MEDI CHEM

Newsletter: July 2010

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

Founded 1972 in Ludwigshafen, Germany
Honorary President: Prof. Dr.med. Dr.h.c. Alfred M. Thiess

Message from the Secretary

Dear Colleagues:

In this newsletter we will say good-bye and thank you to two long-standing MEDICHEM Board members – Dr. Andreas Flueckiger and Professor Dr. Todor Popov. On a personal note, in the time that I have been Secretary, I have benefited greatly from Andreas's helpful assistance and from Teo's support and wisdom. I look forward to their continued active participation as MEDICHEM members.

I would also like to personally welcome on behalf of the Board our new Board Members – Dr. Karolina Lyubomirova and Dr. Martina Piasek.

A final thanks to Dr. Michael Nasterlack for his assistance in compiling this Newsletter – as always, he's there to lend a helping hand when needed!

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

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Announcement --
New MEDICHEM Board Members

Following the Call for Candidates, which was sent out with the last Newsletter, the MEDICHEM Secretary received two nominations for the Medichem Board, Dr. Karolina Lyubomirova from Bulgaria and Dr. Martina Piasek from Croatia.

Dr. Thirumalaj Rajgopal had agreed to be a candidate for Chairman for another term of office, with no other nominations received. This year's Board election thus goes as a 'silent vote'.

MEDICHEM owes very special thanks to Andreas Flückiger and Teo Popov for the invaluable service they have provided over many years.

Teo will remain unforgettable as the Varna congress organizer and as the generous supporter of his younger colleagues (many of whom he brought to MEDICHEM); not to forget his unbelievable ability to manage the participation of himself and his disciples at congresses all over the world, even during difficult times before the fall of the iron curtain.

Andreas' contributions to MEDICHEM are beyond praise. He has served on the Board as Secretary and as Treasurer for many years and, with his experience and insight, provided crucial support to individual members and to our membership as a whole. We will certainly miss these two experienced (and - before I forget to say - amiable and dear) colleagues on the Board.

At the same time – (and everything has two sides!) – we are looking forward to working with our new Board colleagues Martina and Karolina. Both are long-standing MEDICHEM members and have shown a keen interest in MEDICHEM's objectives both inside and outside our society. Martina and Karolina - welcome to the Board!

Dr. Michael Nasterlack,
Ludwigshafen (Germany)

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Shiftwork and Worker Risks – New Findings

In December 2007, an expert Working Group convened by the IARC Monographs programme concluded on the basis of "limited evidence in humans for the carcinogenicity of shiftwork that involves nightwork", and "sufficient evidence in experimental animals for the carcinogenicity of light during the daily dark period (biological night)" that shift-work that involves circadian disruption is probably carcinogenic to humans (Group 2A)."

In the July 2008 issue of this Newsletter, Robert Winker and Michael Nasterlack presented a commentary on this evaluation and concluded after reading an additional study (J. Schwartzbaum et al, 2007) and a systematic review by H.A. Kolstad (2008) that the "limited evidence" in humans (IARC, 2007) should rather be regarded as "insufficient evidence."

Unfortunately, more than two years after this preliminary (or premature?) IARC publication the respective monograph is still lacking and, therefore, the scientific discussion of the IARC conclusions is severely hampered. Since then, several new studies have emerged, which add more question marks to the IARC ruling.

Night work and breast cancer - results from the German GENICA study

(Pesch B, Harth V, Rabstein S, Baisch C, Schiffermann M, Pallapies D, Bonberg N, Heinze E, Spickenheuer A, Justenhoven C, Brauch H, Hamann U, Ko Y, Straif K, Brüning T (2010): Scand J Work Environ Health 36:134-141)

These authors have investigated the risk in a German population-based case-control study known as GENICA (gene environment interaction and breast cancer). The GENICA study involved interviews to assess shift work information in 857 breast cancer cases and 892 controls. The risks of employment status and night shift characteristics were estimated using conditional logistic regression models, adjusting for potential confounders.

Resampling and bootstrapping were applied to adjust the risk estimates for a potential selection bias. Among 1749 women, 56 cases and 57 controls worked in night shifts for > or =1 year, usually in the healthcare sector (63.0% of controls).

