TABLE OF CONTENTS

Platform Sessions

SESSION I: PLENARY SESSION

TEMPORAL HORMESIS ASSOCIATED WITH HEART FAILURE AND ANIMAL ASTHMA MODEL

Richard A. Bond, University of Houston, Houston, TX
Zsuzsanna Callaerts-Vegh, University of Houston, Houston, TX

REFLECTIONS ON TWENTY YEARS IN RISK ASSESSMENT: LESSONS LEARNED AND HOW THEY RELATE TO INCORPORATING HORMESIS INTO THE PARADIGM

Dennis J. Paustenbach, ChemRisk, Inc.®, San Francisco, CA

RELATIONSHIP BETWEEN TOXICITY AND HORMESIS IN RATS TREATED WITH VARIOUS DIOXINS

Karl K. Rozman, Ph.D., University of Kansas Medical Center, Kansas City, KS
Margitta Lebofsky, University of Kansas Medical Center, Kansas City, KS
David M. Pinson, University of Kansas Medical Center, Kansas City, KS

HORMESIS: CHANGING THE TOXICOLOGICAL PARADIGM

Edward J. Calabrese, University of Massachusetts, Amherst, MA

TEMPORAL HORMESIS ASSOCIATED WITH HEART FAILURE AND ANIMAL ASTHMA MODEL

Richard A. Bond, University of Houston, Pharmacological and Pharmaceutical Sciences, 521 SR-2 Bldg, Houston, TX, 77204-5037, Tel: 713-743-1210, Fax: 713-743-1229, Email: Rabond@uh.edu
Zsuzsanna Callaerts-Vegh, University of Houston, Pharmacological and Pharmaceutical Sciences, 521 SR-2 Bldg, Houston, TX, 77204-5037, Tel: 713-743-1224, Fax: 713-743-1229, Email: zcallaerts@uh.edu

In the last decade a major therapeutic paradigm shift has occurred in the treatment of congestive heart failure (CHF). Some ß-blockers, a class of drugs originally contraindicated in CHF, have become drugs of choice by reducing mortality and increasing cardiac contractility. These improvements appear after an initial phase of worsening symptoms and reduction of ejection fraction. But over time, the heart recovers and function actually improves (Hall *et al.*, 1995)(Figure 1). We observed a similar phenomenon in a murine model of asthma. Acute and chronic treatment with ß-blocker in this model exhibited opposing effects, with worsening symptoms acutely but decreasing airway hyper reactivity when given chronically (Figure 2). This temporal difference in drug action has been reported in other disease states as well. Antidepressant have been linked to an increased suicidal rate at onset of therapy, while chronically antidepressant have shown to reduce the risk of suicide (Healy *et al.*, 2003). While acutely beneficial drugs are tested for long-term effects, it is assumed that drugs showing acutely adverse effects will also exhibit them chronically. The two examples in CHF and in our model of asthma show, that this extrapolation might not be true.

REFLECTIONS ON TWENTY YEARS IN RISK ASSESSMENT: LESSONS LEARNED AND HOW THEY RELATE TO INCORPORATING HORMESIS INTO THE PARADIGM

Dennis J. Paustenbach, President, ChemRisk, Inc.®, 100 Spear Street, Suite 525, San Francisco, CA 94105, Tel: 415-896-2400, Email: dpaustenbach@chemrisk.com

The publication of the "red book" by NAS (1983) is often heralded as the formal beginning of what we call the modern era of health risk assessment. Much has happened in the field since that time which, by and large, has improved the quality of information conveyed by these analyses. Indications are that the practice of risk assessment is now at a cross roads. On one end of the continuum, it is believed that little more can be learned from the wealth of available toxicology and epidemiology data; and that we must wait for genomics to take our understanding of risk to the next level. On the other, regulatory and litigation forces are dictating that "more needs to be done" and that the pressure on the regulated community to reduce the use of chemicals must continue. In some ways, adoption of various forms of the precautionary principle is a reflection of that school of thought. This paper will discuss ten observations on the evolution of the practice of risk assessment and close by discussing whether hormesis and non-linearity can be incorporated into risk characterization, as well as, regulatory decision making.

RELATIONSHIP BETWEEN TOXICITY AND HORMESIS IN RATS TREATED WITH VARIOUS DIOXINS

Karl K. Rozman, Ph.D., Department of Pharmacology, Toxicology, and Therapeutics, University of Kansas Medical Center, 3901 Rainbow Blvd, Kansas City, KS 66160, Tel: 913-588-7718, Fax: 913-588-7501, Email: krozman@kumc.edu
Margitta Lebofsky, Department of Pharmacology, Toxicology, and Therapeutics, University of Kansas Medical Center, 3901 Rainbow Blvd, Kansas City, KS 66160, Tel: 913-588-7716, Fax: 913-588-7716, E-mail: mlebofsk@kumc.edu
David M. Pinson, Department of Pathology and Laboratory Medicine, University of Kansas Medical Center, 3901 Rainbow Blvd, Kansas City, KS 66160, Tel: 913-588-7351, Fax: 913-588-7277, Email: dpinson@kumc.edu

Chronic toxicity of 1,2,3,4,6,7,8-heptachlorodibenzo-p-dioxin (HpCDD) including its carcinogenicity was studied in female SpragueDawley rats in lifetime experiments. Six single dose and three multiple dose rate experiments were conducted with a single dose corn oil control group and a multiple dose rate corn oil control group, respectively. The lowest dose (1.0 mg/kg) of HpCDD and multiple dose rates of corn oil (4.0 ml/kg biweekly) both prolonged the life of rats by about 2 months over that of single dose corn oil controls, apparently by different mechanisms of action. Higher doses resulted in a predictable shortening of the life of rats after single dose administrations as well as after multiple dose rate administrations. The c x t = k paradigm previously validated for acute toxicity (Rozman, 1999) was confirmed for chronic toxicity including carcinogenicity of HpCDD. The c x t = k product was shown to be independent of dosing regimen. Anemia and squamous cell carcinoma of the lungs were the earliest and most prevalent endpoints of toxicity. At 2.1 mg/kg HpCDD caused 16.6% lung cancer and a dose of 3.1 mg/kg caused 73.3%, an extremely steep dose response (a factor of 1.5). The dose response for HpCDD-induced lung cancer was truncated between 60 and 70% at still higher doses. Liver cancer had a low prevalence and was a very late effect occurring only at doses lethal acutely for most rats in the three highest dosage groups. There was no correlation in the dose-dependence of non-malignant hepatic lesions and liver cancer. It is remarkable that a dose of HpCDD only 2.1 times lower than that which caused 16.6% lung cancer had a life-prolonging hormetic effect without producing a single lung or liver cancer.

HORMESIS: CHANGING THE TOXICOLOGICAL PARADIGM

Edward J. Calabrese, Ph.D. University of Massachusetts, Amherst, MA 01003

The most fundamental concept used in toxicology to estimate risks and to guide regulation is the dose response relationship. Based on guidance from the toxicology and risk assessment communities, regulatory agencies have used the threshold model to estimate risks from non-carcinogens and the linear at low dose model to estimate risks from carcinogens. This presentation will argue that the most frequent model observed in adequately designed toxicological studies is neither the threshold or linear at low dose models but the hormetic dose response model. The toxicological community made an error of profound historic proportions with the rejection of the hormetic mode; this rejection was based in large part upon a regulatory driven agenda to derive LOAELs and NOAELs within a study design framework that emphasized high dose administration and a limit number of doses. Recognition that the hormetic dose response model is more fundamental than the threshold and linear models should force a re-evaluation of how dose response model acceptance affects study design, model and endpoint selection, statistical-power issues as well as reconsideration of default models used in risk assessment.

SESSION II: RADIATION

LOW DOSES OF RADIATION ARE PROTECTIVE *IN VITRO* AND *IN VIVO*

Ron Mitchel, Atomic Energy of Canada Limited, Chalk River, ON, Canada

NON-LINEAR RESPONSE FOR NEOPLASTIC TRANSFORMATION FOLLOWING LOW DOSES OF LOW LET RADIATION

J. Leslie Redpath, University of California Irvine, Irvine, CA

LOW-DOSE RADIATION-INDUCED PROTECTIVE PROCESS AND IMPLICATIONS FOR RISK ASSESSMENT, CANCER PREVENTION, AND CANCER THERAPY

Bobby R. Scott, Lovelace Respiratory Research Institute, Albuquerque, NM
Dale M. Walker, Lovelace Respiratory Research Institute, Albuquerque, NM

UPDATE ON THE DEPARTMENT OF ENERGY LOW DOSE RADIATION RESEARCH PROGRAM

Noelle Metting, Sc.D., U.S. Department of Energy, Washington, D.C.

BIOLOGICAL EFFECTS OF LOW DOSE RADIATION

Philippe Duport, University of Ottawa, Ottawa, Ontario, Canada

LOW DOSE BODY IRRADIATION PREVENTION AND THERAPY OF CANCER

Myron Pollycove, School of Medicine University of California San Francisco

LOW DOSES OF RADIATION ARE PROTECTIVE *IN VITRO* AND *IN VIVO*

Ron Mitchel, Atomic Energy of Canada Limited, Radiation Biology and Health Physics Branch, Chalk River Laboratories, Chalk River, ON, K0J 1J0 Canada, Tel: 613-584-8811 X4721, Fax: 613-584-8217, Email: mitchelr@aecl.ca

The "Linear No Threshold" hypothesis, used in all radiation protection practices, assumes that all doses, no matter how low, increase the risk of human cancer, birth defects and heritable mutations. This hypothesis is also assumed to apply to non-human biota when the effects of radiation in the environment are considered. This talk will present experimental data from human cells and from wild and laboratory animals that test the hypothesis *in vitro* and *in vivo.* Experiments using cells from lower eukaryotes, wild deer, rodents or humans show non-linear adaptive processes in response to low LET radiation, and do not support the hypothesis. These adaptive processes reduced the risk of spontaneous malignant transformation in rodent cells *in vitro*. Environmental exposure of wild frogs to 1 mGy/y increased their ability to repair DNA damage. A single, low, whole body dose (less than about 100 mGy) of low LET radiation given at low dose rate, increased cancer latency and consequently reduced both spontaneous and radiation-induced cancer risk in both genetically normal and cancer-prone mice. This adaptive response lasted for the entire lifespan of all the animals that developed these tumors, and effectively restored a portion of the life that would have been lost due to the cancer in the absence of the low dose. In genetically normal fetal mice, prior low doses could also protect against radiation-induced birth defects. In genetically normal adult male mice, a prior low dose protected the mice from induction of heritable mutations produced by a subsequent large dose, and in genetically cancer prone male mice, reduced the frequency of spontaneous heritable mutations. Overall, the results demonstrate that the assumption of a linear increase in risk with increasing dose is not warranted, and that low doses actually reduce risk.

NON-LINEAR RESPONSE FOR NEOPLASTIC TRANSFORMATION FOLLOWING LOW DOSES OF LOW LET RADIATION

J. Leslie Redpath, University of California Irvine, Department of Radiation Oncology, College of Medicine, Irvine, CA 92697, Tel: 949-824-7395, Fax: 949-824-3566, Email: jlredpat@uci.edu

There are now several independent studies that indicate that the dose-response for the endpoint of radiation-induced neoplastic transformation *in vitro* is non-linear for low LET radiation. At low doses (<10 to 20cGy) the transformation frequency drops below that seen spontaneously. Importantly, this observation has been made using fluoroscopic energy x-rays, a commonly used modality in diagnostic radiology, the practice of which is responsible for the majority of radiation exposure to the general public. Since the transformation frequency is reduced over a large dose range (0.1 to 10 cGy) it is likely that multiple mechanisms are involved and that the relative contribution of these may vary with dose. There are data that suggest that these include killing of a subpopulation of cells prone to spontaneous transformation at the lowest doses, and the induction of DNA repair at somewhat higher doses. A protective effect of low doses of low LET radiation on other cancer-relevant endpoints has also been observed by many independent laboratories. These observations strongly imply that the linear-nonthreshold dose-response model is unlikely to apply to the induction of cancer by low LET radiation in humans and that a threshold model is more scientifically plausible. Such a model is not inconsistent with epidemiologic analyses due to their acknowledged lack of sensitivity at acute doses of low LET radiation <5 cGy.

