

## RESUME

Raymond S. H. Yang  
Department of Environmental and Radiological  
Health Sciences  
Colorado State University  
1680 Campus Delivery  
Fort Collins, CO 80523-1680  
Tel. 970-491-5652  
Fax. 970-491-7569  
E-mail: raymond.yang@colostate.edu

420 Apple Blossom Lane  
Fort Collins, CO 80526  
Tel. 970-226-0294

**EDUCATION:** Cornell University, Postdoctoral Training in Environmental Toxicology  
1970 - 1973

North Carolina State University, Ph.D. (1970), M.S. (1967) -  
Toxicology, Entomology

National Taiwan University, B.S. (1963) - Biology

### EMPLOYMENT RECORD:

**Department of Environmental and Radiological Health Sciences  
College of Veterinary Medicine and  
Biomedical Sciences  
Colorado State University  
Fort Collins, CO 80523-1690**

7/1990 - Present Professor of Toxicology and Cancer Biology  
5/1991 - 12/2004 Director, Center for Environmental Toxicology and Technology  
7/1990 - 6/1995 Head, Department of Environmental Health, College of Veterinary  
Medicine and Biomedical Sciences, Colorado State University  
4/1992 - 12/2000 Program Director and Principal Investigator, Program Project on  
"Integrated Research on Hazardous Waste Chemical Mixtures," (P42  
ES05949) NIEHS Superfund Basic Research Program  
7/1999 - 6/2006 Program Director and Principal Investigator, NIEHS Toxicology Training  
Program (1 T32 ES07321, Quantitative Toxicology and Physiologically  
Based Pharmacokinetic/Pharmacodynamic Modeling)  
7/2006 - 6/2007 Visiting Professor, National Health Research Institutes, Zhunan, Taiwan,  
Republic of China

### Responsibilities and Achievements:

- 1) Professor of Toxicology, Department of Environmental Health;

Director, Center for Environmental Toxicology and Technology;  
Program Director and Principal Investigator, NIEHS Superfund Basic Research Program  
Program Director and Principal Investigator, NIEHS Toxicology Training Program

- \* Established and developed the Center for Environmental Toxicology (CET) in 1991. In the same year, CET was recognized, following university-wide competition, to be an Emerging Center of Research and Scholarly Excellence. In 1995, CET was changed to Center for Environmental Toxicology and Technology (CETT) to allow more participation of colleagues from engineering and other technology based scientific disciplines. Between 1995 and 2003, CETT was identified by the University to be one of the 14 Programs of Research and Scholarly Excellence. I served as the Director of this Center between 1991 and 2004.
- \* Created and built, from ground up, a research and training program on Quantitative and Computational Toxicology -- an interdisciplinary program integrating toxicology and other biomedical sciences with chemical engineering, mathematical/statistical and computer modeling. The central theme of this Program is the application of physiologically based pharmacokinetic/pharmacodynamic (PBPK/PD) modeling, biologically based dose response modeling, and reaction network modeling to pharmacology and toxicology. This computer simulation development has been primarily for the support of our research projects on toxicological interactions of chemical mixtures and multiple stressors. In recent years, these research activities have integrated progressively more functional genomics, proteomics, and metabolomics. I am particularly interested in linking PBPK modeling with biochemical reaction network modeling to simulate the interwoven pharmacokinetics and pharmacodynamics of multiple drug interactions such that the complex biochemical and toxicological processes can be modeled and predicted, by computer, from whole body all the way down to the molecular interaction level. Our research group, Quantitative and Computational Toxicology Group, has consisted of about 10-25 people including 4-8 participating faculty members; the areas of expertise include toxicology, pathology, molecular biology, chemistry, engineering, mathematics, and computer science. Annual research and training grants/contract funding (direct and indirect) is approximately \$0.3 to 1 million.
- \* Created and developed a multidisciplinary team of scientists from 7 academic departments in 3 colleges plus collaborative scientists from outside of Colorado State University. This team competed successfully in 1992 (for a 3-year Program Project totaling \$2.3 million) and again in 1995 (for a 5-year Program Project totaling \$5.8 million) for the NIEHS Superfund Basic Research Program.
- \* Created, developed, and held six International Workshops on Physiologically Based Pharmacokinetic/Pharmacodynamic (PBPK/PD) Modeling and Risk Assessment in 1992, 1994, 1996, 1999, 2001, 2003 at Colorado State University - an intensive hands-on training for two to three weeks in summer and a continuing program. Over 240 international scientists from more than 10 countries were trained in these Workshops. In July 2005, created and held a

PBPK Modeling Workshop for Beginners, a one-week course. Twelve international scientists participated. A shorter version (4-Day Workshop) has been taken on the road to CalEPA, Oakland, CA and Pfizer Inc., Groton, CT. Between August and November 2006, a Beginner's PBPK Workshop was held at the National Health Research Institutes, Zhunan, Taiwan, Republic of China (one afternoon per week for 10 weeks); there were 35 participants. Plans are underway for Dr. Yang to teach this Beginner's PBPK Workshop at USEPA National Center for Environmental Assessment (NCEA) in Cincinnati in the fall of 2007, and at CalEPA Office of Environmental Health Hazard Assessment (OEHHA) early 2008.

- \* Mentored six special appointment assistant professors, one visiting assistant professor, one new tenured track assistant professor and one new full professor; trained 17 postdoctoral and 8 Ph.D. students in toxicology, 1 Ph.D. in chemical engineering (as co-advisor for thesis), 5 M.S. students in toxicology, and 3 M.S. students in chemical engineering (as co-advisor for thesis). Mentor and Sponsor for six successful K-series Career Developmental Awards (1 Temin Award, 2 K08 and 3 K25) from the NIH.
- \* Organized and taught a graduate course in EH648 Environmental Health Risk Assessment. Participated in teaching of eight graduate and undergraduate courses.
- \* Edited and published two books on *Toxicology of Chemical Mixtures. Case Studies, Mechanisms, and Novel Approaches* (Academic Press, 1994), sole Editor, and *Physiologically Based Pharmacokinetics: Science and Applications* (Wiley, 2005) under the joint editorship with Drs. Micaela Reddy, Melvin E. Andersen, and Mr. Harvey Clewell, III. Adding many peer-reviewed publications to a total of over 130 papers.
- \* Many invitational speeches at national and international conferences. Served on many international, national, and regional professional committees and expert panels including USEPA Science Advisory Board/Panel (Consultant, Member), NIEHS Study Section (Environmental Health Sciences Review Committee) on Center Grants and Training Grants, NCI Innovative Toxicology Study Section, Board of Scientific Counselors of ATSDR and CDC/NCEH, and appointment by Governor Romer to serve on Science Advisory Board for Colorado Air Quality Control Commission.
- \* Created, developed, and co-hosted two international conferences on *Current Issues on Chemical Mixtures* and *Application of Technology to Chemical Mixture Research* with the National Institute of Environmental Health Sciences (NIEHS) at Colorado State University, 11-13 August 1997 and 09-11 January 2001, respectively.
- \* Developed successfully with Dr. Julie Campain and other collaborating scientists a Toxicology Training Grant (Institutional National Research Service Award 1 T32 ES07321, Quantitative Toxicology and Physiologically Based Pharmacokinetic/ Pharmacodynamic Modeling; \$1.14 million for five years)

which was awarded by NIEHS in July 1999.

2) Department Head (1990-1995)

Served as the chief administrator for a department of 18 faculty members, about 50 graduate and 160 undergraduate students, 30 to 40 staff members (as of March 1995). The department had a budget of about \$4 million/year of which approximately \$3 million/year is from extramural research grants/contracts.

- \* Turned around and revitalize a department in about three years. A partial indication is the 13.5-fold increase (from \$33,376 in 1990 to \$450,009 in 1993) in "indirect cost recovery" to help the departmental budget.
- \* Led by example and stimulated remarkable growth in extramurally funded research program. Built a quality Environmental Toxicology program from ground up.
- \* Effectively utilized very dedicated teachers and created an infrastructure to strengthen undergraduate and graduate education. Created nurturing and caring atmosphere for students, particularly the undergraduate students. Partially due to this effort, the undergraduate student club, Environmental Health Student Association, organized, on their own, a world-class Scientific Symposium on Hantavirus in 1994 with participation of over 300 national and international scientists.
- \* Improved morale of faculty, staff, and students by implementing effective communication.