Female night workers were more frequently nulliparous and low-educated than day workers (28.6% versus 17.8% and 12.3% versus 9.2%, respectively). Fewer women in night work had ever used post-menopausal hormone therapy (35.7% versus 51.9%). An elevated breast cancer risk was not associated with having ever done shift or night work when compared to women employed in day work only [odds ratio (OR) 0.96, 95% confidence interval (95% CI) 0.67-1.38 and OR 0.91, 95% CI 0.55-1.49, respectively].

In the abstract it is mentioned that women who reported more than 807 night shifts, the third quartile of the distribution among controls, experienced a breast cancer risk of 1.73 (95% CI 0.71-4.22).

Night work for 20 or more years was associated with an OR of 2.48 (95% CI 0.62-9.99) based on 12 cases and 5 controls. The authors conclude that long-term night work was associated with a modestly, but not significantly, increased breast cancer risk, while having ever done night work was not.

On the other hand (and not mentioned in the abstract), a closer look at the data reveals that the respective lower categories of shiftwork exposure are associated with a, albeit not statistically significant, decreased breast cancer risk.

If we do not want to assume that a little nightwork protects against breast cancer while a lot of nightwork causes it, we may want to think about chance findings, residual confounding, etc. In the face of the aforementioned, it comes as a surprise when the authors state that "… our results are in line with the IARC classification that long-term night work in women is probably associated with breast cancer ..."

Night-shift work and breast cancer risk in a cohort of Chinese women

(Pronk A, Ji B-T, Shu X-O, Xue S, Yang G, Li H-L, Rothman N, Gao Y-T, Zheng W, Chow W-H (2010) Am J Epidemiol 171:953-959

The authors investigated the association between night-shift exposure and incident breast cancer in a population-based prospective cohort study of Chinese women. At baseline (1996 - 2000), information on lifetime occupational history was obtained from 73,049 women. Lifetime night-shift exposure indices were created using a job exposure matrix. During 2002 - 2004, self-reported data on frequency and duration of night-shift work were collected.

Hazard ratios and 95% confidence intervals, adjusted for major breast cancer risk factors, were calculated. During follow-up through 2007, 717 incident cases of breast cancer were diagnosed. Breast cancer risk was not associated with ever working the night shift on the basis of the job exposure matrix (adjusted hazard ratio = 1.0, 95% confidence interval: 0.9, 1.2) or self-reported history of night-shift work (adjusted hazard ratio = 0.9, 95% confidence interval: 0.7, 1.1).

Risk was also not associated with frequency, duration, or cumulative amount of night-shift work. There were no indications of effect modification. The lack of an association between night-shift work and breast cancer adds to the inconsistent epidemiologic evidence. The authors concluded that it may be premature to consider shift work a cause of cancer.

At the recent EPICOH-MEDICHEM conference in Taipei, new findings were presented from another large cohort of Chinese women, the Shanghai Textile Workers cohort. The following is taken from the congress abstract book:

Occupational exposure to magnetic fields and shift work, and the risk of breast cancer among female textile workers in Shanghai, China

(Li W, Ray RM, Gao D, Yost M, Davis S, Thomas DB, Breslow N, Wernli KJ, Wong E, Checkoway H: EPICOH-MEDICHEM 2011, abstract no 463)

The etiology of female breast cancer remains poorly understood. Some evidence suggests that exposures to magnetic fields (MF) and light at night, from working night and/or rotating shifts, may increase risk of breast cancer.

Suppression of melatonin by MF and light at night is a plausible underlying mechanism. Epidemiologic support for associations with MF and shift work is inconsistent, however. The objective of this research project was to test the hypothesis that MF and rotating shift work are risk factors for breast cancer among women textile workers in Shanghai.

A total of 1707 incident breast cancer cases diagnosed between 1989 and 2000 were identified in the cohort of 267,400 Shanghai textile workers. The comparison group was a subcohort of 4840 women randomly selected from the entire cohort.

To develop a quantitative job/exposure matrix (JEM), 1155 personal measurements of magnetic field exposure were collected for 146 job categories that were held by the cases and comparison group. Multiple exposure indices were calculated for each job.

Detailed historical shiftwork practices were collected from 502 Shanghai textile factories. The MF exposure, based on arithmetic means, and shiftwork information was linked to the work history records of women.

Cumulative exposures lagged by 0, 5, 10, 15, or 20 years were categorized into quartiles to estimate relative risks and 95% confidence intervals, using proportional hazards modeling adapted for the case-cohort design.