LOW-DOSE RADIATION-INDUCED PROTECTIVE PROCESS AND IMPLICATIONS FOR RISK ASSESSMENT, CANCER PREVENTION, AND CANCER THERAPY

Bobby R. Scott, Lovelace Respiratory Research Institute, 2425 Ridgecrest Drive SE, Albuquerque, NM 87108, Tel: 505-348-9470, Fax: 505-348-8567, Email: bscott@LRRI.org
Dale M. Walker, Lovelace Respiratory Research Institute, 2425 Ridgecrest Drive SE, Albuquerque, NM 87108, Tel: 505-348-9467, Fax: 505-348-8567, Email: dwalker@LRRI.org

We describe a **P**rotective **A**poptosis-**M**ediated (PAM) Process that is turned on in mammalian cells by low doses of genotoxic agents such as ionizing photon (x or gamma rays) radiation. The PAM process leads to selective removal of precancerous cells (e.g., neoplastically transformed cells) and is presumed to also remove other problematic cells (e.g., potentially harmful mutant cells) from the body. The process involves cross-talk between normal and abnormal cells (e.g., transformed cells) and is mediated via reactive oxygen species and specific cytokines. Recent mutagenesis data suggest that a photon radiation threshold of < 0.1 mGy may be required for turning on the PAM process. Photon radiation doses above about 200 mGy delivered at a high dose rate seem to inhibit the PAM process. However, low-dose-rate photon radiations seem to prolong the process and allow it to operate even at doses exceeding 1000 mGy. We attribute each of the following published research observations to the PAM process: (1) the selective removal of problematic mutant and neoplastically transformed mammalian cells *in vitro* after low-dose photon irradiation; (2) protection from alpha radiation-induced mutations *in vitro* following a small adapting photon dose; (3) the hormetic-type dose-response curves found for lung cancer induction in humans after low-dose-rate exposure to photon radiation and after combined chronic, low-dose-rate exposure of Russian nuclear workers to alpha plus gamma radiations; (4) a reduction in cancer mortality (relative to the general public) in Taiwanese citizens chronically exposed to gamma radiation in cobalt-60 contaminated apartments. It is our view that the PAM process likely contributes substantially to cancer prevention in humans. However, new research is needed to improve our understanding of the process. The new research could unlock novel strategies for cancer prevention and novel protocols for low-dose therapy for cancer.

UPDATE ON THE DEPARTMENT OF ENERGY LOW DOSE RADIATION RESEARCH PROGRAM

Noelle Metting, Sc.D., Office of Science / BER, SC-72/Germantown Building, U.S. Department of Energy, 1000 Independence Avenue, SW, Washington, D.C. 20585-1290, Tel: 301-903-8309
Fax: 301-903-8521, Email: noelle.metting@science.doe.gov

The goal of the DOE Low Dose Radiation Research Program is to support research that will help determine health risks from human exposures to low levels of radiation. This information is critical to adequately and appropriately protect people while making the most effective use of our national resources. Extensive research on the health effects of radiation using standard epidemiological and toxicological approaches have been used for decades to characterize responses of populations and individuals to high radiation doses, and to set exposure standards to protect both the public and the workforce. These standards were set by using modeling approaches to extrapolate from the cancers observed following exposure to high doses of radiation to predicted, but not measurable, changes in cancer frequency at low radiation doses. Mathematical models were necessary because of our inability to detect changes in cancer incidence following low doses of radiation. Historically, the predominant approach has been the Linear-no-Threshold model and collective dose concept that assumes each unit of radiation, no matter how small, can cause cancer. As a result, radiation-induced cancers are predicted from low doses of radiation for which it had not been possible to directly demonstrate cancer induction. Over the next 100 years, radiation exposures associated with human activity are expected to be low dose and low dose-rate radiation from medical tests, waste clean up, environmental isolation of materials associated with nuclear weapons, and nuclear power production. The major type of radiation exposures will be from x- and gamma-radiation from fission products. The DOE Low Dose Radiation Research Program is thus concentrating on studies of low-LET exposures delivered at low total doses and low dose-rates, and currently funds research on DNA damage and repair, adaptive response, bystander effects, genomic instability, genetic susceptibility, among other related topics.

BIOLOGICAL EFFECTS OF LOW DOSE RADIATION

Philippe J. Duport, University of Ottawa, Institute of the Environment, International Centre for Low-Dose Radiation Research, 555 King Edward Avenue, P.O. Box 450, Stn. A, Ottawa, Ontario, Canada, K1N 6N5, Tel: 613-562 5800, ext. 1270, Fax: 613-562 5873, Email: pduport@uottawa.ca

The International Centre for Low-Dose Radiation Research (ICLDRR) has assembled all published data on low-dose (less than 1 Gy or any dose when no observable effect) radiation carcinogenesis in mammals. The database contains information on about 88,000 exposed animals ($\approx$ 48,400 cancers) and 40,000 controls ($\approx$ 15,000 cancers). Experiments were conducted with all types of ionizing radiation (doses $\geq$ 10 mGy for gamma rays; $\geq$ 40 mGy for X-ray; $\geq$ 2 mGy for betas; $\geq$ 2 mGy for alphas and $\geq$ 5 mGy for neutrons. There are 800 datasets, each providing a dose-response relationship for animals of a particular species, strain, sex and age exposed to a range of doses delivered under specific conditions. No cancers were observed in the control groups of about 30% of the datasets. When cancer were observed in controls, an apparent risk reduction for cancer was observed at the lowest dose levels in 40% of the neutron datasets, 50% of the X-rays datasets, 53% of the gamma datasets, and 61% of the alpha datasets. An additional study confirms that low-dose irradiation significantly extends the longevity of exposed animals in a statistically significant number of experiments and datasets. It also appears that low-dose irradiation significantly reduces the risk of developing cardiovascular diseases. These observations appear to challenge the general validity of the Linear No Threshold hypothesis (LNT).

LOW DOSE BODY IRRADIATION PREVENTION AND THERAPY OF CANCER

Myron Pollycove, School of Medicine University of California San Francisco

DNA damage control is the central component of the homeostatic system essential for survival of aerobic organisms. Over eons of time, this complex antimutagenic system evolved to control the enormous number of DNA alterations produced by reactive oxygen species generated principally by the leakage of free radicals from cellular metabolism of oxygen. Aging, mortality, and cancer mortality are generally accepted to be associated with stem cell accumulation of permanent alterations of DNA, i.e., accumulation of mutations. In a young adult living in a low LET background of 0.1 cGy/y, the antimutagenic system, after antioxidant prevention of a significant number of DNA alterations, reduces by repair and removal about one million DNA alterations /cell/d to about 1 mutation/cell/d. Subsequently, as these mutations accumulate and gradually deteriorate the antimutagenic system, aging progresses at an increasing rate, mortality increases correspondingly, and cancer increases at the fourth power of age.

During the past three decades genomic, cellular, animal and human data have shown that low-dose ionizing radiation stimulates each component of the homeostatic antimutagenic DNA damage control system: antioxidant prevention, enzymatic repair, and immunologic and apoptotic removal of DNA alterations. High-dose ionizing radiation, on the other hand, suppresses each of these antimutagenic protective components. The biological response to radiation is biphasic, non-linear.

Populations living in high background radiation areas and nuclear workers with increased radiation exposure show lower mortality and decreased cancer mortality than the corresponding populations living in low background radiation areas and rigorously matched nuclear workers without increased radiation exposure. Experimental studies of cancer in animals also show with high statistical confidence the beneficial effects of low-dose radiation.

Current clinical trials in the United States are needed now. After 20 years of intensive research the molecular biology of immune response to low-dose radiation is now well established. Previous clinical trials at Harvard University and at Tohoku University, Japan have documented with high statistical confidence the unequivocal superiority of low-dose body irradiation to chemotherapy of patients with non-Hodgkin's lymphoma. Current confirmation of these results in patients with non-Hodgkin's lymphoma and other cancers by clinical trials in the United States would make low-dose body irradiation therapy available to cancer patients in America.

SESSION III: BIOMEDICAL

HORMESIS IS A MECHANISM UNDERLYING BENEFICIAL EFFECTS OF DIETARY RESTRICTION IN RODENTS

Mark P. Mattson, National Institute on Aging Intramural Research Program, Baltimore, MD
Ruiqian Wan, National Institute on Aging Intramural Research Program, Baltimore, MD
Zhihong Guo, National Institute on Aging Intramural Research Program, Baltimore, MD
Wenzhen Duan, National Institute on Aging Intramural Research Program, Baltimore, MD

HORMESIS IN DOSE-RESPONSE STUDIES WITH FUNGITOXINS AND PHYTOTOXINS

Stephen O. Duke, USDA, ARS, University, MS
Albrecht Michel, Syngenta Crop Protection AG, Stein, Switzerland
Anna Oliva, State Univ. of New York, Stony Brook, NY
Regina G. Belz, Univ. Hohenheim, Stuttgart, Germany

LOW DOSE EFFECTS IN PSYCHOPHARMACOLOGY: ONTOGENETIC CONSIDERATIONS

Linda Patia Spear, Binghamton University, Binghamton, NY

ARE LOW DOSES OF DNA DAMAGING AGENTS ANTI-MUTAGENIC?

Pamela J. Sykes, Flinders University and Medical Centre, Bedford Park, South Australia
Sarah J. Swinburne, Flinders University and Medical Centre, Bedford Park, South Australia
Madhava Bhat, Royal Adelaide Hospital, Adelaide, SA, Australia
John Cormack, Flinders University and Medical Centre, Bedford Park, South Australia
Tanya K Day, Flinders University and Medical Centre, Bedford Park, South Australia
Renate U Domel, Australian Nuclear Science and Technology Organisation, Menai, New South Wales, Australia
William M. Burch, Australian Nuclear Science and Technology Organisation, Menai, New South Wales, Australia
Alexander A. Morley, Flinders University and Medical Centre, Bedford Park, South Australia
Antony M. Hooker, Flinders University and Medical Centre, Bedford Park, South Australia

STRESS IMMUNOLOGY: DIFFERENTIAL DOSE-RESPONSE

Jeffrey A. Woods, Ph.D., University of Illinois at Urbana-Champaign, Urbana IL

HORMESIS IS A MECHANISM UNDERLYING BENEFICIAL EFFECTS OF DIETARY RESTRICTION IN RODENTS

Mark P. Mattson, Laboratory of Neurosciences, National Institute on Aging Intramural Research Program, 5600 Nathan Shock Drive, Baltimore, MD 21224, Tel: 410-558-8463, Fax: 410 558-8465. Email: mattsonm@grc.nia.nih.gov
Ruiqian Wan, Laboratory of Neurosciences, National Institute on Aging Intramural Research Program, 5600 Nathan Shock Drive, Baltimore, MD 21224, Tel: 410-558-8462, Fax: 410-558-8465, Email: wanru@grc.nia.nih.gov
Zhihong Guo, Laboratory of Neurosciences, National Institute on Aging Intramural Research Program, 5600 Nathan Shock Drive, Baltimore, MD 21224, Tel: 410-558-8462, Fax: 410-558-8465, Email: guozh@grc.nia.nih.gov
Wenzhen Duan, Laboratory of Neurosciences, National Institute on Aging Intramural Research Program, 5600 Nathan Shock Drive, Baltimore, MD 21224, Tel: 410-58-8462, Fax: 410-558-8465, Email: duanwe@grc.nia.nih.gov

Dietary restriction (DR; decreased size and/or number of meals) can extend lifespan and can increase resistance to disease in organisms ranging from flys and worms to rats, mice and monkeys. We have found that DR can have profound beneficial effects on cardiovascular and brain function and vulnerability of heart and brain cells to injury and disease. DR is cytoprotective in animal models of myocardial infarction, stroke, Alzheimer's, Parkinson's and Huntington's diseases. DR can stimulate the production of new neurons from stem cells (neurogenesis) and can enhance synaptic plasticity (learning and memory), which may increase the brain's ability to resist aging and restore function following injury. We have found that beneficial effects of DR on result, at least in part, from induction of a mild cellular stress response (hormesis) which results in upregulation of growth factors such as brain-derived neurotrophic factor (BDNF) and stress resistance protein chaperones such as HSP-70 and GRP-78. DR can modify the adverse effects of disease-causing genetic mutations in models of Alzheimer's (presenilin mutations) and Huntington's diseases. Interestingly, our recent data suggest that the beneficial (anti-diabetic) effects of DR on peripheral glucose regulation are mediated, in part, by BDNF signaling in the brain. In many respects the hormetic effects of DR are similar to those of regular vigorous physical exercise. Finally, exposure of neurons or cardiac cells to low amounts of toxins such as cyanide or rotenone can increase the resistance of those cells to ischemic and oxidative injury; apparently by a hormesis-based mechanisms. These findings have important implications of these findings for the prevention and treatment of neurodegenerative and cardiovascular disorders.

HORMESIS IN DOSE-RESPONSE STUDIES WITH FUNGITOXINS AND PHYTOTOXINS

Stephen O. Duke, NPURU, USDA, ARS, P.O. Box 8048, University, MS 38677, Tel: 662-915-1036, Fax: 662-915-1035, Email: sduke@olemiss.edu
Albrecht Michel, Syngenta Crop Protection AG, Basel, Switzerland, Werk Stein (WST-149.E.62), CH-4332 Stein, Switzerland, Tel: +41-61-3231065, Fax: +41-61-3231069,
Email: albrecht.michel@syngenta.com
Anna Oliva, Dept. Molec. Genetics & Microbiology, Life Science, room 130, State Univ. of New York, Stony Brook, NY 11794-5222, Tel: 631-632-8897, Fax: 631-632-9797,
Email: anoliva@ms.cc.sunysb.edu
Regina G. Belz, Univ. Hohenheim, Institute for Phytomedicine 360. Dept. Weed Science,
70593 Stuttgart, Germany, Tel: 011 49 711 459 3444, Fax: 011 49 711-459 2408,
Email: belz@Uni-Hohenheim.DE

The term hormesis was coined by plant pathologists in a 1943 study on the response of a fungus to a fungitoxic phytochemical. Similary, we have found hormesis with the fungitoxic compounds 4-hydroxycoumarin, 7-hydroxycoumarin, 7-methoxycoumarin, and 1-methyl-2-[3',4'-methylenedioxy)phenyl]-4-quinoline from the plant *Ruta graveolens* on the fungal plant pathogen *Phomopsis viticola*. Using a duckweed (*Lemna pausicostata*) bioassay with synthetic herbicides we found chlorpropham, a compound thought to disrupt microtubule organizing centers, to cause hormesis. With natural phytotoxins, such as 2-(3*H*)-benzoxazolinone (BOA), we found marked hormesis in the effects on root growth of alfalfa (*Medicago sativa*). We also found hormesis in dose-response effects of scopoletin D (7-hydroxy-6-methoxy-2H-1-benzopyran-2-one) on the growth of duckweed. In a dose-response experiment in which increasing densities of wheat (and corresponding concentrations of exuded allelochemicals) were tested on mustard (*Sinapis alba*) seedlings, hormesis was seen with one wheat variety's effects on mustard growth. Auscaulitoxin, a phytotoxin produced by a fungal pathogen, caused hormesis in duckweed. Potential mechanisms of hormesis in some of these studies will be discussed, as well as the use of gene expression profiling with whole genome DNA microarrays to differentiate between these mechanisms.

