Newsletter: December 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

Chairman: Dr. Thirumalai Rajgopal
Hindustan Lever Limited
Hindustan Lever House
165/166 Backbay Reclamation
Mumbai - 400 020 (India)
Tel: +91-22-2285 55 83
Fax: +91-22- 2281 91 97

Secretary: Dr. Diane J. Mundt
ENVIRON International Corporation
99 Summer St., Suite 2010
Boston, MA 02110 (U.S.A.)
Tel.: +1-617-946-6100
Fax: +1-617-946-3229

Treasurer: Dr. Steffen Hitzeroth
Procter & Gamble Service GmbH
Sulzbacher Str. 40
65824 Schwalbach / Ts. (Germany)
Tel.: +49-6196-89-5444
Fax: +49-6196-89-2-5444

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Message from the Secretary

Dear Colleagues:

Greetings to you all as we move from 2010 into 2011. I hope it will be a happy and healthy New Year to you and your families.

In this issue, we feature an article about the upcoming June MEDICHEM 2011 meeting in Heidelberg. The organizers have put together an interesting agenda – both scientifically and socially. I hope to see you all there.

And once again – please feel free to contact me at any time with updates or news of interest to the organization.

All the best for 2011.

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

MEDICHEM 2011 --
Time to Register!

A very warm invitation comes from Heidelberg to the MEDICHEM-Family

A high level program of presentations with an A-list of invited speakers, the world famous city of Heidelberg and an attractive social program in the early summer of 2011 – these are some of the attractions waiting for you, the MEDICHEM-Community at the 39th MEDICHEM Congress from 2 – 5 June 2011 in Heidelberg, Germany. A reduced fee of 250 € hopefully meets the desires of our retired colleagues to meet all the old members of their MEDICHEM-Family – Prof. Thiess as honorary president and founder of MEDICHEM will not be the only one who will be very happy to find himself among a great gathering of friends of the last century, including those who were unable to join the congresses in the last years.

The early bird rate for those active in working life is 590 € and is valid until March 15, 2011. Both the retiree and currently employed Congress fees include everything – the scientific program with lunch and coffee breaks throughout the whole congress; an invitation to an excursion of the cradle of MEDICHEM – BASF SE – in Ludwigshafen on Thursday, June 2nd in the morning; the Opening Ceremony, framed by music, with a cold and warm buffet reception on Thursday evening; 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, the 3rd; as well as the Champagne reception at the Castle Gallery, the Gala Dinner in the Castle, and the Giant Firework display on Saturday, the 4th of June, 2011.

January 15 is the date to mark on the calendar for those who would like to share their research findings with colleagues from all over the world, by submitting an abstract. For those who think that the Congress could be a great venue to exhibit and discuss the advantages of their products or to share the work of their companies, please check the Exhibition and Sponsoring Program that is offered at the Congress website www.medichem2011.org. The chair of the organizing team of the Congress and her whole team are looking forward to receiving your registrations and abstract submissions, to answering all questions and to discussing any suggestions. A very warm welcome in the name of the organizing team:

Dr. med. Maren Beth-Huebner,
Heidelberg (Germany)

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MEDICHEM National Occupational Health Award Granted

At the MEDICHEM Board meeting held in Thessaloniki, Greece during October 2009 the Board discussed a proposal for the Austrian Society of Occupational Medicine to provide a NOHA (National Occupational Health Award) at their congress in September 2010 in Villach, Austria. The Board members in attendance unanimously approved this proposal. Details of the NOHA award guidelines were summarized in the March 2010 issue of this newsletter, available on-line at: www.medichem.org.

Congratulations to Dr. Katharina Klien, who was granted the National Occupational Health Award at the annual Austrian Congress in Villach, Austria for her study entitled "The Genotoxic Effects of FeCoB Nanoparticles on Human Fibroblasts Assessed by Comet Assay" (abstract below).

The award of 500 USD was doubled by the board of the Austrian Occupational Society, resulting in a total award to Dr. Klien of 1000 USD and a free MEDICHEM membership for two years. Along with the presentation of Dr. Klien´s study at the Austrian Congress in September, information on MEDICHEM was given in order to promote MEDICHEM in the Austrian Occupational Medicine Society.