**National Health Research Institute  
Division of Environmental Health and Occupational Medicine  
Zhunan Town, Miaoli 350  
Taiwan  
Republic of China**

7/2006 – 6/2007 Visiting Professor (Sponsored and financed by the National Science Council, Executive Yuan, Taiwan, Republic of China, and Colorado State University)

**National Institute of Environmental Health Sciences  
National Toxicology Program  
P. O. Box 12233  
Research Triangle Park, NC 27709**

1983 - 1990 Chemical Manager/Senior Staff Member  
1983 - 1986 Superfund Research Project Director  
1983 - 1990 Principal Investigator, Toxicology of Chemical Mixtures

1984 - 1988 Project Officer of Brookhaven National Laboratory  
1987 - 1990 Principal Investigator, Physiologically Based Pharmacokinetics  
1988 - 1990 Adjunct Professor of Toxicology  
Department of Anatomy, Physiological Sciences and Radiology  
College of Veterinary Medicine  
North Carolina State University  
Raleigh, NC 27606  
Toxicology Program  
North Carolina State University  
Raleigh, NC 27695-7633

Responsibilities and Achievements:

1) Chemical Manager

Served as a central resource of expertise regarding the toxicology of the specified compounds or groups of compounds assigned; and was responsible for the overall toxicological characterization performed under the auspices of the National Toxicology Program. Specific duties included: characterize biological-toxicological effects from acute, subchronic, and chronic exposure to specifically assigned chemicals; planed and provided scientific oversight in the conduct of laboratory studies; evaluated and published results; involvement in the competitive bidding process; evaluated proposals; participated in the contract award process.

2) Superfund Research Project Director

Served as the Project Director of a special multi-million dollar/year "Superfund Project" which was an interagency agreement between the Agency for Toxic Substances and Disease Registry and the National Toxicology Program. Under this Project, the NTP conducted toxicology testing on chemicals that were identified in priority hazardous waste sites or otherwise released into the environment for which adequate toxicology data were not available. Specific duties included: design and implemented toxicological studies to fill in the data gaps for the individual chemicals in this Project; designed and implemented the testing of the toxicology of chemical mixtures as well as toxicological interaction studies; coordinated the effort of other participating scientists; interacted with administrative, budgetary and contract personnel.

3) Project Officer of Brookhaven National Laboratory

Served as the representative of the National Toxicology Program to oversee several Interagency Agreements on the study of inhalation toxicology of various chemicals at the Inhalation Toxicology Facility, Brookhaven National Laboratory. Duties included: reviewed the progress of ongoing inhalation toxicology studies regarding both scientific issues and contract matters to ensure compliance with the work scope, budgets and milestones; provided scientific input and guidance to achieve the goals of the National Toxicology Program; initiated through Contracting Officer appropriate modifications to the contract to meet specified objectives; approved vouchers from the contractor; assured timely delivery of reports from contractor and resolved any technical problems; made

regular site visits and program reviews to assure quality of work.

- 4) Principal Investigator on "Toxicological Studies of Chemical Mixtures of Environmental Concern at the National Toxicology Program"

Projects completed on a 25-chemical mixture simulating groundwater contaminants included: (1) Chemistry Development; (2) Subchronic Toxicity; (3) Immunotoxicology; (4) Biochemical Toxicology; (5) Developmental and Reproductive Toxicology; (6) Genetic Toxicology; (7) Myelotoxicology; (8) Neurobehavioral Toxicology; (9) Hepatotoxicity and Nephrotoxicity; (10) Pharmacokinetics. Approximately 30 studies of varying sizes and durations were completed on this mixture. The co-investigators involved in these collaborative studies came from all over the NIEHS as well as from neighboring EPA/HERL and Research Triangle Institute (RTI). Over twenty papers were published.

Three pesticide/nitrate mixtures representing groundwater contamination in different regions of the Nation were studied toxicologically.

- 5) Principal Investigator of a NTP-Program wide special initiative on Physiologically Based Pharmacokinetics/Computer Modeling and as a "Discipline Expert" on pharmacokinetics on a special NIEHS/NTP program-wide project on methylene chloride.

Setting-up the computer hardware and software, arranging two round-table discussions at the NIEHS with experts in the field, identification and organization of key personnel and resources for this effort, and realization of the experimental and modeling capability. The establishment of the capability of PBPK/computer modeling had proceeded under interbranch support, in parallel with the development and conduct of our methylene chloride pharmacokinetic studies. This included the design and investigation of pharmacokinetic changes in relation to age and chronic dosing of methylene chloride in mice at five time points (1 day, 1, 12, 19 and 24 months postexposure) along the methylene chloride chronic toxicology study.

- 6) Adjunct Professor of Toxicology Program, North Carolina State University. Participated in the teaching of a graduate level toxicology course since 1984.
- 7) Served as a Group Leader and Facilitator on the Committee for Optimal Designs for Conducting Toxicity Studies

This was an NTP-wide planning effort for the future development of the NTP.

**Bushy Run Research Center  
Mellon Institute - Union Carbide Corporation  
R.D. 4, Mellon Road  
Export, Pennsylvania 15632**

1978 - 1983 Manager, Biochemical Toxicology Department  
1978 - 1978 Fellow  
1977 - 1978 Senior Scientist

1976 - 1977 Junior Fellow

1978 - 1983 Adjunct Associate Professor of Toxicology  
Department of Pharmacology and Toxicology  
School of Pharmacy  
University of Pittsburgh  
Pittsburgh, Pennsylvania 15261

Responsibilities and Achievements:

- 1) Program Manager and Study Director of a multi-million dollar comprehensive toxicology program of an industrial chemical.

Sponsors of this program were multi-national corporations (Union Carbide Corp., Dow Chemical USA, Texaco Chemical Co.). The program consisted of approximately 15 projects which included range finding, subchronic studies, combined chronic toxicity/oncogenicity studies, 2-generation reproduction, dominant lethal, teratology studies, dermal carcinogenicity study, pharmacokinetics/metabolism, analytical developmental studies, short-term mutagenicity testings. Scientific and administrative effort included coordination, interaction with and/or supervision of professionals (toxicologists, pathologists, chemists, accountant, administrative personnel, etc.) within our research center and many colleagues of various background and status externally.

- 2) Manager of Biochemical Toxicology Department.

Overall administrative and supervisory functions of the departmental affairs involving 4-7 professionals. Directing and overseeing all scientific projects in the area of biochemical toxicology. Establishment and development of a pharmacokinetics program and a skill center for dermal pharmacokinetics and metabolism studies on foreign compounds.

- 3) Chairman of Toxicology Training Committee.

Development of collaborative, joint, educational programs with local educational institutions (Carnegie-Mellon University, University of Pittsburgh). Participated as a faculty member in the training of graduate and undergraduate students.

- 4) Interaction with governmental agencies and trade associations in an advisory capacity.

**Institute of Comparative and Human Toxicology  
Albany Medical College  
Albany, New York**

1975 - 1976 Assistant Professor

1973 - 1975 Research Associate

Responsibilities and Achievements:

Directed a research program on the Biochemical Toxicology of Hexachlorobenzene.

Participated as a faculty member in a research program grant on the Interaction of Environmental Chemicals. Participated as a faculty member in a Toxicology Training Program for pre- and postdoctoral students. Consultants to EPA on hexachlorobenzene toxicology.

**Cornell University  
Ithaca, New York**

1970 - 1973 Postdoctoral Fellow

**Responsibilities and Achievements:**

Conducted research on the Role of Conjugating Enzymes in Foreign Compound Metabolism. Participated in the teaching of a course in Insecticide Chemistry.

**PROFESSIONAL SOCIETIES:**

Society of Toxicology  
American Association of Chinese in Toxicology  
Society of Sigma Xi  
Society of Phi Sigma

**BOARD CERTIFICATION:**

Fellow, The Academy of Toxicological Sciences (July 2006)

**EDITORIAL BOARDS:**

Fundamental and Applied Toxicology (1988 - 1994)  
Reviews of Environmental Contamination and Toxicology (Feb. 1989 – Jun.2007)  
International Journal of Toxicology (Mar. 1997 - 1999)  
Human and Ecological Risk Assessment (Sept. 2000 – Oct. 2006)

**SIGNIFICANT COMMITTEE WORK:**

1986. Member on the Program Review Team for the Complex Chemical Mixtures Research Program under Department of Energy (DOE)'s sponsorship at the Argonne National Laboratory, Oak Ridge National Laboratory, Battelle Pacific Northwest Laboratory, and Lovelace Inhalation Toxicology Research Institute. Work involved on-site visits, evaluation of presentations, Field Task Proposals, publications, credentials of principal investigators, and other supporting documents of over 35 projects.