LOW DOSE EFFECTS IN PSYCHOPHARMACOLOGY: ONTOGENETIC CONSIDERATIONS

Linda Patia Spear, Department of Psychology and Center for Developmental, Psychobiology Box 6000, Binghamton University, Binghamton, NY 13902-6000, Tel: 607-777-2825, Email: lspear@binghamton.edu

In a number of instances, low doses of psychoactive drugs elicit a behavioral profile in rats opposite that observed following administration of more substantial doses. Our laboratory has observed that these effects are often age-specific. For instance, the dopamine agonist, apomorphine, induces increases in locomotor activity in adult rats when given at moderate-to-high doses (1 and 3 mg/kg), while suppressing locomotor movements at low (0.05 and 0.1 mgkg) doses. Administration of the opiate agonist, morphine, induces hypomobility at doses in the range of 10 mg/kg and greater in adult animals, but stimulates locomotor activity at lower doses. The low dose effects observed with both of these drugs are not apparent early in ontogeny, but emerge only during or following adolescence. A somewhat earlier emergence of a low dose paradoxical effect is seen with the $5HT_{1A}$ receptor agonist, 8-OHDPAT, with late preweanling, but not neonatal, rats showing increases in ingestive behavior at low doses but suppression at higher doses. In contrast to these ontogenetic increases in expression of low dose drug effects, low dose facilitation of social behavior is seen following ethanol only in adolescent rats and not their mature counterparts. Low doses of ethanol (in the range of 0.5 g/kg) stimulate social interactions of adolescent rats when tested in a familiar test situation, with higher doses (1 g/kg or greater) suppressing social behavior. No such low dose facilitation was evident in adults tested identically. Mechanisms postulated to underlie these ontogenetic patterns of low dose effects include delayed development of autoreceptors (apomorphine and 8-OHDPAT) as well as differential ontogeny of neural regions recruited into activity by low versus higher doses of the drugs (morphine and ethanol).

ARE LOW DOSES OF DNA DAMAGING AGENTS ANTI-MUTAGENIC?

Pamela J. Sykes, Department of Haematology and Genetic Pathology, Flinders University and Medical Centre, Bedford Park, South Australia 5042, Australia, Tel: 61 8 82044379, Fax: 61 8 82045450, Email: pam.sykes@flinders.edu.au
Sarah J. Swinburne, Department of Haematology and Genetic Pathology, Flinders University and Medical Centre, Bedford Park, South Australia 5042, Australia, Tel: 61 8 82044139, Fax: 61 8 82045450, Email: sarah.swinburne@flinders.edu.au
Madhava Bhat, Department of Medical Physics, Royal Adelaide Hospital, Adelaide, SA, 5000, Australia, Tel: 61 8 8222 5541, Fax: 61 8 8222 5937, Email: mbhat@mail.rah.sa.gov.au
John Cormack, Department of Medical Imaging, Flinders University and Medical Centre, Bedford Park, South Australia 5042, Australia, Tel: 61 8 82044642, Fax: 61 8 82045450, Email: john.cormack@fmc.sa.gov.au
Tanya K Day, Department of Haematology and Genetic Pathology, Flinders University and Medical Centre, Bedford Park, South Australia 5042, Australia, Tel: 61 8 82044139, Fax: 61 8 82045450, Email: tanya.day@flinders.edu.au
Renate U Domel, Radiation Consequences and Radioecology, Safety and Radiation Science, Australian Nuclear Science and Technology Organisation, PMB 1 Menai, New South Wales 2234, Australia, Tel: 61 2 9717 3839, Fax: 61 2 9717 9264, Email: red@ansto.gov.au
William M. Burch, R&D Radiopharmaceuticals, Australian Nuclear Science and Technology Organisation, PMB 1 Menai, New South Wales, 2234, Australia, Tel: 61 2 9717 9540, Fax: 61 2 9717 9262, Email: wmb@ansto.gov.au
Alexander A. Morley, Department of Haematology and Genetic Pathology, Flinders University and Medical Centre, Bedford Park, South Australia 5042, Australia, Tel: 61 8 82044431, Fax: 61 8 82045450, Email: alec.morley@flinders.edu.au
Antony M. Hooker, Department of Haematology and Genetic Pathology, Flinders University and Medical Centre, Bedford Park, South Australia 5042, Australia, Tel: 61 8 82044139, Fax: 61 8 82045450, Email: tony.hooker@flinders.edu.au

Although mutagens are frequently regarded as being synonymous with carcinogens, nearly all laboratory studies of mutagens involve high levels of exposure, whereas the importance of mutagens and carcinogens for human populations involves the exposure of relatively large numbers of individuals to relatively low doses of the relevant agent. The majority of mutation assays are only capable of detecting mutations at high doses of agents. Therefore, at present, safe levels of environmental and occupational agents are determined largely from hypothetical extrapolation from high doses of agents rather than from true measurements. Extrapolation generally incorporates the linear-no-threshold model, which is based on the conventional paradigm that an agent which produces a harmful effect at a high dose, will produce the same or similarly harmful effect at low doses. The pKZ1 mouse recombination mutagenesis assay enables study of the mutational effect of very low doses of DNA damaging agents in a whole animal model. The mutational end-point studied is chromosomal inversion which is a common mutation in cancer. We have observed a non-linear dose response in chromosomal inversions in spleen tissue of pKZ1 mice exposed to a wide dose range of the DNA damaging agents: etoposide, mitomycin C and X-radiation. For all of these agents an increase in inversions was observed at high doses and a reduction below endogenous inversion frequency was observed at low doses. In the case of X-radiation an induction in inversions was again seen at **very** low doses. These results suggest that some DNA damaging agents may be anti-mutagenic at low doses and that for X-radiation **very** low doses may also be mutagenic. It is likely that bystander effects play a role at the low doses of some of the agents studied here, the mechanism of which is poorly understood at present. If some or all mutagens are anti-mutagenic at low doses then current concepts of low dose population exposure may need substantial revision.

STRESS IMMUNOLOGY: DIFFERENTIAL DOSE-RESPONSE

Jeffrey A. Woods, Ph.D., University of Illinois at Urbana-Champaign, Department of Kinesiology, Freer Hall, 906 S. Goodwin Ave., Urbana IL, 61801, Tel: 217-244-8815,Fax: 217-244-7322, Email: woods1@uiuc.edu

It has long been known that severe psychological and physical stress can result in increased incidence and severity of illness. More recent studies have documented that chronic, uncontrollable stress also impairs many aspects of immune functioning; likely contributing to the increase in illness. However, the dogma that all stress leads to immunosuppression and illness is simplistic. Emerging evidence is shedding new light on the dose-response relationship between stress and immune function. Many studies, including those from our laboratory, have documented that moderate exercise or other forms of modest stress may actually boost various immunological functions. Some evidence also suggests that this translates into a reduced incidence or severity of disease. Unfortunately, the mechanism for this dose-response relationship is not clearly defined. Neural and endocrine factors are likely candidates in that they are activated in response to stress and immune cells are known to express receptors and respond to neuroendocrine signals. Other factors like endogenous ‘danger signals’, metabolic alterations, and free radicals may also play a role.

SESSION IV: TOXICOLOGY

DISTINCT GENE EXPRESSION PROFILES IN LUNG CELLS AT TOXIC VS NON-TOXIC NICKEL DOSES

Robert Y.-S. Cheng, University of Massachusetts Medical School, Worcester, MA
W. Gregory Alvord, Data Management Services, Inc., Ft. Detrick, Frederick,
Lucy M. Anderson, National Cancer Institute at Frederick, Ft. Detrick, Frederick MD

ARSENIC AS AN ENDOCRINE DISRUPTOR: COMPLEX DOSE DEPENDENT EFFECTS OF ARSENIC ON STEROID RECEPTOR SIGNALING

Josh Hamilton, Dartmouth Medical School, Hanover, NH
Jack E. Bodwell, , Dartmouth Medical School, Hanover, NH

CHEMICALLY INDUCED LIVER TUMORS AND THE POSSIBILITY OF HORMESIS

James Klaunig, Indiana University of Medicine, Indianapolis, IN

CHEMICAL MIXTURES: NONLINEAR DOSE-RESPONSE PHENOMENON, PHYSIOLOGICALLY BASED PHARMACOKINETICS, AND REACTION NETWORK MODELING

Raymond S. H. Yang, Colorado State University, Foothills Campus, Fort Collins, CO

THE NON-LINEAR NATURE OF LEAD-RELATED CHANGES IN BEHAVIOR AND NEUROCHEMISTRY

Deborah A. Cory-Slechta, University of Medicine and Dentistry of New Jersey and Rutgers University, Piscataway, NJ

UNIVERSALITY OF J-SHAPED AND U-SHAPED DOSE-RESPONSE RELATIONS IN STOCHASTIC TRANSITION SYSTEMS

Louis Anthony (Tony) Cox, Jr., Cox Associates and University of Colorado, Denver, CO

DISTINCT GENE EXPRESSION PROFILES IN LUNG CELLS AT TOXIC VS NON-TOXIC NICKEL DOSES

Robert Y.-S. Cheng, Division of Urology, Department of Surgery, University of Massachusetts Medical School, Room 504, Lazare Research Building, 364 Plantation Street, Worcester, MA 01604, Tel: 508-856-8104, Fax: 508-856-8699, Email: Robert.Cheng@umassmed.edu
W. Gregory Alvord, Data Management Services, Inc., Building 362, Ft. Detrick, Frederick, MD 21702, Tel: 301-846-5101, Fax: 301-846-6196, Email: gwa@css.ncifcrf.gov
Lucy M. Anderson, Laboratory of Comparative Carcinogenesis, National Cancer Institute at Frederick, Building 538, Ft. Detrick, Frederick MD 21702, Tel: 301-846-5600, Fax: 301-846-5946, Email: andersol@mail.ncifcrf.gov

Occupational exposure to nickel compounds is associated with lung cancer risk; epigenetic effects on gene expression have been suggested as part of the mechanism. We examined acute effects of exposure of cultured cells from the peripheral human lung (HPL1D) to nickel(II) acetate, with regard to gene expression changes as assayed by microarray (~8000 cDNAs, IncyteGenomics chips). Cells were exposed for 24 hr to nontoxic (50, 100 or 200 micromolar) or toxic (400, 800 or 1600 micromolar) Ni(II). A total of 868 genes showed at least 2-fold change in gene expression at any Ni(II) concentration. The data were analyzed by hierarchical and partitioning clustering and by a neural network algorithm. There were two main clusters, which showed marked up- or down-regulation at the highest, toxic Ni(II) concentrations. These were further subdivided into 10 highly cohesive clusters. Remarkably, only 2 of these 10, comprising 163 genes, showed the same dose-response trend at the low nontoxic concentrations as at the high toxic levels. Genes in 7 clusters, a total of 591, showed significantly altered expression only at the toxic concentrations. One cluster of 114 genes exhibited a significant change only at non-toxic doses. Thus, for the majority of genes examined, expression changes at the high toxic Ni(II) concentrations were not predictive of alterations at the lower nontoxic levels. These results are germane regarding mechanistic extrapolation from data obtained with high-dose exposure, to predictions for low-dose effects. Microarray analyses may benefit this thorny issue in risk assessment.

ARSENIC AS AN ENDOCRINE DISRUPTOR: COMPLEX DOSE-DEPENDENT EFFECTS OF ARSENIC ON STEROID RECEPTOR SIGNALING

Joshua W. Hamilton, Dartmouth Medical School, Department of Pharmacology & Toxicology, 7650 Remsen Room 514, Hanover NH 03755, Tel: 603-650-1316, Fax: 603-650-1129, Email: josh.Hamilton@dartmouth.edu
Jack E. Bodwell, Dartmouth Medical School, Department of Physiology, 750W Borwell, DHMC, Lebanon NH 03756, Tel: 603-650-7734, Fax: 603-650-6130, Email: jack.bodwell@dartmouth.edu

Arsenic contamination of drinking water is considered one of the principal environmental health threats in the U.S. and throughout the world. Chronic intake of elevated levels of inorganic arsenic (As) has been associated with a substantially increased risk of cancer, diabetes, vascular disease, cardiovascular disease, and reproductive and developmental problems. Recent studies suggest that levels as low as 5-10 ppb may be associated with significant increases in these health risks. The As levels we used in these studies are directly relevant to those found in New Hampshire, Maine and many other regions of the U.S. As in the range of 0.05 to 1 µM (6 to 120 ppb) showed stimulatory effects on hormone-stimulated, glucocorticoid receptor (GR)-mediated gene activation of both endogenous genes and reporter construct genes containing glucocorticoid response elements transfected into mammalian cells in culture. At only slightly higher concentrations (1 to 3 µM) the effects of As became inhibitory. Thus, over this narrow concentration range the effects of As changed from a two- to four-fold stimulation to a greater than two-fold suppression in activity. The complex pattern of dose-dependent effects of As on GR activity suggest multiple target sites with different affinities that contribute to this effect. Another striking finding of these studies is that the magnitude of GR stimulation and inhibition by As was highly dependent on the cellular level of hormone-activated GR. Similar complex dose-response patterns for As effects have been seen in parallel studies examining gene expression using DNA microarrays and in studies of vascular proliferation and angiogenesis, suggesting this is a common biological response to this environmental agent.

