ISSN 0004-1254

ARHIV ZA HIGIJENU RADA I TOKSIKOLOGIJU

ARCHIVES OF INDUSTRIAL HYGIENE AND TOXICOLOGY

Arh Hig Rada Toksikol • Vol. 63 • No. 2 • pp. 107-246 • ZAGREB, CROATIA 2012

Contents

Cover page:
The cover shows an art graphic by the Croatian computer artist Fabijan Knežević (for more about the artist see Addendum).

FOREWORD TO THE MEDICHEM SECTION

This section brings six articles based on the presentations given at two international meetings in 2011 that were organised by MEDICHEM, the international scientific association for occupational and environmental health in the production and use of chemicals: MEDICHEM 2011 Congress held in June 2011 in Heidelberg, Germany under the motto "Occupational Health in a Changing World" and MEDICHEM Mini Symposium held in November 2011 in Vienna, Austria entitled "Occupational Carcinogens: Exposure Scenarios and Health Risks".

Special thanks go to MEDICHEM Board Chairman, Thirumalai Rajgopal, all Board members, and particularly to Maren Beth-Hübner, chief organiser of MEDICHEM 2011, for accepting the offer of the journal's editors and providing them with the opportunity to ask the Congress participants to submit their congress presentations in the form of manuscripts to be considered for publication in *Archives of Industrial Hygiene and Toxicology*. Extended report on MEDICHEM 2011 by Maren Beth-Hübner is published separately. Furthermore, the help of Robert Winker should also be acknowledged, as he organised 2011 MEDICHEM Mini Symposium in Vienna and extended the same offer of publishing presentations in our journal to the meeting participants.

On behalf of the journal editors, I want to express my gratitude to the authors who submitted their manuscripts to be considered for publication in *Archives of Industrial Hygiene and Toxicology*. By publishing their articles in this theme section, our journal continues to follow the long-standing tradition of its publishing institution, the Institute for Medical Research and Occupational Health (IMROH), Zagreb, Croatia, of being closely connected to the meetings and activities of the International Commission on Occupational Health (ICOH) and MEDICHEM, whose Board acts also as the ICOH Scientific Committee on Occupational Health in the Chemical Industry. These include IMROH's organisation of the ICOH Congress in Croatia 1978 in Dubrovnik, after which Marko Šarić, IMROH's former Director, became an honorary MEDICHEM member. Furthermore, interesting and less known linked fact is that late Birgitta Haeger-Aronsen, who was the first MEDICHEM Secretary in the early 1970s, was also the Corresponding Member of the Department of Medical Sciences at the Croatian Academy of Science and Arts in Zagreb. More recently, in January 2007, IMROH hosted the mid-term meeting of MEDICHEM Board members. This event was followed by a jointly organised half-day Mini Symposium, which embraced professional and scientific presentations from both sides: MEDICHEM Board members and IMROH's researchers.

Last but not least, special gratitude in publishing MEDICHEM papers in this issue goes to the following Board members, who are also the journal's Advisory Board members, for their valuable assistance in connecting MEDICHEM 2011 Congress and Mini Symposium delegates to our journal, as well as for their active participation in writing and/or reviewing the MEDICHEM theme part of this issue, first and foremost to Michael Nasterlack, as well as to Robert Winker, Diane J. Mundt, and Stephen W. Borron.

Archives of Industrial Hygiene and Toxicology looks forward to participating in future MEDICHEM activities.

Martina Piasek,
Guest Editor to the MEDICHEM section

DOI: 10.2478/10004-1254-63-2012-2211

Scientific paper

ANALYSIS OF PROTEIN ADDUCTS AS BIOMARKERS OF SHORT-TERM EXPOSURE TO ETHYLENE OXIDE AND RESULTS OF FOLLOW-UP BIOMONITORING*

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Received in January 2012
CrossChecked in May 2012
Accepted in May 2012

An accidental exposure of six workers to ethylene oxide (EO) provided the rationale for a biomonitoring and follow-up study, whose aim was to analyse protein adduct kinetics and examine the differentiation between accidental and environmental exposure, e.g., from tobacco smoke. For this purpose, the decrease in the concentration of the haemoglobin adduct *N*-2-hydroxyethylvaline (HEV) was followed during a five-month period after the accident, together with *N*-2-cyanoethylvaline (CEV) and urinary cotinine, two well-established biomarkers for smoking. The follow-up study showed that EO adduct concentrations significantly increased after a short but presumably high exposure. Initial biomonitoring revealed HEV levels above 500 pmol g^{-1} globin in all cases, with a maximum of about 2,400 pmol g^{-1} globin. This compares to a German EKA value (exposure equivalent for carcinogenic substances) for a daily 8-h-exposure to 1 ppm EO of 90 µg L^{-1} blood (~3,900 pmol g^{-1} globin). The adduct levels dropped in accordance with the expected zero-order kinetics for a single exposure. After the five-month observation interval, the HEV concentrations in blood reflected the individual background from tobacco smoking. The results of this study show that even a short exposure to ethylene oxide may result in a significant rise in haemoglobin adduct levels. Although protein adducts and their occupational-medical assessment values are considered for long-term exposure surveillance, they can also be used for monitoring accidental exposures. In these cases, the calculation of daily 'ppm-equivalents' may provide a means for a comparison with the existing assessment values.

KEY WORDS: *accidental exposure, haemoglobin adduct kinetics, occupational exposure*

Ethylene oxide (EO) is an important chemical intermediate mainly used for the synthesis of ethylene glycol and its ethers, ethoxylates, ethanolamines, polyoles, and polyesters, or for sterilisation purposes (1). Its acute toxic properties comprise moderate irritation of the eye, the mucous membranes, and the upper respiratory tract with typical symptoms of exposure being headache, dizziness, nausea, and vomiting. EO is a known animal carcinogen and a suspected human carcinogen (2, 3). Due to its hazardous potential, ethylene oxide is usually handled and reacted in closed systems. Its use for sterilisation purposes, e.g., in hospitals and in the production of sterile disposable medical equipment, is strictly controlled in Germany by technical guidelines, and biological monitoring is recommended for health surveillance (4-7).

Ethylene oxide is readily absorbed either by inhalation or through the skin (skin notation). The main metabolic pathway of EO involves a hydrolysis

* Partly presented at the 39th International MEDICHEM Congress on Occupational and Environmental Health in the Production and Use of Chemicals "Occupational Health in a Changing World", Heidelberg, Germany, 2 - 5 June 2011

of the epoxide to yield ethylene glycol and a subsequent sequential oxidation to oxalate, formiate and carbon dioxide, or an enzymatically mediated conjugation to glutathione to form *S*-2-hydroxyethyl mercapturic acid (8, 9). In addition, ethylene oxide binds spontaneously to nucleophilic acids in proteins, namely to haemoglobin in blood. One of these covalently bound addition products, or 'adducts', is the N-terminal *N*-2-hydroxyethylvaline (HEV), a well-established biomarker for ethylene oxide exposure (10-12). In Germany, the Senate Commission for the Investigation of Health Hazards in the Work Area of the German Research Foundation (Deutsche Forschungsgemeinschaft - DFG) has established so-called 'exposure equivalents for carcinogenic substances' (EKA), which describe the correlation between ethylene oxide concentrations in air and HEV concentrations in blood (13). A confounder for this biomarker is smoking, as ethylene oxide is a metabolite of ethene in tobacco smoke (14-16). While nonsmokers usually show HEV levels below 75 pmol g^{-1} globin, levels up to 550 pmol g^{-1} globin are observed in blood samples from smokers (17). One specific aspect in the interpretation of adduct biomonitoring is the fact that assessment and reference values are based on steady-state concentrations. These are achieved only after a regular exposure for at least 120 days, which corresponds to the average life-span of the erythrocytes (18-21). Under constant exposure conditions, the adduct levels continue to increase during this interval until the equilibrium between daily increment of adducts and erythrocyte breakdown has been reached. While protein adducts are valuable markers of a long-term integrated dose, measurement and interpretation of adduct levels after intermittent or single exposures have not yet been well established. In the context of isolated accidental exposures, it would also be interesting to see if the decline of adduct levels follows the expected linear function until the baseline level, e.g., associated mainly with regular smoking habits, has been reached after 120 days. In this case, an extrapolation of adduct concentrations, which were measured weeks or even months after the exposure, would be both possible and advantageous, as it offers a broader time-frame for sample collection than most other biomarkers.

In a study following an accidental exposure of six workers to ethylene oxide in a chemical plant, we investigated the degradation kinetics of the haemoglobin adduct HEV during a period of five months. Furthermore, we calculated the additional exposure following the accident and developed an approach for the interpretation of adduct levels after single or short-term exposures. As the individual background levels from tobacco smoking are to be considered for HEV interpretation, urinary cotinine and *N*-2-cyanoethylvaline (a haemoglobin adduct of acrylonitrile in tobacco smoke) were analysed (17, 22, 23).

MATERIALS AND METHODS

Study group and ethylene oxide exposure

Six male workers from a chemical plant were accidentally exposed to ethylene oxide outside the building. About 40 kg of liquid EO were released through an open valve and evaporated into the surroundings. While there were no specific data available on the concentration of EO in air, the nearby gas alert system was activated, thus indicating that several hundred ppm of EO were detected in the vicinity of the building. Taking into account that the open valve was shut after 2 to 3 min and that a mobile measuring station did not detect any airborne EO after about 15 min, the maximum exposure time of six workers was estimated to be 15 minutes. Immediately after the accidental exposure, the workers were taken care of in the out-patient clinic of the Occupational Medicine & Health Protection Department of the company.

Biomonitoring

Blood and urine samples were collected in the out-patient clinic one day after the accident and thereafter on a monthly basis over a five-month interval. Blood samples were drawn into regular EDTA-containing disposable syringes (Monovettes®, Sarstedt, Germany). The erythrocytes were separated from the plasma fraction by centrifugation (800 × g, 5 min) and washed twice with isotonic saline (addition of 0.9 % sodium chloride, centrifugation, removal of saline) until the supernatant was colourless and clear. The original sample volume was then restored by addition of ultrapure water, while the erythrocytes were lysed by this procedure. To monitor exposure to ethylene oxide and to the tobacco smoke contaminant acrylonitrile, the haemoglobin adducts *N*-2-hydroxyethylvaline (HEV) and *N*-2-cyanoethylvaline (CEV) were quantified in these samples. The protein adduct analyses were carried out in an accredited and

certified contract laboratory (Currenta, Leverkusen, Germany) essentially following a procedure described by van Sittert et al. (17). Globin was isolated from the haemolysates by fractionated precipitation. The dried protein was then subjected to the so-called 'modified or N-Alkyl-Edman method' (10): the adduct-bearing N-terminal amino acid (HEV, CEV) was cleaved off of the protein chain and simultaneously derivatised with pentafluorophenyl isothiocyanate into a thiohydantoin. It was then extracted with diethyl ether, evaporated to dryness, and reconstituted in toluene. Subsequently, the samples were analysed by gas chromatography-mass spectrometry (GC-MS) in the electron impact mode.

Spot urine samples were collected in parallel to the blood specimens in 100 mL polystyrene containers. The nicotine metabolite cotinine was analysed in these samples in the biomonitoring laboratory of the Occupational Medicine & Health Protection Department at BASF SE, Ludwigshafen, Germany, according to a method described by Müller et al. (24). Urine samples were alkalised with sodium hydroxide solution and extracted with dichloromethane after the addition of 2-benzylpyridine as internal standard. The extract was then analysed by GC-MS in the electron impact mode using selected ion monitoring. The method has been tested and certified within several round-robin tests of the German External Quality Assessment Scheme (G-EQUAS, c/o Institute of Occupational, Social and Environmental Medicine of the University of Erlangen-Nuremberg). To correct for diuretic variance, urinary creatinine was analysed by an HPLC-UV method (25) in the BASF laboratory. This parameter was also successfully certified within the G-EQUAS program.

Data processing and calculations

All calculations were carried out with either the Microsoft® Office Excel 2003 software package or with IBM® SPSS® Statistics 19.0.

RESULTS

Four of the six workers exposed to ethylene oxide reported moderate acute effects: mild irritation of the mucous membranes and the upper respiratory tract, dizziness, shortness of breath, cough, and headache. Lung function testing of one worker revealed a slightly reduced peak flow. Two workers with pulmonary symptoms received intravenous corticoids for lung oedema prevention according to the established medical guidelines (26) and stayed in a clinic overnight for observation. Four days after the accidental exposure, two workers still reported general weariness and one of them felt a sunburn-like itchy feeling on some parts of his skin. All observed effects had completely resolved by the time the first follow-up biomonitoring investigation was carried out, four weeks after the accident.

As individual smoking habits are an important factor for further interpretation of the adduct levels of exposure to ethylene oxide, two biomarkers of tobacco smoke, urinary cotinine and haemoglobin adduct CEV, were analysed in order to confirm the self-reported smoker status of the employees (Table 1). Cotinine biomonitoring results for all self-reported smokers (study participants 1, 2, 3, 5, and 6) were always high above the reference values (95th percentiles) of 16 µg g^{-1} creatinine for never-smokers and 53 µg g^{-1}

Table 1 *Results of N-2-cyanoethylvaline and cotinine analyses (-- no sample collected, n.d. not detectable, S smoker, NS nonsmoker)*

Worker	Biomarker	Sample 1	Sample 2	Sample 3	Sample 4	Sample 5	Sample 6	Average
1 (S)	CEV / pmol g^{-1} globin	212	192	204	94	--	106	162
	cotinine / µg g^{-1} creatinine	--	--	--	1,459	--	2,649	2,054
2 (S)	CEV / pmol g^{-1} globin	114	102	94	69	106	90	96
	cotinine / µg g^{-1} creatinine	--	2,086	1,766	2,126	1,989	2,247	2,043
3 (S)	CEV (pmol g^{-1} globin)	147	147	106	53	114	69	106
	cotinine / µg g^{-1} creatinine	--	6,244	1,577	752	1,132	3,879	2,717
4 (NS)	CEV / pmol g^{-1} globin	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.
	cotinine / µg g^{-1} creatinine	--	16	15	10	15	--	14
5 (S)	CEV / pmol g^{-1} globin	200	167	155	49	188	131	148
	cotinine / µg g^{-1} creatinine	--	1,073	678	432	709	2,045	987
6 (S)	CEV / pmol g^{-1} globin	131	118	94	69	139	82	106
	cotinine / µg g^{-1} creatinine	--	--	734	181	893	1,485	823

creatinine for ex-smokers (Third German Environmental Survey) (27). Many samples showed cotinine levels above 1,000 μg g^{-1} creatinine, these results being well in the range of typical smokers. The German Federal Environment Agency reports a cotinine median of 998 μg g^{-1} creatinine and a 95th percentile of 3,340 μg g^{-1} creatinine for a representative sample of smokers (n=1,605) (27). The individual smoking status was further confirmed by the CEV analyses: all adduct levels were above 50 pmol g^{-1} globin, whereas nonsmokers normally show CEV levels below 10 pmol g^{-1} globin (13). Only one worker (study participant 4) declared himself a nonsmoker and biomonitoring results confirmed this: CEV was not detectable in blood samples of this employee and the cotinine levels were between 10 μg g^{-1} and 14 μg g^{-1} creatinine. Both tobacco smoke related biomarkers showed a distinct intra-individual variation during the study interval, with a larger variability of the short-term biomarker cotinine (average: 53 %) as compared to the protein adduct CEV (average: 30 %).

The results of the initial and follow-up biomonitoring of HEV in the six workers are summarised in Table 2. The adduct levels observed one day after the accidental exposure (four days in one case) ranged between 522 pmol g^{-1} and 2,396 pmol g^{-1}. Every worker provided five more samples in the following four months (one sampling time was missed by study participant 1), however not always strictly according to the scheduled 30-day intervals. Nevertheless, the follow-up data showed the expected decline in individual HEV concentrations until the sixth sampling, which took place after 162 days (166 days in one case). The smokers still showed HEV levels in a range between 151 pmol g^{-1} and 276 pmol g^{-1} globin at the end of the study; this is consistent with typical smoker values as reported, for example, by van Sittert et al. (17), Bader et al. (16) and Schettgen et al. (22). This also confirms the results of biomonitoring for urinary cotinine and CEV. In contrast, the nonsmoking employee revealed an HEV level of only 30 pmol g^{-1} globin. According to Törnqvist et al. (28), background levels of HEV in nonsmokers are probably associated with ethene production by intestinal bacteria. Typical HEV levels in nonsmokers are below 50 pmol g^{-1} globin (16, 17, 22).

Due to the average life-span of human erythrocytes of about 120 days, the final HEV concentration of every individual more than 160 days after the accidental exposure was regarded as the tobacco smoke and intestinal ethene related background. This value was therefore subtracted from the initially measured adduct concentration in order to calculate the impact of the additional accidental exposure on HEV levels (Table 3). According to the German EKA values for ethylene oxide, a daily exposure to 1 ppm (1830 μg m^{-3}) EO corresponds to an HEV level of approximately 3,900 pmol g^{-1} globin under steady-state conditions (13), which in turn reflects the average exposure of 60 working days (12). Therefore, an increment of 3,900/60=65 pmol g^{-1} per 8-h-exposure day can be calculated and used to derive 'ppm-equivalents' from the adduct concentrations related to accidental exposure. Following this approach, the adduct levels of the exposed workers correspond to 5 to 36 'ppm-equivalents'.

To analyse adduct kinetics, the initial HEV results were individually adjusted to 100 % after subtraction of the respective background values (Figure 1). A cubic fit (R^2=0.950, $p<0.001$) was applied in this case

Table 2 *Results of N-2-hydroxyethylvaline adduct analyses (-- no sample collected)*

Worker	Biomarker	Sample 1	Sample 2	Sample 3	Sample 4	Sample 5	Sample 6
1	days post-exposure	1	5	28	84	--	166
	HEV / pmol g^{-1} globin	1,961	1,849	1,573	513	--	164
2	days post-exposure	1	28	55	85	140	162
	HEV / pmol g^{-1} globin	522	418	284	259	259	207
3	days post-exposure	1	28	55	85	127	162
	HEV / pmol g^{-1} globin	771	694	440	332	272	233
4	days post-exposure	1	28	55	85	127	162
	HEV / pmol g^{-1} globin	2,396	1,862	1,082	560	142	30
5	days post-exposure	4	28	55	85	127	162
	HEV / pmol g^{-1} globin	642	595	315	319	332	276
6	days post-exposure	1	5	55	85	127	162
	HEV / pmol g^{-1} globin	970	965	392	319	220	151

Table 3 *Initial, tobacco smoke and accidental exposure related HEV concentrations and calculation of 'ppm-equivalents' (ppm-equivalents calculated by dividing the additional accidental exposure by the daily increment of 65 pmol g^{-1} globin × day)*

Worker	HEV / pmol g^{-1} globin first sample	HEV / pmol g^{-1} globin last sample	HEV / pmol g^{-1} globin accidental exposure	ppm-equivalents
1	2,396	30	2,366	36
2	1,961	164	1,797	30
3	970	151	819	13
4	771	233	538	8
5	658	276	382	6
6	522	207	315	5

to visualise the reduction of adduct concentrations and its confidence interval. It is noteworthy that after more than 120 days the HEV values were still higher than the final background values (>160 days). This was also the case with the nonsmoking study participant, thus pointing to a fraction of exposed erythrocytes with a longer than average life-span. According to the assumption of a constant adduct decline following zero-order kinetics during the first 120 days (12, 21), all adjusted HEV results between initial biomonitoring and 130 days post-exposure were subjected to a linear regression analysis (Figure 2). The resulting linear fit was y (% of the initial HEV concentration after a single exposure) = - 0.81 (0.68 to 0.94) × (days post-exposure) + 95 (86 to 104) (with R^2=0.865, p<0.001, numbers in brackets = 95 % confidence intervals). According to this equation, the concentration of HEV after one-time exposure decreases constantly at a rate

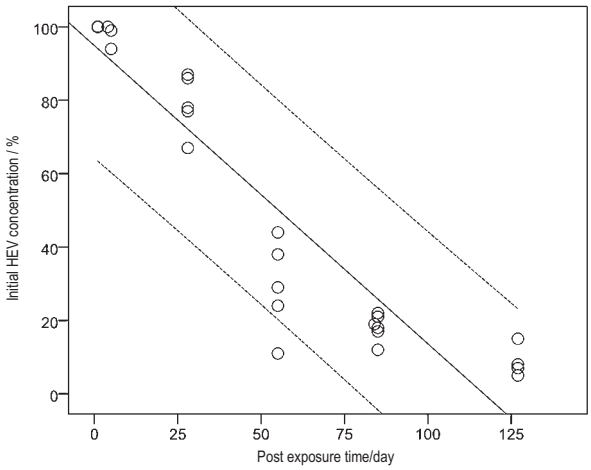

Figure 2 *Linear regression fit of ethylene oxide adducts during the first 130 days post-exposure (y = -0.81 × (days) + 95, R2 = 0.865, p < 0.001; HEV adjusted for background exposure and related to initial adduct concentration)*

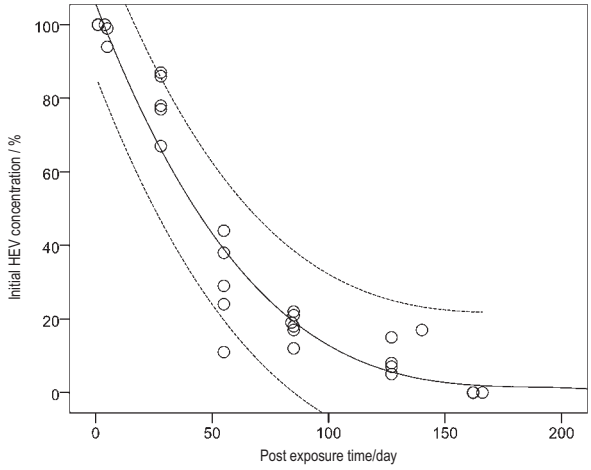

Figure 1 *Time-course of ethylene oxide adducts (cubic fit and 95 % confidence intervals, y = -1.647 x + 0.009 x^2 – 0.00002 x^3 + 106, R^2 = 0.950, p < 0.001; HEV adjusted for background exposure and related to initial adduct concentration)*

of 0.81 % of the initial value per day until the background level is reached after 95/0.81=117 days (or 123 days, in case only the slope of the curve is considered).

DISCUSSION

Six workers of a chemical plant were exposed during a period of approximately 15 min to vaporous ethylene oxide. Although no data on the exposure intensity were available, a rough estimate was made that about 40 kg of liquid EO were released and vapourised rapidly. Ethylene oxide is heavier than air and its distribution within a radius of 50 m and up to a height of 5 m (~39,270 m^3) would result in a mean concentration of about 1,000 mg m^{-3} or 500 ppm,

respectively. This estimated concentration is far above the previous German Technical Guideline Concentration (TRK) for EO of 1 ppm and would explain why the gas alert system in the vicinity of the leak was triggered. Also, the irritative effects and pulmonary symptoms experienced by four workers are consistent with a short but high exposure to ethylene oxide (2).

First of all, ethylene oxide adducts were monitored in order to identify exposed workers and to provide a quantitative measure for the exposure intensity. As the initially measured adduct concentrations were considered to be fairly high in relation to the short exposure time, follow-up biomonitoring was implemented and adduct kinetics was studied to confirm the association of adduct concentrations with the accidental exposure. It was assumed that additional adduct levels would attenuate in a linear fashion down to background levels within 120 days, in accordance with zero-order kinetics (12, 21, 29). While the constant decrease of haemoglobin adducts after a single, or accidental, exposure can be estimated on the basis of the known life-span of erythrocytes, reports on this aspect from human *in vivo* studies are scarce (30, 31). In theory, a single exposure to ethylene oxide during one work shift leads to the formation of covalently bound and chemically stable adducts to erythrocyte haemoglobin in the blood. The total erythrocyte population in humans at a given point in time comprises an equally distributed number of cells between one day and a maximum of 120 days of age, which is the typical life-span of an erythrocyte. After the exposure event, the adducts are removed together with the haemoglobin and erythrocytes at a theoretical rate of 1/120x100=0.83 percent per day until, after about 120 days, all adducts associated with the single exposure have been eliminated. In the case of ethylene oxide adducts, nonsmokers as well as smokers reveal a distinct adduct background due to endogenously formed ethene from intestinal bacteria or from ethene in tobacco smoke, respectively (10, 28, 32). Follow-up biomonitoring in this study has provided new *in vivo* human data to support the above-mentioned toxicokinetic considerations. As can be seen in the Figures 1 and 2, the elimination curve can reasonably be described with a linear fit during the first three post-exposure months, while the attenuation curve seems to level off near the end of and beyond the 120-day interval. As the erythrocytes' life-span may vary to a certain degree, the asymptotically extended curve may be due to a fraction of older erythrocytes with haemoglobin adducts from the accidental exposure. Nevertheless, the linear decline during the first post-exposure months points to an almost complete elimination after about 120 days (range: 101 to 140 days), which is in very good accordance with expected kinetics. In an earlier study by Bader and Wrbitzky (31), a somewhat longer average elimination phase of 148 days was observed for acrylonitrile adducts. However, the database in that investigation was smaller than in the study presented here, as it comprised only samples from four individuals and three sampling times during the 120-day interval.

In this study, urinary cotinine and the acrylonitrile adduct CEV were analysed alongside with the ethylene oxide adducts. Both biomarkers were monitored in order to confirm the self-reported smoker status, but also to provide a measure for constant or changing smoking behaviours of the study participants. While both biomarkers showed a relatively large variability, the results can be interpreted in the way that individual smoking habits of the participants did not change significantly during the study interval. Therefore, the results of the last HEV analyses after about 160 days can reasonably be regarded as the individual adduct background values of the study participants. In one case (worker no. 1), the result of one HEV determination was available from a general survey three months before the accidental exposure. This earlier adduct level was 224 pmol g^{-1} globin as compared to the 164 pmol g^{-1} globin found 166 days after the accidental exposure. The variation of the mean value of these results (30 pmol g^{-1} globin=15 % of the 194 pmol g^{-1} globin mean value) is within the range of the analytical uncertainty of the adduct method. It seems reasonable to assume that both values reflect the same adduct background associated with cigarette smoking and the endogenous exposure.

Another important aspect of linearity of the adduct attenuation curve is that it allows for a back-calculation of the initial post-accidental adduct levels from samples collected several days or weeks after the exposure. The validity of this approach relies, however, on the exposure intensity. As the analytical method has an imprecision of about 12 % (17), the additional adduct formation related to exposure should be at least higher than ~25 % of the background value, otherwise it may go undetected. Therefore, it seems advisable in the case of an accidental exposure to collect at least two samples, one in connection with the exposure and one after the 120-day interval in order to distinguish between additional and background exposure. If the first sample is significantly higher

than the background value, considering the analytical imprecision, an extrapolation to the initial adduct concentration is warranted. Although increased adduct levels may be observed still weeks and even months after the exposure, in particular when the exposure was high, the collection of blood should be carried out as promptly as feasible.

A particularly difficult and yet untackled question is the assessment of adduct concentrations after single or accidental exposures. Current assessment values for adducts such as the EKA of the German DFG are based on the assumption of a steady-state condition, which is reached only after at least 120 days of exposure. Provided, e.g., that an individual is exposed to a similar ethylene oxide concentration for 8 hours a day, the adduct levels will accumulate and rise with a certain daily increment which is reflective of the daily absorbed dose. However, older erythrocytes are also removed constantly from the blood stream. Therefore, a steady-state is achieved only after one life-span of the erythrocytes (120 days) has elapsed, and the corresponding adduct level reflects the cumulative dose of 60 exposure days, or 60 daily increments (12, 21). The German EKA value for a daily exposure to 1 ppm ethylene oxide is 90 µg L^{-1}, or a rounded 3,900 pmol g^{-1} globin (13). Therefore, a daily (8 h exposure) increment or 'ppm-equivalent' of 3,900/60=65 pmol g^{-1} globin can be calculated and used for the assessment of single or accidental ethylene oxide exposures.

In the current study, the initial adduct levels are equivalent to an 8-h-exposure of workers to 5 to 36 'ppm-equivalents'. Considering the 15-min exposure interval (1/32 of an 8-h-shift), these equivalents correspond to a short-term exposure of 160 ppm to 1152 ppm (300 mg m^{-3} to 2000 mg m^{-3}) a value well in line with the estimated EO concentration as discussed above on the basis of the released material, and also in accordance with the activation of the facility's gas alert system. Additionally, acute toxic effects of ethylene oxide as described by the workers are plausible for a short-term exposure to several hundred ppm EO.

In conclusion, the biomonitoring follow-up study has confirmed theoretical considerations on adduct kinetics in humans and enabled the evaluation of 'ppm-equivalents' for the assessment of short-term exposure incidents. This approach may further assist in a more widespread and extended application of protein adduct analysis for the monitoring of exposure to carcinogenic substances, including short-term accidental exposures, with the most significant practical advantage of offering a broad time frame for sampling.

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Sažetak

ANALIZA PROTEINSKIH ADUKATA KAO BIOMARKERA KRATKOTRAJNE IZLOŽENOSTI ETILEN OKSIDU I REZULTATI BIOMONITORINGA

U radu su prikazani rezultati biomonitoringa provedenog neposredno nakon akcidentalnog izlaganja šestorice radnika etilen oksidu i studije praćenja (*follow up*) provedene u cilju procjene kinetike razgradnje proteinskih adukata i utvrđivanja razlika nakon kratkotrajne izloženosti i izlaganja čimbenicima iz okoliša kao što je duhanski dim. U tu smo svrhu tijekom petomjesečnoga razdoblja nakon nezgode pratili smanjenje koncentracije hemoglobinskog adukta *N*-2-hidroksietilvalina usporedo s mjerenjem razina *N*-2-cijanoetilvalina i kotinina u mokraći, koji su pouzdani biomarkeri za dokazivanje pušenja duhana. Studija praćenja je pokazala da su koncentracije adukata etilen oksida značajno porasle nakon kratkotrajnoga izlaganja visokoj razini etilen oksida. U početnom biomonitoringu svih radnika izmjerene su razine *N*-2-hidroksietilvalina iznad 500 pmol g^{-1} globina, s maksimalnom vrijednošću od oko 2400 pmol g^{-1} globina. Ti su podaci usporedivi s vrijednostima njemačkih normi ekvivalenata izlaganja kancerogenim tvarima (EKA) od 90 µg L^{-1} krvi (~3900 pmol g^{-1} globina) kroz osmosatno dnevno izlaganje koncentraciji od 1 ppm etilen oksida. Razine adukata smanjile su se u skladu s očekivanom kinetikom nultoga reda za jednokratno izlaganje. Koncentracije *N*-2-hidroksietilvalina izmjerene u krvi radnika nakon petomjesečnoga praćenja mogu se povezati s njihovim osobnim pušačkim navikama. Rezultati toga istraživanja pokazuju da čak i kratkotrajna izloženost etilen oksidu može znatno povisiti razine adukata hemoglobina. Premda se u zdravstvenom nadzoru u okviru medicine rada proteinski adukti i njihove vrijednosti razmatraju u procjeni dugotrajnoga izlaganja, oni se mogu koristiti i za praćenje akcidentalnih izlaganja. U tim slučajevima izračun dnevnih vrijednosti (tzv. ppm-ekvivalenata) može poslužiti za usporedbu s postojećim procijenjenim vrijednostima.

