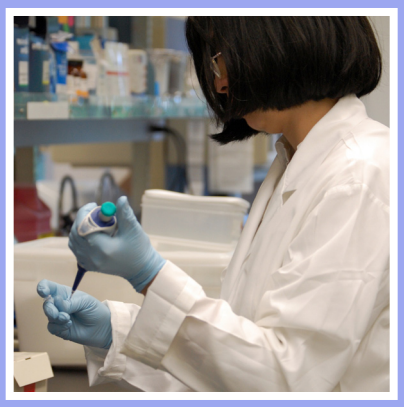
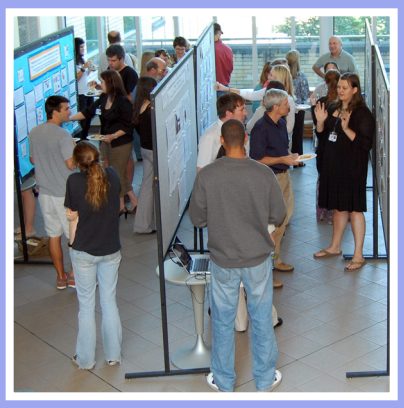
# CROET

Putting science to work for working Oregonians





CROET
2008-2009
BIANNUAL
REPORT

OREGON HEALTH & SCIENCE UNIVERSITY

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# Mission, Purpose, and Mandate

CROET, the Center for Research on Occupational and Environmental Toxicology at OHSU, is dedicated to the promotion of health and safety in the workforce. Through basic and applied research, education, and outreach, CROET seeks to prevent disease and disability among working Oregonians and their families, during their employment years and throughout retirement.

# Message From the Director

There is a reason why a white marble human head sits astride a black plinth outside the Richard T. Jones building that houses CROET, courtesy of construction dollars provided by the Oregon Workers Benefit Fund. Such fine sculpture was made possible by Oregon's Percent for Art Legislation that sets aside "not less than 1% of the direct construction funds of new or remodeled state buildings with construction budgets of $100,000 or greater for the acquisition of art work which may be an integral part of the building, attached thereto, or capable of display in other State Buildings". Distinguished Oregon artist Larry Kirkland, under guidance from the Oregon Arts Commission, created the striking marble head to capture the vision that CROET would initially focus on the role of the brain and behavior in workplace safety and occupational disease.

The neuroscience focus of CROET meshed with the university's ambitions in this then-emerging area of biomedical research. When I arrived at OHSU with my colleagues 21 years ago, we brought a NIH program project grant on toxic probes of neurodegenerative disease; in later years, with an expanded faculty, we were fortunate to win three neuroscience-based center grants in which CROET scientists worked with colleagues across OHSU, the Portland VAMC, and other Pacific Northwest research institutions. Brain Awareness Week was conceived at CROET and nurtured by others into a celebrated annual Portland event. Early in its history, however, the Center's research portfolio expanded beyond the brain and behavior to tackle other problems that compromise the health, safety and productivity of Oregon's workforce.

A key part of the expansion of CROET's portfolio and faculty was the recruitment of Dr. Stephen Lloyd, a leading expert on the mechanisms of DNA damage and repair following exposure to cancer-associated occupational and other chemicals. In addition to a large, nationally funded basic science laboratory, Dr. Lloyd had experience leading multidisciplinary research centers while at the University of Texas Medical Branch. CROET is fortunate to have this combination of scientific and administrative expertise in Interim Director Lloyd, appointed in late 2009, and to have Dr. W. Kent Anger continue in the position of CROET Associate Director. Dr. Anger -- my first recruit to CROET some 20 years ago -- has with his staff played a major role in the Center's development and present standing, as have CROET's Assistant Directors Dr. Gregory Higgins and Janice Stewart, and Dr. Fred Berman, who heads CROET's Toxicology Information Center.

Peter Spencer, PhD, FRCPath

Under my former leadership, CROET engaged the creativity, energy and expertise of a diverse and international workforce, another part of the vision for CROET laid out for artist Larry Kirkland in 1988. This resonated with my own research that took me to remote regions of the world to study little-known neurodegenerative diseases related to conditions found at home. This experience led to my appointment in summer 2007 as interim director of the newly created OHSU Global Health Center (GHC) - since housed temporarily within the space behind Kirkland's marble statue - and the October 2009 transfer of my responsibilities from CROET Director to Director of the GHC.

Respectfully submitted,

Peter S. Spencer, PhD, FRCPath
CROET Director and Senior Scientist
Global Health Center Director,
CROET Senior Scientist,
SOM Professor of Neurology.

# A Message From Dr. Lloyd

After more than 2 decades of service as the founding Director of the Center for Research on Occupational and Environmental Toxicology (CROET), Dr. Peter Spencer accepted the position of Director of the Oregon Health & Science University (OHSU) Global Health Center, effective October, 2009. OHSU has made a commitment to initiate a national search for a new Director of CROET in January, 2010. During this time, I have agreed to assume the role of Interim Director with the primary objective being to maximize CROET's effectiveness in recruiting the best possible individual into the Director's position, an individual whose research program is directly germane to CROET's mission.

Stephen Lloyd, PhD

This time of transition will be characterized by a revitalized and expanded commitment to both OHSU and all Oregonians. Prior to this transition, I led CROET's Strategic Planning committee which proposed an evolution to an increased emphasis of CROET's research on intervention and intervention effectiveness. We have begun to increase CROET's visibility in our local community and across the state through actively seeking partnerships with other organizations whose mandates and missions are to serve all workers within the State. This will be the theme of CROET as we recruit a new Director and plan the hiring of new faculty to implement our strategic plan.

I am privileged that Dr. Kent Anger will continue to serve as the Associate Director of CROET and as such, he will continue to lead an expansion of CROET's outreach program which, together with CROETs applied and intervention research faculty, will continue to find ways to increase our impact at the Oregon Worksite.

I appreciate the opportunity to lead CROET during this transition period Having served as the Director of two Centers in Environmental Health and Medicine at the University of Texas Medical Branch prior to coming to OHSU and having served as the Chair of both the CROET Strategic Planning Committee and Budget Committee, I have an appreciation of the task and potential ahead.

I want to extend CROET's and OHSU's appreciation to Dr. Spencer. As OHSU moves toward greater commitments to address the challenges facing global health issues, OHSU President, Dr. Joe Robertson selected Dr. Spencer to lead the university's efforts in this area based on Dr. Spencer's ongoing interest and expertise in this arena. All of us who have the privilege of working in CROET are very grateful for Dr. Spencer's leadership. He played an integral role in laying the founding principles from which CROET has grown, and his vision and implementation of research, outreach and education. Dr. Spencer will maintain his association with CROET while he takes on this new leadership role in building OHSU's global health initiatives.

As we begin this new chapter for CROET, I look forward to renewing and deepening our commitments and contributions to worker health and safety with the help and support of the CROET faculty and staff.

R. Stephen Lloyd, PhD

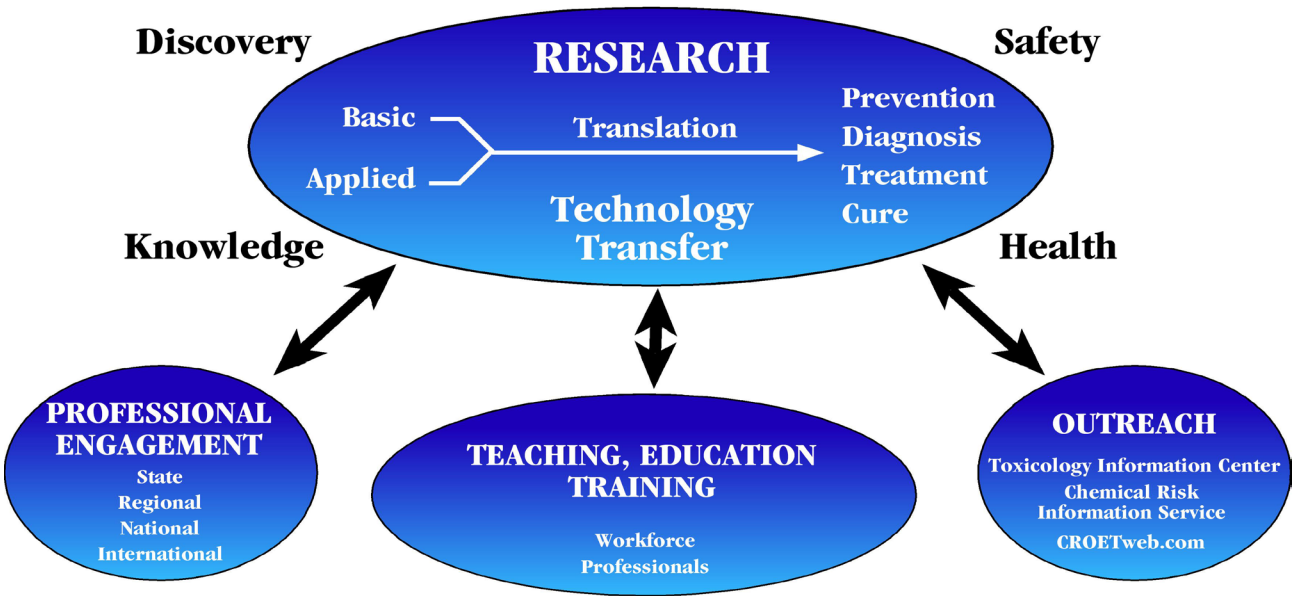
# CROET: a Resource for Oregon

CROET conducts research on the basic biology of workplace-related injury and disease as well as research related to workplace performance and occupational exposure. CROET also participates in doctoral and post-doctoral educational programs to train the next generation of scientists, and provides updates for health and safety specialists to ensure that the latest scientific advances are translated into enhanced workplace safety. Through its outreach efforts, CROET serves as an information conduit to Oregon workers, employers, labor, and the general public.

Applied research addresses workplace hazards, often spurred by specific safety issues of immediate concern to Oregon's workers. Research is focused on surveillance of workplace and environmental problems and on prevention of injury in agriculture, service industries, and construction. This research has short-term payoffs, including, but not limited to: (1) identifying unrecognized trends in Workers' Compensation claims, suggesting new prevention priorities; (2) training effectiveness research has shown that computer-based training can teach topics such as respirator safety, pesticide effects, and supervisor skills to people with severely limited education as well as very well-educated workers; (3) monitoring agriculture workers for exposure to pesticides and adverse nervous system health effects, and giving safety training to these groups; and (4) conducting wellness programs to improve worker health and safety.