1987-1988. Member of Safe Drinking Water Subcommittee on Mixtures, National Research Council/National Academy of Sciences. Work involved the development of an

approach for risk assessment of multiple chemical exposure in drinking water.

- 1988-1990. Member of Toxicology Advisory Panel, City of Denver Water Department. Work involved research direction, experimental design, and evaluation of proposals on the Comprehensive Health Effects Testing Program on the potable water reclaimed from the treatment of secondary sewage by the Potable Water Reuse Demonstration Plant.
- 1988. Invited member of a Workshop on the Toxicology of Complex Mixtures held by the Electric Power Research Institute (EPRI) and served on an "Innovative Working Group" to define research directions on complex mixture related to the coal tar and other wastes relative to "town gas sites" at various manufactured gas plant sites.
- 1989. Member of an Advisory Panel to Office of Health and Environmental Assessment and Office of Research and Development, USEPA, on their effort to revise the Guidelines for Risk Assessment of Chemical Mixture and determining research needs and priorities.
- 1989-1995. Member of a Scientific Advisory Panel to EPRI's complex mixture toxicology program related to the "town gas site" at manufactured gas plant sites.
- 1990. Invited member of a Workshop on Carcinogenic Mixtures by the National Research Council/National Academy of Sciences to provide current information and guidance to the Department of Defense on their hazardous waste problems.
- 1990. Invited member of a Workshop by the USEPA to formulate guidelines for pharmacokinetic studies related to toxicology testing and studies.
- 1990. Member of an Expert Panel to the USEPA/ECAO on the planning of research and development directions.
- 1991. Member of Expert Panels to the USEPA/ECAO on two Workshops on "Weight of Evidence Approach" and "Structural Activity Relationship (SAR) Approach" toward risk assessment of chemical mixtures.
- 1992-1998. Air Quality Science Advisory Board, State of Colorado.
- 1993. Expert Toxicologist and Scientific Advisor to the Water Quality Control Commission, State of Colorado, on rule-making proceedings for diisopropyl methylphosphate (DIMP).
- 1994-1999. Steering Committee Member, Decision Support Methodologies for Human Risk Assessment of Toxic Substances, ATSDR, DHHS.
- 1995-1996. Member of Committee on Interactions of Drugs, Biologics, and Chemicals in Deployed U. S. Military Forces, Institute of Medicine, National Academy of Sciences.

- 1996-1997. Expert Panel Member, Risk Assessment for Mixtures of Drinking Water Disinfection-Byproducts, International Life Sciences Institute/USEPA, Washington, DC.
- 1997- 1998. Screening and Testing Work Group of the Endocrine Disruptor Screening and Testing Advisory Committee, USEPA, Washington, DC.
- 1998- 1999. Commissioned author on Health Risks and Preventive Research Strategy for Deployed U.S. Forces from Toxicologic Interactions Among Potentially Harmful Agents, National Research Council, National Academy of Sciences.
- 1999-2001. Expert Panel Member, Peer Review Process for the Fox River Human and Ecological Risk Assessment, Association for the Environmental Health of Soils, Amherst, MA.
2000. Invited Chair for a Chemical Mixture Workshop, ATSDR, DHHS.
2000. Expert Panel member for Chemical Mixtures, Health Council of the Netherlands.
- 2001-2002. Society of Toxicology Expert Panel on Chemical mixtures.
- 2001-Present. Chemical Mixture Committee member to National Occupational Research Agenda, NIOSH.
- 2001-2005. Environmental Health Sciences Review Committee (Study Section for Center Grants, and Training Grants), NIEHS, NIH, DHHS.
- 2002-2003. USEPA Science Advisory Board, Member (Consultant), for reviewing TCE Health Risk Assessment: Synthesis and Characterization.
- 2003-2005. External Advisory Panel, Centers of Biomedical Research Excellence (COBRE), Mississippi State University.
- 2003-2004. Study Section on Innovative Toxicology, NCI, NIH, DHHS.
- Oct. 2003. External Advisory Panel for a Comprehensive Review of the Department of Environmental and Molecular Toxicology, North Carolina State University
- 2003-2004. USEPA Federal Insecticide, Fungicide, and Rodenticide Act (FIFRA) Science Advisory Panel Member, for reviewing PBPK Modeling Application in Cumulative Risk Assessment of *n*-Methyl Carbamate Pesticide.
- 2004-present. Pacific Northwest National Laboratory Environmental Technology Directorate Review Committee

- 2004-2007. Board of Scientific Counselors, Agency for Toxic Substances and Disease Registry (ATSDR) and National Center for Environmental Health (NCEH), CDC, DHHS
- 2005-2006. Member of Committee on Human Biomonitoring for Environmental Toxins, National Research Council, National Academy of Sciences.
- 2005-2006. ILSI Health and Environmental Sciences Institute (HESI) Technical Committee on Risk Assessment Methodologies Mixture Evaluation Project Steering Team
2006. International Workshop Panel Member on Mixture Toxicity, Society of Environmental Toxicology and Chemistry (SETAC)/NoMiracle (European Union)

#### PUBLICATIONS:

1. Meksongsee, B., Yang, R. S. H., and Guthrie, F. E. 1967. Effect of Inhibitors and Inducers of Microsomal Enzymes on the Toxicity of Carbamate Insecticides to Mice and Insects. *J. Econ. Ent.* 60:1469-1471.
2. Yang, R. S. H. and Kare, M. R. 1968. Taste Response of a Bird to Constituents of Arthropod Defensive Secretions. *Ann. Ent. Soc. Amer.* 61:781-782.
3. Yang, R. S. H. and Guthrie, F. E. 1969. Physiological Responses of Insects to Nicotine. *Ann. Ent. Soc. Amer.* 62:141-146.
4. Yang, R. S. H., Dauterman, W. C., and Hodgson, E. 1969. Enzymatic Degradation of Diazinon by Rat Liver Microsomes. *Life Sci.* 8:667-672.
5. Folsom, M. D., Hansen, L. G., Philpot, R. M., Yang, R. S. H., Dauterman, W. C., and Hodgson, E. 1970. Biochemical Characteristics of Microsomal Preparations from Diazinon-Resistant and -Susceptible Houseflies. *Life Sci.* 9:869-875.
6. Yang, R. S. H., Hodgson, E., and Dauterman, W. C. 1971. Metabolism in vitro of Diazinon and Diazoxon in Rat Liver. *J. Agr. Food Chem.* 19:10-13.
7. Yang, R. S. H., Hodgson, E., and Dauterman, W. C. 1971. Metabolism in vitro of Diazinon and Diazoxon in Susceptible and Resistant Houseflies. *J. Agr. Food Chem.* 19:14-19.
8. Yang, R. S. H. and Wilkinson, C. F. 1971. Conjugation of p-Nitrophenol with Sulfate in Larvae of the Southern Armyworm (*Prodenia eridania*). *Pesticide Biochem. Physiol.* 1:327-339.
9. Yang, R. S. H. and Wilkinson, C. F. 1972. Enzymic Sulphation of p-Nitrophenol and Steroids by Larval Gut Tissues of the Southern Armyworm (*Prodenia eridania*) Cramer). *Biochem. J.* 130:487-493.

