

1999 Annual Report

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

Cincinnati, Ohio

March 2000

Dear Trustees:

Calendar year 1999 was good for our corporation. We hired Ms. Caitlin McArleton to replace Mr. Jason Unrine, who went to graduate school. A biographical sketch for Ms. McArleton can be viewed at www.tera.org. 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 ~800 hours of time to pro bono activities, including the State Hazard Evaluation Lending Program (StateHELP) and scientific organizations. Unfortunately, we also posted a loss of ~\$51,207. Our balance of profit/nonprofit work was 34/66.

The attached agenda includes a number of important items for discussion, including approval of the 2000 budget and short and long-term goals. We seek input on suggestions for appropriate individuals to replace the folks that will be retiring at the end of this year from our board. 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

3/24/00

Annual Meeting Board of Trustees

Toxicology Excellence for Risk Assessment

Time: 3:00 pm, April 5th, 2000

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 (J. Patterson)
- Peer Review (M. Dourson)
- Education and Outreach (J. Dollarhide)
- Research (K. Poirier)
- Financial Report of 1999 & Proposed 2000 Budget (M. Dourson)
- Other?

New Business

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

Good and Welfare (*TERA* staff and Trustees)

Adjourn at 5:00 pm

Dinner: 6:30 Open House with invitations to risk assessment folks from Cincinnati and surrounding areas

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. In 1999, *TERA* continued to do a mix of straight hazard identification work and work involving analysis of the mechanism of action and dose-response.

In 1999, several assessments were undertaken as a part of the *VERA* project. Highlights of these projects include:

- **Soluble Nickel Salts.** *TERA* completed the assessment begun in 1998 and submitted the final product (an IRIS Toxicological Review and support IRIS files) for review through EPA's IRIS process. The final assessment reflected results and input of the independent peer review. The project was jointly sponsored by U.S. EPA's Office of Water, by Health Canada, and by the Metal Finishing Association of Southern California (MFASC, an industry group). In this support document cancer and noncancer assessments via the oral and inhalation routes were conducted.

Based on the assessment, *TERA* scientists made comments at a meeting of the South Coast Air Management District, and submitted written comments to NIEHS and to CalEPA/OEHHA, all on a pro bono basis. *TERA* scientists also received an invitation to make a presentation about the nickel assessment at 6th International Symposium on Metal Ions in Biology and Medicine, and submitted for publication two articles based on the assessment, to *Regulatory Toxicology and Pharmacology*: [L.T. Haber, L. Erdreich, G.L. Diamond, A.M. Maier, R. Ratney, Q. Zhao, and M.L. Dourson. Hazard identification and dose response of inhaled soluble nickel salts] and [L.T. Haber, G.L. Diamond, Q. Zhao, L. Erdreich, and M.L. Dourson. Hazard identification and dose response of ingested soluble nickel salts.]

- **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 in the protocol development and as a study monitor for a number of studies.
 - Reviewed EPA's Draft Perchlorate Risk Assessment. Worked with other consultants to PSG to prepare written comments on the assessment which were submitted to EPA on behalf of the PSG.
 - Attended the public Peer Review Meeting of Perchlorate Risk Assessment sponsored by U.S. EPA in CA, February 1999. Gave oral comments on risk assessment at the meeting.