KLJUČNE RIJEČI: *akcidentalna izloženost, kinetika adukata hemoglobina, profesionalna izloženost*

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DOI: 10.2478/10004-1254-63-2012-2200

Professional paper

WORKER PROTECTION DURING MERCURY ELECTROLYSIS CELL PLANT DECOMMISSIONING*

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Received in January 2012
CrossChecked in May 2012
Accepted in April 2012

This article brings information on how to protect worker health during the decommissioning of mercury-based electrolysis facilities. It relies on the Euro Chlor document "Health 2, Code of practice, Control of worker exposure to mercury in the chlor-alkali industry" that provides protection guidelines for both normal production and decommissioning activities, and on hands-on experience gained during chlor-alkali plant decommissioning operations.

Decommissioning and dismantling of mercury-containing chlorine production plants presents challenges to industrial hygiene and health protection that are usually not present during normal operations. These involve meticulous training and enforcement of the appropriate use of personal protective equipment to prevent excessive mercury exposure.

The best practice guidelines and recommendations available from Euro Chlor can help employers and occupational physicians to manage these challenges, as they provide state-of-the-art procedures. Our experience is that rigorous implementation of these procedures and worker training ensured acceptable hygiene at the workplace and prevented mercury-related adverse health effects.

Key words: *chlor-alkali industry, chlorine, industrial hygiene, medical surveillance*

Chlorine production usually involves three processes using either mercury, diaphragm, or more recently, membrane technologies (1). Mercury has been used since the 19th century, even though no new mercury plant has been built since the 1980s due to the hazards of mercury for human health and the environment. Euro Chlor, a professional organisation representing the European chlorine producers, has agreed a voluntary commitment with its members to shut down European chlor-alkali mercury electrolysis plants by 2020 at the latest. Further to this agreement, several plants have switched to the membrane process. At the same time, many mercury plants have been decommissioned and others will follow in the near future.

The aim of this article is to provide information on how to protect worker health during the decommissioning of mercury-based electrolysis facilities. It is based on the feedback from recently decommissioned plants, as Euro Chlor has not yet identified published data from decommissioning mercury electrolysis plants.

Mercury-based chlorine production plants use large amounts of mercury to produce chlorine; about 100 t of mercury is used to produce 50,000 t of chlorine. Heavy exposure is imminent unless workers use efficient means of prevention and protection (2-4).

In practice, occupational safety at mercury-based electrolysis plants has been improving steadily over

* Partly presented at the 39th International MEDICHEM Congress on Occupational and Environmental Health in the Production and Use of Chemicals "Occupational Health in a Changing World", Heidelberg, Germany, 2 - 5 June 2011

the last decades, so much so that exposure to mercury and individual mercury body burden are usually kept below the applicable limits (5). However, exposure can be much higher during decommissioning than during normal production. The amount of mercury creating this exposure represents the "difference to balance", which is the difference between the quantity of mercury in the waste sent to deposit and in the products (chlorine, hydrogen, caustic soda) and the quantity of mercury added to the electrolysis cells in order to maintain a constant amount in the process. It may have been deposited on girders and other materials for decades, and only be mobilised during dismantling or decommissioning operations. At these moments, mercury air concentrations may exceed the Occupational Exposure Limit (OEL) of 20 μg m^{-3} by a factor of 10 to 20.

The pattern of exposure is also different. During production, exposure is generally stable, while during decommissioning, exposure can vary significantly from one day to another. This puts a lot of strain on managing exposure.

The best way to assess mercury exposure in occupational medicine is by biomonitoring, where urinary mercury measurement is the method of choice. During normal operations, urinary mercury in workers slowly increases for several months until it reaches steady-state. During decommissioning, we once observed a result breaching limit values after only three working days.

Euro Chlor has published a document named "Health 2, Code of practice, Control of worker exposure to mercury in the chlor-alkali industry". It focuses on occupational health and industrial hygiene aspects in running mercury-based electrolysis plants (6). This article follows its structure and brings additional information and hands-on experience specific to decommissioning.

Organisation and management

Decommissioning is not simply destroying a plant; it must be planned properly. A written policy is required which includes a system for health management of mercury-related processes with continuous improvement as far as it is possible during the months, sometimes more than a year, necessary to remove everything that has been contaminated by mercury. Obviously, this policy for decommissioning is different from that used during production. It should contain the names, responsibilities and tasks of each technician, and their mobile phone numbers. It should also provide details about and responsibilities of the plant's physician and each contractor's physician.

Laboratories which measure mercury in air and urinary mercury should have high quality control procedures. They should participate in a national or international quality control scheme to maintain reliable results (7).

Regarding the medical department, a policy should be established to handle medical surveillance when the physician or nurse is absent due to holidays or for any other reason. Workers should know to whom to refer to in case of a problem.

Health hazards and personal hygiene standards

It is important to provide workers with sufficient information on mercury toxicity. Pregnant women must be excluded from work where there is a risk of exposure to mercury.

The risk of acute mercury exposure is usually not relevant while the electrolysis cells are running. During decommissioning however, this risk is real. One of the procedures that may involve high exposure is blowtorch cutting of steel that has been contaminated by mercury for years.

Chronic risk is under control in normally operating electrolysis plants in developed countries, as exposure is more or less stable. Again, decommissioning brings the risk of much higher and more varied exposure.

Workers should receive specific training in personal hygiene and adopt efficient working and housekeeping practices, including decontamination procedures. In exposed areas, workers should always wear proper work clothing. This includes disposable unwoven overalls. Our experience in several plants tells us that workers should change their overalls each time they stop working, which means two overalls in the morning and two in the afternoon. Obviously, work clothes should never be brought home but washed on site to ensure that wastewater is properly treated.

Changing facilities should be separated into "clean" and "dirty". Dining facilities should be located in clean areas. Additional facilities may be necessary for extra workers during the dismantling period. They should be designed to allow easy cleaning. All areas should be washed with bleach every day.

Smoking materials like cigarettes, pipes or tobacco should never be carried in work clothes, because they might become contaminated and lead to additional inhalatory mercury exposure, if smoked.

Taking a shower is necessary at the end of each work shift, one before lunch and one at the end of the day.

Footwear should be impervious to mercury and resistant to corrosives such as caustic soda. Gloves should also be impervious to mercury and replaced on a regular basis; they should never be carried in the pockets; leather gloves are out of question. Respirators should be stored in a mercury-free environment and decontaminated properly after each use.

Biomonitoring of mercury exposure

The method of choice for individual monitoring of mercury exposure is the determination of mercury in urine, adjusted to urinary creatinine concentration (8). Mercury in ambient air cannot reliably predict individual mercury uptake (5). Mercury in blood mainly reflects organic mercury uptake, primarily resulting from dietary exposure to fish (9).

Workers should be taught how to give urine samples and should be aware of exposure limits, medical surveillance programme, and biological monitoring. During decommissioning, they should receive each urine test result with a medical comment.

Urinary mercury should be tested more often during decommissioning than during production due to the higher level of exposure. Weekly testing is recommended, not only for personnel working in the cell rooms, but also for those handling contaminated waste.

Samples should be taken at approximately the same time of the day. A sample taken before starting work or after showering at the end of a shift is preferred to minimise the risk of sample contamination.

Baseline testing is necessary before decommissioning begins and the last test should take place after decommissioning activities are over to see whether workers have ever been overexposed between these two time points.

Table 1 shows courses of action related to the measured mercury urinary levels during normal plant operation and decommissioning.

More rigorous rules recommended in the latter case take into account the possibility of a very quick increase in urinary mercury levels. For example, with a weekly monitoring frequency, a case has been observed where, starting from a level below 35 μg g^{-1} creatinine, one week later the urinary mercury excretion had increased to 105 μg g^{-1} creatinine. An early intervention performed in this case most likely helped to prevent strong mercury effects. Clinical signs of mercury exposure do not usually occur in workers with urinary mercury below 300 μg L^{-1}, except in case of renal disease (10). This level corresponds to around 200 μg g^{-1} creatinine, as urinary creatinine is generally around 1.5 μg L^{-1} (0.3 μg L^{-1} to 3 μg L^{-1}). A new worker would reach the level of 25 μg g^{-1} creatinine after six to 15 weeks of exposure and the level of 35 μg g^{-1} creatinine between nine and 33 weeks. In all our cases, the results dropped below 35 μg g^{-1} creatinine soon after the end of exposure.

Monitoring mercury in air

Eight-hour urinary measurements should be performed according to European regulation. Results are to be expressed as time-weighted average and compared to the OEL of 20 μg m^{-3} (11).

Because systematic measurements during a demolition process are difficult to perform and unexpected exposure to mercury can happen, it is advisable to have portable equipment to do frequent spot measurements of mercury concentration in air.

These measurements proved to be most helpful in practice. Air mercury was measured three times a day. As expected, it would increase by the afternoon (Figure 1) and was also higher on sunny than on cloudy days. In fact, air mercury levels correlated with the temperature recorded at the nearby weather station (Figure 2).

Table 1 *Action requirements according to urinary mercury findings*

Urinary mercury / μg g^{-1} creatinine		Management action
Normal operation (ref. 6)	**Decommissioning**	
<30	< 25	no action
30 to 50	25 to 35	review of employee work practice
>50	> 35	remove from exposure to mercury until below 30 μg g^{-1} creatinine

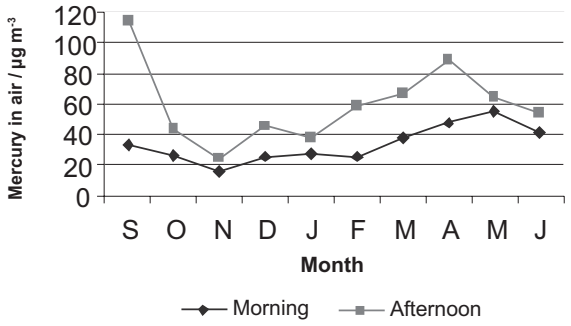

Figure 1 *Morning and afternoon mercury air concentrations measured over the ten months of decommissioning in 2007-2008*

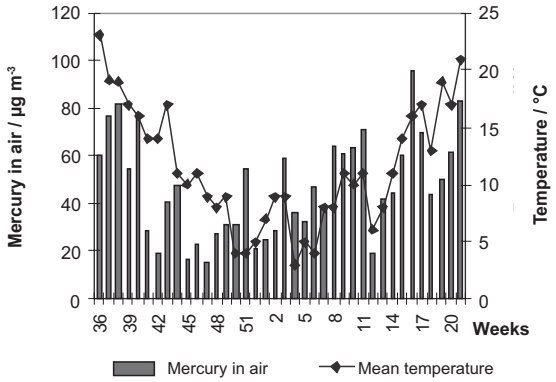

Figure 2 *Mercury air concentrations and mean temperature over the ten months of decommissioning (Weeks = week of the year)*

Thanks to these observations, the work shift was rescheduled to begin at 5 a.m. and end early to avoid the hottest hours. To explain this organisational change the workers were presented with the mercury air measurements.

Further to these observations, it is recommended not to do decommissioning during the summer, or at least avoid activities with the highest exposure potential.

In addition, mercury air measurements have shown that mercury levels rise with the number of decommissioning operators who happen to stir it up with their activity. Therefore each area has a limitation put on the number of workers allowed.

Risk assessment and management

Each step of dismantling has to be assessed, in particular the differences from regular production. As some activities have a higher exposure potential than others, the plant management should make sure that the workers are aware of these. This particularly refers to cutting with a blowtorch, whereas washing presents the lowest exposure risk.

The first assessment of the contamination should involve examination of the area for mercury droplets. Washing the most contaminated places usually requires large amounts of water. Covering mercury with water is useful as it limits evaporation.

What follows risk assessment is taking precautions to protect workers. As a rule, the use of personal protective equipment will be indispensable in several dismantling operations. However, without an efficient prevention plan, personal protective equipment may not be sufficient. This plan should be published in an understandable way and available to all.

Health examination and health-related actions in case of overexposure

Exposure to high levels of inorganic mercury vapour mainly results in nephrotoxicity and neurotoxicity (12, 13). Occupational medical surveillance should be sensitive enough to detect early signs of toxicity in these organ systems.

At pre-placement examination, the examining physician has to be aware that the worker will be exposed to mercury. The aim of this examination is to establish the baseline levels for new workers and for third-party contractors. In some cases, a contracted company could be specialised in demolition, and the workers may have been exposed to mercury before without knowing it.

Beside the regular medical examination and tests, the baseline examination should include urinary mercury analysis and the history or clinical signs of renal insufficiency and neurological or psychiatric disturbances as exclusion criteria. In the EU, urine mercury levels in occupationally unexposed persons are usually less than 5 µg g^{-1} creatinine (14).

Similar to biomonitoring, the last examination after dismantling operations are over is to establish whether there are signs of mercury toxicity.

Between these two time points, examination is due whenever overexposure is suspected or documented. The first objective of this intermittent examination is to establish the current health status of the exposed person. The second is to provide a new information to the affected person by the physician or the nurse. The third objective is to discuss the real working conditions in a one-on-one conversation with the worker in order to identify potential shortcomings in the current operations which the worker might otherwise address in the presence of a manager.

Information, training, record keeping, and auditing

The training should address all the topics covered so far. Results from the audits should also be communicated to the workers. This should be done using a language and in a way understandable to all the workers. It should be repeated in case of overexposure or modification of the working process.

Every worker should sign a training participation list, which is to evidence that all decommissioning workers have been properly informed of the exposure risks and countermeasures.

Records should be kept for medical surveillance, for future medical research, and for handling insurance claims or lawsuits for several decades. They should be organised so that an outside body could understand how the processes were managed. The knowledge related to the hazards, hygiene, biomonitoring, and risk assessment is so valuable that it should not fade when all European mercury electrolyses have been decommissioned.

At least an internal audit system is necessary to monitor and continuously improve the working conditions. The *Euro Chlor document Health 6, Audit questionnaire mercury* is being updated to take include the specificities of dismantling operations (15).

CONCLUSION

Decommissioning and dismantling of mercury-containing chlorine production plants poses to industrial hygiene and health challenges usually not present during normal operations. The best practice guidelines and recommendations available from Euro Chlor help employers and occupational physicians to manage these challenges through state-of-the-art procedures. Experience gathered during decommissioning operations has confirmed that rigorous implementation of procedures and communication with the involved workers successfully maintained acceptable workplace hygiene and helped to avoid mercury-related adverse health effects.

Acknowledgements

We thank Jean-Pol Debelle and Shaun Presow, both from Euro Chlor, for their helpful comments and support in preparing this manuscript.

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Sažetak

ZAŠTITA RADNIKA TIJEKOM GAŠENJA POGONA ZA ELEKTROLIZU POMOĆU ŽIVE

Cilj je ovoga rada pružiti informacije o načinu na koji se može zaštititi zdravlje radnika kod gašenja pogona u kojima se obavlja elektroliza pomoću žive. U ovu je svrhu korišten dokument Euro Chlor-a *Zdravlje 2, Pravilnik, Kontrola izloženosti živi kod radnika koji rade u kloralkalnoj industriji* (eng. *Health 2, Code of practice, Control of worker exposure to mercury in the chlor-alkali industry*) kao podloga: navedeni se dokument odnosi na redovitu proizvodnju, ali i na aktivnosti gašenja pogona. Preporuke koje su ovdje dane podupiru i iskustva koja su stečena i prikupljena tijekom radnji gašenja kloralkalnih postrojenja.
Gašenje i rastavljanje klornih proizvodnih postrojenja koja sadrže živu izazovi su za higijenu rada i zdravlje koji inače ne postoje kod redovitih poslova. Ako ne postoji odgovarajuća izobrazba u svezi s korištenjem odgovarajuće zaštitne opreme te ako se takve mjere ne provode rigorozno, može doći do prekomjernoga izlaganja živi.
Smjernice i preporuke za najbolju praksu koje se nalaze na stranicama Euro Chlor-a mogu pomoći poslodavcima i liječnicima medicine rada u suočavanju s navedenim izazovima. Pri tome im stoje na raspolaganju vrhunski suvremeni postupci. Naše osobno iskustvo stečeno tijekom gašenja takvih postrojenja navelo nas je na zaključak da stroga provedba ovakvih postupaka uz odgovarajuću komunikaciju s radnicima omogućuje održavanje primjerene higijene na radnom mjestu i sprječava nuspojave vezane za živu.

KLJUČNE RIJEČI: *higijena rada, kloralkalna industrija, klor, zdravstveni nadzor*

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DOI: 10.2478/10004-1254-63-2012-2212

Professional paper

PSYCHOSOCIAL RISKS IN THE WORKPLACE: AN INCREASING CHALLENGE FOR GERMAN AND INTERNATIONAL HEALTH PROTECTION*

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Received in February 2012
CrossChecked in May 2012
Accepted in March 2012

Occupational health in a changing world has to face up to psychosocial risks to protect the health of employees now and in the future. Faster production, service and communication processes, a service- and knowledge-based society, an increasing proportion of intellectual work, growing complexity of work-related demands, new technologies and constant availability, mobility demands, and job insecurity contribute to the problem of psychosocial risks in the workplace. Psychosocial risks affect both physical and psychosocial health. There is scientific evidence of the link between psychosocial work-related stress and cardiovascular diseases, affective disorders or musculoskeletal disorders, especially chronic back pain.

The Framework Directive on Safety and Health makes it very clear that employers are obliged "to ensure the safety and health of workers in every aspect relating to work". In spite of these far reaching obligations, a kind of taboo sometimes makes it hard to focus on topics that have psychosocial implications. A large number of models, instruments and methods are now available to gauge psychosocial risks in the workplace. Given the clear contrast between knowledge and application, there is not a lack of knowledge in this regard, but rather a lack of application.

In Germany, statutory accident insurance institutions are guided by two key principles: putting prevention before rehabilitation and rehabilitation before compensation. To prevent work-related health risks the BG RCI has developed several prevention tools to help employers and employees deal with psychosocial risks in the workplace.

KEY WORDS: *affective disorders, cardiovascular diseases, musculoskeletal disorders, work-related stress*

Good old times and brave new world?

Psychosocial risks in the workplace and the increasing challenge these present for health protection was not only the subject of intensive discussions at last year's MEDICHEM congress in Heidelberg, Germany, on 2-5 June 2011. In fact, experts all over the world agree that occupational health in a changing world has to face up to psychosocial risks to protect the health of employees now and in the future. An expert forecast by the European Agency for Safety and Health at Work identified emerging psychosocial risks, such as work intensification or high emotional demands at work (1). When comparing the working conditions of 20, 50 or 100 years ago with the situation today, most people would also agree that psychosocial risks, such as time pressure, interruptions in the work

* Partly presented at the 39th International MEDICHEM Congress on Occupational and Environmental Health in the Production and Use of Chemicals "Occupational Health in a Changing World", Heidelberg, Germany, 2 - 5 June 2011

flow or work-family conflicts, have increased. Nearly 50 percent of the 20,000 people in gainful employment selected on a representative basis in Germany indicated that "stress and work pressure" have increased. One in six even said that they "often had to work to the limits of their ability" (2).

When we compare our stressful times with the working conditions of the "good old days" we may sometimes wish we worked some 50 years ago. Nevertheless, we should be careful not to glorify the old times too much. In the "good old days", many accidents happened. Health protection was therefore there to save lives by preventing accidents. In Germany and in other parts of the world, we have been very successful in preventing accidents in recent decades. Today, the challenge of our time - and of the future - seems to be the prevention of psychosocial risks.

Psychosocial risks in the workplace are sometimes called "soft factors". In a way, this description is suitable because there are indeed some difficulties in measuring them. There is no technical device that can be put into a factory or any kind of building indicating that there are "2,500 square meters of stress" or "four tons of mobbing". But most of us would agree that these so-called "soft factors" can have very hard implications.

Essentials of this brave new world

There are many parts to this problem. Some of the factors underlying psychosocial risks were dealt with at the European Union conference on "Promoting mental health and well being in workplaces" (3). In short, the conference summarised the following aspects that contribute to the problem of psychosocial risks in the workplace:

- Faster production, service and communication processes
- Increasing proportion of intellectual work
- Trend towards a service- and knowledge-based society
- Growing complexity of work-related demands
- New technologies and constant availability
- Mobility demands and job insecurity
- Instability in social relationships

If everything seems to be faster than before - production, service and communication processes - it comes as no surprise that many people are shorter of breath in a psychosocial sense. If work-related demands appear to be more complex - and social and emotional demands form a core part of a wide variety of jobs these days - the health implications are consequently more complex as well.

If constant availability is a condition *sine qua non*, then the idea of going home and relaxing after work is becoming more and more of a pipedream. New technologies ensure we are available regardless of where we are. And just switching off the mobile phone could be a big mistake if we want to climb the career ladder or - more modestly - just want to keep our jobs. Following the rules of our time, we therefore all of a sudden have to move to another town - and once we feel settled, we might have to move to another, as flexibility seems to be the credo of this brave new world.

Definition and facts: psychosocial risks affect both physical and psychosocial health

The following definition describes psychosocial risks as "those aspects of work design and the organisation and management of work, and their social and environmental contexts, which have the potential for causing psychological or physical harm" (4).

Psychosocial risks affect both physical and psychosocial health. The link between psychosocial work-related stress and health problems has been a subject of global discussion since the early 1980s and has been proved using various work-related stress models. There is substantial evidence that psychosocial risks can lead to hypertension and cardiovascular diseases. The job strain model by Karasek and Theorell (5) as well as the effort-reward imbalance model by Siegrist (6) inspired a great amount of research that produced significant results highlighting the link between psychosocial risks and cardiovascular diseases.

High job demands combined with low job control must be considered a risky combination. Evidence has shown that there is a higher risk of becoming ill if a person's workload is high and there is little he/she can do to manage it effectively (7). The power of social support was integrated into this paradigm in the later stages of research (8). This showed that social support is a health resource - and that we are put at even greater risk if no social support is available.

Based on the effort-reward imbalance model, Siegrist (9) and other researchers showed that a so-called gratification crisis can also lead to a higher risk of cardiovascular diseases. Gratification crises emerge if we work hard and are committed - but no one seems to notice. Esteem is an important part of the salutogenic

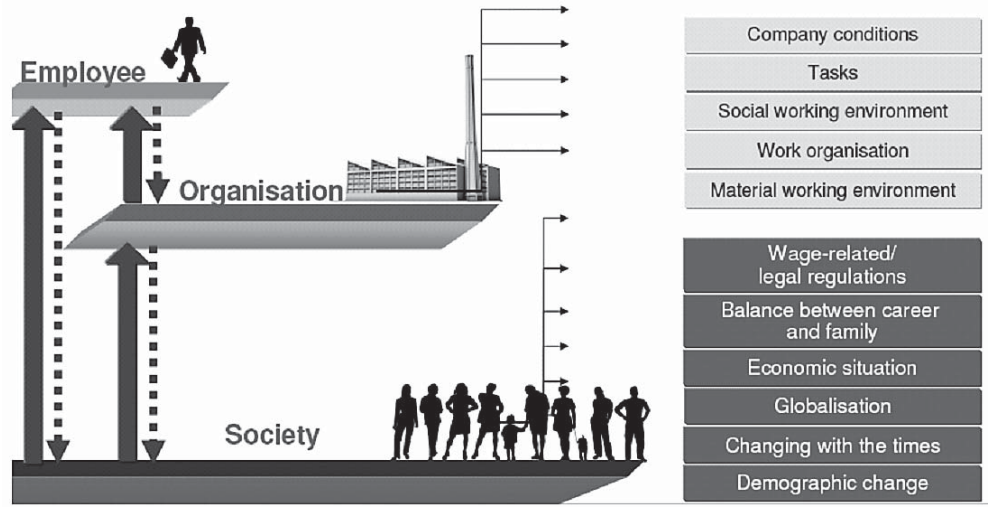

Figure 1 *Three-level model of mental workload (19)*

power of work. High effort combined with low reward is undoubtedly a serious risk.

There is therefore scientific evidence of the link between psychosocial work-related stress and cardiovascular diseases and affective disorders (6, 10). There is also a strong link between high work intensity, low job security, and a lack of social recognition on the one hand, and depression on the other (11). The increase in psychosocial risks at the workplace is closely linked with an increasing prevalence of mental disorders in Germany (12) and throughout Europe. In 2011, the BAUA (Bundesanstalt für Arbeitsschutz und Arbeitsmedizin) reported for Germany that 11.4 percent of sick leave days are due to mental disorders such as depression and anxiety. Of course, this increase does not derive solely from problems in the workplace, as mental health disorders usually develop from multifactorial causation. Nevertheless, psychosocial risks in the workplace often play an important part in the processes leading to anxiety, burnout or depression (13).

There is also a link - and a very complex relationship - between musculoskeletal disorders, especially chronic back pain, and psychosocial factors (14). There is also evidence of the impact of psychosocial factors, especially in later stages of the pain process. When forced to feel pain again and again, the power of catastrophising thoughts can be huge, activating the vicious circle of chronic pain and thereby leading to a close relationship between chronic pain and mood disorders such as depression.

The quality of scientific research into psychosocial risk and health has improved significantly in the last ten years (for example, comprehensive longitudinal studies, use of objective health indicators), to the extent that there is no longer any doubt as to the existence of a causal link between psychosocial work-related stress and health (15, 16).

Is working bad for your health? Is working good for your health?

Can we therefore say that "working is bad for your health" today?

When asking this question, we must be careful to consider the health situation of the unemployed as well. In these cases, being out of work seems to be much worse than working (17). For example, Wacker & Kolobkova (18) identified strong links between unemployment and health problems or negative self-esteem. Generally speaking, having a job seems to be consistently better for your health than not having a job, particularly in the long term (19) (Figure 1).

There is sufficient evidence to suggest that, under the right conditions, work can be good for your health in a number of ways (20). The right working environment lets people show what they are capable of and is therefore a positive factor (21). In a good working environment, employees are also given the resources they need, including organisational and social resources (20). Organisational resources include a variety of tasks, complete activities and opportunities for participation. Social resources include a good working environment, staff oriented management behaviour and social support.

It is also interesting to remember what Sigmund Freud said when asked what a healthy human being should be able to do. He answered: "To love and to

work". In a similar vein, Alexander von Humboldt wrote that work was just as basic a need as eating and sleeping. Even today, working still has a high salutogenic potential. We therefore need to take a closer look at what factors have the potential to cause psychological or physical harm. But sadly, agreeing on this point does not necessarily translate into practice.

A kind of taboo

Occupational health and safety professionals from different companies agree that it is very important to deal with psychosocial risks in the workplace. On the other hand, the answers vary greatly. When asked how much emphasis is placed on psychosocial factors in the workplace, different companies seem to have different approaches - the majority pay little to medium attention to the topic while only a minority pay great attention to psychosocial risks in the workplace. Why is this?

As shown in the three-level model (22), interaction between the individual, the organisation and society is very complex. Individual thoughts and feelings have not yet been dealt with as key themes for occupational safety and health. Over time, most working people encounter some problems concerning some aspects of their working situation, but not all of them want to talk about these problems. This kind of taboo sometimes makes it hard to focus on topics that have psychosocial implications. Corporate decision-makers sometimes hope to get to grips with the topic with low-threshold measures based on the motto: "Wash me but please don't get me wet!" (23). Enterprises and employers who are not willing to deal with psychosocial risks argue that either the individual or society - or both - is the cause of the problem. This is correct in part, as long as the enterprise also admits to playing a crucial part in the mix. In this case, it is important to identify the psychosocial risks in the workplace and ask what can be done about them.

The European perspective: Framework Directive on Safety and Health

European legislation states that this is exactly what needs to be done. The Framework Directive on Safety and Health makes it very clear that employers are obliged "to ensure the safety and health of workers in every aspect relating to work".

The general principles of prevention aim to avoid risks or to evaluate risks that cannot be avoided, thereby combating the risks at source. "Developing a coherent overall prevention policy that covers technology, organisation of work, working conditions, social relationships, and the influence of factors relating to the working environment" - these are the far-reaching obligations that form the basis for a holistic health management system that goes far beyond individual training courses.

Where and when to act?

There's nothing wrong with seminars on stress management or communication. Studies show that cognitive-behavioural stress training is very effective and successful (24). The key is to take action on both

Where to act?	And when to act?	
	Preventive	**Corrective**
Individual level	Seminars on stress management Communication training courses Team training Leadership training	Dealing with (mental) health disorders
Organisational level	Risk assessment on psychosocial risks Health management Health policy / culture	Rehabilitation management

Figure 2 *Where to act and when to act: preventive and corrective, on both individual and an organisational level (25).*

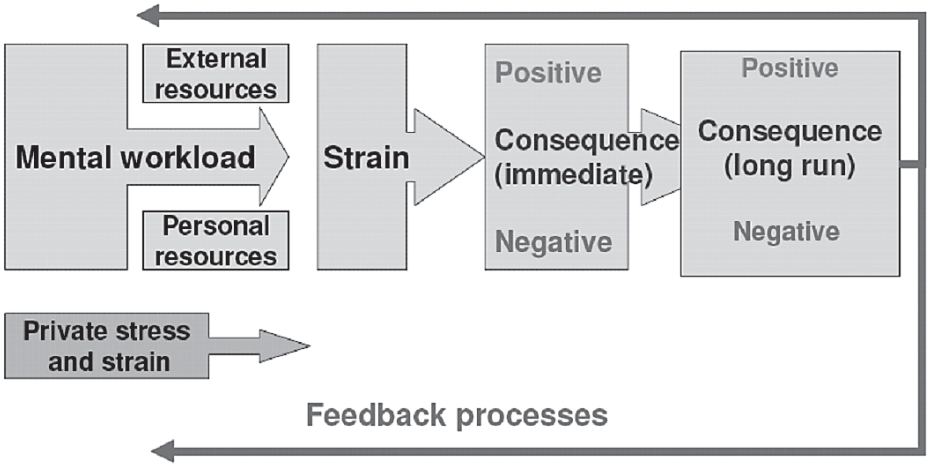

Figure 3 *Mental workload and strain - DIN EN ISO 10075 (30)*

individual and organisational level (25) (Figure 2). Risk assessments should form the starting point for systematic health management (26, 27). Preventive action is usually more effective and less cost-intensive than corrective action. Nevertheless, dealing with mental health disorders, especially systematic rehabilitation management, is an essential part of modern health protection. One step ahead of mental disorders are support systems provided by some firms enabling their employees to get in touch with psychological experts anonymously and in the strictest confidence. Today Employee Assistance Programs (EAP) have become common among many firms but no matter how effectively they may work - they can only be one part of the whole of the preventive approach as set out in the cited European legislation.

