

2001 Annual Report

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

Cincinnati, Ohio

February 2002

Toxicology Excellence for Risk Assessment (*TERA*) is a non-profit corporation dedicated to the best use of toxicity data for risk assessment. *TERA* was founded in 1995 to help public and private organizations and companies to find common ground through the application of good science to risk assessment. In fostering successful partnerships with and among our sponsors, improvements in the science and practice of risk assessment will follow.

TERA provides aid with the following risk assessment tasks:

- developing new risk values,
- conducting original risk assessment research,
- reviewing assessments prepared by other parties,
- analyzing risk positions, regulatory, and other approaches of government agencies and industry,
- preparing educational or training materials
- designing toxicological and exposure studies.

Toxicology Excellence for Risk Assessment is organized under section 1702.01 et seq. of the Ohio Revised Code, Non-Profit Corporation and has been granted tax-exempt status under section 501(c)(3) of the Internal Revenue Code by the Internal Revenue Service. *TERA* is organized exclusively for scientific purposes, including for such purposes, the making of distributions to other organizations that qualify as exempt under section 501(c)(3) of the Internal Revenue Code, or the corresponding section of any future federal tax code. Contributions to *TERA* are tax deductible to the full extent allowed by the law. *TERA* has chosen to organize as a non-profit corporation as a way to facilitate successful partnerships between environmental, industry and government groups.

This report presents selected accomplishments in our five program areas:

1. Assessments on chemicals and other substances conducted in our Verifiable Estimates for Risk Assessment (VERA) program
2. International Toxicity Estimates for Risk (*ITER*) database of risk assessment values
3. Independent peer review and consultation program
4. Education program of training courses, scientific support and the State Hazard Evaluation Lending Program (StateHELP)
5. Research program to develop methods for conducting human health risk assessment

A list of *TERA* Trustees follows, along with the agenda for the 2001 Annual Meeting.

VERA

(Verifiable Estimates for Risk Assessment)

Long-term Goals

- Be known for developing partnerships and fostering cooperation between industry and government in the development of risk values.
- Be known for expertise in developing noncancer and cancer toxicity values using the best science.
- Increase our activity in several areas (international risk values, occupational risk value development, and consumer products).

2001 Selected Accomplishments

- Continued analysis of multiple toxicology issues related to perchlorate, providing technical support on perchlorate risk assessment issues and acting as a study monitor for a number of toxicity studies
- Presented talks and posters on several projects at national scientific meetings
- Continued our work on a number of Drinking Water Criteria Documents on disinfectant byproducts for EPA, revising the documents in response to internal EPA and external peer review.
- The IRIS Toxicological Reviews for phenol and nickel were shepherded through EPA review processes in 2001 and subsequently revised to respond to comments.
- Prepared a Drinking Water Summary Document for Cyanobacterial Toxins for EPA's Office of Water. The document addressed cyanobacterial toxin synthesis and factors affecting synthesis, environmental fate, toxicity, and toxicokinetics.

ITER

International Toxicity Estimates for Risk Database

International Toxicity Estimates for Risk (*ITER*) is a free Internet database (www.tera.org/iter) that contains risk values for 560+ 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. In 2002, RIVM (The Netherlands) risk values will also be available on *ITER*. 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 Peer Review Program.

Overall Goal

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

2001 Selected Accomplishments

- Completed over two-dozen updates or additions to chemical entries currently on *ITER*. These were based on new releases or updates from ATSDR and EPA, as well as newly released data from Health Canada for 7 chemicals, and data for one chemical from the Chemical Industry Institute of Toxicology (under the *ITER* column). Additionally, we have added 7 new chemicals to *ITER* based on new releases from ATSDR and EPA.
- Established partnership with RIVM to add its data to *ITER*; began initial preparation of files. During 2001, RIVM directly added much of its data into *ITER*, and provided *TERA* with RIVM-related information to update the other sections of the database (such as the glossary and methods sections, which *TERA* completed). We expect to complete this project and make all of the RIVM data publicly available on *ITER* during 2002
- Improved tracking of hits to database to better characterize and quantify usage. During 2001, the number of daily users of *ITER* (starting from the *ITER* home page) increased by 30% as compared to 2000

Independent Peer Review Program

Overall Goal

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

2001 Selected Accomplishments

- Began a five-year cooperative agreement with the U.S. EPA to develop a peer consultation program and conduct peer consultation meetings on risk assessment issues, particularly characterizing the risk to children.
- Continued exploring the feasibility and desirability of review of occupational values and issues and discussed feasibility with ACGIH.
- Individual *TERA* staff served as expert peer reviewers for a number of assessments and meetings. For the Ontario Ministry of the Environment, a *TERA* scientist served as an expert peer reviewer for a report on the health effects of community exposure to soil contaminated with nickel and other metals. For the International Life Sciences Institute (ILSI Europe) several *TERA* staff have participated in the EC Concerted Action on Food Safety in Europe (FOSIE): Risk Assessment of Chemicals in Food and Diet.
- *TERA* scientists have reviewed derivation of risk values, identification of appropriate effect levels and other evaluation of risk assessment documentation for both private and public sponsors. For example, for a private company *TERA* provided advice on derivation of reference doses (RfDs) for several contaminants that had been found in drinking water wells.
- *TERA* scientists evaluated the data for the RfD for methylmercury to determine how to reduce uncertainties and prepared a report for the Electric Power Research Institute. As a follow-up to this report, a paper was published in *NeuroToxicology*.
- Presented poster on issues in organizing peer reviews at the Society for Risk Analysis 2001 Annual Meeting.

