Vol. 10, No. 2, 2002

CROET

Center for Research on Occupational and Environmental Toxicology

NEWSLETTER

This issue features the work of Corvallis artist Marie Le Glatin-Keis

INSIDE

CROET Scientists Reveal Unusual Properties of Organic Solvents

It has long been recognized that certain organic solvents have the potential to damage peripheral nerves. Equally well established was that other organic solvents of similar chemical structure lack this property. Recently, however, a research team led by CROET scientists Dr. Mohammad Sabri and Dr. Peter Spencer has shown this dogma to be incorrect. The CROET team has shown that certain solvents are not only potent neuropathic agents, that damage the nervous system, but also have the remarkable property of turning tissue blue and urine green! This property is called chromogenicity.

That solvents could be both chromogenic and neurotoxic first surfaced in the early 1900's when children and adults were reported to excrete green urine and develop acute central nervous system toxicity after exposure to waxes and varnishes that contained the chemical tetralin. By 1960, several widely used solvents were shown to be chromogenic, but their neurotoxic

OHSU
OREGON HEALTH & SCIENCE UNIVERSITY

potential was not assessed. Later, around 1980, a derivative of tetralin used in fragrances and foods was withdrawn from the market after it was shown to cause spinal cord and peripheral nerve damage in rats. These and a number of other tetralin compounds can now be found in trace quantities in water, sediments and fish.

Many widely used non-chlorinated solvents (benzene, o-xylene, diethyl-benzene, triethyl-benzene) are reported to have chromogenic properties, but have not been assessed with modern analytical methods. Solvents such as these are among the most common contaminants of soil and water at Superfund sites all over the country, including Oregon. If chromogenicity and neurotoxicity are linked, then these chromogenic solvents should be tested for their neurotoxic potential.

Knowledge about the mechanism of the chromogenic effects could provide valuable insights into the fundamental mechanisms of solvents that damage the nervous system. Moreover, knowledge that the colored compound appears in tissues and is excreted in urine before neurological damage occurs could be utilized to assay or measure exposure to these chromogenic compounds. A clear understanding of this relationship could be valuable to risk assessors and public health officials, and ultimately reduce the risk of nervous system damage caused by solvents found in the workplace.

Doctors Sabri's and Spencer's research team is working to understand the relationship between the chromogenicity and neurotoxicity of non-chlorinated organic solvents. This work is funded by the National Institute of Environmental Health Science (NIEHS) Superfund Basic Research Program (SBRP) in conjunction with the NIEHS Neuro-Toxicogenomics Research Center, both of which are housed in CROET. The studies focus on the chromogenic benzene derivative 1,2-DEB and a product of its metabolism, 1,2-DAB. The researchers have shown that the colorless 1,2-DAB forms a blue pigment on contact with proteins, skin and other tissues. Repeated exposure to 1,2-DAB produces swellings in nerves of the spine in rats that results in limb weakness. A similar pattern of spinal pathology is reported in amyotrophic lateral sclerosis (Lou Gehrig's disease); however, while the neurons controlling movement degenerate in Lou Gehrig's disease, nerve degeneration has not been observed in 1,2-DAB-treated rats.

Further work at CROET showed that 1,2-DAB reacts chemically with proteins within nerves to form what are called protein adducts of high molecular weight (i.e. polymers). Similar changes are produced by another solvent metabolite, 2,5-HD, which is responsible for peripheral nerve damage in humans exposed to the solvents n-hexane or methyl n-butyl ketone. These solvents are used in glues to make shoes as well as other processes, although their uses are now severely restricted.

The CROET scientists are investigating the structure-activity relationships for the chromogenic and nerve damaging properties of the above solvents. They have compared the reactivity of diacetylbenzene (DAB) and hexanedione (HD) with amino acids and proteins both in tissue preparations and in live animals. They found that:

* 1,2-DAB forms blue-purple pigments with amino acids and proteins and induces tissue discoloration, behavioral changes and peripheral neuropathy in rats.

* 1,3-DAB (a slightly different compound) does not react with proteins, is not chomogenic and is not toxic to nerves.