CHEMICALLY INDUCED LIVER TUMORS AND THE POSSIBILITY OF HORMESIS

James Klaunig, Indiana University, Department of Pharmacology and Toxicology, 635 Barnhill Dr., MS551, Indianapolis, IN 46202, Tel 317-274-7799, Fax 317 2747787, Email: jklauni@iupui.edu

In rodents, liver tumors are the most common neoplasia detected in chronic carcinogenicity studies. Chemically induced hepatocarcinogenesis involves a multi-step process that incorporates both mutational and cell proliferation events. The cellular and molecular mechanisms involving this multistage process have been extensively studied in rodents. The initial stage involves genomic DNA damage that if un-repaired may result in the formation of a mutated, intitiated cell (initiation stage). The initiated cell requires subsequent clonal expansive growth to form a preneoplastic lesion (promotion). For these preneoplastic cells to progress to neoplasia, additional DNA damaging events need to occur (progression). Multiple investigations have clearly defined many of the mechanisms involved in liver neoplasm induction by chemicals. Initiated cells may be produced through either un-repaired DNA damage following carcinogen adduct formation or through spontaneous DNA mutation. The promotion stage involves the selective increase in preneoplastic cell population though either increased cell proliferation and/or decrease cell apoptosis, both of which involve modulation of gene expression by the chemical agent. Multiple biological process including, changes in methylation status, receptor mediated events, blockage of cell to cell communication, and increased oxidative stress have bee associated with the selective preneoplastic cell growth. It is clear that the cellular and molecular mechanisms involved in this multi-step hepatocarcinogenesis process are dose dependent and exhibit well defined thresholds. These processes are also inducible and thus it is not surprising that a protective effect (hormesis) is observed in studies employing low doses. The presence of dose response, threshold, and low dose protective effects of chemicals on liver neoplasia development is further supported in several chronic carcinogen bioassays where multiple doses have been employed.

CHEMICAL MIXTURES: NONLINEAR DOSE-RESPONSE PHENOMENON, PHYSIOLOGICALLY BASED PHARMACOKINETICS, AND REACTION NETWORK MODELING

Raymond S. H. Yang, Quantitative and Computational Toxicology Group, Center for Environmental Toxicology and Technology, Colorado State University, Foothills Campus, 3195 Rampart Road, Fort Collins, CO 80523-1690
Tel: 970-491-5652, Fax: 970-491-8304, Email: Raymond.yang@colostate.edu

The focus of this presentation is on chemical mixtures and their related non-linear dose response relationship; in doing so, we attempt to demonstrate a number of concepts. First, the concept of dose-dependent toxicological interactions: Using human keratinocytes, our studies revealed that toxicological responses of metal mixtures consisting of arsenic, cadmium, chromium, and lead are highly dose-dependent. From very low dose levels (about 0.3 to 10 ppb) to the highest dose levels (about 200 ppb to 8 ppm), the responses varied from a growth stimulatory effect (hormesis), to additive, synergistic, and finally antagonistic cytotoxicity (Bae *et al.,* 2001; Gennings *et al.,* 2002). Second, the concept of interaction threshold: Using an interactive physiologically based pharmacokinetic (PBPK) model for human and under specific exposure conditions near threshold limit values (TLVs), we estimated "interaction thresholds" under these exposure conditions for ternary and binary mixtures of volatile organic solvents. We also found that increases in trichloroethylene (TCE) blood levels due to competitive inhibition of TCE metabolism by other solvents [tetrachloroethylene (PERC) and 1,1,1-trichloroethane (MC)] led to higher availability of TCE for glutathione conjugation, a metabolic pathway associated with kidney toxicity/carcinogenicity (Dobrev *et al.,* 2001; 2002). Third, the concept of biochemical reaction network and "second generation physiologically based pharmacokinetic/pharmacodynamic (PBPK/PD) models": Integrating PBPK modeling with reaction network modeling, a proven chemical/ petroleum engineering technology for complex systems such as an oil refinery, we intend to develop a computer modeling tool for simulations (*i.e., in silico* biology, or virtual human) on whole body PK/PD all the way down to the level of interwoven molecular interactions.

THE NON-LINEAR NATURE OF LEAD-RELATED CHANGES IN BEHAVIOR AND NEUROCHEMISTRY

Deborah A. Cory-Slechta, Environmental and Occupational Health Sciences Institute, Robert Wood Johnson Medical School, University of Medicine and Dentistry of New Jersey and Rutgers University, 170 Frelinghuysen Road, Piscataway, NJ 08854, Tel: 732-445-0205, Fax: 732-445-0131, Email: dcs@eohsi.rutgers.edu

Recent findings suggest a non-linear relationship between blood lead (Pb) concentrations and intelligence quotient scores in children. Brain regions known to play critical roles in such cognitive functions include prefrontal cortex and nucleus accumbens, with dopamine and glutamate as key neurotransmitters in these areas. In accordance with the studies in children, a well-characterized low-level chronic postweaning Pb exposure model in rats has repeatedly demonstrated that behavioral performances mediated by these brain regions likewise exhibit non-linear changes in response to Pb. On a Fixed Interval (FI) schedule of reinforcement, a behavioral baseline considered to be a surrogate of impulsivity in children, response rates are markedly increased by low levels, but decreased at higher Pb levels. Such effects can be related mechanistically to levels of dopamine in nucleus accumbens since administration of an irreversible dopamine antagonist directly into nucleus accumbens in normal rats demonstrates that dopamine systems are critical to the mediation of FI performance. Moreover, dopamine function in nucleus accumbens is also influenced by Pb in a non-linear fashion. Using in vivo electrochemistry, low Pb exposures increase potassium-evoked DA release while higher levels decrease release. These findings indicate an inverse U-shaped relationship between nucleus accumbens dopamine and FI performance that could underlie the non-monotonic effects of Pb on this behavioral baseline. Non-linear trends in Pb-associated learning impairments in this model may be related to blockade of NMDA glutamatergic receptors in nucleus accumbens, since intra-nucleus accumbens injection of the non-competitive antagonist MK-801 in normal rats produces a profile of learning impairments mimicking those of Pb. Furthermore, the MK-801 dose-effect function itself is non-linear, with more pronounced reductions in learning accuracy at lower than higher doses. Collectively, these studies are consistent with a biological basis for the non-linear dose-effect functions associated with the adverse effects of Pb exposure on the central nervous system.

UNIVERSALITY OF J-SHAPED AND U-SHAPED DOSE-RESPONSE RELATIONS IN STOCHASTIC TRANSITION SYSTEMS

Louis Anthony (Tony) Cox, Jr., Cox Associates and University of Colorado, 503 Franklin Street, Denver, CO, 80218, Tel: 303-388-1778, Fax: 303-388-0609, Email: tony@cox-associates.com

Dose-response data for benzene and many other chemical carcinogens exhibit multiple apparent concentration thresholds. A relatively small increase in exposure concentration near such a threshold disproportionately increases incidence of a specific tumor type. Yet, most mathematical models of carcinogenesis do not explain such threshold-like behavior. For example, the traditional multistage (MS) model of carcinogenesis and the Moolgavkar-Venzon-Knudson (MVK) two-stage stochastic model of carcinogenesis typically yield smooth dose-response curves without thresholds.

This paper introduces a general mathematical modeling framework that includes the MVK and MS model families as special cases. Stochastic transitions of stem cells among stages represent genotoxic or clastogenic damage. Cell proliferation, cell killing and apoptosis can occur at different stages. Key components include:

1. An effective number of stem cells undergoing active cycling and hence vulnerable to stochastic transitions representing somatically heritable transformations. (These need not occur in any special linear order, as in the MS model.)
2. A random time until the first malignant stem cell is formed. This is the first order-statistic, $T = \min\{T1, T2,\ldots, Tn\}$ of n random variables, interpreted as the random times at which each of n initial stem cells or their progeny first become malignant.
3. A random time for a normal stem cell to complete a full set of transformations converting it to a malignant one. This is interpreted very generally as the first passage time through a random network of stochastic transitions, possibly with very many possible paths.

In this very general family of models, threshold-like (J-shaped or multi-threshold) dose-response nonlinearities naturally emerge even without cytotoxicity, as consequences of stochastic phase transition laws for traversals of random transition networks. With cytotoxicity present, U-shaped as well as J-shaped dose-response curves can emerge. These results are universal, i.e., independent of specific biological details represented by the stochastic transition networks.

SESSION V: REGULATORY / RISK SESSION

IMPLICATIONS OF THE HORMESIS RESPONSE FOR CANCER RISK ASSESSMENT
Jonathan Borak, Yale University, New Haven, CT

THE SEARCH FOR NON-LINEAR EXPOSURE-RESPONSE RELATIONSHIPS AT AMBIENT LEVELS IN ENVIRONMENTAL EPIDEMIOLOGY
Morton Lippmann, New York University School of Medicine, Tuxedo, NY

PUBLIC POLICY IMPLICATIONS OF HORMESIS
Joseph V. Rodricks, Ph.D., DABT, ENVIRON International Corporation, Arlington, VA

SOME IMPLICATIONS OF NONLINEAR DOSE-RESPONSE RELATIONSHIPS FOR QUANTITATIVE RISK ASSESSMENT
Robert L. Sielken Jr., Ph.D., Sielken & Associates Consulting, Inc., Bryan, TX

PRECAUTIONARY PRINCIPLES, ANTICIPATORY ACTIONS AND HORMESIS: SOCIETY GAINS A NEW REGULATORY PARADIGM
Paolo F. Ricci, University of San Francisco and University of Queensland, San Francisco, CA
Thomas R. MacDonald, University of San Francisco and University of Queensland, San Francisco, CA

IMPLICATIONS OF THE HORMESIS RESPONSE FOR CANCER RISK ASSESSMENT

Jonathan Borak, Yale University, Departments of Medicine and Epidemiology & Public Health, 234 Church Street (#1100), New Haven, CT 06510, Tel: 203-777-6611, Fax: 203-777-1411, Email: jborak@jborak,com

Standard methods for cancer risk assessment (e.g., *Draft Final Guidelines for Carcinogen Risk Assessment,* US EPA, 2003) proscribe linearized extrapolation when data indicate: 1) that such extrapolation is appropriate; 2) when the agent is DNA-reactive or has a mode of action expected to be linear at low doses; 3) when body burdens are so high that incremental doses are expected to affect the linear portion of the dose-response cure; 4) when available data are insufficient to establish the mode of action. Unfortunately, there are few agents for which sufficient experimental data exist to document low-dose non-linearity. A barrier to developing such data is the standard design of NTP bio-assays, which rarely include the numbers of low-range doses necessary to demonstrate hormesis. Nevertheless, empirical data suggest that the low-dose response curves of some carcinogens do reflect a hormetic model. Among these are initiators (e.g., radiation, MNNG), promoters (e.g., TCDD), and carcinogens of uncertain modes of action (e.g., cadmium). Such findings raise the possibility that the default linearized model is overly conservative. To evaluate the public health importance of that possibility, future research will need to demonstrate: 1) that hormetic dose-response curves pertain for a variety of carcinogenic agents; and, 2) that such non-linear dose responses occur at public health-relevant exposure levels, (i.e., at levels greater than the reference doses or other exposure limits that are calculated on the basis of linearized models).

THE SEARCH FOR NON-LINEAR EXPOSURE-RESPONSE RELATIONSHIPS AT AMBIENT LEVELS IN ENVIRONMENTAL EPIDEMIOLOGY

Morton Lippmann, New York University School of Medicine, Nelson Institute of Environmental Medicine, 57 Old Forge Road, Tuxedo, NY 10987, Tel: 845-731-3558, Fax: 845-351-5472
Email: lippmann@env.med.nyu.edu

The traditional paradigm for setting standards for exposures to environmental toxicants has involved the use of either experience from exposed workers or laboratory animals. The data have been used to determine or estimate a no-or lowest observable adverse effect level (NOAEL), and a margin of safety (safety factor) has been applied to account for the limitations of the available exposure and effects data. For animal test data, these limitations include: species differences; high-to-low dose extrapolations; and differences in susceptibility between healthy pure bred animals and a more diverse human population with various susceptibilities. For occupational experience, the limitations are: very limited data on exposure; and the data being limited to a population of relatively healthy adults (usually men only).