- Completed the rat 2-generation study of ammonium perchlorate in drinking water; submitted final report to U.S. EPA. This study was conducted by Primedica Argus Laboratory, Philadelphia, PA
 - Worked with other PSG consultants to design and monitor human studies on ammonium perchlorate.
 - Developed protocol and initiated 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. The study is being conducted by Gary Burlison, Burlison Research Labs, RTP, NC, and will be completed in May 2000.
 - Developed protocol, sought bids, and awarded contract to conduct another extensive developmental study of perchlorate in rats. This study is 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 that were not answered by earlier studies. The study design includes a guidelines 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. The contract was awarded to Primedica Argus and the study was initiated on Dec. 28, 1999. Work on this study will progress through 2000.
 - TERA staff was either primary or secondary authors of abstracts of four perchlorate studies that were presented at the 1999 SOT and Wright-Patterson AFB Risk Assessment meetings. In addition, work was started on developing manuscripts on the rabbit developmental study, the rat 2-generation study, and the mutagenicity studies for submittal to peer-reviewed journals. These manuscripts will be completed and submitted in early 2000
- **Haloacetonitriles, Halopicrins, and Cyanogen Chloride.** *TERA* won a contract with EPA's Office of Water, as a subcontractor to the Albuquerque-based small business GRAM, Inc. In collaboration with GRAM, Inc., *TERA* is developing criteria documents for the drinking water disinfectant byproducts cyanogen chloride and the haloacetonitriles. Due to the lack of data on cyanogen chloride, data on its metabolites and potential metabolites are also being considered. A shorter summary is being prepared for chloropicrin. Multiple exposure durations and exposure routes are being considered. Modes of action and sensitive subpopulations are also being considered in the development of health advisories, RfDs, and cancer assessments.
 - **Phenol.** *TERA* wrote the IRIS Toxicological Review for phenol, under contract to EPA's Office of Solid Waste. A number of new toxicity and toxicokinetic studies became available in 1999, including an oral developmental toxicity study, a subchronic oral neurotoxicity study, a 2-generation reproduction study, a new toxicokinetics study via multiple routes, and a 2-week inhalation study. These new studies were incorporated into the development of the RfD, RfC, and cancer assessment. A particularly interesting aspect of the assessment was the importance of exposure route (e.g., drinking water vs. gavage) and of gavage volume in determining toxic potential.

- **Lanthanides.** *TERA* developed RfDs and RfCs for the non-cancer, non-radiological human health risk resulting from human exposure to the rare earth elements known as the lanthanides. This mixture may include such rare earth elements as neodymium (Nd), cerium (Ce), scandium (Sc), yttrium (Y), dysprosium (Dy) and lanthanum (La). RfDs for lanthanum, europium and yttrium, and RfCs for cerium and gadolinium, were developed. The ultimate goal of the project was to develop RfDs for a mixture composed primarily of lanthanum and cerium. This mixture is the primary material mined by Molycorp at the Mountain Pass Mine site, Mountain Pass, California, on Bureau of Land Management (BLM) land. The toxicology literature on all lanthanides was reviewed as part of the assessment. The Bureau of Land Management and Molycorp sponsored this work.
- **NIOSH Profiles.** *TERA* developed five chemical-specific Hazard Profile Documents for the National Institute for Occupational Safety and Health (NIOSH), propylene glycol, 2-biphenylol, stearyl alcohol, potassium carbonate, and N-bis(hydroxyethyl) cocoamide. 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.”
- **Flame Retardants.** *TERA* was engaged by the National Academy of Sciences (NAS) to provide the draft cancer and noncancer assessments on 16 different chemical or chemical classes of upholstery flame retardants (FR). The request came about in response to the public concern regarding the safety of FR chemicals. Congress, in the fiscal year 1999 appropriations report for the Consumer Product Safety Commission (CPSC), requested that the National Research Council (NRC) conduct an independent study of the health risks posed by exposure to 16 FR chemicals (or chemical classes) that are likely to be used in residential upholstered furniture to meet regulations proposed by CPSC for flame resistance. The FR chemicals reviewed constitute a diverse group of substances, including brominated compounds, metal compounds, inorganic and organic compounds. The NRC assigned the project to the Committee on Toxicology (COT), which convened a Subcommittee on Flame-Retardant Chemicals, which prepared the final report. *TERA* collaborated with two other organizations (Syracuse Research Corporation and Oak Ridge National Laboratory) to provide the complete assessments to the COT. *TERA* personnel worked directly with staff members at the NRC and also with the COT to provide direction and amendments to the documentation. The assessments included oral, dermal, and inhalation exposures. The most likely routes of exposure will be dermal and oral, but inhalation can also be of concern because the disintegration of worn-out FR-treated upholstery might cause fabric particles to become airborne. Although the subcommittee developed the methodology for conducting health risk assessments for FR chemicals, the methodology used is similar to the risk assessment processes previously recommended by NRC and other regulatory agencies. The final report will be published in 2000.

