MEDICHEM

NEWSLETTER

March 2008

Obituary in Memoriam of Dr. Leo Djerassi

It is with very deep regret that I have to announce to all Medichem members that our honorary member Leo Djerassi, from Israel, passed away on 11th October 2007.

I received this sad news from his wife Mrs Haia Adam Djerassi; my Christmas letter in December hadn't reached Leo any more. In the name of the Medichem Board and the whole membership I expressed to Mrs Djerassi in January our deep condolences and sympathy.

Medichem and I personally owe Leo deep gratitude. He was a co-founder of Medichem in 1972 and belonged to the first Board. A nice photo from London in the Library of Shell shows him amidst the other Board members. Leo was always deeply engaged within Medichem and organized our 4th Conference in Haifa 1976, the beautiful city of Mount Carmel, literally the vineyards of God. In his opening address he cited "…that the prophet Elisha, closely related to the Carmel and pupil of Elijah carried out the first successful mouth to mouth resuscitation when he raised the dead boy in the prophet's chamber".

180 participants from 18 countries were present and discussed the main topics "Neurotoxicity in the Chemical Industry and Institutional Co-operation in Defining Medical Hazards in the Chemical Industry."

The congress and the social program, with visits to Jerusalem, Nazareth, the Golan Heights, Masada, etc. were outstanding events. Leo belonged to the Board from 1972 to 1987 and was also present on all following conferences, always with a paper presentation or skilled discussions. He brought us in close contact with the difficult situation of his country. To all of us it was obvious that he was not an ordinary person; Leo always had a voice of authority. He was a colleague with a clear incentive mind and represented a "doctor of the old school." Leo Djerassi will remain in the great family of Medichem, a lasting inspiration, he will forever be remembered. For me he was a truly faithful friend. Thank you Leo.

Prof. Alfred Thiess
(Founder and Honorary President of Medichem)

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

Founded 1972 in Ludwigshafen, Germany

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A meta-analysis of occupational trichloroethylene exposure and liver cancer

The most common causes for liver cancer are infections with Hepatitis B or C and leading unhealthy lifestyles - for example smoking or drinking alcohol. Yet, it is furthermore assumed by various physicians that there exists a direct relationship between an occupational exposure to trichloroethylene (TCE) and liver cancer. TCE has been widely used as an industrial solvent and degreasing agent for over 70 years and, although its usage has decreased, it is still present at some workplaces, as for example at aircraft and aerospace industries, electronics industries, dry-cleaning and, in general, in industries that involve metal degreasing. Several studies were conducted about liver cancer and TCE exoosure, but the findings were inconsistent. The aim of this meta-analysis of various studies is to find out, if there actually is a relationship between liver cancer and TCE.

Fourteen occupational cohort studies and one case-control study, which deal with cancer cases in workplaces where TCE exposure may be present or is clearly identified, were chosen. They were then separated into two groups, at which Group I, - consisting of nine studies that identified TCE as a workplace exposure - had a subgroup of eight studies in which the cohorts were clearly exposed to TCE. Group II included five studies that either mentioned TCE, but did not imply any documentation of an actual exposure, or identified TCE, but did not give precise data or consisted of aerospace and aircraft workers, who were presumably exposed to TCE. Summary relative risk estimates (SRRE) were evaluated for primary liver cancer, biliary tract cancer and for liver and biliary tract cancer combined. Meta-analyses were carried out for all 15 studies together and separately for Group I and the eight subcohort studies. The Subgroup was also stratified by occupation, geographic study location and the type of study outcome, for example, if there were incidence or mortality endpoints.

The results for a combined liver and biliary tract cancer in all 15 studies displayed a SRRE of 1.08, whereas Group I had a SRRE of 1.14. Group II showed a SRRE of less than 1.0 and the Subgroup had a SRRE of 1.30. Removing of one or the other study that seemed to have a significant impact on the outcome did not change the overall SRRE. The individual analysis of the Subgroups studies resulted in a SRRE of 0.97 for the US aerospace and aircraft workers and a SRRE of 1.38 for the four European incidence cohort studies, conducted in various industries. This significant difference in relative risk estimates between the US and Europe led to debates if the TCE exposure is higher in Europe than in the US. Assessments of differences in the exposure level showed that the US and Europe have likely similar levels and that generally US standards allow a higher exposure level. The reason for the difference could either be that the European studies used incidence data whereas US studies used mortality data, or the fact that Europeans are more likely to smoke or drink alcohol and that cancer is therefore caused by their lifestyle and not by a TCE exposure. Furthermore most of the studies failed to consistently observe an exposure-response trend. Due to these inconsistencies the meta-analysis can not definitely say, if there actually is a relationship between trichloroethylene and liver cancer.

