MEDI CHEM

NEWSLETTER

July 2005

Medichem 2005 Board of Directors

With the March Newsletter you received the call for candidates for this year's Medichem Board election. Thanks very much to all of you who answered.

The Board members Peter Boogaard (Netherlands), Jiin Ger (Taiwan), Frank Rose (UK), and Les Yee (USA), agreed to stand again for another term of office. The following Medichem members were newly nominated to the secretary and consented to stand as new Board candidates: Elpida Emmanouil-Nikoloussi (Greece), Jorge Morales (Mexico), and André Kotzé (South Africa).

Board members Hans van der Merwe, Samir Guirguis and Robert Garnier decided not to run as candidates again for personal reasons. Thus, there are as many candidates as there are vacancies on the Board, and this year's Board election goes with a "silent vote". The newly elected members will serve on the Board from September 2005.

On behalf of the whole Medichem Board I want to take this opportunity to express our deep gratitude to Hans, Sam and Robert who have given us so much support and personal friendship in the past. We trust that we will maintain close relations, and we are looking forward to each event where we will meet again in the future.

Dr. Michael Nasterlack
(Ludwigshafen, Germany)

Contact Lens Use in a Chemical Environment

Since the 1978 Standards Completion Program, the National Institute for Occupational Safety and Health (NIOSH) has recommended that workers not wear contact lenses during work with chemicals that present an eye irritation or injury hazard. Recently, several professional groups have issued guidelines removing restrictions in the industrial environment. NIOSH has reviewed these guidelines, company policies on contact lens use and injury incidents, and the limited literature on contact lens use in a chemical environment. Injury data are lacking to indicate that contact lens wear should be restricted during work with hazardous chemicals, and thus NIOSH recommends that contact lens wear be permitted provided that the safety guidelines presented in this Current Intelligence Bulletin (CIB) are followed.

The full document is available for free at:
http://www.cdc.gov/niosh/docs/2005-139/pdfs/2005-139.pdf.

Dr. Jonathan B. Borak
(New Haven, USA)
Dr. Stephen W. Borron
(Paris, France)

Short introduction of Medichem's new Board members

Elpida-Niki Emmanouil-Nikoloussi is Associate Professor of Histology-Embryology at the Faculty of Medicine of the Aristotle University of Thessaloniki, Greece. Ph.D. on oral medicine, oral surgery, oral pathology, Faculty of Dentistry, Ph.D. on Histology-Embryology, Faculty of Medicine, both of Aristotle University of Thessaloniki.

André B. Kotzé is Group Medical Adviser for AECI Ltd. in South Africa. MBChB from the University of Pretoria and Diploma in Occupational Health from the University of Witwatersrand.

Jorge A. Morales is Associate Medical Director for Latin America and Globally for the Snacks and Beverage Business (The Procter & Gamble Company). Master Degree on Occupational Health (Faculty of Medicine UNAM) and Master in Business Administration (IPADE). Professor of Occupational Health, Faculty of Medicine (UNAM) and Medical Director of Advanced Hazardous Materials Life Support courses (University of Arizona) in Mexico.

All three of them hold memberships in various national and international scientific societies and associations, and all are National Representatives of Medichem in their respective countries.

Managing uncertainty: Nanotechnology facts and fiction

"In the Nevada desert, an experiment has gone horribly wrong. A cloud of nanoparticles -- micro-robots -- has escaped from the laboratory. This cloud is self-sustaining and self-reproducing. It is intelligent and learns from experience. For all practical purposes, it is alive. It has been programmed as a predator. It is evolving swiftly, becoming more deadly with each passing hour. Every attempt to destroy it has failed. And we are the prey." Source: HaperCollins.com, describing the novel "Prey" by Michael Crichton

"Society is not ready for the technological and economic upheaval that nano-scale technologies will deliver. Government regulation is not enough: society must be fully engaged in a discussion of the socio-economic as well as health and environmental implications of nano-scale technologies." Source: ETC Group Communiqué May/June 2004 Issue # 85 Nanotech News in Living Colour: An Update on White Papers, Red Flags, Green Goo, Grey Goo (and Red Herrings)

The above two quotations pertaining to "nanotechnology" were found on the internet – the first trying to sell a novel by a popular American author, the other stating a view of a concerned activist group. What is fiction and what is fact when is comes to understanding the health effects of nanomaterials? What *are* the health consequences of manufactured nanoparticles, and do we know enough to be sure workplaces and the environment are safe? Are these nanoparticles "new," or just smaller versions of "old" materials? Do we understand enough to regulate? Do we have the capacity to evaluate and derive science-based controls and regulations?