Knowing that risk assessment of psychosocial risks is both a legal obligation and a matter of management intelligence, it is interesting to take a look at how far we've come in Germany in integrating psychosocial risks in the risk assessment of occupational health and safety. A survey of works councils (28) showed that just 20 percent of larger businesses with a works council and at least 20 employees take into account psychological stress in their risk assessment. In the case of smaller businesses, a survey of owners showed that this figure is much lower, at just six percent (29).

Although traditional aspects of health and safety seem to be taken into account, psychosocial risks appear to have been largely forgotten or deliberately neglected.

What can be done? To overcome the aforementioned taboo, it is useful to take a closer look at how mental workload is defined and which aspects of the workload strain process should be factored into the risk assessments of modern workplaces.

Mental workload and strain

To achieve the essential aim of preventing health risks, mental workload factors must be analysed and evaluated alongside the humanised design of work.

Mental workload is defined in a European and an international ISO standard. Mental workload is described as "the sum of all assessable influences acting on a human from external sources and affecting it mentally" (DIN EN ISO 10 075-1).

According to this neutral and far-reaching definition of mental workload and its possible consequences, there can be both short-term and long-term consequences that can be either positive or negative (30) (Figure 3).

The advantage of this standardised model is that the psychosocial factors can be taken out of the "taboo zone" and we can explain both positive and negative outcomes. Nevertheless, possible causes of mental overload or underload and appropriate measures need to be addressed.

What to do? Contributions of German Statutory Accident Insurance institutions

Most employers must continue - or maybe even start - getting to grips with these demanding tasks. International organisations such as the World Health Organization (WHO) and the International Labour Organization (ILO) are trying to help (31, 32). In Germany, the Joint German Occupational Safety and

Health Strategy ("Gemeinsame Deutsche Arbeitsschutzstrategie", GDA) is currently focusing on the challenging task of dealing with mental workload and psychosocial risks.

A large number of models, instruments and methods are now available to gauge psychosocial risks in the workplace (33-35). Given the clear contrast between knowledge and application, we can - and must - therefore no longer talk about a lack of knowledge in this regard, but rather a lack of application.

The "Berufsgenossenschaft für Rohstoffe und chemische Industrie" (BG RCI) is the Institution for Statutory Accident Insurance and Prevention for Raw Materials and the Chemical Industry in Germany. It is part of the comprehensive social security system in Germany. The Statutory Accident Insurance institutions in Germany are public-law bodies - institutions whose legal authority derives from public law ("Sozialgesetzbuch VII" (36) is a part of the German Social Code). They are different, for example, to private-law institutions such as associations. The legal basis for such institutions is the BGB (Civil Code).

Industrial institutions for statutory accident insurance and prevention have the statutory duty to prevent occupational accidents, occupational diseases and work-related health risks. We provide comprehensive assistance to companies in all occupational safety matters, train insured employees, investigate causes of accidents, and test technical equipment (37).

BG RCI insures 1.3 million employees and is responsible for 36,000 companies of various sizes. The three main tasks of statutory accident insurance institutions in Germany are:

1. To prevent accidents, occupational diseases and work-related health risks.
2. To treat and reintegrate victims of accidents or diseases.
3. To pay benefits in the event of a permanent reduction in earning capacity.

Statutory accident insurance institutions are guided by two key principles: putting prevention before rehabilitation and rehabilitation before compensation. To prevent work-related health risks, the BG RCI has developed several prevention tools to help employers and employees deal with psychosocial risks in the workplace.

In the field of adult education, the BG RCI offers large training centres at four locations where you can learn everything you need to know about health and safety, promotion of occupational health, explosion protection, machine and plant safety, personnel management, communication, and much more besides. Insured persons can attend a wide variety of seminars and workshops at attractive locations throughout Germany. Topics at these workshops and seminars include leadership, stress management, communication, moderation, working together, mobbing and mediation, risk assessment, and many others.

People can also specialise in psychological topics and work towards a certificate which they can obtain by attending a few psychological seminars and heading up an occupational project on psychosocial factors in their own enterprise. They are supported by occupational psychologists from the BG RCI. Qualified multipliers who improve prevention at their enterprises are another important piece of the puzzle. They are necessary if psychosocial risks are to be prevented in the workplace.

Last but not least, people can also ask for counselling to find the right strategy to deal with psychosocial risks in their own specific working environment. The BG RCI's psychologists are happy to help them find the right psychosocial solutions for the specific circumstances of their own enterprises.

CONCLUSION

In conclusion, when it comes to psychosocial risks in the workplace, I believe…

- enough is known – now we have to act.
- we have to focus on working conditions and the organisation and management of work in a social context.
- we need to act at organisational level, including systematic approaches to leadership, health and safety management and organisational development.
- we need interdisciplinary cooperation between psychological, medical and technical experts.
- we need to talk about our experiences and learn from one another.

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Sažetak

PSIHOSOCIJALNI RIZICI NA RADNOM MJESTU: RASTUĆI IZAZOV ZAŠTITE ZDRAVLJA U NJEMAČKOJ I SVIJETU

Moderna medicina rada mora se suočiti s psihosocijalnim rizicima kako bi se sada i ubuduće zaštitilo zdravlje radnika. Brža proizvodnja, uslužni i komunikacijski procesi, društvo koje se temelji na uslugama i znanju, veći intelektualni napor, rastuća složenost zahtjeva povezanih s radom, novi tehnološki postupci, stalna raspoloživost, zahtjevi mobilnosti i nesigurnost posla doprinose psihosocijalnim opasnostima na radnom mjestu. Postoje znanstveni dokazi koji idu u prilog povezanosti radnoga psihosocijalnog stresa i afektivnih ili mišićno-koštanih poremećaja, a naročito kroničnih bolova u leđima.
U okvirnoj *Direktivi o sigurnosti i zdravlju* izrijekom se navodi da poslodavci imaju obvezu "zajamčiti sigurnost i zdravlje radnika u svim radnim aspektima". Unatoč takvim dalekosežnim obvezama postoje određeni tabui zbog kojih se ponekad teško usredotočiti na teme koje imaju psihosocijalne implikacije. Postoji veliki broj modela, instrumenata i metoda kojima se u današnje vrijeme mogu mjeriti radni psihosocijalni rizici. S obzirom na to da postoji jasna razlika između samog znanja i njegove primjene, možemo reći da u ovom smislu ne nedostaje znanje, već primjena postojećega znanja.
Njemačke državne osiguravajuće kuće slijede dva ključna načela: stavljaju sprječavanje ispred rehabilitacije, a rehabilitaciju ispred kompenzacije. Kako bi se spriječili radni zdravstveni rizici, njemačka državna osiguravajuća ustanova za sirovine i kemijsku industriju (BG RCI) osmislila je nekoliko preventivnih mjera kojima nastoji pomoći poslodavcima i zaposlenicima u suočavanju s psihosocijalnim rizicima na radnom mjestu.

KLJUČNE RIJEČI: *afektivni poremećaji*, *kardiovaskularne bolesti*, *mišićno-koštani poremećaji, stres na radu*

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DOI: 10.2478/10004-1254-63-2012-2213

Professional paper

GENOTOXICITY OF METAL NANOPARTICLES: FOCUS ON *IN VIVO* STUDIES*

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Received in February 2012
CrossChecked in February 2012
Accepted in May 2012

With increasing production and application of a variety of nanomaterials (NMs), research on their cytotoxic and genotoxic potential grows, as the exposure to these nano-sized materials may potentially result in adverse health effects. In large part, indications for potential DNA damaging effects of nanoparticles (NPs) originate from inconsistent *in vitro* studies. To clarify these effects, the implementation of *in vivo* studies has been emphasised. This paper summarises study results of genotoxic effects of NPs, which are available in the recent literature. They provide indications that some NP types cause both DNA strand breaks and chromosomal damages in experimental animals. Their genotoxic effects, however, do not depend only on particle size, surface modification (particle coating), and exposure route, but also on exposure duration. Currently available animal studies may suggest differing mechanisms (depending on the duration of exposure) by which living organisms react to NP contact. Nevertheless, due to considerable inconsistencies in the recent literature and the lack of standardised test methods - a reliable hazard assessment of NMs is still limited. Therefore, international organisations (e.g. NIOSH) suggest utmost caution when potential exposure of humans to NMs occurs, as long as evidence of their toxicological and genotoxic effect(s) is limited.

KEY WORDS: *adverse health effects, chromosomal damage, coating, DNA damage, nanomaterials, rodents*

Nanomaterials have always been released into air by various natural phenomena, e.g. volcano ashes or wild fires, and this is how they unintentionally come into contact with humans, animals, and the environment. Besides, anthropogenic NMs set free by diesel engine exhaust, combustions, welding or cigarette fume are part of the plausible exposure to nano-sized particles.

LIST OF ABBREVIATIONS

ATP	Adenosine triphosphate
Bw	Body weight
MRI	Magnetic resonance imaging
NIOSH	National Institute for Occupational Safety and Health
NM	Nanomaterial
NP	Nanoparticle
OECD	Organisation for Economic Co-operation and Development
ROS	Reactive oxygen species
UV irradiation	Ultraviolett irradiation

* Partly presented at the MEDICHEM Mini Symposium on „Occupational Carcinogens: Exposure Scenarios and Health Risks“, Vienna, Austria, 8 November 2011.

However, over the past years the production and application of a wide variety of NMs have aroused great interest due to their very unique and industrially favourable physico-chemical properties that differ remarkably from bulk materials of the same composition. Due to these properties, materials produced from (or with) nanoparticles boast durability, flexibility, electrical conductivity or numerous other promising features. Metal nanoparticles are the most frequently produced NMs, as they are already widely applied in nanotechnology. Incorporated metal NPs not only improve consumer products like cosmetics and sport goods, but also positively affect contrast agents for magnetic resonance imaging. Another great field of interest is their future application in diagnostic and therapeutic medicine for drug delivery and hyperthermia treatments (1,2).

NMs, which is the umbrella term for other nano-sized morphologies such as NPs, nanofibers, and nanotubes, are defined as very small materials having at least one dimension below 100 nm in size. They can be synthesised by two primary strategies: the top-down fabrication, which crushes bulk material into smaller particles, and the bottom-up method, which uses chemical reactions to originate NPs from atoms or molecules (3).

The smaller the particles are, the bigger their total surface area per unit mass (the surface area of particles involved in biological interactions) (4) becomes. In fact, when the size of (nano-)particles diminishes, their number per unit of mass increases (5). The abovementioned increase in the surface area also increases the number of atoms on the particle surface, which leads to an increased biological reactivity and an extremely different behaviour compared to bigger particles consisting of the same material (6). For instance, while 5 nm gold particles absorb light strongly at 520 nm, bulk gold in turn reflects the light (7). Titanium dioxide (TiO_2) particles, on the other hand, lose their white colour when downsized below 50 nm (4). These remarkably different and favourable behaviours of small particles have brought about a concern that intentionally engineered NMs may at the same time cause adverse health effects when they come in contact with living organisms. Persons primarily exposed to engineered NMs are not only consumers of nanoproducts, but also employees in the field of nanotechnology who may potentially come in contact with NMs during the synthesis or further treatment and application of such materials. Nanomaterials may also be released during transportation and cleaning of production equipment where the primary exposure route is inhalation (8).

Toxicological information on the frequently engineered (metal) NMs is of pivotal importance in terms of risk assessment and management, as these are either already in use (e.g. contrast agents for MRI, cosmetics, and textiles) or may in future be applied in numerous further fields of interest. Nanotoxicological research on the potential adverse health effects of NMs, and especially NPs, has investigated only some of the numerous available NP types.

However, most of the cytotoxic and genotoxic effects of NPs have been documented in *in vitro* studies only. Titanium dioxide NPs (21 nm), which are approved as UV-absorbent substances in sunscreens (9), induced genotoxic effects in mouse lymphoma cells after simultaneous UV irradiation (10). Yet, further *in vitro* studies have provided evidence that UV irradiation is not necessarily required for the DNA damaging potential of TiO_2 NPs. Wang et al. (11) exposed human B-cell lymphoblastoid cells to TiO_2 NPs with a particle diameter of 6.57 nm, which resulted in DNA and chromosomal damages after an exposure duration of 24 and six hours, respectively. The negative size effect of NPs was clearly demonstrated by Gurr et al. (12) who exposed human bronchial epithelial cells to various sizes of TiO_2 NPs (10 nm and 20 nm, ≥200 nm, respectively). Interestingly, the two smaller TiO_2 NPs, sized 10 nm and 20 nm, at a concentration of 10 $\mu g\ ml^{-1}$ induced significant oxidative DNA and chromosomal damages, while the bigger (200 nm or above) TiO_2 NPs with the same composition and concentration did not. This size effect was confirmed by another recent study: on the one hand, it showed comparable DNA damages of nano-sized anatase (<25 nm) and fine rutile (<5 μm) TiO_2 particles in human bronchial epithelial cells, but on the other hand, significant chromosomal damages were only caused by the smaller nano-sized anatase TiO_2 particles (13).

In addition to the size, coating of an NP appears to be crucial in terms of both cellular toxicity and genotoxicity. NPs are coated with various coverings (i.e. polymers, amino acids) in order to obtain improved solubility in fluids, higher biocompatibility, and lower toxicity (14,15). As these coatings modify the particle surface, they may also alter the particle's (geno-)toxicity or inflammatory effects depending on the coating material (14,16). The effect of coating was investigated by Hong et al. (17) who revealed that positively charged coatings of iron oxide NPs resulted

in increased DNA strand breaks of fibroblasts, while negatively charged coatings did not show any significant genotoxicity. As an explanation for this behaviour, the authors assumed that only positively charged particles penetrated the nucleus and interacted with the DNA.

Likewise, polysaccharide coated silver NPs (25 nm) elevated the amount of DNA damage repair proteins and upregulated the tumour suppressor protein p53 in mouse cells. On the contrary, uncoated silver NPs of the same size did not result in altered protein expression (18). The authors refer to the plausibility that the coating of NPs with polysaccharides prevents their tendency to agglomerate, which results in an increased surface area and facilitated contact with cell membranes (18).

Besides TiO_2 NPs, sunscreens and other nanotechnology-based cosmetics frequently contain zinc oxide (ZnO) NPs. Alike TiO_2 NPs, ZnO NPs seem to induce genotoxic effects *in vitro*. They were able to induce DNA strand breaks and downregulate mitochondrial activity in different cell lines. It was further possible to illustrate their concentration and time dependent cellular internalisation (19).

Moreover, cobalt chromium (CoCr) NPs appear to be genotoxic under *in vitro* conditions due to significantly increased single and double DNA strand breaks and chromosomal damages in human fibroblasts (20).

In large part, *in vitro* investigations conducted up to this moment have demonstrated direct interaction between the NM and the DNA *per se* but have not considered genotoxic mechanisms which originate from intercellular processes. Nonetheless, there are indications that genotoxicity might result from indirect DNA damage by the cellular production of reactive oxygen species (ROS), the depletion of antioxidants or the altered synthesis of DNA repair proteins (5). If the indirect DNA damaging mechanism were to be confirmed, NPs would not necessarily need to come into direct contact with their target cells. A very sophisticated cell model conducted by Bhabra et al. (21) showed this possible indirect way of genotoxicity. In this study, the target fibroblasts, which functioned as monitoring cells, were placed underneath an intact cell barrier consisting of inert placenta cells and lying on a microporous membrane. The intact cell barrier may be comparable with the intact human blood-brain barrier. Following the exposure of the cell barrier to CoCr NPs, a significant DNA damage was detected in fibroblasts, although they had never been in direct contact with the NPs. Due to further experiments, the authors postulate that these genotoxic effects were induced by an increased ATP-release of the barrier cells. This increased ATP-release damaged the fibroblasts' DNA, reaching them via gap junctions and hemichannels.

In summary, there is evidence that a variety of metal NP types may be genotoxic to cultured cells *in vitro,* even though there are clear inconsistencies in the recent literature. Nevertheless, results of *in vitro* experiments may not fully reflect the natural genotoxic potential of NMs. Under *in vivo* conditions, NPs and NMs in general may act considerably different than under *in vitro* conditions. Furthermore, *in vivo* concentrations of NMs may differ from those *in vitro*.

Thus, researchers have started to investigate potential adverse health effects of NMs *in vivo* in order to obtain information on their behaviour in living organisms. Additionally, information on the mechanisms by which they interact and possibly interfere with cellular components is of utmost importance.

To our knowledge, there is only one review about the genotoxicity of metal NPs, which was published in 2011. Numerous further investigations on nanoparticulate genotoxicity have since been conducted. In this paper, we will give an overview on *in vivo* genotoxicity research undertaken up to this point, with a focus on metal NPs.

METHODS

Papers were retrieved from the open literature by a systematic search of databases MEDLINE and SCOPUS. The keywords for search included *metal nanoparticles*, *DNA damage*, *genotoxiciy*, *comet assay*, *micronucleus*, in vivo, *mice*, *rats*, *inhalation,* and *instillation* until May 2012. Language was restricted to German and English. This resulted with 17 references which are included in this paper (Table 1).

In terms of quantifying cellular genotoxicity *in vitro* and *in vivo*, the comet assay and the micronulceus test are the most commonly applied methods in nanotoxicology. Under *in vivo* conditions, the (alkaline) comet assay measures single and double DNA strand breaks in cells of exposed animals, which can visually be quantified by electrophoresis and fluorescence microscopy in the form of comet-like

Table 1 In vivo *studies on the genotoxicity of metal nanoparticles (NPs). bw body weight, TiO_2 titanium dioxide, Au gold, Co cobalt, ZnO zinc oxide, Al_2O_3 aluminium oxide, 8-OHdG 8-hydroxydeoxyguanosine, RPE retinal pigment epithelium,*

Authors	Nanoparticle and size	Concentration and exposure duration	Exposure and species	Assays	Results
Naya et al., 2012 (28)	TiO_2 NPs 5 nm	1.0 mg kg^{-1} and 5.0 mg kg^{-1} bw (single instillation),	Intratracheal instillation, rats	Histopathology	Increase in alveolar macrophages and neutrophils at 5 mg kg^{-1}
				Alkaline comet assay	No increase in DNA strand breaks (% tail DNA)
		0.2 mg kg^{-1} and 1.0 mg kg^{-1} bw (repeated instillation, once per week for 5 weeks)		Histopathology	Significant increase in alveolar macrophages and neutrophils at 1.0 mg kg^{-1}
				Alkaline comet assay	No increase in DNA strand breaks (% tail DNA)
Sycheva et al., 2011 (25)	Microsized TiO_2 particles (TDM) 160 nm	40 mg kg^{-1}, 200 mg kg^{-1} and 1000 mg kg^{-1} bw, daily for 7 days	Oral gavage, mice	Comet assay	Increase in DNA strand breaks (% tail DNA) in bone marrow (TDM, TDN) and liver cells (TDN)
	Nanosized TiO_2 NPs (TDN) 33 nm			Karyological assay	Increase in micronuclei in bone marrow (TDM), increase in mitotic index and apoptosis in forestomach, colon, atypical nuclei of spermatids (TDM, TDN) and apoptosis in forestomach (TDN)
Trouiller et al., 2012 (24)	TiO_2 NPs 160 nm	50 mg kg^{-1}, 100 mg kg^{-1}, 250 mg kg^{-1} and 500 mg kg^{-1} bw for 5 days	Oral gavage, mice	Alkaline comet assay	Increase in DNA strand breaks (tail moment) at 500 mg kg^{-1} bw
				Micronucleus test	2.1 fold increase in micronuclei at 500 mg kg^{-1}
				γ-H2AX immunostaining	Increase of γ-H2AX formation at 50 mg kg^{-1}, 100 mg kg^{-1}, 250 mg kg^{-1} and 500 mg kg^{-1} bw
				8-OHdG	Increase in 8-OHdG at 500 mg kg^{-1} bw
	TiO_2 NPs 160 nm	500 mg kg^{-1} for 10 days for pregnant mouse dams	Oral gavage, pregnant mouse dams	DNA deletion assay	Fetuses: increase in eyespots per RPE
Saber et al., 2011 (45)	2 coated rutile TiO_2 NPs, one uncoated anatase TiO_2 NPs	54 μg, single dose	Intratracheal instillation, mice	Comet assay	Increase in DNA damage in lung lining fluid

Table 1 *Continued*

Saber et al., 2012 (26)	Coated rutile TiO_2 NPs ($NANOTiO_2$) 20.6 nm	18 μg, 54 μg, 162 μg, single dose	Intratracheal instillation, mice	Alkaline comet assay	No increase in DNA strand breaks (normalized tail length) of broncho-alveolar cells
	Sanding dust of paint with TiO_2 NPs (Indoor-TiO_2) 10 nm to 1.7 μm			Alkaline comet assay	Increase in DNA strand breaks (normalized tail length) of liver tissue by 162 μg of $NANOTiO_2$
Landsiedel et al., 2010 (27)	ZnO NPs 30 nm to 200 nm	15 mg kg^{-1}, 30 mg kg^{-1}, 60 mg kg^{-1} bw, single dose	Intraperitoneal administration, mice	Micronucleus test	No increase in micronuclei in bone marrow cells
	TiO_2 NPs 10 nmx50 nm	0.5 mg m^{-3}, 2 mg m^{-3}, 10 mg m^{-3}, 6h on 5 consecutive days	Head-nose inhalation, rats	Alkaline comet assay	No increase in DNA strand breaks in broncho-alveolar cells
Hwang do et al., 2012 (33)	Silica-coated and uncoated cobalt ferrite NPs 50 nm and 35 nm, respectively	500 μg, single dose	Intravenous injection, mice	RT-PCR	Uncoated cobalt ferrite NPs enhanced expression of 17 genes related to DNA damage or repair, apoptosis, carcinogenesis, inflammation, oxidative stress and growth arrest
Girgis et al., 2012 (34)	Au and Au-Co NPs 15 nm	80 mg kg^{-1}, 160 mg kg^{-1}, 320 mg kg^{-1} bw, once daily for 7 and 14 days, respectively	Oral gavage, mice	RNA extraction	Alteration in tumor-initiating genes (CYP3A, p27, p53) by gold-cobalt NPs (160 mg kg^{-1} and 320 mg kg^{-1} bw) and Au-NPs (320 mg kg^{-1} bw)
				Micronucleus test	Increase in MN formation of bone marrow cells by Au-Co NPs (160 mg kg^{-1} and 320 mg kg^{-1} bw) and Au-NPs (320 mg kg^{-1} bw)
				Glutathione peroxidase activity	Decrease in glutathione peroxidase activity by Au-Co NPs (320 mg kg^{-1} bw) and Au-NPs (320 mg kg^{-1} bw)
				8-OHdG	Increase in 8-OHdG of hepatic mice genome by Au NPs and Au-Co NPs
Schulz et al., 2011 (41)	Gold NPs 2 nm, 20 nm, and 200 nm	18 μg, single dose	Intratracheal instillation, rats	Alkaline comet assay	No increase in relative tail intensity
				Micronucleus test	No increase in MN formation

Table 1 *Continued*

Sharma et al., 2012 (29)	ZnO NPs 30 nm	50 mg kg^{-1} and 300 mg kg^{-1} bw, 14 days	Oral administration	Fpg-Comet assay	Increase in % tail DNA and Olive tail moment by 300 mg kg^{-1} ZnO NPs
Tiwari et al., 2011 (36)	Ag NPs 15 nm to 40 nm	4 mg kg^{-1}, 10 mg kg^{-1}, 20 and 40 mg kg^{-1} bw, 5-day interval for 32 days	Repeated intravenous injection, rats	Alkaline Comet assay	Increase in DNA strand breaks (tail migration) by 40 mg kg^{-1}
Choi et al., 2010 (37)	Ag NPs 5 nm to 20 nm	30 mg L^{-1} Ag, 60 mg L^{-1} Ag and 120 mg L^{-1} Ag, 24h	Oral gavage, zebrafish	Western blot	Increase in γ-H2AX and dose-dependent increase in p53 mRNA
Ahamed et al., 2010 (38)	Polysaccharide-coated Ag NPs 10 nm	50 μg mL^{-1} and 100 μg mL^{-1}, 24h and 48h	Oral gavage, Drosophila melanogaster	Western blot	Increase in p53 and p38 proteins by 50 μg mL^{-1} and 100 μg mL^{-1} and after 24 h and 48 h exposure
Kim et al., 2008 (39)	Ag NPs 60 nm	30 mg kg^{-1}, 300 mg kg^{-1} and 1000 mg kg^{-1} bw, 28 days	Oral gavage, rats	Micronucleus test	No increase in MN formation of erythrocytes
Kang et al., 2011 (44)	Nickel hydroxide NPs 5 nm	79 μg m^{-3} Ni, 5h/day for 1 week or 5 days/week for 5 months	Whole-body inhalation, (ApoE-/-) mice	Long PCR assay	Increase in damaged mitochondrial DNA of the aorta only after 5 months of exposure
Balasubraman-yam et al., 2009 (42)	Al_2O_3 NPs 30 nm and 40 nm, bulk Al_2O_3 particles 50 μm to 200 μm	500 mg kg^{-1}, 1000 mg kg^{-1} and 2000 mg kg^{-1} bw, single dose	Oral gavage, female Wistar rats	Micronucleus test Chromosomal aberrations analysis	Significant increase in MN formation of bone marrow erythrocytes by Al_2O_3 NPs (1000 mg kg^{-1} and 2000 mg kg^{-1}) Significant increase in chromosome aberrations of bone marrow cells by 30 nm-Al_2O_3 (1000 mg kg^{-1} and 2000 mg kg^{-1}) and 40 nm-Al_2O_3 (2000 mg kg^{-1})

Table 1 *Continued*

Balasub-raman-yam et al., 2009 (43)	Al_2O_3 NPs 30 nm and 40 nm, bulk Al_2O_3 particles 50 μm to 200 μm	500 mg kg^{-1}, 1000 mg kg^{-1} and 2000 mg kg^{-1} bw, single dose	Oral gavage, female Wister rats	Micronucleus test	Significant dose-dependent increase in MN of bone marrow erythrocytes by 30 nm - Al_2O_3 and 40 nm - Al_2O_3 (1000 mg kg^{-1} and 2000 mg kg^{-1})
				Alkaline comet assay	Significant dose-related increase in DNA breakage (% tail DNA) by 30 nm - Al_2O_3 and 40 nm - Al_2O_3 (1000 mg kg^{-1} and 2000 mg kg^{-1})

cell nuclei (22). The micronucleus test measures general chromosomal damages. The detected micronuclei represent chromosomal fragments, which arise in daughter cells during mitosis (23).

RESULTS

Genotoxic potential of titanium dioxide NPs

The *in vivo* genotoxicity of TiO_2 NPs has been investigated in six studies which treated both rats and mice by intratracheal instillation and oral gavage. Four of these animal studies were positive. Trouiller et al. (24) determined several genotoxic endpoints after the oral treatment of male mice with TiO_2 NPs. At very high mass fractions (500 mg kg^{-1} bw), 160 nm TiO_2 NPs caused DNA strand breaks, a 2.1 fold increase in micronuclei, and inflammatory reactions in respect of changes in cytokine expression. Likewise, oxidatively induced DNA damage was significantly increased. *In utero* treatment of mouse fetuses showed a significant increase in DNA deletion frequency suggesting possible genome rearrangements. Due to these study results, it is likely that TiO_2 NPs may cause both direct and indirect DNA damage, the latter being due to oxidative stress.

The second positive animal study with similar TiO_2 NPs and the same particle size (160 nm) confirmed the increase of DNA strand breaks and micronuclei formation in bone marrow cells of treated mice. However, animals were exposed by daily oral gavage for seven days. Smaller TiO_2 NPs with a size of 33 nm showed similar genotoxic results, even if they additionally increased DNA strand breaks of mouse liver cells and apoptosis in forestomach cells (25).

Saber et al. (26) compared the inflammatory and genotoxic effects of pure TiO_2 NPs and TiO_2 NPs added to paints. While pure TiO_2 NPs induced significant inflammatory response in broncho-alveolar fluid cells of intratracheally instilled mice, TiO_2 NPs incorporated in paint matrix did not. Only pure TiO_2 NPs additionally caused an increase in DNA damage of liver cells. Authors assume that a relevant exposure to nanoparticulate TiO_2 incorporated in paints does not occur during the use of product, as single NPs are not released.

Nevertheless, two studies were clearly negative regarding genotoxicity *in vivo*. Although single intratracheal instillation of 5 nm TiO_2 NPs caused inflammatory responses in rats, these NPs did not enhance DNA damage neither after single, nor after repeated exposure. Landsiedel et al. (27) considered the recommended OECD test methods for NMs by including the Ames test with Salmonella, the micronucleus test, and comet assay *in vitro* and *in vivo*. Unexpectedly, parallel *in vitro* and *in vivo* (inhalatory exposure to mice) studies showed that zinc oxide and TiO_2 NPs were not genotoxic. These findings corroborate the above-mentioned absent genotoxicity in rats after intratracheal administration of TiO_2 NPs (28).

Genotoxic potential of zinc oxide NPs

Besides TiO_2 NPs, ZnO NPs are applied in cosmetics, UV-absorbent sunscreens, and food packaging. Despite its progressive use, the DNA damaging potential of ZnO NPs has so far been

investigated *in vivo* only once. Sharma et al. (29) orally exposed mice for 14 consecutive days. The exposures resulted in elevated liver enzymes, and oxidatively induced DNA breakage.

Genotoxic potential of cobalt NPs

Cobalt-based NPs may, on the one hand, embody a realistic (future) exposure hazard for humans because they are released by mechanical wear of orthopedic implants (30) and by further medical applications. On the other hand, they may also be dangerous because of their application in technical devices such as data storage and catalysts (31, 32).

Still, the DNA damaging potential of Co NPs has rarely been considered *in vivo*. One recent rodent study investigated genotoxicity of Co NPs dependent on surface coating. The authors showed that both silica-coated and uncoated cobalt ferrite ($CoFe_2O_4$) NPs, intravenously injected into mice, accumulated in liver tissue, while only uncoated $CoFe_2O_4$ NPs resulted in enhanced expression of genes related to DNA damage and repair, carcinogenesis, cell death, growth arrest, oxidative stress, and inflammation. In comparison with the coated NPs, uncoated $CoFe_2O_4$ NPs even induced a 45-fold expression ratio of cyp4a10 - a gene related to oxidative stress (33).

Similar results, partly overlapping, have been achieved in a study where mice were orally treated with 15 nm gold NPs and gold-cobalt (Au-Co) NPs for seven and 14 days. Both NP types caused alterations in tumour-initiating genes, micronucleus formation, and oxidative DNA adducts. Nevertheless, Au-Co NPs showed a much higher effect at already lower concentrations compared to Au NPs. These greater effects of Au-Co NPs regarding genotoxicity may be explicable by the fact that Co-based Au NPs are able to induce greater oxidative stress. A possible size and concentration effect can widely be excluded due to equal experimental conditions as described by the authors (34).

Genotoxic potential of silver NPs

The antibacterial property of silver (Ag) NPs has frequently been used for numerous applications such as wound dressings, other medical devices, textiles or plastics as they fight both Gram positive and Gram negative bacteria, as well as fungi and viruses (35). The actual mechanism of their bactericide property has not been fully clarified yet. This uncertainty and the high number of applications yield studies on the possible cytotoxic and genotoxic effects of Ag NPs.