* 2,5-HD, but not a closely similar chemical, is weakly chromogenic, reacts with proteins at higher concentrations than 1,2-DAB; and

damages peripheral nerves rather than the spinal cord.

As part of their SBRP-funded project, the CROET team is collaborating with researchers at Battelle Research Institute, which directs the Pacific Northwest National Laboratories, to understand the relationship between the protein chemical reactivity and neurotoxic properties of these various solvents. Additional research on the nerve protein targets of this class of chemicals is underway with collaborating scientists at Oregon State University, which houses an NIEHS-funded Environmental Toxicology Center.

The research conducted by the CROET researchers has led to significant new findings with respect to the role of molecular structure in the genesis of peripheral neuropathy and the relationship between chromogenicity and neurotoxicity. Specifically, the CROET team has shown that:

* 1,2-DAB is a potent nerve damaging solvent, whereas compounds of similar structure lack this property.

* While closely related chemical solvents share neurotoxic mechanisms, those with unique structural characteristics have a much higher potency for producing nerve damage in rodent studies.

* Because chromogenicity and neurotoxicity are closely related properties, other chromogenic solvents in widespread use should be tested for neurotoxic properties.

* Chromogenicity (green urine) precedes nerve damage and might therefore be a useful marker for exposure to organic solvents with neurotoxic potential.

For More Information Contact:

Mohammad I. Sabri, Ph.D.
Peter S. Spencer, Ph.D., F.R.C.Path.
Center for Research on Occupational and Environmental Toxicology, L606
Oregon Health & Science University
3181 SW Sam Jackson Park Road
Portland, OR 97201
E-mail: sabri@ohsu.edu; spencer@ohsu.edu

Recent Publications:

Kim MS, SB Hashemi, PS Spencer, and MI Sabri (2002) Amino acid and protein targets of 1,2-diacetylbenzene, a potent aromatic gamma-diketone that induces proximal neurofilamentous axonopathy. *Toxicology and Applied Pharmacology 183(1):55-65.*

Kim MS, MI Sabri, VH Miller, RJ Kayton, DA Dixon, and PS Spencer (2001) 1,2-diacetylbenzene, the neurotoxic metabolite of a chromogenic aromatic solvent, induces proximal axonopathy. *Toxicology and Applied Pharmacology* 177:121-131.

Spencer PS, MS Kim, and MI Sabri (2002) Aromatic as well as aliphatic hydrocarbon solvent axonopathy. *International Journal of Hygiene and Environmental Health* 20:131-136.

Zhan CG, DA Dixon, MI Sabri, MS Kim, and PS Spencer (2002) Theoretical determination of chromophores in the chromogenic effects of aromatic neurotoxicants. *Journal of the American Chemical Society* 12:2744-2752.

This article was originally published as a brief by the National Institute of Environmental Health Sciences (NIEHS)

Illicit Methamphetamine Laboratories

The use of methamphetamine (meth), an illegal and dangerous drug with unpredictable effects on users, has risen dramatically over the last decade. Along with this increase has been a rise in seizures by law enforcement of illicit laboratories that produce meth, as well as other drugs. In Washington State, the magnitude of this rise has been staggering - in 1990, 38 labs were reported by law enforcement to the Washington Department of Ecology - but by 2001, the rate of illicit lab seizures had grown to greater than 1700 per year. Oregon witnessed 209 illicit drug lab seizures in 2000 and 327 in 2001. As large as these numbers may be, however, it is estimated that three illicit drug laboratories remain undetected for each that is discovered.

THE HAZARDS

Meth labs have been found in a variety of places, including motel rooms, private residences, campgrounds, boats and motor vehicles. These labs present serious occupational health risks to law enforcement and other personnel who are charged with securing and cleaning up these hazardous environments. First, there is the risk of violence from meth lab "cooks" and their associates, who may be armed and "strung out" on meth. It is also not uncommon for law enforcement to discover meth labs that have been booby trapped. Second, there is the risk of exposure to a wide variety of caustic, volatile and toxic chemicals that are used in the production of methamphetamine. For every pound of meth produced, an estimated six pounds of chemical waste is generated. These chemicals become a threat to all who come in contact with them when they are released into the air, septic systems, water and soil, or when they permeate the furniture, carpets, walls, floors and air vents of dwellings. Finally, there is the risk of infection from biological agents, such as HIV, hepatitis or tetanus, which may be incurred through puncture wounds from used needles or broken glassware.