Cumulative exposures to MF and night shifts did not show any significant effects on risk of breast cancer. For the MF exposure, the relative risks for three high quartiles compared to the lowest quartile, adjusted for age and reproductive factors was 1.02, 1.07, and 0.99, respectively.

The adjusted relative risks for having worked on shift work for 1 - <10 years, 10 - < 20 years, and 20+ years compared with less than 1 year were 0.99, 1.0, and 0.92, respectively. There was no dose-response trend observed. The results did not change significantly when the exposures were lagged by 5, 10, 15, or 20 years.

The authors came to the conclusion that their findings to date do not suggest any associations between the work-place exposures to MF or shiftwork and the risk of breast cancer. While more in-depth analyses of the study are ongoing, they believe that the findings will unlikely change substantially.

If the findings persist, this study will offer some reassurance that workplace exposure to magnetic fields and shiftwork are unlikely to be associated with the risk of breast cancer.

The current situation is thus far from unequivocal and less than satisfactory. Nevertheless, at the EPICOH-MEDICHEM conference H. Kolstad and co-workers reported that in Denmark, breast cancer has already been recognized as an occupational disease on the basis of the IARC classification. At least sixty women, who had worked a night shift at least once a week for more than 20 years, have received compensation.

This has caused public concern and prompted demands for setting limits for duration of night shift work. Kolstad et al. therefore reviewed exposure-response data for night shift work and breast cancer risk based on previously published epidemiological data, to answer the question:

Should we warn against long-term night shift work to avoid breast cancer?

(Kolstad HA, Erlandsen M, Frost P, Bonde JP: EPICOH-MEDICHEM 2011, abstract no 356)

The authors identified eight epidemiological studies with data on risk of breast cancer in relation to duration of night shift work (range 1 - ≥30 years) and conducted a dose-response meta-analysis. We fitted weighed least squares regression models. The natural log of the reported risk estimates were assigned to the midpoint of the lower and upper boundaries of the corresponding duration categories. The models took account of the correlation between estimates within each study.

The authors observed no increasing risk of breast cancer by increasing years of night shift work (log OR 1.0 (95% CI 0.9-1.1). Analyses that dichotomized night shift work by successively increasing duration (0, 5, 10, 15, 20, 25 years) did not reveal any threshold level.

The authors concluded that this limited epidemiological data do not indicate an exposure-response relationship between night shift work and breast cancer. Furthermore, the data do not provide empirical arguments for the 20 years criterion applied for compensating breast cancer in Denmark. No threshold level that could guide the regulation of night shift work is indicated. Therefore, they regard warnings against long-term night shift as not evidence-based.

Having said all that: where shall we go from here? Erren et al. have provided insightful comments on the current situation and the necessity to perform further studies in other industrial populations, not limited to breast cancer or prostate cancer risk, taking into account different patterns of shiftwork, and not dependent on retrospective assessment of shiftwork status (Erren TC, Morfeld P, Stork J, Knauth P, von Mülmann MJ, Breitstadt R, Müller U, Emmerich M, Piekarski C (2009) Shift work, chronodisruption and cancer? - The IARC 2007 challenge for research and prevention and 10 theses from the Cologne Colloquium 2008. Scand J Work Environ Health 35:74-79). Such cohorts exist in Germany (Morfeld et al., 1997; Ott et al., 2009) and probably also in other parts of the world.

Dr. Michael Nasterlack,
Ludwigshafen (Germany)

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The following article: Guidotti, TL. 2010. The Regulation of Occupational Exposure to Nanomaterial: A Proposal, Archives of Environmental and Occupational Health; is reprinted with the permission of the publisher (Taylor & Francis Ltd, http://www.informaworld.com).

The Regulation of Occupational Exposure to Nanomaterials: A Proposal

Nanomaterials represent a major challenge in occupational health protection.[1] Uncertainty over the best way forward is causing delay in regulation despite rapidly growing use of nanomaterials by industry and widespread distribution in consumer products. By the time a satisfactory approach to risk assessment, standards setting, and risk management is agreed upon, "nano" could well be a mature technology.[2]

Nanomaterials are artificial objects on a scale of 100 nm (10^{-7} m) or below, smaller than most bacteria and in the size range of viruses and larger molecules.[1,3] There are many nanomaterials that are of significance in environmental health, the mostly familiar perhaps being fine particulate air pollution and the more exotic products of combustion known as fullerenes (the 60- and 80-carbon structures named after inventor Buckminster Fuller).