Basic research is focused on nerve and muscle damage and repair, occupational/environmental exposures and their consequences, DNA damage, and cancer. This research requires prolonged commitment and synergy among investigators and has a long-term payoff. It is applicable to many diseases and disorders, including those that begin in the workplace and those that arise or are exacerbated by other causes (e.g., genetic, environmental) that plague Oregonians during their working years and into retirement. While this is important for Oregonians, it obviously has a wider impact. Thus, most of the funding for CROET's research in these areas is supported by grants from the National Institutes of Health, Centers for Disease Control, National Institute of Occupational Safety and Health, and from other federal sources. CROET's influence and impacts are depicted in the graphic below and in this report that follows.

***State Mandate:***
***Conduct basic and applied research, outreach and education to address Oregon's occupational health needs***



# CROET's Areas of Emphasis

## Education and Outreach programs

### CROET's Education and Outreach Programs have four goals:

- Provide scientifically accurate information on Oregon's occupational issues — continuously on the Internet and daily with scientific interpretation of complex issues through the Toxicology Information Center (TIC)
- Offer educational programs on Oregon's occupational needs to health and safety specialists and medical providers
- Train health professionals who will investigate Oregon's occupational safety and health issues in the future
- Provide the scientific expertise to help Oregon industry and labor evaluate occupational safety and health questions

## Research

### Applications and Outreach

- Cellular mechanisms that control sleep-wake cycles relevant to shift workers
- Computer-based and other training methods to enhance worker safety training
- Agricultural, construction, high tech, office-related and transportation industries

### Injury and Recovery of the Nervous System and Muscles

- Image analyses of nerve cell protein dynamics using imaging
- The use of nanotechnology to enhance nerve growth
- Factors that govern the accuracy of nerve synapse formation
- Genetic models of nerve maldevelopment

### Chronic Disease and Working Safely

- Biomarkers of pesticide exposures and assessment of pesticides on behavior
- Toxicants that disrupt protein transport in neurons
- Development of models of chronic disease (asthma, neurodegenerative, diabetes)

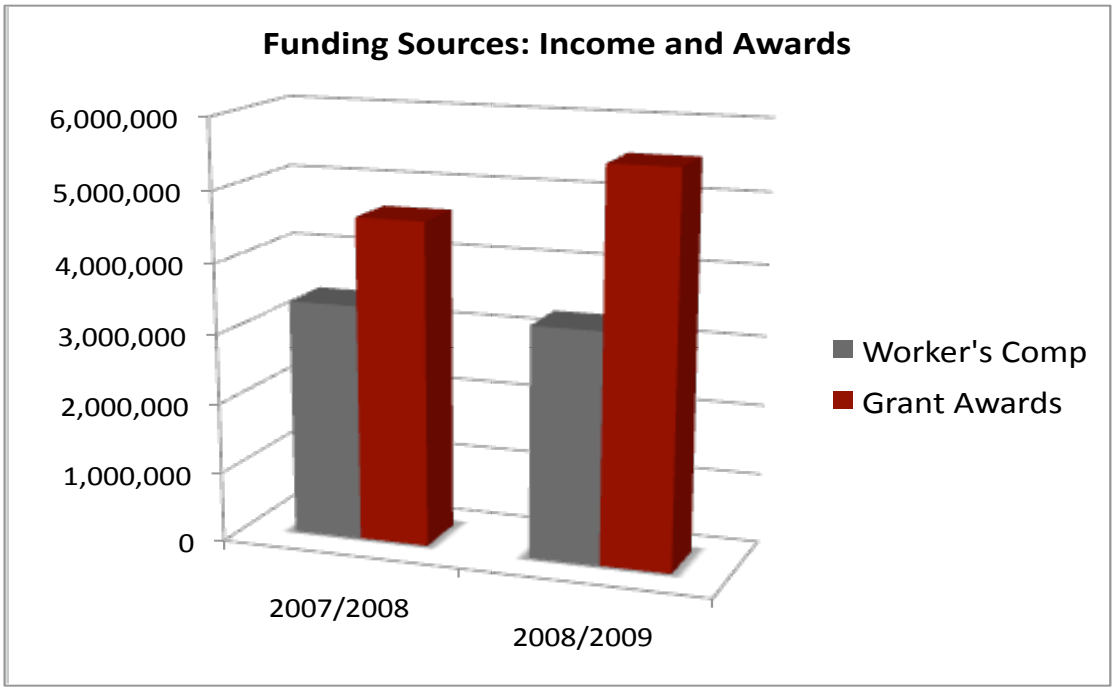
### Integrity of DNA (DNA damage, genetic alterations, and disease)

- Role of DNA repair in protecting the nervous system from chemical exposures
- Gene silencing and cancer
- Mutations induced by ionizing irradiation, oxidative stress, and other genotoxins
- Ion channel mutations that underlie diseases

# CROET Highlights

## CROET brings federal dollars into the Oregon economy

CROET receives base operations funding from the Oregon Workers' Compensation System that, year after year, CROET scientists have successfully leveraged to win federal and other research dollars. For every dollar invested by the State's Workers' Benefit Fund in the current biennium, CROET's world-class scientists brought an average $1.52 of federal and private grant funding into the Oregon economy (see chart below). Federal dollars for research in Oregon have a significant positive impact on the state's economy. Expenditures for goods and services, as well as the salaries of scientific and support personnel, produce a multiplier effect on the purchase of goods and services and creation of businesses that support the needs of Oregon's research institutions. Moreover, research coming out of CROET has a greater than average impact on the state's economy from the new technologies and jobs that spin off from productive research. In a study conducted by Oregon State University, multiplier effects on the economy from the infusion of federal grant funds were estimated to range from 2 up to 10 dollars per federal dollar received.




## Workplace studies and applications research

CROET conducts workplace surveys so that prevention and research needs can be identified, and applications research to bring the benefits of science to the workplace floor. It also reaches out to provide education and information to the Oregon workforce and beyond.

### Oregon Fatality Assessment and Control Evaluation (OR-FACE) Program

The Oregon Fatality Assessment and Control Evaluation (OR-FACE) Program is designed to prevent occupational fatalities through surveillance, targeted investigation, assessment, and outreach that are associated with traumatic work-related deaths in Oregon. Headed by Gary Rischitelli MD, JD, MPH, OR-FACE is one of nine state FACE programs funded by the National Institute for Occupational Safety and Health (NIOSH). OR-FACE Preliminary data for 2008 and 2009 indicates 117 work-related fatalities in 108 incidents.

During 2008-2009, OR-FACE produced the OR-FACE 2006 Annual Report, six investigational reports on particular incidents, a safety brochure for agriculture in both English and Spanish (Can You Identify Fatal Hazards on Your Farm or Ranch?), a second edition of the safety booklet, Young Workers: Stay Alive on the Job!, and three posters for conference presentations related to young workers, logging, and commercial crab fishing. OR-FACE also collaborated with

Oregon's Young Worker Health and Safety coalition, attended meetings and events with educators and safety professionals, and gave safety presentations for young audiences.

OR-FACE expanded activity in logging safety by completing a pilot study with camera-mounted hardhats, funded by the Pacific Northwest Agriculture Safety and Health Center ("Fallers Point of-view Video Observation Study"). OR-FACE also completed two logging safety projects funded by Oregon OSHA: one to update the Oregon OSHA Yarding and Loading Handbook, and another to produce an OR-FACE Yarding Logging Safety booklet as a companion volume to the OR-FACE Fallers Logging Safety booklet.

In May 2009, OR-FACE hosted the Annual National FACE Program meeting, bringing together federal and state public health workers and academic researchers from across the country. Representatives of the state FACE programs, including Dr. Rischitelli, presented updates on their research activities, discussed regional trends and factors that affect worker fatalities, and shared outreach and education methods.

OR-FACE investigational reports and other publications are available on the program's website (http://www.ohsu.edu/xd/research/centers-institutes/croet/outreach/or-face/). Investigation reports from Oregon and other FACE states are also available through the National Institute for Occupational Safety and Health (www.cdc.gov/niosh/face).

## Safety and Health Interventions for Lone Workers

Dr. Ryan Olson's research is focused on safety and health interventions for lone workers, and on behavioral self-management methods. The overarching goal of this research is to understand how organizations can best protect and promote health among workers who are physically isolated from their peers. Olson's work is also concerned with understanding workplace and personal factors that help individual's self-regulate and engage in prevention behavior.

## Promoting Health and Preventing Injuries Among Truck Drivers

Commercial truck drivers have overweight and obesity rates that are nearly 20% higher than the general population. However, prior efforts to promote weight loss and healthful behaviors with this population had been minimally effective. Dr. Olson led the development and pilot testing of a new health promotion intervention for truck drivers, called SHIFT (Safety & Health Involvement For Truckers). The intervention engages drivers in health promotion with a weight loss and safe driving competition that is supported with computer-based training and motivational interviewing (see www.ohsushift.com for more information). In the pilot test, drivers lost an average of one unit of body mass index and made significant changes to healthful and safe behaviors. The pilot test was completed in 2008 and published in 2009. The study also won 1st place in the "Best Practices Intervention Evaluation Competition" at Work, Stress, and Health 2009, which is an international conference sponsored by the American Psychological Association (APA) and National Institute for Occupational Safety and Health (NIOSH).

Musculoskeletal injuries in commercial truck drivers account for 8% of annual injuries in the US. However, research on drivers' exposures to injury hazards during material handling tasks is extremely limited because of the isolated nature of the work. Olson and colleagues used video-based assessment and driver self-assessments to study three drivers over a 6-month period. The resulting analyses identified four environmental predictors of severe back postures among short-haul truck drivers during material handling tasks.

Olson, R., Anger, K., Elliot, D. L., Wipfli, B., & Gray, M. (2009). A new health promotion model for lone workers: Results of the SHIFT pilot study (Safety & Health Involvement for Truckers). Journal of Occupational and Environmental Medicine, 51(11), 1233-1246.