Dr. Klien's paper will be published in the "Austrian Journal Österreichisches Forum Arbeitsmedizin (ÖFAM)." The journal is published in German and not Medline accessible, but is widely distributed to all Austrian physicians.

Dr. Robert Winker,
Vienna (Austria)

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The Genotoxic Effects of FeCoB Nanoparticles on Human Fibroblasts Assessed by Comet Assay

Below is the abstract, title above, of the award-winning paper presented by Dr. Katharina Klien to the Austrian Occupational Medicine Society.

Intentionally engineered nanoparticles (NPs) have recently focused researchers' attention on them as epidemiological as well as *in vivo* and *in vitro* studies have supposed their toxicological and genotoxic effects on human cells. Magnetic NPs such as iron cobalt boron (FeCoB) NPs – which were investigated in this thesis – mainly find or may in the future find, applications in medical fields (e.g. tumor targeting or magnetic resonance imaging). This may not only affect patients and consumers coming in contact with NPs but also employees working with nanotechnology where NPs could possibly be released into air.

The aim of the present study was to determine whether genuine FeCoB NPs and two types of surface modified FeCoB NPs, including FeCoB +PAA and FeCoB +L-Cys NPs, with a size of 5-15 nm at three concentrations (0.1, 1.0, and 10 µg/ml) each induce DNA damages in normal human fibroblasts. The exposure time was 48 hours and genotoxicity was assessed by alkaline comet assay, which is a suitable method to register single strand- and double strand-DNA breaks.

The capacity to induce genotoxicity was observed in all three NP types (FeCoB, FeCoB +PAA, FeCoB +L-Cys) which, however, differed depending on the particle surface and the concentration. The

uncoated FeCoB NPs and the coated FeCoB +L-Cys NPs caused DNA damage only at the highest concentration of 10 μg/ml whereas the coated FeCoB+PAA NPs induced genotoxicity at 1μg/ml and 10 μg/ml.

The comparison between the original and the coated NPs revealed that the high concentrations of coated NPs induced more DNA damages than the uncoated NPs of the same composition, implying that the surface chemistry of NPs may play a decisive role in the mechanism of DNA damage. It was further observed that all NP types showed a dose-dependent correlation between NP concentration and genotoxicity, suggesting a dose-dependent manner of concentration.

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Nanoparticles and Pulmonary Damage – Should We Worry?

An article by Song et al. (2009) has created quite a bit of commotion and has been widely cited both in scientific circles and in the public media. Many interpreted it as evidence for the long awaited but hitherto never conclusively demonstrated deadly hazards coming with the use of nanomaterials. This is the abstract of the article:

Exposure to nanoparticles is related to pleural effusion, pulmonary fibrosis and granuloma

(Song Y, Li X, Du X (2009): Eur Respir J 34: 559-567)

Nano materials generate great benefits as well as new potential risks. Animal studies and *in vitro* experiments show that nanoparticles can result in lung damage and other toxicity, but no reports on the clinical toxicity in humans due to nanoparticles have yet been made. The present study aimed to examine the relationship between a group of workers' presenting with mysterious symptomatic findings and their nanoparticle exposure.

Seven young female workers (aged 18-47 yrs), exposed to nanoparticles for 5-13 months, all with shortness of breath and pleural effusions were admitted to hospital. Immunological tests, examinations of bacteriology, virology and tumour markers, bronchoscopy, internal thoracoscopy and video-assisted thoracic surgery were performed. Surveys of the workplace, clinical observations and examinations of the patients were conducted.

Polyacrylate, consisting of nanoparticles, was confirmed in the workplace. Pathological examinations of patients' lung tissue displayed nonspecific pulmonary inflammation, pulmonary fibrosis and foreign-body granulomas of pleura. Using transmission electron microscopy, nanoparticles were observed to lodge in the cytoplasm and caryoplasm of pulmonary epithelial and mesothelial cells, but are also located in the chest fluid. These cases arouse concern that long-term exposure to some nanoparticles without protective measures may be related to serious damage to human lungs.

