2005 Annual Report

Toxicology Excellence for Risk Assessment (*TERA*)

Cincinnati, Ohio

April 2006

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

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

Dear Dr. Dourson:

Having completed my term as Chair of *TERA*'s Board of Trustees, I feel a great sense of satisfaction that I was able to witness the efforts and progress of the past year. While I feel an approaching sense of 'separation anxiety,' I know – beyond doubt – that you and your colleagues will carry on in the fine tradition that *TERA* has established. At the risk of repeating myself, it is yours and *TERA*'s commitment to scientific excellence that sets you apart.

My confidence in *TERA*'s future is further bolstered by knowing the exceptional panel of professionals who make up the Board. Jim Wilson will be a fine Chair, and I'm proud to 'pass the gavel' to him. Your plans to advance *TERA*'s business are ambitious, to be sure…but, just as surely, in good hands. I know that I can speak for Jim and the entire Board in wishing you and the organization the very best.

On behalf of the entire Board of Trustees, I congratulate you. And, please accept my personal thanks for this extraordinary experience. I am honored to have had the opportunity to serve.

Very truly yours,

/s/

Steven C. Lewis, Ph.D., DABT

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Introduction

Toxicology Excellence for Risk Assessment (*TERA*) is a nonprofit organization established in 1995 with a mission to protect public health by developing and communicating risk assessment values, sponsoring peer reviews and consultations, improving risk methods through research and educating the public on risk assessment issues. *TERA* was established as an independent corporation to improve the science of risk assessment through a focus on partnerships among *all* members of the risk assessment community. *TERA* focuses on high quality science and building bridges among diverse stakeholder groups.

Highlights of 2005

An Alliance for Risk Assessment

Since its inception, *TERA* has provided technical assistance to many States under our StateHELP Program. Recognizing growing needs in this area, we have initiated an *Alliance for Risk Assessment* to expand significantly our help to the risk assessment community. We are developing processes with the National Library of Medicine under which diverse stakeholder groups from government, industry, and others provide a pool of funds that are used as a shared resource to address issues most relevant to state and local risk assessors. Technical projects completed under the expanded program will include the development and peer review of risk values, research in new risk methods, training in risk methods, and documentation of risk assessment information in a free online database of risk values (*ITER*). A hazard assessment notification system (*HANS*) to enhance communication on risk assessment activities and needs is also envisioned. Contact Dr. Andrew Maier (maier@tera.org) for details.

Cooperative Research and Development Agreement (CRADA) to Improve Cancer Risk Assessment

TERA, the Food and Drug Administration's National Center for Toxicological Research (NCTR), and ENVIRON have established a collaborative relationship (Cooperative Research and Development Agreement) for informing mode of action analysis for cancer risk assessment. This collaboration seeks to investigate a new approach to quantitatively compare mutation data with tumor data. The essence of the approach involves comparing the *in vivo* mutagenicity dose-response (using transgenic *in vivo* shuttle vector models) in the tumor target tissue with the tumor dose response in the same rodent strain. Preliminary collaborative work between NCTR and Bruce Allen and Annette Shipp of ENVIRON has found promising results for distinguishing the role of mutagenesis in carcinogenicity by chemicals that act via multiple modes of action. We invite companies and government agencies to join us by participating in and/or sponsoring studies investigating the best approach for experimentally obtaining and quantitatively analyzing *in vivo* mutagenicity data for use in cancer risk assessment. For further details, see http://www.tera.org/news/ or contact Dr. Lynne Haber (Haber@tera.org).

Building Quantitative Structure Activity Relationships Expertise

In recognition of the growing need to develop hazard and risk assessments for the huge number of chemicals that lack traditional toxicity testing data, *TERA* has developed in-house capacity in the development and use of Structure Activity Relationships (SAR) and Quantitative Structure Activity Relationship Expertise (QSAR) approaches. This expertise provides a vital resource for risk assessment through the development of structure-based toxicity sorting rules, for selection of structural analogs for use as toxicological surrogates, and direct computational chemistry and QSAR development. A series of free QSAR Issue Papers are available from *TERA* that provide information on current approaches and future research needs. Contact Dr. Andrew Maier (Maier@tera.org) for details.