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

***ITER* Database Development**

During 1999, *TERA's* International Toxicity Estimates for Risk (*ITER*) database was greatly expanded to nearly 500 chemicals. *ITER* is a compilation of risk values from U.S. EPA, Health Canada and ATSDR. *TERA* initiated and created this database to serve the needs of risk assessors and managers worldwide for current and reliable risk value information. A pilot version of *ITER* with 39 chemicals was introduced in 1996 with support from the Chemical Manufacturers Association, Health Canada, Syracuse Research Corporation, and U.S. Borax. In 1998 *ITER* was redesigned and expanded to over 100 chemicals, through a collaborative venture between *TERA* and *CTC*. This expansion was funded through the National Defense Center for Environmental Excellence (NDCEE) operated by *CTC*. During 1999 *TERA* has added more data to *ITER* supported by funding and/or in-kind assistance from additional organizations, including the Cinergy Foundation, Cytec Industries Inc., the Formaldehyde Epidemiology, Toxicology and Environmental Group, Inc. (FETEG), and U.S. Borax.

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. *ITER* is available on the Internet at <http://www.tera.org/iter>.

During 1999 *TERA* decided that if we were to continue providing this database it must be expanded to include at least all of EPA's IRIS risk values. When no outside funding was left, *TERA* development reserve funds were used to extract the IRIS data, perform quality control, and continue to publicize the program. In the fall of 1999, *TERA* staff undertook a major effort to seek additional support to complete the addition of IRIS data and bring the expanded version of the database to the risk assessment community's attention. Requests for support were sent to over 75 individuals and organizations, numerous briefings were given, and additional funds were received from three organizations.

TERA seeks to have *ITER* serve the risk assessment and risk management communities by providing a comprehensive database of risk values from a variety of agencies and independent sources worldwide. Therefore, it is imperative to include risk values from the major organizations. During 2000, *TERA* plans to add information from the remaining 100 Toxicological Profiles of ATSDR. In addition, *TERA* will continue to solicit funds as a tax-exempt [501(c)(3)] organization to include risk values from the World Health Organization (WHO) and the International Programme on Chemical Safety (IPCS), along with government agencies such as RIVM in the Netherlands. High quality assessments for hundreds of risk values are available from these organizations, but the public does not have easy access to this information. As an on-line source of these assessments, *ITER* makes them more accessible to the scientific and regulatory community, as well as furthering international harmonization.

***ITER* Peer Review Meetings**

For the *ITER* Peer Review program, *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 1999 four meetings were held and six chemical assessments were reviewed.

January 1999 - An assessment for soluble salts of nickel was reviewed in a two-day meeting

In work jointly funded by the Metal Finishing Association of Southern California, U.S. EPA, and Health Canada, *TERA* assessed the potential cancer and noncancer human health risks of oral and inhalation exposure to soluble salts of nickel, using EPA risk guidelines. With newer studies and analyses that focused on soluble nickel, risk values for noncancer exposures were developed. In addition, the review panel concluded that the carcinogenicity of soluble nickel via the inhalation route cannot be determined because of conflicting data, while the carcinogenicity via oral exposures cannot be determined because there are inadequate data to perform an assessment.

A subgroup of the *TERA* Board of Trustees selected the peer review panel and a *TERA* Trustee, Dr. James Wilson, chaired the meeting. These unusual measures were taken to minimize the potential for conflict of interest.

May 1999 - An assessment of carbon disulfide developed by Health Canada under the Priority Substances Program was reviewed in a one-day meeting in Ottawa.

Health Canada proposed an inhalation tolerable concentration for carbon disulfide based on decreased motor nerve conduction velocity seen in an occupational study. The panel discussed the choice of critical effect (nervous system vs. cardiovascular risk factor endpoints) and agreed that decreased motor nerve conduction velocity is the endpoint is an appropriate basis for the tolerable concentration, because it does indicate that axonal damage has occurred. Other issues discussed included the appropriate choice of the benchmark response (BMR) and background adverse response level for the benchmark concentration modeling, and the choice of uncertainty factors and the associated rationales.

June 1999 - A one and one-half day meeting was held to discuss arsenic and barium.

Elf Atochem, North America, Inc. presented to a peer review panel the results of a review of the developmental toxicity literature on arsenic, including a number of additional laboratory animal studies sponsored by Elf Atochem that were designed to evaluate the ability of inorganic arsenic to induce prenatal structural malformations. Based on the new, regulatory guideline-compliant studies of arsenic trioxide and arsenic acid in mice, rats, and rabbits, the panel concluded that repeated oral and inhalation exposures to these forms of inorganic arsenic did not induce structural malformations, even at doses that elicited frank maternal toxicity and lethality.