Int Arch Occup Environ Health (2207) 81:127-143
Dominik D. Alexander et al.

Biological monitoring of occupational exposure to polycyclic aromatic hydrocarbons (PAH) by determination of monohydroxylated metabolites of phenanthrene and pyrene in urine

In addition to a certain amount of exposure to polycylcic aromatic hydrocarbons (PAH) caused by anthropogenic sources as well as by natural

sources, exposure at some industrial workplaces is much higher. When, for instance, looking at sites for the production of coke, graphite electrodes, carbon products, refractories or sites for the distillation of coal tar, it can be assumed and proved that the PAH levels employees are exposed to on these particular sites are much higher than the ones the general population is exposed to normally.
Previously carried out studies had already shown that PAH mixtures which were released unintentionally as well as those materials which were used for industrial production (coal tar, coal tar pitch) showed carcinogenic properties. Thus, many countries (e.g.Germany) started to introduce measurements of the PAH concentration in work place air (ambient monitoring). Yet, it does not seem to be enough to measure the uptake of PAH by inhalation only, but one should also consider measuring the oral and dermal uptake (biological monitoring).
Whereas the marker 1-hydroxypyrene (1-OH-Pyr), an urine metabolite of pyrene (Pyr), had been widely used for biological monitoring within many studies, hydroxylated metabolites of phenanthrene (Phe) have become more popular for these studies recently.

For this particular study, the internal and the external PAH exposure was determined in a number of 255 male workers aged from 19 to 62 years. The workers were exposed to PAH during their working hours in coke production (n=40), production of graphite electrodes (n=92) and production of refractory materials (n=123). Data was assessed via a questionnaire, via air samplers and via post-shift urine samples.
All workers were equipped with personal air samplers for, at least, a period of 2 hours. Acenaphthene, acenaphthylene, anthracene, benz[*a*]anthracene, benzo[*b*]fluoranthene, benzo[*k*]fluoranthene, benzo[*ghi*]perylene, BaP, chrysene, dibenz[*ah*]anthracene, fluoranthene, fluorene, indeno[1,2,3-*cd*]pyrene, naphthalene, Phe and Pyr were measured with the help of these air samplers and the external exposure was thus determined. Additionally, filters and XAD-2 sorbent tubes were used to collect particulate bound and gaseous PAH.
For the internal exposure to PAH post-shift urine samples were collected after a period of three consecutive workdays. The day of collection was the same as the day on which the air measurements took place. PAH metabolites 1,2+9-,3-,4-hydroxyphenanthrene and 1-hydroxypyrene were determined (modified method of Lintelmann and Angerer).
Creatinine and cotinine in the urine were determined photometrically and by gas chromatography.

This study showed a median total PAH exposure and exposure to BaP of 30.62 and 0.27 g/m^3. In all branches the median excretions of 1-hydroxypyrene and hydroxyphenanthrenes (sum) were 6.68 and 11.22 g/g creatinine. The total ambient PAH and the excretion of hydroxyphenanthrenes in urine correlated very closely, whereas Phe metabolites and the carcinogenic BaP did not.
Hydroxyphenanthrenes in urine reflected only an uptake of lowly condensed volatile PAH and not so strongly an incorporation of highly condensed PAH like BaP. Highly condensed PAH should be reflected by 1-hydroxypyrene.A further determination of hydroxyphenanthrenes could, additionally used to the marker 1-hydroxyprene, offer new ways of determination of workplace-related exposures to PAH.
Int Arc Occup Environ Health (2007) 81:221-229
Bernd Rossbach et al.

Evaluation of dermal and protective effectiveness or respirators for xylene in spray painters

The aim of this study was to find out to which degree the exposure dose of xylene and ethyl benzene used for spray painting was dermally absorbed by spray painters and to further find out how effective the use of respirators for the protection of the lungs of spray painters was.

This study was carried out among 18 spray painters who work on a shipyard. In August 2005 these workmen were monitored via reported-measures study design over a 3-day-work period.