Nanotechnology is generally defined as research and technology development at the atomic, molecular or macro-molecular levels, which involves creating and using structures, devices and systems that have novel properties and functions because of their small size. Nanoparticles (<100 nm diameter) are either natural (e.g., motor vehicle emissions, combustions products) or manufactured (created under controlled conditions) in shapes that can best match their functions. For example, manufactured carbon nanotubules can be single or multi-walled to serve as "building blocks" for use in various industry settings; or, they can be three-dimensional, known as fullerenes or "buckeyballs" consisting of 60 carbons shaped in the form of a European football, which may be used as "delivery devices" for other materials.

The development of this technology offers an incredible range of potential to many industries, because by the nature of the size and shape of these particles, they possess unique chemical and physical properties, as well as enormous surface areas. Utilizing these properties, those developing nanomaterials have started to find avenues into the market-place. For example, in medicine nanoparticles are being developed for drug delivery and diagnostic purposes. Sports equipment and tires can be made more durable with a longer life, fabrics can be made stain and wrinkle resistant, and cosmetics can be made to be absorbed more quickly with no residual film. These small particles are also being developed to assist in the environment – "eating up" more harmful substances or toxic spills. The health and environmental impacts of these substances, however, remains largely unknown. For some nano-sized materials (carbon black, titanium dioxide, air pollution ultrafine particulates), there are some toxicological and epidemiological studies available, although a consensus pertaining to understanding the health effects remains unclear. Compared to their larger scale versions, nano-sized particles of the same substance have a greater surface area, greater chemical reactivity on the surface, possibly a greater penetration into the respiratory tract, and may be more likely to pass through nature's barriers such as cell walls and the blood/brain barrier.

The fact is that the health effects and identification of potential hazards of nano-sized particles are not known – so by what mechanism do we regulate or control their production? Are manufactured particles "new" because of size and surface area properties that impart new properties? Or are they smaller-scaled versions of known substances? The lack of information leaves plenty of room for "fiction" to move in and create a fearful or overly cautious result. Currently, the United States Environmental Protection Agency regulations apply to manufactured materials, although the United States National Toxicology Program is investigating the potential hazards of these materials. The EU *current* frameworks are sufficiently broad to cover products in use now, and therefore a separate framework at this point has been determined to be unnecessary. In February 2005, the government of the United Kingdom responded to a document produced by the Royal Academy in 2004, indicating that because of their novel properties, nanoparticles and nanotubules should be treated as new chemicals, and that industry should publish details of safety tests, showing these novel properties have been taken into account.

Although substantial funds have been allocated for nanotechnology by governments and private, industry sponsors around the globe, the proportion allocated to study and understand potential health impacts has been small. Regulatory decisions need to be made based on scientific fact, and not possible fiction. Strategies are underway to move the science forward and to share information. One example is the announcement in this newsletter of the 2nd International Symposium of Occupational Health and Nanotechnology to be held in US in 2005. This meeting will include an industry forum, which will be a unique opportunity for those in occupational health from industry to discuss the current state of the science.

Future strategies are, perhaps, more critical, and definitely more challenging. For the occupational health practitioner, one challenge is to anticipate and define the types of outcomes that might be expected to result from exposure to nanoscale materials, and what constitutes a "health effect." If "baseline" measurements of health are to be recorded or surveillance systems developed, determining which measurements should be taken, and how frequently pose additional challenges. Yet, the initiation of surveillance methods that establish clinical baselines for laboratory tests, spirometry, etc., will be critical to understanding changes – however they are defined – that might occur in the future. Challenges are also faced by the industrial hygienist required to measure and monitor exposures to nanomaterials – both through inhaled and dermal routes – as current techniques and technologies are likely to prove inadequate. Additionally, the development of safe work practices, including adequate personal protection equipment and disposal procedures – understanding the "cradle to grave" aspects of the industry -- will be critical to protecting employee and public health.