Olson, R., Hahn, D. I., & Buckert, A. (2009). Predictors of severe trunk postures among short-haul truck drivers during non-driving tasks: An exploratory investigation involving video-assessment and driver behavioural self-monitoring. Ergonomics, 52 (6), 707-722.

## Understanding Factors that Promote Prevention Behaviors

One third of all construction fatalities are falls, and 34% of fatal falls are due to a failure to wear personal protective equipment (PPE) that was available at the relevant worksite at the time of the incident. An additional 13% of

fatal falls are due to improper use of PPE. One factor that affects the proper use of PPE is whether or not peers are positive social models of the behavior. Prior research had shown that exposure to a single social model wearing PPE had positive effects. However, in the work place an individual is likely to observe the aggregate behavior of their entire work group to decide if wearing PPE is encouraged or discouraged in their work environment. In 2009, Olson and colleagues published the first evidence showing that the aggregate behavior of multiple social models influences PPE use.

Behavioral self-monitoring (BSM) methods, where individuals repeatedly observe, evaluate, and record aspects of their own behavior, can produce valuable assessment data about injury hazards and near misses. In 2008, Olson and Winchester published the first quantitative literature review of BSM methods applied in workplace settings.

Many jobs require workers to perform sustained visual searching to identify threats or hazards to personal and public safety (e.g., commercial driving, quality control in manufacturing, airport baggage screening). In collaboration with colleagues at Santa Clara University, Olson formalized and produced further evidence for the Vigilance Reinforcement hypothesis, which is the notion that the chance to detect an error or threat actually reinforces vigilant search behaviors.

Olson, R., Grossheusch, A., Wipfli, B., & Schmidt, S. (2009). Observational learning and workplace safety: The effects of viewing the collective behavior of multiple social models on the use of personal protective equipment. Journal of Safety Research, 40 (5), 383-387.

Olson, R. & Winchester, J. (2008). Behavioral self-monitoring of safety and productivity in the workplace: A methodological primer and quantitative literature review. Journal of Organizational Behavior Management, 28 (1), 9-75

Hogan, L., Bell, M., & Olson, R. (2009). A preliminary investigation of the reinforcement function of signal detections in simulated baggage screening: Further support for the Vigilance Reinforcement Hypothesis. Journal of Organizational Behavior Management, 29 (1), 6-18.

## Computer-based Supervisor and Worker Protection Training

CROET's research on computer-based training effectiveness in agriculture has been extended to (1) teach complex capabilities--supervisor skills--to workers with limited education and (2) to identify the need for more frequent repeat training about the Worker Protection Standard than is legally required by the Environmental Protection Agency (EPA). This research was conducted by Drs. Kent Anger and Diane Rohlman of CROET, in collaboration with community partner RN Leda Garside of Tuality Healthcare, ¡Salud! Services, and several Oregon vineyards. The supervisor skills training was developed out of concern that employees with limited education may be excluded from advanced training due to (we believe unfounded) assumptions that the typical agricultural employee might not learn rapidly. The study, published in the Journal of Agricultural Safety and Health, demonstrated that providing computer-based training in supervisor skills to Latino agricultural workers with an average education of 6.4 and 8.2 years (in our intervention and control groups, respectively) did improve performance in a face-to-face workshop designed to teach supervisor skills given on the following two days. The training produced a large positive effect size, much larger than the average effect size reported in workplace training studies. This result suggests that limited educational attainment is not a barrier to learning the complex skills required to supervise employees.

Other research, published in the Journal of Agromedicine, examined Worker Protection Standard (WPS) training, which is one of EPA's primary methods for preventing pesticide exposure to agricultural workers. EPA requires retraining of the WPS at 5-year intervals, meaning the knowledge must be retained for that long. Vineyard workers completed a test of their baseline WPS knowledge, computer-based training on WPS, a post-test immediately after training and a re-test 5 months later. There was a relatively high level of baseline knowledge of WPS information, training increased the knowledge and produced a large effect size. Re-test performance at 5 months revealed a return towards but not back to the pre-test levels. Shorter re-training intervals for the WPS were recommended in the publication.

The work funded by the National Institute for Occupational Safety and Health (NIOSH) used cTRAIN, developed

at CROET, and licensed by OHSU to a company owned by Drs. Anger and Rohlman. OHSU and Drs. Anger and Rohlman have a significant financial interest in Northwest Education Training and Assessment, LLC, a company that may have a commercial interest in the results of this research and technology. This potential conflict has been reviewed and managed by OHSU and the Integrity Program Oversight Council. Two new research grants employing this computer-based training technology were funded in 2008-2009 (1) to study the effectiveness of training to address the effects of domestic violence in the workplace in Oregon counties and (2) to provide prevention training to home care workers to avoid and prevent violence from their clients or client families.

## Research on Pesticides and Terrorism

Organophosphorus (OP) pesticides used in Oregon and worldwide in agriculture are also predicted to be likely terrorism agents that could be used against the US. CROET's Drs. Kent Anger and Pam Lein began studying this chemical in parallel human and animal studies aimed at identifying tests and measures (called biomarkers) that can effectively and quickly determine if humans have been harmed by exposures to these pesticides. The immediate effects of exposure to these OP pesticides at concentrations that cause fatal poisonings (if not treated) are well studied. Drs. Anger and Lein are investigating lower-concentration exposures that may produce silent or unobservable damage--but damage that affects the brain and nervous system. Pesticide exposures in Oregon occur at much lower concentrations than exposures or damage that would be expected following a terrorism event, so the human research led by Dr. Anger is being conducted in Egypt's cotton fields during pesticide application, where the highest workplace exposures ever reported are found (demonstrated in an article by the research team in press in NeuroToxicology). Dr. Lein is conducting the animal research under controlled exposures that reproduce the same degree of internal dosing and the same pattern of exposures as the human exposures that were measured in the first year of this research in Egypt. This research is funded by the National Institute of Environmental Health Sciences. Dr. Lein moved to the University of California at Davis after this work was funded and the collaboration continues between her, Dr. Anger of CROET (the two lead investigators on the project), Drs. Rohlman (CROET) and Matt Lattal (OHSU) and investigators at the University of Washington, University of Buffalo and Menoufia University in Egypt. The outcomes of the research will relate to anyone who is exposed to organophosphorus pesticides, whether at the low concentrations experienced on farms or in high concentrations that could be experienced if used as a weapon.

## Assessment of Health Effects of Children Living in an Agricultural Community

There is increasing concern regarding the use of pesticides in agricultural communities and potential impacts on public health. Organophosphate (OP) pesticides are among those of greatest concern, due to their persistence once in the home and their established effects on the nervous system. Neurobehavioral tests (e.g. of memory and attention) have identified deficits in adult populations exposed to and poisoned by OP pesticides on farms. However, little research has examined OP pesticide exposure in children. While the neurotoxic effects of acute exposure to OP pesticides are well established, chronic low-level exposures are not well studied in adults and very few studies provide evidence of neurobehavioral deficits in farmworker children compared to controls. Children of farmworkers are presumed to be exposed to pesticides throughout development, and this exposure may produce subtle health effects that would not be detected by clinical examinations nor recognized by parents. A study conducted by Dr. Diane Rohlman and funded by the National Institute of Occupational Safety and Health (NIOSH) through the Pacific Northwest Agricultural Safety & Health Center, examines health effects in children living in an agricultural community to determine if they are associated with current home pesticide exposure or an estimate of lifetime exposure. Children's exposure to pesticides from the parent's work or residence in an agricultural community is measured through questionnaires and dust samples collected from the home. Children will be evaluated a second time, one year later, to obtain longitudinal data that will be used to characterize developmental progress and relate that progress to exposure estimates.

## Assessing Vulnerability of the Adolescent Brain to Organophosphorus Pesticides

There is compelling evidence that repeated (chronic) low-level occupational and environmental pesticide exposures are associated with neurobehavioral performance deficits (e.g. in memory and attention) in adults. Adolescents working in agriculture are exposed to the same risks as adults, but it is unknown whether their risk is equivalent to or greater than that of adults. Experimental animal studies indicate that the developing brain is more susceptible to the neurotoxic effects of OPs than the adult brain, and low-level exposures to OP pesticides cause significant neurobehavioral deficits in animal research. Adolescents (ages 15-18) in Egypt are legally hired

as seasonal workers to apply pesticides to the cotton crop. The pesticide application to the cotton crop is highly regulated and standardized across Egypt, and is limited primarily to OP pesticides (generally chlorpyrifos) and pyrethrins. This provides a unique opportunity to examine the impact of a highly consistent known OP pesticide exposure on the adolescent and their developing nervous system. Recent research in this adolescent Egyptian population found increasing reports of symptoms, depressed cholinesterase, and extensive neurobehavioral deficits in adolescents applying chlorpyrifos (vs. controls). While we have preliminary evidence of some of the highest reported exposure concentrations from dermal patch and urinary samples in adult Egyptian applicators, there is no quantitative exposure data available in adolescents. Furthermore, what is not established is if these exposure-related nervous system effects accumulate across time, if the effects increase with repeated exposure, and if they reverse after exposure ends. The goal of this project is to examine the dose-related response of the adolescent nervous system to OP pesticides, to determine if repeated exposures produce a progressive deficit and to determine if this deficit is reversible. The Egypt project is funded by NIEHS through the Fogarty International Center. It expands upon some of the work we have done with adolescents in Oregon.

Rohlman DS, Lasarev M, Anger WK, Scherer J, Stupfel J, McCauley L. Neurobehavioral performance of adult and adolescent agricultural workers. Neurotoxicology. 2007 Mar;28(2):374-80. Epub 2006 Dec 4.

Abdel Rasoul GM, Abou Salem ME, Mechael AA, Hendy OM, Rohlman DS, Ismail AA. Effects of occupational pesticide exposure on children applying pesticides. Neurotoxicology. 2008 Sep;29(5):833-8.