10. Yang, R. S. H. and Wilkinson, C. F. 1973. Sulphotransferases and Phosphotransferases in Insects. *Comp. Biochem. Physiol.* 46B:717-726.
11. Yang, R. S. H., Pelliccia, J. G., and Wilkinson, C. F. 1973. Age-Dependent Arylsulphatase and Sulphotransferase Activities in the Southern Armyworm -- A Possible Insect Endocrine Regulatory Mechanism? *Biochem. J.* 136:817-820.
12. Gil, D. L., Rose, H. L., Yang, R. S. H., Young, R. G., and Wilkinson, C. F. 1974. Enzyme Induction by Phenobarbital in the Madagascar Cockroach, *Grophadorhina portentosa*. *Comp. Biochem. Physiol.* 47B:657-662.
13. Yang, R. S. H., Coulston, F., and Golberg, L. 1975. Binding of Hexachlorobenzene to Erythrocytes: Species Variation. *Life Sci.* 17:545-549.
14. Yang, R. S. H., Coulston, F., and Golberg, L. 1975. Chromatographic Methods for the Analysis of Hexachlorobenzene and Possible Metabolites in Monkey Fecal Samples. *J. Assoc. Off. Anal. Chem.* 58:1197-1201.
15. Yang, R. S. H. Enzymatic Conjugation and Insecticide Metabolism, in "*Insecticide Biochemistry and Physiology*," Edited by C. F. Wilkinson, Plenum Publishing Corporation, New York, New York, pp. 177-225, 1976.
16. Yang, R. S. H., Grace, H. K., Golberg, L., Coulston, F., and Mueller, W. G. 1976. Hexachlorobenzene Contamination in Laboratory Monkey Chow. *J. Agr. Food Chem.* 24:563-565.
17. Rourke, D. R., Mueller, W. F., and Yang, R. S. H. 1977. Hexachlorobenzene Contamination in Laboratory Nalgene Wash Bottles. *J. Assoc. Off. Anal. Chem.* 60:233-235.
18. Yang, R. S. H., Pittman, K. A., Rourke, D. R., and Stein, V. B. 1978. Pharmacokinetics and Metabolism of Hexachlorobenzene in the Rat and the Rhesus Monkey. *J. Agr. Food Chem.* 26:1076-1083.
19. Yang, R. S. H. and Tallant, M. J. 1982. Metabolism and Pharmacokinetics of Ethylenediamine in the Rats Following Oral, Endotracheal or Intravenous Administration. *Fundam. Appl. Toxicol.* 2:252-260.
20. Yang, R. S. H., Garman, R. H., Maronpot, R. R., McKelvey, J. H., Weil, C. S., and Woodside, M. D. 1983. Acute and Subchronic Toxicity of Ethylenediamine in Laboratory Animals. *Fundam. Appl. Toxicol.* 3:512-520.
21. Slesinski, R. S., Guzzie, P. J., Hengler, W. C., Watanabe, P. G., Woodside, M. D., and Yang, R. S. H. 1983. Assessment of Genotoxic Potential of Ethylenediamine: In Vitro and In Vivo Studies. *Mutation Res.* 124:299-314.

22. Chu, S. C., Tallant, M. J., and Yang, R. S. H. 1983. Quantitative Determination of Ethylenediamine in a Laboratory Rodent Diet by High-Performance Liquid Chromatography. *J. Chromatogr.* 280:394-399.
23. Yang, R. S. H., Garman, R. H., Weaver, E. V., and Woodside, M. D. 1984. Two Generation Reproduction Study of Ethylenediamine in Fischer 344 Rats. *Fundam. Appl. Toxicol.* 4:539-546.
24. DePass, L. R., Fowler, E. H., and Yang, R. S. H. 1984. Dermal Carcinogenicity Studies on Ethylenediamine (EDA) in Male C3H Mice. *Fundam. Appl. Toxicol.* 4:641-645.
25. Yang, R. S. H., Tallant, M. J., and McKelvey, J. A. 1984. Age-Dependent Pharmacokinetic Changes of Ethylenediamine in Fischer 344 Rats Parallel to a Two-Year Chronic Toxicity Study. *Fundam. Appl. Toxicol.* 4:663-670.
26. Yang, R. S. H. 1986. 1,3-Dichloropropene. *Residue Rev.* 97:19-35.
27. Yang, R. S. H. 1986. The Toxicology of Methyl Ethyl Ketone. *Residue Rev.* 97:121-143.
28. Yang, R. S. H., Huff, J. E., Boorman, G. E., Haseman, J. K., Kornreich, M., and Stookey, J. L. 1986. Chronic Toxicology and Carcinogenesis Studies of Telone II by Gavage in Fischer 344 Rats and B6C3F1 Mice. *J. Toxicol. Environ. Health* 18:377-392.
29. Yang, R. S. H. 1987. Propylene Chlorohydrins: Toxicology, Metabolism, and Environmental Fate. *Rev. Environ. Contam. Toxicol.* 99:47-59.
30. Yang, R. S. H. 1987. Acute Versus Chronic Toxicity and Toxicological Interactions Involving Pesticides, in "*Pesticides: Minimizing the Risks*," Edited by N. N. Ragsdale and R. J. Kuhr, ACS Symposium Series No. 336, American Chemical Society, Washington, DC, pp. 20-36.
31. Yang, R. S. H., Anuskiewicz, C. M., Chu, S. C., Garman, R. H., McKelvey, J. A., and Tallant, M. J. 1987. Biochemical and Morphological Studies on the Percutaneous Uptake of <sup>14</sup>C-Ethylenediamine in the Rat. *J. Toxicol. Environ. Health* 20:261-272.
32. DePass, L. R., Yang, R. S. H., and Woodside, M. D. 1987. Evaluation of the Teratogenicity of Ethylenediamine Dihydrochloride in Fischer 344 Rats by Conventional and Pair-Feeding Studies. *Fundam. Appl. Toxicol.* 9:687-697.
33. Yang, R. S. H. and Rauckman, E. J. 1987. Toxicological Studies of Chemical Mixtures of Environmental Concern at the National Toxicology Program: Health Effects of Ground Water Contaminants. *Toxicology* 47:15-34.
34. Yang, R. S. H. 1987. A Toxicological View of Pesticides. *CHEMTECH* 17:698-703.
35. Yang, R. S. H., and Rauckman, R. E. 1987. Toxicological Studies of Chemical Mixtures of Environmental Concern at the National Toxicology Program: Health Effects of Ground

- Water Contaminants, Proc. 16th Conf. Toxicol., Harry G. Armstrong Aerospace Medical Research Laboratory, Air Force Systems Command, Dayton, OH, pp. 30-49.
36. Yang, R. S. H. 1988. Hexachloro-1,3-butadiene: Toxicology, Metabolism and Mechanisms of Toxicity. *Rev. Environ. Contam. Toxicol.* 101:121-137.
  37. Eustis, S. L., Haber, S. B., Drew, R. T., and Yang, R. S. H. 1988. Toxicology and Pathology of Methyl Bromide in Rats and Mice Following Repeated Inhalation Exposure. *Fundam. Appl. Toxicol.* 11:594-610.
  38. Dunnick, J. K., Graham, D. G., Yang, R. S. H., and Haber, S. B. 1989. Subchronic Toxicity Study of n-Hexane in B6C3F1 Mice After Inhalation Exposure. *Toxicology* 57:163-172.
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  134. Lohitnavy, M., Lu, Y., Lohitnavy, O., Chubb, L. S., Hirono, S., and Yang, R. S. H. A possible role of multidrug-resistance-associated protein 2 (Mrp2) in hepatic excretion of PCB126, an environmental contaminant: PBPK/PD modeling. *Pharmacol. Res.* Submitted for publication.
  135. Lee, S. K., Hamer, D., Bedwell, C. L., and Yang, R. S. H. Investigation of pharmacokinetic interactions for the lactational transfer of methyl mercury and PCB congeners by physiologically-based pharmacokinetic modeling. *Toxicol. Sci.* Submitted for publication.
  136. Lin, P. P., Chen, J. W., Chang, L. W., Wu, J. P., Redding, L., Chang, H., Yeh, T. K., Yang, C. S., Tsai, M. H., Wang, H. J., Kuo, Y. C., and Yang, R. S. H. 2007. Computational and structural toxicology of a nanoparticle, Quantum Dot 705, in mice. *Nature Nanotechnol.* Submitted for publication.
  137. Kim, K. H., Bae, D. S., Reardon, K. F., Yang, R. S. H., Campain, J. A., and Lee, K. H. Proteomics of malignant cellular transformation in human epidermal keratinocytes treated with MNNG. Manuscript in review.
  138. Lee, S. K., Belisle, J. T., and Yang, R. S. H. Differential expression of cerebellar proteins in the developing brain of mice exposed to MeHg and PCBs through perinatal transfer: A proteomics approach. Manuscript in review.

#### **BOOKS:**

1. Yang, R. S. H. 1994. *Toxicology of Chemical Mixtures: Case Studies, Mechanisms, and Novel Approaches*, Academic Press, San Diego, CA, 720 pp.
2. Reddy, M., Yang, R. S. H., Clewell III, H. J., and Andersen, M. E. 2005. *Physiologically Based Pharmacokinetics: Science and Applications*, John Wiley & Sons, 420 pp.