THE CHEMICALS

Methamphetamine production is a simple process that doesn't require specialized equipment, knowledge or expertise. A broad variety of hazardous chemicals may be used, including: solvents, such as benzene, chloroform, pyridine and toluene; chemical precursors, such as acetaldehyde, ephedrine, methylamine, phenyl-2-propanone and phenylacetylchloride; metal reagents containing aluminum, iron, lead, copper and mercury; non-metal reagents, such as iodine and phosphorous; acids, including hydrochloric and perchloric acid; and bases, such as ammonia and sodium hydroxide.

In addition to these primary chemicals, meth lab operations invariably produce a variety of secondary chemical byproducts and contaminants, depending upon the production method used and how controlled and sophisticated the process is. Over- or under heating, or improper mixing of the chemical reactants can generate toxic compounds such as lead oxide, aluminum hydroxide, mercury vapor, iodine and phosphine gas. Some of these byproducts are volatile and explosive. In fact, it was reported in 1989 that approximately 30 percent of drug labs found by police in Oregon were discovered secondary to mysterious explosions or fires.

EMERGENCY RESPONSE PROCEDURES

Because of the hazards to people and the environment, the State of Oregon has developed statutes and administrative rules that govern emergency response procedures and the cleanup of toxic contamination from illegal drug manufacturing. In compliance with these laws and rules, the Oregon Occupational Safety and Health Administration (OR-OSHA), in co-operation with

police and fire departments, has developed a multi-agency plan for responding to suspected clandestine drug labs. This plan covers all phases involved in the seizure of suspected drug labs, as well as procedures to follow if a scene is classified as chemically contaminated. Such a designation usually occurs if a lab is found to be in operation, chemical containers are open, spilled or leaking, or if personnel complain of chemical odors, watering eyes, skin or soft tissue irritation, and breathing problems or other difficulties. Once so designated, all personnel are notified and advised of the hazard, a hot zone is established, and a decontamination corridor is set up through which all people exiting the hot zone must pass. Persons requiring medical attention are decontaminated before treatment and removal from the site. After arrests are completed, only properly trained and equipped HAZMAT technicians are allowed within the hot zone.

REMOVING THE CHEMICALS

Once a drug lab site has been secured, law enforcement officials are faced with the costly process of removing and properly disposing of hazardous chemicals. This is often accomplished through the services of the Oregon Department of Environmental Quality (DEQ). When contacted to assist in drug lab cleanups, DEQ is responsible for collecting, packaging and removing the chemicals, and hauling them off site to a state-approved waste disposal facility. Funding for this service comes from several possible sources: the Drug Lab Asset Forfeiture Fund, recovery costs from property owners, or through voluntary cost reimbursement agreements between DEQ and local law enforcement agencies. Obviously, it is desirable to have perpetrators pay for cleaning up hazardous drug lab materials; however, the resources of the Drug Lab Asset Forfeiture Fund are extremely limited. As these funds become depleted, DEQ notifies all state law enforcement agencies that hazardous waste disposal costs must then be recovered through property owners or through pre-approved reimbursement agreements with DEQ. In this situation, DEQ cannot accept requests for drug lab cleanup assistance without such agreements already in place. Alternatively, police agencies have the option of contracting with licensed waste management companies to remove hazardous chemicals.

THE FINAL CLEAN-UP

According to Oregon law, when a property is raided by the police and an illegal drug lab found, the property becomes designated as "Unfit for Use". The property is then off limits to everyone until it has gone through an assessment and cleanup procedure administered by the Oregon Public Health Service's Clandestine Drug Lab Cleanup Program. A licensed drug lab decontamination contractor must be used for the assessment and cleanup, and the property is not to be entered, used or occupied until a Certificate of Fitness is issued by the Oregon Health Services. Costs for property decontamination are borne by the owner.