Three studies regarding genotoxicity of Ag NPs showed positive results. Tiwari et al. (36) assessed increased single and double DNA breakage in rats after intravenous injection of 40 mg kg^{-1} bw of Ag NPs. In the second *in vivo* study, zebrafish were treated with oral Ag NPs (5 nm to 20 nm), which resulted in high levels of γ-H2AX - a marker for double DNA strand breaks. Moreover, the exposure to Ag NPs resulted in a non-significant dose-dependent increase in hepatic p53 mRNA - the precursor of the tumour suppressor protein and an indirect DNA damage marker (37). Likewise, polysaccharide-coated Ag NPs (10 nm) heightened the level of DNA damage markers (p53 and p38 proteins) in *Drosophila melanogaster* (38).

So far, there is one study which obsevered the effect of extended exposure periods in rats that were orally treated with various levels (maximum 1000 mg kg^{-1}) of 60 nm Ag NPs. This, however, resulted in slight liver damage but did not show a significant increase in genotoxicity (39).

Genotoxic potential of gold NPs

Bulk gold is considered biologically inert, whereas nanoparticulate Au particles seem to be genotoxic under *in vitro* conditions (40). *In vivo* genotoxicity however has only once been investigated. Single intratracheal instillation of Au NPs was not genotoxic in rats - as assessed by the comet assay and the micronucleus test. Genotoxicity could not be identified after the treatment with three different particle sizes: 200 nm, 20 nm, and 2 nm (41).

Genotoxic potential of aluminium NPs

Engineered aluminium (Al)-based NPs were investigated *in vivo* by Balasubramanyam et al (42, 43). In orally exposed rats, the authors observed significant dose related DNA breakage, dose dependent micronuclei formation, and chromosome aberrations by 30 nm and 40 nm aluminium oxide (Al_2O_3) NPs. In contrast, these genotoxic effects were not observed by bulk Al_2O_3 particles with a size of 50 µm to 200 µm.

Genotoxic potential of nickel NPs

The DNA damaging potential of nickel (Ni) NPs was a small part of a whole-body inhalation study. The experimental animals were hyperlipidemic and apoprotein E-deficient (ApoE-/-) mice which received treatment with 5 nm nickel hydroxide (NH) NPs.

Besides pulmonary and systemic inflammatory reactions, and atherosclerosis as a long-term effect, mice showed heightened levels of mitochondrial DNA damage in the aorta. Interestingly, mitochondrial DNA damage was (similar to atherosclerosis) only detected after long-term exposure of five months (44). As oxidative stress was induced simultaneously with mitochondrial genotoxicity, a potential relation between these two effects has to be taken into consideration.

DISCUSSION

Currently available data on NP genotoxicity *in vivo* indicate a potential for DNA damaging effect of various NP types, primarily in mice and rats. However, these *in vivo* investigations are rare and inconsistent. While some of the present *in vivo* studies on nanoparticulate genotoxicity are positive, others do not confirm genotoxic effects. Some NP types such as titanium dioxide, cobalt, zinc oxide, silver, aluminium, and nickel NPs indicate a possible DNA damaging potential in rodents.

So far, TiO_2 NPs are the most frequently investigated NPs in terms of genotoxicity. Still, some studies have revealed genotoxic effects by TiO_2 NPs, while others regard them as being non-genotoxic in particular animals. One reason for the above-mentioned negative study results may be the exposure route which differed from all other studies. Additionally, authors adhered to the recently published OECD recommendations on genotoxicity testing of soluble materials. In the negative study by Landsiedel et al. (27), animals were exposed by inhalation, whereas other studies primarily treated animals by oral gavage - which could have resulted in much higher incorporated NP concentrations. Indeed, inhalation is the most natural and relevant way of human exposure. So far, there are insufficient *in vivo* studies involving inhalatory exposure.

Contrary effects were also observed with surface coatings. Polysaccharide-coated Ag NPs increased the expression of tumour suppressor proteins but uncoated Ag NPs did not (18, 38). The opposite effect was seen with cobalt-based NPs. While silica-coated cobalt ferrite NPs were non-genotoxic, uncoated cobalt ferrite NPs significantly increased the expression of genes associated with DNA damage and repair (33). As mentioned above, the increased genotoxic effect of polysaccharide-coated NPs might be due to the inhibition of particle agglomeration (18). Coatings based on silica might prevent the oxidatively damaging capability of cobalt ferrite NPs. Uncoated cobalt ferrite NPs might release metal ions due to direct interaction with cell membranes, which in turn could result in oxidative stress and consequent DNA damage. Another possibility might be a genotoxic mechanism that depends on the electrical charge of the particle surface. Therefore, further investigations on particle coating and surface modification are needed.

Another determining fact in genotoxicity testing might be the varying exposure durations. Short exposure durations ranging between one and two days caused DNA breakage by Ag NPs. Surprisingly, long-term exposure (28 days) to Ag NPs was not genotoxic to rats. However, the differences in methods have to be considered, as the studies with shorter exposure durations assessed genotoxicity by potentially reversible DNA breakage, while the long-term exposure study determined irreversible chromosome breakage.

These inconsistent results on NP genotoxicity indicate that there are great challenges regarding risk assessment, as *in vivo* studies are, unfortunately, comparable among each other only to a limited extent. The problematic interpretation of nanotoxicological results arises out of the following circumstances:

First, a considerable number of various NMs and NP types are being produced. Thus, nanomaterials greatly differ one from the other by either core material, size, surface area, shape, stability, coating or electrical charge. Hence, these characteristics have a great impact on possible interactions with living cells or tissues and determine cytotoxicity and damage to DNA. Second, *in vitro* and *in vivo* studies may or may not reflect the actual effect of NMs in living organisms when spontaneous contact occurs. Hence, these studies may or may not be relevant for humans. Applied exposure dosages under experimental conditions might exceed the potential (occupational) exposure of humans. Within the framework of animal experiments, exposure routes such as oral gavage may be administered. Gastrointestinal intake of NMs may indeed occur through nanotechnological food, packaging or medical applications. Still, inhalation accounts for the majority of NM exposure routes in humans, as NMs can be released into air in occupational settings. Third, the comparison across different nanotoxicological studies remains questionable due to different dose metrics (i.e. $\mu g\ m^{-3}$ and $mg\ kg^{-1}$ bw) applied. Some authors additionally do not mention the concentration which study animals indeed received.

Finally, the applied NMs are frequently not sufficiently characterised in their chemical composition, physico-chemical properties, agglomeration status in the cell medium, and surface charge. For that reason, the OECD recently developed the "Guidance Manual for the Testing of Manufactured Nanomaterials" aiming at "high science-based, internationally harmonised standards" and the validation of test methods. Following these recommendations, researchers are requested, beyond other standardised procedures, to give detailed information on applied NMs, including their physico-chemical properties, as well as to evaluate their environmental fate and toxicity in mammals. In the end they should provide an explicit study report (46).

Thus, at present there is a lack of *in vivo* studies corresponding to *in vitro* studies with identical NMs, identical methods, and identical endpoints, which are necessary to gain knowledge of possible cytotoxic, genotoxic, and inflammatory effects of NMs on living cells and organisms. Due to the current uncertainties regarding adverse health effects of NMs, NIOSH (National Institute for Occupational Safety and Health) and other international organisations suggest caution when there is an imminent risk of potential exposure of humans to NMs , as long as there is limited evidence available (47). Thus, for the present moment, international organisations recommend a precautionary occupational safety approach, which regards NPs as potentially genotoxic to humans (47, 48). Furthermore, it is recommended to establish exposure registries for workers who handle NMs in order to systemically monitor those who are potentially exposed and who are possibly at risk. As the use of nanotechnology has increased, such exposure registries have gained importance and have been attributed high priority because conventional epidemiological studies on potential health effects of NMs are difficult to conduct (49).

CONCLUSIONS

Several metal NPs may have genotoxic potential *in vivo*. However, inconsistencies in the literature on nanotoxicology do exist; while TiO_2 and Ag NPs have been found to be genotoxic to rodents in large part, other metal NPs, which have rarely been studied *in vitro* and *in vivo*, showed diverging genotoxic effects. Nanoparticulate coatings seem to have a relevant impact on genotoxicity, as they may not only alter the particles' surface charge, but also their agglomeration status by which they gain total surface area. The currently available animal studies may also suggest differing genotoxic mechanisms depending on the duration of exposure.

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Sažetak

GENOTOKSIČNOST METALNIH NANOČESTICA: OSVRT NA PODATKE ISTRAŽIVANJA *IN VIVO*

S povećanjem proizvodnje i primjene niza različitih nanomaterijala (NM) raste i potreba istraživanja njihovih mogućih citotoksičnih i genotoksičnih učinaka kao i drugih štetnih učinaka na zdravlje u uvjetima profesionalne ili opće izloženost ljudi. Indikacije potencijanog oštećenja DNA kojeg uzrokuju nanočestice u velikoj mjeri proizlaze iz nedosljednih *in vitro* ispitivanja. Kako bi se razjasnili ti učinci, naglašena je potreba provedbe *in vivo* ispitivanja. Ovaj pregledni rad sažima rezultate procjene genotoksičnih učinaka nanočestica koji su objavljeni u novijoj stručnoj i znanstvenoj literaturi. Navedeni rezultati pokazuju da određene nanočestice uzrokuju lomove u molekuli DNA i oštećuju kromosome u eksperimentalnim životinjama. Njihovi genotoksični učinci ne ovise samo o veličini čestice, modifikaciji površine (oblaganje čestice) i načinu izlaganja, već i o trajanju izloženosti nanočesticama. Postojeća istraživanja provedena na životinjama upućuju na različite mehanizme koji ovise o trajanju izlaganja i pomoću kojih živi organizmi reagiraju na doticaj s nanočesticama. Međutim postoje brojne nedosljednosti u novijoj literaturi, a standardne testne metode nisu dostupne pa je stoga pouzdanija procjena opasnosti od izlaganja nanomaterijalima u ljudi još uvijek veoma ograničena. Stoga se u međunarodnim dokumentima savjetuje oprez prilikom svakog izlaganja ljudi nanomaterijalima kako bi se spriječili mogući opći toksični genotoksični učinci.

KLJUČNE RIJEČI: *eksperimentalne životinje, nanomaterijali, neželjni učinci na zdravlje, oblaganje čestice, oštećenje DNA, oštećenje kromosoma*

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DOI: 10.2478/10004-1254-63-2012-2199

Review

OTOTOXIC SUBSTANCES AT THE WORKPLACE: A BRIEF UPDATE*

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Received in January 2012
CrossChecked in April 2012
Accepted in April 2012

Ototoxic chemicals can impair the sense of hearing and balance. Lately, efforts have been intensified to compile evidence-based lists of workplace agents with ototoxic properties. This article gives a rough overview of the latest relevant publications, which confirm that toluene, styrene, and lead should receive particular attention as ototoxic substances at the workplace. Moreover, there is sufficient evidence that occupational exposure to trichloroethylene, mercury, carbon monoxide, and carbon disulfide can affect the ear. Based on the existing information, industrial hygienists should make sure that occupational health professionals and the workforce are made aware of the risks posed by ototoxic substances; support their replacement or new technical measures to reduce exposure; make these substances a part of regular screening, develop tools that can early diagnose chemically induced hearing impairment, and investigate further into the ototoxic properties of these substances. Further research should focus on quantifying the combined effects of ototoxic substances and noise.

KEY WORDS: *carbon disulfide, carbon monoxide, hearing impairment, evidence-based risk assessment, lead, mercury, styrene, toluene, trichloroethylene, xylene*

Noise is not the only potential cause of hearing loss from damage to the inner ear. Certain chemical substances can also have reversible or irreversible effects that impair the sense of hearing and balance. They can affect the structure and/or the function of the inner ear (auditory and vestibular apparatus) and the neural pathways from the inner ear to the auditory cortex in the brain.

The first reports on ototoxic effects concerned pharmaceuticals (1). Some 1000 years ago, the Persian philosopher and medical scholar Avicenna warned that the treatment with mercury vapour against head lice could deafen the host. In the 19th century, antimalarial drugs chloroquine, quinine, and salicylates were found to temporarily damage the ear. Other examples with clinical relevance are the ototoxic side-effects of aminoglycoside antibiotics or the loop diuretic furosemide.

The European Physical Agents Directive (2) stipulates that "the employer shall give particular attention, when carrying out the risk assessment, to (…) any effects on workers' health and safety resulting from interactions between noise and work-related ototoxic substances."

This review focuses on common workplace substances that are assumed to have ototoxic effects. These have come to the fore only in the last few decades and mostly include organic solvents, several metals, and asphyxiants like carbon monoxide. It mostly summarises the findings of three recently

* Partly presented at the 39th International MEDICHEM Congress on Occupational and Environmental Health in the Production and Use of Chemicals "Occupational Health in a Changing World", Heidelberg, Germany, 2 - 5 June 2011

published comprehensive literature reviews, one by the Canadian Institut de recherche Robert-Sauvé en santé et en sécurité du travail (IRSST) (3), one by the European Agency for Safety and Health at Work (4), and one jointly presented by the US National Institute for Occupational Safety and Health (NIOSH) and the Nordic Expert Group (5).

It also includes information from the latest articles (published between 2009 and 2011) indexed in PubMed and other biomedical research abstracts that have not been mentioned in the three reviews referred to above.

RESULTS

Canadian Institute IRSST is a private, non-profit agency in the province of Quebec. It published its report on ototoxic chemicals at the workplace in 2009, although it had presented the main results earlier at international conferences. In collaboration with Montreal University, searches were performed in the existing literature for evidence of ototoxic properties of all 695 chemicals listed in Quebec's occupational safety and health regulation. Promising scientific pointers were found for more than two dozen substances. The documents were evaluated only for exposure concentrations up to the domestic short-term exposure limit or ceiling value, which is five times the eight-hour time-weighted average (TWA) occupational exposure limit (OEL) for humans. In animal studies, concentrations of up to 100 times the TWA were taken into consideration. Each substance was classified as either "ototoxic", "possibly otoxic", "non-conclusive", or "no evidence", according to the score combining human and animal data. Only lead (and its inorganic salts) and the organic chemicals toluene, styrene, and trichloroethylene were ranked as "ototoxic".

In an annex to the report, the authors presented *fiches toxicologiques* (toxicological cards) for 27 substances, making transparent the rationale behind the decisions by giving very brief statements on the evaluated human and animal data, followed by a short conclusion. The full report is available in French only; an English article in a scientific journal was published more than two years later (6).

The European Agency for Safety and Health at Work (EU-OSHA) is a so-called policy agency governed by the EU public law, with its own legal personality. It was established by the European Council in 1994. EU-OSHA commissioned an international team of authors to compile information on combined exposure to noise and ototoxic substances. Realising that little information was available on these combined effects, the authors proceeded to develop another classification scheme for ototoxic substances, that led to three categories: "confirmed", "suspected", and "questionable ototoxic substance". Their weight-of-evidence approach was based on the methodological quality, quantity (magnitude of effect, number of studies from different centres or research groups, and sample size), and consistency of results published by different laboratories.

As a rule, human data were given priority over animal data, but EU-OSHA criticised the poor quality of the majority of epidemiological studies. Indeed, a clear relationship between industrial chemicals and hearing impairment is not easy to assess in humans, given the complexity of workplace environments where noise and various chemicals may be present simultaneously. Most of the published epidemiological studies have a cross-sectional design and relate chronic effects to currently measured exposures.

As EU-OSHA used a qualitative weight-of-evidence approach and relied predominantly on animal experiments, the lists of substances classified as

Table 1 *Classification of ototoxic substances by the Institut de recherche Robert-Sauvé (IRSST), the European Agency for Safety and Health at Work (EU-OSHA), and the Nordic Expert Group (NEG).*

SUBSTANCE	IRSST (2009)	EU-OSHA (2009)	NEG (2010)
Toluene	ototoxic	confirmed	Category 1
Styrene	ototoxic	confirmed	Category 1
Trichloroethylene	ototoxic	confirmed	Category 3
Mercury	non-conclusive	confirmed	Category 1
Lead	ototoxic	confirmed	Category 1
Carbon disulfide	possibly ototoxic	confirmed	Category 1
Carbon monoxide	no evidence	confirmed	Category 1

ototoxic is much longer and includes all the chemicals identified by IRSST, plus several nitriles (acrylonitrile, 3-butenenitrile, *cis*-2-pentenenitrile, *cis*-crotononitrile, 3,3'-iminodipropionitrile), carbohydrates (*n*-hexane, *p*-xylene, ethylbenzene, *n*-propylbenzene, methylstyrenes), hydrogen cyanide and its salts, carbon monoxide, carbon disulfide, and compounds of mercury, germanium, and tin.

Most interestingly, only *p*-xylene, and not its *ortho*- or *meta*-isomers, seem to be ototoxic. This observation is also documented in IRSST's *fiche toxicologique* on xylene, although the Canadian authors consider "xylene (*o*-, *m*-, *p*-isomers)" as "possibly ototoxic" in the original version of their review. In the subsequent English journal article this ranking was limited to *p*-xylene alone (6).

The most comprehensive report was delivered by the Nordic Expert Group (NEG). This is a collaborative effort between the Nordic countries of Denmark, Sweden, Norway, and Finland to reach consensus and set up criteria documents on chemicals for occupational exposure limits. Their recent review on ototoxic substances was drawn up in cooperation with a Brazilian specialist, then working at the National Institute for Occupational Safety and Health (NIOSH) in the United States.

The Nordic Expert Group chose a quantitative approach, meticulously comparing the "no observed" or "lowest observed" effect levels with occupational exposure limits from various countries. Their criteria for the classification scheme with three categories are self-explanatory:

- Category 1: Human data indicate auditory effects below or near the existing OELs. There are also robust animal data supporting an effect on hearing resulting from exposure.
- Category 2: Human data are lacking, whereas animal data indicate an auditory effect below or near the existing OELs.
- Category 3: Human data are poor or lacking. Animal data indicate an auditory effect well above the existing OELs.

According to these criteria, toluene, styrene, carbon monoxide, carbon disulfide, lead and mercury were classified to Category 1, and *p*-xylene, ethylbenzene, and hydrogen cyanide to Category 2.

Publications issued since 2009 do not focus on particular substances, but rather on complex mixtures such as organic solvents (7, 8), on exposure to chemicals in a steel company (9), or even on the complex environment of military forces (10). Remarkably, an increasing number of publications has covered combined exposure to noise and ototoxic chemicals (7-12).

DISCUSSION

As ototoxic substances are a heterogeneous group of chemicals that cause hearing impairment in various toxicological modes of action, risk identification and risk assessment present a challenge of their own. Several hundreds of chemical agents have been associated with ototoxic health effects, including diffuse classes like "solvents" or "pesticides". In this context, the effort of collecting, combining, evaluating and condensing the available scientific data may well contribute to a clearer understanding for non-experts.

Even though the three institutions IRSST, EU-OSHA, and NEG applied differing classification criteria, their key findings match quite well and yield a short list of workplace substances with sufficient scientific evidence of relevant ototoxic properties (Table 1). The seven substances compiled in this synoptic table rank the most ototoxic by at least two institutions. Three of them – toluene, styrene, and lead – are regarded by all three institutions as proven ototoxic substances of the highest category.

A few discrepancies are discernible in Table 1. In general, IRSST (3) tends to be more restrictive than the two other institutions. The most striking mismatch concerns carbon monoxide, which IRSST has ranked as "no evidence" while EU OSHA (4) and NEG (5) classify it as a proven ototoxic agent. The obvious reason is that carbon monoxide interacts synergistically with noise-induced hearing impairment, but apparently is not an ototoxic agent *per se*.

Trichloroethylene is a well-known disruptor of certain structures in the inner ear. Since these effects tend to occur only at high exposure concentrations, NEG has classified this halocarbon as Category 3 ototoxic substance in compliance with its own quantitative scheme (see above). With regard to mercury, it seems that IRSST has based its differing assessment on a smaller body of data.

An obvious step would be to call for the lowering of the established OELs on the grounds of the substances' ototoxic effects, but this should be undertaken prudently within the approved procedures**.** As a matter of course, every toxicological endpoint including ototoxicity has to be taken into account when

setting limit values. The point of departure for deriving OELs is usually the so-called "critical effect", i.e. the most sensitive health effect caused by a substance. However, we are not aware of any workplace substance for which ototoxity has been identified as the critical effect. Usually, ototoxicity seems to be a phenomenon of higher exposure concentrations. This observation is not necessarily in contradiction to the NEG statement that human data indicate auditory effects below or near the existing OELs for at least six chemicals. On the one hand, the reference lists in the NEG report reflect a wide range of OELs for a given substance, including relatively high limit values, for which newer information concerning various toxicological endpoints require urgent revision and lowering. On the other hand, most field studies lack a proper characterisation of historic exposure, thus hampering the use of these data for a sound OEL derivation.

Another regulatory problem is the interaction with noise, which has not been investigated in a satisfactory manner. This issue has recently been tackled systematically in another literature review by IRSST. In the English abstract of their French publication (13), the IRSST authors state: "The result is that it is very difficult to combine all of the data to arrive at solid conclusions. Of all the articles consulted, there are only two cases of interaction with noise: toluene and noise acting synergistically, and carbon monoxide possibly potentiating the effect of noise. This does not exclude the possibility that other chemical substances can worsen hearing losses due to noise." Again, IRSST's assessment seems to be rather conservative and refers to selected agents exclusively. There is further evidence, for instance, that a broad range of volatile lipophilic solvents can exacerbate noise-induced hearing impairment to a certain extent (4, 11).

CONCLUSIONS

All the substances listed in Table 1, namely toluene, styrene, lead, trichloroethylene, mercury, carbon monoxide, and carbon disulfide, deserve special attention with regard to their ototoxic properties when deciding on appropriate risk management measures in occupational settings.

Having examined the existing information, two specialised working groups of the German Social Accident Insurance (DGUV) have concluded that the risk of hearing impairment may become high if the current German OELs for ototoxic substances are exceeded. These working groups have made the following recommendations (14), which may serve as a general guideline for industrial hygienists:

- Occupational health professionals and the workforce should be made aware of the risks posed by ototoxic substances. Employers and workers should be advised accordingly.
- Risk management measures aimed at reducing exposure to ototoxic substances should be encouraged.
- Ototoxicity should make part of occupational health-screening activities.
- Appropriate tools should be developed for early diagnosis of chemically induced hearing impairment.
- Suitable scientific investigations into ototoxic properties should be encouraged such as longitudinal epidemiological studies. Further research should focus on quantifying the combined effects of ototoxic substances and noise.

However, the European statistics on occupational diseases and their prevalent causes clearly indicate that ototoxic substances should not divert risk managers' attention from the fundamental requirements in combating noise-induced hearing loss at the workplace that still has priority over chemically-induced hearing impairment.

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Sažetak

OTOTOKSIČNE TVARI NA RADNOM MJESTU: KRATAK UVID U STANJE

Ototoksične kemikalije mogu narušiti osjetilo sluha i ravnotežu. Nedavno su uloženi dodatni napori u izradu znanstveno utemeljenih popisa tvari koje su prisutne na radnom mjestu, a koje imaju ototoksična svojstva. Ovaj rad daje kratak uvid u najnovije publikacije objavljene na ovu temu. Usporedba navedenih publikacija potvrđuje da bi toluen, stiren i olovo trebalo razmatrati kao izrazito bitne ototoksične tvari koje postoje na radnom mjestu. Nadalje, postoje dovoljni dokazi koji potvrđuju da ototoksične tvari poput trikloretilena, žive, ugljikova monoksida i disulfida u radnom okruženju mogu oštetiti sluh. Temeljem postojećih informacija stručnjaci u području higijene rada trebali bi upozoravati stručnjake u području medicine rada i same radnike na rizike koje ototoksične tvari predstavljaju; poticati ih na zamjenu takvih tvari ili uvođenje novih mjera za smanjenje izlaganja; uključiti ototoksične tvari u redoviti program praćenja i osmisliti mjere za rano otkrivanje oštećenja sluha zbog izloženosti kemijskim tvarima; dodatno istražiti ototoksična svojstva ovih tvari. Buduća istraživanja trebala bi se usredotočiti na izračun ukupnih učinaka ototoksičnih tvari i buke.

KLJUČNE RIJEČI: *ksilen, olovo, oštećenje sluha, procjena rizika koja se temelji na znanstvenim činjenicama, stiren, toluen, trikloretilen, ugljikov disulfid, ugljikov monoksid, živa*

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DOI: 10.2478/10004-1254-63-2012-2209

Review

SHIFT WORK AND CANCER: STATE OF SCIENCE AND PRACTICAL CONSEQUENCES*

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Received in January 2012
CrossChecked in January 2012
Accepted in April 2012

In 2007, an expert Working Group convened by the IARC Monographs Programme concluded that shift work that involves circadian disruption is probably carcinogenic to humans (Group 2A). We scrutinised the epidemiological basis for this conclusion, with a focus on, but not limited to, breast and prostate cancers. We further considered practical consequences for shift workers in our industry against the background of new findings.

We carried out a literature search including the epidemiological studies cited by IARC and newer available literature on shift work and cancer.

Since the IARC assessment, eleven new studies have emerged, ten of which have already been published, with inconclusive results. Heterogeneity of exposure metrics and study outcomes and emphasis on positive but non-significant results make it difficult to draw general conclusions. Also, several reviews and commentaries, which have been published meanwhile, came to equivocal results. Published evidence is widely seen as suggestive but inconclusive for an adverse association between night work and breast cancer, and limited and inconsistent for cancers at other sites and all cancers combined.

At this point in time it can not be ruled out that shift work including night work may increase the risk for some cancers in those who perform it. However, shift schedules can be organised in ways that minimise the associated health risks, and the risks may be further reduced through the implementation of structured and sustained health promotion programs specifically tailored to the needs of shift workers.

KEY WORDS: *breast cancer, circadian disruption, night work, prostate cancer*

Nearly 20 % of the working population in Europe and North America works in shifts and because of the nature of the production processes involved - the chemical industry is particularly dependent on this type of work organisation. In 2007, an expert Working Group convened by the International Agency for the Research on Cancer (IARC) Monographs Programme concluded on the basis of "limited evidence in humans for the carcinogenicity of shift work that involves night work", 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) (1). This ruling, which was only published as a short "policy watch" notice, was soon challenged by other scientists on the basis of a systematic review of the relevant literature (2). However, an in-depth discussion of the IARC assessment has only recently become possible due to the fact that the full monograph was only published three years after the first communication (3). In this article we will shortly summarise the epidemiological basis for the IARC assessment and address some

* Partly presented at the 39th International MEDICHEM Congress on Occupational and Environmental Health in the Production and Use of Chemicals "Occupational Health in a Changing World", Heidelberg, Germany, 2 - 5 June 2011

inconsistencies, which in our opinion had been given too little weight by IARC. We will then summarise the new literature on this topic and finally, based on practical experience from a major chemical company in Germany, address the question of consequences for the shift work organisation in industry. For the purpose of this article, shift work is always considered as work involving night work.

THE IARC ASSESSMENT

The IARC ruling was mainly based on two types of study populations; first, the published cancer experience from nurse cohort members with and without shift work, and second, the respective findings in flight attendants and pilots. In the latter case, long-haul flights across time zones were taken as a proxy for shift work, because they were considered to cause "circadian disruption", a concept which IARC sees as instrumental for the development of cancer in so exposed persons. Noteworthy, on the 200 pages of the monograph the term "circadian disruption" occurs approximately 40 times, with no definition provided. For the purpose of the following discussion we may tentatively assume that it refers to desynchronisation of two or more of the more than hundred known physiological processes, which show circadian periodicity in humans. However, IARC leaves open the question of which ones may be of relevance, and to which degree such a disruption would have to occur to be of biological significance.

As a matter of fact, most of IARC's ruling is thus based on the reports of female breast cancer. In evaluating the evidence in humans, IARC offers a very straight-forward approach: six out of eight studies (excluding female flight attendants) included in the review have shown modestly elevated risks, and the incidence of breast cancer was also modestly increased in most cohorts of female flight attendants (1). The following Table 1 with the main results from the eight studies in "non-aircraft" populations shows that this simplified comparison may not represent the full picture.

Elevated breast cancer risks appear either after having worked in shifts for 30 years (4, 9), or after a cumulative exposure to shift work of only six months (8). They also appear after having worked in shifts for a little more than three years, but only in women aged 50 years or more (7). Thus, even in this small subset of studies there is considerable heterogeneity regarding dose metrics and dose-response relations.

IARC scrutinised nine studies on breast cancer in aircraft crew (12-20). Most risk estimates from these studies are in the range between 1 and 2, but only four out of the nine studies reach at least borderline statistical significance (12, 14, 16, 18). IARC acknowledges the fact that aircraft crew is exposed to other possible carcinogenic agents, most notably cosmic radiation. Indeed, most of the aircraft crew studies were originally targeted at the effects of cosmic radiation, estimating cumulative radiation doses as exposure of interest. IARC explicitly assumes that the number of flights across several time zones, which is used as a proxy of frequency of circadian rhythm disruptions, correlates with the dose of cosmic radiation. Therefore, according to IARC, the estimates of cancer risk in cumulative radiation dose categories could also be interpreted to roughly reflect the frequency of circadian rhythm disruptions. This assumption, however, disregards that daytime flights in the north-south direction, thus along one meridian, would contribute to the radiation dose but per definition not lead to "circadian disruption".

The prostate cancer incidence in aircraft crews has been found elevated for pilots, but not for cabin crew, in several of the older studies. This excess risk has decreased over time and is, according to IARC, probably attributable to the use of prostate specific antigen (PSA) testing, which was common in pilots much earlier than in the general population. The two largest and most recent studies available in this category have found no elevated risks for prostate cancer mortality (20, 21). Only two reports on prostate cancer risks from other shift-working populations have been considered by IARC. In one study, a relative risk (RR) of 2.3 based on three cases was seen in persons working in fixed night shifts, while a RR of 3.0 (confidence interval (CI) 1.2 to 7.7; seven cases) resulted for rotating shift workers (22). The other study found an odds ratio (OR) of 1.19 (CI 1.0 to 1.42) for persons who "normally worked full-time rotating" shift, but it did not explain what "normally" meant (23). Contrary to IARC's reading of the paper there was no apparent trend with cumulative shift exposure. A third study did not enter into this comparison, which reported standardised incidence ratios close to unity for persons who worked in occupations with >40 % shift workers (6).

The evidence found by IARC for other cancers is even weaker and will not be discussed in detail in this

article. The picture gained so far, however, provokes the question whether there was indeed enough evidence for the carcinogenicity of shift work at the time of the IARC assessment to warrant a classification of this link as "probable". We may also ask whether this ruling, if warranted, should apply to all cancers or only to female breast cancer.