Education, State HELP and Pro Bono Programs

Long-term Goals:

- To develop the risk communication and public services aspects of the Education program
- Have *TERA* scientists participate in a wide range of educational forums, both pro bono and for a fee.

2001 Selected Accomplishments

- *TERA* continues to provide support to Cinergy Corporation on assessing risk from power plant emissions and communicating risk to the public. *TERA* began 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 year 2000 emissions.
- Development of a white paper on the potential health risks of bromate in bottled water that meets the FDA standard of 10 ppb.
- *TERA* scientists completed several *pro bono* articles in 2001, including:
 - An invited paper on Internet and World Wide Web resources for human health risk assessment, to be published in *Toxicology*.
 - *TERA* scientists were lead authors on three *Comments in Toxicology* articles, one on biomarkers, one of categorical regression and the other on evolution of risk assessment practice.
 - Publication of paper on Applications of Mechanistic Data in Risk Assessment -- The Past, Present, and Future in *Toxicological Sciences*.
- *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:
 - Reviews of two papers from the NIOSH meeting last August "Future Research for Improving Risk Assessment Methods: of Mice, Men, and Models"
 - Review several articles for peer-reviewed journals, including *Regulatory Toxicology and Pharmacology*, *Risk Analysis*, *Human and Ecological Risk Assessment*, *Critical Reviews in Toxicology* and *Human and Experimental Toxicology*.
- *TERA* scientists were invited to make presentations on a variety of risk assessment topics in several different forums. Selected presentations include:
 - Presentation at the Toxicology Forum on whether the RfD protects children

- Lectures to the environmental toxicology course at University of Cincinnati on basic risk assessment
- Presentation to CalEPA/OEHHA and the California Air Resources Board on nickel speciation
- Seminar and course lectures at the Department of Environmental Health at University of Cincinnati on basic risk assessment, mode of action analysis, and use of biological markers in risk assessment.
- *TERA* scientists are active members of professional societies including the Society of Toxicology, the Society for Risk Analysis, and the Society of Environmental Toxicology and Chemistry, and the American Industrial Hygiene Association. Several *TERA* staff has also held leadership roles in these societies. For example, Mike Dourson was President of SOT's Specialty Section on Risk Assessment and served as vice chair of the NSF International Health Advisory Board. Lynne Haber was Vice President of SRA's Dose Response Specialty Group.
- *TERA* scientists played active roles in developing educational programs for various professional societies:
 - Reviewed or developed courses and symposia for SOT's 2002 annual meeting. Served as media resource specialist in risk assessment for the SOT.
 - Served as a co-chair of an SOT continuing education course on Incorporation of Pharmacokinetic and Pharmacodynamic Data into Risk Assessments, to be taught at SOT 2002 annual meeting
 - Served as co-chair of session at SRA on Implications of Human Variability for Risk Assessment, and presented a talk at that session
 - For the Ohio Chapter of SRA, organized a one-day training course in PBPK modeling held in Dayton Ohio. Both lecture and hands-on sessions were part of this well-received workshop
- Bert Hakkinen serves on the Scientific Advisory Panel of the Mickey Leland National Urban Air Toxics Research Center.
- *TERA* scientists provide risk assessment support in 2001 to several states under the StateHELP program
 - Continued to 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 through early 2001 by responding to questions from the group on issues related to the critical effect of copper and interactions of copper and other metals.

- Participated in a review of Draft Human Health Risk Assessment Guidance Document, prepared by the State of Ohio. *TERA*'s review focused on issues related to risk assessment for exposure to chemical mixtures.
- For the State of New York, provided guidance on the route-to-route extrapolation for MTBE risk assessment.
- Provided guidance to the State of Michigan on cancer assessment for MTBE.
- Reviewed a draft guidance document from the Ohio EPA on ecological risk assessment.
- For the State of Ohio Voluntary Action Program, developed guidance on assessment of, oral-to-dermal extrapolation, portal-of-entry effects, and data appropriate for deriving dermal cancer potency estimates.
- Through the website and feedback forms, responded to many general questions from citizens on issues related to toxicology, risk assessment, and occupational toxicology.

Risk Assessment Research Program

TERA's research program includes two major components: chemical-specific research, and methods development. The methods development portion of our program expanded significantly in 2001, with a variety of new projects on topics such as children's risk, incorporating information on genetic polymorphisms into risk assessment, and scientific criteria for the development of occupational exposure levels (OELs). Chemical-specific work included an analysis of the mode of carcinogenic action for 1,3-dichloropropene (a project with broader implications for risk assessment methods), and continued research on the acute nausea threshold for copper.