Easier Access to *TERA* Peer Review and Peer Consultations

To make peer reviews and consultations more publicly available and transparent, *TERA* has been experimenting with broadcasts of peer review and consultation meetings over the Internet using webcast technology. *TERA* webcast the latest Voluntary Children's Chemical Evaluation Program (VCCEP) meeting on xylenes held in December 2005, along with a peer consultation on approaches to derive database and toxicodynamic uncertainty factors to protect children's health. In November 2004, a peer input meeting on Health Canada's Complex Exposure Tool (ComET) was webcast, allowing participants to see and hear about the ComET model. Contact Ms. Jacqueline Patterson (Patterson@tera.org) for details.

Development of a Biomarker Decision Support System

TERA is conducting a study with National Institute for Occupational Safety and Health (NIOSH) to develop and demonstrate a system for integrating complex data from emerging technologies with traditional toxicity data, validating biomarkers using Bayesian networks and other graphical modeling techniques, and incorporating the biomarkers in occupational risk assessments, including exposure limit development. Biomarkers spanning the exposure-disease continuum are validated or rejected by analyzing the strength of the dependencies among exposure, the potential biomarkers, and disease. Traditional regression analysis approaches as well as Bayesian network methods are used to validate biomarkers and to analyze dose-biomarker-response relationships to define an effective dose for risk assessment. The approach is demonstrated using benzene as a case study, and preliminary results have been presented at a number of scientific meetings, including at an Society of Toxicology (SOT) sponsored workshop on use of probabilistic methods in risk assessment. Additional case studies are planned. Contact Mr. Eric Hack (Hack@tera.org) for details.

Children's Risk Issues

TERA scientists have developed two documents addressing broad issues related to children's risk. One document addresses the relative tissue dose in adults and children following inhalation exposures by presenting a framework for evaluating whether children would have a higher dose than adults for a given exposure scenario. The second document compiles data related to the database uncertainty factor, with particular attention to the size of the uncertainty factor needed to address the lack of reproductive or developmental toxicity studies. This document also evaluates application of the chemical-specific adjustment factors (CSAFs) concept to reproductive and developmental

toxicity. For details, see http://www.tera.org/peer/adultchildtk/actkwelcome.htm and http://www.tera.org/peer/UFD/UFDWelcome.htm

Summary of *TERA* Program Activities

Peer Consultations and Peer Reviews

TERA's Peer Consultation and Review Program provides sponsors with high quality independent, expert scientific review of risk assessment related documentation through panel meetings or other venues. *TERA* uses a transparent and public process for peer reviews and consultations to facilitate maximum sharing of information and credibility of conclusions. *TERA*'s role is to manage all aspects of the peer consultation or review, including independent selection of the panel, identification of conflict of interest and bias issues, development of the panel charge, conducting the meetings, all logistical and facility arrangements and preparation of meetings reports. We have provided this service to the risk assessment community since 1996, having organized and conducted over two dozen panel reviews and numerous paper reviews.

- VCCEP Peer Consultation on Xylenes - December 13-14, 2005
- Peer Consultation on the Scientific Rationale for Approaches to Derive Database and Toxicodynamic Uncertainty Factors to Protect Children's Health - September 19, 2005
- Peer Review of Methodology Document for the TCEQ - June 27-28, 2005 in Austin, Texas
- Framework for Use of Quantitative Structure Activity Relationships (QSAR) for Genotoxicity and Carcinogenicity
- Approach to Evaluate Adult-to-Child Toxicokinetic Differences - Peer Consultation, March 31, 2005 in Cincinnati, OH
- Evaluation of plans for dioxin bioavailability studies and use of results, for the state of Michigan