STUDIES SINCE THE IARC ASSESSMENT

We carried out a PubMed literature search using the search term "shift work OR night work OR circadian disruption AND cancer" for the period between 2007 and the end of 2011. This search yielded 363 hits, which were then restricted to ten original epidemiologic studies in humans; excluding reviews, studies targeting exposures that may include but go beyond shift work (e.g., light at night), and studies examining surrogates for effects (e.g., cancer biomarkers) (Table 2). One additional study, which was presented at the International EPICOH and MEDICHEM Meeting in Taiwan but has not been published to date, is further mentioned as personal communication.

Since 2007, six new studies have emerged which can shed more light on the possible link between shift work and female breast cancer. One study in a population-based Chinese cohort found a hazard ratio (HR) of 1.0 (CI 0.9 to 1.2) for ever working night shifts on the basis of a job exposure matrix; the HR was 0.9 (CI 0.7 to 1.1) on the basis of self-reported history of night shift work (24). In 2010, data from a nested case-control study in a different cohort consisting of 267,000 Chinese textile workers were presented for the first time in Taiwan. The RR for

Table 1 *Heterogeneity in exposure metrics and thresholds in female breast cancer studies (non-aircraft) quoted in the IARC assessment; *RR/OR = relative risk or odds ratio, as applicable; CI = confidence interval*

Study type	Population	Risk estimate (OR/RR; CI)*	Exposure to shift work	Source (ref number)
Cohort	Nurses, NHS (n=121,701)	1.36 (1.0 to 1.78)	≥30 years	Schernhammer et al. 2001 (4)
Cohort	Nurses, NHS II (n=116,087)	1.79 (1.06 to 3.01)	≥20 years	Schernhammer et al. 2006 (5)
Cohort	General population (n=1,148,661)	0.97 (0.67 to 1.40)	occupation with >40 % shift workers	Schwartzbaum et al. 2007 (6)
Nested case-control	Radio and telegraph operators, 50 cases, 4-7 matched controls	0.9 (0.3 to 2.9) 4.3 (0.7 to 26.0)	age <50 and shift work >3.1 years age ≥50 and shift work >3.1 years	Tynes et al. 1996 (7)
Case-control	General population, 7035 cases, one matched control per case	1.5 (1.2 to 1.7)	≥0.5 year in ≥1 trade in which ≥60 % of the female responders had night time schedules	Hansen 2001 (8)
Nested case-control	Nurses, 537 cases, 4 matched controls per case	1.3 (0.8 to 2.0) 2.2 (1.1 to 4.5)	15 to 29 years ≥30 years	Lie et al. 2006 (9)
Case-control	General population, 813 cases, 792 age matched controls	1.4 (1.0 to 2.0)	ever night shift (at least 3 nights per week)	Davis et al. 2001 (10)
Case-control	General population, 576 cases, 585 age matched controls	0.55 (0.3 to 0.9) 1.2 (0.9 to 1.6)	any overnight shift evening shift only	O'Leary et al. 2006 (11)

Table 2 *Studies on shift work and cancer, published after the IARC assessment; *RR/OR/HR = relative risk, odds ratio or hazard ratio, as applicable; CI = confidence interval*

Study type and cancer of interest	Population	Risk estimate (OR/RR/HR; CI)*	Exposure metric	Source (ref number)
Cohort Female breast	General population, Shanghai Women's Health Study, (n=73,049)	1.0 (0.9 to 1.2) 0.9 (0.7 to 1.1)	ever night shift (job exposure matrix) ever night shift (self-report)	Pronk et al. 2010 (24)
Case-control Female breast	General population, 857 cases, 892 controls	0.98 (0.74 to 1.29) 1.01 (0.68 to 1.50) 0.91 (0.38 to 2.18) 2.49 (0.87 to 7.18)	ever shift work ever night work 10 to 19 years night ≥20 years night	Pesch et al. 2010 (25)
Case-control Female breast	General population, 1230 cases, 1315 controls	1.4 (0.9 to 2.1) 2.4 (0.9 to 6.0) 1.5 (0.9 to 2.6)	employed >10 years as nurse textile workers tailors/dressmakers	Villeneuve et al. 2011 (26)
Nested case-control Female breast	Danish nurses, 310 cases, 4 age matched controls per case	0.9 (0.4 to 1.9) 1.8 (1.2 to 2.8) 2.9 (1.1 to 8.0)	ever evening shift, never night ever after midnight rotating shift, never permanent night ever permanent night in addition to rotating night shifts	Hansen and Stevens 2011 (27)
Nested case-control Female breast	Norwegian nurses, 699 cases, 895 frequency matched controls	1.1 (0.8 to 1.6) 1.2 (0.8 to 1.7) 1.8 (1.1 to 2.8)	worked ≥5 years with ≥3 consecutive night shifts worked <5 years with ≥6 consecutive night shifts worked ≥5 years with ≥6 consecutive night shifts	Lie et al. 2011 (28)
Cohort Prostate	4995 male industry workers, age 49 to 65 years (4168 daytime workers, 827 shift workers, 4 exposed cases)	1.79 (0.57 to 5.68)	three-shift work for >80 % of career	Kubo et al. 2011 (29)
Cohort Prostate	General population (15 million, 339,973 cases)	All risks for occupations with shift work around unity	Occupation with high probability for night work	Pukkala et al. 2009 (30)
Cohort Ovarian	Nurses, NHS I+II (n=181,548), 718 cases	1.28 (0.84 to 1.94) 0.80 (0.51 to 1.23)	15 to 19 years rotating night shift ≥20 years rotating night shift	Poole et al. 2011 (31)
Cohort Skin melanoma	Nurses, NHS I (n=68,336), 10,799 cases	0.80 (0.51 to 1.23) skin cancer 0.56 (0.36 to 0.87) melanoma	>10 years rotating shift	Schernhammer et al. 2011 (32)
Cohort Non-Hodgkin's lymphoma	General population (n=1,669,272), 6,307 NHL cases	1.10 (1.03 to 1.19)	Occupation with high probability for night work	Lahti et al. 2008 (33)

having worked shifts for 1 to <10 years, 10 to <20 years, and 20+ years compared with less than 1 year were 0.99, 1.0, and 0.92, respectively (W. Li, personal communication). In a re-analysis of case-control data originally gathered for a different set of risk factors, shift work (ever vs. never) had an OR for female breast cancer of 0.98 (CI 0.74 to 1.29); night work (ever vs. never) was associated with an OR of 1.01 (CI 0.68 to 1.50); there were non-significantly reduced risk estimates for exposure metrics below the median, and non-significantly increased risks above the median. The OR was 2.49 (CI 0.87 to 7.18) for more than 20 years of night shift work, while all other risk estimates were below unity (25). Surprisingly, the authors of this study concluded that their findings were "in line with the IARC classification." In a French case-control study on occupation as a risk factor for breast cancer, an OR of 1.4 (CI 0.9 to 2.1) emerged for women employed for more than 10 years as nurses. An overall OR of 2.4 (CI 0.9 to 6.0) was reported in textile workers and 1.5 (CI 0.9 to 2.6) in tailors/dressmakers, with no information available on working time schedules of these occupational groups (26). In a nested case-control study from a cohort of Danish nurses, significantly increased ORs ranging between 1.8 and 2.9 were found when work after midnight was compared with permanent day work (27). There was no apparent effect of evening work, if night work was excluded. An interesting new aspect was added by the re-analysis of data from a Norwegian case-control study (9, 28). Here, a significantly increased OR of 1.8 (CI 1.1 to 2.8) was seen in nurses who worked ≥5 years with ≥6 consecutive night shifts.

Two new studies have emerged regarding prostate cancer. An OR of 1.79 (CI 0.57 to 5.68), based on only four exposed cases, was seen in persons who had performed three-shift work for >80 % of their career, if compared to persons who had never worked shifts (29). On the other hand, no indication of an association with occupation was seen among 339,973 prostate cancer cases in a cohort of 15 million people aged 30 to 64 years in the 1960, 1970, 1980/1981 and/or 1990 censuses in Denmark, Finland, Iceland, Norway and Sweden (30).

Little new information has emerged for other cancer types. In one study, the HR for ovarian cancer was 1.28 (CI 0.84 to 1.94) in women who performed 15 to 19 years of rotating night shifts, and 0.80 (CI 0.51 to 1.23) for those with more than 20 years of shift work (31). A 14 % decreased risk of skin cancer, and 44 % decreased risk of melanoma, was seen after more than 10 years of rotating night shifts (32). The RR for non-Hodgkin's lymphoma was 1.10 (CI 1.03 to 1.19) for men who worked night shifts, and it increased to 1.28 (CI 1.03 to 1.59) when a lag period of 10 years was applied (33).

CONSEQUENCES FOR SHIFT WORKERS IN INDUSTRY - EXPERIENCE FROM A LARGE CHEMICAL COMPANY

While we agree with the conclusion drawn by Wang et al. (34) in their in-depth review that "heterogeneity of study exposures and outcomes and emphasis on positive but non-significant results make it difficult to draw general conclusions" from the existing literature on shift work and cancer, this lack of evidence should not lead to complacency in the persons who are responsible for workers' health. Recommendations for measures to counteract expected negative effects of night work are more often "eminence-based" than "evidence-based" (35). These recommendations include a selection of "shift tolerant" individuals, favouring of forward rotating shift schedules (morning - afternoon - night) over backward rotation (night - afternoon - day), avoidance of multiple night-shifts in a row, interventions through bright light or medication, physical exercise, and others.

Given that shift work is simply unavoidable in many occupations and industries, it is the duty of occupational physicians and scientists to examine the potential risks associated with this kind of work organisation. Health risks, if any, have to be minimised as far as possible and, where they can not be avoided, means of intervention and - if necessary - compensation have to be discussed. To this end we performed studies in more than 17.000 shift and 13.000 day workers at a major chemical site in Germany. We compared the acute and chronic illness experience, the accident rates, and the overall mortality across these groups of workers with the surprising result of generally more favourable outcomes for shift workers, after adjusting for smoking habits and other known relevant confounders (36, 37). Even the overall cancer incidence was reduced in shifts if compared to day workers. It has to be emphasised, however, that owing to German data protection legislation our database is weak regarding cancer incidence, and our conclusions regarding the question of carcinogenicity of shift work in our workforce are preliminary. There are several

possible explanations for the unexpected lack of adverse health effects of shift work in this study population. First, the shift system in place never requires more than one night shift in a row. Second, it is forward rotating, with night work always followed by a resting period of 24 (old system) or 48 hours (new system). With regard to the IARC concept of "circadian disruption", we hypothesise that desynchronisation of circadian biological rhythms does not occur to a sizable degree under these circumstances. This assumption can further be supported by the observation that workers in both shift systems did not complain about subjective health impairment more than day workers with the same socio-economic background (38). Whether health promotion programs for workers result in long-term health benefits is equivocal (39, 40), but it may reasonably be assumed provided such programs are not only offered on a one-time basis. We were indeed able to demonstrate that shift workers in our studied populations were more often participating in such programs than day workers, and participation in health promotion activities was associated with reduced overall mortality, if compared to non-participation (41). However this reduced mortality was not apparently triggered by reduced cancer incidence in participants (RR 1.07; CI 0.84 to 1.36).

CONCLUSION

Based on the literature available, it can not be confidently ruled out that shift work including night work may, possibly depending on the way how it is organised, increase the risk for some cancers in those who perform it. However, at this point in time there is no reason to believe that shift-workers in general face an increased cancer risk. In any case, shift schedules can probably be organised in ways that minimise the associated health risks, and the risks may be further reduced through the implementation of structured and sustained health promotion programs specifically tailored to the needs of shift workers. The recommendation to use fast forward rotating shift schedules with no more than one or two subsequent night shifts can be supported on the basis of our experience.

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Sažetak

RAD U SMJENAMA I RAK - ZNANSTVENE SPOZNAJE I PRAKTIČNE POSLJEDICE

Stručna radna skupina, koju je okupio Program monografija Međunarodne agencije za istraživanje raka (eng. *International Agency for Research on Cancer*, krat. IARC), 2007. godine zaključila je da je rad u smjenama, koji uključuje prekid cirkadijurnoga ritma, najvjerojatnije kancerogen za ljude (skupina 2A). Procijenili smo epidemiološku osnovu takvoga zaključka i usredotočili se na rak dojke i rak prostate između ostalih malignih bolesti. Nadalje, razmatrali smo praktične posljedice koje rad u smjenama ima na radnike u kemijskoj kompaniji BASF u okvirima novih spoznaja na tom području.

Istražili smo literaturu, uključujući i epidemiološka istraživanja studije koje citira IARC kao i noviju literaturu o povezanosti rada u smjenama i raku.

Od zaključka IARC-a nastalo je jedanaest novih istraživanja, a deset ih je već objavljeno. Njihovi rezultati ipak ne dovode do konačnoga i jednoznačnoga zaključka. Heterogenost mjerenja izloženosti i ishoda istraživanja i naglasak na pozitivne, ali ne uvijek i značajne rezultate, otežavaju postavljanje općih zaključaka. Jednako tako u nekoliko nedavno objavljenih recenzija i komentara ne iznose se jednoznačni rezultati. Objavljeni znanstveno utemeljeni dokazi samo upućuju, ali ne dovode u očiglednu vezu noćni rad i rak dojke. Nadalje, ograničeni su i nedosljedni za malignome na drugim lokacijama u tijelu, kao i za sve malignome zajedno.

U ovom trenutku nije moguće odbaciti hipotezu da smjenski rad (uključujući noćni rad) može povećati rizik nastanka određenih malignih bolesti. Međutim, raspored smjena se može organizirati na način da se opasnosti za zdravlje svedu na najmanju moguću mjeru. Rizici se također mogu dodatno smanjiti provedbom strukturiranih programa promicanja održivoga zdravlja koji bi bili posebno osmišljeni prema potrebama radnika.

KLJUČNE RIJEČI: *noćni rad, prekid cirkadijurnog ritma, rak dojke, rak prostate*

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DOI: 10.2478/10004-1254-63-2012-2186

Scientific Paper

EFFECTS OF EXPOSURE TO MIXED ORGANIC SOLVENTS ON BLOOD PRESSURE IN NON-SMOKING WOMEN WORKING IN A PHARMACEUTICAL COMPANY

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Received in December 2011
CrossChecked in December 2011
Accepted in March 2012

Some studies suggest that exposure to industrial solvents can affect blood pressure. The objective of this study was to investigate the effect of a mixture of organic solvents on blood pressure in women working in a pharmaceutical company in Iran. Four hundred and thirty-three women were included in the study. Women working in packing units (group 1) were not exposed to the mixture of organic solvents, women in new laboratory units (group 2) were exposed to the mixture within the permitted range and women working in old laboratory units (group 3) were exposed to the mixture above the permitted limit. We compared systolic and diastolic blood pressures (SBP & DBP) and prevalence of hypertension and pre-hypertension among groups. The results revealed a significant difference in SBP and pre-hypertension ($p<0.001$) and hypertension ($p<0.05$) prevalence between the exposed and the control group, but DBP did not differ significantly. Logistic regression analysis showed a significant association between hypertension and exposure to mixed solvents. Odds ratio for hypertension in the group 2 and group 3 (exposed) workers was 2.36 and 3, respectively, compared to controls. Our results suggest that exposure to a mixture of organic solvents may increase SBP and hypertension and pre-hypertension prevalence in drug manufacture workers. Therefore, more attention should be paid to workers that work in such settings by periodically measuring blood pressure and implementing accurate and comprehensive programs to reduce exposure to organic solvents.

KEY WORDS: *hypertension, industrial solvents, occupational exposure*

According to the Seventh Report of the Joint National Committee on Hypertension of 2003, hypertension was a major public health concern affecting about 50 million people in the USA and about one billion people all over the world (1). Hypertension is still a serious public health concern and is a major risk factor for heart failure, myocardial infarction, and some cerebrovascular diseases such as stroke (2). Therefore, priority should be given to the recognition, treatment, and control of this public health problem (3).

Organic solvents are frequently used in the production of dyes, plastic and rubber, and in the printing industry (4). According to NIOSH (National Institute for Occupational Safety and Health), 9.8 million American workers were exposed to solvents in the first half of the 1970s (4). A number of studies have shown that organic solvents are associated with

auditory (5), visual (6), cardiovascular (7), neurological (8), and other complications (9-11). Some suggested that chronic exposure to industrial solvents can affect blood pressure (12-16). Bener et al. (13) investigated the prevalence of hypertension among workers who were exposed to gasoline vapour in their workplace; 71.4 % of the exposed group and 28.6 % of the control group had taken medications for the treatment of hypertension, and the difference was statistically significant ($p<0.001$). The 90th percentile of systolic blood pressure in the exposed group was 140 whereas in the control group it was 130. In a study by Kotseva et al. (7) occupational exposure to high levels of xylene and benzene increased the prevalence of hypertension in workers. In a study by Mørck et al. (17), a significant rise in systolic blood pressure was found among workers occupationally exposed to toluene. After six weeks without exposure, systolic blood pressure decreased. However, other studies found an insignificant increase in blood pressure in workers exposed to mixed organic solvents compared to control (18, 19).

The exact mechanism of the effect of solvents on blood pressure is still unclear. In a study on rats, Sun et al. (20) examined endothelial nitric oxide synthase (eNOS) activity and blood pressure level following exposure to trinitrotoluene (TNT). They found that TNT inhibited eNOS activity and increased systolic blood pressure (20).

Evaluating exposure to a single organic solvent is rather difficult because workers are normally exposed to varying concentrations of mixtures of organic solvents over different time spans (21). However, there are only a few studies on the relation between mixture of solvents and blood pressure.

The pharmaceutical industry employs more than 350 thousand people all over the world in various operations including marketing, sales, manufacturing, and research and development. People most likely to be exposed to drug substances and chemical precursors in their occupational setting are those working in research and development and manufacturing (22). Solvent use is common in pharmaceutical industry and consistently accounts for between 80 % and 90 % of mass utilisation in a typical pharmaceutical batch chemical operation (23).

The objective of the present study was to examine the effect of a mixture of organic solvents on blood pressure in women working in a pharmaceutical company.

MATERIALS AND METHODS

Study design and subjects

We conducted a cross-sectional study in a pharmaceutical plant in Iran during 2010-2011. It included all workers with at least one year of working experience in the company, 449 in total. All the workers were women. From the records and interviews we gathered the following data for all of them: age, length of service, work schedule, second or previous occupation, personal habits, regular exercise, cigarette smoking, tea and salt consumption habits, systemic disease history (such as diabetes mellitus, cardiac or renal diseases), family history of hypertension and drug history. Regular exercise was defined as at least half an hour of physical activity three or more times a week (24). Responses to the question on dietary salt were classified into three groups: low intake (lower than usual: no adding salt when cooking), moderate intake (usual: no adding salt when eating) and high intake (more than usual: adding salt when eating). Work schedule was divided into shift work and day work. Fixed day shift was considered day work, and other schedules were considered shift work (25).

Exclusion criteria were pre-employment history of hypertension or known chronic illnesses such as diabetes mellitus, cardiovascular and cerebrovascular diseases and exposure to organic solvents in past jobs, second jobs or because of personal habits (26). After applying these criteria, 16 women were excluded and 433 remained in the study: 212 in packing units (group 1 - unexposed controls), 146 in new laboratory units (group 2 - low exposure), and 75 in old laboratory units (group 3 - high-exposure). All women participated voluntarily and signed the informed consent form. The study was approved by the ethics committee of Tehran University of Medical Sciences.

All workers were interviewed and examined by an occupational medicine physician.

Blood was collected and blood pressure measured under fasting conditions between 8:00 and 9:00 am, just before starting work. Blood pressure was taken with each subject sitting on a chair after at least five minutes of rest.

Systolic and diastolic blood pressure (SBP and DBP, respectively) were measured twice in the right arm, using a standard mercury sphygmomanometer. The mean value of the two blood pressure measurements was used for this study. We defined hypertensive

subjects as those who reported diagnosed hypertension or those whose mean resting SBP and resting DBP were ≥140 mm Hg and ≥90 mm Hg, respectively. Pre-hypertension was defined as mean resting SBP between 120 mm Hg and 139 mm Hg or mean resting DBP between 80 mm Hg and 89 mm Hg. Furthermore, for each subject, we measured fasting blood sugar (FBS), lipid profile including cholesterol, triglycerides, low-density lipoprotein (LDL) and high-density lipoprotein (HDL), as well as liver function including alanine transaminase (ALT), aspartate aminotransferase (AST), and alkaline phosphatase (ALP). Workers' heights and weights were used to calculate body mass index (BMI).

Exposure assessment

The company's occupational hygiene team performed air monitoring for all existing solvents in the working environment. In order to determine solvent exposure in each location, the team also performed an analysis of workplaces and identified a set of job descriptions for each workplace. All eight-hour time-weighted measurement averages were based on environmental sampling for each workplace. Air was monitored continuously over the eight hour shift. Air samples were collected on charcoal tubes with constant flow (100 mL min^{-1}) pumps (SKC 226-01, Gulf Coast Inc., USA) at 42 stations designed for the new laboratory units, 29 stations designed for the old laboratory units and 36 stations designed for the packing units. According to the NIOSH analytical method 1501 for aromatic hydrocarbons, the charcoal tubes were located at a height of 1.5 m (27). Subsequently, gas chromatography (Hewlett-Packard 5890, Avondale, PA, USA) was used to analyse the samples and the average concentration of each solvent was identified.

The solvents present in all laboratory units of the factory were toluene, xylene, formaldehyde, phenol, *n*-hexane, and chloroform.

The American Conference of Governmental Industrial Hygienists (ACGIH) equation was used to evaluate occupational exposure of workers to the organic solvents mixture (28).

$$E_m = C_1/L_1 + C_2/L_2 + \ldots. + C_n/L_n$$

where E_m is the equivalent exposure for the organic solvents mixture, C is the mean concentration level of organic solvents in the air of the workstation, and L is the exposure limit for organic solvents. In this equation, E_m above 1 indicates that the level of organic solvent mixture in the workplace is higher than the permissible limit (28). Since the equation of mixed organic solvents can only be used for solvents with identical adverse effects on target organs or systems, we only inserted solvents with similar adverse effects on cardiovascular system into the equation; these organic solvents were toluene, xylene and phenol.

Mean concentrations of toluene, xylene, and phenol in new laboratory units were12.3 mg m^{-3}, 53 mg m^{-3}, and 0.98 mg m^{-3}, respectively, and the concentrations in old laboratory units were 90 mg m^{-3}, 278 mg m^{-3}, and 1.99 mg m^{-3}, respectively. The exposure limit for toluene, xylene and phenol is 192 mg m^{-3}, 442 mg m^{-3}, and 19.6 mg m^{-3}, respectively.

In the high-exposure group (old laboratory units), E_m ranged from 1.094 to 2.820 and its median value was 1.202. In the low-exposure group (new laboratory units), E_m was between 0.183 and 0.631 and its median value was 0.234. E_m values indicated that the concentration of mixed organic solvents in old laboratory units was above the permitted limit whereas in new laboratory units it was within the permitted range.

Finally, in the non-exposure group (packing units) the concentrations of organic solvents were negligible.

Statistical analysis

We calculated mean, range and standard deviation (SD) of quantitative variables and used ANOVA to compare these variables between the groups. Chi-square was used to compare qualitative variables. Logistic regression analysis with confounding variables eliminated was used to establish the correlation between hypertension and exposure to mixed organic solvents. Continuous variables of age, length of service and body mass index were categorised based on the median of each variable. The level of significance was set at $p<0.05$. We also used odds ratio (OR) with 95 % confidence intervals (95 % CI) to express the results of our analysis. All study variables were analysed using SPSS 11 software.

RESULTS

We evaluated 433 women working in a drug manufacturing plant. The workers' mean age was 31.72 years, range (22 to 55) years. Their average

Table 1 *Demographic variables and risk factors for hypertension in study groups*

Variable	Unexposed (control) group (N=212)	Low-exposure group (N=146)	High-exposure group (N=75)	p-value
[a]Age / year	32.3±4.6	31.6±5.1	30.5±5.8	0.049
[a]Length of service / year	9.5±5.4	8.7±5.0	7.9±4.8	0.051
[a]Body mass index / kg m^{-2}	24.1±3.3	23.5±3.5	23.0±3.4	0.065
[b]Tea consumption / Yes	132 (62.2)	87 (59.5)	45 (60.0)	0.923
[b]Dietary salt				
Low	103 (48.6)	85 (58.2)	39 (52.0)	0.365
Moderate	77 (36.3)	39 (26.7)	24 (32.0)	
High	32 (15.1)	22 (15.1)	12 (16.0)	
[b]Regular exercise / Yes	36 (16.9)	25 (17.1)	11 (14.6)	0.881
[b]Shift work / Yes	46 (21.6)	31 (21.2)	16 (21.3)	0.914
[b]Family history of hypertension / Yes	15 (7.0)	10 (6.8)	5 (6.6)	0.992

[a]*Data are expressed as mean±SD*
[b]*Data are expressed as number of persons and percent of N*

Table 2 *Prevalence of hypertension and pre-hypertension and mean SBP* & DBP** in studied groups*

Study groups	SBP / mm Hg Mean±SD	DBP / mm Hg Mean±SD	Hypertension n (%)	Pre-hypertension n (%)
Non-exposure group (N=212)	125.1±14.0	75.6±12.6	18 (8.4)	34 (16.0)
Low-exposure group (N=146)	127.5±15.7	77.5±13.8	21(14.3)	67 (45.8)
High-exposure group (N=75)	133.9±9.7	79.2±13.3	14 (18.6)	39 (52.0)
p-value	< 0.001	0.145	0.024	< 0.001

* *Systolic blood pressure*
** *Diastolic blood pressure*
n = number of persons

length of service was 9.04 years, range (1 to 26) years and average BMI was 23.75 kg m^{-2}, range (17.21 to 32.14) kg m^{-2}. In our study, 93 workers (21.5 %) were shift workers. Table 1 summarises the demographic variables and potential risk factors for the study groups. There were no statistically significant differences between the groups in the length of service, body mass index, tea consumption, dietary salt, regular exercise, shift work, and family history of hypertension. However, the mean age was higher in group 1 ($p<0.05$). There were no statistically significant differences between the groups in FBS, lipid profiles (cholesterol, triglycerides, LDL and HDL), and liver function tests (ALT, AST and ALP).

Mean resting SBP and DBP were 127.28 mm Hg, range (90 to 160) mm Hg and 76.27 mm Hg, range (50 to 110) mm Hg, respectively. Fifty-three (12.2 %) workers were hypertensive and 140 (32.3 %) pre-hypertensive. Table 2 shows mean SBP and DBP and hypertension and pre-hypertension prevalence in the studied groups. There was a significant difference between the control group and groups 2 and 3 in SBP and prevalence of pre-hypertension ($p<0.001$) and hypertension ($p<0.05$), but there was no significant difference in DBP (Table 2). The difference between groups 2 and 3 was only significant in terms of SBP ($p<0.05$).

Logistic regression analysis with adjustment of confounding variables showed that occupational solvents exposure was significantly associated with high blood pressure ($p<0.05$). Compared to the unexposed group, the odds ratio (OR) for hypertension was 3.00 in the group that was exposed to a higher than the permitted level, and it was 2.36 in the group that was exposed to the permitted range (Table 3).

In this study, there was a significant association between hypertension and variables such as age, high dietary salt intake, length of service, BMI, regular exercise, and shift work ($p<0.05$), but there was no association between hypertension and family history of hypertension (Table 3).

DISCUSSION

Our findings suggest that exposure to mixed organic solvents can affect blood pressure. Low-exposure and high-exposure groups have significantly elevated odds ratios for hypertension. No group differed in the length of service, smoking, BMI, and other variables, except average age, which was higher in the control group. Therefore, the correlation between hypertension and exposure to a mixture of organic solvents was not affected by the above mentioned confounding factors.

We observed significantly higher mean SBP between workers with high exposure and low exposure to mixed organic solvents, 8.8 mm Hg and 2.4 mm Hg respectively, compared to the control group.

Gericke et al. (29) studied a group of printers who had been exposed to toluene for more than 20 years and found that chronic exposure to toluene can increase SBP. However, this study did not consider many probable confounders.

In our study, DBP was higher in groups 2 and 3 than in the control group, but this difference was not significant. In a study by Egeland et al. (16) involving 410 male textile workers, 165 of whom were exposed and 245 not exposed to carbon disulphide (CS_2), SPB was not affected by exposure but diastolic blood pressure was. Kaukiainen et al. (12) studied 26 workers with chronic exposure to organic solvents and 19 unexposed volunteer workers. After adjusting for confounding factors such as age, sex, alcohol consumption, cigarette smoking, and BMI, SBP turned out to be significantly higher in the exposed workers, suggesting that lifetime exposure to organic solvents can increase systolic blood pressure.

In our study, the prevalence of pre-hypertension and hypertension was significantly higher in the exposed groups (2 and 3) compared to the control group.

Regression analysis with eliminating confounding factors confirmed the correlation between hypertension and exposure to a mixture of solvents. Compared to the group with no exposure, the odds ratio (OR) for hypertension was 3.00 in the group with exposure above the permitted level, and 2.36 in the group with exposure within the permitted range.

Table 3 *Relationship between hypertension and study variables using logistic regression analysis*

Variable	Status	Adjusted OR	95 % CI	p-value
Study groups	Non-exposure (N=212)	1.00	----------	------
	Low-exposure (N=146)	2.36	1.14-4.82	0.021
	High-exposure (N=75)	3.00	1.30-6.91	0.010
Age / year	≤ 31 (n=223)	1.00	----------	-------
	> 31 (n=210)	2.99	1.24-6.86	0.035
Length of service / year	≤ 9 (n=207)	1.00	----------	-------
	> 9 (n=226)	2.54	1.07-6.09	0.034
Body mass index / kg m^{-2}	≤ 23.4 (n=214)	1.00	----------	-------
	> 23.4 (n=219)	2.03	1.04-3.96	0.038
Dietary salt	Low (n=227)	1.00	----------	------
	Moderate(n=140)	2.41	1.06-4.99	0.047
	High (n=66)	3.35	1.46-7.70	0.004
Regular exercise	Yes(n=72)	1.00	----------	-------
	No(n=361)	4.33	1.27-14.77	0.019
Shift work	No (n=93)	1.00	----------	-------
	Yes (n=340)	2.83	1.18-5.71	0.033
Family history of hypertension	No (n=403)	1.00	----------	-------
	Yes (n=30)	1.48	0.40-5.41	0.551

In another study, Kaukiainen et al. (14) investigated the prevalence of symptoms related to solvent exposure among building painters and found that chronic exposure was associated with hypertension and arrhythmia.

In a study by Wiwanitkit (15), the prevalence of hypertension was significantly higher in the group with high levels of benzene exposure (100 %) than in the group with lower levels of benzene exposure (49 %). This study suggests that disturbance of the nitric oxide process may account for benzene-induced hypertension.

Chang et al. (19) studied 20 workers in a synthetic leather manufacturing company to see if there was an association between hypertension and co-exposure to N,N-dimethylformamide, toluene and noise. They found no significant difference in ambulatory blood pressure between solvent-exposed workers, noise-exposed workers, and workers to this combination compared to the low-exposure group.

