MEDICHEM

NEWSLETTER

March 2005

Medichem 2005 Board Elections – Call for Candidates

This year, the following Medichem Board members arrive at the end of their term of office:
Peter Boogaard, Robert Garnier, Jiin Ger, Samir Guirguis, Frank Rose, Hans van der Merwe and Leslie Yee.
Thus, seven seats on the Medichem Board are to be distributed.
Board member Robert Garnier has already indicated that due to other obligations he will not be available for another term of office.

You, Medichem members in good standing, are now asked to nominate candidates for the Board, if you want to do so.

A nomination form has been sent to you along with this Newsletter.
According to Article 5 Sect. 4.1 of the Medichem Constitution, each Board member shall be from a different country. This rule does not apply for those holding the offices of Chairman, Vice Chairman, Secretary, Treasurer, and immediate Past Chairman.

*Members from **Argentina, Austria, Bulgaria, Germany, India, Japan** or **Nigeria,** cannot be candidates in this year's Board election.*

All **candidates must be Medichem Members in good standing**, and **also ICOH members in good standing**, or **at least agree to join ICOH if elected**. Furthermore, the nomination shall only be valid if it is sent in along with written acceptance of the nomination from the candidate himself or herself. Nominations must be sent to the Secretary of Medichem, Dr. Michael Nasterlack, by mail or fax (+49 621 60 43322). They must be in possession of the secretary no later than May 31st, 2005. The ballot form for the election will be sent out along with the next Newsletter in July 2005.

ICOH Membership

The Medichem Board acts as the "Scientific Committee on Occupational Health in the Chemical Industry" of the International Commission on Occupational Health, ICOH. While all Medichem Board members therefore also have to be ICOH members in good standing, this is not mandatory for other Medichem members. The Medichem Board, however, strongly encourages every Medichem member to also join ICOH and thus participate in the fostering of scientific progress, knowledge and development of occupational health and safety in all its aspects.
Find out more about ICOH and ICOH membership at www.icoh.org.sg/membership.html

Dr. Michael Nasterlack
(Ludwigshafen, Germany)

MEDICHEM - Occupational and Environmental Health in the Production and Use of Chemicals

Severe Lead Poisoning in the Plastics Industry: a Report of Three Cases

Lead stabilizers (e.g., lead sulfate, lead stearate) are common additives in plastics used in electrical devices. In 1997, three plastics compounders at one California company were severely lead-poisoned. The poisonings were investigated by interviewing the workers, employer, and treating physician and reviewing medical records and environmental monitoring results. In addition to measuring blood lead levels (BLLs), noninvasive K X-ray fluorescence was used to measure bone lead concentration of the index case. Blood lead concentrations of the three workers at time of diagnosis were 159, 114, and 108 microg/dl. The worker with highest exposure presented with clinical findings of crampy abdominal pain, constipation, normocytic anemia, fatigue, and reversible azotemia. Bone lead concentration in his tibia, calcaneous, and patella were 102, 219, and 182 ppm, respectively. The poisonings resulted from uncontrolled use of powdered lead sulfate stabilizer. Clinicians should be aware of potential serious overexposure to lead in compounding of plastics.

(P. Coyle et al., Am. J. Ind. Med. 2005, 47: 172-175)

Dr. Michael Nasterlack
(Ludwigshafen, Germany)

Allergies and asthma, being constantly on the rise in "western lifestyle" countries, belong to the most troublesome diseases which affect our children in particular. The reasons for this development remain to be elucidated. After Germany's re-unification, and thus the end of a historical mass experiment, scientific research made obvious that simplistic theories causally attributing allergies and asthma to "chemical pollution" were insufficient to explain this complex matter. Some still seem not to have heard about this.

Frequent Use of Chemical Household Products is Associated with Persistent Wheezing in Pre-school Age Children

In the UK and other developed countries the prevalence of asthma symptoms has increased in recent years. This is likely to be the result of increased exposure to environmental factors. A study was undertaken to investigate the association between maternal use of chemical based products in the prenatal period and patterns of wheeze in early childhood.