2005 Highlights

The cooperative agreement with the U.S. EPA to develop peer consultation concepts completed its fourth year on September 1. One peer consultation was held under the VCCEP Program in 2005 (xylenes in December). Two additional peer consultations in the area of children's risk assessment were held under this program in 2005. These were open to the public and attended by scientists from government, industry and other affiliations. The second meeting was webcast for those who could not attend. The first of the two children's risk peer consultations was held in March on an approach to compare the tissue dose in children and adults for a given exposure level, as part of an evaluation of the relative sensitivity of children and adults. *TERA* prepared materials and analyses that were discussed at the meeting by a panel of expert scientists who provided suggestions for improvement and further work. A second peer consultation on children's risk issues was held in September on the scientific rationale for selection of uncertainty factors to address issues associated with developmental, neonatal, child, or reproductive toxicity studies when deriving reference doses (RfDs). *TERA* prepared two data compilations to help frame this discussion.

A number of other peer reviews and consultations were organized in 2005 (see the text box).

TERA continued to develop improved procedures for peer consultations and reviews and shared this knowledge broadly. We evaluated the final Office of Management and Budget (OMB) Bulletin on peer review for the federal government and how its requirements differ from *TERA's* current procedures for selection of panels and identification of conflicts of interest (COI). We subsequently revised our COI policy and procedures on panel selection and COI to adopt the NAS definitions

and demonstrate consistency with OMB guidance. We presented posters on peer consultation and lessons learned from VCCEP at the joint DOD/EPA/ATSDR Risk Assessment meeting. We also presented a poster on comparing peer review, peer consultation and expert elicitation at the 2005 Society for Risk Analysis (SRA) Annual Meeting, along with a organizing a symposium on uses of peer consultation to improve children's risk. We submitted a manuscript on peer consultation and results from the VCCEP pilot to *Risk Analysis*. Findings from this paper were presented at the SOT meeting in March 2005 and SRA in December 2005.

TERA scientists have also provided review and comment on risk documentation for both government and private-sector sponsors. These included serving as expert peer reviewers for EPA Integrated Risk Information System (IRIS), provisional toxicity value (PPRTV) documents, and Board of Scientific Counselors Land Subcommittee program review; Minnesota's Health Risk Limits rule for 3M Corporation; and proposed Peer Review Procedures for FDA-CFSAN Food Safety Risk Assessments. We also assisted a number of government and private sponsors with reviews of the technical basis for chemical analyses, exposure assessments, and methodological approaches, including providing comments on the Israel Ministry of the Environment report on Chlorpyrifos for a pesticide industry sponsor.

International Toxicity Estimates for Risk (*ITER*) Database

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

ITER* Webstats

Average Users per Day
2005 - 240 users
2004 - 185 users

Average Length of Visit
2005 – 34 minutes
2004 – 31 minutes

Average Hits per Day
2005 – 2906 hits
2004 – 2407 hits

* Webstats account for users of the original *ITER* database and do not include users of *ITER* on TOXNET

During 2005, we made 149 updates or additions to chemicals in the *ITER* database. This expansion of *ITER* included the addition of data for nearly 60 chemicals from NSF International. This work also included adding or updating data from ATSDR, EPA, RIVM, and IARC. We also added data to the *ITER* column for resorcinol from a peer reviewed assessment developed by AMEC Earth and Environmental, Inc. on behalf of Beazer Inc. This assessment underwent peer review through *TERA's* program.

Research in Risk Assessment Methods

TERA's Research Program strives to move the science of risk assessment forward by improving the application of current methods, developing and defining new methods, obtaining the data to support such applications, and educating the scientific community and the general public about advances in risk assessment research. *TERA* scientists bring together a practitioner's knowledge of the issues and pitfalls involved in the day-to-day application of methods for developing risk values, along with expertise in cutting-edge risk assessment methods.

The research program works closely with our chemical assessment program in identifying and addressing key issues related to risk assessment methods. While many of the research projects have traditionally been on the border between methods development and application to risk assessment, we are increasing work on fundamental risk assessment methods issues. Areas of particular interest include improved incorporation of mechanistic data (including molecular toxicology data) in risk assessment, quantitative methods, and children's risk.