For a limited number of environmental toxicants, for which there are widespread exposures among the general population, such as the criteria air pollutants (PM, O_3, CO, NO_2, SO_2, and Pb), standards have been set on the basis of human experience with a focus on susceptible subsegments of the population, and there have been relatively thorough, albeit unsuccessful, examinations of evidence for the existence of thresholds and non-linearities in the exposure-response relationships. In most cases, the risk-assessments have been based on best-fit linear, non-threshold, models fitted to the available, population-based, low-dose exposure-response data. In this paper, the use of these approaches for particulate matter, ozone, lead, and for dioxin and related compounds will be reviewed and compared.

PUBLIC POLICY IMPLICATIONS OF HORMESIS

Joseph V. Rodricks, Ph.D., DABT, ENVIRON Health Sciences Institute, ENVIRON International Corporation, 4350 North Fairfax Drive, Suite 300, Arlington, VA 22203, Tel: 703-516-2316, Fax: 703-516-2393, Email: jrodricks@environcorp.com

Development of experimental or epidemiological data sufficient to ascertain whether any or all of the manifestations of toxicity produced by specific substances exhibit hormetic dose-response relationships would require studies having designs that would greatly exceed, in complexity and cost, those now typically undertaken. It thus becomes critical, if hormesis is to become an influential component of risk assessment, to ascertain the extent to which the available information supports hormesis as a general phenomenon in toxicology. Criteria for generalizability need to be developed, and the available information need to be evaluated against them. If such phenomena are common, but not general, then are there specific indicators that can be used to differentiate responses that are hormetic from those that are not? If the issue of generalizability can be resolved, then additional questions arise regarding the models appropriate for low dose risk assessment. Policy issues regarding the quality and quantity of evidence necessary to document low dose "protective" effects for humans also need to be examined and resolved. It will be useful to set forth all of the specific steps that need to be taken to move what is clearly a common (but perhaps not general?) phenomenon in toxicology from the purely scientific to the public health and regulatory realms.

SOME IMPLICATIONS OF NONLINEAR DOSE-RESPONSE RELATIONSHIPS FOR QUANTITATIVE RISK ASSESSMENT

Robert L. Sielken Jr., Ph.D., Sielken & Associates Consulting, Inc., 3833 Texas Avenue, Suite 230, Bryan, Texas 77802, Tel: 979-846-5175, Fax: 979-846-2671, Email: SielkenAssoc@aol.com

The existence of nonlinear dose-response relationships should impact quantitative risk assessment in at least seven fundamental ways. (1) The dose-response models for bioassay and epidemiological data should have greater flexibility to fit the observed shape of the dose-response data and no longer be forced to always be linearly increasing at low doses. (2) Experimental designs should be altered to provide greater opportunity to identify the nonlinear component of a dose-response relationship. (3) Rather than a lifetime average daily dose or its analog for shorter time periods, dose scales or metrics should be used that reflect the age or time dependence of the dose level. (4) Low-dose risk characterization should include the likelihood of beneficial effects and the likelihood that a dose level has reasonable certainty of no appreciable adverse health effects. (5) Exposure assessments should make greater efforts to characterize the distribution of actual doses from exposure rather than just upper bounds. (6) Uncertainty characterizations should be expanded to include both upper and lower bounds, and there should be an increased explicit use of expert judgment and weight-of-evidence based distributional analyses reflecting more of the available relevant dose-response information and alternative risk characterizations. (7) Risk should be characterized in terms of the net effect of a dose on health rather than a dose's effect on a single factor affecting health -- for example, risk would be better expressed in terms of mortality from all causes combined rather than a specific type of fatal disease.

PRECAUTIONARY PRINCIPLES, ANTICIPATORY ACTIONS AND HORMESIS: SOCIETY GAINS A NEW REGULATORY PARADIGM

Paolo F. Ricci, University of San Francisco and University of Queensland, 2130 Fulton St., San Francisco, CA 94114, Tel: 510-282- 9014, Fax: 415-422-6387, Email: apricci@earthlink.net
Thomas R. MacDonald, University of San Francisco and University of Queensland, 2130 Fulton St., San Francisco, CA 94114, Tel: 415-422-5895, Fax: 415-422-6387, Email: macdonaldt@usfca.edu

Precautionary and anticipatory principles drive environmental health choices and require science and law to intersect and account for incomplete, heterogeneous, and complex biological evidence. Those principles concern policy-making when a hazard can cause severe or irreversible consequences, but they leave the task to default values and scientific conjectures developed and implemented by regulatory agencies. We find that those principles cannot guide policy choices when science is unable to provide accurate and incontrovertible answers. Acting on scientific conjecture and defaults - a priori acceptable by society for low stake outcomes - can result in unfair, costly and even detrimental outcomes when stakes are large. The situation can be improved through a formal, and thus replicable and generalizable, causal framework. We describe and exemplify how hormesis and probabilistic reasoning merge into a unified causal framework that bridges the gap between potential future irreversible or severe harm and incomplete scientific evidence. The framework, which can account for direct stimulation and for overcompensation mechanisms of action at low doses, is particularly appropriate for policy-making, because it results in more confident and resilient societal choices and is consistent with modern law of evidence and substantive regulatory law.

POSTER SESSION

AN OVERVIEW OF THE HORMESIS DATABASE

Robyn B. Blain, University of Massachusetts, Environmental Health Sciences, Amherst, MA 01003, Tel: 413-533-6339, Fax: 413-545-4692, Email: JRJBLAIN@aol.com
Edward J. Calabrese, University of Massachusetts, Environmental Health Sciences Amherst, MA 01003, Tel: 413-545-3164, Fax: 413-545-4692, Email: edwardc@schoolph.umass.edu

LOW-DOSE RADIATION AND DIABETES

Lu Cai, Departments of Medicine, Pharmacology & Toxicology, University of Louisville School of Medicine, 511 South Floyd Street, MDR 533, Louisville, Kentucky 40202, USA and Department of Toxicology, Jilin University School of Preventive Medicine, 6 Ximin Street, Changchun, Jilin 130021, PR China, Tel: (502) 852-5215, Fax: (502) 852-6904, Email: lcai1@hotmail.com

NON-LINEAR EFFECT OF RADIATION ON ERYTHROCYTE IMMUNITY

Guangjun Wang, Department of Hematology & Oncology, The First Hospital, Jilin University School of Medicine, 2 Ximin Street, Changchun, Jinin 130021, PR China, Tel: 086-(431) 5612815Fax: 086-(431) 8526281
Lu Cai, Departments of Medicine, Pharmacology & Toxicology, University of Louisville School of Medicine, 511 South Floyd Street, MDR 533, Louisville, Kentucky 40202, USA and Department of Toxicology, Jilin University School of Preventive Medicine, 6 Ximin Street, Changchun, Jilin 130021, PR China, Tel: (502) 852-5215, Fax: (502) 852-6904, Email: lcai1@hotmail.com

DETECTING CAUSAL NONLINEAR EXPOSURE-RESPONSE RELATIONS IN EPIDEMIOLOGICAL DATA

Louis Anthony (Tony) Cox, Jr., Cox Associates and University of Colorado, 503 Franklin Street, Denver, CO, 80218, Tel: 303-388-1778, Fax: 303-388-0609, Email: tony@cox-associates.com

LOW-DOSE NONLINEARITY OF HEMATOPOIETIC DOSE-RESPONSE RELATIONS

Louis Anthony (Tony) Cox, Jr., Cox Associates and University of Colorado, 503 Franklin Street, Denver, CO, 80218, Tel: 303-388-1778, Fax: 303-388-0609, Email: tony@cox-associates.com

BIPHASIC DOSE-RESPONSE RELATIONSHIPS IN HUMAN EXPERIMENTAL EXPOSURE TO SOLVENTS

Ivo Iavicoli , Catholic University of Sacred Heart, Institute of Occupational Health, Largo Francesco Vito, 1, 00168 Rome, Italy, Tel: +39-06-30154486, Fax: +39-06-3053612, Email: iavicoli.ivo@rm.unicatt.it
Giovanni Carelli, Catholic University of Sacred Heart, Institute of Occupational Health, Largo Francesco Vito, 1, 00168 Rome, Italy, Tel: +39-06-30154487, Fax: +39-06-3053612, Email: gcarelli@rm.unicatt.it

REGULATION OF GLUTATHIONE BY OXIDATIVE STRESS IN BOVINE PULMONARY ARTERY ENDOTHELIAL CELL

Regina M. Day, Ph.D, Departments of Medicine and Phamacology, Georgetown University Medical School, SE401 Medical-Dental Building, 3900 Reservoir Rd, Washington DC 20057, Tel: 202-687-8464, Fax: 202-687-2585 / 617-636-5953, Email: reginamday@hotmail.com
Yuichiro J. Suzuki, Ph.D., Department of Phamacology, Georgetown University Medical School SE401 Medical-Dental Building, 3900 Reservoir Rd, Washington DC 20057, Tel: 202-687-8090, Fax: 202-687-2585, Email: yuichirosuzuki@hotmail.com
Barry L. Fanburg, M.D., Department of Medicine, Tufts-New England Medical Center, Tupper Research Institute, 750 Washington St, #257, Boston, MA 02147, Tel: 617-636-8283, Email: bfanburg@tufts-nemc.org

EFFECTS OF A CHRONIC EXPOSURE TO LEAD ACETATE ON IMMUNE FUNCTION IN SWISS MICE

Ivo Iavicoli, Catholic University of Sacred Heart, Institute of Occupational Health, Largo Francesco Vito, 1, 00168 Rome, Italy, Tel: +39-06-30154486, Fax: +39-06-3053612, Email: iavicoli.ivo@rm.unicatt.it
Giovanni Carelli, Catholic University of Sacred Heart, Institute of Occupational Health, Largo Francesco Vito, 1, 00168 Rome, Italy, Tel: +39-06-30154487, Fax: +39-06-3053612, Email: gcarelli@rm.unicatt.it

LOW DOSES OF PHENOLIC COMPOUND CAN BE USEFUL IN QUICK RECOGNITION THEIR AFFINITY TO LACCASE

Elżbieta Malarczyk, Maria Curie-Sklodowska University, Biochemistry Department, M.Curie-Sklodowska square, 3, Poland 20-031 Lublin, Tel: +48 81 537 57 70, Fax: +48 81 537 51 02
Janina Kochmanska-Rdest, Maria Curie-Sklodowska University, Biochemistry Department M.Curie-Sklodowska square, 3, Poland 20-031 Lublin, Tel: +48 81 537 57 70, Fax: +48 81 537 51 02
Anna Jarosz-Wilkolazka, Maria Curie-Sklodowska University, Biochemistry Department M.Curie-Sklodowska square, 3, Poland 20-031 Lublin, Tel: +48 81 537 57 35, Fax: +48 81 537 51 02

REGULATION OF VERATRATE DEMETHYLATION IN *RHODOCOCCUS ERYTHROPOLIS* CELLS BY LOW DOSES OF FORMALDEHYDE

Elżbieta Malarczyk, Maria Curie-Sklodowska University, Biochemistry Department, M.Curie-Sklodowska square, 3, Poland 20-031 Lublin, Tel: +48 81 537 57 70, Fax: +48 81 537 51 02
Marzanna Pazdzioch-Czochra, Maria Curie-Sklodowska University, Biochemistry Department, M.Curie-Sklodowska square, 3, Poland 20-031 Lublin, Tel: +48 81 537 57 35
Fax: +48 81 537 51 02
Janina Kochmanska-Rdest, Maria Curie-Sklodowska University, Biochemistry Department M.Curie-Sklodowska square, 3, Poland 20-031 Lublin, Tel: +48 81 537 57 70, Fax: +48 81 537 51 02

REGULATION OF VERATRATE DEMETHYLATION IN *RHODOCOCCUS ERYTHROPOLIS* CELLS BY LOW DOSES OF FORMALDEHYDE

Elżbieta Malarczyk, Maria Curie-Sklodowska University, Biochemistry Department, M.Curie-Sklodowska square, 3, Poland 20-031 Lublin, Tel: +48 81 537 57 70, Fax: +48 81 537 51 02
Marzanna Pazdzioch-Czochra, Maria Curie-Sklodowska University, Biochemistry Department, M.Curie-Sklodowska square, 3, Poland 20-031 Lublin, Tel: +48 81 537 57 35 Fax: +48 81 537 51 02
Janina Kochmanska-Rdest, Maria Curie-Sklodowska University, Biochemistry Department M.Curie-Sklodowska square, 3, Poland 20-031 Lublin, Tel: +48 81 537 57 70, Fax: +48 81 537 51 02

THIMEROSAL FOR THE TREATMENT OF INFLUENZA AND HERPES VIRUS INFECTIONS

John McMichael, The Institute for Therapeutic Discovery, P.O. Box 127, Delanson, NY 12053, Tel: 518-872-1144, Fax: 518-872-0753
Allan D. Lieberman, Center for Occupational and Environmental Medicine, 7510 Northforest Drive, North Charleston, SC 29420, Tel: 843-572-1600, Tax: 843-572-1795, Email: allanlsc@yahoo.com