In the population based Avon Longitudinal Study of Parents and Children (ALSPAC), the frequency of use of 11 chemical based domestic products was determined from questionnaires completed by women during pregnancy and a total chemical burden (TCB) score was derived. The products chosen (and the percentages of women using them) were: disinfectant (87.4%), bleach (84.8%), carpet cleaner (35.8%), window cleaner (60.5%), dry cleaning fluid (5.4%), aerosols (71.7%), turpentine/white spirit (22.6%), air fresheners (spray, stick or aerosol) (68%), paint stripper (5.5%), paint or varnish (32.9%), and pesticides/insect killers (21.2%). A simple score for frequency of use of each product was derived (0=not at all, 1=less than once a week, 2=about once a week, 3=most days, 4=every day) and the scores for each product were summed to produce a total chemical burden (TCB). Four mutually exclusive wheezing patterns were defined for the period from birth to 42 months based on parental questionnaire responses (never wheezed, transient early wheeze, persistent wheeze, and late onset wheeze). Multinomial logistic regression models were used to assess the relationship between these wheezing outcomes and TCB exposure while accounting for numerous potential confounding variables. Complete data for analysis was available for 7,019 of 13,971 (50%) children.

The mean (SD) TCB score was 9.4 (4.1), range 0-30. Increased use of domestic chemical based products was associated with persistent wheezing during early childhood (adjusted odds ratio (OR) per unit increase of TCB 1.06 (95% confidence interval (CI) 1.03 to 1.09)) but not with transient early wheeze or late onset wheeze. Children whose

mothers had high TCB scores (>90th percentile) were more than twice as likely to wheeze persistently throughout early childhood than children whose mothers had a low TCB score (<10th percentile) (adjusted OR 2.3 (95% CI 1.2 to 4.4)).
These findings suggest that frequent use of chemical based products in the prenatal period is associated with persistent wheezing in young children. Follow up of this cohort is underway to determine whether TCB is associated with wheezing, asthma, and atopy at later stages in childhood.
(A. Sherriff et al., Thorax 2005, 60: 45-49)

I can hardly think of an exposure metric less meaningful from a toxicological point of view than "total chemical burden", derived from the use of "chemicals-based" household products. The authors didn't seem to bother, which "chemicals" they were looking at, and why they had been used in first place. Does the reported use of pesticides indicate a generally unhealthy environment, e.g. the presence of animal (roach?) antigens? Or, on the contrary, is the frequent use of household cleaners and disinfectants a surrogate for "excessive hygiene" (the authors didn't even mention the "hygiene hypothesis" in their discussion)? Were the authors aware that they possibly only looked at total VOC (irrespective of their "natural" or "chemical" origin), and that they did not – as they claimed – examine in-utero exposure, because the prenatal use of household products is probably strongly correlated with postnatal use as well?
This is science at its poorest. Multivariate statistics alone are not enough for sound epidemiology!

Dr. Michael Nasterlack
(Ludwigshafen, Germany)

Although the following is not exactly related to the chemical industry, those of us who counsel frequent travellers may occasionally be confronted with questions regarding the use of melatonin.

AHRQ Issues Report on Safety and Effectiveness of Melatonin Supplements

A new evidence review by the Agency for Healthcare Research and Quality (AHRQ) found that melatonin supplements, which people often take for problems sleeping, appear to be safe when used over a period of days or weeks, at relatively high doses and in various formulations. However, the safety of supplements used over months or years is unclear. For most sleep disorders, the authors found evidence suggesting limited or no benefits from melatonin supplement use. But the authors say that firm conclusions cannot be drawn until more research is conducted. The report was requested and funded by the National Center for Complementary and Alternative Medicine, a part of the National Institutes of Health.
The report's authors reviewed the scientific evidence to date for the benefits of melatonin supplements used for disorders due to sleep schedule alterations and primary and secondary sleep disorders. Among those problems for which melatonin supplements appear to provide little benefit are jet lag and working night shifts. In contrast, the authors found evidence to suggest that melatonin supplements may be effective when used in the short term to treat delayed sleep phase syndrome in persons with primary sleep disorders.
Melatonin supplements do not appear to have an effects on sleep efficiency in persons with primary sleep disorders, and the effects of the hormone do not seem to vary by the individual's age, type of primary sleep disorder, dose, or length of treatment. Furthermore, melatonin supplements do not appear to affect sleep quality, wakefulness after sleep onset, total sleep time, or percent of time spent in rapid eye movement (REM) sleep.
"Sleep disorders can affect a person's quality of life and job performance, which can translate into decreased productivity, motor vehicle and industrial accidents, and even medical errors", said AHRQ Director Carolyn Clancy, MD. Estimates show that at least 40 million Americans each year suffer from chronic sleep disorders, and an additional 20 million experience occasional problems.