#### **EDITOR FOR SPECIAL VOLUMES OF JOURNALS:**

1. Yang, R. S. H. and Suk, W. A. 1998. Current Issues on Chemical Mixtures. *Environ. Health Perspect.* Volume 106, Supplement 6.

2. Yang, R. S. H. and Suk, W. A. 2002. Application of Technology to Chemical Mixture Research. *Environ. Health Perspect.* Volume 110, Supplement 6.

#### **ABSTRACTS AND PRESENTATIONS:**

A total of about 225 abstracts and presentations as of March 2007.

#### **TECHNICAL REPORTS:**

Between 1977 and 1983, twenty-four reports have been prepared from the work under my supervision at Bushy Run Research Center in the following areas. Much of the data generated were never published because of the proprietary nature of the information.

1. Pharmacokinetics and Metabolism of Carbaryl in Dogs.
2. Inhalation Toxicity Study on an Experimental Agricultural Chemical DTX77-0001 (Diamond Shamrock Corp.)
3. Pharmacokinetics and Metabolism of Ethylenediamine in Rats.
4. Range Finding Toxicity Studies on Ethylenediamine Dihydrochloride.
5. Ethylenediamine Dihydrochloride Subacute and Subchronic Toxicity Studies.
6. Chronic Toxicity/Carcinogenicity Studies on Ethylenediamine and Ethylenediamine Dihydrochloride.
7. Development of Analytical Methodology on Carbaryl and Ethylenediamine.
8. In Vitro Mutagenicity Testing on Ethylenediamine.
9. Two-Generation Reproduction Study on Ethylenediamine in Rats.
10. Dominant Lethal Study on Ethylenediamine.
11. Pharmacokinetics and Metabolism of Diethylenetriamine in the Rat.
12. Dermal Carcinogenicity Study on Ethylenediamine.

At the National Toxicology Program, the following Technical Reports were prepared, peer-reviewed, and approved.

1. NTP TR 269 Carcinogenesis Studies of Telone II [Technical Grade 1,3-Dichloropropene (CAS No. 542-75-6) containing 1.0% Epichlorohydrin as a Stabilizer] in F344/N Rats

- and B6C3F1 Mice (Gavage Studies). National Toxicology Program Technical Report Series No. 269, May 1985.
2. NTP TS 3 Toxicity Studies of Hexachloro-1,3-Butadiene in B6C3F1 Mice (Feed Studies). March 1989
  3. NTP TR 385 Toxicology and Carcinogenesis Studies of Methyl Bromide (Bromomethane) (CAS No. 74-83-9) in B6C3F1 Mice (Inhalation Studies). National Toxicology Program Technical Report Series No. 385, peer-reviewed and approved by the NTP Board of Scientific Counselors, Technical Reports Review Subcommittee on November 19, 1990.
  4. NTP TS 35 Toxicity Studies of a Chemical Mixture of 25 Groundwater Contaminants. Administered in Drinking Water to F344/N Rats and B6C3F<sub>1</sub> Mice. Peer-reviewed and approved by the NTP Board of Scientific Counselors, Technical Reports Review Subcommittee on December 2, 1992.
  5. NTP TS 36 Toxicity Studies of Pesticide/Fertilizer Mixtures. Administered in Drinking Water to F344/N Rats and B6C3F<sub>1</sub> Mice. Peer-reviewed and approved by the NTP Board of Scientific Counselors, Technical Reports Review Subcommittee on December 2, 1992.

**INVITED SPEECHES AND SCHOLARLY ACTIVITIES NATIONALLY AND INTERNATIONALLY (in the latest 5 years):**

2002. Application of Computer Modeling to Biological Consequences of Multiple Stressors, **International Conference on the Combined Effects of Environmental Factors**, Taketsuki City-Osaka, Japan, August 28-31, 2002.
2002. Integration of Computer Modeling and Experimental Toxicology to Studies of Mixed Waste, **Radiation Effects Research Foundation**, Hiroshima, Japan, September 4, 2002.
2002. Chemical Mixture Toxicology: From Descriptive Toxicology to *In Silico* Toxicology, Invitational Keynote Speech at the **International Conference on Chemical Mixtures**, Atlanta, GA, September 10-11, 2002.
2002. Reaction Network Modeling of Benzo[a]pyrene, **International Congress of Toxicology/University of Chile**, Santiago, Chile, September 30 – October 2, 2002.
2003. Application of Biologically Based Computer Modeling to the Study of Chemical Mixtures, **USEPA, Office of Research and Development, National Center for Environmental Assessment**, Cincinnati, OH, June 10, 2003.
2004. Chemical Mixtures: Nonlinear Dose-Response Phenomenon, Physiologically Based Pharmacokinetics, and Reaction Network Modeling, **International Conference on Non-Linear Dose-Response Relationships In Biology, Toxicology And Medicine**, Amherst, MA, June 8-10, 2004.

2004. Uptake and Toxicokinetics: Some Current Issues on PBPK and Reaction Network Modeling, **International Workshop "Internal Exposure - Linking Bioavailability to Effects,"** Ascona, Switzerland, August 22-27, 2004
2004. Assessing Multiple Exposures and Chemical Mixtures, **Environmental Lecture Series. Science, Policy, and Engineering of Hazardous Waste Sites,** Amherst, MA, November 18, 2004.
2005. Is there a general relationship between thresholds of toxicity for individual chemicals and interaction thresholds for chemical mixtures? **Society of Toxicology's Continuing Concepts in Toxicology Workshop. Charting the Future: Building the Scientific Foundation for Mixtures Joint Toxicity and Risk Assessment,** Atlanta, GA, February 16-17, 2005.
2005. Integration of PBPK and Reaction Network Modeling: Predictive Xenobiotic Metabolomics. **5<sup>th</sup> World Congress on Alternatives and Animal Use in the Life Sciences,** Berlin, Germany, August 21-25, 2005
2005. Predictive Xenobiotic Metabolomics: Integrating Biochemical Toxicology with Computer Modeling. **ACS Agrochemical Div. Symposium,** Washington, DC, August 29, 2005.
2006. The Application of PBPK Modeling to Cumulative Risk Assessment and Special Life Stages. **CalEPA, OEHHA,** Oakland, CA, February 14, 2006.
2006. Invitational Participants to a Workshop on Chemical Mixtures organized by **SETAC** (Society of Environmental Toxicology and Chemistry) and **the European Integrated Project "NoMiracle"** (Novel Methods for Integrated Risk Assessment of Cumulative Stressors in Europe), Krakow, Poland, April 3-6, 2006.
2007. Roundtable Discussion on Chemical Mixture: Is the "Problem" Solvable? **Society of Toxicology Annual Meeting,** Charlotte, NC, 29 Mar 2007.
2007. Computational Toxicology and Chemical Mixtures, Distinguished Chinese Toxicologist Lectureship Award **by the American Association of Chinese in Toxicology,** Charlotte, NC, 29 Mar 2007.
2007. Physiologically-Based Pharmacokinetic Modeling of Lactational Transfer of PCB 153 in Humans, **Lawrence Berkeley National Laboratory,** Berkeley, CA, 02 Apr 2007.
2007. Invitational speaker at a Symposium organized by the **Institute for Risk Assessment Sciences, Utrecht University,** on Chemical Mixture Toxicology: Physiologically-Based Pharmacokinetic and Biochemical Reaction Network Modeling, Utrecht, The Netherlands, 18 Jun 2007.