ADAPTIVE IMMUNE RESPONSES TO LONG-TERM LOW-LEVEL RADIATION EXPOSURE: FEASIBILITY STUDY ON DOG MATERIAL FROM ARGONNE

Viktor Meineke, Institute of Radiobiology, German Armed Forces, Neuherbergstrasse 11, 80937 Munich, Germany, Tel: +49-89-3168-2764, Fax: +49-89-3168-2635, Email: ViktorMeineke@bundeswehr.org
Kerstin Müller, Institute of Radiobiology, German Armed Forces, Neuherbergstrasse 11, 80937 Munich, Germany, Tel: +49-89-3168-3269, Fax: +49-89-3168-2635, Email: Kerstin2Mueller@bundeswehr.org
Karin M. Greulich-Bode, Institute of Radiobiology, German Armed Forces, Neuherbergstrasse 11, 80937 Munich, Germany, Tel: +49-89-3168-3286, Fax: +49-89-3168-2635, Email: KarinGreulichBode@bundeswehr.org
Dirk van Beuningen, Institute of Radiobiology, German Armed Forces, Neuherbergstrasse 11, 80937 Munich, Germany, Tel: +49-89-3168-2749, Fax: +49-89-3168-2635, Email: InstitutfuerRadiobiologie@bundeswehr.org
Thomas E. Fritz, 503 White Oak Drive, Naperville, Illinois 60540, USA, Tel: +1-630-355-4728, Fax: +1-630-355-0274, Email: imaloon2@eudoramail.com
Theodor M. Fliedner, Radiation Medicine Research Group and WHO Collaborating Center for Radiation Accident Management, University of Ulm, Helmholtzstrasse 20, 89081 Ulm, Germany, Tel: +49-731-500-22900, Fax: +49-731-500-22902, Email: theodor.fliedner@medizin.uni-ulm.de
Ludwig E. Feinendegen, Wannental 45, 88131 Lindau, Germany, Tel: +49-8382-75673, Fax: +49-8382-947626, Email: Feinendegen@gmx.net

CARDIORENAL DOSE RESPONSE RELATIONSHIP OF CADMIUM

V.N.Puri, S.Saha, Division of Pharmacology, Central Drug Research Institute, Lucknow, India

A COMPARATIVE STUDY OF DRUG STANDARDIZATION IN HORMETIC OBSERVATIONS AND HOMEOPATHIC PROVINGS

Jahangir Satti, Ph.D., Chief Medical Physicist and Radiation Safety Officer, Department of Radiation Physics, St. Joseph's Medical Center, 1800 North California St., Stockton, CA 95213-9008, Tel: 209 467 6405, Fax: 209 461 5150

COMPLEMENTARY NANO-SCALE THERAPEUTIC APPROACH THROUGH FREQUENCY BASED BIO-SYNCHRONIZATION.

Jahangir Satti, Ph.D., Chief Medical Physicist and Radiation Safety Officer, Department of Radiation Physics, St. Joseph's Medical Center, 1800 North California St., Stockton, CA 95213-9008, Tel: 209 467 6405, Fax: 209 461 5150

ALCOHOLIC BEVERAGE *HORMESIS* FOR CATARACT AND ATHEROSCLEROSIS IS RELATED TO PLASMA OXIDATIVE CONDITION

Claire D. Prickett, Research Assistant, Department of Biochemistry, Faculty of Medicine & Dentistry, University of Western Ontario, London, Ontario, Canada, N6A 5C1, Tel: 519-661-3074/3063(lab), Fax: 519-661-3175, Email : cdpricke@uwo.ca
Erin Lister, B.Sc., Research Assistant, Department of Biochemistry, Faculty of Medicine & Dentistry, University of Western Ontario, London, Ontario, Canada, N6A 5C1, Tel: 519-661-3074/3063(lab), Fax: 519-661-3175, Email: e_lister@hotmail.com
Michelle Collins, Research Assistant, Department of Biochemistry, Faculty of Medicine & Dentistry, University of Western Ontario, London, Ontario, Canada, N6A 5C1, Tel: 519-661-3074/3063(lab), Fax: 519-661-3175, Email :mcollin6@uwo.ca
Colleen Trevithick-Sutton, B.Sc., Research Assistant, Department of Pharmacology and Toxicology, Faculty of Medicine & Dentistry, University of Western Ontario, London, Ontario, Canada, N6A 5C1, Tel: 519-661-3074/3063(lab), Fax: 519-661-3175, Email: colleen@chem.ucla.edu
Maurice Hirst, Ph.D., Professor, Department of Pharmacology and Toxicology, Faculty of Medicine & Dentistry, University of Western Ontario, London, Ontario, Canada, N6A 5C1,
Tel: 519-661-3315, Fax 519-661-3175, Email: mhirst@uwo.ca
Earl Noble, Ph.D., Professor, School of Kinesiology, Faculty of Health Sciences, University of Western Ontario, London, Ontario, Canada, N6A 5C1, Tel: 519-661-8365, Fax 519-661-2008, Email: enoble@uwo.ca
Joe A. Vinson, Ph.D., Professor, Department of Chemistry, University of Scranton, Scranton, PA, Tel: 570-941-7551, Fax 570-941-7510, Email: vinson@UofS.edu
John R. Trevithick, Ph.D., Professor, Department of Biochemistry, Faculty of Medicine & Dentistry, University of Western Ontario, London, Ontario, Canada, N6A 5C1, Tel: 519-661-3074/3063(lab), Fax: 519-661-3175, Email: trevjohn@uwo.ca

AN OVERVIEW OF THE HORMESIS DATABASE

Robyn B. Blain, University of Massachusetts, Environmental Health Sciences,
Amherst, MA 01003, Tel: 413-533-6339, Fax: 413-545-4692, Email: JRJBLAIN@aol.com
Edward J. Calabrese, University of Massachusetts, Environmental Health Sciences
Amherst, MA 01003, Tel: 413-545-3164, Fax: 413-545-4692, Email: edwardc@schoolph.umass.edu

A relational-retrieval database has been developed compiling toxicological studies that assess the occurrence of hormetic dose responses and their quantitative characteristics. This database permits an evaluation of these studies over numerous parameters, including the study design and dose-response features as well as physical/chemical properties of the agents. The database currently contains approximately 5600 dose-response relationships satisfying evaluative criteria for hormesis across over about 500 agents from a broadly diversified spectrum of chemical classes. The assessment reveals that hormetic dose-response relationships occur in males and females of numerous animal models in all principal age groups as well as across species, displaying a broad range of differential susceptibilities to toxic agents. The biological models are quite extensive, including plants, bacteria, fungi, insects, fish, birds, rodents, and primates, including humans. The spectrum of endpoints displaying hormetic dose responses is also quite broad being inclusive of growth, longevity, metabolic parameters, disease incidences (including cancer), and immune responses amongst others. The quantitative features of the hormetic dose response reveal that the vast majority of cases display a maximum stimulatory response less than two-fold greater than the control while the width of the stimulatory response is typically less than 100-fold. The database also contains a quantitative evaluation component that differentiates amongst the various dose responses concerning the strength of the evidence supporting a hormetic conclusion. This evidence is based on study design features, magnitude of the stimulatory response, statistical significance and reproducibility of findings. While the database was originally designed to assess the hypothesis concerning whether hormesis was a demonstrable phenomenon that was reproducible, the database has not only provided a means to affirmatively address this question but to also permit significant insight into the nature of the dose response in the sub-NOAEL zone and its broad-based generalizability by biological model, endpoint and chemical/physical stressor agent.

LOW-DOSE RADIATION AND DIABETES

Lu Cai, Departments of Medicine, Pharmacology & Toxicology, University of Louisville School of Medicine, 511 South Floyd Street, MDR 533, Louisville, Kentucky 40202, USA
and Department of Toxicology, Jilin University School of Preventive Medicine, 6 Ximin Street, Changchun, Jilin 130021, PR China, Tel: (502) 852-5215, Fax: (502) 852-6904, Email: lcai1@hotmail.com

Induction of hormesis (low doses of radiation are beneficial) and adaptive response (preexposure to a low dose of radiation protects against a subsequent high dose) by low-dose radiation has been extensively indicated. It was shown that adaptive response by low-dose radiation was not only resistant to damage induced by high-dose radiation, but also cross resistant to other non-radiation challenges such as chemicals. Mechanisms by which low-dose radiation induces the preventive effect on animal tissues includes the induced or up-regulated protective proteins such as heat shock proteins and antioxidants. Since oxidative injuries of tissues are known to play a major role in many human diseases including diabetes. In order to explore the application of the adaptive mechanism induced by low-dose radiation, this review will search the published data on the effect of low-dose radiation on diabetes and also on the therapeutic role of low-energy laser on diabetic cardiovascular complications. The available data indicated that pre-exposure of mice to low-dose radiation reduced the incidence of alloxan-induced diabetes, and also delayed the onset of hyperglycemia in diabetes-prone non-obese diabetic (NOD) mice. Exposure of spontaneous developed type II diabetic mice to chronic low-dose radiation also offered a reverse effect on hyperglycemic mice, showing the attenuation of hyperglycemia in these diabetic mice. In search of the mechanisms by which low-dose radiation prevents and reverses diabetes, which is unclear now though, major reason may includes the induction of antioxidants in the pancreatic tissues and preserves the capacity of insulin secretion of beta cells. In addition, low-intensity laser has been used to cure diabetic skin, and retinopathy. There is documentation, low-intensity laser is also efficient in curing infarction injury in the myocardium, and whether it is also extrapolated to diabetic cardiomyopathy is need to be investigated. In summary, low-dose radiation, and low-energy laser will become an alternated approach to prevention of diabetes and its complications. (Supported in part by Philip Morris USA, Inc.).

NON-LINEAR EFFECT OF RADIATION ON ERYTHROCYTE IMMUNITY

Guangjun Wang, Department of Hematology & Oncology, The First Hospital, Jilin University School of Medicine, 2 Ximin Street, Changchun, Jinin 130021, PR China, Tel: 086-(431) 5612815
Fax: 086-(431) 8526281
Lu Cai, Departments of Medicine, Pharmacology & Toxicology, University of Louisville School of Medicine, 511 South Floyd Street, MDR 533, Louisville, Kentucky 40202, USA
and Department of Toxicology, Jilin University School of Preventive Medicine, 6 Ximin Street, Changchun, Jilin 130021, PR China, Tel: (502) 852-5215, Fax: (502) 852-6904, Email: lcai1@hotmail.com

Induction of hormesis, in particular hormetic effect on mammalian immunity, by low-dose radiation was extensively indicated. However, effect of low-dose radiation on erythrocyte immunity has been paid less attention. The present study was undertaken to investigate the effect of radiation at 0 – 6 Gy X-rays, including low doses of 25, 50, 75 and 100 mGy, on erythrocyte immunity by measuring C3b and IC receptor rosette as well as IL-2 production. Mice were exposed to indicated doses of X-rays, and 24 to 72 later blood were collected for C3b and IC receptor rosette assays. Result showed that both 1 Gy and 6 Gy X-rays induced significant suppression of RBC-C3b and RBC-IC rosette formation at 24 to 72 post-radiation, while low-doses of X-rays (25 to 100 mGy) all induced significant increases in RBC-C3b and RBC-IC rosette formations at 24 to 72 post-radiation as compared to control. Measurement of IL-2 indicated that all doses of 25 mGy to 1000 mGy X-rays induced significant stimulation of IL-2 production with the optimal effect at 75 mGy X-rays from 24 to 120 hr post-radiation. These results suggest that low-dose radiation caused a distinct hormetic effect from inhibitory effect by high-dose radiation on erythrocyte immunity, ie. non-linear effect. Although IL-2 has been suggested to play an important role in erythrocyte immunity, no direct association of IL-2 with RBC-C3b and RBC-IC rosette formation was found in the present study. (Supported by National Natural Scientific Foundation of PR China).

DETECTING CAUSAL NONLINEAR EXPOSURE-RESPONSE RELATIONS IN EPIDEMIOLOGICAL DATA

Louis Anthony (Tony) Cox, Jr., Cox Associates and University of Colorado, 503 Franklin Street, Denver, CO, 80218, Tel: 303-388-1778, Fax: 303-388-0609, Email: tony@cox-associates.com

The possibility of hormesis in individual dose-response relations undermines traditional epidemiological criteria and tests for causal relations between exposure and response variables. Non-monotonic exposure-response relations in a large population may lack aggregate consistency, strength, biological gradient, and other hallmarks of traditional causal relations. For example, a u-shaped or n-shaped curve may exhibit zero correlation between dose and response. Thus, possible hormesis requires new ways to detect potentially causal exposure-response relations.

This paper introduces information-theoretic criteria for identifying potential causality in epidemiological data that may contain nonmonotonic or threshold dose-response nonlinearities. Roughly, exposure variable X is a potential cause of response variable Y if and only if: (a) X is INFORMATIVE about Y (i.e., the mutual information between X and Y, I(X; Y), measured in bits, is positive. This provides the required generalization of statistical association measures for monotonic relations); (b) UNCONFOUNDED: X provides information about Y that cannot be removed by conditioning on other variables. (c) PREDICTIVE: Past values of X are informative about future values of Y, even after conditioning on past values of Y; (d) TEMPORAL ORDERING: Entropy of Y $\geq$ joint entropy of its direct causes (its parents in a causal graph); (e) CAUSAL ORDERING: Y is conditionally independent of the parents of X, given X. These criteria yield practical algorithms for detecting potential causation in cohort, case-control, and time series data sets. We illustrate them by identifying potential causes of campylobacteriosis in past data sets in which low exposures to suspected risk factors (e.g., raw milk, chicken) have been paradoxically associated with statistically significant *reductions* in risk. We also discuss the application of the new criteria in resolving ambiguities and apparent contradictions in past analyses of epidemiological data sets for benzene and other chemical carcinogens.