The cooperation and co-ordination of the industry sector internationally is essential to understanding and moving the health science forward in this exciting new arena. Pro-active approaches on the part of industry are equally essential to de-fuse images from popular science fiction and to curtail as yet unfounded fears in the public eye. Although the toxicology, epidemiology, and occupational medicine lag far behind the technical advances, we can learn to manage uncertainties. Many decisions and management strategies pertaining to occupational health are implemented where the underlying knowledge is lacking or unclear. Regulatory mechanisms exist that can handle what is known, but because health effects are mostly unknown, concerted, focused, and accelerated efforts for objective health and environmental research are needed – now.

Dr. Diane J. Mundt
(Amherst, MA, USA)

Reproductive toxicology in occupational settings: an update

Since the beginning of the 20th century there has been a consistent increase in the number of involuntarily childless marriages in nearly all industrialized countries. About 10 to 15 % of all couples remain unvoluntarily childless. The causes of sterility are divided as follows. The woman is the reason for involuntary childlessness in 39% of cases while the man is the cause in 20%; in 26% of cases the reason is to be found in both spouses. In 15% of cases the clinician is unable to identify a disorder. However, this so-called idiopathic sterility is a diagnosis by exclusion – it is not to be equated with psychological causes of undesired childlessness.

Reproductive toxicology is the discipline that determines which compounds are toxic to reproduction and which mechanisms are responsible. From an Occupational Medicine point of view, a basic distinction must be made between the following entities:

- Toxic influences for which threshold values (MAK and BAT values) have been established in occupational medicine. These include effects on fertility and lactation.
- Developmental effects such as abortions, malformations, developmental disorders and poor postnatal performance. These endpoints are not necessarily covered by MAK and BAT values.
- Genetic change in the germ line, which lead to genetic malformations or to genetic diseases.

The objective of this short article is to deal with toxic influences on fertility in occupational settings.

About one hundred thousand different compounds are used in the diverse occupational settings. The risk potential of no more than a fraction of these has been established by systematic investigations or long-term observations. The MAK value is the highest permissible concentration of an atmospheric substance at the workplace, which in general does not impair the health of employees/workers even if it is active during the entire period of work; thus, the MAK value implicitly includes toxic fertility disorders. Employees misleadingly imagine themselves to be in safety in respect of more than 500 substances, which have been included in the MAK list (Germany), and the threshold value regulation (Austria). This is because of the substantial method-based difficulties faced by epidemiologic and experimental research.

Firstly there are different epidemiological parameters of end points for fertility. The most accurate index of impaired fertility is the measurement of time to conception. However, recall problems may make this an unreliable measure for retrospective studies and its usefulness in prospective studies has yet to be demonstrated in the occupational setting. Other often-used end points are the standardized birth ratio, which is the ratio of observed to expected birth rates, and the infertility rate. Infertility is the inability to produce a clinically recognizable pregnancy after 1 year of unprotected intercourse.

Secondly epidemiologic research in the field of occupational exposures on fertility is influenced by publication bias, which was recently reviewed. The review criticized that reported associations are inconsistent, more positive than negative associations are reported, the most reports are about solvents and defects are grouped into larger categories, with little biological meaning.

Taking toxic influences on fertility into account is, thirdly, also especially problematic because of the major risk factors of fertility disorders in men and women, which may act as confounders in some studies. These are mainly in men Drugs, alcohol, heavy smoking, anatomical variants of the genital organs, cryptorchidism even after surgical correction, and so forth. In women also mainly Drugs, alcohol, heavy smoking and ovulatory dysfunction, endometriosis, hyperandrogenism and hormonal disorders. In the chosen study design one must also take the so-called infertile worker effect into consideration: a much larger percentage of childless women tend to be fully occupied with their profession compared to women with children. This may cause a distortion of the results as to the influence of occupational toxic substances on fertility.