2005 Highlights

TERA continues to use our expertise in quantitative work and physiologically-based pharmacokinetic (PBPK) modeling, including *de novo* development of PBPK models. In a project sponsored by Syngenta in the U.K., we are collecting data and building models that will aid in predicting fetal dose from maternal exposure levels. Initial work involves collection of parameters and building a generic model, to be followed by development of models for case-study chemicals. In another modeling project, conducted for the Indiana Department of Environmental Management (IDEM), *TERA* used the harmonized trichloroethylene (TCE) PBPK model developed previously as part of a peer consultation to develop a slope factor for TCE, using a stratified regression approach to combine disparate mouse data sets. Results of this analysis were used as the basis of IDEM's draft rule for TCE.

As part of *TERA*'s work in fundamental risk assessment issues, current efforts are in the areas of children's risk, QSAR modeling, PBPK modeling, Bayesian analysis, and molecular toxicology. Progress in the areas of molecular toxicology, PBPK modeling, and Bayesian analysis were described above and in the overall *TERA* highlights sections. Other developments include an evaluation of current approaches for extrapolating from experimental animal data to develop an Immediately Dangerous to Life or Health Concentration (IDLH) for NIOSH. This included evaluation of how well a factor of 0.1 applied to the LC_{50} protects against lethality or other severe or escape-impairing effects in humans. Separate analyses were conducted for different modes of action and the results are being prepared as a manuscript. We also published two manuscripts on chlorpyrifos, one evaluating lower birth weight as a potential critical effect for chlorpyrifos exposure, in light of the available epidemiological and animal data, and a second manuscript reviewing issues in the dose-response assessment of chlorpyrifos. A significant part of the research program has continued to be the development of effectiveness and risk characterizations for nonlethal weapons, and the methods for doing so, based on data sets of varying quality.

Development of Chemical Risk Assessments

The Verifiable Estimates for Risk Assessment (*VERA*) program continues to provide our government and industry sponsors with a source of high quality risk assessments developed using state of the science approaches. *TERA* staff worked on over 20 separate assessment projects during 2005. The program has maintained a diverse portfolio of work, including in the development of comprehensive toxicological reviews, screening assessments, and occupational toxicology projects. Roughly two-thirds were for industry sponsors with the reminder mostly for government agencies.

2005 Highlights

TERA staff continued to be active in support of EPA risk assessment development. *TERA* developed a draft Toxicological Review document on decabromodiphenyl ether and conducted additional dose-response modeling for two additional related chemicals under contract to the EPA Office of Water. Also for the Office of Water, *TERA* we provide support for the development of provisional RfDs for developmental and reproductive toxicity endpoints and for revisions of several other IRIS assessments. For EPA's National Homeland Security Research Center, we developed a database of dose-response information to support the development of new QSAR models, and provided support for development of provisional advisory limits.

TERA conducted a number of projects in 2005 that demonstrated our technical leadership in risk assessment development. In work for a private sponsors, *TERA* has conducted benchmark dose and categorical regression modeling to evaluate the human health effects of acute exposures to inorganic borates for deriving an occupational exposure limit, for vapor exposures to chloropicrin from its agricultural use in support of NIOSH Immediately Dangerous to Life or Health Value derivation, and for deriving occupational exposure limits for active pharmaceutical ingredients.

We also continue to share our experience and knowledge by training others in risk assessment methods and techniques. *TERA* received a contract from EPA to enhance their Benchmark Dose (BMD) Software, presented training on this software with EPA staff at the 2005 SRA meeting, and has received additional funding to further develop models and to develop training modules for EPA's BMD software and categorical regression software in 2006. *TERA* collaborated with EPA and Health Canada on the development and delivery at the 2005 SRA meeting of a course on the IPCS approach for chemical-specific adjustment factors (CSAFs). *TERA* is also expanding its training to state and local risk assessors, in work that both establishes the organization as a technical leader and supports our mission by helping to raise the general quality of toxicological risk assessment. *TERA* has received funding from the State of Indiana to present both basic and advanced risk assessment methods training at the MidWest Risk Assessment Symposium, and will be providing training in 2006 to the technical staff of the Texas Commission for Environmental Quality, as a follow-up to an earlier round of training provided to this group in 2004.