Some solvents are associated with cardiovascular diseases (30-32); for example, methylene chloride, styrene and carbon disulfide with coronary artery disease (CAD) and fluorocarbons and tricholoroethane with cardiac arrhythmia. Benzene and xylene have been associated with arterial hypertension (7), and solvent exposure with hypertension in pregnancy (10, 33). According to the study by Xiao and Levin (31), exposure to solvents can cause neurotoxic and neuropsychiatric symptoms and sleep disturbance. This can lead to increased personal stress, which, in turn, can affect blood pressure. Disturbance of the nitric oxide process is the likely mechanism triggering hypertension (15, 20). Using animal models, Leong et al. (34) showed that 50 μL of 10 % phenol injected into the renal cortex of rats may lead to acute hypertension because of the renal sympathetic nerve activation.

In our study, we found an association between hypertension and variables such as age, length of service, BMI, dietary salt, regular exercise, and shift work (Table 3). These findings are similar to the results reported in some earlier studies (26, 35-36).

In our study, the odds ratio for hypertension in shift workers was significantly higher than in daytime workers. Nazri et al. (26) investigated the relationship between shift work and hypertension in workers in a semiconductor manufacturing company. In that study, the prevalence of hypertension among shift workers was significantly higher compared to day workers.

In our study, the odds ratio for hypertension in workers with higher BMI and in workers with irregular physical activity was higher than in the control group. Leung et al. (35) conducted a study among 6193 Chinese students to determine the prevalence and patterns of hypertension. They have suggested that obesity is a predictor of hypertension, while physical activity is a protective factor.

We found that the prevalence of hypertension in workers with moderate and high dietary salt intake was significantly higher than in workers with low dietary salt intake. Cook et al. (36) investigated the effect of a training and consultation program for reducing dietary salt intake on cardiovascular diseases. The results of this study showed that sodium reduction may lead to blood pressure decrease.

Pharmacologically active agents used in pharmaceutical plants can cause adverse health effects, unless occupational exposure is controlled enough (37). Pharmaceutical workers are potentially at risk for occupational asthma, pharmacological effects, adverse reproductive outcomes, dermatitis, and other adverse health effects (22).

This study may have some limitations. First, a cross-sectional design may restrict causal relations. This can be addressed in a prospective cohort study. Another limitation is that in evaluating solvent exposure we relied on environmental monitoring alone. Workers were in separate working environments, which facilitated group classification and exposure assessment, but further studies should consider using biological monitoring instead. Besides, we were not able to calculate cumulative occupational exposure because the information on previous levels of exposure was not available.

We investigated the effects of mixed organic solvents on hypertension, but not the effects of single solvents. However, organic solvent mixtures are more common in workplaces.

CONCLUSION

Our study suggests that exposure to organic solvent mixtures may increase the prevalence of hypertension and pre-hypertension in drug manufacturing workers. Therefore, more attention should be paid to workers that work in such settings by periodically measuring blood pressure and implementing accurate and comprehensive programmes to reduce exposure to organic solvents.

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Sažetak

UTJECAJ IZLOŽENOSTI MJEŠAVINI ORGANSKIH OTAPALA NA KRVNI TLAK NEPUŠAČICA KOJE RADE U FARMACEUTSKOJ TVRTKI

Neka su istraživanja pokazala da izloženost industrijskim otapalima može utjecati na krvni tlak. U ovom smo istraživanju nastojali ispitati utjecaj mješavine organskih otapala na krvni tlak žena koje rade u farmaceutskoj tvrtki u Iranu. Četiristo trideset i tri žene bile su uključene u istraživanje. Žene koje rade u pakirnicama (G1) nisu bile izložene mješavini organskih otapala, žene koje rade u novim laboratorijskim jedinicima (G2) bile su izložene dozvoljenoj granici mješavine, a žene u starim laboratorijskim jedinicama (G3) bile su izložene količini mješavine koja je viša od dozvoljene granične vrijednosti. Usporedili smo sistolički i dijastolički krvni tlak (eng. *systolic blood pressure*, krat. SBP i eng. *diastolic blood pressure*, krat. DBP) i prevalenciju hipertenzije i prehipertenzije između navedenih skupina. Otkrili smo značajnu razliku u vrijednostima SBP-a i prevalencije prehipertenzije ($p<0,001$) i ($p<0,05$) hipertenzije između skupina G2 i G3, te kontrolne skupine (G1), ali se vrijednosti za DBP nisu značajno razlikovale. Logistička regresijska analiza pokazala je značajnu poveznicu između hipertenzije i izlaganja mješavini otapala. U usporedbi s radnicama koje nisu bile izložene mješavini, omjer izgleda za nastanak hipertenzije u skupini G2 iznosio je 2,36, a u skupini G3 3. Naši rezultati pokazuju da izlaganje mješavini organskih otapala može povisiti vrijednost SBP-a i prevalencije hipertenzije i prehipertenzije kod radnika koji rade u proizvodnji lijekova. Stoga je potrebno posvetiti veću pozornost osobama koje rade u takvim okruženjima, a mjere koje bi valjalo poduzimati uključuju redovito mjerenje krvnog tlaka i provedbu preciznih i sveobuhvatnih programa za smanjenje izlaganja organskim otapalima.

KLJUČNE RIJEČI: *hipertenzija, industrijska otapala, izloženost na radu*

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DOI: 10.2478/10004-1254-63-2012-2140

Scientific Paper

PROFESSIONAL STRESS AND HEALTH AMONG CRITICAL CARE NURSES IN SERBIA

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Received in July 2011
CrossChecked in August 2011
Accepted in April 2012

The aim of this study was to identify and analyse professional stressors, evaluate the level of stress in nurses in Intensive Care Units (ICU), and assess the correlation between the perception of stress and psychological and somatic symptoms or diseases shown by nurses. The research, designed as a cross-sectional study, was carried out in the Intensive Care Units (ICU), in health centres in Serbia. The sample population encompassed 1000 nurses. Expanded Nursing Stress Scale (ENSS) was used as the research instrument. ENSS revealed a valid metric characteristic within our sample population. Nurses from ICUs rated situations involving physical and psychological working environments as the most stressful ones, whereas situations related to social working environment were described as less stressful; however, the differences in the perception of stressfulness of these environments were minor. Socio-demographic determinants of the participants (age, marital status and education level) significantly affected the perception of stress at work. Significant differences in the perception of stressfulness of particular stress factors were observed among nurses with respect to psychological and somatic symptoms (such as headache, insomnia, fatigue, despair, lower back pain, mood swings etc.) and certain diseases (such as hypertension, myocardial infarction, stroke, diabetes mellitus etc). In view of permanent escalation of professional stressors, creating a supportive working environment is essential for positive health outcomes, prevention of job-related diseases and better protection of already ill nurses.

KEY WORDS: *professional stressors, psychological and somatic symptoms, questionnaires, workplace*

Stress is one of the most severe occupational risks in the European Union. After back pain and musculoskeletal diseases, it is the second most prevalent work-related health problem (1). According to WHO Expert Committee (1985), work-related diseases are defined as a "wide spectrum of diseases of multifactorial aetiology, which are partly associated with profession or working conditions" (2). In addition to well-known physical, chemical and ergonomic factors, indirect mechanisms such as psychosocial factors and chronic professional stress may play an important role in the development of such diseases (2).

Occupational stress occurs when demands of the working environment overpower the capacities of workers to cope with them. It can affect all categories of workers and all professional areas (1, 3). Professional stress can also be defined as a "pattern of emotional, cognitive, behavioural and physiological reactions to adverse and harmful aspects of work content, work organisation and the working environment" (4, 5).

Recent studies suggest that 50 % to 60 % of all lost working days are related to professional stress (1, 6). According to conclusions of the majority of available research, a higher rate of professional stress is established among middle-aged population, widowed, divorced or separated individuals and among professional groups such as nurses, teachers, and managers (7-9).

Professional stress in nurses

There seems to be a general agreement that work-related stress: decreases the quality of nursing and nursing care, negatively affects job satisfaction (10), increases psychiatric morbidity (high rate of anxiety and depression) (11, 12), and triggers the development of some physical disorders, particularly cardiovascular (13) and locomotor diseases (14, 15).

Research on professional stress in nurses focuses mainly on nurses employed in hospital settings. Early investigations by Gray-Toft and Anderson (16, 17) identified seven major sources of stress among nurses: *facing death and dying*, *conflicts with physicians*, *inadequate preparation to meet emotional needs of patients and their families*, *lack of support*, *conflicts with other nurses and supervisors*, *labour standards* and *uncertainty concerning treatment*. The results of their studies correspond to the results of later research, which then added several other stress factors to the list: *fear of making mistakes*, *limitations on organisational level*, *work in shifts* and *disproportion between work and reward* (8, 18-23).

Some authors investigated if the sources of stress usually reported in literature were identical or similar for all nurses employed in hospitals, or they differed across hospital departments and nursing specialities (24-26). Results of these studies revealed significantly higher values of stress factors in relation to the items such as *conflicts with physicians*, *problems with supervisors,* and *uncertainty concerning treatment* in nurses in Intensive Care Units (ICU) compared to other departments. Stress situations such as *performing procedures that are painful for the patient* and *fear of making mistakes* were also recurrent in critical care nurses (24-26).

ICU nurses are expected to have superior professional knowledge and skills, be familiar with modern technical equipment and dedicated to the patient (27). Requirements for working in ICUs differ from one country to another. Contrary to most European countries, particular education and training for this type of nursing is not available in Serbia. Nurses acquire knowledge and training through experience rather than by advanced and specialised ICU education.

According to the data of the Serbian Chamber of Nurses and Medical Technicians, there are 91.3 % of secondary school nurses and only 9.7 % of nurses with high professional qualifications (baccalaureate). However, the curricula and syllabi of the secondary four-year nursing schools (which students attend after eight-year primary school) lack training on intensive care methods and patient-oriented health care systems. In such work environment, professional stressors are expected to appear, leading to a number of different diseases.

The aim of the study

The aim of this study was to identify and analyse professional stressors, evaluate the level of stress in nurses in ICUs, and assess the correlation between the perception of stress and psychological and somatic symptoms or diseases shown by nurses.

METHODS

Samples and settings

The research was carried out in the ICUs in twenty-two health centres in Serbia, which provide secondary and tertiary level health services. The ICUs were centralised (general) and specialised (surgery, internal medicine and paediatrics) depending on the type of healthcare institution. The study was designed as a cross-sectional study, using an opinion poll method. The randomised sample population encompassed 1000 nurses.

A working group made of nurses from the Serbian Association of Nurses and Technicians of Intensive Care, Anaesthesia and Reanimation distributed the questionnaires and collected the data for the population. A total of 1150 questionnaires were sent out and 1000 of them were considered for final processing; the remaining questionnaires were either not returned or returned incomplete, lacking majority of required data. In the questionnaires with only a few missing items, responses were replaced by the average value for a given item obtained in this sample. Therefore, the overall response rate for participation in the study was 86.9%.

Instruments

To assess and analyse professional stressors, we applied the Expanded Nursing Stress Scale (ENSS)

(28). The ENSS is an expanded and updated version of the classic Nursing Stress Scale (NSS) developed by Gray-Toft & Anderson (1981). The NSS scale was the first instrument to target nursing stress rather than general job stress. The original 34 items of NSS measured the frequency and major sources of stress in patient care situations (16). Major changes in health care delivery and work environment of nurses stimulated French et al. (2000) to identify stressful situations not reflected in the NSS scale and develop an expanded version useful for various work settings. The researchers then tested the 59 item ENSS on a larger sample (N=2.280) after which two items were removed from the instrument. The final ENSS contained 57 items in nine subscales related to: physical, psychological, and social working environments. The 57 items were arranged in a 5 point Likert response scale. The offered response options were: 'does not apply' (0), 'never stressful' (1), 'occasionally stressful' (2), 'frequently stressful' (3) and 'extremely stressful' (4). The response (0) indicated that the respondent had never faced the situation described by the item, and therefore the final calculation of total score for this respondent was (0). Calculation of the average value was performed excluding zero values. Internal consistency reliability was assessed using Cronbach's coefficient alpha. The 57-item ENSS showed improved reliability (α=0.96) over the original NSS (α=0.89). Individual subscale reliability ranged from α=0.88 (problems with supervisors) to α=0.65 (discrimination) (28).

The questionnaire was in this case cross-culturally adapted to meet the criteria of the research (29). The instrument was translated into Serbian, and back translation (from Serbian to English) was provided as a validity check. One author (DM) resolved language discrepancies.

Besides the ENSS scale, we applied a supplementary questionnaire to obtain socio-demographic data (gender, age, marital status, material status and housing problems), data related to workplace (service length, night shift work, duties, temporary assignment to other duties, and continuous professional education possibilities) and data on presence/absence of psychological and somatic symptoms and diseases in the previous six months. In addition to these, the questionnaire included the data on smoking and excessive coffee ingestion habits because these were considered to be a behavioural disorder caused by chronic professional stress and a risk factor for a variety of multifactorial diseases including work-related diseases.

General characteristics of sample population

Our sample population included 951 women (95.1 %) and 49 men (4.9 %). The average age of participants was (33.2±8.5) years. Five hundred and sixty-five nurses (56.5 %) were married, 576 had one or more children (57.6 %), and 557 nurses (55.7 %) described the material status of their families as "average".

Most participants completed secondary education (842; 84.2 %), while 158 (15.8 %) achieved higher-level education. As far as their workplace and duties were concerned, most nurses (747; 74.7 %) said they worked in shifts.

Ethical consideration

The study was examined and approved by the Research Ethics Committee of the Faculty of Medicine where the researchers currently work, as well as by hospitals' administrators. Nurses were contacted and invited by their nurse managers to participate in the current study but the nature of their participation was voluntary. Each potential subject was informed about the nature of the study in an introductory letter. Nurses' anonymity and the confidentiality of their information were guaranteed. No code numbers or any other identifying marks were printed on the questionnaires. Code numbers were placed on the questionnaires once these were returned.

Statistical analysis

The Statistical Package for Social Sciences (SPSS, Version 14) was used to generate descriptive and inferential statistics. Minimum significance level was set to 0.05. Means, standard deviations and frequencies were reported for the sample's variables. Each group of stress factors was analysed in relation to the workplace and socio-demographic determinants using the ANOVA test. The respondents were stratified into four groups according to age (20 to 29, 30 to 39, 40 to 49, 50 and over), education level (secondary, higher education), marital status (married, divorced, widowed, single), and smoking status (smoker, non-smoker, ex-smoker). The independent samples *t*-test and nonparametric Mann-Whitney U-test test were applied to common habits, such as excessive coffee consumption (up to 3 or more than 3 cups per day), and health status determinants. The independent samples *t*-test was used to determine differences in the perception of diverse stressogenic situations between respondents with certain symptoms of disease

and those without the symptoms. A small number of respondents reported history of diabetes, angina, malignant diseases, stroke, and infarction, thus the analysis of stress perception between such respondents and those without mentioned diseases was performed using the nonparametric Mann-Whitney U-test. This helped us to define particular factors, i.e. stress situations differently perceived by nurses, depending on the existence or absence of some psychological and somatic symptoms or diseases. Cronbach's α (alpha) and inter-item correlation was used as a measure of internal consistency and reliability. Confirmatory factor analysis (CFA) was used to determine if the number of factors conformed to what was expected on the basis of the pre-established hypothesis.

RESULTS

ENSS revealed a valid metric characteristic within our sample population. Cronbach alpha for the entire scale was (α=0.94), and >0.70 for all subscales except the categories *conflicts with physicians* (α=0.65) and *inadequate preparation* (α=0.59). The average inter-item correlation was 0.22, whereas item-total correlation ranged between 0.20 and 0.60.

The theoretical background of factorial structure of the questionnaire was confirmed by CFA. The initial factorial analysis, which included 57 items, revealed nine factors that highly corresponded to the nine subscales of ENSS. These nine factors accounted for 52 % of nursing stress variance. The second-order factor analysis discerned three factors: physical, psychological, and social working environments. Physical working environment was described by the subscale *workload*, while psychological working environment was described by the following subscales: *death and dying*, *inadequate preparation,* and *uncertainty concerning treatment*. The third factor - social working environment - was described by the following subscales: *conflicts with physicians*, *problems with peers*, *problems with supervisors*, *patients and their families,* and *discrimination.*

Stress situation analysis

A descriptive analysis of arithmetic means with respect to three dimensions of work environment and nine subscales of the questionnaire and their comparison (Table 1) lead us to conclude that critical care nurses rated situations related to physical and psychological working environments as the most stressful ones, whereas situations related to social working environment were seen as less stressful. However, differences in the perception of a stressogenic level of these working environments were small. The analysis of stress situation groups revealed that nurses rated the *death and dying* group situations as the most stressful, M=2.87; SD=0.92, whereas the *problems with peers* group situations were rated M=2.09; SD=0.93 and were considered the least stressful (Table 1).

The analysis of all 57 potentially stressful situations in ICUs revealed that working in conditions that might endanger their health and safety was the most stressful experience for nurses (M=3.17; SD=0.91), as was the death of a patient with whom they developed a close relationship (M=3.13; SD=1.02).

Separate ANOVA analysis showed significant differences in the perception of each of nine stressful situations in relation to age, marital status, and education level. The results revealed that married nurses experienced a higher level of stress at work in the situations of the *death and dying* (p=0.01) and *workload* (0.03) subscales compared to divorced or single nurses. With respect to age, certain differences were observed as regards the *problems with colleagues* (p=0.00) and *problems with supervisors* (p=0.01) subscales, which showed that nurses in the age category 30 to 39 years experienced a higher stress level compared to their younger or older co-workers. As far as education level is concerned, considerable differences appeared in the domain of *discrimination* (p=0.02) and *problems with supervisors* (p=0.03). These situations were found to be more stressful by the nurses with secondary education level than by those with a higher-level education.

Analysis of nurses' common habits and health statuses

Average coffee consumption among nurses participating in the poll was 2.8 cups (SD=1.7). One third of nurses, 322 (32.2 %), declared themselves as non-smokers, 452 (45.2 %) as smokers, and 226 (22.6 %) as ex-smokers. However, further analysis did not reveal any significant differences in the perception of stressfulness of different situations at the workplace between nurses with these common habits and those without them.

Less than half of nurses reported headache and lower back pain, 424 (42.4 %) and 406 (40.6 %), respectively. Mood swings (280; 28.0 %) and fatigue

Table 1 *Mean values for intensity of all stress situation categories*

Subscales and number of items	Mean	SD	Min.	Max.
DD - Death and dying - 7 items	2.87	0.92	0	28
CP - Conflict with physicians - 5 items	2.52	0.94	0	20
IP - Inadequate preparation - 4 items	2.19	0.84	0	16
PP - Problems with peers - 6 items	2.09	0.93	0	24
PS - Problems with supervisors - 7 items	2.56	0.99	0	28
WL - Workload - 9 items	2.55	1.01	0	36
UT - Uncertainty concerning treatment - 8 items	2.57	0.93	0	32
PF - Patients and their families - 8 items	2.71	1.02	0	32
D - Discrimination - 3 items	2.58	1.14	0	12
Dimensions of the work environment and the number of subscales contained	**Mean**	**SD**	**Min.**	**Max.**
Physical - 1-subscale	2.55	1.01	0	36
Psychological - 3 subscales	2.54	0.89	0	76
Social - 5 subscales	2.49	1.04	0	116
Physical (WL), psychological (DD; IP; UT) and social working environment (CP; PP; PS; PF; D).				

(271; 27.1 %) were observed in one-quarter of polled nurses.

Table 2 shows the differences in the perception of stressfulness of different situations in participants with and without certain symptoms. Significant differences were observed among nurses with respect to psychological and somatic symptoms, such as headache, insomnia, fatigue, despair, lower back pain, frequent mood swings, excessive sweating, and shortness of breath, chest pain and palpitations. Interestingly, insomnia, fatigue, and headache are symptoms related to the perception of the most stressful situations given in the questionnaire. However, the participants who felt anxiety and anger and those with appetite disturbances did not differ significantly with respect to the perception of stressfulness of any of the stress factors at work.

Nurses who had been experiencing lower back pain and headache for the past six months considered situations in the social working environment to be significantly more stressful (*conflicts with physicians*, *problems with supervisors*, *problem with peers,* and *patients and their family members*) than other situations compared to the nurses without these symptoms. Nurses suffering from insomnia, fatigue, and headache perceived situations in the domain of physical and psychological working environments (all subscales) and *problems with supervisors* subscale from the social working environment as significantly more stressful than other situations compared to the nurses without these symptoms.

Table 2 shows that the perception of certain stressogenic situations at work is closely related to certain symptoms and problems, while other types of stressful events are not related to any of the examined symptoms. The perception of *discrimination at work* and *problems with patients and their families* are not connected with any symptoms. Stressful situations in the realm of the *conflicts with physicians*, *problems with supervisors*, *uncertainty of treatment,* and *workload* subscales are connected with almost all symptoms, while stressful situations from other subscales are only connected with a few symptoms.

Table 3 shows the differences in the perception of stressfulness of nine situational factors between participants with and without diseases.

Out of the total number of investigated nurses, 84 (8.4 %) reported hypertension, 75 (7.5 %) peptic or duodenal ulcer disease, 52 (5.2 %) gallbladder inflammation or gallstones, 30 (3.0 %) chronic bronchitis / asthma, and 17 (1.7 %) diabetes.

It is important to emphasise that nurses who had at least one of the examined diseases perceived the events from the domains of *death and dying*, *problems with supervisors* and *discrimination problems* as highly stressful. Both, nurses with and without diseases, equally perceived stressogenic effects of the situations from the domains of *workload*, *competence at work* and *problems with patients and their families*.

Table 2 *Differences in the perception of stressfulness of different stress situations between participants with and without certain symptoms*

Symptoms	N	DD	CP	IP	PP	PS	WL	UT	PF	D
		t	t	t	t	t	t	t	t	t
Despair	36	1.41	3.05**	1.63	2.57**	2.06*	1.77	2.18*	0.89	0.76
Anxiety	108	1.39	0.11	0.27	0.35	1.91	1.64	0.64	0.03	0.41
Mood swings	280	1.32	2.22*	1.16	0.39	1.97*	3.35**	1.67	1.87	0.34
Sweat	73	0.78	2.76**	0.34	1.67	1.28	1.35	0.66	0.03	0.21
Insomnia	122	3.29**	4.46**	2.14*	1.22	4.24**	3.67**	2.95**	1.89	0.12
Appetite changes	127	0.28	0.49	0.05	1.30	0.26	1.34	1.13	0.66	0.70
Anger	136	0.38	1.27	0.28	0.35	0.29	1.76	0.62	0.57	0.12
Fatigue	271	2.41**	3.19**	0.33	1.75	3.02**	2.61**	3.87**	0.55	0.41
Lower back pain	406	1.19	2.64**	2.30*	1.26	1.98*	1.95	2.02*	0.75	0.32
Palpitation	218	2.55	2.05*	1.82	0.65	1.40	1.96*	1.61	0.25	0.82
Dyspnoea	87	0.003	1.16	1.34	1.07	0.02	1.96*	2.06*	0.42	0.73
Chest pain	87	2.89**	2.22*	2.53**	0.95	1.49	1.17	1.53	0.49	0.32
Headache	424	3.02**	2.32*	1.39	2.77**	4.02**	2.76**	2.78**	2.09*	1.14

**Significance level p<0.05*
***Significance level p<0.01*
DD - Death and dying; CP - Conflict with physicians ; IP - Inadequate preparation; PP - Problems with peers; PS - Problems with supervisors; WL - Workload; UT - Uncertainty concerning treatment; PF - Patient and his family; D - Discrimination;
N - number of respondents who reported symptoms
t - t-test

Table 3 *Differences in the perception of stressfulness of nine stress situations between participants with and without disease*

Disease	N	DD	CP	IP	PP	PS	WL	UT	PF	D
		t	t	t	t	t	t	t	t	t
Gallbladder inflammation or gallstones (gallbladder surgery)	52	1.07	2.32*	1.64	1.31	0.27	1.36	0.63	1.92	0.83
Stomach ulcer or duodenal ulcer	75	1.11	0.40	0.70	1.82	0.35	1.47	0.05	0.38	1.16
Chronic bronchitis or asthma	30	2.07*	0.10	0.14	0.37	1.88	0.39	0.75	0.77	2.11*
Hypertension	84	1.94	2.92**	2.09*	1.80	2.08*	1.59	1.82	1.78	1.21
Disease	**N**	**DD**	**CP**	**IP**	**PP**	**PS**	**WL**	**UT**	**PF**	**D**
		U	**U**	**U**	**U**	**U**	**U**	**U**	**U**	**U**
Malignant disease	3	149*	856	761	258	105*	479	755	354	132*
Diabetes mellitus	17	17189*	20818	19953	20000	16931*	20171	19073	18613	16901*
Stroke	3	163*	352	287	374	142*	612	518	441	120*
Myocardial infarction	3	147*	760	286	112*	108*	552	534	601	116*
Angina pectoris	6	2722	2457	2955	2766	2521	2034	2040	2558	2769

**Significance level p<0.05*
***Significance level p<0.1*
DD - Death and dying; CP - Conflict with physicians ; IP - Inadequate preparation; PP - Problems with peers; PS - Problems with supervisors; WL - Workload; UT - Uncertainty concerning treatment; PF - Patient and his family; D - Discrimination;
N - number of respondents who reported symptoms
t - t-test
U - Mann-Whitney U-test

DISCUSSION

The effects of job-factors on the occurrence of professional diseases are well established, yet their role in the development and outbreak of work-related diseases is still unclear. Work-related diseases can be prevented, and recognizing and understanding all risk factors is of paramount importance. In that respect, this research aimed at analysing professional stress in ICU nurses as a potential risk factor for work-related diseases, and implementing appropriate preventive measures.

Nurses are exposed to various stress sources from physical, psychological and social working environments. Furthermore, socio-demographic determinants of the participants in our study (age, marital status and education level) proved to significantly influence stress perception at work. Nurses who are married experience higher stress level than single nurses. It has been suggested that such higher stress levels result from multiple and complex roles that these women have to perform: wife, mother, employee and housekeeper (30).

The most intense stressors for critical care nurses are related to their psychological working environment, such as *death and dying*, which corresponds to the results obtained by other authors, and distress related to this domain is reported to persist approximately a week after patients die (16, 20, 31).

Furthermore, other significant stressors for nurses in ICUs are related to their physical working environment, i.e. *workload* (overtime work, shift work, inappropriate work/rest regimens, and pressure to have something done in a very short time).

A simple distribution analysis of items pertaining to the factor *problems with supervisors and peers* revealed that the lack of support from direct supervisors, difficulties in working with peers, and the impossibility of exchanging experiences and feelings with other staff are important professional stressors. Another significant work-related stressor is the problem with patients and their families: working with patients seems to cause excessive workload because nurses must provide psychological support and/or respond to the patient's' dissatisfaction or complaints.

The results of this study indicated a close connection between work-related stress factors and psychosomatic health. The most commonly reported psychological and somatic symptoms were: headache, lower back pain, fatigue, mood swings and insomnia. These findings are similar to those of other researchers (12, 15, 33-35).

Headache is one of the symptoms of professional stress and is usually associated with general fatigue and sleep disturbance (32). Our results are consistent with this implication. Stressful situations such as heavy workload, and problems with peers and superiors are correlated with high incidence of headache. It seems that these results are similar to the results of a research conducted in Taiwan, where worsening of the patient's condition, poor patient-nurse relations, poor doctor-nurse relations and poor interpersonal relations among nurses, as well as insufficient medical knowledge were reported as possible causes of headache in nurses (32). High prevalence of headache could also be attributed to novel technologies, as complex technical equipment in ICUs requires rapid update of knowledge and skills, which along with constant time pressure leads to "techno-stress" (36). This type of mental strain leads to the sense of insecurity and confusion associated with fear of making mistakes, pronounced anxiety, and difficulties in relaxing after work (37).

Lower back pain is the second most reported somatic problem in nurses participating in this study. The high frequency of lower back pain can be explained not only by physical factors at work, but with psychosocial factors too. These results are similar to Yip's study (33), in which working in a team with poor relations was associated with an increased risk of lower back pain.

Significant differences in the perception of stressfulness were observed among nurses with respect to psychological and somatic symptoms and diseases, particularly those from the group of work-related diseases such as malignant diseases, diabetes mellitus, and cardiovascular diseases. This suggests that such perception is considerably associated with occurrence of certain symptoms and diseases in nurses. In spite of limited supporting evidence, psychosocial stress at workplace can be considered an independent predictor of type 2 diabetes, and chronically elevated cortisol levels during chronic psychosocial stress play a crucial role in explaining this correlation (37). The relationship of work-related stress and malignant diseases is the subject of an intensive ongoing investigation, thus work stress and shift work are considered new individual risk factors for cancer (38).

The results of this study strongly suggest introducing new strategies and measures into the working environment in ICUs to improve psychosocial and

physical health of nurses. The first measure to undertake is to improve psychosocial work climate by providing more social and emotional support to nurses by their associates and supervisors. In view of permanent escalation of professional stressors, creating a supportive working environment is essential for positive health outcomes, prevention of job-related diseases and better protection of already ill nurses, which is in line with results and recommendations of other researchers (39).

Likewise, critical care nurses need to be trained through a stress-management program. This would help boost their confidence and develop abilities to communicate with doctors, chief nurses, and other nurses, which would improve overall teamwork. Managerial skills acquired this way could also reduce stress caused by bureaucratic and organisational tasks in the ward. Providing other forms of continuous professional training and acquiring techniques for handling new and modern equipment represent an important part of workplace safety. The implementation of these strategic measures is responsibility of the health facility management, team of experts implementing workplace safety, and nurses.

Limitations of the study

Although a large number of respondents participated in the study, it is not free from limitations. This study is fundamentally a cross-sectional study and shows the current status quo in regard to our test problem. In order to establish the cause-effect relations, it is necessary to conduct longitudinal studies.

CONCLUSION

It is widely accepted that nurses are exposed to various stress sources from physical, psychological and social working environments.

Our research underlined that:

- Socio-demographic determinants of participants (age, marital status and education level) significantly affect perception of stress at work.
- Stress situations related to psychological working environment, particularly facing suffering and dying, are significant professional stressors for critical care nurses in Serbia. This emphasises the need to learn to accept death as a part of everyday life rather than experience it as a clinical failure.
- There is a close connection between perception of stress at work and psychosomatic health of nurses.

Acknowledgments

The authors would like to thank The Association of Nurses - Technicians of Intensive Care, Anaesthesia and Reanimation of Serbia for organisational and financial support in collecting and analysing data.