Chemical Products Corporation sponsored the review of an oral reference dose for barium and compounds which was written by Drs. Dallas and Williams of the University of Georgia. The RfD was based on kidney effects seen in the 1994 National Toxicology Program (NTP) drinking water studies of barium chloride dihydrate in rats and mice. The peer review panel reached unanimous

consensus that available human studies were of lesser quality and the 1994 NTP study was the most appropriate choice basis for a RfD. The panel also unanimously agreed that kidney effects, rather than cardiovascular effects, are the critical effect for barium.

August 1999 - Assessments on N-nitrosodimethylamine (NDMA) and ethylene oxide developed by Health Canada under the Priority Substances Program were reviewed in a one-day meeting in Ottawa.

Health Canada evaluated the toxicity data for NDMA and derived Tumorigenic Doses₀₅ (i.e., the dose level which causes a 5% increase in tumor incidence over background) for hepatic biliary cystadenomas, hepatic carcinomas, and hepatic hemangiosarcomas.

For ethylene oxide, the peer review panel agreed with Health Canada's characterization of the human and animal data and agreed that the animal data are the appropriate basis for deriving TC_{05S}. The panel agreed that there is clear evidence of carcinogenicity in laboratory animals and that human studies provide suggestive, but inconclusive, evidence of increased risk for hematological cancers. There was significant discussion regarding the human studies and the genotoxicity data. Health Canada calculated based on several carcinogenesis bioassays in F344 rats and one in B6C3F1 mice.

During 1999, risk values for three new chemicals were added to *ITER* upon the recommendation of peer review panels. The risk values derived in the Dow AgroSciences assessment of Telone II (1,3-dichloropropene) that had been reviewed during 1998 were added to *ITER*. The peer review panel conclusions on arsenic have been included in the non-cancer sections of the arsenic file on *ITER*. Risk values from the soluble nickel salts assessment were included in the nickel sulfate, nickel chloride and nickel soluble salts (not otherwise classified) files of *ITER*.

The *TERA* peer review program has been operating since 1996. Review panels consist of scientists from government, industry, consulting, academia, and environmental groups who meet face-to-face to share experience and insights. The review process is open and transparent. Conflicts of interest are identified and avoided. Potential conflicts of interest are discussed and recorded. Meetings are held four times per year and are open to the public; the results are made available on *TERA's* home page (<http://www.tera.org/peer>). Because the peer review panels include scientists with expertise in the broad range of disciplines required for each assessment, and because the ensuing discussions are thoroughly documented, these meeting summaries have served as a valuable resource for scientists conducting related assessments.

Independent assessments will continue to be added to *ITER* as the peer review panels make recommendations. To meet further needs the peer review program and *ITER* database may expand into occupational and ecological risk values, provided additional financial support and the collaboration of interested colleagues is secured.

TERA has created the peer review program as a service to the risk assessment community. While the peer review program received high praise from sponsors and peer reviewers, the program has yet to break even on expenses. 1999 fees were \$15,000 (\$10,000 for government) for a half day meeting. *TERA* will charge higher rates in 2000 to more accurately reflect true program costs.

Selected Education/Pro bono

Support to Cinergy Corporation on Toxic Release Inventory Reporting. *TERA* has conducted an independent risk assessment of emissions from 10 coal-fired power plants for our local gas and electric utility company, Cinergy. 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. *TERA* wrote a report of this work that is tailored to the general public and an abstract used as a press release. The report is available on *TERA's* web site and *TERA* staff fielded questions from the public on the report. *TERA* provided ongoing support to the utility company by

- Working with utility company's public relations firm to develop newsletters and brochures that are distributed to power plant neighbors
- Attending meetings with local health departments and citizen groups to give presentations on results of risk assessment.
- Attending a press conference held to accompany release of utility company's TRI data.

Work on this project with Cinergy continues during the year 2000.

Legal. For the law firm Dunetz, Marcus, Brody & Weinstein, L.I.C., *TERA* reviewed the 1992 Block Drug X-14 acute inhalation study and provided comment on the study with particular attention to the use of acute lethal studies in toxicology. *TERA* provided some background material that explained the expected results in LC50 studies and put the data provided in context of the standard protocol. In addition *TERA* examined the X-14 labeling from 1992 and provided a summary of its compliance with the regulatory requirements of the Federal Hazardous Substances Act. After submitting this material to the sponsor, the case was settled and no further action was required on *TERA's* part.