## Organophosphorus Pesticides May Alter the Incidence of Asthma

Organophosphorus pesticides (OPs) are widely used in agriculture and other pest control environments, including orchards in Oregon. Recent epidemiologic studies have identified OPs as occupational and environmental factors potentially contributing to the increase in asthma prevalence over the last 25 years. In support of this hypothesis, Dr. Pam Lein's research group previously demonstrated that real-world concentrations of OPs induce airway hyper-reactivity in guinea pigs. Sensitization to allergens is a significant contributing factor in asthma; therefore, Dr. Lein wanted to determine whether allergen sensitization similarly influences OP-induced airway hyper-reactivity. Non-sensitized and allergen-sensitized guinea pigs were injected subcutaneously with the OP, parathion. Allergen sensitization decreased the threshold dose for parathion-induced airway hyper-reactivity and exacerbated parathion effects on nerve stimulation-induced bronchoconstriction. Pretreatment with antibody to interleukin (IL-5) prevented parathion-induced hyper-reactivity in sensitized, but not in non-sensitized guinea pigs. These results show that antigen sensitization increases vulnerability to parathion-induced airway hyper-reactivity by a mechanism that is dependent on IL-5. Since sensitization to allergens is characteristic of 50% of the general population and 80% of asthmatics (including children), these findings have significant implications for OP risk assessment, intervention, and treatment strategies.

Becky J. Proskocil, Donald A. Bruun, Jesse K. Lorton, Kirsten C. Blensly, David B. Jacoby, Pamela J. Lein, and Allison D. Fryer. Antigen Sensitization Influences Organophosphorus Pesticide–Induced Airway Hyperreactivity. Environmental Health Perspectives 116(3), 2008: 381-388

## Effects of Developmental Exposure to PCBs Explored

The "developmental origins of adult disease" hypothesis was originally derived from evidence linking low birth weight to cardiovascular diseases, including stroke. Subsequently, it has been expanded to include developmental exposures to environmental contaminants as risk factors for adult-onset disease. Polychlorinated biphenyls (PCBs) are an important class of environmental contaminant widely used as dielectric fluids in transformers, capacitors, and coolants. Due to PCB's toxicity, the United States Congress banned their production in 1979; however, PCB's continue to present an exposure risk as persistent organic pollutants. Dr. Pam Lein is interested in the hypothesis that developmental exposure to PCBs alters stroke outcome in adults. To test this, pregnant rats were exposed to low levels of the PCB mixture Aroclor 1254 (A1254) in the diet throughout gestation and lactation. Cerebral stroke was induced in the offspring at 6–8 weeks of age, after which the concentrations of PCB congeners were quantified in brain tissue, and expression of the PBC-inducible metabolic enzymes, Bcl2 and Cyp2C11 were quantified. Interestingly, Dr. Lein found that developmental exposure to A1254 significantly decreased infarct size in females and males, whereas effects of developmental A1254 exposure on Bcl2 and Cyp2C11 expression did not correlate with effects on infarct volume. These data provide proof of principle that developmental exposures to contaminants found in the workplace and larger environment influence the response

of the adult brain to ischemic injury and thus represent potentially important determinants of stroke susceptibility.

Suzan Dziennis, Dongren Yang, Jian Cheng, Kim A. Anderson, Nabil J. Alkayed, Patricia D. Hurn, and Pamela J. Lein. Developmental Exposure to Polychlorinated Biphenyls Influences Stroke Outcome in Adult Rats. VOLUME 116 | NUMBER 4 | April 2008 • Environmental Health Perspectives 116(4), 2008: 474-480

Neurodevelopmental disorders are associated with altered patterns of connections between neurons. A critical determinant of neuronal connectivity is the dendritic morphology of individual neurons, which is shaped by experience. The identification of chemical exposures that interfere with dendritic growth and plasticity may, therefore, provide insight into environmental risk factors for neurodevelopmental disorders. Dr. Lein's group tested the hypothesis that polychlorinated biphenyls (PCBs), found in electrical transformers, alter dendritic growth and/or plasticity by promoting the activity of ryanodine receptors (RyRs), which are the major cellular mediators of calcium-induced calcium release in animal cells (a mechanism important to dendritic growth and plasticity). The Morris water maze was used to induce experience-dependent neural plasticity in weanling rats exposed to either vehicle or the PCB mixture Aroclor 1254 (A1254) in the maternal diet throughout gestation and lactation. Developmental A1254 exposure promoted dendritic growth in cerebellar and neocortical neurons among untrained animals but attenuated or reversed experience-dependent dendritic growth among maze-trained littermates. These structural changes coincided with subtle deficits in spatial learning and memory, increased [3H]-ryanodine binding sites and RyR expression in the cerebellum of untrained animals, and inhibition of training-induced RyR upregulation. A congener with potent RyR activity, PCB95, but not a congener with negligible RyR activity, PCB66, promoted dendritic growth in primary cortical neuron cultures and this effect was blocked by pharmacologic antagonism of RyR activity. These results show that developmental exposure to PCBs interferes with normal patterns of dendritic growth and plasticity, and these effects may be linked to changes in RyR expression and function. These findings identify PCBs as possible risk factors for neurodevelopmental disorders, especially in children with heritable deficits in calcium signaling.

Dongren Yang, Kyung Ho Kim, Andrew Phimister, Adam D. Bachstetter, Thomas R. Ward, Robert W. Stackman, Ronald F. Mervis, Amy B. Wisniewski, Sabra L. Klein, Prasada Rao S. Kodavanti, Kim A. Anderson, Gary Wayman, Isaac N. Pessah, and Pamela J. Lein. Developmental Exposure to Polychlorinated Biphenyls Interferes with Experience-Dependent Dendritic Plasticity and Ryanodine Receptor Expression in Weanling Rats. Environmental Health Perspectives 117(3), 2009: 426-435

## Outreach and Education

CROET has been proactively engaged in providing timely occupational health and safety information to employees, employers, health and safety professionals, doctors and nurses.

### CROETweb.com

CROETweb.com is an occupational safety and health resource directory that contains links to over 1200 occupational safety and health resources focusing on day-to-day workplace issues. CROETweb serves thousands of users who regularly bookmark this resource, those who subscribe to the monthly electronic newsletter, and those searching by search engine (e.g. Google) for occupational health and safety topics on the web. It is widely recognized and respected by industrial health and other safety professionals as well as the general public, based on feedback from user groups. CROETweb was accessed an average 12,000-16,000 times per month for a total of 194,676 'hits' in 2008. This monthly average hit rate has increased almost every year since the inception of CROETweb.

- The most popular pages visited for 2008-09 included Materials for Safety Talks, Hospitality, Construction and Office Ergonomics

  New topics 2008: Automotive; Indoor Air Quality

  New topics 2009: Mass Transit; H1N1/Swine Flu; MRSA; Fishing; Hospitality – Hotel, Restaurant and Kitchen; Landscaping; Logging & Forestry; Acids & Bases; Chromium; Avian Flu; Occupational Asthma; Occupational Reproductive Hazards; Materials for Safety Talks; OSH Professional Development; and Safety, Language and Culture.

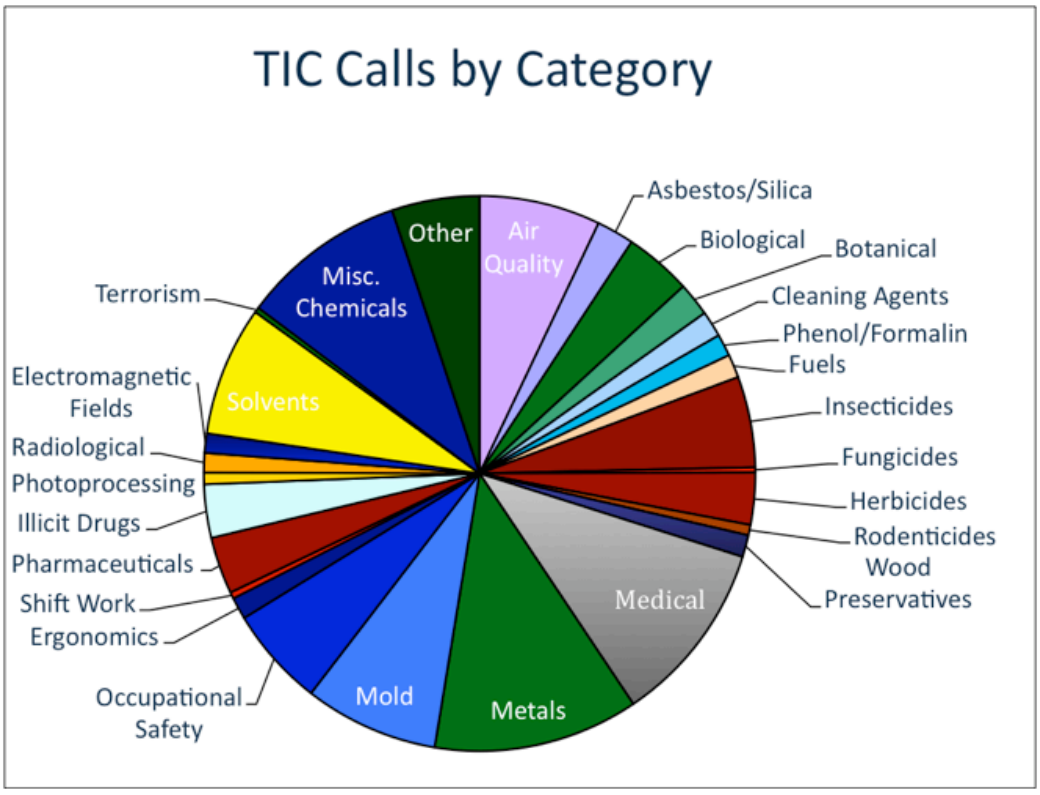
- Annual page hits – 2006: 162,838
  2007: 166,134
  2008: 194,676
  2009: 158,218

- More than 1,250 links are posted on CROETweb.com, including Oregon-specific information from OR-OSHA.

  As of the end of 2009, CROETweb contains 3500 links and 80 main topic pages.

## Toxicology Information Center (TIC)

CROET's Toxicology Information Center, directed by Dr. Fred Berman, provides free scientifically accurate information for those with questions or concerns about chemical, biological, physical or other agents encountered in the workplace and elsewhere. In 2008-2009, Dr. Berman handled hundreds of consultation requests from occupational safety and health professionals, business owners, government agencies, physicians and nurses, the media, and the general working public. Inquiries covered a variety of issues, as shown on the chart. Chemical agents of concern included solvents, heavy metals, insecticides, fungicides, and herbicides. Physicians often called seeking information on a variety of potentially occupation-related health complaints. Calls in regard to indoor mold were common as were calls related to acute and chronic medical problems that were attributed to exposure to chemical agents. Each request took from less than an hour up to several days to respond to fully. The TIC is open from 7:30 a.m. to 4:00 p.m., Monday through Thursday. Walk-in visitors have access to a variety of resources, including computers, databases, government reports, textbooks, and journals that are devoted to toxicology-related issues and occupational health.