## **GRANTS AND CONTRACTS:**

Current Support:

- 1) Agency for Toxic Substances and Disease Registry (ATSDR), Cooperative Agreement #U61/ATU881475, Application of Toxicogenomics to Hazard Identification of Chemical Mixtures. Integration of Mechanistic Carcinogenicity Studies with PBPK/PD Modeling for Health Assessment of Hazardous Waste Chemical Mixtures. Budget: \$30,000 (direct and indirect for 9/30/05 to 9/29/06; originally funded at about \$750,000 for 5 years; currently under severe budget cut). Project period: 2002-2007. PI, 2.5 % Effort. This is a project to develop an efficient and scientifically credible approach for the assessment of carcinogenicity of chemical mixtures found at hazardous waste sites using gene profiling technology.
- 2) CSU Act. No. 2-69350. Bi-annual. PI, No salary effort. Budget: Registration fees & other sources \$17,250-70,000 (approximation). 1992, 1994, 1996, 1999, 2001, 2003, & 2005 International Workshop on Physiologically-Based Pharmacokinetic/Pharmacodynamic (PBPK/PD) Modeling and Risk Assessment. The major goal of this project is to provide a hands-on intensive training workshop on physiologically-based pharmacokinetic modeling and its application to risk assessment. In 2003, the 10-day workshop consisted of lectures (AM) and computer laboratory (PM) every day. The July 2005 PBPK Workshop for Beginners is for one week.
- 3) 1 K25 ES012909-01A1. Mentored Quantitative Research Career Developmental Award for Dr. Arthur Mayano. Proposed Budget: \$735,162 (total direct and indirect). Project period: 05/01/05 - 04/30/10. No salary effort for Dr. Yang (Mentor).

An interdisciplinary research career development program where Dr. Mayano, under the mentorship of Drs. Yang and Reisfeld, will integrate chemical engineering modeling technology and biochemistry, physiology, and pharmacology/toxicology to characterize the cytochrome P450 catalyzed metabolic reaction networks of selected PCB congeners.

- 4) NIH PA-02-127. Mentored Quantitative Research Career Developmental Award for Dr. John Volckens. Budget: \$745,375 (total direct and indirect). Project period: 02/01/06 - 01/31/11. No salary effort for Dr. Yang (Mentor).

An interdisciplinary research career development program where Dr. Volckens, under the mentorship of Dr. Yang and Dr. Dan Costa of the USEPA, will integrate engineering technology and biochemistry, physiology, and pharmacology/toxicology to develop a realistic, 3-D, solid-state physiological model for *in vitro* studies of air pollutant deposition and lung cellular inflammatory responses.

- 5) EPA STAR R833451. An Integrated Computational Framework for the Interpretation of Organophosphorus Pesticide Biomarkers. Budget: \$748,582 (total direct and indirect). Project period: 10/01/07 - 09/30/10. No salary effort for Dr. Yang (Co-investigator/Consultant; PI: Brad Reisfeld).

The objective of this project is to create a computer-assisted framework to aid in the identification, characterization, and understanding of biomarkers resulting from human exposure to mixtures of OP insecticides, using chlorpyrifos and diazinon as the initial test compounds. The framework will use existing human biomarker data, along with

information about population and exposure variability and uncertainty, to reconstruct absorbed dose and exposure scenarios, as well as to predict levels of biomarkers resulting from known exposures to one or multiple OP insecticides.

Pending:

- 1) EPA-G2007-STAR-D1. International Center for Computational Toxicology of Chemical Mixtures. Budget: \$3,400,000 (total direct and indirect). Project period: 07/01/08 - 06/30/12. PI: Dr. Yang (25% effort total).

Adopting a central theme of "*Predictive Toxicology for Chemical Mixtures Using Computational Technology and Systems Biology*," the overall goal of our proposed "International Center for Computational Toxicology of Chemical Mixtures" is to carry out cutting-edge research and training in biologically-based computer modeling and simulation, utilizing leading experts in their fields, to assist the USEPA to fulfill its mission "...to protect human health and the environment..."

- 2) USEPA, National Center for Environmental Assessment (NCEA). Interagency Personnel Action for Dr. Raymond S. H. Yang to work 50% time at NCEA Cincinnati based on three months rotation between NCEA, Cincinnati and Colorado State University, Fort Collins. Budget: \$139,033 (total direct and indirect). Project period: 09/01/07 - 08/31/08. PI: Dr. Yang (50% effort).

Completed Projects:

- 1) U. S. Air Force research contract, F33615-91-C-0538. Physiologically Based Pharmacokinetic/ Pharmacodynamic Modeling of Chemical Mixtures, Budget \$608,624. 1991-1996. Co-PI (with J. D. Tessari, Co-PI, 10%), 10%. This is a research contract to conduct physiologically based pharmacokinetics/pharmacodynamics and computer modeling in rats of chemical mixtures relevant to the Air Force's Installation Restoration Program.
- 2) NIEHS. P42 ES05949. PI and Program Director, Program Project on "Integrated Research on Hazardous Waste Chemical Mixtures." Budget: approximately \$2,300,000 (direct and indirect)/3 years. Project period: 1992-1995. This Program Project consists of two Cores (Administrative, Analytical Chemistry) and five research projects (3 in biomedical sciences, 1 ecology, and 1 engineering). PI, 15% (Core A: Administrative). Project 5: Age- and Chronic Dosing Related Changes in Pharmacokinetics, Biochemical Markers, Cell Proliferation, and Histopathology in F344 Rat Exposed to a Chemical Mixture, PI, 10%. This is a Program Project to conduct interdisciplinary research on "Chemical Mixtures Related to Hazardous Waste Disposal" under the NIEHS Superfund Basic Research Program.
- 3) U. S. EPA/ECAO, Cooperative Agreement CR 821922-01-0, Physiologically Based Pharmacokinetic/Pharmacodynamic (PB-PK/PD) Modeling of Benzo(a)pyrene and PAH (Polycyclic Aromatic Hydrocarbon) Mixtures. Budget: \$50,000 (direct and indirect).

Project period: 1993-1996. PI, 10 % Effort. This is a project to develop an innovative approach for the risk assessment of chemical mixtures of polycyclic aromatic hydrocarbon (PAHs) by utilizing PB-PK/PD and computer modeling.

- 4) U. S. Navy research contract, F3360195MSA05, Application of Physiologically Based Pharmacokinetic/Pharmacodynamic (PB-PK/PD) Modeling to Human Health Hazard Assessment to U. S. Navy Personnel with Potential Exposure to JP-5. Budget: \$49,979 (direct and indirect). Project period: 1995-1996. PI, 2.1 % Effort. This is a feasibility study of applying PBPK/PD modeling and sophisticated statistical methods (such as response surface methodology and isobolographic analysis) to study the toxicity of JP-5 as a prototypical complex mixture.
- 5) Air Force Office of Scientific Research, Research Grant No. F49620-94-1-0304, An Interdisciplinary and Alternative Approach to Assess Carcinogenicity of Chlorobenzenes. Budget: \$526,047 (direct and indirect). Project period: 1994-1997. PI, 10 % Effort. This is a project to develop an interdisciplinary approach in predictive toxicology based on the integration of several state-of-the-art techniques for the accurate prediction of carcinogenic activity for chlorobenzenes.
- 6) Agency for Toxic Substances and Disease Registry (ATSDR), Cooperative Agreement #U61/ATU881475, Application of Physiologically Based Pharmacokinetic/Pharmacodynamic (PBPK/PD) Modeling to Human risk Assessment. Budget: \$480,537 (direct and indirect). Project period: 1994-1997. PI, 10 % Effort. This is a project to develop an innovative approach for the risk assessment of chemical mixtures of 4 groundwater contaminants from hazardous waste disposal sites in the states of Illinois, Indiana, and Michigan by coupling PBPK/PD modeling, focused experimental toxicology, with statistical/mathematical modeling such as isobolographic analysis and response surface methodology.
- 7) NIEHS/ATSDR/USEPA/US Army, Conference Support for *Current Issues on Chemical Mixtures*. Budget: approximately \$80,000 including registration income. Project period: 1996-1997. PI, no salary effort. The purpose for this conference is to bring scientific advances worldwide up to date on a variety of issues related to chemical mixtures (e.g., health effects, new advances on methodologies to deal with toxicology and risk assessment of chemical mixtures, remediation and ecological impact of chemical mixtures, chemical-chemical, chemical-physical agent, chemical-biological interactions).
- 8) 1 K01 CA75955-01A1 (PI: Gustafson)      07/01/98 - 06/30/03      No salary effort  
 NCI Howard Temin Award                      \$481,846 (direct)  
 An interdisciplinary research career development program where Dr. Gustafson, under the mentorship of Dr. Yang, will integrate the discipline of toxicology, pathology, and biomedical engineering in the realm of PBPK/PD modeling of combination chemotherapy for breast cancer. Dr. Gustafson's long-term goal is to develop a computer modeling approach for the accurate prediction of dosimetry for cancer chemotherapy combination protocols in target tissues to achieve maximal therapeutic efficacy with minimal side effects. Since 01 July 1999, Dr. Gustafson has assumed a tenured-track position at the University of Colorado Health Sciences Center in Denver and this grant has been transferred accordingly.