LOW-DOSE NONLINEARITY OF HEMATOPOIETIC DOSE-RESPONSE RELATIONS

Louis Anthony (Tony) Cox, Jr., Cox Associates and University of Colorado, 503 Franklin Street, Denver, CO, 80218, Tel: 303-388-1778, Fax: 303-388-0609, Email: tony@cox-associates.com

To clarify the possible shapes of dose-response relations between low-level exposures to benzene and other volatile organic compounds (VOCs) and resulting risk of chemically induced acute myeloid leukemia, we introduce an integrated pharmacokinetic-pharmacodynamic-MVK (PBPK-PD-MVK) dynamic model of (a) the proliferative responses of hematopoietic stem cell populations during and following exposures; and (b) the resulting number of initiated and malignant cells formed over time. The model identifies how the timing of exposures affects predicted hematotoxicity and expected number of malignant stem cells formed. It represents hematopoietic progenitor cell, granulocyte-macrophage (GM)-committed stem cells, and more mature blood cells linked by nonlinear feedback control loops and susceptible to cell-killing by cytotoxic metabolites. The hematotoxicity portion of the model has been partly validated by testing its predictions against experimental and clinical data for blood cell counts during and following administration of cyclophosphamide to mice, dogs, and humans. It successfully explains apparent anomalies and patterns in previously published data, including the fact that smaller cumulative doses can cause larger hematotoxic responses. The model predicts threshold-like nonlinearities in toxic and carcinogenic responses as a function of exposure concentration and/or weeks of exposure and shows how low (linear PBPK) concentrations of myelotoxic VOC mixtures can produce U-shaped dose-response relations. Different combinations of concentrations and days between consecutive exposures greatly affect (e.g., by 7-fold) the predicted carcinogenic risk for the same total AUC of administered dose or exposure. These possibilities are robust to several model uncertainties.

BIPHASIC DOSE-RESPONSE RELATIONSHIPS IN HUMAN EXPERIMENTAL EXPOSURE TO SOLVENTS

Ivo Iavicoli , Catholic University of Sacred Heart, Institute of Occupational Health, Largo Francesco Vito, 1, 00168 Rome, Italy, Tel: +39-06-30154486, Fax: +39-06-3053612, Email: iavicoli.ivo@rm.unicatt.it
Giovanni Carelli, Catholic University of Sacred Heart, Institute of Occupational Health, Largo Francesco Vito, 1, 00168 Rome, Italy, Tel: +39-06-30154487, Fax: +39-06-3053612, Email: gcarelli@rm.unicatt.it

Previous studies carried out in the field of experimental toxicology have shown the evidence of biphasic dose-response relationships for different experimental models, endpoints and chemicals tested. As these studies excluded humans as the experimental model, we examined the literature of the last three decades in order to verify data concerning the human experimental exposure with the aim of highlighting possibile biphasic dose-response relationships. The substances used for the experimental exposures included hydrocarbons, esthers, alcohols, ketones, ethers, glycoethers, halogenated hydrocarbons, and carbon sulphide. In all the studies the absorption route was inhalation. Some metodological limitations prevented us a more detailed examination of experimental data and in any case biphasic dose-response relationships were not observed.
Frequently the limitations were as follows:

1. Endpoints have not been reported.
2. A single exposure dose was administered.
3. The time corse of levels has been fluctuating during the exposure session.
4. The presence of workload (both constant and variable) complicated the concept of "exposure level".
5. There was a lack of adequate statistical analysis.
6. There was a lack of tabular data for additional analysis.
7. In any case, a NOAEL has not been assigned.
8. Sometimes, there was the coincidence of 2 or more limitations.

Therefore we have concluded that the available experimental data do not allowed us to support evidence of biphasic dose-response relationships in the human experimental exposure to the above mentioned chemical substances.

REGULATION OF GLUTATHIONE BY OXIDATIVE STRESS IN BOVINE PULMONARY ARTERY ENDOTHELIAL CELL

Regina M. Day, Ph.D, Departments of Medicine and Phamacology, Georgetown University Medical School, SE401 Medical-Dental Building, 3900 Reservoir Rd, Washington DC 20057, Tel: 202-687-8464, Fax: 202-687-2585 / 617-636-5953, Email: reginamday@hotmail.com
Yuichiro J. Suzuki, Ph.D., Department of Phamacology, Georgetown University Medical School SE401 Medical-Dental Building, 3900 Reservoir Rd, Washington DC 20057, Tel: 202-687-8090, Fax: 202-687-2585, Email: yuichirosuzuki@hotmail.com
Barry L. Fanburg, M.D., Department of Medicine, Tufts-New England Medical Center, Tupper Research Institute, 750 Washington St, #257, Boston, MA 02147, Tel: 617-636-8283, Email: bfanburg@tufts-nemc.org

Glutathione plays important roles as an intracellular antioxidant and in the maintenance of cellular thiol-disulfide balance. In addition, glutathione may regulate cell growth signaling induced by oxidative stress. We previously reported that cellular glutathione is up-regulated by bleomycin in bovine pulmonary artery endothelial cells. The present study examined effects of hydrogen peroxide (H2O2) on cell growth and glutathione levels. Exogenous addition of H2O2 induced biphasic effects on cell growth; 1 mM was stimulatory and >10 mM was inhibitory. However, both growth-promoting and inhibitory levels of H2O2 increased cellular glutathione levels. Whereas 1 mM H2O2 moderately but significantly increased glutathione, 30 mM caused a more substantial increase. Like bleomycin, both concentrations of H2O2 activated DNA binding to the antioxidant response element (ARE), a regulatory element in the promoter of the g-glutamylcysteine synthetase heavy chain, a key regulator of glutathione synthesis. However, only high concentrations of H2O2 activated p44/p42 mitogen-activated protein kinase (MAPK). Thus, cellular glutathione is up-regulated by H2O2, perhaps via activating ARE-binding factors in a mechanism independent of MAPK. H2O2-mediated increase in glutathione and activation of ARE binding may play important roles in growth and death of pulmonary artery endothelial cells.

EFFECTS OF A CHRONIC EXPOSURE TO LEAD ACETATE ON IMMUNE FUNCTION IN SWISS MICE

Ivo Iavicoli, Catholic University of Sacred Heart, Institute of Occupational Health, Largo Francesco Vito, 1, 00168 Rome, Italy, Tel: +39-06-30154486, Fax: +39-06-3053612, Email: iavicoli.ivo@rm.unicatt.it
Giovanni Carelli, Catholic University of Sacred Heart, Institute of Occupational Health, Largo Francesco Vito, 1, 00168 Rome, Italy, Tel: +39-06-30154487, Fax: +39-06-3053612,
Email: gcarelli@rm.unicatt.it

Lead (Pb), a widely toxicant, has been shown to exert toxic effects during early development. Furthermore a number of studies documented that the Pb exerts immunotoxic effects on T lymphocytes.

One day after mating 6 female Swiss mice were administered six different diets containing Pb acetate (0.02, 0.06, 0.11, 0.2, 40 and 400 ppm). During lactation the mothers received the same feed given during pregnancy and the same diets were given to the offsprings (n=72; 12 for each group) after weaning for nine months. During the experiment, air Pb level was determined in the environment where the mice were caged. At the end of exposure, blood Pb level was determined in all the animals to provide a biological exposure index, and possible changes in two type-1 cytokines (IL-2, INF-) and one type-2 cytokine (IL-4) in the serum were measured. At higher levels (40 and 400 ppm) a significant increase in IL-4 production was associated with a decrease in IFN-γ production, while at lower level (0.02 ppm) we observed an increased IFN-γ production with a significant decrease in IL-4 production. Concerning Th1 and Th2 responses, our findings suggest that at these levels Pb acetate causes biphasic dose-response relationships.

LOW DOSES OF PHENOLIC COMPOUND CAN BE USEFUL IN QUICK RECOGNITION THEIR AFFINITY TO LACCASE

Elżbieta Malarczyk, Maria Curie-Sklodowska University, Biochemistry Department, M.Curie-Sklodowska square, 3, Poland 20-031 Lublin, Tel: +48 81 537 57 70, Fax: +48 81 537 51 02
Janina Kochmanska-Rdest, Maria Curie-Sklodowska University, Biochemistry Department
M.Curie-Sklodowska square, 3, Poland 20-031 Lublin, Tel: +48 81 537 57 70, Fax: +48 81 537 51 02
Anna Jarosz-Wilkolazka, Maria Curie-Sklodowska University, Biochemistry Department
M.Curie-Sklodowska square, 3, Poland 20-031 Lublin, Tel: +48 81 537 57 35, Fax: +48 81 537 51 02

Laccase belongs to oxidative extracellular enzymes which take part in the degradation of wood lignin. However the substrate range of laccase is not limited to phenolic subunits of lignin. It oxidizes also polycyclic aromatic hydrocarbons, anthracene and benzopyrene, hydroxybezotriazole, ABTS and many others. Some of these compounds are known as mediators in the free radical dependent process of delignification with participation of laccase. We used the crude enzyme of fungal laccase from *Cerrena unicolor* as the object for study of the changes in activity when the small amounts of phenolics known as substrate as well as mediators were present in the reaction mixture during determination of the laccase activity. All these substances were diluted in 75% ethanol in the range from 100^{0} to 100^{-20} mol/L and respective dilutions were added to the reaction mixture one hour before the colorimetric determination. The activity of laccase distinctly changes in the presence of tested substances and the shape of curves was depended on the kind of diluted compound. After mathematical analysis of curve shapes it could be observed that the similarity with theoretical curve was the highest only for substances known as a good substrates or good mediators of laccase. It came to the conclusion that the application of low doses of unknown substance in the test on laccase activity can be useful for the quick looking after the mediatory or substrate important for intensification of delignification processes.

REGULATION OF VERATRATE DEMETHYLATION IN *RHODOCOCCUS ERYTHROPOLIS* CELLS BY LOW DOSES OF FORMALDEHYDE

Elżbieta Malarczyk, Maria Curie-Sklodowska University, Biochemistry Department, M.Curie-Sklodowska square, 3, Poland 20-031 Lublin, Tel: +48 81 537 57 70, Fax: +48 81 537 51 02
Marzanna Pazdzioch-Czochra, Maria Curie-Sklodowska University, Biochemistry Department, M.Curie-Sklodowska square, 3, Poland 20-031 Lublin, Tel: +48 81 537 57 35
Fax: +48 81 537 51 02
Janina Kochmanska-Rdest, Maria Curie-Sklodowska University, Biochemistry Department
M.Curie-Sklodowska square, 3, Poland 20-031 Lublin, Tel: +48 81 537 57 70, Fax: +48 81 537 51 02

The reversible process of demethylation is very important for all living cells and can be regulated by limitation not only by various sources of carbon, nitrogen and oxygen but also by presence of low molecular effectors. Numerous microorganisms as bacteria, *Actinomycetes* and fungi take part in biodegradation of natural methoxyphenolics during many vital processes, among them in various steps of lignification and delignification. These organisms are very convenient for studying oxygen dependent demethylation processes very sensitive to concentration of formaldehyde (HCHO), ATP, GSH and so on. The effect of low doses of HCHO on demethylation of veratrate was observed for *Rhodococcus erythropolis* during 10 hours incubation of cells with mild shaking. At the beginning of incubation the small quantities of HCHO dilutions from 100^{-1} to 100^{-20} mol/L were added and the products of partial demethylation as vanillic and isovanillic acids, were monitored colorimetrically every two hours. The concentration of these acids changed in the sinusoidal manner with two maxima, for dilutions 100^{-5} and 100^{-15} and two minima for100^{-10} and 100^{-20} mol/L. The highest value of demethylation was observed after 6-8 hours. The electron microscopic observation showed the characteristic changes in vacuole morphology, different for the cells with maximal and minimal demethylation activity.The above results confirmed the overcompensation effect accompanying the action of formaldehyde particle on the oxygen-dependent process of veratrate demethylation. The power of these reaction was on the same level for the 100^{-5} and 100^{-15} mol/L dilutions and manifested also as distinct morphological changes.

THIMEROSAL FOR THE TREATMENT OF INFLUENZA AND HERPES VIRUS INFECTIONS

John McMichael, The Institute for Therapeutic Discovery, P.O. Box 127, Delanson, NY 12053, Tel: 518-872-1144, Fax: 518-872-0753
Allan D. Lieberman, Center for Occupational and Environmental Medicine, 7510 Northforest Drive, North Charleston, SC 29420, Tel: 843-572-1600, Tax: 843-572-1795, Email: allanlsc@yahoo.com

The World Health Organization estimates that nearly a third of the world's human population will suffer a herpesvirus infection this year, and a significant, though smaller, percentage will contract an influenza virus infection. With either type of virus, infection can range in severity from mild to life-threatening, and in the case of several of the herpesviruses, repeated expression of infection is common. We have found that a relatively low concentration of thimerosal administered systemically can reverse the course of disease induced by influenza or herpes viruses beginning within a matter of minutes of the first dose. This therapeutic dose is several hundred times less than the concentration of thimerosal used as a preservative in vaccines, is constant among hundreds of patients, and is effective for influenza A and B of different strains, herpes simplex types I and II, zoster, cytomegalovirus, infectious mononucleosis virus, and other herpes agents. Likewise, it has been shown effective for the treatment of herpes infections in dogs, cows, horses, and rabbits at this same concentration. Thimerosal has not proven efficacious for the treatment of parainfluenza or other virus infections.