## Chemical Risk Information Service (CRIS)

OSHA regulations require employers to maintain Material Safety Data Sheets (MSDS) for hazardous chemicals used in their workplace. This often proves to be a difficult record-keeping task, and it can be burdensome to ensure that employees have quick access to health and safety information in the workplace when they need it. Since 1998, CROET's Chemical Risk Information Service, directed by Dr. Gregory Higgins, has helped a grow-

ing number of local and international industries manage and distribute chemical safety information through its internet-based MSDS management system. CROET's working relationship with the Oregon Poison Center also ensures that employees covered by the program have ready access to medical information in the event of exposure. During 2008-2009, the Chemical Risk Information Service added four new clients, and now provides MSDS management services to 40 municipal, construction, and service companies, most of which are Oregon-based. An enhanced program was developed for our new client Portland METRO, which allows METRO to evaluate and rank the human health, environmental, and physical hazards of the products used in their facilities. We are also developing a website tool for METRO to help ensure "green" products are chosen for their facilities. Enhancements were made to the website and database during this period. CROET continues to provide expert MSDS management services at a reasonable cost, which is attractive to both small and large organizations.

## Health and Safety Training Symposia

CROET provides two health and safety symposia per year, one sponsored jointly with Portland State University. Topics are determined based on solicited and unsolicited feedback from the Oregon occupational health and safety professional community. The target audience includes health and safety professionals, occupational nurses and physicians, loss control specialists and human resource representatives, although the targeted group varies based on the symposium topic. The purpose of the symposia is to provide timely, up-to-date presentations, forums and discussions on workplace safety and health issues. CROET presented the following symposia series in 2008-2009:

**Managing the Aging Workforce: Implications for Workplace Stress, Health, Safety and Performance**
Presented by CROET and Portland State University
October 30, 2009

**Oregon's Workplace Health and Safety: Looking Forward to 2020**
Presented by CROET and Oregon OSHA
September 24, 2009

**The Body's Response to Environmental Stress**
May 29, 2009

**Work-Family Stress: Implications for Safety and Health**
Presented by CROET and Portland State University
November 7, 2008

**Driving Safety at Work**
Held at the UA 290 Plumbers Steamfitters Training Center, Tualatin, OR.
June 6, 2008

## Regional Health and Safety Conferences

OR-OSHA sponsors the majority of health and safety conferences that CROET attends; these conferences are an important means by which CROET reaches out to working Oregonians. Workers and businesses learn about CROET and what it has to offer, and CROET personnel learn about the needs and concerns of workers and the industries that employ them. Moreover, CROET scientists are often asked to give health and safety presentations in addition to providing conference exhibits. Overall, conferences represent a tremendous networking opportunity for CROET outreach personnel. The following are safety and health conferences attended by CROET during 2008-2009:

**2008**
- Oregon Employers Traffic Safety Conference
- 15th Annual Oregon Small Business Fair
- Blue Mountain Occupational Safety & Health Conference
- Cascade Occupational Safety & Health Conference
- Workers' Compensation Division 2008 Educational Conference
- Oregon Tradeswomen, Inc.'s 2008 Women in Trades Conference

- Central Oregon Occupational Safety & Health Conference
- Southern Oregon Occupational Safety & Health Conference
- Mid-Oregon Construction Safety Summit
- Willamette Valley Ag Expo
- Western Pulp & Paper Workers Safety & Health Conference
- New Paths - Health and Safety in Western Agriculture
- Oregon Employers Traffic Safety Conference

**2009**
- Oregon Governor's Occupational Safety & Health Conference
- Blue Mountain Occupational Safety & Health Conference
- Central Oregon Occupational Safety & Health Conference
- Southern Oregon Occupational Safety & Health Conference
- NW Environmental Health Conference: Bridging Research, Care and Policy
- 2009 Women in Trades Career Fair
- Public Health Week at OMSI - "Crack the Case of Good Health"
- Oregon Small Business Fair
- Oregon Employers Traffic Safety Conference
- Oregon Workers' Compensation Division Educational Conference

## OHSU Health Discoveries Program: Let's Get Healthy!

A "Research to the Public" exhibit titled "Lets Get Healthy!" has been developed by Jackie Shannon, Ph.D. Originally titled "Nutrition World", the exhibit debuted for 2 weeks in 2007 at the Oregon Museum of Science and Industry (OMSI) in Portland, in conjunction with the museum's Body Worlds 3 exhibit. In 2008-2009, Let's Get Healthy! was expanded into a popular interactive education and research exhibit that allows community members to learn important information about their body while contributing to science. The exhibit not only educates the public about relationships among diet, weight and chronic disease, but also introduces attendees to biomedical research and invites them to become research participants by providing them an opportunity to obtain tailored feedback on their diet. This included measurements of height, weight, waist circumference and percent body fat, measurements of blood glucose, HDL, LDL and total cholesterol levels. Participants can contribute their health information anonymously to a population database that researchers use to study the relationship between eating habits, body composition and genetics. Now, schools and communities have access to the anonymized data that can be used to encourage healthy living in the community or teach scientific inquiry to students using real data. The program also partners with schools to help teachers meet Oregon's state standards in health education. "Let's Get Healthy" is housed within the Health Discoveries Program, a program designed to support research, data collection and data analysis activities resulting from implementation of the exhibit.

In 2008-2009, the Oregon Clinical and Translational Research Institute (OCTRI) and OHSU's Science Education Partnership Award (SEPA) program became engaged in furthering the development and promotion of the exhibit. OCTRI and SEPA were awarded two National Institutes of Health (NIH) administrative supplement grants to take "Let's Get Healthy!" to rural Oregon communities. The grants have supported a partnership between OCTRI and SEPA at OHSU, OMSI, and the Oregon State University School of Pharmacy. Two new partners were also brought into the project: Oregon Area Health Education Centers (AHECs) and the Oregon Rural Practice-based Research Network (ORPRN). ORPRN and AHEC are helping to bring the "Let's Get Healthy!" exhibit to the rural communities that they serve, and are facilitating direct community access to the data – in both community venues and medical facilities – thereby serving the interests of the communities, OCTRI and OMSI investigators. This work supports CROET's goal of improving the health of the Oregon workforce.

## The Global Health Center (GHC)

The newly formed Global Health Center (GHC), initially housed in the CROET Toxicology Information Center, facilitates OHSU collaboration with the global health community to promote quality and equity in health care at home and abroad. Through the GHC, CROET and OHSU are working with domestic and international communities to develop programs for students, faculty, staff and partners that will promote global health awareness, research, education and advocacy. Dr. Peter Spencer serves as Director of the Global Health Center. Dr. Spencer has long studied the causes and solutions to neglected human diseases in developing countries, and hopes to spawn a new generation of medical and research professionals certified in global health. Built on the principle

that there can be an effective two-way exchange on matters such as cultural competency, health education, research opportunities and clinical practice, the long-range goal of the GHC is to maintain a compact, efficient operation on the campus and invest in building healthcare capacity in global communities. In 2008, the GHC was awarded a 3-year Fogarty Framework for Global Health research education award.

## Injury and Recovery of the Nervous System and Muscles

CROET scientists conduct basic research that examines the causes of injury to nerves and muscles in order to identify protective, preventative, and recovery methodologies for such injuries.

### Nerve Support Protein Plays Unique Role in Neuromuscular Development

Neuromuscular injuries are the largest cause of workplace disability, and Bruce Patton, PhD, is interested in identifying signaling pathways in nerve and muscle cells that control their regeneration. Nerves and muscles have the capacity to regenerate, but typically do so slowly and with errors and internal scarring that result in lingering disability. Nerves include two primary types of cells. Long neuronal axons connect the brain and spine to muscles and other tissues. Schwann cells normally wrap the axons in a supportive sheath (myelin) and support re-growth of injured axons. Results from the Patton lab show how a family of extracellular matrix proteins made by Schwann cells ensure that every axon becomes ensheathed by the proper number and sub-type of Schwann cell. In 2008-2009, these studies were extended to show how one of these proteins, called laminin alpha2, works in part by polymerizing to create a mesh-like scaffold of protein  along the surface of the growing nerve fiber, which controls how the Schwann cells proliferate and differentiate as the nerve develops or re-grows.  In further work, the lab has discovered that these matrix proteins also play critical roles the growth and maturation of neuronal pathways in the brain. Finally, the lab made an unexpected discovery that defects in maintaining the expression of one of the matrix proteins contributes to chronic kidney disease. These results have implications for treatment strategies for recovery from neurological injuries, as well as diseases such as ALS and multiple sclerosis.

### Chronic Disease and Working Safety

Chronic disease takes a significant toll on our workforce just as it does in the broader community. CROET research seeks to discover causes of chronic diseases that are produced or exacerbated by workplace factors and identifies processes or procedures that can prevent or ameliorate those diseases and improve workplace safety.

### Can Fruit Flies Get Alzheimer's Disease?

Alzheimer's Disease is the most common form of dementia, with approximately 26 million people suffering worldwide. It is also expected that with the increase in life span this number will quadruple over the next four decades, and people will continue working later in life than they do today. Starting with memory loss, AD eventually leads to severe mental impairment, and although therapeutic drugs can slow down the progression of cognitive decline, there is currently no cure.

One of the hallmark features of Alzheimer's Disease is the accumulation of amyloid plaques which consist of small protein segments called amyloid beta (Ab). Ab is cleaved from the larger Amyloid Precursor Protein (APP) by several enzymes, which in addition to Ab results in the production of several other protein fragments. The normal physiological function of APP and its fragments as well as its interaction with other proteins are, however, still not well understood. Due to methodological difficulties and ethical concerns, studies in humans have obvious limitations. Therefore, the Kretzschmar lab uses a well-established biological model system, the fruitfly Drosophila, to model this condition.

