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- The Definition of Hormesis and its Implications for *In Vitro* to *In Vivo* Extrapolation and Risk Assessment



Symposium on Challenges in Environmental Toxicology in Australasia, Melbourne, 13-14 July 2006

Organised by Australian Centre for Human Health Risk Assessment (ACHHRA), in conjunction with the recently formed Australasian College of Toxicology and Risk Assessment (ACTRA) and Journal of Toxicology and Environmental Health (JTEH).

The Symposium will focus on identifying the major contemporary issues surrounding environmental health and the need to develop risk-based approaches to control environmental threats in Australasia. The primary aim of the symposium will be to showcase Australia's commitments to quality science in toxicology and environmental health to an international audience.

The topics will highlight the latest scientific findings concerning critical issues relating to the toxicological effects and implications of anthropogenic and natural contaminants in air, soil, water and food.

More information next page -

<http://www.med.monash.edu.au/epidemiology/achhra/>

Symposium Challenges in Environmental Toxicology in Australasia

13 to 14th
July 2006

Eden on the Park
Melbourne



Organised by the Australian Centre for Human Health Risk Assessment (ACHHRA), in conjunction with the Australasian College of Toxicology and Risk Assessment (ACTRA) and Journal of Toxicology and Environmental Health (JTEH).

The symposium will focus on contemporary issues surrounding environmental health and the need to develop risk-based approaches to control environmental threats in Australasia. This programme will be of high interest to professionals from all sectors, including practicing toxicologists, health care professionals, risk assessors, health and safety administrators and environmental scientists.

Registration fee A\$300 (incl GST)

For a registration form go to <http://www.med.monash.edu.au/epidemiology/achhra/conference2006.html>

CALL FOR ABSTRACTS

The official language of the symposium will be English. People interested to present their work are invited to submit an abstract in English, together with the registration form, by **19th May 2006** (deadline for receipt of abstracts).

The selection of oral presentations will be made on the basis of an evaluation of abstracts by the scientific committee, while those not selected for oral presentations will be asked to present posters.

Each speaker will be allocated 20 minutes (incl. 5 min. of discussion). Authors will be notified by **1 June 2006** as to whether papers will be selected for oral or poster presentations.

Selected reviewed manuscripts will be published in the *Journal of Toxicology and Environmental Health*, in a special issue of the journal devoted to the symposium. The symposium offers a unique opportunity to showcase Australia's commitment to quality science in environmental toxicology and health risk assessment to an international audience.

Information on registration and abstract preparation at <http://www.med.monash.edu.au/epidemiology/achhra/> or contact Dr Jennifer Ong - jennifer.ong@adelaide.edu.au or phone 61 8 303 5163

Other events

Society for Risk Analysis
Australian & NZ Chapters

17 to 19th July 2006

University of Melbourne

School of Botany Building
Turner Theatre

Hosted by the Australian Centre of Excellence for Risk Analysis (ACERA).

On Day 1 the conference will focus on 'Biosecurity risk analysis'. Days 2 and 3 will focus on general topics in risk analysis.

Registration fee A\$110 (incl GST)

The conference will be limited to 120 participants

Presentations by -

Dr Mark Lonsdale (CSIRO)

Professor Jean Cross (UNSW)

Professor Hugh Possingham (UQ)

Professor Colin Thompson (UM)

Dr Mick McCarthy (ARCUE)

Dr Janet Gough (ERMANZ)

For more information email Dolla Boutros -

dollab@unimelb.edu.au

The Australian Health &
Medical Research Congress
Melbourne Convention Centre

26th November - 1st December

The five-day Congress program will cover a broad cross-section of topical areas in a thematic structure.

International and local scientists will present cutting-edge research in plenary sessions and integrated, multi-society symposia. In addition, the Congress will provide a framework for free oral and poster communications, and a host of smaller focused meetings. The level and diversity of participation is anticipated to encourage a large trade presence. <http://www.ahmrcongress.org.au>

Recent Published Literature

Interact Air Water and Earth Conference (2006)

Burswood Convention Centre, Perth; 24-28 September 2006

<http://www.promaco.com.au/conference/2006/raci/> for further information. The participating groups in this conference are Royal Australian Chemical Institute (Analytical Chemistry Division, Environmental Chemistry Division and Electrochemistry Division), Australasian Society for Ecotoxicology and Clean Air Society of Australia and New Zealand (CASANZ).