The women came from farm families living near the factory, received no safety training, and were protected only by cotton face masks, worn occasionally (if ever). The report said they handled paint materials in the factory for eight to 12 hours every day, and for five to 13 months. The women worked in a 70 square meter workshop with a door but no windows. Every day, they put about 6 kilos of polyacrylic paste into a pressure sprayer and sprayed it on polystyrene boards or glass. The pressure used was as high as 100 - 120 KPa. The boards were heated to between 75 to 100 degrees

Celsius, with emissions reportedly vented. However, five months before the women fell sick, the sprayer's vent was broken and the door kept closed to conserve heat.

The exposure situation at the workplace has only poorly been characterized. The exact composition of the spraying emulsion has not been reported and the presence of nanosized objects in the emulsion has not been examined. Thus, no clear picture can be derived of the possible exposures at this workplace. Dust measurements have either not been performed or the results have not been made available. A rough calculation (assuming the total space of the workshop to be approximately 200 m^3) leads to an estimated maximum aerosol concentration of up to 30 mg/m^3 by the end of a workday, enough to produce effects of dust overload. In this given situation the question whether nanomaterials were involved in the process may no longer be important.

This does of course not mean that health problems after an exposure should never be attributed to the fact that this exposure occurred at the nano size. But the problem may not be related to some novel type of toxicity. Recently, another interesting paper was published which may illustrate this thought.

Pulmonary and systemic toxicity following exposure to nickel nanoparticles

(Phillips JI, Green FY, Davies JCA, Murray J (2010): Eur Respir J 34: 559-567)

Nanoparticles are being used in ever increasing numbers in a range of industrial and medical products. Questions surrounding their potential to cause toxic effects in humans have been raised. Although animal experiments predict that nanoparticles are more toxic than their larger counterparts there are few descriptions in the literature of human exposure.

A case described in 1994 has been re-examined from a pathology perspective. The subject, a 38-year-old previously healthy male, inhaled nanoparticles of nickel while spraying nickel onto bushes for turbine bearings using a metal arc process. Although he was provided with a half face mask he was observed to remove it during the spraying process which lasted approximately 90 minutes. Immediately after operating the process he complained of feeling unwell.

The following day he developed cough, shortness of breath and symptoms of a “tight chest.” He died 13 days after being exposed and the cause of death at autopsy was adult respiratory distress syndrome (ARDS). Nickel particles <25 nm in diameter were identified in lung macrophages using transmission electron microscopy. High levels of nickel were measured in his urine and his kidneys showed evidence of acute tubular necrosis.

It was actually interesting to see the results of retrospectively reconstructed nickel air concentrations (up to 380 mg/m^3) and the nickel concentration determined in the urine of the unfortunate victim (780 µg/L). The latter value was as high as the ones reported from several fatal cases of Ni-tetracarbonyl intoxications which occurred in the late fifties of last century in a BASF plant. These cases had developed the same symptoms as the person described in the aforementioned report.

Thus, the assumption of the authors Phillips et al. that “nanoparticles are more toxic than their larger counterparts” appears to be a misconception. It might be rephrased to “nanoparticles show a higher bioavailability and can thus easier elicit toxic effects than the respective bulk materials.”

The cases of both reports, by the way, could probably easily have been avoided by implementation of some basic occupational hygiene measures. And this is what worries me most …

Dr. Michael Nasterlack,
Ludwigshafen (Germany)

Cycloheximide and Teratogenesis, Embryotoxicity and Carcinogenesis

The following article was submitted by Dr. Elpida Nikoloussi, MEDICHEM Board member. Full bibliography available by contacting MEDICHEM Secretary.

Elpida-NN Emmanouil-Nikoloussi and E. Frangou-Massourides; Faculty of Medicine; Aristotle University of Thessaloniki. Greece

Introduction. Cycloheximide [4-{(2R)-2-[(1S,3S,5S)-3,5-dimethyl-2-oxocyclohexyl]-2-hydroxyethyl}piperidine-2,6-dione] and molecular formula $C_{15}H_{23}NO_4$; is a highly toxic agent and a protein synthesis inhibitor that acts specifically on the 60S subunit of eukaryotic ribosomes. It has previously been shown that a short incubation of *Dictyostelium discoideum* amoebae in cycloheximide eliminates fluid phase endocytosis and also some isolates of Chlamydia pecorum from sheep feces failed to produce inclusions on passage in cycloheximide-treated monolayers, (Philips et al. 1995, Clotworthy et al. 2006).