The personal exposures to xylene and ethyl benzene inside and outside of masks were tested by using two 3 M model 3500 organic vapor monitors. The workers clipped two samplers to their collars. One sampler was first fixed into the respirator while the worker was spray painting and then, when the respirator was not in use, the sampler was taken out of the respirator and attached to the collar.

Additionally, urine was collected before and after the work shift in order to trace urinary methylhippuric acid (MHA) within it. The urine samples were then stored in plastic bottles and frozen at –20°C until they were finally analysed. The urine concentrations of methylhippuric acid were measured by high performance liquid chromotography (HPLC).

The results of the study showed that wearing respirators could reduce the inhalation of xylene by 96% and the inhalation of ethyl benzene by 94%. Furthermore, big differences between the results of workers who wore their respirators on a permanent basis and those who didn´t could be clearly shown in figures: the geometric WPF for xylene ranged from 2,5 to 279 and for ethyl benzene from 2,2 to 239. Xylene and ethyl benzene concentration inside the masks were 2.09 +- 2.74 and 1.79 +- 2.16 ppm and the median workplace protection factors of respirators for xylene and ethyl benzene were 25.0 and 17.4.

The total urinary MHA concentration was 240.2 +- 42.3 (mean +- SE) mg/g creatinine absorbed with 202.1+- 40.1 mg/g creatinine purely dermally absorbed.
Thus, this study clearly showed that dermal exposure played the major part of the total body burden of solvents and it can therefore be strongly recommended that not only the workers faces and lungs, but also their entire bodies should be protected from the intake of xylene and ethyl benzene. It is also very important that the respirators fit the workers faces to such degree that the lowest possible exposure to xylene and ethyl benzene can be guaranteed.
Int Arch Occup Eviron Health (2007) 81:145-150
Fu-Kei Chang et al.

Production of silicon alloys is associated with respiratory symptoms among employees in Norwegian smelters

This study was carried out in order to develop a qualitative exposure classification of employees in Norwegian smelters, on one hand, and, on the other hand, to further find out which relationship exists between respiratory symptoms and exposure at the workplaces of the employees

The idea behind this study was that Norwegian smelters produces ferrosilicon alloys (FeSi), silicon metal (Si-metal), alloys of ferromanganese (FeMn), silicomanganese (SiMn) and ferrochromium (FeCr), silicon carbide (SiC), titanium (II) oxide (TiO_2), pig iron and calcium carbide (CaC_2). People whose workplace is in and around the smelters are exposed to various forms of air pollution, such as inorganic dusts, organics - like polycyclic aromatic hydrocarbons (PAH) – and various gases, such as nitrogen oxides (NOx), sulphur dioxide (SO_2) or carbon monoxide (CO). These forms of air pollution may harm the airways of the employees working in and around smelters. Connections of a prevalence of respiratory symptoms such as “bronchitis symptoms”, dyspnoea, wheeze, cough and phlegm and workers in smelters had been reported before, but as the numbers of participants in these former studies were rather restricted (less than 200), the outcomes have not been regarded as absolutely significant.

However, the number of participants in this study was 3924. All participants were employees in one of the 24 Norwegian smelters, maintenance or related companies, which are all members of the Federation of Norwegian Industries. The age

of the people ranged from 20 to 55 years. The groups of employees ranged from line operators over non-line operators to non-exposed employees

The forms of assessment of data were spirometry and a self-administered questionnaire. Smelting groups were subdivided into 1) FeSi and Si-metal, 2) FeMn, SiMn and FeCr, 3) Sic and 4) Other. Parts of the emission in this group consisted of TiO_2, CaC_2 and Ceramite.

. The respiratory symptoms during the last year, as they were described in the questionnaire, were: dyspnoe, dyspnoe and wheezing, cough without a cold, cough for more than 3 months and phlegm when coughing.

Further points that were investigated via the questionnaire were familial asthma, previous or current allergy, asthma diagnosed by a doctor, smoking habits and previous occupational exposure to dust, fumes and gases. This questionnaire was a modification of an already existing questionnaire by Kongerud et al.

Data was analysed via the association between each outcome variable (respiratory symptoms) and the relevant covariates (gender, age, category, familial asthma, allergy, doctor-diagnosed asthma, smoking status, job categories and previous exposure).

Then, a multivariate logistic regression model was used with the intention to find out the association of respiratory symptoms and exposure.