Long-term Goals

- Be known for doing innovative 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

- In work partly funded by the American Crop Protection Association, *TERA* developed a two-part publication on children's risk with Bob Scheuplein and Gail Charnley. The first paper focused on the biological differences between children and adults. The second paper focused on regulatory aspects of this biological difference, the use of animal models to explore potential differences in risk, and the proposed additional 10-fold factor (the FQPA safety factor) for the extra protection of children when estimating safe exposures.
- In a project sponsored by the International Council on Mining and Metals, *TERA* is surveying the methods used by a number of organizations to develop limits on occupational exposure for metals, metal compounds, and other compounds related to mining operations.
- In collaboration with Environ, in work sponsored by the American Chemistry Council, *TERA* is researching the use of data on human polymorphisms and variability in risk assessment. In Phase I, case studies were developed that integrated 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 the chemical. Results of the first phase were accepted for publication in 2002, in *Regulatory Toxicology and Pharmacology*. In Phase II, Monte Carlo analysis was combined with PBPK modeling for two of the case study chemicals, warfarin and parathion, to determine the total variability in human tissue dose, and the amount of this variability that can be attributed to metabolic variability (due to the polymorphism) versus physiological variability. Phase III will consider the implications of the results of Phase II for the intraspecies uncertainty factor for noncancer risk assessment.

- In a project sponsored by Dow AgroSciences, *TERA* conducted a critical analysis of the mechanistic data underlying cancer risk assessments for 1,3-dichloropropene (1,3-DCP), with the goal of facilitating the application of mode of action (MOA) data in future cancer risk assessments. The analysis will be submitted for publication in a peer-reviewed journal.
- The second phase of the human copper acute NOAEL study was completed. This phase of the study was designed to (1) corroborate the findings of phase I (completed and published in 2000), (2) determine if water volume or concentration of copper or both affect the previously determined NOAEL, and (3) determine the effects of copper in bottled, potable drinking water. The study was successful in answering all of the objectives and the results will be submitted for publication in 2002.
- In work related to children's risk, for the Pest Management Regulatory Agency of Health Canada, *TERA* reviewed methods used by Health Canada, USEPA, and IPCS for hazard identification, dose-response assessment, and exposure assessment, with particular attention to how children's risk issues are handled.
- A white paper, funded by a grant from NIEHS, U.S. EPA/Office of Research and Development, and the International Copper Association, was prepared on the assumptions used in dose-response. The project is led by Hugh Spitzer, a visiting scientist with *TERA*, and Dr. James Wilson, of Resources for the Future.
- In a project for Applied BioSystems, *TERA* developed an occupational risk assessment procedure that provides a systematic process for assessing and documenting potential toxicological hazards of newly purchased/manufactured chemicals prior to introduction into the work area. The procedure uses a decision flow process that allows for deriving qualitative risk potential ratings based on diverse data sets. The procedure is being presented at a national industrial hygiene conference, and is being planned as a published manuscript.

Managerial and Financial Report for Fiscal Year 2001

Report on Adopted Resolutions and Recommendations of the Board of Trustees

- The Board of Trustees emphasizes that *TERA* management achieve revenues in excess of expenses and staff *TERA* projects appropriately.

Financial objectives for 2001 were achieved. A *VERA* program lead was hired from within *TERA*. Other project leaders were identified and used as appropriate. Two new experienced staff were brought on as visiting scientists. Their integration into *TERA* has been very fruitful.

- *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.

Audits for FY 1999 and 2000 were accomplished and reports submitted to board at appropriate times. An audit of the 2001 books is planned.

- 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.

***TERA* received a cooperative agreement of \$2.5 million (total) for the next five years to conduct peer consultations. *TERA* also started a new *VERA* project with NIOSH on “Immediately Dangerous to Life or Health Values.” Task is slated at about \$100K and spans approximately 1 year.**

TERA'S BOARD OF TRUSTEES

TERA's Board of Trustees consists of nine members who serve 3-year rotating terms. 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 2002. The date in parenthesis indicates the year each member joined *TERA's* Board of Trustees.

Board of Trustees

Daniel Acosta, University of Cincinnati (2002)
Gail Charnley, HealthRisk Strategies (2002)
Robin Corathers, Mill Creek Restoration Project (2002)
Michael Dourson, Toxicology Excellence for Risk Assessment (1995-indefinite member)
Elaine Dorward-King (2001)
Steven Lewis, ExxonMobil Biomedical Sciences, Inc. (2001)
Roger McClellan, Chemical Industry Institute of Technology (2000)
Jennifer Orme-Zavaleta, U.S. Environmental Protection Agency (2001)
James Wilson, Resources for the Future (2000)

Scientific Advisor

Frank Lu, Biomedical and Environmental Sciences

Meetings of the Board of Trustees

The Board of Trustees held a meeting on February 28, 2001 to discuss the 2000 Annual Report and the plans and budget for 2001. This meeting was held in Cincinnati, Ohio and convened at 9:00 am Eastern. The Board also held a conference call meeting later in the year to discuss *TERA's* progress. February 13, 2002 is the date of the Board of Trustees meeting to discuss the 2001 Annual Report and the plans and budget for 2002. This meeting is in Cincinnati, Ohio and convenes at 10:00 am.