Mitomycin C (MMC) and cycloheximide (CHX) are known for their apoptotic and antitumor activity. Cycloheximide (CHX) is also known for its property to inhibit protein synthesis and to reduce cytotoxicity of various antitumor drugs, i.e. inducing an adaptive survival response (ASR) (Bajic et al. 2005).

Cyclohexamide is involved in the inhibition of truly mitochondrial protein synthesis (Satav et al. 1997). Cycloheximide , as a protein synthesis inhibitor, was studied in breast cancer cell lines. Therefore, studies on breast cancer epithelial cell lines from Mullauer et al. (2000) on Fas (CD95/Apo-1) ligand, which is a cell membrane receptor that upon binding by its ligand (FasL), triggers a signal resulting in apoptotic cell death, includes the application of cycloheximide on those breast cancer cell lines.

Results of this study, indicate that co-treatment of breast cancer cell lines with cycloheximide, which is an inhibitor of protein translation, rendered the resistant cell line sensitive.

Cycloheximide and cellular apoptosis. Cycloheximide (CHX) can contribute to apoptotic processes, either in conjunction with another agent (e.g. tumor necrosis factor-alpha) or on its own. However, the basis of this CHX-induced apoptosis has not been clearly established (Tang et al., 1999).

To determine whether CHX-induced apoptosis was mediated by a Fas-associated death domain (FADD)-dependent mechanism, a FADD-DN protein was expressed in cells prior to CHX treatment. Its expression effectively inhibited CHX-induced cell death, suggesting that CHX-mediated apoptosis primarily involves a Fas-associated death domain (FADD)-dependent mechanism (Tang et al., 1999).

According to Tsuchida et. al (2002), cultured rat astrocytes were incubated in the presence of cycloheximide (CHX) in dosage levels of 20 microg/mL,can operate as a potent neuroprotective agent. Results of this study nevertheless, suggest that although CHX has been shown to be useful as a neuroprotective agent against ischemic neuronal death at dosage level of 20 microg/mL , astroglial toxicity may be problematic, depending on CHX concentration. Therefore, a prudent use of this compound is recommended (Tsuchida et. al 2002).

CHX as a regulator of apoptosis has been studied in astrocytes. An in vitro ischemia model was established and the effect of the metabolic inhibitors cycloheximide (CHX) and actinomycin D (ActD) on apoptosis in astrocytes under ischemia .This study proved that cycloheximide (CHX) can reduce

the expression of bcl-2 (alpha and beta) but can increase bax and Ice expression in astrocytes (Yu et al. 2003).

It is hypothesized that the balance of proapoptotic (Bad, Bax) and antiapoptotic (Bcl-2, Bcl-Xl) proteins determines apoptosis. The data suggest that the ratio of Bcl-2/Bad in astrocytes following ActD and CHX treatment does not decrease as much in untreated cells during ischemia. Data of this study, indicate that it is the ratio of Bcl-2 family members that plays a critical role in determining ischemia-induced apoptosis. It is also important to note that ischemia-induced apoptosis involves the regulation of RNA and protein synthesis (Yu et al. 2003, van Kooten et al. 2006).

In van Kooten et al. (2006) study, a new application for cycloheximide is indicated, as concerning cataract surgery, suggestions were made that the implantation success of accommodating lenses is hampered by the occurrence of capsular opacification (PCO) due to lens epithelial cell (LEC) growth. In order to prevent LEC proliferation, a treatment regime using actinomycin D, cycloheximide and water was developed. The writers conclude that exposure to actinomycin D and cycloheximide, resulted in a lasting inhibition of lens conversion and consequently cell proliferation.

Treatment with actinomycin D containing solutions, however, resulted in a nearly complete absence of cells on the capsular wall. Long-term administration of cycloheximide on rat liver mitochondria resulted in inhibition of total cellular protein synthesis including that of mitochondria while, at short-term intervals, 8-10% of mitochondrial protein synthesis was cycloheximide-resistant. The observed inhibition of mitochondrial protein synthesis by cycloheximide was not due to either inhibition of energy metabolism or alteration of amino-acid pool (Satav et al. 1997).