To study the toxicity of APP, the Kretzchmar lab created flies that express APP and produce Ab. These flies show accumulations of Ab in the brain, neuronal cell death, and behavioral deficits similar to Alzheimer patients. In fact, Dr. Kretzschmar has shown that Drosophila contains its own version of APP and Ab that also cause these defects. Having established that the deleterious effects of APP and Ab are conserved in flies, the Kretzschmar lab is using this system to identify genetic factors that influence the severity of these effects and are performing drug tests to find treatments that could eventually lead to increased quality of life and productivity of workers in retirement.

I. Greeve, D. Kretzschmar, J. Tschäpe, A. Beyn, C. Brellinger, M. Schweizer, R. Nitsch and R. Reifegerste. Alzheimer's disease-like neuropathology in transgenic Drosophila. Journal of Neuroscience, 24, 3899-3906, 2004.

K. Carmine-Simmen, T. Proctor, J. Tschäpe, B. Poeck, T. Triphan, R. Strauß and D. Kretzschmar. Neurotoxic effects induced by Ab peptides derived from the Drosophila Amyloid Precursor Protein (APP) suggest a conserved toxic function of APP proteins. Human Molecular Genetics, 33, 274-281, 2009.

L. Wang, H. Ankati, S. Akubathini, M. Balderamos, C. Storey, A. Patel, V. Price, D. Kretzschmar, E. Biehl, and S. D'Mello. Identification of novel 1, 4- benzoxazine compounds that are protective in tissue culture and in vivo models of neurodegeneration. Journal of Neuroscience Research, epup 2010.

## Discoveries of Circadian Clock Function Leads to Enhanced Understanding of Sleep-Wake Cycles

Circadian rhythms are physiological processes that cycle with a period of twenty-four hours. In humans, these rhythms are set so that we are active during the day and sleep at night, which has significant ramifications in our 24 hr. society. Approximately 1 in 5 workers have jobs that require them to work outside of the traditional 8-5 workday. This work schedule requires these workers to be awake when their internal clock is telling them to sleep. Short-term disruption of the circadian system can lead to higher rates of on-the-job accidents, impairments in cognitive function, hormone activity, and gastrointestinal distress. Long-term disruption of the circadian system contributes to the development of breast and colorectal cancer, cardiovascular disease, mood disorders and a number of metabolic derangements. Biological circadian rhythms are controlled by a small brain region structure called the suprachiasmatic nucleus (SCN), which contains a molecular time-keeping mechanism. The signals from this biological clock are sent throughout the body and drive circadian rhythms in multiple tissues and organs. The long-term goal of Dr. Charles Allen's basic research program is to identify the cellular mechanisms underlying the generation and entrainment of circadian rhythms. Successful completion of this work will provide a better understanding of the mechanisms underlying regulation of circadian processes such as sleep. This knowledge can lead to better and more rationale treatment of circadian-based sleep and mood disorders.

The master circadian pacemaker located in the suprachiasmatic nucleus (SCN) is reset by light intensity–dependent signals transmitted via a direct nerve pathway from the eye's retina to the SCN. Short-term plasticity at nerve synapses in this pathway was studied using stimuli that simulated the activity of light sensitive retinal cells. In addition, neuronal communication within the suprachiasmatic nucleus (SCN) network facilitates light-induced phase changes and synchronization of individual nerve oscillators. Using calcium imaging techniques to record changes in the intracellular calcium concentration ([Ca2+]i) in the SCN neural network, Dr. Allen's group studied the role of the neurotransmitter GABA in interneuronal communication and modulation of optic nerve stimulations that mimic light input signals. Stimulation of the retinohypothalamic tract (RHT) evoked divergent Ca2+ responses in neurons that varied regionally within the SCN with a pattern related to that evoked by applications of GABA. Application of a GABA receptor antagonist induced changes in baseline [Ca2+]i in a direction opposite to that evoked by GABA, and similarly altered the RHT stimulation-induced Ca2+ response. The GABA induced Ca2+ response varied in time and region within the SCN network. GABA-A and GABA-B receptor agonists and antagonists were used to evaluate components of the GABA-induced changes in [Ca2+]i. These results suggest that physiologic GABA induces opposing effects on [Ca2+]i in the SCN network and may play an important role in neuronal Ca2+ balance, synchronization and modulation of light input signaling.

## Organic Solvents Illuminate our Understanding of Neurological Disorders

Workers exposed to certain organic solvents (such as n-hexane and 1,2-diethylbenzene) can develop nerve and spinal cord damage that leads to a crippling disease known as peripheral neuropathy. While n-hexane neuropathy is all too common today in certain low- and middle-income countries, improved workplace practices have virtually banished the disease from U.S. industry. Now, the neurotoxic metabolites of n-hexane and 1,2-diethylbenzene are used here as valuable laboratory tools with which to probe the vulnerabilities of the nervous system. This is important as much for occupational as for general medicine because peripheral neuropathy complicates prevalent metabolic diseases of Americans, notably diabetes. Understanding why nerves degenerate in metabolic syndromes would be a huge stride forward toward prevention and treatment. Previous experimental work on this subject (see CROET Report 2006-7) has provided compelling evidence that nerve proteins are targeted in

metabolic and toxic diseases. The CROET team of Staff Scientist Desire Tshala-Katumbay, Emeritus Faculty Mohammad Sabri, and Senior Scientist Peter Spencer has now revealed the identity of some of the targeted proteins. They have identified 34 proteins in the spinal cord proteome that are markedly modified after exposure to the solvent metabolites. Additional work showed a significant alteration in the expression of an enzyme involved in protein folding, the proper activity of which is an absolute requirement for the proper functioning of the nervous system. Modifications were also seen in the further processing of proteins through a system called post-translation modification. While these observations have advanced knowledge of the molecular mechanisms that precede the onset of nerve degeneration, precisely how the cascade of events culminates in breakdown of nerve tissue remains to be shown.

Tshala-Katumbay D, Desjardins P, Sabri M, Butterworth R, Spencer P. New insights into mechanisms of gamma-diketone-induced axonopathy. Neurochem Res. 2009 Nov;34(11):1919-23. Epub 2009 Apr 29.PMID: 19404740

Tshala-Katumbay D, Monterroso V, Kayton R, Lasarev M, Sabri M, Spencer P. Probing mechanisms of axonopathy. Part II: Protein targets of 2,5-hexanedione, the neurotoxic metabolite of the aliphatic solvent n-hexane. Toxicol Sci. 2009 Feb;107(2):482-9. Epub 2008 Nov 25.PMID: 19033394

Tshala-Katumbay D, Monterroso V, Kayton R, Lasarev M, Sabri M, Spencer P. Probing mechanisms of axonopathy. Part I: Protein targets of 1,2-diacetylbenzene, the neurotoxic metabolite of aromatic solvent 1,2-diethylbenzene. Toxicol Sci. 2008 Sep;105(1):134-41. Epub 2008 May 22.PMID: 18502740

## Integrity of DNA (DNA damage, genetic alterations and disease)

Human health and risk for disease ultimately depend on the integrity of our DNA, the genetic material that provides the body's blueprint for manufacturing proteins that carry out the function of cells and organs. Aberrant forms of DNA can produce inherited diseases, and changes in DNA during life are believed to trigger cancer and many other chronic diseases. Such changes can result from exposure to certain chemicals found in the workplace and others in the diet and medications, and to sunlight in outdoor workers. Two broad types of DNA changes are recognized: DNA damage and DNA silencing.

### Insights Into Mechanisms That Lead to Cancer

Cancer is a leading cause of death and morbidity in Oregonians, and essentially all human populations. Cancer occurs when a cell's genome undergoes subtle or major alterations that cause critical proteins to be made incorrectly or not at all. A cell's genome contains DNA, which acts as the blueprint for construction of the cell. The critical proteins altered in cancer cells normally function to control cell growth and to maintain the integrity of the genome. An important question in cancer biology is how cellular DNA is altered leading to development of the cancerous cell. An alteration in DNA, commonly termed a mutation, is a change in the primary sequence of the DNA. Many different types of occupational and environmental exposures cause mutations. These exposures cause cancer because of the link between mutation and cancer.

Research in the laboratory of Dr. Mitchell Turker has been directed towards identifying the types of mutations that occur spontaneously or are induced by environmental exposures. Most of this work is done with mouse kidney cells because current methodologies allow mutations to be induced and detected in cultured kidney cells and/or within the intact mouse kidney. One example of a study with cultured kidney cells showed that the types of mutations caused by ultraviolet radiation are different when the cells are first exposed to oxidative stress. Ultraviolet radiation found in sunlight is a major contributor to skin cancer. Another study compared the types of mutations induced by ionizing radiation in cultured kidney cells with mutations induced by radiation exposure in mouse kidneys. This study showed that some types of mutations were induced in both the cultured cells and in the intact kidney, but other types were only observed in the exposed kidney. Moreover, mutant cells from the kidneys exhibited unstable genomes. In total, this study showed mutagenic effects from ionizing radiation exposure, such as from sunlight, and that these effects are best studied in the intact organism.

Gene inactivation in cancer cells also occurs via a second pathway termed gene silencing, which involves loss of protein production without a DNA mutation. Gene silencing is analogous to a car motor that has stalled and then shuts down. It may be possible to restart such a gene, but repairs are required. Research in the Turker laboratory established that a stalling of the gene predisposes it to undergo silencing. Additional work demonstrated a way to

prevent silencing from occurring. Prevention of gene silencing could lead to approaches to prevent cancer.

Skinner AM and Turker MS High Frequency Induction of CC to TT Tandem Mutations in DNA Repair Proficient Mammalian Cells. Photochemistry and Photobiology 84:222-227, 2008.

Oyer JA, Chu A, Brar S, and Turker MS Aberrant Epigenetic Silencing Is Triggered by a Transient Reduction in Gene Expression. PLoS ONE 4: e4832. doi:10.1371/journal.pone.0004832, 2009.

Kronenberg A, Gauny S, Kwoh, E, Connolly L, Dan C, Lasarev M, and Turker MS Comparative Analysis of Cell Killing and Autosomal Mutations in Mouse Kidney Epithelium Exposed to 1 GeV/amu Fe Ions In Vitro and In Situ. Radiation Research 172:550-557, 2009.

Turker MS, Connolly L, Dan C, Lasarev M, Gauny S, Kwoh E, and Kronenberg A, Comparison of Autosomal Mutations in Mouse Kidney Epithelial Cells Exposed to Fe ions In Situ or in Culture. Radiation Research 172:558-566, 2009.