Because of these difficulties, several years ago the WHO initiated an assessment of the existing data on the impact of the working environment on fertility. The conclusion of the report was, that only 10% of the reviewed studies (out of 80 positive associations) fulfill the criteria of good study design. Therefore there are only few substances, which are proven to influence fertility in occupational medicine: These are lead, organic mercury compounds, manganese, carbon disulfide, 2-bromopropane and dibromochloropropane.

Dibromochloropropane (DBCP) is the classical compound, which markedly and unquestionably impairs fertility in males. This substance was developed in the 1950's. Animal experiments conducted as early as in 1961 showed that DBCP leads to drastic alterations in testicular tissue. As late as in 1977 it became known that the substance may also irreversibly inhibit spermiogenesis in humans. Of concern is also the category of glycol ethers along with a methyl or ethyl group in primary position. These substances are mainly used in water-soluble varnishes. Glycolethers (Ethoxyethanol, ethoxyethanol acetate, 2-methoxyethanol and 2-methoxyethanol acetate) are, in fact, now classified by the European Union as toxic to reproduction.

The toxic effects of metals on reproduction will be addressed in the following: Workers with lead concentrations of 40 to 60 µg in plasma were found to have poor sperm quality and have as a result thereof an impaired fertility. Some studies were focused on workers who were exposed to inorganic mercury. This exposure was considered to be associated with a reduced concentration of testosterone in serum.

As to the toxic effect of manganese on fertility, two epidemiological studies with different results have been published. Lauwerys et al. found reduced fertility while Gennart et al. were unable to prove this phenomenon. One explanation for these differing results is the fact that the manganese values in urine were lower in the latter study, which signifies lower exposure levels in the investigated workers.

In a series of studies, which were focused on exposure to organic solvents, in addition to limitations in fertility, several other toxic effects on reproduction were identified (increased number of spontaneous abortions and cancers). Carbon disulfide at elevated concentrations above the current threshold value in Austria (30mg/m^3) is associated with spermatic effects as well. However, low exposure to carbon disulfide under the threshold level showed no effect on semen quality or on the pregnancy outcome of the wives of exposed workers.

In summary all substances with established toxic influence on fertility within concentrations, which can be seen at the workplace are lead, organic mercury compounds, 2-Bromopropan and Dibromochloropropane.

Experience has shown that the most potent occupational reproductive hazard was reported by the workforce rather than detected by occupational health screening. In a few cases the identifying of toxic substances to reproduction was possible because of their high toxicity, as it was the case of DBCP. In others, the specific toxic effect was observed among workers with high exposures. A great number of confounder and possible biases have to be accounted for.

But the decreasing fertility of women in Western countries compared to developing countries (15% vs 5%), can be explained by the increasing female reproduction age in the Western World, rather than by occupational exposures. For women between the age of 19 and 25 years, the likelihood of becoming pregnant by normal sexual intercourse during one cycle is 30%. For women between the ages of 25 and 33 years it is only 18%. This could be explained by the reduced fecundability of the oocyte with advancing age. Other sources mention gametogenesis disorders and/or impairment or death of the fertilized egg due to changes in cell organelles after successful syngamy as the cause of this phenomenon.

In addition a reduction of male fertility, by sperm-parameters is also doubtful. This is also reflected in a recent re-evaluation of a data from a French multicenter study. We should be aware that the sperm concentration in itself is not the chief determinant of male fertility. Besides, there is little to no evidence that male fertility is declining: According to the Princeton National fertility Study and the National Center for Health Statistics in the National Survey of Family Growth, rates of fecundity have remained constant.

Exposure to chemicals may cause reversible or irreversible damage to the fertility of the female or male organism. Generally, however, reproduction toxicity in humans has been proven for a very small number of substances. Among other study design factors, this is because the effects in humans are always accompanied by a significantly high "spontaneous rate" of fetal loss (abortions, malformations, etc.). In conclusion occupational exposures are not a significant factor for the 15% of couples, who remain involuntarily childless. Also the other figures, which were mentioned in the introduction concerning spontaneous abortions and birth defects cannot be explained by industrial exposures at the workplace.