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Sažetak

STRES NA RADU I ZDRAVLJE MEDICINSKIH SESTARA U JEDINICAMA INTENZIVNE NJEGE U SRBIJI

Cilj je ovoga rada bio identificirati i analizirati profesionalne stresore, procijeniti razinu stresa kod medicinskih sestara u jedinicama intenzivne njege te procijeniti korelaciju između percepcije stresa i prisutnosti psiholoških i somatskih simptoma ili bolesti kod medicinskih sestara. Istraživanje je provedeno u obliku studije presjeka u Jedinicama intenzivne njege u zdravstvenim centrima u Srbiji. Uzorak se sastojao od 1000 medicinskih sestara-tehničara. Za procjenu i analizu profesionalnih stresora korišten je upitnik Expanded Nursing Stress Scale (ENSS), koji je pokazao validne metrijske karakteristike na našoj ispitanoj populaciji. Medicinske sestre u Jedinicama intenzivne njege ocijenile su situacije iz fizičkoga i psihološkoga radnog okruženja kao izrazito opterećujuće, a situacije iz socijalnoga radnog okruženja kao manje opterećujuće. Razlika u percepciji stresogenosti navedenih radnih okruženja nije bila statistički značajna. Sociodemografske determinante ispitanika (dob, bračno stanje i stupanj obrazovanja) značajno utječu na percepciju stresa na radnom mjestu. Utvrđena je statistički značajna razlika u opažanju stresogenosti pojedinih stresnih situacija na radnom mjestu između medicinskih sestara u odnosu na postojanje psihosomatskih simptoma (kao što su glavobolja, nesanica, umor, očaj, bol u leđima, česte promjene raspoloženja) ili određenih bolesti (kao što su povišena hipertenzija, infarkt miokarda, cerebrovaskularni inzult, šećerna bolest). Zbog sve izraženije prisutnosti profesionalnih stresora nužno je poduzeti određene strateške mjere kod medicinskih sestara u Jedinicama intenzivne njege. Strateške mjere podrazumijevaju unaprjeđenje psihosocijalne radne klime, što bi unaprijedilo njihovo zdravlje i spriječilo nastanak bolesti u svezi s radom, ali i omogućilo bolju zaštitu već oboljelim medicinskim sestrama.

KLJUČNE RIJEČI: *profesionalni stresori, psihološki i somatski simptomi, radno mjesto, radno opterećenje, upitnici*

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DOI: 10.2478/10004-1254-63-2012-2191

Scientific Paper

CONCENTRATION OF LEAD, CADMIUM, AND IRON IN SEDIMENT DUST AND TOTAL SUSPENDED PARTICLES BEFORE AND AFTER INITIALISATION OF INTEGRAL PRODUCTION IN IRON AND STEEL WORK PLANT ZENICA*

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Received in December 2011
CrossChecked in January 2012
Accepted in May 2012

Poor air quality is a common fact for all areas with base industry. The city of Zenica was once the metallurgical centre of Ex-Yugoslavia and is therefore highly polluted at present. Air pollution peaked in 1987 when average concentration of pollutants was extremely high (daily average concentration of SO_2 was 1800 μg m^{-3}). With the beginning of the war in 1992, integral production in the steel work plant was shut down, to be re-launched in 2008. Limit values for iron do not exist, but iron has been monitored in Zenica for the past 28 years because of the presence of steel works. Concentrations of cadmium and lead have also been measured because they are very much present in polluted areas with steel works. The concentration of mentioned elements in air deposit and total suspended particles before and after integral production in the steel work plant was re-launched is the subject of this paper. Total suspended particles were measured in two locations using German standard VDI 2463 Blatt 4. Sediment dust was measured in nine locations using Bergerhoff method. The concentration of iron, lead, and cadmium was performed in the chemical laboratory of the Metallurgical Institute "Kemal Kapetanović" Zenica using standard methods. Higher concentrations of these parameters during the period of integral production clearly point to the impact of steel works on Zenica valley.

KEY WORDS: *air pollution, atmospheric dust, temperature inversion, Zenica*

Air quality was and still is the subject of many research studies. Because of a large number of industrial sources of pollution, ambient air in the city of Zenica is very highly polluted. This problem deteriorates in winter because of the heating season and temperature inversion, which impedes dispersion of pollutants (1, 2). When analysing air quality measurements performed in the past decades, one can conclude that metrological conditions have changed: periods with inverse layers of atmosphere have become longer. For example, in December 1989, there was a period with temperature inversion of about 10 days, during which daily average concentration of SO_2 reached the value of 1800 μg m^{-3} (3). This occurred again in December 2007, when the period with temperature inversion lasted for about 7 days, and daily average concentration of SO_2 reached the value

* Partly presented at the 7th Croatian Scientific and Professional Assembly "Air Protection '11" in Šibenik, Croatia, 13-17 September 2011

of 900 μg m^{-3} (3). Highly polluted ambient air in Zenica district compelled local companies to assess the impact of their sources of pollution on air quality. Following this line of reasoning, Steel Works Zenica, the biggest air polluter in the area, developed an impact study in which it looked into its main sources of air pollution with sulphur dioxide. The study showed that under the conditions of low dispersion (winter period - inverse layers of atmosphere), these sources had no major impact on air quality in the city of Zenica thanks to their high chimneys (4). A much bigger problem were industrial sources with low chimneys, house stows, boilers in small factories, steam locomotives, and vehicles. This study can be confirmed with the daily average concentration of 900 μg m^{-3} SO_2 measured in December 2007, at a time when Steel Works Zenica had no integral production. Integral production is characterised by a network of interdependent material and energy flows between various production units (sinter or pelletisation plant, blast furnace, coke oven plant, basic oxygen furnace plant or electric arc furnace plant with subsequent casting). Blast furnace is the main operational unit with primary reduction of oxide ores leading to liquid iron. Sinter or pelletisation is a process of preparation of blast furnace charge, which involves agglomeration of blast furnace burden. Essentially this is a physical and metallurgical preparation of blast furnace burden, which improves permeability and reducibility. Coke oven is a production unit which produces coke from coal by means of dry distillation. Coke has better chemical and physical characteristics than coal. Basic oxygen furnace is a unit where carbon content of liquid iron is lowered to less than 1 %, thereby resulting in steel. Electric arc furnace is a production unit in which direct smelting of materials containing iron is performed. High voltage electric arc is used for smelting materials.

When we consider metal in total suspended particles (TSPs) and in sediment dust (SD), the situation is not flattering for the city, especially for the areas around Steel Works Zenica. This is because TSPs and SD contain a lot of heavy fractions which literally "cross the fence" of Steel Works.

In order to determine air quality in the city of Zenica, Metallurgical Institute has been performing measurements of air quality for more than 20 years. Air pollution is determined by measuring the concentration of sulphur dioxide, total suspended particles, and suspended dust, as well as by measuring the concentration of metals in total suspended particles and in sediment dust. Air quality measurements used to be performed quite intensively before the war. However, during the war (1992-1995), measurements were only performed at the Institute and they focused on the concentration of SO_2 and the quantities of TSPs and SD, with no chemical analyses. Since 2006, measurements have continued, but to a smaller extent compared to the pre-war period.

In this paper three periods are considered: 1) the period of intensive work of Steel Works Zenica (up to 1992), when it produced two million tons of steel annually; 2) the period characterised by an interruption of integral production (the period between 2006, when air quality measurements were again performed, and 2008 when integral production in Steel Works was re-launched); and 3) the period from 2008 until the end of 2010 when integral production reached its planned capacity of 800 000 tons of steel per year.

MATERIALS AND METHODS

The measurement of the concentration of total suspended particles (24-hour samples) was performed according to guidelines VDI 2463, Blatt 4. Samples were collected in two locations using the sample device Lib Filter Gerath.

Measurements of sediment dust (monthly samples) were performed according to Bergerhoff method. Samples were collected in nine locations using the sample device. Measurement locations are shown in Figure 1.

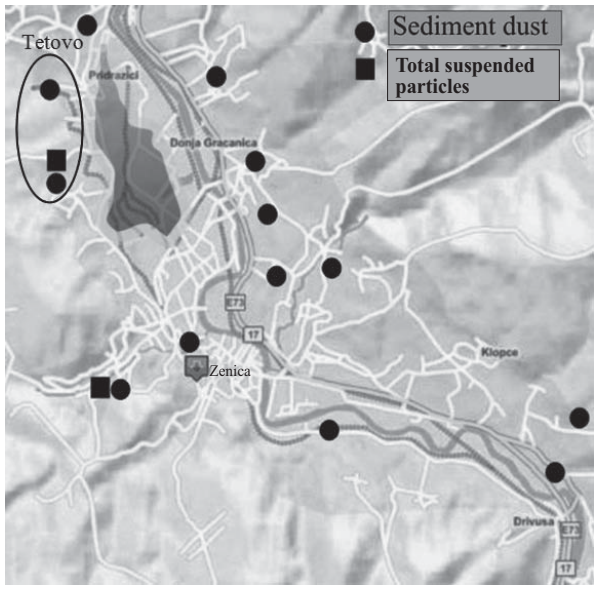

Figure 1 *Measurement sites in Zenica city*

The analysis of the composition of total suspended particles and sediment dust was performed using standard PERKING ELMER Analytical Methods for Atomic Absorption Spectrometry in the chemical laboratory of the Metallurgical Institute.

All data concerning TSPs, SD, and the content of toxic metals are the outcome of measurements of the Metallurgical Institute "Kemal Kapetanović" Zenica.

RESULTS AND DISCUSSION

Annual averages of total suspended particles are shown in Figure 2. It is evident that the amount of TSPs significantly reduced after Steel Works closed its integral production. After re-launching the production, there was no significant increase of TSPs. A reason for such a small increase of TSPs is the ore which is used in the production process, as it was the only thing that was changed in the production process. It can be also noticed that in the period without integral production in Steel Works Zenica, the concentrations of TSPs at both measurement sites were almost identical, which was not the case for the period before 1990. Comparing the period of integral production shutdown and the period with intense production before 1990, it can be said that 50 % to 60 % of total suspended particles in the city came from Steel Works. It is also noticeable that the concentration of TSPs at the measuring site "Tetovo", which is located near the Steel Works, was constantly higher by about 40 % than the concentration at the measuring site "Institute", which is located in the city. Higher concentration of TSPs at the measuring site near Steel Works means that TSPs consist of heavy particles which can not be easily transported long distances. This could be the reason for the 300 % higher TSP concentration at "Tetovo" compared to the period with no integral production at Steel Works. After the re-launch of integral production in Steel Works, TSPs increased at both measuring sites, "Institute" and "Tetovo". The measuring site "Institute" is located in the city, but its location is in the path of a northern wind, which blows

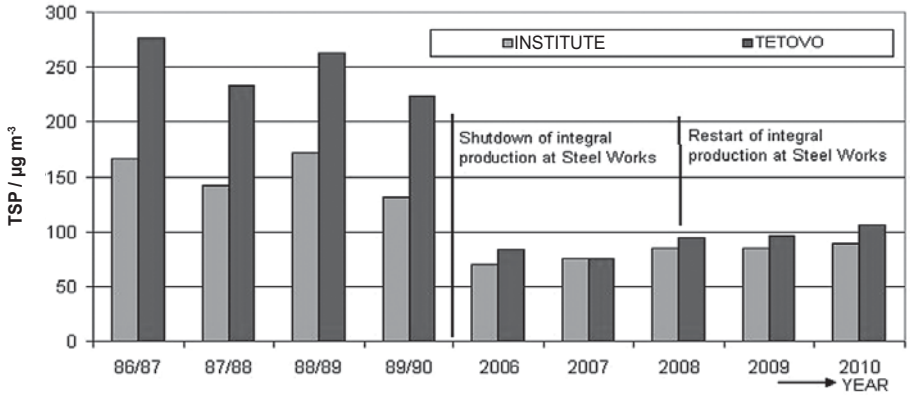

Figure 2 *Annual average of total suspended particles (TSPs)*

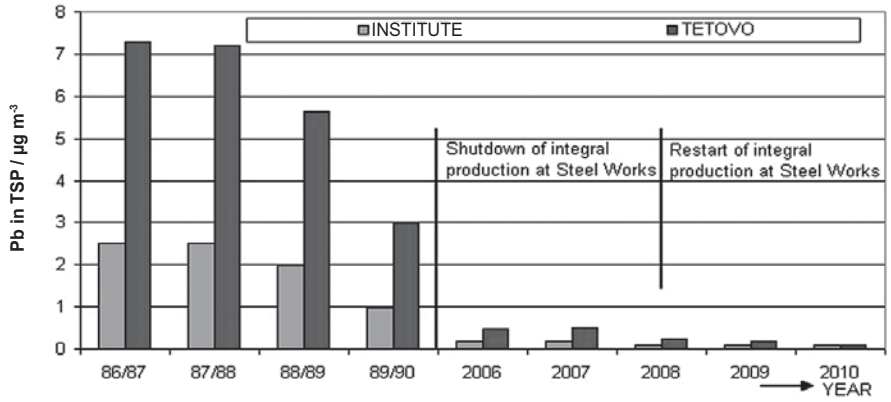

Figure 3 *Amount of lead (Pb) in total suspended particles (TSPs)*

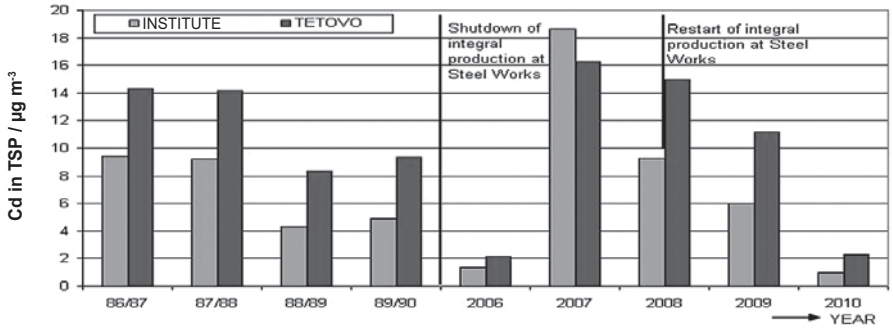

Figure 4 *Amount of cadmium (Cd) in total suspended particles (TSPs)*

over Steel Works Zenica towards the city and which according to the wind rose blows 14 % of the time. This is the reason why the measuring site "Institute" was taken as a reference point for the city. If the concentration of pollutants is high at this site, their concentration is also high in the city.

Figures 3, 4, and 5 show the concentrations of lead, cadmium, and iron in total suspended particles.

In the period before 1990, when Steel Works Zenica was producing two million tons of primary products, the amount of iron, lead, and cadmium in total suspended particles and sediment dust was much higher than in the post-war period. In the measuring location "Tetovo", annual average concentration of lead in total suspended particles for the period April 1986 - March 1987 was 7.3 µg m^{-3} (limit value is 2 µg m^{-3}). The reason for this high value was an ore from the mine Vareš which contained high concentration of lead (average value of Pb 0.12 %) (5). Because of these high concentrations of lead in the ore blast furnace, Steel Works Zenica produced a considerable amount of lead as a by-product.

It can be seen from Figures 3 and 5 that concentrations of lead and iron in total suspended particles decreased significantly after the integral production in Steel Works Zenica was shut down. In this period, lead concentration in TSPs was 15 times lower than in the period of integral production, with a decreasing tendency even in the period after 2008, when integral production was re-launched and when the concentration of TSPs rose. Less lead in the ore used for the production process is connected with less lead in total suspended particles. The concentration of iron in TSPs also decreased by 15 times after the integral production was closed. Once integral production was re-launched, iron in TSPs increased by about 4 times. This increase points to the extent of the impact of Steel Works on the pollution in the city; as for the present level of production, the concentrations of TSPs are 3 to 5 times higher on both measuring sites than before integral production re-start (Figure 5).

Figure 4 shows that concentration of cadmium in TSPs significantly decreased after integral production

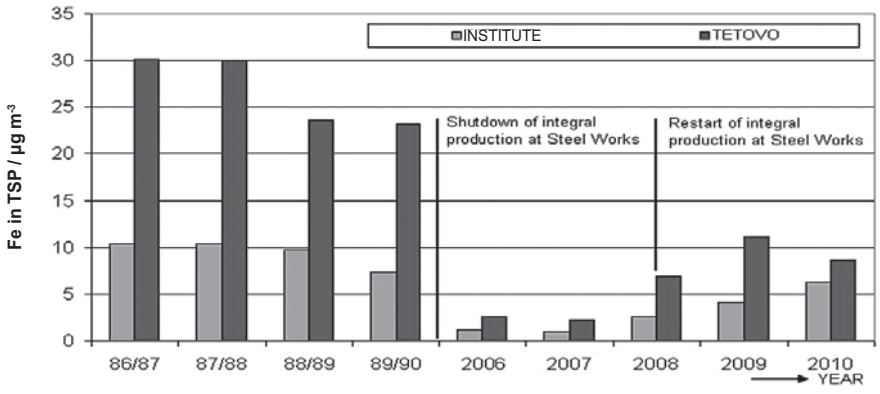

Figure 5 *Amount of iron (Fe) in total suspended particles (TSPs)*

had been interrupted. However, the amount of cadmium in TSPs in 2007 was higher than in the period before 1990. High level of cadmium is connected with the production of steel in electric arc furnace 100 tons (EAF 100 tons). It is not known which components are used to produce steel in electric arc furnace 100 tons, but it is noticeable that the concentration of cadmium began to subside as the amount of steel produced in EAF decreased. As it can be seen from Figures 4 and 7, the concentration of cadmium after 2007 reduced in TSPs but at a slower pace than in SD. The probable reason for this is a bag filter installed on EAF 100 tons through which only fine particles can escape. Fine particles are dispersed on greater surfaces so they have more impact on TSPs and less on SD. The amount of cadmium determined in 2007 in the measuring location "Institute" is the highest amount measured for all three analysed periods. We speculate that this extra amount of cadmium could have come from two foundries located in the city.

Average concentration of sediment dust (SD) is shown in Figure 6. After Steel Works' integral production was brought to a standstill, a significant decrease of SD was noticed, especially in measuring locations near Steel Works ("Tetovo"), because dust emitted from Steel Works consisted mostly of heavy fractions which could not be transported long distances. Shutting integral production down resulted in identical sediment dust values in all locations, whereas the subsequent restarting of integral production raised the concentrations mostly on sites near Steel Works Zenica.

In the period 1986-1990, the amount of lead and cadmium in sediment dust was very high and there was almost no area in Zenica valley with concentrations of lead and cadmium in SD below the limits for vegetation (except for vegetation with roots) (2).

Annual average cadmium in sediment dust can be seen in Figure 7. The amount of cadmium in SD decreased significantly with the shutdown of integral production in Steel Works, and then gradually even more so when the production subsided. The increase in the amount of cadmium in SD in 2007, as was the case with TSPs, is connected with 100 tons electric furnace. With its shutdown by the end of 2009, when basic oxygen furnace yielded its planned capacity, concentrations decreased significantly. The amount of iron in sediment dust was not subjected to analysis because limit values do not exist. The amount of iron in total suspended particle was measured in order to

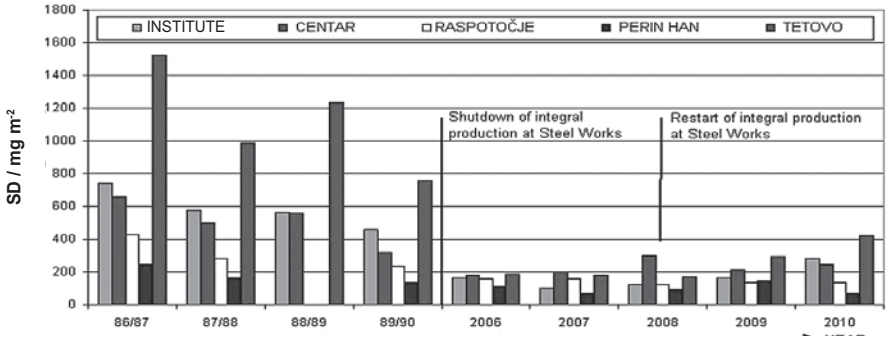

Figure 6 *Annual average of sediment dust (SD)*

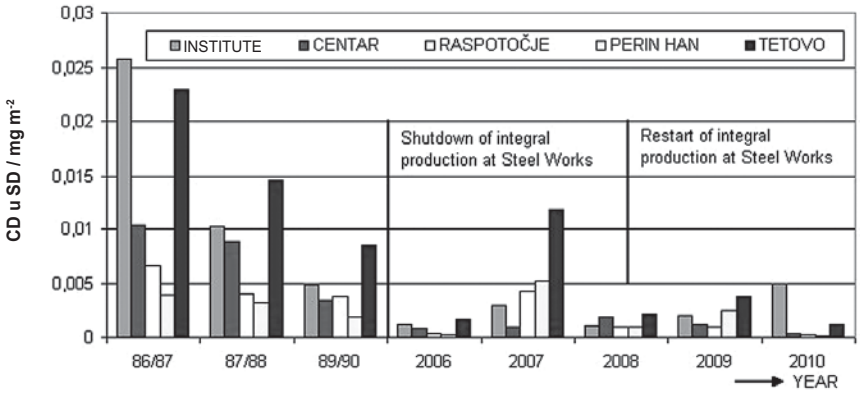

Figure 7 *Amount of cadmium (Cd) in sediment dust (SD)*

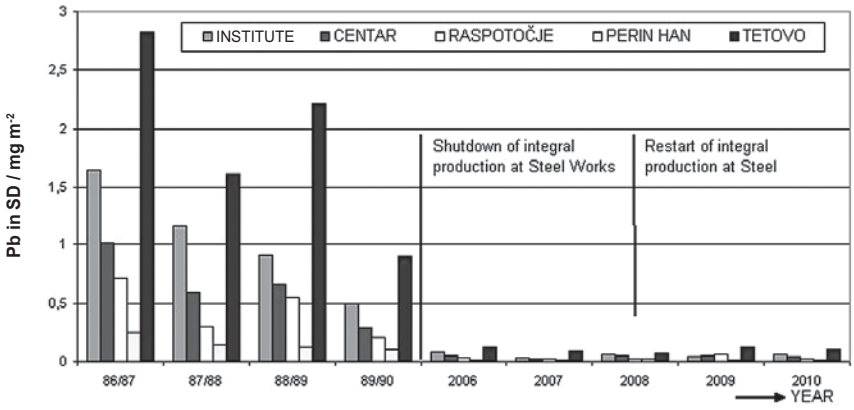

Figure 8 *Amount of lead (Pb) in sediment dust (SD)*

monitor the impact of Steel Works Zenica on environmental pollution.

The analysis of soil from the areas near Steel Works (in 2009), performed by the Federal Institute for Agropedology, showed that soil was contaminated with toxic metals, especially with lead, zinc, nickel, chrome, and cadmium (8, 11). Concentrations of these elements were several times higher than limit values. Toxic elements in soil accumulate in plants, which is then detrimental for both humans and animals (9, 11).

Ten years after integral production had been shut down (in 1999), the amount of toxic metals in soil in the area around Steel Works (6) was smaller than in the period before shutdown. This is the result of a long period of shutdown, during which these metals were transported from soil by the plants and washed out with water (6). Soil analysis performed in 2009 by the Federal Institute for Agropedology in the same areas around Steel Works showed that concentrations of lead and cadmium were higher than in 1989, and the immission values of toxic metals were much lower (8). This calls for an additional analysis of possible sources of toxic metals. Industrial and communal waste disposal sites, containing all kinds of wastes that are disposed of without any control, are located in the proximity of the examined areas. The communal disposal site is now closed but is still active, and uncontrolled fires break out there quite often. In the past ten years, the industrial waste disposal site has been intensively dug around in search for scrap iron and coal.

Irrespective of reduced concentrations of metals in SD and TSPs, the amount of metals in soil is still beyond limit values (8, 11). This means that we are still paying the price for having polluted the soil in the period when Steel Works was producing two million tons of steel, and for having allowed uncontrolled disposal of industrial and communal waste in the most polluted part of the city.

CONCLUSION

On the basis of the analyses for the presence of lead, cadmium, and iron in sediment dust and total suspended particles before and after integral production in Steel Works Zenica, the following conclusions can be derived:

- Air quality assessed by the amount of metals in total suspended particles and sediment dust in the city of Zenica was poorer when Steel Works was producing two million tons of steel annually.
- When metals are considered, most contaminated locations are those surrounding Steel Works Zenica.
- Integral production shutdown in Steel Works caused a significant drop of SD, TSPs, and the amount of metals in them.
- Restart of integral production did not cause a considerable increase in SD and TSPs. The concentration of iron augmented, lead remained at the same level as before the re-start of integral production, cadmium reached a level higher than where it was in the period in which Steel Works produced two million tons of steel annually.
- Comparing the results of soil analyses from the areas near Steel Works, which were performed in 2009, and those from 1990, it is clear that soil was more contaminated with toxic metals, especially with lead,

zinc, nickel, chrome, and cadmium in 2009 when the immisson values of toxic meals were significantly lower than in 1990.

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Sažetak

SADRŽAJ OLOVA, KADMIJA I ŽELJEZA U TALOŽNOM PRAHU I UKUPNIM LEBDEĆIM ČESTICAMA PRIJE I NAKON POKRETANJA INTEGRALNE PROIZVODNJE U ŽELJEZARI ZENICA

Opće je poznato da sredine s baznom industrijom imaju lošu kvalitetu zraka. Zenica kao centar crne metalurgije bivše Jugoslavije pripada najzagađenijim gradovima. Onečišćenje zraka dosegnulo je vrhunac 1987. godine kada su prosječne koncentracije bile izrazito visoke (npr. koncentracija SO_2 bila je oko 1800 $\mu g\ m^{-3}$). Početkom rata integralna željezara je prestala s radom, ali je 2008. godine ponovno pokrenuta integralna proizvodnja u željazari. U ovom radu je prikazana analiza sadržaja olova, kadmija i željeza u taložnom prahu i lebdećim česticama za razdoblja prije pokretanja integralne proizvodnje u Željezari Zenica, danas, Arcelor Mittal Zenica, i poslije pokretanja te proizvodnje. Norme za sadržaj željeza ne postoje, ali se njegova koncentracija u lebdećim česticama i taložnom prahu u Zenici određuje već 28 godina, upravo zbog željezare. Sadržaj olova i kadmija se također određuje jer su ta dva elementa, a naročito olovo, dosta prisutni u zeničkoj kotlini. U radu je prikazan sadržaj navedenih elemenata u taložnom prahu i lebdećim česticama prije pokretanja integralne proizvodnje u željezari i poslije toga. Mjerenje ukupnih lebdećih čestica obavlja se na dva mjesta a prema VDI 2463 Blatt 4. Taložni prah se određuje prema metodi Bergerhoffa na 9 mjernih mjesta, a određivanje sadržaja željeza, olova i kadmija vršeno je standardnim metodama u kemijskom laboratoriju Metalurškog instituta "Kemal Kapetanović" u Zenici. Povećan sadržaj ovih parametara u vrijeme rada integralne proizvodnje u Željezari u odnosu na period njezinoga mirovanja, jasno pokazuje utjecaj na kvalitetu zraka zeničke kotline.

KLJUČNE RIJEČI: *onečišćenje zraka, atmosferska prašina, temperaturna inverzija, Zenica*

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DOI: 10.2478/10004-1254-63-2012-2159

Professional paper

CONFLICT BETWEEN WORK AND FAMILY ROLES AND SATISFACTION AMONG NURSES IN DIFFERENT SHIFT SYSTEMS IN CROATIA: A QUESTIONNAIRE SURVEY

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Received in October 2012
CrossChecked in January 2012
Accepted in April 2012

The objective of this study was to examine the perception of conflict between work and family roles and job, family, and life satisfaction among nurses in Croatia. One hundred and twenty-nine nurses (married mothers) working in hospitals in Zadar, Šibenik, and Split were divided in four groups according to their worktime schedule. The participants completed a survey, which included a set of sociodemographic-type questions, questions about the level and allocation of family responsibilities between spouses, and scales measuring the perceived negative effects of worktime, psychological demands of the work, work-family conflict, and semantic differential scales for measuring the affective and cognitive-evaluative component of job, family, and life satisfaction. This was the first study in Croatia to deal with work-family conflict among nurses or workers with different shift systems.
The results of this study indicate that nurses working morning shifts only experienced less conflict between work and family than other groups of nurses, who worked the morning, afternoon, and the night shift. The cognitive-evaluative component of job satisfaction was the highest among morning shift nurses and the lowest in nurses who worked 12-hour shifts, while the affective component of life satisfaction was the lowest in nurses working irregular and backward rotated shifts. These results confirm that shiftwork makes the work-family role conflict even worse. They also support the view that the type of shift rotation matters.

KEY WORDS: *family satisfaction, job satisfaction, life satisfaction, nursing, shiftwork, work-family conflict*

Women and worktime stress

Although the number of working women is increasing and attitudes about gender roles are changing, the society still expects women to take responsibility for most childcare and household tasks (1). Research results show that women indeed see themselves as more responsible for the family domain than men (2). This "woman's work" often takes priority over other duties and can not be delayed (3). Studies show that levels of stress hormones such as epinephrine, norepinephrine, and cortisol remain high in women after the work day is over, women with children in particular (4). Certain types of work schedules can be a significant stressor for a working mother. For example, shift work has been shown to have negative effects on physical health, sleep quality, and mental health (5-7).

The problems of shift workers derive from having to work with inadequate levels of 'stress' hormones such as cortisol and catecholamine, which can have a more rapid impact on health than prolonged exposure to stressful events (8). Shift work has many effects on nurses' health. For example, the risk of breast cancer and metabolic syndrome is higher among nightshift workers (9-11). The risks of making an error at work were significantly increased when work shifts were longer than twelve hours, when nurses worked overtime, or when they worked more than forty hours per week (12). Extended daily working hours have both negative (example fatigue) and positive effects (more time for the family, social life, and domestic duties) (13-17).

Women are particularly susceptible to interrole conflict, which refers to the experience of multiple, conflicting expectations from different people. Increased workload cancels opportunities for relaxation and threatens the physical and mental health of women.

Conflict between work and family roles and worktime schedules

Different roles can affect each other if performed at the same time. This interaction can be complementing or conflicting and can become a source of stress when the roles are not compatible or when they exceed the capabilities of an individual. Since two important focal points of adult life are family and work, most research has dealt with the interaction between these two domains (18): conflict due to the disrupting interference of work to family life (*work-to-family conflict*) and conflict due to the disrupting interference of family to work life (*family-to-work conflict*).

Today's almost universally accepted so-called integrative model of conflict between work and family roles suggests that the structural, social, and psychological demands of work and family contribute to increasing levels of work-family conflict by increasing demands at work and work-to-family conflict and increasing demands of the family and family-to-work conflict (18, 19). This source of stress leads to distress/dissatisfaction with work and family, and these two forms of distress cause general discontent and depression in particular.

Structural work requirements, such as shift work (20) and extended working hours (21, 22), as well as social and psychological demands, such as the amount of responsability, a variety of tasks, workload, and psychological pressure, are associated with a higher degree of work-to-family conflict, with important consequences such as the subjective experience of work stress, work dissatisfaction, and poor functioning at work (23, 24). Likewise, structural and social requirements of the family (number and age of children, care for children, care for elders, marital status, quality of family member relationships) were associated with higher levels of family-to-work conflict (25, 26), with important consequences such as the subjective feeling of family stress, dissatisfaction with family and fatigue, inefficiency in marital and parenting functions (19, 23).