Sleep disorders cost an estimated $16 billion in medical costs alone each year. Indirect costs due to lost or substandard work productivity, accidents, resulting litigation, and other factors may increase overall costs. The National Highway Traffic Safety Administration, for example, estimates that 100,000 motor vehicle accidents a year are caused by driver fatigue from sleep deprivation, which is one result of some sleep disorders, and that more than 1,500 people are killed and another 71,000 injured annually as a result.

The report was prepared by a team of researchers led by Terry Klassen, MD, director of AHRQ's University of Alberta/Capital Evidence-based Practice Centre in Edmonton, and Chair of Pediatrics for the University's Faculty of Medicine and Dentistry.

A summary of *Melatonin for Treatment of Sleep Disorders* is on line at www.ahcpr.gov/clinic/epcsums/melatsum.htm. Or, download the full 310-page report at www.ahcpr.gov/downloads/pub/evidence/pdf/melatonin/melatonin.pdf

(taken from ACOEM Report November/December 2004, p. 4-5)

Dr. Michael Nasterlack
(Ludwigshafen, Germany)

Many of you may already be aware of the following article which appeared in Science, thus, not in the least reputable scientific journal on the market.

Hematotoxicity in Workers Exposed to Low Levels of Benzene

Benzene is known to have toxic effects on the blood and bone marrow, but its impact at levels below the U.S. occupational standard of 1 part per million (ppm) remains uncertain. In a study of 250 workers exposed to benzene, white blood cell and platelet counts were significantly lower than in 140 controls, even for exposure below 1 ppm in air. Progenitor cell colony formation significantly declined with increasing benzene exposure and was more sensitive to the effects of benzene than was the number of mature blood cells. Two genetic variants in key metabolizing enzymes, myeloperoxidase and NAD(P)H:quinine oxidoreductase, influenced susceptibility to benzene hematotoxicity. Thus, hematotoxicity from exposure to benzene occurred at air levels of 1 ppm or less and may be particularly evident among genetically susceptible subpopulations.
(Q. Lan et al., Science 2004, 306: 1774-1776)

Disquieting indeed, if benzene levels below 1 ppm should exert significant hematotoxicity in exposed workers. However, this study suffers from several inconsistencies and shortcomings, some of which shall be addressed in the following.

The authors' conclusion is obviously not supported by the data provided in the article. The distinction between low (< 1 ppm) and moderately (< 10 ppm) exposed workers is quite arbitrary. Obviously, the differences reported between these two groups are not very impressive (fig. 1, data taken from table 1 of the article).

This lack of a dose-response in the low exposure range is probably due to misclassification: workers assigned to the low exposure group (based on exposure measurement in the month before phlebotomy) in fact might have had higher intermittent exposures in the past. This assumption is further supported by the reported details of the exposure assessment (Vermeulen et al. (2004) Ann. Occup. Hyg. 48, 105). There, table 3 reveals a considerable variability of benzene levels within job categories, where only one job title (cutting, factory B) appears to be more or less consistently associated with benzene levels below 1 ppm. However, only 30 workers were in this job category, thus, at least 79 allegedly low-exposed workers in the study in fact weren't low exposed according to the definition.