Dr. Robert Winker
Prof. Hugo W. Rüdiger
(Vienna, Austria)

Neuro-reproductive toxicities of 1-bromopropane and 2-bromopropane

2-Bromopropane was used as an alternative to chlorofluorocarbons in a Korean electronics factory and caused reproductive and hematopoietic disorders in male and female workers. This causality was revealed by animal studies, and target cells were identified in subsequent studies. After identification of 2-bromopropane toxicity, 1-bromopropane was introduced to the workplace as a new alternative to ozone-depleting solvents. 1-Bromopropane was considered less mutagenic than 2-bromopropane, but, in contrast, animal experiments revealed that 1-bromopropane is a potent neurotoxic compound compared with 2-bromopropane. It was also revealed that 1-bromopropane has reproductive toxicity, but the target cells are different from those of 2-bromopropane. Exposure to 1-bromopropane inhibits spermiation in male rats and disrupts the development of follicles in female rats, in contrast to 2-bromopropane, which targets spermatogonia and oocytes in primordial follicles. After the first animal study describing the neurotoxicity of 1-bromopropane, human cases were reported. Those cases showed decreased sensation of vibration and perception, paresthesia in the lower extremities, decreased sensation in the ventral aspects of the thighs and gluteal regions, stumbling and headache, as well as mucosal irritation, as the initial symptoms. The dose-response of bromopropanes in humans and mechanism(s) underlying the differences in the toxic effects of the two bromopropanes remain to be determined.

(G. Ichihara, Int. Arch. Occup. Environ. Health 2005, 78: 79-96)

Dr. Michael Nasterlack
(Ludwigshafen, Germany)

Autonomic function linked to job cardiac risk

A study of British government employees supports the belief that low-status jobs are linked to increased coronary risk through abnormal autonomic cardiac function. A low employment grade was associated with a higher heart rate and lower heart rate variability, which appeared to be mediated by behavioral factors such as smoking and drinking, and psychosocial factors such as job control, as well as components of the metabolic syndrome. Harry Hemingway (University College London Medical School) and colleagues compared the autonomic effects of employment grade among 2197 men aged 45 to 68 years who were working as civil servants, and participating in the Whitehall II study.

Individuals were categorized at three levels in the work hierarchy: senior civil servants (executive officers), middle grades, and low grades (clerical and support staff).

The team found that low-grade employment was associated with low heart-rate variability over a period of 5 minutes, which was used as a measure of cardiac parasympathetic function (standard deviation of N-N intervals and high-frequency power 0.15-0.40 Hz), and the influence of sympathetic and parasympathetic function (low-frequency power 0.04-0.15 Hz, age-adjusted trend $p \leq 0.02$ in both cases). The heart rates of men with low-level positions were also an average 3.2 beats per minute faster than those in top-level positions. Age-adjusted mean low-frequency power was 319 ms^2 for participants in the lowest third of work hierarchy compared with 379 ms^2 for those in the other two grades ($p=0.004$). Adverse health-related behaviors were associated with adverse heart rate and heart rate variability, the researchers note, such as smoking, little exercise, poor diet, and high alcohol consumption.

Heart rate variability had a strong linear association with components of the metabolic syndrome such as hypertension, large waist circumference, dyslipidemia, and hyperglycemia. However, Hemingway et al. (2005) note that the association between social grade and the metabolic syndrome was lost after adjusting for low-frequency power, behavioral factors, and the participant's reported control over daily tasks.

Writing in the journal Circulation, they conclude: "This provides population evidence for the hypothesis that disturbances of the autonomic nervous system are involved in mediating the excess coronary risk associated with low social position."

Dr. Robert Winker
(Vienna, Austria)