## Mechanisms Behind Insulin Secretion Diseases Being Uncovered

ATP-sensitive potassium (KATP) channels are gated by the intracellular nucleotides ATP and ADP, the major energy molecules within cells. As such, they couple cell metabolism to membrane excitability and regulate a variety of physiological processes including insulin secretion, vasodilatation, neurotransmitter release, and cell defenses against cardiac and brain ischemia (stroke). Malfunction of KATP channels due to genetic mutations has been shown to cause congenital hyperinsulinism, diabetes, and delayed cardiomyopathy, all diseases that can affect productivity in the workplace. The primary research focus of Show-Ling Shyng, PhD is to understand the role of KATP channels in health and disease, in particular with regard to the regulation of insulin and glucose homeostasis. A recent highlight of her research is the demonstration that patients diagnosed with congenital hyperinsulinism in childhood as a result of dominant KATP channel mutations are not more susceptible to type II diabetes, contrary to what was proposed previously by others. The large-scale clinical and basic science study, published in the Journal of Clinical Investigation in 2008, was a collaborative effort of researchers from OHSU and the Children's Hospital of Philadelphia. The work has significant impact on our understanding of the biochemical characteristics of dominant mutant KATP channels associated with congenital hyperinsulinism and the course of disease development. Her ultimate goal is to develop therapeutic strategies to combat diseases caused by KATP channel dysfunction resulting from genetic mutations or environmental/occupational exposures.

Sara E. Pinney, Courtney MacMullen, Susan Becker, Yu-Wen Lin, Cheryl Hanna, Paul Thornton, Arupa Ganguly, Show-Ling Shyng, and Charles A. Stanley. Clinical characteristics and biochemical mechanisms of congenital hyperinsulinism associated with dominant KATP channel mutations. J. Clin. Investigation 118(8): 2877-2886, 2008

## Insights Into a Cause of Metabolic Syndrome and Cancer

It is estimated that greater than 45 million Americans suffer from a constellation of at least three out of four of the following diseases: obesity, hypertension, diabetes, and fatty liver disease. Collectively, these are known as the Metabolic Syndrome. The annual health care costs associated with the treatment and ongoing care of these diseases is an enormous health care burden with costs exceeding 100 billion dollars, and seriously increase sick leave and limit workplace productivity.

Research in the laboratories of Drs. Stephen Lloyd and Amanda McCullough has been directed toward ascertaining the most fundamental mechanisms that initiate cellular changes that ultimately result in metabolic syndrome and cancer. A unifying hypothesis to explain the origins of all of these diseases is the following: the body naturally produces reactive chemical species that can damage the cell's genetic material; these chemical byproducts (reactive oxygen species) not only are generated as part of normal energy production and cellular defense mechanisms, but also are produced from exposure to many environmental toxicants and radiation. These reactive oxygen species damage the cells genetic material (DNA) and if not repaired to its original state, the damage could lead to mutations that would trigger the initiation of metabolic syndrome and/or cancer. Since cells contain DNA in both the nucleus and mitochondria (location of energy production), it is essential to repair damage in both cellular locations.

To investigate these hypotheses, the Lloyd and McCullough laboratories have created mice that lack the ability to initiate DNA repair following challenge with reactive oxygen species. Mice that lack one of these repair proteins

(NEIL1) are very prone to obesity, fatty liver disease, and insulin resistance (Vartanian et al, 2006). Further, the DNA located within the mitochondria of these mice is severely damaged. In addition to the metabolic syndrome diseases, mice that lack NEIL1 and another repair enzyme (NTH1) were shown to be very prone to spontaneous cancer formation (Chan et al, 2009). Greater than 70% of mice that were deficient in both repair proteins spontaneously developed lung adenomas and carcinomas and nearly 50% also developed liver carcinomas (Chan et al 2009). These data establish for the first time a common link between cellular deficiencies in DNA repair with both cancer and metabolic syndrome.

Vartanian V, Lowell B, Minko IG, Wood TG, Ceci JD, George S, Ballinger SW, Corless CL, McCullough, AK, Lloyd RS. The metabolic syndrome resulting from a knockout of the NEIL1 DNA glycosylase. Proc Natl Acad Sci U S A. 103(6):1864-9, 2006.

Chan, M.K., Ocampo-Hafalla, M.T., Vartanian, V., Juruga, P., Kirkali, G., Koenig, K.L., Brown, S., Lloyd, R.S., Dizdaroglu, M., Teebor, G.W. Targeted deletion of the genes encoding NTH1 and NEIL1 DNA N-glycosylases reveals the existence of novel carcinogenic oxidative damage to DNA. DNA Repair (Amst) 8(7):786-94, 2009.

## Cellular Responses to Acute and Chronic Formaldehyde Exposure

The laboratory of Dr. Amanda McCullough is interested in the regulation and roles of DNA repair in cellular responses to occupational and environmental stress and how genetic variation and defects in these systems modify the risk of cancers and other disease states in humans.

Formaldehyde exposure occurs both in occupational settings and household environments. Formaldehyde is a respiratory irritant associated with asthma and “sick building syndrome”, and exposure is associated with the occurrence of nasopharyngeal cancers and DNA damage. In order to identify and characterize the biochemical mechanisms for repair of formaldehyde-induced DNA damage, the McCullough lab is utilizing a yeast model system that allows the entire genome to be screened for genes that confer formaldehyde sensitivity. These studies have identified specific biochemical pathways that protect cells from the cytotoxic effects of acute and chronic formaldehyde exposures; results that will impact the assessment of safe human exposure limits in the workplace and from some consumer products. This work was published in the journal DNA Repair in 2009.

Bendert de Graaf, M.S., Clore, A.J., McCullough, A.K. Cellular Pathways for DNA Repair and Damage Tolerance of Formaldehyde-Induced DNA-Protein Crosslinks. DNA Repair, 2009; 8:1207-14.

## DNA Repair-based Therapeutic Strategies for the Prevention of Skin Cancer

Exposure of human skin to ultraviolet light (UV) triggers a progression of events that is initiated by DNA damage and immune suppression and can ultimately result in mutagenesis, actinic keratoses, and skin cancers. The number of affected individuals is rapidly increasing, with over 1 million new skin cancers diagnosed in the United States annually. The carcinogenic effects of UV light, such as from sunlight, are directly mediated by dipyrimidine DNA photoproducts. Human cells have only one mechanism to repair these DNA lesions, while lower organisms possess multiple pathways to repair the deleterious consequences of UV-induced DNA damage. In order to implement proactive strategies to treat and prevent several human diseases that can be directly attributed to inefficient repair of UV-induced DNA lesions, including skin cancer, the McCullough and Lloyd laboratories have discovered and characterized multiple DNA repair enzymes that possess activities that can initiate an additional repair pathway in human cells.

Experimental reduction to practice was demonstrated in 2008-2009 by the following technological breakthroughs: 1) purification and encapsulation of patented enzymes in specific targeting vesicles that are used for topical skin delivery and 2) demonstration of the efficacy of the enzymes to localize to damaged cells and to initiate DNA repair using a fully-differentiated human skin model system and human keratinocyte cell cultures. These findings make it possible to develop topical treatments for UV-induced DNA damage in populations excessively exposed to sunlight, such as outdoor workers.

# Fiscal Year 2007/2008

| Workers' Compensation Expenditures | | Federal and Other Grant Expenditures | |
|---|---|---|---|
| **Salaries** | | **Salaries** | |
| Salaries - research (22% of all salaries) | 1,136,912 | Salaries - research (55% of all salaries) | 2,793,917 |
| Salaries - outreach (8% of all salaries) | 437,020 | Salaries - outreach (0% of all salaries) | 0 |
| Salaries - education (3% of all salaries) | 156,256 | Salaries - education (<1% of all salaries) | 6,293 |
| Salaries - administration (9% of all salaries) | 457,342 | Salaries - administration (2% of all salaries) | 110,074 |
| Salaries - core services[1] (1% of all salaries) | 19,486 | Salaries - core services (0% of all salaries) | 0 |
| **Supporting Services (includes cores)** | | **Supporting Services (includes cores)** | |
| Supplies and equipment | 682,067 | Supplies and equipment | 1,274,761 |
| Miscellaneous support[2] | 170,517 | Miscellaneous support[2] | 18,892 |
| **Outreach and Education** | | **Outreach and Educ Outreach and Education** | |
| Services, supplies and equipment | 316,855 | Services, supplies and equipment | 20,271 |
| **Other Expenses** | | **Other Expenses** | |
| Bond principal & interest | 353,481 | Building operations & maintenance | 0 |
| OHSU administrative charges | 106,942 | OHSU administrative charges | 250,573 |
| Total | $3,836,878 | Total | $4,474,781 |

# Programs
# Fiscal Year 2007/2008

| | Amount paid by W/C | Amount paid by grants | Total Cost |
|---|---|---|---|
| **Outreach and Education** | | | |
| Information dissemination (e.g., TIC[3], website, newsletters, brochures) | 712,433 | 20,271 | 732,704 |
| Education & training programs (professional & para-professional) | 180,392 | 186,155 | 366,547 |
| Chemical risk information service[5] | 17,306 | 0 | 17,306 |
| | | | |
| **Basic and Applied Research** | | | |
| Factors that affect workplace performance | 290,658 | 495,444 | 786,102 |
| Damage and repair of the nervous system and muscle | 484,211 | 725,153 | 1,209,364 |
| Occupational/environmental exposures and their consequences | 471,678 | 884,759 | 1,356,437 |
| DNA damage, genetic alterations & disease | 313,127 | 1,775,430 | 2,088,557 |
| Core services support[1] | 167,902 | 0 | 167,902 |
| Non-program-specific expenses[4] | 1,199,171 | 387,569 | 1,586,740 |
| | | | |
| **Total Expenses** | $3,836,878 | $4,474,781 | $8,311,659 |