Engineered nanoparticles are fabricated objects on this scale that are designed for a purpose. Their commercial applications have grown from low-tech, as an ingredient in sunscreen, to highly sophisticated. Engineered nanomaterials are now used or in the final stages of development for biomedical research, medication delivery systems, oilfield stimulation, cosmetics, composite materials, antiseptics, smart textiles, advanced metal alloys, catalysts, filters, and photovoltaic devices, and this is just the beginning. They come in many different configurations: spherical structures, tubes or wires, sheets, cages trapping metal ions, crystals, and branching structures.

Next on the horizon are nano-scale machines, with engineered parts. Many of the applications of nanomaterials are fundamental to “green” and energy-conserving technology, so slowing down development would not be a viable option even if it were possible.

However, nanomaterials have properties that raise concerns for environmental and occupational health. Like fine particulate air pollution, their potential for toxicity is disproportionate to their mass, because material so finely divided has an enormous surface area relatively to its weight.

Particles this small stay airborne for a very long time, and disperses rapidly and widely at a relatively homogeneous concentration compared to familiar particulate pollution or contamination. Nanoparticles in open air will spread quickly throughout a workplace environment, will be readily inhaled, will penetrate deeply into the respiratory tract, and will have the potential to cause unpredictable problems.

Although they are small solid particles, it is most useful to think of nanoparticles as a different state of matter, from the point of view of regulatory policy. This is because they are so small that the familiar properties of their composite materials in bulk become irrelevant and new properties govern their behavior, including quantum effects that have no counterpart on a macro-scale. (For example, on a nano scale, gold is not shiny and yellow: it is red.)

It seems fairly clear, because of the enormous range of sizes and variations in configuration that are possible with nanomaterials, not to mention engineered activity such as electrical properties (some nanparticles have semiconductor properties) and mechanical action, that nanomaterials cannot be regulated as a single class.

There must be individual attention, with each nanomaterial treated as a new product. But is it possible to make at least some generalizations so that nanmaterials can at least be regulated in groups rather than one at a time, seemingly presenting regulatory nightmare?

The risk presented by some nanoparticles may resemble that of fine and ultrafine particulate air pollution, which show an exposure-response relationship but no toxicity threshold, have the capacity to migrate in the body to reach target organs other than the lung, and exert their effects even in non-susceptible population subgroups.

There may also be similar issues involving immune responses, oxidant load, intracellular overload, and inflammation. There are no clear studies so far that characterize the risks of nanoparticles under reasonable operating conditions. One human study of an egregious exposure situation, although confounded by exposure to other contaminants,[4] and several animal studies suggest that health risk may be driven by respiratory, cardiovascular, and neurodegenerative outcomes.

There is always the risk of cancer to be concerned about, and, for these novel materials, the possible risk of significant problems with allergy and direct inflammation. At present, there is no consensus on how to measure exposure to nanoparticles. Simple measurement of mass is the only practical measurement for routine monitoring but is difficult on that scale, requiring a cumbersome technology called a tapered element oscillating microbalance, the only practical use of which has been in stationary air pollution monitors. (On the other hand, passive diffusion monitors may be very feasible in the future for nanoparticles with well-defined chemical or physical characteristics.)

Mass, as has been noted, is not even a particularly good metric for the biological hazard of a nanoparticle. Particle counts, aggregate surface area (calculated), aggregate particle volume, and particle sorting have all been suggested and it is obvious that both the configuration and the chemistry (including, importantly, composition, the "corona" of adsorbed constituents, metal content and trapping, and surface activity, such as charge) will be more important in some nanomaterials than in others.

So what to do?

One approach might be to anchor the regulatory approach, conservatively, by analogy to a nanomaterial that is already known and at least moderately understood. The Canadian Council of Ministers of the Environment has adopted a Canada-wide standard (CWS) for $PM_{2.5}$ (fine particulate matter at or below 2500 nm, which is above the upper range of nanoaterials but includes the size range) of 30 $\mu g/m^3$ 24-hour average, as the 98^{th} percentile of the range permitted over any three year period, to take effect in 2010.