Public Service

TERA staff continued to dedicate significant effort supporting scientific development through *pro bono* activities and our *TERA* Developmental Reserve funds. Examples of *pro bono* efforts of the staff included, but were not limited to:

- *TERA* staff provided support in response to requests under our StateHELP Program and in response to requests from the general public. For example, *TERA* assisted the city of Memphis with a local risk assessment issue and provided support to the State of Indiana on TCE risk assessment issues.
- Served as peer reviewers of submitted manuscripts for journals including, *Regulatory Toxicology* and *Pharmacology*, *Human* and *Experimental Toxicology*, *Critical Reviews* in *Toxicology, Journal* of *Toxicology* and *Environmental Health*, and the *Journal* of *Children's Health*. Staff also served on editorial boards for several of these journals.
- Numerous articles written for the *Encyclopedia of Toxicology*.
- Presentations at national meetings, such as the Society of Toxicology Annual Meeting, Society for Risk Analysis Annual Meeting and the Toxicology and Risk Assessment Conference, as well as at several other regional or topical meetings;
- Served on numerous scientific committees, including: NAS subcommittees on Chemical Warfare Agents and on "Ethical Issues in Housing-Related Health Hazard Research Involving Children," AIHA Workplace Environmental Exposure Levels (WEEL) Committee, NSF International External Peer Review committee, and the Underwriters Laboratory External Peer Review committee.
- *TERA* staff members are officers in the Society for Risk Analysis Ohio Chapter, as well as the Risk Assessment Specialty Section (RASS) of SOT.

***TERA* Publications and Reports**

TERA is dedicated to sharing the results of our work widely. We published and prepared a number of papers in 2005 for journals as well as reports on numerous projects. Copies of many of these are available on our website at http://www.tera.org/pubs/welcome.htm .

DOLAN, D., B. NAUMAN, E. SARGENT, **A. MAIER**, and **M. DOURSON**. 2005. Application of the threshold of toxicological concern concept to pharmaceutical manufacturing operations. Reg. Toxicol.Pharmacol. 43: 1-9.

HABER, L.T. and **J. PATTERSON**. 2005. Report of an independent peer review of an acrylonitrile risk assessment. Human & Exp. Tox. 24(10): 487-527.

HACK, E. 2005. Bayesian analysis of physiologically-based toxicokinetic and toxicodynamic models. Toxicology. 221: 241-248.

MAIER, A., B. GADAGBUI, E. HACK, Q. ZHAO, A. PARKER, A. WEINRICH, and C. GERACI. 2005. Use of animal acute toxicity data to derive immediately dangerous to life or health concentrations: Extrapolating to human effect thresholds. In preparation.

MAIER, A., P. NANCE, P. PRICE, C. SHERRY, J.P. REILLY, G.J. KLAUENBERG AND J.T. DRUMMOND. 2005. Human effectiveness and risk characterization of the electromuscular incapacitation device – A limited analysis of the TASER (Public Version). U.S. Air Force Research Lab/Human Effects Center of Excellence. Submitted to Advanced Information Engineering Services.

MAIER, A. and **L.T. HABER**. 2005. Toward the goal of harmonizing occupational exposure limits: Approaches for enhancing derivation methods. In preparation.

MAIER, A., E. HACK, Q. ZHAO, L.T. HABER and **M.L. DOURSON**. 2005. Derivation of an occupational exposure limit for inorganic borates using a weight of evidence approach. In preparation.

NANCE, P., M. DOURSON, J. PATTERSON, P. PRICE AND B.J. KLAUENBERG. 2005. The non-lethal weapons human effectiveness & risk characterization (HERC) framework. NATO Advanced Research Workshop, ASRW 980724, Prague, October. In press.

SCHOENY, R., **L. HABER** and **M. DOURSON**. 2005. Data considerations for regulation of water contaminants. Toxicology. 221 (2-3): 217-224.

STRAWSON, J., **M.L. DOURSON** and **Q.J. ZHAO**. 2005. The NAS perchlorate review: Is the RfD acceptable? Env. Health Perspect 113(11):A729-30; Nov. Author reply A730-2.