For more information on:

OR-OSHA's clandestine drug lab response plan, visit http://www.cbs.state.or.us/external/osha/interps/subject.htm

DEQ's drug lab cleanup program, see http://www.deq.state.or.us

Oregon Public Health Service's Clandestine Drug Lab Cleanup Program, call 503-731-4012 or see http://www.healthoregon.org/esc/druglab/procedures.htm

Grants and Awards

Genes & Environment: New Education To Involve Communities (GENETIC)

GENETIC, a new initiative headed by CROET's Linda McCauley, has been funded by the National Institute of Environmental Health Sciences (NIEHS) and the National Human Genome Research Institute. In recognition of the potential impact of genetic science developments in the 21st century, this unique five-year project is aimed at promoting public understanding of the social, ethical and legal implications of research on genetic susceptibility to environmental toxicants. Key personnel in this consortium are: CROET's Dr. McCauley, Gary Rischitelli and Fred Berman; Jeri Sundvall, of the Portland Environmental Justice Action Group (EJAG); Steven Hecker and Marc Weinstein, from the University of Oregon's Labor Education and Research Center (LERC); and Eda Davis-Butts and Liz Peirce Cassell, from Oregon State University's Science and Math Investigative Learning Experience (SMILE) Program. Each of these four groups brings a unique and valuable view to the development of outreach and educational programs around issues of gene-environmental susceptibility, education and research. The project will assess community readiness to focus on this issue, develop community-driven educational and outreach programs, and develop mechanisms for ongoing dialogue as the science progresses and community issues emerge. The broader view of this project is that these activities will provide an arena for the various societal communities to come together and share their perspectives on the issues of importance in areas of gene-environmental susceptibility. The project will begin with work within each community partner and build to activities in which the communities work together to share each other's perspectives on the emergent issues of interest surrounding the science of genetic research.

Determining the Prevalence of Multiple Sclerosis Near Hanford

William Lambert, Ph.D., has received funding for a three-year research project to determine the prevalence of multiple sclerosis (MS) in eastern Washington counties. This research is designed in response to a request by the Agency for Toxic Substances and Disease Registry (ATSDR) for the development of methods to quantify the number of existing cases of MS in populations living near hazardous waste sites. Population-based registries for this disease and most other neurological diseases are not maintained by State and local public health agencies. Therefore, when ATSDR is asked to investigate a concern about a perceived excess of MS, or a cluster, in a community, it must rely on very time consuming and expensive reviews of medical records.

Dr. Lambert, in collaboration with Drs. Dennis Bourdette and Bridget Bagert of OHSU Department of Neurology, will investigate the use of a technique called "capture-recapture method" to more efficiently estimate the numbers of cases at the county level. If the term reminds you of the type of science you hear about on nature documentaries, you are correct. The method was originally developed by field biologists to estimate the total number of animals in an area by capturing, tagging, releasing, and later recapturing the animals. Dr. Lambert and his team will use electronic databases from hospitals, diagnostic and treatment centers, and local service organizations to develop counts of cases. Statistical models will then be used to determine proportions of overlap and differences between counts from the separate sources, and estimate the total number of cases in each county.

The study will be performed near the Hanford Nuclear Reservation, a site where releases of radiation and chemicals to the environment have occurred over the past 50 years. The ATSDR and the Centers for Disease Control and Prevention (CDC) have conducted many public health studies in this area, primarily focusing on thyroid disease. However, a new concern for MS has arisen. Client data from local chapters of the National Multiple Sclerosis Society suggest higher than expected numbers of self-reported MS patients in the Tri-City area and Spokane. Quantifying the occurrence of MS is a first step. Should high prevalence be confirmed, this will support the need for other analytical epidemiological studies to evaluate potential causes. This research should ultimately benefit Oregonians as well, inasmuch as Oregon is reported to have higher than average rates of occurrence of neurodegenerative diseases, including MS, amyotrophic lateral sclerosis (ALS) and Parkinson's disease.