ADAPTIVE IMMUNE RESPONSES TO LONG-TERM LOW-LEVEL RADIATION EXPOSURE: FEASIBILITY STUDY ON DOG MATERIAL FROM ARGONNE

Viktor Meineke, Institute of Radiobiology, German Armed Forces, Neuherbergstrasse 11, 80937 Munich, Germany, Tel: +49-89-3168-2764, Fax: +49-89-3168-2635, Email: ViktorMeineke@bundeswehr.org
Kerstin Müller, Institute of Radiobiology, German Armed Forces, Neuherbergstrasse 11, 80937 Munich, Germany, Tel: +49-89-3168-3269, Fax: +49-89-3168-2635, Email: Kerstin2Mueller@bundeswehr.org
Karin M. Greulich-Bode, Institute of Radiobiology, German Armed Forces, Neuherbergstrasse 11, 80937 Munich, Germany, Tel: +49-89-3168-3286, Fax: +49-89-3168-2635, Email: KarinGreulichBode@bundeswehr.org
Dirk van Beuningen, Institute of Radiobiology, German Armed Forces, Neuherbergstrasse 11, 80937 Munich, Germany, Tel: +49-89-3168-2749, Fax: +49-89-3168-2635, Email: InstitutfuerRadiobiologie@bundeswehr.org
Thomas E. Fritz, 503 White Oak Drive, Naperville, Illinois 60540, USA, Tel: +1-630-355-4728, Fax: +1-630-355-0274, Email: imaloon2@eudoramail.com
Theodor M. Fliedner, Radiation Medicine Research Group and WHO Collaborating Center for Radiation Accident Management, University of Ulm, Helmholtzstrasse 20, 89081 Ulm, Germany, Tel: +49-731-500-22900, Fax: +49-731-500-22902, Email: theodor.fliedner@medizin.uni-ulm.de
Ludwig E. Feinendegen, Wannental 45, 88131 Lindau, Germany, Tel: +49-8382-75673, Fax: +49-8382-947626, Email: Feinendegen@gmx.net

Between 1964 and 1992 the Argonne National Laboratory (ANL, Chicago, IL, USA) performed a unique large-scale experiment on dogs to analyze the effects of long-term low-level radiation exposure. The dose rates ranging from 3 mGy to 37.5 mGy per day whole body exposure of low LET radiation were applied over 22 hours daily. First investigations revealed that at the lowest dose rate, the incidence of myeloproliferative disorders was not significantly increased as compared to controls. However, significant changes were observed regarding the fractional distribution of peripheral blood cells. Based on above results the question towards the mechanisms underlying the system tolerance in complex tissues was raised. Therefore, the US Department of Energy funded a feasibility study to evaluate the formalin-fixed, paraffin-embedded ANL tissues for their suitability to investigate radiation effects. The study revealed that various methods such as histological staining, immunohistochemistry, telomere-specific fluorescence *in situ* hybridization and terminal deoxynucleotidyl transferase method can be successfully applied. Even intact RNA can be isolated from certain tissues and further subjected to reverse transcriptase-polymerase chain reaction. Although it was not the primary intention of the feasibility study to identify parameters pointing to specific effects of low dose rate radiation, extremely promising data on the immune system emerged. It was shown by immunohistochemistry, that different markers related to the immune system as well as to cell proliferation and differentiation were significantly increased in the groups irradiated with 3 mGy and 18.8 mGy per day as compared to both the control group and the group irradiated with 37.7 mGy per day. Signals were mainly detected in walls and near the blood vessels. Intense staining was observed in the lymphatic tissues suggesting a radiation-induced stimulation of immune parameters involving the whole organism. Our findings indicate non-linear dose rate-dependent adaptive immune responses in complex tissues that need further investigations.

CARDIORENAL DOSE RESPONSE RELATIONSHIP OF CADMIUM

V.N.Puri, S.Saha, Division of Pharmacology, Central Drug Research Institute, Lucknow, India

Low doses of cadmium are known to produce hormetic effects (Science, 302, 376, 2003). Low doses of cadmium produce inverted U shaped dose response curve. Dose response relationship with higher doses of cadmium has not been investigated by many groups. Therefore, we performed studies on Sprague - Dawley (S-D) rats (220-250 g) to evaluate the effects of higher cadmium (0.1 - 0.32,1.0 mg /Kg i.v.) dose response relationship on some cardio renal functions of pentobarbitone anesthetized rats. Cadmium produced dose dependent hypertensive effect, while heart rate changed differently. Cadmium failed to produce dose dependent inhibition of serum angiotensin converting enzyme (ACE), while tissue renal ACE levels were inhibited. Cortical ACE inhibition was not dose dependent. However, medullary ACE levels were decreased dose dependently ($P<0.01$). Cadmium concentrations in these two tissues were devoid of any significant correlation. In addition cadmium produced inverted U shaped dose response curve on glomerulus, while in proximal and distal tubules no such dose response relationship was observed. These results indicate that cadmium produced cardio renal modulation on some cardiac functions and renal enzyme kinetics. Cadmium induced reverse hormetic effects need additional studies.

A COMPARATIVE STUDY OF DRUG STANDARDIZATION IN HORMETIC OBSERVATIONS AND HOMEOPATHIC PROVINGS

Jahangir Satti, Ph.D., Chief Medical Physicist and Radiation Safety Officer, Department of Radiation Physics, St. Joseph's Medical Center, 1800 North California St., Stockton, CA 95213-9008, Tel: 209 467 6405, Fax: 209 461 5150

Homeopaths use sub-toxic doses of drugs to stimulate the organism. Earlier experiments on animals and human beings yield data based on accidental exposures to toxic materials and intentional drug provings. The drug doses and their stimulatory levels were never standardized based on scientific metrics. Hahnemann, the founder of homeopathy, experimented with different dilutions and devised different mechanisms in a bid to standardize the medicine. He used simplistic dilution methods and ignored the scientific approach based on Avogadro's principle, who happened to be his contemporary. Literature search shows that earlier homeopathic drug proving experiments and observations of hormetic effects were carried out within the similar concentration ranges. Hahnemann's earlier provings were conducted with drug strengths in ranges of $1.25x10^{-6}$ to 4 grams during 1796-98. He used drug strengths of 1ppm (10^{-6}) by 1799 and later diluted his drugs further with a hope to standardize them. Despite Hahnemann's pioneering work in provings, the drug standardization method was open to questions at all levels. Hahnemann's centesimal method proved inadequate and his faithful disciple Hering devised another method based on decimal scale. Later it was found that Hahnemann devised another method known as LM scale. Similarly scientists observed hormesis with sub-toxic doses of certain compounds but failed to quantitatively standardize them on scientific basis. Hormetic observations were made with compounds in the ranges of 1-720 ppm for sodium arsenate, lead arsenate, Paris green, zinc arsenate and sodium arsenate. These observations were made on plants, bacteria and yeast. Computer simulations have been carried out to standardize homeopathic chemical drugs in which a single scale (i.e., 30S) of every drug carries the same number of medicinal atoms/molecules. Such drug standardization will help reproduce the results much more accurately than the existing methods. It will also provide standard drug quantization across the board for emerging nano-scale medicine.

COMPLEMENTARY NANO-SCALE THERAPEUTIC APPROACH THROUGH FREQUENCY BASED BIO-SYNCHRONIZATION.

Jahangir Satti, Ph.D., Chief Medical Physicist and Radiation Safety Officer, Department of Radiation Physics, St. Joseph's Medical Center, 1800 North California St., Stockton, CA 95213-9008, Tel: 209 467 6405, Fax: 209 461 5150

Recent research has shown that most materials in the range between single atom and bulk rate have different physical, chemical, electrical, magnetic, vibrational and biochemical characteristics. It is projected that such a nano-scale material development between single and 20 atoms will transform the industry during this century. It is also an established scientific fact that ionizing radiation and chemical compounds at sub-toxic levels have beneficial effects on living organisms which is also known as hormesis. Cells in a living organism react to external and internal stimuli through different mechanisms. The effects of temperature, pressure, light, metabolism, and other inputs result in different cellular reactions. Such biological reactions are quantitatively observed in circadian rhythms. These reactions are affected by both conventional and complementary approaches. The conventional mechanism is based on quantitative amount or concentration of a chemical that macroscopically affects the amplitude of cellular rhythms. Sometimes such a desired change needs concentrated chemicals approaching toxic levels. On the other hand, a weak signal is required to produce detuning in a biosystem. The adaptation of a living organism to its environment through evolutionary changes is a proof that cosmic bio-synchronization is vital for survival. Bio-synchronization means that different organs maintain a specific rhythm, which is not necessarily harmonious, and has a cooperative pattern for any biological function. Any deviation from this synchronization may result in sickness. Health is the adaptive capability of a living organism to withstand cosmic evolutionary changes of its environment. One can help cellular rhythm synchronize with its system by carefully applying a weak signal. Tuning a system at the cellular level may result in healing without undue side effects from mega doses of chemical drugs. Further it can be equally effective either in maintaining biorhythms at cellular levels inside an organ or establishing a coupling rhythm among organs.

ALCOHOLIC BEVERAGE *HORMESIS* FOR CATARACT AND ATHEROSCLEROSIS IS RELATED TO PLASMA OXIDATIVE CONDITION

Claire D. Prickett, Research Assistant, Department of Biochemistry, Faculty of Medicine & Dentistry, University of Western Ontario, London, Ontario, Canada, N6A 5C1, Tel: 519-661-3074/3063(lab), Fax: 519-661-3175, Email : cdpricke@uwo.ca
Erin Lister, B.Sc., Research Assistant, Department of Biochemistry, Faculty of Medicine & Dentistry, University of Western Ontario, London, Ontario, Canada, N6A 5C1, Tel: 519-661-3074/3063(lab), Fax: 519-661-3175, Email: e_lister@hotmail.com
Michelle Collins, Research Assistant, Department of Biochemistry, Faculty of Medicine & Dentistry, University of Western Ontario, London, Ontario, Canada, N6A 5C1, Tel: 519-661-3074/3063(lab), Fax: 519-661-3175, Email :mcollin6@uwo.ca
Colleen Trevithick-Sutton, B.Sc., Research Assistant, Department of Pharmacology and Toxicology, Faculty of Medicine & Dentistry, University of Western Ontario, London, Ontario, Canada, N6A 5C1, Tel: 519-661-3074/3063(lab), Fax: 519-661-3175, Email: colleen@chem.ucla.edu
Maurice Hirst, Ph.D., Professor, Department of Pharmacology and Toxicology, Faculty of Medicine & Dentistry, University of Western Ontario, London, Ontario, Canada, N6A 5C1,
Tel: 519-661-3315, Fax 519-661-3175, Email: mhirst@uwo.ca
Earl Noble, Ph.D., Professor, School of Kinesiology, Faculty of Health Sciences, University of Western Ontario, London, Ontario, Canada, N6A 5C1, Tel: 519-661-8365, Fax 519-661-2008, Email: enoble@uwo.ca
Joe A. Vinson, Ph.D., Professor, Department of Chemistry, University of Scranton, Scranton, PA, Tel: 570-941-7551, Fax 570-941-7510, Email: vinson@UofS.edu
John R. Trevithick, Ph.D., Professor, Department of Biochemistry, Faculty of Medicine & Dentistry, University of Western Ontario, London, Ontario, Canada, N6A 5C1, Tel: 519-661-3074/3063(lab), Fax: 519-661-3175, Email: trevjohn@uwo.ca

Objectives: To correlate the oxidative state of post-absorptive blood plasma after consumption of one or three drinks of different beverages with known J-shaped epidemiological risk curves.

Design: the plasma antioxidant or pro-oxidant activity was determined after volunteers consumed one or three drinks containing equivalent amounts of alcohol (except for an alcohol-free stout used as a control for stout).

Results: One drink of red wine, lager beer, or stout(5% alcohol v/v, and alcohol-free) increased significantly the average antioxidant activity, in plasma samples obtained from volunteers averaged over 240 min. Three drinks of red wine, lager beer, or stout(5% alcohol v/v, and alcohol-free) increased significantly the average pro-oxidant activity, in plasma samples obtained from volunteers averaged over 360 min. For a solution of alcohol three drinks resulted in pro-oxidant plasma on average, while one drink did not significantly affect the plasma oxidative status. Two volunteers, who showed a significantly increased time to metabolize ethanol after ingestion of lager beer and red wine, had elevated antioxidant activity in plasma.

Conclusions: One drink of red wine, beer, or stout provided equivalent increases in plasma antioxidant activity. Three drinks of red wine, beer, or stout provided equivalent increases in plasma pro-oxidant activity. This may explain at least in part, the decreased risk of cataract and atherosclerosis from daily consumption of one drink of different types of alcoholic beverages as well as the increased risk from daily consumption of three drinks of alcoholic beverages. The plasma pro-oxidant activity appears to be due to ethanol metabolism, while the antioxidant activity may be due to the absorption of polyphenols in the beverages. Consistent with this, the

LDL oxidation lag time in participants increase after consumption of stout. Stout itself was shown to destroy superoxide by electron spin resonance spin trapping.