TERA provided assistance to the law firm of McCullough and Sherrill, LLP, with research on nitrate for the case *Adams v The City of Albany*, File No. 7127.1. *TERA* provided general information on the RfD method and the meaning of the RfD; basis for and meaning of the nitrate RfD; potential for adverse effects at doses below and above the RfD; and relative contribution of nitrate from drinking water and other sources of nitrate exposure.

TERA conducted some follow up analysis for the law firm Orrick, Herrington & Sutcliffe on PCB contamination at the Paoli Rail Yard Superfund Site in Pennsylvania. *TERA* reviewed comments received by the law firm on our earlier work and provided guidance on how to respond to these comments.

Pro bono Articles Written. *TERA* scientists completed several *pro bono* articles in 1999, including:

- "Noncancer Risk Assessment: Principles and Practice in Environmental and Occupational Settings" in the 5th edition of Patty's Toxicology.
- "Persistent Environmental Pollutants" in *Environmental Health Secrets*, Hanley & Belfus, Inc., Publishers.

- An article on hormesis for the BELLE Newsletter
- Presentation of seven posters at the 1999 Annual Meeting of the Society of Toxicology

***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:

- "An evaluation of Modeled Benzene Exposure and Dose-estimates Published in the Chinese-National Cancer Institute Collaborative Epidemiology Studies" by Budinsky, R.A. et al. for Regulatory Toxicology and Pharmacology.
- A Risk Assessment of Sulfur Mustards for the U.S. Army
- "Comparison of the Acute Hematotoxicity of 2-butoxyethanol in Male and Female Rats" for Human and Experimental Toxicology.

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:

- A presentation on uncertainty factors was given to the National Academy of Sciences
- A presentation on the toxicology of soluble nickel was made to the Southern California Air Quality Management District
- A presentation on the common mechanisms/methods for cancer and noncancer risk assessment was given to the Society of Toxicology
- A lecture on developing a Reference Dose was given to the University of Ulster
- *TERA* conducted a Symposium on Comparative Dietary Risk at 1999 Annual Meeting of the Society of Risk Analysis
- *TERA* conducted a Roundtable Discussion on Peer Review at 1999 Annual Meeting of the Society of Risk Analysis
- Lectures on noncancer and cancer risk assessment were given to graduate students and medical 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. Also, *TERA* hosted a brown bag lunch meeting of the Ohio chapter of the Society for Risk Analysis where Mike Dourson presented *TERA*'s work on Comparative Dietary Risk. Several *TERA* staff has also held leadership roles in these societies:

- Mike Dourson served as President of American Board of Toxicology, Vice President Elect of the Risk Assessment Specialty Section of the Society of Toxicology, and as a member of the Health Advisory Board for the National Sanitation Foundation
- Jacqueline Patterson served as President of the Ohio Chapter of the Society for Risk Analysis.
- Lynne Haber was elected Vice President for Education of the Dose-Response Specialty Group of the Society for Risk Analysis.
- Ken Poirier was elected Treasurer of the Ohio Chapter of the Society for Risk Analysis.

State Hazard Evaluation Lending Program (StateHELP). *TERA* scientists provide risk assessment support in 1999 to several states under the StateHELP program.

- Develop a toxicity value and Preliminary Remediation Goal (PRG) for the State of Nevada – *TERA* scientists reviewed the toxicity data on dichlorobenzil and helped to derive a provisional RfD based on qualitative structure activity relationship analysis using dichlorobenzophenone as a surrogate. This work is continuing in the year 2000.
- Develop risk assessment methods approach for the State of Ohio – *TERA* scientists developed an approach for developing dermal RfDs and cancer potency values based on extrapolation from oral data.
- Prepare a definition of Reference Dose that can be used for nonscientific audiences for the State of Vermont
- Provided guidance to the State of Michigan on the selection of appropriate uncertainty factors to apply in the development of a toxicity value for 2,3,7,8-TCDD.
- Provided assistance to the State of Michigan on the development of risk assessment values for telone.
- Provided guidance on the appropriate choice of uncertainty factors in developing a RfD for boron to the U.S. EPA, Office of Research and Development in Cincinnati, OH.
- Provide general consultation in risk assessment for a number of states on small issues.