Center for Research on Occupational and Environmental Toxicology

CROET, the Center for Research on Occupational and Environmental Toxicology at Oregon Health & Science University, conducts research, provides consultations and offers information on hazardous chemicals and their health effects. CROET includes approximately 100 scientists and research staff exploring a range of questions relating to health and the prevention of injury and disease in the workforce of Oregon and beyond. CROET's Toxicology Information Center is open to the public and is staffed to answer Oregonians' questions about hazardous substances in the workplace and elsewhere. CROET's Web site also provides answers to questions about industries found in Oregon through links on a series of pages devoted to industry-specific topics.

How to Contact Us

MAIL ADDRESS

CROET
Oregon Health & Science University
3181 SW Sam Jackson Park Rd, L606
Portland, OR 97201-3098

Web site

http://www.CROETWEB.com

TELEPHONE

Main CROET number
(503) 494-4273
Facsimile
(503) 494-4278
Toxicology Information Center
(800) 457-8627

E-MAIL
Toxicology Information Center
croettic@ohsu.edu

You may share your comments regarding this publication by calling (503) 494-2514, by e-mailing us at brownjo@ohsu.edu or by faxing us at (503) 494-4278

Directors and Scientists

DIRECTOR AND SENIOR SCIENTIST

Peter S. Spencer, PhD, FRCPath

ASSOCIATE DIRECTOR AND SENIOR SCIENTIST

W. Kent Anger, PhD

ASSOCIATE DIRECTOR FOR FINANCE AND PLANNING

J. Robert Williams, MBA

ASSISTANT DIRECTORS

Janice Fisher, BS
Gregory Higgins, PhD

FACULTY

Charles Allen, PhD
W. Kent Anger, PhD
Gary Banker, PhD
Bruce Gold, PhD
Glen Kisby, PhD
Dennis Koop, PhD
Doris Kretzschmar, PhD
William Lambert, PhD
Linda McCauley, RN, PhD, FAAN
Valle Nazar-Stewart, PhD
Bruce Patton, PhD
Gary Rischitelli, MD, JD, MPH, FACOEM
Show-Ling Shyng, PhD
Peter S. Spencer, PhD, FRCPath
Mitchell Turker, PhD

INVESTIGATORS

Gregory Higgins, PhD
Mohammad Sabri, PhD
Christopher Wallace, PhD
Ginger Withers, PhD

SCIENTIFIC STAFF

Daniel Austin, MS
Frederick Berman, DVM, PhD
Etienne Cartier, MD
Karen Fujimoto, BS
Taiping Jia, MD
Stefanie Kaech Petrie, PhD
Robert Kayton, PhD
Sihyun Kim, PhD
Hoa Lam, MS
Mike Lasarev, MS
Elaine Mahoney, RN, MPH
Sarah Michaels, MS
Juan Muñiz, MS
Anthony Oliva, PhD
Diane Rohlman, PhD
Joan Rothlein, PhD
Bernard Sampo, PhD
Jennifer Scherer, MPH
Holly Sherburne, MS
Michael Silverman, PhD
Diana Sticker, MPH
Daniel Storzbach, PhD
Jan Voda, MD
Dong Ren Yang, PhD
Phillip Yates, PhD

Artwork by Marie Le Glatin-Keis

OUTREACH

CROET will provide exhibits at the following conferences.

Oregon Governor's
Occupational Safety & Health Conference
March 3-6, 2003
Oregon Convention Center
Portland, Oregon

Oregon Self Insurers Association Annual Meeting
July 16-18, 2003
Wilsonville, Oregon

Join our monthly E-mail list

Join CROET's e-mail list for monthly updates about what's new on the CROET Web site, news and upcoming events. To subscribe or read past updates, go to http://www.ohsu.edu/croet/about/croetml/.

OHSU

Oregon Health & Science University
CROET, the Center for Research on Occupational
and Environmental Toxicology
3181 SW Sam Jackson Park Rd., L606
Portland, OR 97239-3098

Non-Profit Org.
U.S. Postage
PAID
Permit No. 722
Portland, OR