NANOTOX 2006

1st International Conference on Nanotoxicology in Miami, florida, 29 Jan to 1 Feb 2006

The meeting was promoted by the organisers from University of Pittsburgh as the first international conference focussing on nanotoxicology. The invited speakers were primarily from the 5 or 6 US and German organisations which comprised the Organising Committee or worked closely with them. Some of the key speakers who had been advertised in the initial promotional brochures had withdrawn from the meeting. Notably absent were: Vicki Colvin (Rice CBEN), Vivian Howard (UK) and Eva Oberdorster (Texas). However, some of the leading lights did attend (e.g. Gunter Oberdorster, Eileen Kueml, Nancy Monteiro-Riviere, Peter Hoet and Vince Castranova) and there were some quality presentations from some of the US, German, Swedish and UK scientists.

A full report by Professor Brian Priestly is available at <http://www.med.monash.edu.au/epidemiology/achhra>

ACHHRA is a consortium of four Australian Universities with expertise in human health risk assessment.

Its establishment was funded by a grant from the Australian Government Department of Health and Ageing through the Innovations Program of the Public Health Education and Research Program (PHERP).

Partners in ACHHRA are -

- Department of Epidemiology and Preventive Medicine, Monash University
- Department of Environmental Health, Flinders University
- National Research Centre for Environmental Toxicology
- School of Environmental Studies, Griffith University

A Case for Revisiting the Safety of Pesticides: A Closer Look at Neurodevelopment

Theo Colborn; *Environmental Health Perspectives*; Jan 2006; Vol. 114, Issue1, pg. 10-17.

Many studies have shown that adults, children and fetuses are exposed to mixtures of numerous pesticides, some of which have been banned in Western countries. There is also mounting evidence that some pesticides can cause detrimental effects on foetal and early childhood brain development, with serious consequences for adulthood. This article focuses on the toxicity testing of the acetylcholinesterase inhibitor, chlorpyrifos, and the discovery of a number of alternate mechanisms not initially recognised. There are also examples of other herbicides, insecticides and fungicides affecting various aspects of brain development. These findings have been made using more subtle endpoints than those currently used by the regulatory bodies such as the USEPA. In light of these reports, the author criticises the use of "crude" traditional endpoints of toxicology and stresses the need for more functional endpoints. Consequently, there are calls for regulatory bodies to accept non-guideline, open literature in the risk assessment of chemicals.

Estimates of exposures to perchlorate from consumption of human milk, dairy milk, and water, and comparison to current reference dose.

Cal Baier-Anderson, Benjamin C. Blount, Judy S. LaKind, Daniel Q. Naiman, Sharon B. Wilbur, Shirlee Tan; *Journal of Toxicology and Environmental Health; Part A*, Feb 2006, Vol. 69, Issue 4, pg. 319-330.

Recent studies in the US have shown that perchlorate is detectable in milk and other foods. Exposure to high levels of perchlorate results in hypothyroidism and reduced production of the thyroid hormones T₃ and T₄, which are particularly critical for normal fetal and neonate development. Exposure to perchlorate in milk and tap water was evaluated using several different exposure scenarios and results were compared to the NRC reference dose (RfD). The data indicated that infants exposed to perchlorate via the consumption of either human milk or infant formula (made with perchlorate-contaminated tap water) may exceed the RfD. However, the authors did not recommend changing the public health recommendation for breastfeeding but highlight the importance of screening neonates for thyroid function.

Personal Exposure to Ultrafine Particles and Oxidative DNA Damage.