Kuo et al. (2007) was undertaken a study to identify the requirement of protein synthesis in the learning and memory aspect of the conditioned place preference induced by cocaine and methamphetamine, two abused drugs of choice in local area. Cocaine-induced Drug-induced conditioned place preference (CPP) was mitigated by cycloheximide (15 mg/kg/injection), a protein synthesis inhibitor, pretreatment, whereas methamphetamine-induced CPP remained intact by such pretreatment (Kuo et al. 2007).

Mierzejewski et al. (2006) had performed a similar study in rats with lower dosage levels of cycloheximide (3 mg/kg, s.c./injection), studying the role of cycloheximide in memory protein synthesis and concluded that this process requires de novo protein synthesis. Grummer et al (2000) in their study explore the hypothesis that perturbations caused by ethanol on the regulatory role of retinoids in brain development may be a mechanism involved in the neuropathology of foetal alcohol syndrome and concludes that cycloheximide abolished only the glial fibrillary acidic protein (GFAP) response to ethanol, showing that an interrelationship between ethanol and retinoids exists in the astrocyte and that this interrelationship can be intermediated by cycloheximide.

Oretti et al (1996) suggests that cycloheximide (20 mg/kg body wt, given intraperitoneally at-1 and 3 h after withdrawal of an ethanol-containing liquid diet) prevents the activation of liver tryptophan pyrrolase, the consequent inhibition of synthesis of brain 5-hydroxytryptamine, and the audiogenic seizures observed at 7 h after alcohol withdrawal; suggesting that a rapidly-turning-over protein mediates the alcohol withdrawal syndrome and discuss the possible role of liver tryptophan pyrrolase.

Lary et al (1982) has proved that cycloheximide is teratogenic in litters treated with this and the teratogenic manifestations that produces are polydactyly, oligodactyly, and a variety of skeletal abnormalities including incidence of taillessness, as well as gross malformations and total skeletal

malformations were identified. Prenatal mortality and decreased foetal weights was also observed in treated litters.

Estrogenic expression was also discussed at the abnormalities presented, which several times are resembling the malformations of the studies of Ma et al (1998) and Block et al. (2000). Riter et al. (1982) in their study on acetazolamide and inhibitors of DNA synthesis (hydroxyurea, 5-fluoro-2'-deoxyuridine), RNA synthesis (actinomycin D), and protein synthesis (cycloheximide, emetine), which were each administered to pregnant rats together with caffeine at doses where each agent alone caused minimal embryotoxicity suggest that caffeine co-administered with any of the other agents induced a powerful potentiative response.

According to the writers, is not clear from their study, whether much lower caffeine dosage, as normally encountered in humans, would potentiate embryotoxicity due to other agents. Freddi et al. (2000) have shown that reverse transcription polymerase chain reaction (RT-PCR) was performed on the illegitimate transcripts of accessible cells (lymphoblasts and fibroblasts), which were pre-incubated with cycloheximide to prevent nonsense-mutation-induced mRNA decayin ocular malformartions caused by the molecular basis of Stickler syndrome.

Concerning studies on retina neuronal loss Yoon et al. (2000) suggest that glutamate antagonists, an antioxidant (trolox), or cycloheximide, did not attenuate either vacuolar changes or neuronal loss in retina. Contrary to the current theories, ethambutol-induced retinal cytotoxicity in the present study is mediated not by excitotoxicity or zinc deficiency but by a mechanism requiring intracellular zinc. In addition, features of the ethambutol-induced cell death were not consistent with those of apoptosis (Yoon et al. 2000).

Cycloheximide and estrogen receptors. Estrogen has been closely associated with the genesis and malignant progression of breast cancer. However, the molecular mechanism underlying the effects of estrogen is far from being completely clarified Inoue et al (2004).

Estrogenic expression was also discussed at the expression of cycloheximide producing breast cancer at studies published from Ma et al. (1998) and Block et al. (2000). Swami et al (2000) have studied the estrogen receptor (ER) plays a key role in breast cancer progression and supports that overall suggestions that the antiproliferative effects of 1,25(OH)2D3 and its analogues on MCF-7 cells could partially be mediated through their action to down-regulate ER levels and thereby attenuate estrogenic bioresponses, including breast cancer cell growth.