Although exposure measurements were taken during the 16 months prior to phlebotomy, the authors only used the exposure samples from the month directly preceding phlebotomy to categorize the workers into exposure groups. By doing so they ignored the exposure categorization that had been published earlier by this group. There is no

justification why this peculiar approach has been taken as exposure categorization based on the 16 month of exposure allows for more robust categorizations as well takes into account the exposure in the previous months that my have resulted in the observed effects.

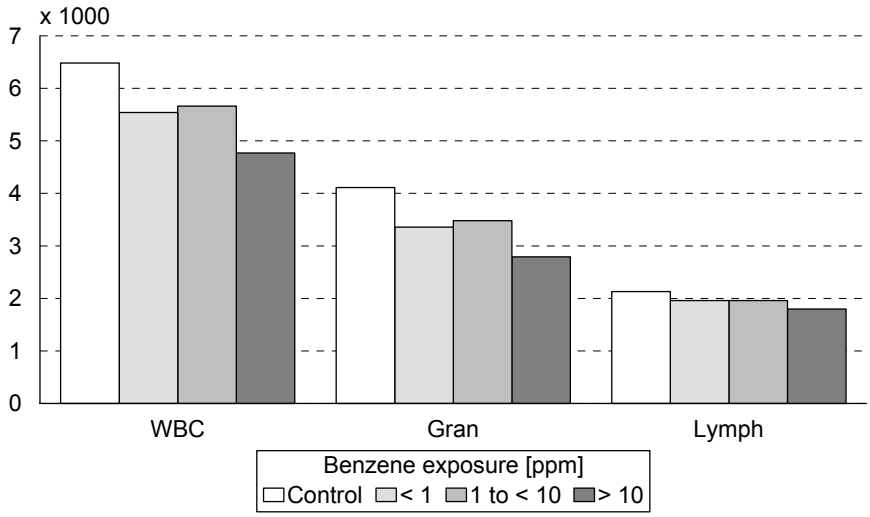

Fig 1: Data from Lan et al., Science 306: 1774-1776 (2004)

Furthermore it is not understood why the lifetime exposure doses that have been estimated according to the SOM where not used in the analyses either. In addition there is uncertainty about the contribution of skin uptake. Although it has been mentioned that the preliminary analyses indicated that this route of exposure did not contribute substantially to the total benzene doses received in this population, it is clear that the impact can vary significantly from job title to job title and that it can be expected that skin uptake has remained unaffected in situations where the inhalatory exposure was reduced by the application of local exhaust ventilation. Therefore it is plausible that the contribution of skin exposure may have seriously affected the exposure doses of particularly the low exposed groups where inhalatory exposure was mitigated by local exhaust ventilation. Biomonitoring results that are available but have not been utilized may have provided some better understanding.

Second, reports from the same research group clearly document that benzene exposures in China in the past have been much higher and that these exposures have decreased over time. Data reported in 1996 indicate that for gluers, a profession in the shoemaking industry, average exposures have decreased from between 60 and 70 ppm in 1965 to 1969 to exposures between 20 and 30 ppm in 1985 to 1987. Even these exposure assessments have been criticized by others for being underestimates of the actual exposure concentrations.

Third, earlier reports on hematological effects from benzene exposure in Chinese shoemakers indicated that aplastic anemia was 5.8 times more prevalent, clearly documenting that these cohorts have experienced high benzene exposures. These reports are in close agreement with reports from Turkish shoemakers, in whom the same health effects, including decreased blood cell counts were observed thirty years ago. Workers exposed to high benzene concentrations in the past may still suffer from the consequences and may still show hematological effects from these past exposures, even if the exposure concentrations have been reduced.

Valid information on possible health effects from low level benzene exposure can only be collected from workers who have not experienced high benzene concentrations in the past. In the population studied by Lan et al. high benzene concentrations in the past are likely. Other studies specifically focused on workers with low benzene exposures have not found evidence for hematotoxicity.

I have compiled this text from several statements from several persons whom I don't name, because the documents used are partly classified as confidential. I just don't want to claim that I did all the work myself.

Just one more conclusion, in order to prevent misunder-standing: I strongly believe that, where substitution is possible, benzene-containing

materials should not be handled in workplaces at all.