Vinzents Peter S, Møller Peter, Sørensen Mette, Knudsen Lisbeth E, Hertel Ole et al., *Environmental Health Perspectives*; Nov 2005, Vol. 113 Issue 11, pg. 1485-1490. Even though exposure assessment is difficult, ultrafine particles (UFPs) from vehicle exhaust have been related to risk of cancer, as well as cardiovascular and pulmonary diseases. These authors studied personal exposure using portable instruments in six 18-hr periods in 15 healthy non-

smoking subjects. Exposure contrasts of outdoor pollution were achieved by bicycling in traffic for 5 days and in the laboratory for 1 day. Oxidative DNA damage was assessed by quantifying strand breaks and oxidized purines in peripheral monocytes the morning after exposure measurement. They reported that cumulated outdoor and cumulated indoor exposures to UFPs were independent predictors of the level of purine oxidation in DNA but not of strand breaks. Furthermore, ambient air concentrations of PM_{10} , nitrous oxide, nitrogen dioxide, carbon monoxide, and/or number concentration of UFPs at urban background or busy street monitoring stations was not a significant predictor of DNA damage. However, personal UFP exposure was correlated with urban background concentrations of CO and NO_2 particularly during bicycling in traffic. The results indicated that biologic effects of UFPs occurred at modest exposure, such as that occurring in traffic, which supports the relationship of UFPs and the adverse health effects of air pollution.

Thyroid-Hormone-Disrupting Chemicals: Evidence for Dose-Dependent Additivity or Synergism.

Crofton, Kevin M., Craft, Elena S., Hedge, Joan M., Gennings, Chris., Simmons, Jane E., Carchman et al. *Environmental Health Perspectives*; Nov 2005, Vol. 113 Issue 11, pg. 1549-1554.

Endocrine disruption from environmental contaminants has been linked to a broad spectrum of adverse outcomes. One concern is that mixtures of endocrine-disrupting xenobiotics have the potential for additive or synergistic (i.e., greater-than-additive) effects. To address this, a short-term dosing model to examine the effects of environmental mixtures on thyroid homeostasis has been developed. Prototypic thyroid-disrupting chemicals (TDCs) such as dioxins, polychlorinated biphenyls (PCBs), and polybrominated diphenyl ethers have been shown to alter thyroid hormone homeostasis in this model, primarily by up-regulating hepatic catabolism of thyroid hormones via at least two mechanisms. The authors tested the hypothesis that a mixture of TDCs will affect serum total thyroxine T_4 concentrations in a dose-additive manner. They used young female Long-Evans rats, which were dosed via gavage with 18 different polyhalogenated aromatic hydrocarbons for 4 consecutive days. Doses of individual chemicals that were associated with a 30% TH decrease from control (ED_{30}). Additionally, predicted mixture outcomes were calculated using a flexible single-chemical-required method, which was applicable to chemicals with differing dose thresholds and maximum-effect asymptotes.

Workgroup Report: Drinking-Water Nitrate and Health—Recent Findings and Research Needs.

Ward, Mary H., deKok, Theo M., Levallois, Patrick., Brender, Jean., Gulis, Gabriel., Nolan, Bernard T., VanDerslice, James, *Environmental Health Perspectives*; Nov 2005, Vol. 113 Issue 11, p1607-1614.

Human alteration of the nitrogen cycle has resulted in steadily accumulating nitrate in our water resources. The U.S. maximum contaminant level and World Health Organization guidelines for nitrate in drinking water were promulgated to

protect infants from developing methemoglobinemia, an acute condition. Some scientists have recently suggested that the regulatory limit for nitrate is overly conservative. The few epidemiologic studies that have evaluated intake of nitrosation precursors and/or nitrosation inhibitors have observed elevated risks for colon cancer and neural tube defects associated with drinking-water nitrate concentrations below the regulatory limit. The role of drinking-water nitrate exposure as a risk factor for specific cancers, reproductive outcomes, and other chronic health effects must be studied more thoroughly before changes to the regulatory level for nitrate in drinking water can be considered.



Development of a Preliminary Framework for Informing the Risk Analysis and Risk Management of Nanoparticles

Kara Morgan, *Risk Analysis*; Dec 2005, Vol 25, Issue 6, pg 1621-1635.

Presently, safety assessment for a product containing engineered nano-scale particles is a very poorly structured problem, as decisions are often made even when there is uncertainty about the possible outcomes. Many fields of study may inform the safety assessment of such particles (e.g., ultrafines, aerosols, debris from medical devices), but engineered nano-scale particles may present such unique properties that extrapolating from other types of studies may introduce, and not resolve, uncertainty. Some screening-level health effects studies conducted specifically on engineered nano-scale materials have been published and many more are underway. A framework has been developed from expert interviews of nanotechnology researchers. The analysis organizes the information as a system based on the risk assessment framework, in order to support the decision about safety. In the long term, this framework is designed to incorporate research results as they are generated, and therefore serve as a tool for estimating the potential for human health and environmental risk.