Estrogens and androgens influence many properties of breast cancer cells; hence, regulation of local estrogen and androgen levels by enzymes involved in steroid hormone biosynthesis and metabolism would impact signaling by these hormones in breast cancer cells (Harrington et al. 2006). UDP-glucuronosyltransferase (UGT) enzyme UGT2B15, a member of the UGT family of phase II enzymes involved in the glucuronidation of steroids and xenobiotics, is a novel, estrogen-regulated gene in estrogen receptor (ER)-positive human breast cancer cells (MCF-7, BT474, T47D, and ZR-75). UGT2B15 is the only UGT2B enzyme up-regulated by estrogen, and marked estradiol stimulation of UGT2B15 mRNA levels is observed, in a time- and dose-dependent manner. UGT2B15 stimulation by estradiol is blocked by the antiestrogen ICI182,780, but not by the translational inhibitor cycloheximide, indicating that UGT2B15 is likely a primary transcriptional response mediated through the ER.

UGT2B15 up-regulation is also evoked by other estrogens (propylpyrazoletriol, genistein) and by the androgen 5alpha-dihydrotestosterone working through the ER, but not by other steroid hormone receptor ligands (Harrington et al. 2006). Treatment of cells with cycloheximide converted the

phenotype of resistant cell lines from Fas-resistant to Fas-sensitive, and enhanced the sensitivity of Fas-sensitive cell lines. These results suggest that the Fas-resistance is dependent on the presence of labile proteins that determine resistance to Fas-mediated apoptosis and the apoptotic machinery is already in place in Fas-resistant cell lines (Kim et al. 2000).

Zhang et al. (2007) examined the steroidal regulation of estrogenic receptors within the mouse uterus with pretreatment with a transcription inhibitor actinomycin D or translation inhibitor cycloheximide. Their study indicates that Estrogenic receptor (2) regulates uterine epithelial cells at multiple points, involving transcriptional and posttranscriptional control as well as modulation of inhibitor activities.

Collectively, these data suggest that E(2) regulates uterine epithelial cells expression and activity in vivo via a complex mechanism. This estrogen regulation of uterus epithelial cells activity may play an important role in uterine tissue remodeling. (c).

The effect of apigenin in increasing alkaline phosphatase (ALP) activity and collagen content was completely prevented by the presence of 10(-6) M cycloheximide and 10-6 M tamoxifen, suggesting that apigenin's effect results from a newly synthesized protein component and might be partly involved in estrogen action (Choi 2007).

Experiments with actinomycin D and cycloheximide suggested that estrogen induction of vascular endothelial growth factor (VEGF) mRNA is dependent on the synthesis of new mRNA and increased mRNA half-life. The antiestrogen ICI 182.780 inhibited E2 stimulation of vascular endothelial growth factor(VEGF), suggesting that the effect was mediated by the estrogen receptor.

Results from Ruohola et al. (1999) suggest that both estrogen and androgen stimulate the expression of VEGF by increasing gene transcription and mRNA stability. In addition, the antiestrogens tamoxifen and toremifene also increased VEGF expression.

Estrogen and androgen induction of vascular endothelial growth factor (VEGF) expression and promotion of new vessel formation may be an important paracrine mechanism by which these hormones contribute to the early phase of tumour growth of hormonal cancer (Ruohola et al. 1999).

Welcome to New Members

Dr. **Sebastien Jotterand**, Merck-Serono (Switzerland)

Dr. **Katharina Klien**, (Austria)

Mark your Calendar!!

2011 MEDICHEM Congress: Occupational Health in a Changing World

Heidelberg, Germany,

2-5 June 2011

Conference fee is inclusive of all program events and meals Conference Fee – 590 Euro; 250 Euro (for retired members)

Heidelberg Marriott Hotel

Special rates of 118 Euro (single); 138 Euro (double), including breakfast buffet if booked before 15 April 2011.

Congress registration and booking information can be found here:
http://cwp.marriott.com/hdbmc/medichem/
Phone: +49 (0)6221 908-692 or +49 (0)6221 908-610

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

Dr. Maren Beth-Hübner
BG RCI
P. O. Box 10 14 80
69115 Heidelberg Germany
Phone: +49 (0)6221 523-400; Fax: +49 (0)6221 523-420; E-mail: medichem2011@bgrci.de