For completion a final multivariate model was applied and the analyses of all data was performed by the Statistical Package for the Social Sciences (SPSS Inc., Chicago).

Results proved that the prevalence of respiratory symptoms was higher among employees with previous exposure to dust, fumes or gases compared to employees without any previous exposure whatsoever.

Furthermore, a direct relationship between respiratory symptoms and tabacco consumption was proved. The prevalence of all symptoms was increased in current smokers.

The most interesting fact was that previous exposure was more important and influential than current exposure.

Only “cough for more than 3 months last year” and “phlegm” in the SiMn, FeMn and FeCr production groups showed a direct association between respiratory symptoms and job category.

Even though this study could clearly show a strong relationship between previous exposure and respiratory symptoms, it could not allow a further and detailed investigation of respiratory symptoms and occupational exposure. For this investigation a longitudinal study would be necessary.

Int Arch Occup Environ Health (2008)81:451-459

H. Laier Johnsen

Biomonitoring of two types of chromium exposure in an electroplating shop

The aims of this study were to define the daily variations of chromium (Cr) concentration in urinary samples of employees in an electroplating shop and to clarify if these variations are in a relationship with the Cr exposure. Chromium can be present in the body as Cr (III) and Cr (VI) and especially Cr (VI) can cause toxic effects which may lead to diseases.

Nine volunteers took part divided into two groups. The first group, consisting of four male electroplaters, worked in an adjacent, but separated room to the finishing shop where the second group, consisting of four female brush-operators, were working. One storekeeper, also taking part, was located between these two groups. Pollution extraction systems worked continuously throughout the study operation and aerosol samples were collected on filters attached to the operators. During the seven days of the study 6-7 urine samples were collected per day.

The aerosol measurements showed that in the electroplating shops water soluble Cr (VI) was present in low concentrations, while it was practically undetected in the other workshop. A low concentration in the electroplating and a higher

concentration in the polishing shop was recorded for water insoluble Cr. The total soluble Cr was registered in low concentration in both shops.
The study also included the measurement of the size of the particles, which showed, that the emitted dust is fine enough to reach deep into the lung.
The urinary sampling displayed that the urinary Cr values were at the minimum at the start of the work shift and rose rapidly as soon as the exposure started. At the end of the shift the value was at its maximum. Although the airborne concentration of Cr differed between the workshops, the quantities in the urine of both groups appeared to be closely comparable.

Until now there have almost only been studies about biological limit values of Cr in stainless steel welding, but this new study revealed that the relationships between exposure and excretion are different in electroplating shops. In this case, Urinary Cr is uncorrelated with soluble Cr (VI), but it is effectively related to the soluble fraction of airborne chromium.
Int Arch Occup Environ Health (2008) 81:461-472
Francis Pierre et al.

Evaluation of biomarkers of occupational exposure to toluene at low levels

Toluene, which is present at solvent workplaces, for example at printing or glue-application shops, has a toxic effect on the central nervous system. From earlier studies it is known that hippuric acid in urine (HA-U) is the biomarker of choice with regard to a high occupational exposure to toluene (Tol). The aim of this survey was to find out if this is also true for a low level of Tol, or if un-metabolized toluene in urine (Tol-U) and peripheral blood (Tol-B) would be the better biomarker.

During a period of eight years the survey was carried out at 16 different workplaces on 473 male workers, who were aged 18 – 58 years. Urine and blood samples were taken in the second half of the week at the end of the working shift. To measure the time-weighted average intensity of solvent exposure diffusive samplers were placed on the working uniform of the participants and stayed there during their whole working shift.

The analysis of the samplers showed that the solvent concentration in the workplace air, although it varied, was generally low.
Regarding the evaluation of the biomarker concentrations in urine and blood it turned out that the geometric mean (GM) for HA-U was highest in workplace B, although the Tol exposure was not the most intensive there, whereas in workplace G, with the most intensive Tol exposure the GM was highest for Tol-B and Tol-U. The biomarker concentrations further displayed that in comparison the coefficients were highest for Tol-U and then for Tol-B. Although all three biomarkers had significant coefficients it clearly confirmed that Tol-U is the biomarker of choice for low levels of occupational exposure to toluene.
Int Arch occup Environ Health (2008) 81:253-262
Toshio Kawai et al.