Principles and practices of health risk assessment under current EU regulations

Christina Rudé, *Regulatory Toxicology and Pharmacology*, Feb 2006, Vol. 44, Issue 1, pg 14-23.

Risk assessments serve as the foundation of regulatory decision-making and this article briefly outlines the principles of the European Union process for risk assessments, as defined by legislations and official guidelines. The actual workings of this system are exemplified by the results from case studies of the risk assessment processes for trichloroethylene and for acrylamide. The analysis and comparison of these two cases illustrated; (1) that generation of a large amount of data does not ensure consensus among risk assessors, (2) that controversy can regard different levels of detail, (3) that controversy can arise at different organizational and theoretical levels, (4) that risk assessments may be subject to (public) criticism even if the experts agree, and (5) that “scientific” controversies have a significant policy component.



Effect of environmental contaminants on male reproduction (B. Saradha and P.P. Mathur.

Environmental Toxicology and Pharmacology, Jan 2006, Vol. 21, Issue 1, pg. 34-41.

There has been a substantial body of evidence accumulated in recent years that consistently indicate various adverse effects of environmental contaminants on human health. Decreasing trend of male fertility in terms of sperm counts and sperm quality, along with other changes in male reproductive health, including congenital malformations and testicular cancer in humans, and similar problems in wildlife have been correlated to the exposure to environmental contaminants. Many environmental chemicals have been reported to cause these reproductive abnormalities by eliciting changes in endocrine control of reproduction; however the specific underlying mechanisms are poorly understood. The present review summarizes recent studies concerning environmental contaminants and associated possible mechanism leading to adverse effects on male reproduction. Numerous studies have demonstrated the interaction of environmental toxicants with steroid receptors and thereby causing interference with developmental and functional aspects of testis, epididymis and accessory sex organs. Induction of reactive oxygen species (ROS) by environmental contaminants and associated oxidative stress also have role in defective sperm function and male infertility.



Endocrine Disruption Induced by Organochlorines (OCs): Field Studies And Experimental Models.

Ropstad, Erik., Oskam, Irma C., Lyche, Jan L. et al., *Journal of Toxicology & Environmental Health: Part A*; Jan 2006, Vol. 69, Issue 1/2, pg. 53-76.

Long-range transport of persistent organic compounds by air and ocean currents from industrialized areas resulted in high levels of these pollutants in food webs in the Svalbard area. The authors aimed to test if organochlorine (OC) exposure in free-living polar bears from Svalbard affected their plasma steroid hormone concentrations. They reported that polychlorinated biphenyls (PCBs) were associated with increased progesterone levels in females. Using a goat model, their second objective was to study the effects of selected OCs (i.e., PCB 153 and PCB 126) on animal health (i.e. reproduction and immunity) as a consequence of endocrine-disruption. The results indicated that exposure to low doses of PCB 153 *in utero* and in the suckling period influenced reproductive functions. Additionally, both PCB 153 and PCB 126 exerted immunomodulatory effects on the offspring, while acute exposure of adult mice had only minor effects on male reproductive function.

The Definition of Hormesis and its Implications for In Vitro to In Vivo Extrapolation and Risk Assessment

Hester van der Woude, Gerrit M. Alink, Ivonne M. C. M. Rietjens., *Critical Reviews in Toxicology*, July 2005, Vol. 35, Issue 6, pg. 603 – 607.

This article comments on some of the basic questions on hormesis. There seems to be a need for a better definition of the concept itself and reconsideration of whether all biphasic dose-response curves should be considered representative for hormesis. Improvement of risk assessment strategies should take into account physiologically based pharmacokinetic (PBPK) models as well as biphasic dose-response curves. Hormesis is an important phenomenon, especially from the scientific point of view, but that its consequences for risk assessment and the possibilities for *in vitro* to *in vivo* extrapolation may remain limited without additional mechanistic insight.