- 9) NIEHS 1RO3 ES10116-01 ZES1, Mixture Effect on CNS Development: Integrated Approach. Budget: \$100,000 (total direct). Project period: 09/01/99 - 08/30/01. PI, 2.5% Effort. In this RO3 grant, we tried to complete first of the two phases of our strategy to integrate both biological and computational methods to a coherent and predictive program for the effects of a chemical mixture (methylmercury and PCBs) on central nervous system (CNS) development.
- 10) NIEHS/ATSDR/American Chemistry Council, Conference Support for *Application of Technology to Chemical Mixture Research*. Budget: approximately \$75,000 including registration income. Project period: 2000-2001. PI, no salary effort.

The purpose for this conference is to bring scientific advances worldwide up to date on a variety of issues related to the application of technology, including biotechnology, to chemical.

- 11) NIEHS. P42 ES05949. PI and Program Director, Program Project on "Integrated Research on Hazardous Waste Chemical Mixtures." Budget: approximately \$5,800,000 (direct and indirect)/5 years. Project period: 1995-2000 (extended to 12/31/01). This Program Project consists of three Cores (Administrative, Analytical Chemistry and Molecular Biology, and GIS and Statistics) and six research projects (3 in biomedical sciences, 2 ecology, and 1 engineering). PI, 15% (Core A: Administrative). Project 1: Toxicologic Interaction Studies in Chemical Mixtures Using Physiologically Based Pharmacokinetics/ Pharmacodynamics (PB-PK/PD) Coupled with Statistical/Mathematical Modeling, PI, 10%. This is a renewal of the Program Project to conduct interdisciplinary research on "Chemical Mixtures Related to Hazardous Waste Disposal" under the NIEHS Superfund Basic Research Program.
- 12) 1 K08 CA72396 (PI: Pott). 03/01/97 - 02/28/02. No salary effort. NCI \$245,307 (direct) Mentored Clinical Scientist Developmental Award. An interdisciplinary research career development program where Dr. Pott, under the mentorship of Dr. Yang, will integrate the discipline of toxicology, pathology, and biomedical engineering in the realm of cancer research. Dr. Pott's immediate goals involve: (1) to evaluate the carcinogenic effects of subchronic exposure to three common groundwater contaminants - arsenic, 1,2-dichloroethane, and vinyl chloride, individually and in combination, in the development of hepatic angiosarcoma; (2) to use data from these studies for PBPK/PD and other statistical/mathematical modeling for health risk characterization.
- 13) NIEHS 1 F32 ES 05901, Individual National Research Service Award to Dr. Carol Belfiore, Budget: \$120,084 (direct and indirect). Project period: 09/01/99 - 08/31/02. Dr. Yang serves as the Mentor for Dr. Belfiore; No salary effort  
PBPK/PD Model of Kepone: Mechanisms of Toxic Interaction

A postdoctoral training program where Dr. Carol Belfiore, the applicant, under the mentorship of Drs. Raymond S. H. Yang and Melvin E. Andersen, will integrate mechanistic toxicology and computer modeling. Dr. Belfiore's research will involve the refinement and improvement of the PBPK/PD model for toxicologic interactions between

Kepone and carbon tetrachloride by incorporating pharmacokinetics and pharmacodynamics of Kepone into the integrated model.

- 14) Agency for Toxic Substances and Disease Registry (ATSDR), Cooperative Agreement #U61/ATU881475, Integration of Mechanistic Carcinogenicity Studies with PBPK/PD Modeling for Health Assessment of Hazardous Waste Chemical Mixtures. Budget: \$800,730 (direct and indirect for 9/30/97 to 9/29/02). Project period: 1997-2002. PI, 10 % Effort. This is a project to integrate mechanistic toxicology and biologically based computer modeling of chemical mixtures for hazard identification of chemicals in waste sites.
- 15) NIEHS 3 RO1 ES-09655-01S1, Minority Supplemental Award, Budget: \$117,041 (direct and indirect). Project period: 08/15/98 - 08/14/03. PI, No salary effort. This was an award supplemental to a R01 grant specifically to support graduate training for Mr. Damon S. Perez, a Hispanic minority student, leading toward a Ph.D. degree in toxicology.
- 16) USEPA 3C-R102-NTEX. Method of Analysis to Perform a Tissue-Based Cumulative Risk Assessment for Mixtures of Chemicals. Proposed Budget: \$90,893 (total direct and indirect). Project period: 04/02/03 - 12/31/03 (no cost extension to 05/31/04). PI: 20% effort.

This primary goal of this research proposal is to develop an integrated approach using computer modeling and experimental toxicology for cumulative risk assessment of chemical mixtures.

- 17) NIEHS RO1 ES-09655, Developing a Predictive Strategy for Chemical Mixtures, Budget: \$1,396,653 (direct and indirect). Project period: 08/15/98 - 08/14/03 (no cost extension to 08/14/04). PI, 10% Effort.

This is a unique interdisciplinary research program for the integration of mechanistic toxicology, molecular and cellular biology related to mutagenicity and carcinogenicity, and the petroleum engineering concept and technique of structure oriented lumping (SOL) plus QSAR modeling. The long-term goal is to develop an interdisciplinary approach based on mechanistic toxicology and chemical engineering concepts for the prediction of mutagenic and carcinogenic potentials of petroleum hydrocarbons and mixtures.

- 18) NIOSH/CDC. 1 RO1 OH07556-01, Physiologically-Based Pharmacokinetic/Clonal Growth Modeling: Predicting Cancer Potential of Chemical Mixture. Budget: \$783,278 (total direct and indirect). Project period: 06/01/01 - 05/30/04 (no cost extension to 05/30/05). PI, 15% Effort.

We propose to develop a biologically based modeling approach for predicting the cancer potential of chemical mixtures. This will be accomplished by integrating a time-course hepatocarcinogenic assay at the tissue, cellular, and molecular levels with physiologically based pharmacokinetic (PBPK) and clonal growth modeling.

- 19) NIEHS 1 T32 ES 07321, Institutional National Research Service Award, Budget:\$1,144,381 (direct and indirect). Project period: 07/01/99 - 06/30/04 (no cost extension to 06/30/06). PI, 25% Effort (no salary). The purpose of the proposed program is to provide pre- and post-doctoral training in mechanistically based quantitative toxicology to qualify individuals for research and teaching positions in universities and medical institutions, or research positions in national laboratories and other governmental agencies. Because of the uniqueness of the proposed training program in quantitative toxicology and its potential application in science-based risk assessment, it is conceivable that our trainees will be sought after by industry as well. The major research emphasis is **toxicologic interactions of chemicals and physical agents**. The endpoints to be studied are mutagenesis and carcinogenesis. Mechanistic studies will be integrated with physiologically based pharmacokinetic/pharmacodynamic (PBPK/PD) modeling and biologically based dose response (BBDR) modeling.

- 20) 01 K25 ES11146. Mentored Quantitative Research Career Developmental Award for Dr. Bradley Reisfeld. Proposed Budget: \$677,403 (total direct and indirect). Project period: 11/01/01 - 10/31/06. No salary effort for Dr. Yang.

An interdisciplinary research career development program where Dr. Reisfeld, under the mentorship of Drs. Yang and Reardon, will integrate chemical engineering modeling technology and molecular, biochemical, and cellular biology to elucidate the chemical reaction networks of Cytochrome P450 2E1 and its toxicologically significant substrates.

- 21) USEPA Contract DE-AC05-00OR22750. 1,1,1-Trichloroethane: EPA IRIS Support PBPK Modeling. Proposed Budget: \$66,129 (total direct and indirect). Project period: 12/27/04 - 09/30/06. PI: 2.5% effort.

The primary goal of this research is to support USEPA's effort in updating 1,1,1-trichloroethane risk assessment in its Integrated Risk Information System (IRIS) program.

- 22) NSC 95-2811-B-400-002 (National Science Council, Taiwan, Republic of China). Visiting Professor/Scientist Award. Budget: NT\$5,746,000 (USD\$179,563; Direct and Indirect). Project period: 07/01/06 - 06/30/09. PI: 100% effort (sabbatical leave).

