recommendation to the Trustees for confirmation this choice by electronic ballot.
5. The *TERA* Trustees also recommended that for FY2001 the *TERA* management limit its contributions to internal developmental reserves and to not give money away to other nonprofit organizations. *TERA* effort should be in the use of pro bono time and not donated cash.

***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. Based in part on feedback from the last trustee meeting and our own deliberations, we list them again here for your comment and enhancement.

Long Term Technical and Financial Goals of *TERA*

Technical Goals

- *TERA* To Be Known For...

Moving The Science Of Risk Assessment Forward

High Quality, Unbiased And Neutral Work

(As) Customer Friendly but Science Driven

(As) The Supreme Court Of Toxicity Values

(As) The Employer Of Choice

- Success For *TERA* Would Be...

Highly Valued By Both Government And Industry Clients

The First Name In The Minds Of Clients

To Be Able To Focus Exclusively On Mission Related Work

Recognition Of Both Individuals And The Organization

- Develop Relationships with Other Groups That Share A Common Mission

Financial Goals

- Develop 50% of Projects that are long term with...

ITER Peer Review

VERA Projects

Long Term Partners As “On Call” Risk Assessors

Funding For *ITER* Development

Funding For Risk Assessment Research

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

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

In-House Expertise

No Cumbersome Bureaucracy

TERA'S BOARD OF TRUSTEES

TERA's Board of Trustees consists of 10 members who serve 3-year rotating terms. The Board has not elected to have officers. Michael Dourson, Director of *TERA*, serves on the Board and also serves as the President, Treasurer, and Secretary. Listed below are *TERA's* Board members for 2000. We need to elect 3 new Board members this year to replace Lynn Goldman, Steve Lewis and Jennifer Orme-Zavaleta. The date in parenthesis indicates the year each member joined *TERA's* Board of Trustees.

Board of Trustees

Robert Bornschein, University of Cincinnati (1999)
Gail Charnley, HealthRisk Strategies (1999)
Michael Dourson, Toxicology Excellence for Risk Assessment (1995-indefinite member)
Lynn Goldman, The Johns Hopkins University (2000) retiring
Michael Keller, Independent Consultant (1999)
Steven Lewis, ExxonMobil Biomedical Sciences, Inc. (1998) rotating off
Roger McClellan, Chemical Industry Institute of Technology (2000)
Jennifer Orme-Zavaleta, U.S. Environmental Protection Agency (1998) rotating off
Denise Robinson, International Life Sciences Institute (1999)
James Wilson, Resources for the Future (2000)

Scientific Advisor

Frank Lu, Biomedical and Environmental Sciences