This may seem convoluted but it is convenient as a benchmark because represents an upper bound for an "almost" worst case scenario. Being an environmental standard, the CWS seems appropriate for a hazard for which no threshold applies, that affects persons who are not susceptible, and no healthy worker effect is relevant.

Assuming that the objective is not to exceed this exposure level on the job or outside the workplace, one can adopt (although not derive, because the time over which the average are calculated are not comparable) a benchmark occupational exposure level (not an occupational exposure limit, or OEL) of 30 $\mu g/m^3$ 8-hour time-weighted average.

Is this arbitrary?

Yes, but not unreasonable. The worst case scenario for the environmental exposure simply becomes a benchmark for the maximum allowable concentration in the workplace. Assuming that the objective is not to add to community risk and that there is no firm scientific evidence to do anything else, it at least provides a place from which to start, a benchmark for nanoparticles not otherwise characterized. This is a very low level of exposure, and would undoubtedly drive control technology toward containment for many or most processes.

In practice, this benchmark exposure level would be applied to nanoparticles that are believed to be relatively inert (such as TiO_2), at least until such time as their safety could be evaluated. For nanoparticles with more biological activity, demonstrated or predicted, additional uncertainty or safety factors could be applied to reduce this benchmark level, using the traditional factors of 0.1 or something else (such as 0.3 – there are not enough data to know what is best).

The features which might require application of a safety factor could be demonstrated biological activity, metal content, resemblance to a known hazard, and fibrous shape. The resulting modified exposure level would become the provisional standard until sufficient data became available to evaluate the specific product.

This provisional system would have many advantages. It is stringent but not unrealistic and can be loosened in the future if research demonstrates less risk for specific classes of nanomaterials, but in the meantime it is precautionary. It would drive technology for control in the long run although individual protection would be attainable with personal respiratory protection (available respirators have a dip in efficiency at this size range but are still highly effective). It would drive monitoring technology, powerfully.

Perhaps best of all, it would give the industry a firm basis for planning and the "level playing field" so important for anticipating regulatory issues in a competitive sector. This is a technology that should be encouraged because of its promise but precisely because it will become ubiquitous and will change our lives it should be regulated to prevent unanticipated consequences.

Is this a reasonable approach or not? Does anyone among our readers have a better idea?

Tee L. Guidotti, MD, MPH

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Taipei EPICOH-MEDICHEM 2010 – Mother Nature Wins

From April 21 to 25, the joint EPICOH-MEDICHEM congress took place in Taipei, Taiwan. It featured many interesting presentations covering a wide range of topics, from old but still pertinent issues like asbestos to the new challenges associated with globalization, migration, etc. While the conference was well attended mostly by delegates from Asian countries, many delegates especially from Europe but also from other parts in the world were not able to make it this time: the reason being the ash cloud produced by Iceland's Eyjafjallajökull. As one more side-effect of this event, for the first time in many years there were not enough MEDICHEM members in good standing present to have a General Assembly. This is why this July issue does not provide a respective report or minutes.

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Mark your Calendar!!

2011 MEDICHEM Congress: Occupational Health in a Changing World
Heidelberg, Germany, 2-5 June 2011.

25 years after the last congress in Germany in 1986 the 39th MEDICHEM congress will be held in the city of Heidelberg. This place with its romantic townscape is an event in itself. It is home to Germany's oldest university which will be celebrating its 625th anniversary also in 2011. The harmonious ensemble of the world-famous castle ruins, the Old Town and the Neckar River nestling among the hills continues to fascinate until today millions of visitors from all over the world.

The **conference fee will be 590 Euro**, which also includes all social events like Opening Ceremony with cold and warm buffet reception on Thursday, an organ concert in the Church of the Holy Spirit in the heart of Heidelberg's famous Old Town and the reception by the Mayor of Heidelberg at the Town Hall just opposite the church on Friday, as well as the Champagne reception on the Castle Gallery, the Gala Dinner in the Castle, and the Giant Firework display on Saturday, and the catering during the conference itself.

To especially facilitate their participation in the congress a reduced fee of 250 Euro is offered to our retired colleagues, all inclusive.

Additional details are available at http://www.medichem2011.org or contact:

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The **30th Congress**

of the

International Commission on Occupational Health (ICOH)

Monterrey, Mexico

Sunday, March 18 to Friday, March 23, 2012