Selected Research Projects

Copper Studies in Humans. *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. *TERA* has identified four research institutions of excellence and has written two research protocols to attempt to provide a dose response in humans that shows a threshold for bolus ingestion of copper in drinking water. The first protocol was approved for use at three research centers originally identified to participate in the study. This study was unique in the use of three separate populations on three different continents. In addition, the study was designed to help nutritional toxicologists understand the potential toxic effects of ingesting copper in dietary supplements. This is the first study to provide data on the acute ingestion of copper in drinking water over a very narrow and well-controlled dose range. *TERA* has inspected each research facility to insure compliance to Good Laboratory and Clinical Practices and each institution's Institutional Review Board policies for human subject studies. *TERA* is also overseeing the research, coordinating the compilation and statistical analysis of the results, and writing report summaries. The results of the phase 1 are complete and *TERA* is coordinating the incorporation of the data from the three sites and will be submitting the manuscript to *Environmental Health Perspectives*.

The results of phase 1 have clearly delineated a NOAEL and LOAEL for the acute bolus exposure to copper in drinking water in human volunteers which has not been reported previously. These data will be of importance to regulatory agencies that are grappling with establishing drinking water guidelines for copper and possible for other regulatory agencies with concerns of excess copper ingestion from nutritional supplementation products. 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. Addressing the effect of copper concentration in the drinking water is of particular importance, since the effect occurs at the portal of entry (the stomach). This raises the question of whether the critical determinant of toxicity is the total daily dose (as in traditional RfDs), or the concentration of copper in the drinking water. The phase 2 study is designed to address this question.

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. The project Director is Hugh Spitzer, a visiting scientist with *TERA*, and the Co-Director is Dr. James Wilson, of Resources for the Future.

Scientists and risk assessment practitioners are currently being interviewed to determine:

- how the use of default assumptions has changed over time;
- ongoing research that will impact dose-response assumptions; and
- ongoing efforts to harmonize practices used by North American, Asian, and European regulatory agencies.

Based on the information collected, the authors, in consultation with an advisory committee, will identify issues for workshops on default assumptions.

Cadmium - Susceptibility Of Occupational Vs. General Populations. Occupational studies are often used in risk assessment and applied to the general population. However, the dose-response data

from occupational studies may not be directly applicable to the general public, due to such reasons as a healthy worker effect, or a hardened worker effect, in which some workers may adapt to more or less continuous exposures, a situation that is not likely to take place in the general population. There is a substantial body of occupational data on the effects of cadmium, but the cadmium RfD and RfC are based on general population data. In this study, cadmium nephrotoxicity in the general population and occupational cohorts were compared.

Comparative Dietary Risks: Balancing the Risks and Benefits of Fish Consumption. A comparative dietary risk framework was developed under a Cooperative Agreement with U.S. Environmental Protection Agency for comparing the possible health risks of consuming contaminated fish, while considering the potential health benefits lost by not eating fish. The framework was designed to provide information for a range of fish consumption rates, allowing a user to roughly estimate the range of consumption rates at which people may have a net benefit, a net risk, and the consumption rate at which no net change in the health index would be likely.

This framework is an initial attempt to evaluate risks and benefits (qualitatively and quantitatively) on a common scale. Constructing this framework identified numerous areas that need further research and development. Two needs seemed paramount. First, better estimations of benefits are needed for the general population and its sensitive subgroups. Second, better risk information is needed on the chemicals that commonly contaminate fish, specifically estimating risks above the RfD for certain chemicals is essential for this framework to be most effective. This work won an award at the annual SOT meeting in 1999. Publications are planned for 2000.

Financial Report for 1999 and Proposed 2000 Budget

During 1999 *TERA* had income of ~\$926,277 and expenses of ~\$977,484. The net loss for 1999 was ~\$51,207. *TERA* will work in 2000 to erase this loss. The proposed budget for 2000 is \$1,200,000. This budget was approved at the April 5, 2000 meeting of the trustees. This budget does not include pass through funds to pay for the toxicity studies on perchlorate.

***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. A second page of goals for year 2000 is also included.

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

- Maintain A Base Of Work 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