Re-assessment of the influence of polymorphisms of phase-II metabolic enzymes on renal cell cancer risk of trichloroethylene-exposed workers

Due to findings of increased cases of renal cell cancer in trichloroethylene-exposed persons a re-investigation of a hospital-based case-control study (by Brüning 2003) was conducted. This new study was initiated by the assumption that genetic polymorphisms of glutathione S-transferase isoenzymes (GST) may be responsible for differences in the individual susceptibility to trichloroethylene-induced nephrocarcinogenicity. If this is true, it could affect the legal compensation of renal cell cancer patients who had been

occupationally exposed to trichloroethylene in the past. Genes of the glutathione S-transferases GSTT1, GSTM1 and GSTP1 were included in this new evaluation since the respective isoenzymes are present in the renal tissue. Polymorphisms of the NAT2 gene were also taken into consideration because of a potential involvement in the detoxication of reactive trichloroethylene (TCE) metabolites.

The re-assessment was conducted on Brüning's study and two additional control groups. Brüning's study consisted of 134 renal cell cancer cases and 401 non-cancer controls. 99 diseased persons and 325 non-diseased consented to blood sampling. The study was originally carried out to investigate the relationship between occupational exposures to chlorinated solvents, TCE in particular, and the development of renal cell cancer. The two additional control groups were also not diseased. The frequencies of genetic polymorphisms had been determined for these groups. The blood samples were stored at -20°C until DNA isolation, and further, genotyping methods were performed. All three groups had the same age structure.

The results did not suggest that the deletion polymorphisms of GSTT1 and GSTM1 are involved in the renal cancer pathogenesis. The same can be said of the NAT2 rapid/slow acetylator states. Although still not statistically significant, the outcomes showed a higher proportion of the homozygous GSTP1 313A wild type (GSTP1*A). The hypothesis of Brüning, that the deletion polymorphisms of the glutathione S-transferases GSTT1 and GSTM1 have an influence on renal cell cancer development caused by TCE exposure, has not been affirmed. The re-assessment proved that the individual sensitivity to renal cell cancer, due to TCE exposure, is genetically influenced, although many polymorphisms in metabolic cancer susceptibility genes have not shown a consistent role as cancer risk factors, when only main effects were examined. Concluding it can be said that it is not operable to use individual genotyping data for questions of legal compensation concerning occupational TCE-caused renal cancer.

Based on the article of the same title by:
Bernd Wiesenhütter; Silvia Selinski; Klaus Golka; Thomas Brüning; Hermann M. Bolt
Published online: 4th May 2007

Boook Review: Occupational Medicine Case Series

J. Shamsul Bahrin et al, published by SOEM Malaysian Medical Association (2007), ISBN: 978-983-99128-2-1

This book is not a classical textbook, but emerged from case presentations delivered and discussions performed during CME events of the Society of Occupational and Environmental Medicine in Malaysia. It reflects the practical challenges occurring in the daily life of an OM practitioner, well beyond occupational toxicology and questions regarding occupational diseases. Case descriptions, accompanied by photographs and other illustrations, are presented with differential diagnoses and discussed regarding aspects of work-relatedness, eligibility as occupational disease, consequences for employ-ability, etc.

Here, the discussion reflects not always unanimously accepted scientific evidence, but also personal views and inclinations of the authors of the respective chapters. The chapters about mercury poisoning, interstitial lung disease, and organic solvent toxicity might well trigger lively discussions among experts in these fields. However, this is exactly what this book can provide: not tailored solutions that "fit for all", but an incentive to discuss

and further investigate. Not only medical students and postgraduate students of occupational medicine, but also medical professionals working in other specialties – and interested in looking over the "fence line" – can benefit from reading this book and critically re-thinking the reasoning provided therein.

Dr. Michael Nasterlack
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Welcome to new members

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Forthcoming Events

The 36th Medichem Congress **Innovation in Occupational Health** will take place Sept. 10th to 11th in Amsterdam. Deadline for abstract submission is 1 May, 2008.

Preceding the congress, on 8th and 9th September 2008 an Advanced Hazmat Life Support (AHLS) Provider course will be held. This is a 16 hour, two-day course that gives health professionals a timely and effective response strategy in the medical management of hazmat incidents. Participants will receive a four-year verification status upon successful completion of the course.

Find more information and the registration form at http://www.medichem.org/medichem2008.