Dr. Michael Nasterlack
(Ludwigshafen, Germany)

Formaldehyde Exposure and Leukaemia

Formaldehyde is currently classified by IARC as a probable human carcinogen based on animal studies with neoplastic lesions at the point of contact, the nasal cavity, but limited evidence of human respiratory tract carcinogenicity. This IARC classification is based on several long term chronic bioassays, mechanistic information developed over 20 years, and 39 epidemiology studies. The studies on formaldehyde carcinogenicity represent one of the more extensive databases that IARC has reviewed.

Formaldehyde causes nasal cavity tumours in rats and at higher exposure levels in mice. The mechanistic information seems to indicate that formaldehyde at high airborne concentrations increases the occurrence of damage to the nasal cavity and this damage contributes to "the subsequent development of cancer". However, there is thought to be no or little transport of formaldehyde beyond the point of contact since formaldehyde is rapidly metabolised and detoxified on contact with the upper respiratory tract. Thus, the focus of formaldehyde epidemiology for many years has been on cancers of the upper respiratory tract as evinced by 25 case-control studies examining formaldehyde exposure and sinonasal cancer, nasopharyngeal cancer, lung cancer, and cancers of oral cavity, oropharynx, and hypopharynx, and 14 cohort studies examining exposure-response relations largely among the cancers of the respiratory tract. Rates of other cancers distant from the respiratory tracts have been increased in some of the cohort studies; these findings have not received much attention.

The cohort studies of workers with formaldehyde exposures have been conducted in three broad occupational groups that have the potential to receive significant formaldehyde exposure – embalmers, anatomists, and industrial workers. The industrial worker studies have more direct and quantified estimates of formaldehyde exposure relative to the other groups. While embalmers and anatomists have higher rates of brain cancer, lymphatic or haematopoietic cancers, and pancreatic cancers in some studies, the lack of higher rates of these cancers in the studies of industrial workers has been used to argue against a causal association. The industrial worker studies in general have leukaemia rates close to expected levels.

Two recent updates of large industrial studies, conducted in the United States by Hauptmann et al. and Pinkerton et al., have found a positive association between selected measures of formaldehyde exposure and increased leukaemia rates, but a recent large industry-wide study of industrial workers with formaldehyde exposure by Coggon et al. in the UK failed to confirm the finding. This study, which had more workers with higher exposures than both the Hauptmann et al. and the Pinkerton et al. studies combined, found no increase in risk of leukaemia in the highest exposure category. There are two areas where the findings leukaemia risk conflict with our current understanding of formaldehyde carcinogenicity, the lack of consistency of the data across epidemiology studies and biological plausibility.

For many putative occupational and environmental carcinogens, there is scant mechanistic information to help focus the research or contribute to causal assessment. However, this is not the case for formaldehyde as the mechanism for cancer in laboratory animals is well understood. The proposed association between formaldehyde and leukaemia does not appear consistent with the current biological evidence. In particular:

(1) no evidence of toxicity at sites remote from the respiratory tract has been found, despite multiple long term inhalation animal bioassays;

(2) no DNA-protein crosslinks have been discovered in the bone marrow of rats exposed to high concentrations of formaldehyde;

(3) formaldehyde does not occur in increased concentrations in blood when humans, monkeys, or rats are exposed to airborne formaldehyde; and

(4) even very high concentrations of formaldehyde do

not seem to cause cytogenetic damage in the lymphocytes and bone marrows of rats.
New scientific findings in this well established field are useful because they force us to reconsider the evidence and determine what additional research may be needed to improve our understanding of the causal process. In the case of formaldehyde exposure and leukaemia, two research approaches seem possible. First, the two recent industrial studies which report a leukaemia effect should be critically reviewed to rule out uncontrolled confounding as far as possible and to assess the appropriateness of the comparison group that led to such unexpected findings. This approach could be pursued quickly, but would probably not bring the issue to resolution. Second, all of the available information should now be evaluated systematically to specify the additional research we need. Such additional research might include a formal evaluation of the leukaemia risk in previously published cohort epidemiological studies, updating some of the older investigations, formally analysing leukaemia rates by exposure level in all of the cohort studies, and investigating which mechanisms, if any, would allow formaldehyde to cause leukaemia. This approach, however, may take years to advance understanding. We are certain today that formaldehyde at high exposure levels increases nasal cancer in rats and mice. We are still debating whether or not humans exposed to far lower levels of formaldehyde are at any increased risk of cancer of the upper respiratory tract. As for the new leukaemia hypothesis, I suspect we are many years from resolution, but we do not have the "freedom to ignore the knowledge we already have, or to postpone the action that it appears to demand".
(J.J. Collins, Occup. Environ. Med. 2004, 61: 875-876)