💣☜☟✋👍☝☜💣

Host factors in occupational diisocyanate asthma: a Swiss longitudinal study

The objective of the study was to investigate the usefulness of surrogates for individual susceptibility to organic diisocyanates in occupational asthma. Subjects were all new cases declared to the Swiss National Accident Insurance Company (SUVA) for establishment of a case for compensable occupational disease during 1993. Sixty-nine persons, of whom three were women, were suspected of having occupational asthma due to isocyanates. Of these, 47 subjects fulfilled the criteria to be accepted as an occupational disease case. All subjects were studied clinically and gave a blood sample for the phenotyping of their alpha-antitrypsin status and for immunological studies. The subjects were also given a peroral dose of caffeine for the determination of their N-acetylation capacity. Finally, those with an occupational disease were subjected to the methacholine provocation test. The following results are described: Forty-four persons with occupational disease, out of 47, were heterozygous antitrypsin carriers and/or slow acetylators of primary amines. In the bronchial provocation with methacholine, 12 of these subjects had an unaltered response and seven had a mild reaction, 13 a moderate one and 15 a severe reaction. According to the authors the study confirms the finding that slow N-acetylators are susceptible to asthma from exposure to common diisocyanate monomers at work. The same applies to heterozygous antitrypsin-phenotype carriers. The authors conclude that the use of these markers may reinforce the diagnostic procedure, but they cannot completely replace the immunological tests.

(M. Berode et al., Int. Arch. Occup. Environ. Health 2005, 78: 158-163)

Dr. Michael Nasterlack
(Ludwigshafen, Germany)

💣☜☟✋👍☝☜💣

People and Events

The National Federation of Health at Work in Mexico (Federación Nacional de la Salud en el Trabajo) has bestowed on our new Board member **Jorge A. Morales** the honour of proclaiming him "Occupational Health Professional of the year 2005". This is the most prestigious award for a person working in the field of occupational medicine in this country. Our heartiest congratulations to Jorge for this outstanding achievement.

Medichem activities

On the occasion of its Board mid-term meeting on April 1st in Sofia, Bulgaria, Medichem organized a Mini-Symposium for local toxicologists, public health specialists and occupational health professionals. The symposium, which was organized by Board member Todor Popov from the National Centre of Hygiene in Sofia, was well attended by some 50 participants. The presenters and their topics were: Stephen Borron: “Preparedness for Chemical Emergencies”, Koichi Kono: “Toxicity of hydrofluoric acid and biological monitoring of HF exposed workers”, Frank Rose: “The sustainable development and the role of occupational health”, Peter Boogard: “Registration, Evaluation and Authorisation of Chemicals (REACH)”, Shrinivas M. Shanbhag: “Project CASH: Rejuvenating safety & health at the workplace – a Reliance initiative”, and Thirumalai Rajgopal: “Occupational health strategy in Unilever”. Prof. Ivanov, Head of the National Centre of Hygiene, very much appreciated Medichem's initiative and expressed his thanks to the Medichem Board for fostering the knowledge and development of occupational health and safety in Bulgaria.

Dr. Stephen W. Borron
(Paris, France)
Dr. Michael Nasterlack
(Ludwigshafen, Germany)

Forthcoming Events

XXXIII. Medichem 2005 - Goa

The XXXIII Medichem Congress will be held on September 20-23, 2005 at the Goa Marriot Resort Hotel. The theme for the Congress is "Occupational Health and Safety in Chemical Industries in Transitional Economies." Further information and registration form can be obtained from:

Dr. C.S. Gulvady
Reliance Industries Ltd.,
19, Walchand Hirachand Marg,
Ballard Estate,
Mumbai 400038,India.
Tel: +91-22-30327064
Fax: +91-22-30327662
e-mail: chaitanya.gulvady@ril.com

or on the Congress website
www.medichem2005.com

2nd International Symposium on Nanotechnology and Occupational Health

The Second International Symposium on Nanotechnology and Occupational Health will be the premier global meeting of 2005 addressing the potential implications and applications of nanotechnologies in the workplace. Building on the success of the First International Symposium on Nanotechnology and Occupational Health held in the UK in October 2004, it will provide a multi-stakeholder forum for presenting, assimilating, and discussing the latest breakthroughs and activities in addressing nanotechnology and worker safety and health.
Symposium registrations will be accepted online at www.cce.umn.edu/nanotechnology.
Please check the Web site for a complete list of fees and to register online. For more information, please contact
Katie Kjeseth
Tel (+1) 612 624 3708
conferences5@cce.umn.edu

Welcome to New Members

Dr. **George Efthimiopoulos**, General Hospital Papageorgiou, Katerini (GREECE),
Prof. **Helen Frangou-Massourides**, Aristotle University of Thessaloniki (GREECE),
Dr. **Andreas J. Rickauer**, Statutory Accident Insurance for the Chemical Industry, Nürnberg (GERMANY)