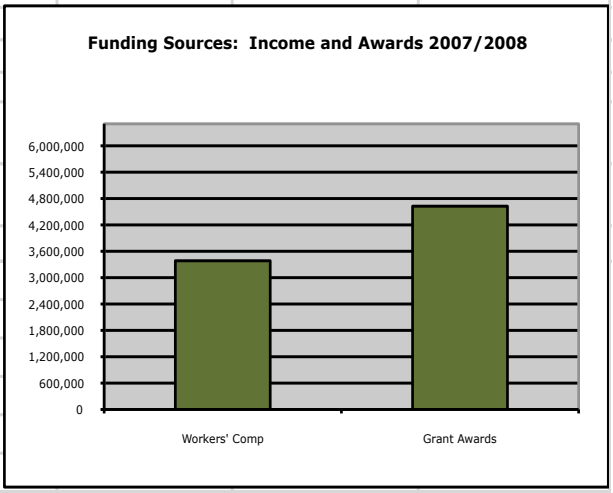
[1] core services - centralized graphics, statistics, imaging, tissue culture and and morphology (pathology)

[2] e.g., office supplies, equipment maintenance and repair, phone rental and line charges

[3] Toxicology Information Center

[4] includes supporting services, administrative salaries, bond principal and interest, OHSU administrative charges, building operation and maintenance

[5] Chemical risk information service is self-suppoting and uses carry forward from prior years if needed



# CROET Expenditures
# Fiscal Year 2008/2009

| Workers' Compensation Expenditures | | Federal and Other Grant Expenditures | |
|---|---|---|---|
| **Salaries** | | **Salaries** | |
| Salaries - research (37% of all salaries) | 848,673 | Salaries - research (33% of all salaries) | 2,488,038 |
| Salaries - outreach (5% of all salaries) | 104,064 | Salaries - outreach (0% of all salaries) | 0 |
| Salaries - education (3% of all salaries) | 73,488 | Salaries - education (0% of all salaries) | 0 |
| Salaries - administration (17% of all salaries) | 394,997 | Salaries - administration (5% of all salaries) | 110,851 |
| Salaries - core services[1] (<1% of all salaries) | 19,095 | Salaries - core services (0% of all salaries) | 0 |
| **Supporting Services (includes cores)** | | **Supporting Services (includes cores)** | |
| Supplies and equipment | 878,981 | Supplies and equipment | 1,185,544 |
| Miscellaneous support[2] | 219,745 | Miscellaneous support[2] | 18,527 |
| **Outreach and Education** | | **Outreach and Education** | |
| Services, supplies and equipment | 402,162 | Services, supplies and equipment | 0 |
| **Other Expenses** | | **Other Expenses** | |
| Bond principal & interest | 353,481 | Building operations & maintenance | 0 |
| OHSU administrative charges | 150,552 | OHSU administrative charges | 222,345 |
| Total | $3,445,238 | Total | $4,025,305 |

# Programs
# Fiscal Year 2008/2009

| | Amount paid by W/C | Amount paid by grants | Total Cost |
|---|---|---|---|
| **Outreach and Education** | | | |
| Information dissemination (e.g., TIC[3], website, newsletters, brochures) | 424,384 | | 424,384 |
| Education & training programs (professional & para-professional) | 101,778 | 49,211 | 150,989 |
| Chemical risk information service[5] | 53,552 | | 53,552 |
| **Basic and Applied Research** | | | |
| Factors that affect workplace performance | 422,989 | 430,334 | 853,323 |
| Damage and repair of the nervous system and muscle | 544,962 | 172,500 | 717,462 |
| Occupational/environmental exposures and their consequences | 486,839 | 1,088,622 | 1,575,461 |
| DNA damage, genetic alterations & disease | 264,867 | 1,949,548 | 2,214,415 |
| Core services support[1] | 46,460 | 0 | 46,460 |
| Non-program-specific expenses[4] | 1,099,407 | 335,090 | 1,434,497 |
| **Total Expenses** | $3,445,238 | $4,025,305 | $7,470,543 |

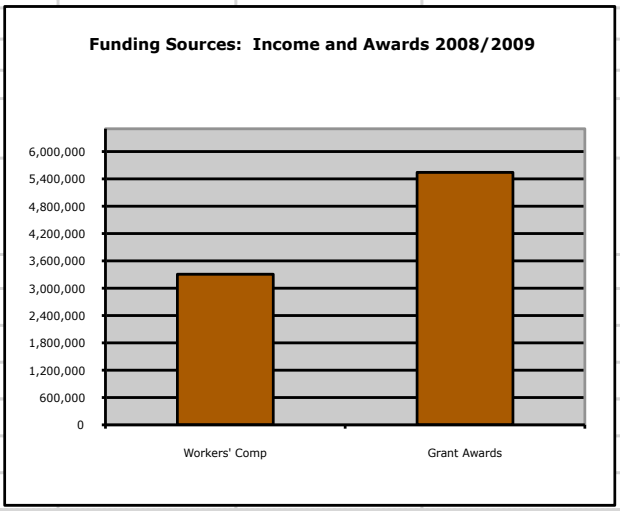
[1] core services - centralized graphics, statistics, imaging, tissue culture and and morphology (pathology)

[2] e.g., office supplies, equipment maintenance and repair, phone rental and line charges

[3] Toxicology Information Center

[4] includes supporting services, administrative salaries, bond principal and interest, OHSU administrative charges, building operation and

[5] Chemical risk information service is self-supporting. This amount reflects current year expenses and income only, however, prior year carry forward was used to cover all costs.



# CROET

The Center for Research on Occupational and Environmental Toxicology (CROET) conducts research, trains health professionals, provides consultation, and offers the public information on hazardous chemicals and their health effects. CROET includes scientists and research staff exploring a range of questions relating to prevention of injury and disease, and promotion of health, in the workforce of Oregon and beyond. CROET's Toxicology Information Center (TIC) is staffed to answer Oregonians' questions about chemical and other occupational exposures, and the Center's CROETweb web site makes health and safety information continuously available.

## How to Contact Us

### Mail Address

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For additional copies of this report, call CROET at the numbers listed above or visit www.ohsu.edu/croet and clikc on "About"

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### Associate Director and Senior Scientist

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### Assistant Director for Operations

Gregory Higgins, PhD

### Assistant Director for Business Affairs

Janice Stewart, BS

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Bernard Sampo, PhD
Vladimir Vartanian, PhD
Izabela Wojnarowicz, MS
Feifei Yan, PhD
Erika Zoller, BS

## FRONT COVER

### Top Photo

Wine grapes are a major part of Oregon agriculture. This photo documents Dr. Kent Anger's research project on training effectiveness in vineyard workers.

### Middle Photo

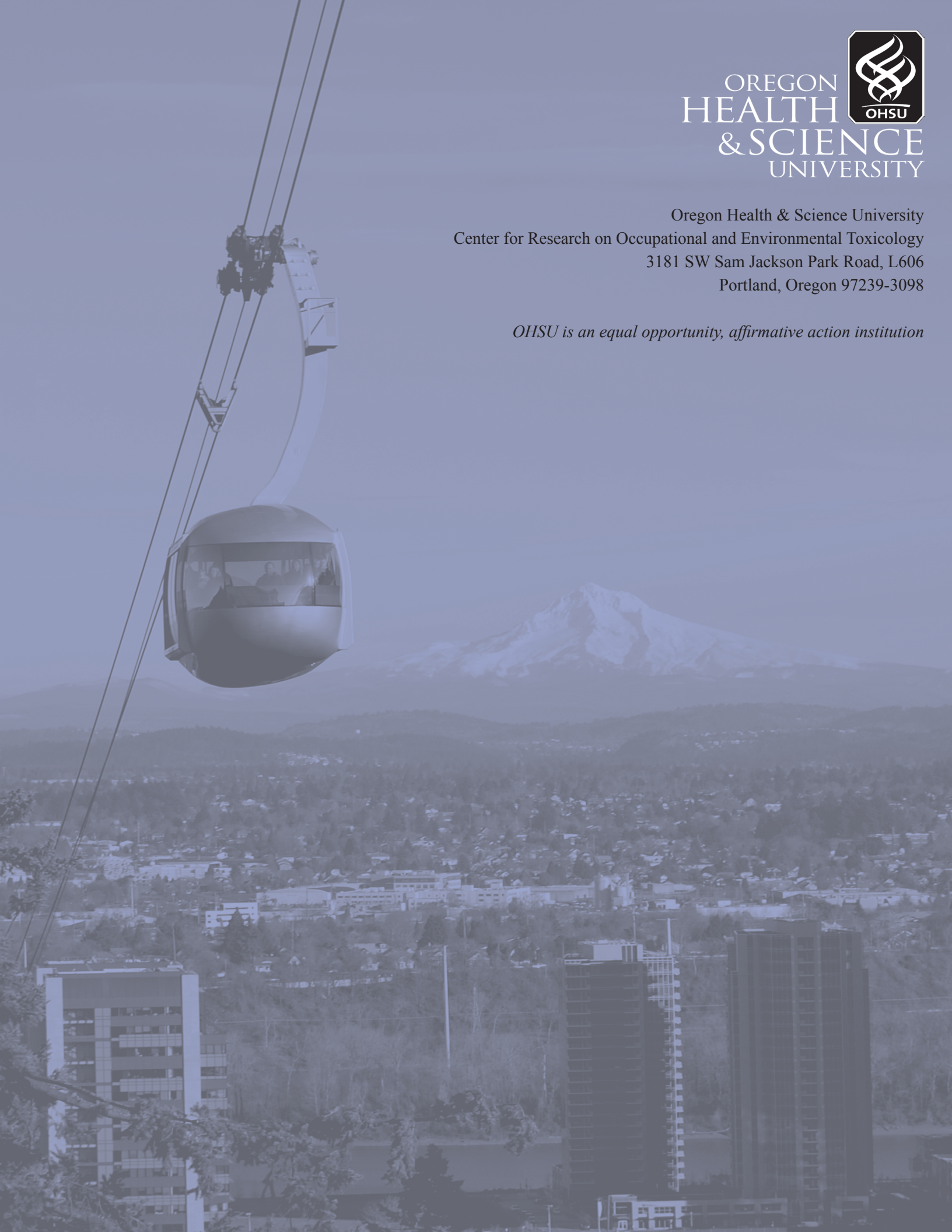
Basic research on occupational illness is just one of the means by which CROET seeks to prevent disease and disability among working Oregonians and their families.

### Bottom Photo

Scene from the Annual CROET Summer Student Poster Session, where student interns share their research results with peers and receive constructive criticism from CROET faculty.

## BACK COVER

The OHSU Tram with Mount Hood and Portland's South Waterfront in the background. (*photo by Dan Austin*).



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