This Visiting Professor/Scientist Award is to support Dr. Yang for his teaching and research at the Division of Environmental Health and Occupational Medicine, National Health Research Institutes, Zhunan, Taiwan. Initial period is from 01 July 2006 to 30 June 2007, with an Award of NT\$1990,000 (USD\$62,188). This Award is renewable for two additional years, if needed; no competition is necessary for renewal. As it turned out, Dr. Yang returned to Colorado State University in July 2007 after one year sabbatical leave and did not renew this Award for a second year.

## **POSTGRADUATE AND GRADUATE TRAINING:**

### **MENTORING FACULTY MEMBERS**

Dr. Henk J. M. Verhaar, Visiting Assistant Professor from RITOX, Utrecht University, Utrecht, The Netherlands (March to August 1996)  
 Dr. Daniel L. Gustafson, Research Assistant Professor (November 1996 to June 1999)  
 Dr. Julie Campain, Research Assistant Professor (January 1998 to December 2004)  
 Dr. Melvin E. Andersen, Professor (January 1999 to 2000)  
 Dr. Brad Reisfeld, Assistant Professor (September 2001 to 2006)  
 Dr. Micaela Reddy, Research Assistant Professor (August 2003 to March 2005)  
 Dr. John Volckens, Assistant Professor (October 2004 to present)  
 Dr. Arthur Mayeno, Research Assistant Professor (May 2005 to present)  
 Dr. Mike Lyons, Research Assistant Professor (June 2006 to present)  
 Dr. Pin Pin Lin, Associate Principal Investigator, National Health Research Institutes, Zhunan, Taiwan, Republic of China (July 2006 to Present)

POSTDOCTORAL FELLOWS, RESEARCH ASSOCIATES, OR GUEST SCIENTISTS

Dr. In-Young Hwang (July 1992 to March 1995)  
 Dr. Hisham Elmasri (July 1994 to April 1996)  
 Dr. Wendy A. Pott (September 1994 to present)  
 Dr. Shakil A. Saghir (August 1995 to May 1997)  
 Dr. Daniel L. Gustafson (February 1996 to October 1996)  
 Dr. Harold S. Butler (April 1996 to January 1997)  
 Dr. Ivan Dobrev (January 1999 to March 2001)  
 Dr. Ying Ou (September 1998 to May 2001)  
 Dr. Carol Belfiore (November 1998 to present)  
 Dr. Smadar Lapidot (May 2000 to October 2001)  
 Ms. Christine Rabideau (July 2001 to November 2002)  
 Mr. Manupat Lohitnavy (July 2001 to January 2002)  
 Dr. Robert Davidson (January 2002 to March 2003)  
 Dr. Ying Zhang (January 2002 to August 2003)  
 Dr. Micaela Reddy (September 2002 to July 2003)  
 Dr. Arthur Mayeno (May 2002 to April 2004)  
 Dr. Jim Dennison (June 2004 to Sept. 2005)  
 Dr. Mike Lyons (September 2005 to June 2006)

GRADUATE STUDENTS

		<u>Graduation Date or Expected Graduation Date</u>
Mr. Hisham Elmasri	Ph.D. (Toxicology)	May 1994
Mr. Alex Constan	Ph.D. (Toxicology)	Dec. 1995
Ms. Betsy Smith	M.S. (Toxicology)	July 1995
Ms. Jenny Phillips	M.S. (Toxicology)	May 1996
Mr. Sean Hays	M.S. (Chemical Engineering Co-Advisor with Dr. Reardon)	July 1996
Ms. Teresa Smith	M.S. (Chemical Engineering Co-Advisor with Dr. Reardon)	Sept. 1997
Mr. Russell Thomas	Ph.D. (Toxicology)	Dec. 1997
Mr. Lixin Feng	M.S. (Toxicology)	Jun. 1999

Ms. Heike Newman	M.S. (Toxicology)	Jun. 1999
Mr. Ken K. Liao	M.S. (Chemical Engineering Co-Advisor with Dr. Reardon)	Dec. 1999
Ms. Sandra Troncoso	M.S. (Toxicology)	Jul. 2002
Ms. Doon-song Bae	Ph.D. (Toxicology Co-Advisor with Dr. Campaign)	Sept. 2002
Wendy A. Pott, DVM	Ph.D. (Toxicology)	Nov. 2003
Mr. Jim Dennison	Ph.D. (Toxicology Co-Advisor with Dr. Andersen)	May 2004
Mr. Ken K. Liao	Ph.D. (Chemical Engineering Co-Advisor with Dr. Reardon)	Aug. 2004
Mr. Sun Ku Lee	Ph.D. (Toxicology)	May. 2004
Mr. Damon Perez	Ph.D. (Toxicology Co-Advisor with Dr. Campaign)	Dec. 2004
Ms. Elizabeth Perrigo	M.S. (Toxicology)	Dec. 2005
Mr. Yasong Lu	Ph.D. (Toxicology)	Dec. 2006
Mr. Manupat Lohitnavy	Ph.D. (Toxicology)	Dec. 2007
Ms. Ornratt Lohitnavy	Ph.D. (Toxicology)	May. 2008

#### GRADUATE COMMITTEE MEMBER

Ms. Can-Can Deng	M.S. (Radiological Health Sciences)	May 1993
Dr. Andrea Bohn	Ph.D. (Pathology)	Dec. 1997
Mr. Changsin Lee	Ph.D. (Radiological Health Sciences)	1999
Dr. Charley Dean	Ph.D. (Pathology)	Apr. 2003

#### STUDENT/POSTDOCTORAL FELLOW/MENTORED FACULTY AWARDS:

- Alex Constan. 1992. The Bagby Award, Department of Environmental Health, Colorado State University
- Alex Constan. 1995. Society of Toxicologic Pathology Young Investigator Award.
- Russell Thomas. 1996. Ciba-Geigy Graduate Student Fellowship from the Society of Toxicology
- Ying Ou. 2000. Outstanding Presentation, The Risk Assessment Specialty Section, the Society of Toxicology.
- Ying Ou. 2000. Best Abstract Award, The American Chinese Toxicology Society.
- Ying Ou. 2001. Best Student Award, The Biological Modeling Specialty Section, the Society of Toxicology.
- Ying Ou. 2001. Best Abstract Award, The American Chinese Toxicology Society.
- Jim Dennison. 2001. Best Abstract Award, The Risk Assessment Specialty Section, the Society of Toxicology.
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- Brad Reisfeld. 2003. Best Abstract, The Risk Assessment Specialty Section, the Society of Toxicology.
- Sun K. Lee. 2004. Best Student Award, The Biological Modeling Specialty Section, the Society of Toxicology.
- Jim Dennison. 2005. Best Student Abstract Award, The Biological Modeling and the Occupational and Public Health Specialty Sections, the Society of Toxicology.
- Jim Dennison. 2005. Blue Ribbon Best Abstract Award, The Risk Assessment Specialty Section, the Society of Toxicology.
- K. H. Liao. 2005. Best Student Abstract Award, The Biological Modeling Specialty Section, the Society of Toxicology.
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## REFERENCES:

- Dr. John D. Zimbrick, Head, Department of Environmental and Radiological Health Sciences, College of Veterinary and Biomedical Sciences, Colorado State University, 122A Environmental Health Building, Fort Collins, CO 80523, Tel. 970-491-7038, Fax. 970-491-2940, E-mail: [zimbrick@colostate.edu](mailto:zimbrick@colostate.edu)
- Dr. John S. Reif, (Head 1996-2003), Department of Environmental and Radiological Health Sciences, College of Veterinary and Biomedical Sciences, Colorado State University, 148A Environmental Health Building, Fort Collins, CO 80523, Tel. 970-491-6074, Fax. 970-491-2940, E-mail: [john.reif@colostate.edu](mailto:john.reif@colostate.edu)
- Dr. Melvin E. Andersen, Director, Division of Computational Biology, CIIT Centers for Health Research, 6 Davis Drive, P.O. Box 12137, Research Triangle Park, NC 27709-2137, Tel. 919-558-1205, Fax. 919-558-1404, E-mail: [MAnderсен@ciit.org](mailto:MAnderсен@ciit.org)
- Dr. Anna Fan, Chief, Pesticide and Environmental Toxicology Section, Office of Environmental Health Hazard Assessment, California Environmental Protection Agency, 1515 Clay Street, 16<sup>th</sup> Floor, Oakland, CA 94612, Tel: 510-622-3165, Fax: 510-622-3218, E-mail: [afan@oehha.ca.gov](mailto:afan@oehha.ca.gov)

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