WILLIAMS, P., **D. BRIGGS**, and **J. PATTERSON**. 2006. VCCEP Pilot: Progress on Evaluating Children's Risks and Data Needs. Risk Anal. In press.

ZHAO, Q., B. GADAGBUI, and **M. DOURSON**. 2005. Lower birth weight as a critical effect of Chlorpyrifos: A comparison of human and animal data. Reg. Toxicol. Pharmacol. 42: 55-63

Other *TERA* Reports

Use of Benchmark Concentration Modeling and Categorical Regression to Evaluate the Effects of Acute Exposure to Chloropicrin Vapor – August, 2005.

VCCEP Peer Consultation on Xylenes - December 13-14, 2005

Peer Consultation on the Scientific Rationale for Approaches to Derive Database and Toxicodynamic Uncertainty Factors to Protect Children's Health - September 19, 2005

Peer Review of Methodology Document for the TCEQ - June 27-28, 2005

Framework for Use of Quantitative Structure Activity Relationships (QSAR) for Genotoxicity and Carcinogenicity

Approach to Evaluate Adult-to-Child Toxicokinetic Differences - Peer Consultation, March 31, 2005.

Financial Report

TERA's 2005 income was $1,804,971 and actual expenses totaled $1,802,038. This resulted in net income of $2,933.

TERA conducts work for both public and private sector sponsors. In 2005 *TERA* conducted a large percentage of work for government agencies and other non-profits (82%). 18% percent of our work was for private sector sponsors. While 2005 was heavy on government, this ratio varies from year to year dependent upon the needs of sponsors and other conditions. Over the ten years of *TERA's* operations, we have devoted a yearly average of 62.8% percent to government work and 37.2% to private sector (see Figure 1 below for details).

Percentage of Profit and Nonprofit Work for Billed Hours and Percent of Probono Effort for Total Hours

	1995	1996	1997	1998	1999	2000	2001	2002	2003	2004
Nonprofit Billable	67%	37%	55%	63%	66%	59%	48%	72%	79%	82%
Profit Billable	33%	63%	45%	37%	34%	41%	52%	28%	21%	18%
ProBono	7%	12%	7%	5%	5%	7%	5%	4%	7%	7%

Figure 1. Percentage of Profit and Nonprofit Work for Billed hours.
The percent of Total Hours that are Probono is also shown.

TERA's Board of Trustees and Officers

TERA's Board of Trustees consists of up to 10 members who serve 3-year rotating terms. Listed below are *TERA's* Board members for 2005. New members began their three year terms 1/1/2005. The date in parenthesis indicates the year each member completes their current term on *TERA's* Board of Trustees.

Board of Trustees - 2005

Michael Dourson (permanent member)
Steven Lewis (2006) Chair
Roger O. McClellan (2007), Past Chair
Joyce Martin (2005)
Jennifer Orme-Zavaleta (2006)
Jerry Rice (2006)
Chad B. Sandusky (2007), Treasurer
James D. Wilson (2007)

On April 10, 2005, the Board of Trustees met for a retreat with *TERA* staff, followed by its annual meeting on April 11, 2005, to discuss the 2004 Annual Report and the plans and budget for 2005. Both the retreat and the annual meeting were held in Cincinnati, Ohio. The Board held its midyear conference call meeting on October 19, 2005. This meeting was held in Cincinnati, Ohio.

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

Jim Wilson, Chair of the Board of Trustees (also re-elected for two-year board term)
Roger McClellan, Emeritus Chair of the Board of Trustees (also re-elected for two-year board term)
Chad Sandusky, Chair of the Board Finance Committee (also re-elected for two-year board term)
Michael Dourson, Corporate President (one-year term)
Jacqueline Patterson, Corporate Vice President and Secretary (one-year term)
Lynne Haber, Corporate Treasurer (one-year term)

The Board unanimously approved the following new trustees for terms beginning January 1, 2006.

Michael Fremont
Sam Kacew
Randy Manning
Sue Ross