I am not sure what this last sentence means. Shall we ban formaldehyde from human metabolism on the basis of the precautionary principle?

Dr. Michael Nasterlack
(Ludwigshafen, Germany)

Female breast cancer and pesticides: another topic of ongoing hot debate. Here are two recent publications on this issue.

Pesticide Use and Breast Cancer Risk among Farmers' Wives in the Agricultural Health Study

The authors examined the association between pesticide use and breast cancer incidence among farmers' wives in a large prospective cohort study in Iowa and North Carolina. Participants were 30,454 women with no history of breast cancer prior to cohort enrollment in 1993-1997. Information on pesticide use and other information was obtained by self-administered questionnaire at enrollment from the women and their husbands. Through 2000, 309 incident breast cancer cases were identified via population-based cancer registries. Rate ratios were calculated for individual pesticides using Poisson regression, controlling for confounding factors. Breast cancer standardized incidence ratios were 0.87 (95% confidence interval: 0.74, 1.02) for women who reported ever applying pesticides and 1.05 (95% confidence interval: 0.89, 1.24) for women who reported never applying pesticides. There was some evidence of increased risk associated with use of 2,4,5-trichloro-phenoxypropionic acid (2,4,5-TP) and possibly use of dieldrin, captan, and 2,4,5-trichlorophenoxyacetic acid (2,4,5-TP), but small numbers of cases among those who had personally used the pesticides precluded firm conclusions. The authors found no clear association of breast cancer risk with farm size or washing of clothes worn during pesticide application, but risk was modestly elevated among women whose homes were closest to areas of pesticide application. Further follow-up of this cohort should help clarify the relation between pesticide exposure and breast cancer risk.
(L.S. Engel et al., Am. J. Epidemiol. 2005, 161: 121-135)

Dr. Michael Nasterlack
(Ludwigshafen, Germany)

Breast Cancer Risk and Historical Exposure to Pesticides from Wide-area Applications Assessed with GIS

Pesticides are of interest in etiologic studies of breast cancer because many mimic estrogen, a known breast cancer risk factor, or cause mammary tumors in animals, but most previous studies have been limited by using one-time tissue measurements of residues of only a few pesticides long banned in the United States. As an alternative method to assess historical exposures to banned and current-use pesticides, we used geographic information system (GIS) technology in a population-based case-control study of 1,165 women residing in Cape Cod, Massachusetts, who were diagnosed with breast cancer in 1988-1995 and 1,006 controls. We assessed exposures dating back to 1948 (when DDT was first used there) from pesticides applied for tree pests (e.g., gypsy moths), cranberry bogs, other agriculture, and mosquito control on wetlands. We found no overall pattern of association between pesticide use and breast cancer. We found modest increases in risk associated with aerial application of persistent pesticides on cranberry bogs and less persistent pesticides applied for tree pests or agriculture. Adjusted odds ratios for these exposures were 1.8 or lower, and, with a few exceptions, confidence intervals did not exclude the null. The study is limited by uncertainty about locations of home addresses (particularly before 1980) and unrecorded tree pest and mosquito control events as well as lack of information about exposures during years when women in the study lived off Cape Cod and about women with potentially important early life exposures on Cape Cod who were not included because they moved away.

(J.G. Brody et al., Environ. Health Perspect. 2004, 112: 889-897)

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:

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or at Medichem's website **http://www.medichem.org/congresses.html**

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. **Ron Stout**, Procter & Gamble, Mason Oh (U.S.A.),