One study showed that shift workers, in comparison with daily workers, had a greater amount of work interference with family life (work-to-family conflict), and the amount of interference increased with time (27). However, an impact on family-to-work conflict can not be excluded. Shift workers may sacrifice sleep quality to spend more time with the family, and thereby diminish their efficiency at work.

As the type of shift rotation also affects workers' well-being (28-31), it should be taken into account in studying the work-family conflict. Grosswald (32) found that work-to-family spillover was the highest in workers with the rotating shift system in comparison with those in permanent night shifts, permanent afternoon shifts, and split shifts. It is not difficult to understand why rotating shift systems have a negative impact on household and family duties. Even childcare becomes a big problem, as it is needed at different times of the day. Moreover, in a 32-month follow-up, Amelsvoort et al. (33) found that employees in the backward rotating shift system have a greater need for recovery, poorer health status, poorer sleep quality, and greater work and family interrole conflict than forward rotating shift workers.

Research conducted on nurses gave similar results (34, 35). Workload and irregular work-time schedules were significant predictors of work-to-family conflict, and the conflict between work and family roles was associated with lower levels of job and life satisfaction. The issue has been studied thoroughly through the European Nurses Early Exit Study (NEXT) (36), whose aim is to see why nurses leave their profession early, often earlier than other professions. The NEXT study has included more than 77,000 nurses in 10 European countries. They

concluded that attempts to retain nurses in their profession should take into consideration the work-to-family conflict (WFC), the regularity of working time in particular, and overtime issues.

Study objective

Very little research has been done on the conflict between work and family roles in societies like ours, where most women still assume the traditional homemaking role. This points to an increased risk of a conflict between women's professional role and her role as a mother and a housewife. If their job includes shiftwork, which tends to affect many aspects of life and involve problems such as sleep disturbances, fatigue, lower performance, and disturbed family and social relationships, this conflict can be even more pronounced. Additional sources of stress such as understaffed night shifts and overnight patient crises put even more strain on the work-to-family conflict and satisfaction with job, family, and life.

The objective of this study was to establish the perception of the conflict between work and family roles and life satisfaction among nurses in Croatia working different shifts. This is the first research of the kind in Croatia.

SUBJECTS AND METHODS

Participants

The study included 128 married nurses (all having children) from the General Hospital in Zadar and Šibenik and Clinical Hospital Center in Split, as our focus was on the conflict between work and family roles. They were between 19 and 59 years old and worked shifts which rotated every two days (so-called fast-rotating shifts), as follows:

- Forward rotation (morning-afternoon-night-day off), 8 hours (N=37)
- Backward rotation (night-morning-afternoon-day off), 8 hours (N=29)1
- Forward rotation (day, night, day off), 12 hours (N=25)
- The fourth was the control group of nurses working only the eight-hour morning shift (N=37).

Questionnaires and response evaluation

We used a questionnaire, which opened with a set of sociodemographic questions about the participant age, education, marital status, number of children, overall years of service at the current workplace, the type of shifts they worked, and overtime work. There were also three questions about the level and distribution of responsibilities in childcare and housework between the spouses.

A Scale of the psychological demands of work used for this study included 12 items about the autonomy of the job, role conflict, role ambiguity, and work overload. Examples of the items are: "I have enough materials and the necessary instruments to perform my job properly" and "I have enough time to complete my job". The reliability of this scale, expressed with Cronbach's alpha coefficient, was 0.78. The participants were asked to rate their responses on a seven-point scale (1-strongly disagree, 7-strongly agree). Higher score indicates a higher level of perceived psychological demands. The average scores ranged from 1.4 to 6.9.

The *Scale of the negative effects of worktime* is an adapted translation of the original scale by Ahasan et al. (37). It covers effects of worktime on family life, social life, and health, with questions such as "My worktime disturbs my family life" or "My worktime restricts my social life". Scale reliability, expressed with Cronbach's alpha coefficient, was 0.89. The participants were to rate their responses on a seven-point scale (1-strongly disagree, 7-strongly agree). Higher score reflects a higher level of perceived negative effects of shift organisation on family and social life and general health. The scores ranged from 1 to 7.

The translated and modified *Conflict between work and family roles scale* developed by Netemeyer et al. (38) was used for measuring the perceived level of conflict between work and family roles, taking into account time and strain as the causes of conflict. It consists of two sets of six items, the first focusing on the *work-to-family conflict* (WFC; example: "Due to the time needed for my job, I do not have enough time to participate in family activities") and the second on the *family-to-work conflict* (FWC; example: "Due to the time spent for family activities, I often have to delay and modify

[1] A group of nurses working in irregularly organized shifts were included here, since frequent change of there rapidly changing shifts is most similar to a backward rotation shift system.

my work activities"). Reliabilities were satisfactory (around 0.8). Again the participants rated their responses on a seven-point scale (1-strongly disagree, 7-strongly agree) and higher scores reflected a greater level of perceived negative impact of work on family and vice versa. The scores on the WFC scale ranged from 1 to 7 and on the FWC scale from 1 to 6.8.

Semantic differential items for measuring job, family, and life satisfaction were developed by Gregov (39). Each semantic differential item consisted of bipolar pairs of adjectives listed on opposite ends of seven-point scale ranging from -3 to +3. Affective and cognitive-evaluational components of satisfaction were determined for all three domains (job, family, life). The *affective component of job satisfaction* (ACJS) included 13 items and the cognitive-evaluational component (CCJS) seven. The *affective component of satisfaction with the family* (ACFS) included 14 items and *cognitive-evaluative component* (CCFS) five. Finally, the *affective component of life satisfaction* (ACLS) included 14 items and the *cognitive-evaluative component* (CCLS) five.

The reliabilities of these components were all satisfactory, with Cronbach's alpha coefficients ranging from 0.82 to 0.96. To evaluate the -3 to +3 range scores we had to recode them into the 1 to 7 range, in which 1 corresponded to the adjective indicating the most negative attitude and 7 to the adjective indicating the most positive attitude. In other words, the higher the score the greater the satisfaction**.** The score ranges were as follows: for ACJS from 1.8 to 7, for CCJS from 1 to 7, for ACFS from 4 to 7, for CCFS from 1 to 7, for ACLS from 2.2 to 7, and for CCLS from 1 to 7.

Data collection

First we contacted hospital directors and head nurses by phone to obtain their consent to carry out the study. Department head nurses were contacted in person to help distribute the questionnaires. We aimed for married nurses to make the majority of the sample and for an equal distribution of questionnaires between shift types.

The questionnaires were distributed and returned in envelopes for the sake of anonymity and greater sincerity in responses. One of the researchers collected them in person from each participant from February to March 2008. The response rate was about 80 %, which is relatively high. Out of 174 questionnaires collected results of 128 nurses who were married we used for the purpose of this study.

Ethical approval

This research was approved by the Ethics Committee for research in psychology of the University of Zadar. It followed the ethical principles of the Croatian Psychological Society, which are in accordance with the ethical principles of the American Psychological Association and the British Psychological Society.

RESULTS AND DISCUSSION

Sociodemographic profile of nurses in different shift systems

Table 1 shows that the groups of nurses did not differ in the years of service at the current workplace. Nurses working the morning shift alone were on average significantly older and had more years of service than the nurses working 12-hour shifts. There were more nurses with higher education in the morning shift group than in the other groups (chi-square=5.07; p=0.024). Furthermore, nurses working morning shifts alone less often reported overtime work than the nurses working 12-hour shifts (chi-square=7.24; p=0.007). These differences should be taken into account when interpreting the differences in work-to-family conflict and satisfaction. Parkes (40) suggests that older shift workers experience more problems than younger shift workers, because the circadian adaptation declines with age. It is therefore possible that most of the workers who now work the morning shift alone worked the night shift before, and were transferred to the morning shift because of accumulated health problems.

Perceived job characteristics and family responsibilities

Earlier studies suggest that housework and the care for children and the elderly are related to family-to-work conflict and the level of stress in families (18, 27). In our study, we observed no differences in these family tasks between the nurse groups.

Perceived psychological demands of work have previously been shown to correlate with stress

Table 1 *Sociodemographic characteristics of nurses working different shifts.*

Variable	Form of shift organization								df = 3/128 – 3/124	
	Morning shift only		Forward rotation, 12-hour shifts		Forward rotation, 8-hour shifts		Backward rotation plus irregular 8-hour shifts			
	M	sd	M	sd	M	sd	M	sd	F	p
Age / years	44.54	7.99	36.96	5.75	40.25	8.57	39.17	8.78	5.08	0.002
Total work experience / years	24.08	8.41	16.28	5.89	19.54	8.59	17.61	9.22	5.53	0.001
Current service / years	12.32	9.22	11.29	7.79	13.95	9.25	12.59	9.22	0.46	0.709
Overtime per week / hours	0.92	2.69	3.32	5.63	1.86	4.16	1.37	4.12	1.76	0.158
Number of children	2.05	0.71	1.96	1.06	2.14	0.98	2.14	0.99	0.23	0.875

M = mean
sd = standard deviation
F = F-ratio
df = degrees of freedom

experienced at work and with work-to-family conflict (18, 35). Nurses who worked morning shifts alone estimated psychological demands of work and the negative effects of worktime on social and family life, and general health significantly lower than the other three groups of nurses (Table 2). This was expected, given that earlier studies show greater negative effects of night and shift work on health status (6) and on family and social life (42). Working night shifts requires extra effort to stay awake and be effective; this alone puts a lot of stress on the body and can cause health problems and fatigue. Moreover, night shifts are often not aligned with the worktime and the responsibilities of other family members, friends, and the social environment in general.

In addition, morning shift nurses were the oldest group of nurses. A number of them might have been transferred from shiftwork to permanent morning shifts because their capability to adapt to circadian changes and other role-related demands declined with age.

Work-to-family and family-to-work conflict

Morning shift nurses perceived the level of work-to-family conflict significantly lower from the other three groups (Table 2). This is consistent with earlier research that established a correlation between nightshifts and work-to-family conflict (3, 35).

On the other hand, the groups did not significantly differ in the level of family-to-work conflict (Table 2), which is not surprising considering that these groups share similar sources of stress in the family (at least those taken account in this research) and considering the results of previous studies which show the same (19, 23, 25). The average perceived level of family-to-work conflict was very low, especially in comparison with work-to-family conflict. It is possible that this is related to the importance of the family for women in Croatia and to their traditional family roles. Again, the age difference should be taken into account, since it is very likely that the morning shift nurses have older children, who are not so dependent any more, and their obligations at home are fewer.

Satisfaction with work, family, and life

Morning shift nurses had the highest and 12-hour forward rotating shift nurses the lowest scores on the scale of the cognitive-evaluative component of job satisfaction. This means that, while nurses are generally happy with their jobs (the average affective component of job satisfaction was 5 points on the assessment scale), the nurses on 12-hour shifts have a more negative attitude toward shift organisation, as they not only have to work shifts but also work longer hours and thus feel more fatigued (43).

No significant differences were observed between the groups in the cognitive or affective components of satisfaction with family life (Table 2). This supports the findings by Mott et al. (44) who showed that, shift work does not significantly affect the level of marital and family happiness.

Concerning life satisfaction the significant difference between nurses was found for its affective component (Table 2). Nurses working backward

Table 2 *Descriptive parameters and one-way analyses of some perceived characteristics and aspects of family, work, and life in general in nurses with different forms of shift organization*

Variable	Form of shift organization									
	Morning shift only		Forward rotation, 12-hour shifts		Forward rotation, 8-hour shifts		Backward rotation plus irregular 8-hour shifts			
	N=37		N=25		N=37		N=29			
	M	sd	M	sd	M	sd	M	sd	F	p
Childcare	3.43	0.68	3.52	0.50	3.37	0.68	3.33	0.55	0.437	0.727
Household	3.64	0.82	3.84	0.74	3.51	0.76	3.58	0.62	0.980	0.401
Psychological work demands	3.64	1.00	3.75	1.30	3.77	1.15	4.34	0.93	2.541	0.054
Worktime organisation effects	3.00	1.43	4.90	0.93	4.84	1.42	4.95	1.31	17.32	0.000
Work-to-family conflict	3.43	1.27	4.36	1.21	4.61	1.41	4.97	1.05	9.352	0.000
Family-to-work conflict	1.94	0.78	1.72	0.76	2.28	1.52	2.15	1.35	1.316	0.272
My job (cogn.)	3.70	1.62	2.34	1.11	2.66	1.57	2.81	1.52	4.371	0.006
My job (aff.)	5.31	0.92	4.87	1.15	5.08	1.07	4.65	1.52	1.581	0.198
My family (cogn.)	5.61	1.22	5.65	1.06	5.75	0.86	5.28	1.50	0.743	0.529
My family (aff.)	6.40	0.57	6.58	0.43	6.50	0.58	6.18	0.81	1.890	0.135
My life (cogn.)	4.72	1.40	4.53	1.27	4.56	1.50	4.40	1.71	0.225	0.879
My life (aff.)	6.17	0.58	6.31	0.56	6.28	0.80	5.61	1.27	3.707	0.014

Legend: Childcare – a 5-degree scale where 1 is 'completely the responsibility of my spouse' and 5 is 'completely my responsibility'; Household – a 5-degree scale where 1 is 'completely the responsibility of my spouse' and 5 is 'completely my responsibility'; Psychological work demands – a 7-degree scale with a higher result showing a higher level of negative work characteristics; Worktime organisation effects – a 7-degree scale with a higher result showing a higher level of negative effects of worktime on health, family, and social life; Work-to-family conflict – a 7-degree scale with a higher result showing a higher level of negative interference of work to family life; Family-to-work conflict – a 7-degree scale with a higher result showing a higher level of negative interference of family to work life; My job (cogn.) – a 7-degree scale with a higher result showing a higher level of the cognitive evaluative component of job satisfaction; My job (aff.) - a 7-degree scale with a higher result showing a higher level of the affective component of job satisfaction; My family (cogn.) - a 7-degree scale with a higher result showing a higher level of the cognitive evaluative component of family satisfaction; My family (aff.) - a 7-degree scale with a higher result showing a higher level of the affective component of job satisfaction; My life (cogn.) - a 7-degree scale with a higher result showing a higher level of the cognitive evaluative component of life satisfaction; My life (aff.) - a 7-degree scale with a higher result showing a higher level of the affective component of life satisfaction.
M = mean
sd = standard deviation
F = F-ratio

rotating or irregular shifts scored it lower than other groups. This to some extent may reflect the differences in the level of negative effects of shift work on family life. It is likely that unpredictable distribution of working hours adversely affects functioning off work. This has partly been supported by Amelsvoort et al. (33), who have shown that backward rotating shift workers have a greater need for recovery, poorer health status, and poorer quality of sleep. In our earlier study (45), nurses in irregular and backward rotating shifts evaluated their health status as poorer than did the other groups of nurses.

CONCLUSION

This study is the first to investigate work-family interference among nurses from Croatia. In fact, no similar study has been performed in Croatian shift workers in general. It has shown that working three shifts is viewed as more difficult and stressing on other life domains. At the same time, the level of family-to-work conflict was very low in all four groups, which is in line with the findings in countries that highly value family as an institution (36).

When it comes to satisfaction, the cognitive-evaluative component of job satisfaction was the highest in morning shift and the lowest in 12-hour shift nurses, while the affective component of life satisfaction was the highest in the morning shift and the lowest in nurses working irregular and backward rotating shifts. Family members and organisations of women working stressful jobs such as nurses should take into account the factors that may cause their higher fatigue and dissatisfaction and provide different types of support. Our findings can help to improve shift work efficiency and management. Working night, prolonged, and irregular shifts is obviously most stressful for working mothers. Since shift rotation and night work are almost inevitable in health institutions, organisations could at least minimise irregular shift work. The working time schedule should be determined and well known well in advance. In addition shiftwork schedules should allow a degree of flexibility to accommodate employee needs. Employees too could reduce adverse effects of shift work by maintaining a healthy lifestyle, which includes a healthy diet, exercise, and avoiding cigarettes and alcohol. They should also be more flexible about their priorities and try to shift a part of their traditional load to their partners.

Limitations and future research

The main limitation of this study is that the comparisons between nurses working shifts are obscured by different age of the groups. Another limitation is the small size of the groups compared, which renders interpretation of results less reliable and applicable in general.

Furthermore, the relative importance of family and work in the nurses' lives was not measured, which, for example, Carlson and Kacmar (46) found to be associated with the levels of work-to-family and family-to-work conflict and which may be important in interpreting our results.

We also have not taken into account worktime preferences and the morningness/eveningness type of personality in our nurses. Some people recover better after night shifts than others, and we believe that some of our nurses worked night shifts of their own choice.

It would have also been useful to include in the comparison a group of workers with morning and afternoon shifts or afternoon shifts alone to see whether night or afternoon shifts had a greater influence on the work-to-family conflict than the rest, as many family activities take place in the afternoon. Future research should address all these limitations.

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Sažetak

SUKOB RADNIH I OBITELJSKIH ULOGA I ZADOVOLJSTVA U MEDICINSKIH SESTARA U HRVATSKOJ S RAZLIČITIM SUSTAVIMA SMJENSKOGA RADA

Cilj je ovoga istraživanja bio ispitati percepciju sukoba između radnih i obiteljskih uloga i radno, obiteljsko i životno zadovoljstvo kod medicinskih sestara s obzirom na različite vrste organizacije radnoga vremena. 129 udatih medicinskih sestara majki koje rade u bolnicama u Zadru, Šibeniku i Splitu podijeljeno je u 4 skupine s obzirom na vrstu organizacije radnoga vremena. Sudionice su ispunile upitnik koji je uključivao set pitanja sociodemografskoga tipa, pitanja o količini i raspodjeli obiteljskih odgovornosti među supružnicima i skale koje mjere percipirane negativne efekte radnoga vremena, psihološke zahtjeve posla, sukob između radne i obiteljske uloge te skale semantičkoga diferencijala za mjerenje afektivne i kognitivno-evaluativne komponente radnog i obiteljskog zadovoljstva i života općenito. Ovo je prvo istraživanje provedeno u Hrvatskoj u kojem je ispitivan sukob radne i obiteljske uloge kod medicinskih sestara ili općenito radnika s različitim sustavima smjenskoga rada.
Rezultati pokazuju da sestre koje rade u stalnim jutarnjim smjenama doživljavaju manje sukoba zbog ometajućih utjecaja rada na obitelj od grupe medicinskih sestara koje su radile u tri smjene (u koje je uključena noćna smjena). Kognitivno-evaluativna komponenta zadovoljstva poslom bila je najviša kod medicinskih sestara s jutarnjim smjenama, a najniža kod onih koje su radile u 12-satnim smjenama. Afektivna komponenta zadovoljstva životom bila je najniža kod medicinskih sestara koje su radile u iregularnim i unatrag rotiranim smjenama. Ovi su rezultati dodatan pokazatelj različitih i više ili manje negativnih efekata smjenskoga rada na sukob između radnih i obiteljskih uloga te dodatno upozoravaju na važnost uzimanja u obzir vrste rotacije smjena.

KLJUČNE RIJEČI: *smjenski rad, sukob radne i obiteljske uloge, zadovoljstvo obiteljskim životom, zadovoljstvo poslom, životno zadovoljstvo*

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DOI: 10.2478/10004-1254-63-2012-2204

Professional Paper

RESPIRATORY SYMPTOMS IN FISH PROCESSING WORKERS ON THE ADRIATIC COAST OF CROATIA

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Received in January 2012
CrossChecked in May 2012
Accepted in May 2012

This article describes respiratory symptoms and lung function in 98 fish processing female workers employed in a fish processing plant located on the Croatian Adriatic coast and 95 matching controls. The study included chronic and acute respiratory symptoms which developed during the shifts. Lung function measurements included forced vital capacity (FVC), one-second forced expiratory volume (FEV_1) and maximal expiratory rates at 50 % and the last 25 % (FEF_{50}, FEF_{25}). Chronic respiratory symptoms were significantly dominant in fish processing workers compared to controls. The most common chronic symptoms were hoarseness (57.1 %), nasal catarrh (51.0 %), chronic cough (42.9 %), chronic phlegm (34.7 %), and frequent chest cold (35.7 %). Exposed smokers and nonsmokers had a similar prevalence of chronic respiratory symptoms. Acute symptoms over the work shift were high, with headache in lead (smokers: 62.5 %; nonsmokers: 56.1 %). Most of the ventilatory capacity parameters were significantly lower than predicted, FEF_{25} in particular, indicating obstructive changes predominantly in the smaller airways. These findings suggest that fish processing workers are prone to developing acute and chronic respiratory symptoms as well as to lung function changes. This calls for medical and technical preventive measures to be introduced in the work environment of the fish processing plant.

KEY WORDS: *bioaerosols, occupational respiratory diseases, prevention*

Fisheries along the Croatian Adriatic coast have a long tradition in processing fish such as tuna, sea bass, and sardines. Processing in the studied plant mostly includes manual handling of seafood. In Croatia, fish processing has been regulated by the Croatian veterinary and health regulation for breeding, production and marketing of fish and fish products (1, 2). According to these regulations, fish has to be sorted and cooled down to the temperature between 0 °C to +4 °C or frozen to -18 °C. Fish processed in factories should be exsanguinated, decapitated, stripped of fins and entrails, and finally cooled or frozen.

There is an increasing demand for seafood in the world which has led to increased harvesting. The Adriatic Sea offers a great opportunity for the development of fisheries and related processing industry. Workers employed in fish processing industry are exposed to a variety of harmful environmental agents including cold and humidity, allergens, and aerosols of histamine, fish flour and other toxins. These agents may cause a number of adverse reactions.

There are few reports on the respiratory reactions in workers occupationally exposed to harmful agents in fish processing industry. Common occupational symptoms in fish processing workers include asthma, chronic bronchitis, conjuctivitis, rhinitis, angioedema, and rash (3).

This article presents a study of respiratory function in workers employed in a fish processing plant in coastal Croatia.

SUBJECTS AND METHODS

Subjects

The study included 98 women who worked in a sardine processing plant located near the town of Zadar, Croatia. Their mean age was 44 years (range: 19 to 56 years), mean height 163 cm (range: 155 cm to 188 cm) and mean years of service in fish processing industry 20 (range: 1 to 34 years). Over half the workers (52 of 98; 53.1 %) smoked on average 18 pack-years. As their jobs involved a variety of tasks they could not be grouped according to the working process.

The control group consisted of 95 female food packers from another plant unexposed to known bioaerosols to control for the prevalence of chronic respiratory symptoms. They matched the exposed group in age, years of service, and smoking habits.

Respiratory symptoms

Chronic respiratory symptoms were established using the Medical Research Council Questionnaire (MRCQ) (4) on respiratory symptoms and additional questions on occupational asthma, as described by Godnić-Cvar (5). All workers gave a detailed occupational and smoking history. The definitions of symptoms were taken from (4), as follows:

- *Chronic cough or phlegm*: cough and/or phlegm to a minimum of three months a year;
- *Chronic bronchitis*: cough and phlegm for a minimum of three months a year and for not less than 2 successive years;
- *Dyspnea grades*: grade 3 - shortness of breath when walking with other people at an ordinary pace on level ground; grade 4 - shortness of breath when walking at their own pace on level ground;
- *Occupational asthma*: recurring attacks of dyspnoea, chest tightness, and pulmonary function impairment of the obstructive type diagnosed by physical examination, and spirometry during or after the shift (a drop in FEV by more than 15 %), confirmed by the medical records from industrial physician.
- *Chest cold*: frequent cold during or after the shift for at least three months a year.

Acute symptoms that developed during the shift were also recorded in all fish processing workers, but not controls. Symptoms included cough, wheezing, chest tightness, dyspnoea, irritation or dryness of the throat, secretion, dryness or bleeding of the nose, eye irritation, and headache. Special attention was paid to register the symptoms of the reactive airways dysfunction syndrome (RADS) including cough, nasal symptoms, chest tightness, wheezing, dyspnoea, hoarseness, and throat irritation or dryness.

Ventilatory capacity

Ventilatory capacity was measured only in fish processing workers by recording maximum expiratory flow-volume (MEFV) curves on a Jaeger Pneumoscreen spirometer (Wurzburg, Germany). The MEFV curves provided information on the forced vital capacity (FVC), one-second forced expiratory volume (FEV_1), and maximum flow rates at 50 % and the last 25 % of the vital capacity (FEF_{50} and FEF_{25}, respectively). These readings were taken during the morning shift. The spirometer was calibrated on a daily basis. Lung function was tested according to Quanjer et al. (6). At least three MEFV curves were recorded for each subject and the best the three curves used for interpretation. Ventilatory capacity was compared with the predicted normal values proposed by Quanjer et al. (7).

Statistical analysis

Chi-square test (or when appropriate Fisher's exact test) was used to test differences in the prevalence of respiratory symptoms between the fishery and control workers . Odds ratios and 95 % confidence intervals (CI) were calculated using a logistic regression analysis for each respiratory symptom (variables) and age, length of employment and smoking as predictors (8). Ventilatory capacity was analysed with the paired *t*-test by comparing baseline to predicted values (matched by sex, age, and height). Multiple regression analysis was used to adjust the predicted FVC, FEV_1, FEF_{50}, and FEF_{25} for sex, age, years of service, and smoking (9). A level of $P<0.05$ was considered statistically significant.

RESULTS

Table 1 shows that the prevalence of most chronic respiratory symptoms was significantly higher in fish processing workers than in controls (P<0.01), ranging from 57.1 % for hoarseness to 2 % for dyspnoea grade 3 and 4. No case of occupational asthma was recorded in either group.

Differences in chronic respiratory symptoms between smoking and nonsmoking fishery workers are presented in Table 2. Only chronic cough was significantly higher in smokers (56.3 %) than in nonsmokers (36.4 %) (P<0.05).

Acute symptoms in the fishery workers recorded during the shift did not differ significantly between smokers and nonsmokers, except for eye irritation, which was higher in nonsmokers (57.6 %) than smokers (31.5 %, P<0.05, Table 3). No case of wheezing or chest tightness was recorded in either subgroup.

Table 4 presents the odds ratios for chronic and acute respiratory symptoms in relation to age, length of occupational exposure (years of service), and smoking. Statistically significant were the ratios for chronic cough, chronic phlegm, chronic bronchitis, and dyspnoea for smokers and for dyspnoea, nasal catarrh, acute cough, throat irritation, nasal secretion, dry nose, and headache for the length of occupational exposure (years of service).

Ventilatory capacity in fishery workers was significantly lower than predicted for all parameters, FEF_{25} in particular. This points to obstructive changes in the smaller airways (Table 5).

Regression analysis showed that FVC and FEV_1 were significantly related to years of exposure

Table 1 *Prevalence of chronic respiratory symptoms in 98 female fish processing workers and 95 controls*

Respiratory symptoms	No. (%) of subjects		P
	Fish workers* (n=98)	Controls† (n=95)	
Chronic cough	42 (42.9)	6 (6.1)	<0.01
Chronic phlegm	34 (34.7)	5 (5.3)	<0.01
Chronic bronchitis	26 (26.5)	4 (4.2)	<0.01
Dyspnoea grades 3 & 4	2 (2.0)	0 (0)	NS
Sinusitis	31 (31.6)	2 (2.1)	<0.01
Nasal catarrh	50 (51.0)	1 (1.1)	<0.01
Hoarseness	56 (57.1)	0 (0)	<0.01
Chest cold	35 (35.7)	0 (0)	<0.01

** Mean age (43.7±5.9) years; mean years of service (20.0±7.5)*
†Mean age (42.5±4.9) years; mean years of service (19.3±6.2)

Table 2 *Prevalence of chronic respiratory symptoms in 98 female fish processing workers by smoking habit*

Respiratory symptoms	No. (%) of subjects		P
	Smokers* (n=32)	Non-smokers† (n=66)	
Chronic cough	18 (56.3)	24 (36.4)	<0.05
Chronic phlegm	14 (43.8)	20 (30.3)	NS
Chronic bronchitis	12 (37.5)	14 (21.2)	NS
Dyspnoea grades 3 & 4	1 (3.1)	1 (1.5)	NS
Sinusitis	10 (31.3)	21 (31.8)	NS
Nasal catarrh	15 (46.9)	35 (53.0)	NS
Hoarseness	17 (53.1)	39 (59.1)	NS
Chest cold	12 (37.5)	23 (34.9)	NS

† Mean age (44.4±5.4) years; mean years of service (20.9±7.9)
** Mean age (42.3±6.6) years; mean years of service (19.0±7.3)*

Table 3 *Prevalence of acute symptoms reported during shift in 98 female fish processing workers by smoking habit*

Respiratory symptoms		No. (%) of subjects		P
		Smokers* (n=32)	Non-smokers† (n=66)	
Cough		1 (3.1)	1 (1.5)	NS
Dyspnoea		1 (3.1)	1 (1.5)	NS
Throat	irritation	12 (37.5)	19 (28.8)	NS
	dryness	16 (50.0)	32 (48.5)	NS
Eye irritation		10 (31.3)	38 (57.6)	<0.01
Nose	secretion	4 (12.5)	13 (19.7)	NS
	dryness	5 (15.6)	12 (18.2)	NS
	bleeding	5 (15.6)	8 (12.1)	NS
Headache		20 (62.5)	37 (56.1)	NS

** Mean age (42.3±6.6) eayrs; mean years of service (19.0±7.3)*
† Mean age (44.4±5.4) years; mean years of service (20.9±7.9)

Table 4 *Chronic respiratory and acute symptoms in 98 female fish processing workers in relation to age, years of service,and smoking by log regression*

Symptoms	OR (95 % CI)		
	Age	Exposure	Smoking
Chronic cough+	1.055 (0.964 to 1.155)	0.950 (0.887 to 1.017)	1.096* (1.010 to 4.071)
Chronic phlegm+	1.001 (0.914 to 1.096)	0.990 (0.924 to 1.061)	1.102* (0.081 to 5.076)
Chronic bronchitis+	1.034 (0.937 to 1.141)	0.975 (0.907 to 1.049)	1.040* (1.000 to 1.092)
Dyspnoea+	0.902 (0.596 to 1.365)	1.077* (1.011 to 4.525)	1.032* (1.023 to 6.153)
Sinusitis+	1.053 (0.957 to 1.159)	0.985 (0.920 to 1.055)	1.004 (0.959 to 1.051)
Nasal catarrh+	0.973 (0.888 to 1.067)	1.103* (1.097 to 5.149)	0.980 (0.936 to 1.026)
Hoarseness+	1.072 (0.975 to 1.179	1.019 (0.951 to 1.091)	0.969 (0.926 to 1.014)
Chest cold+	0.965 (0.879 to 1.060)	1.020 (0.950 to 1.096)	1.000 (0.954 to 1.048)
Acute cough++	0.358 (0.074 to 1.744)	2.550* (1.135 to 1.207)	0.849 (0.410 to 1.755)
Throat irritation++	0.943 (0.844 to 1.054)	1.188* (1.085 to 7.173)	1.030 (0.980 to 1.081)
Dry throat++	1.018 (0.933 to 1.111)	1.011 (0.926 to 1.056)	0.996 (0.953 to 1.042)
Eye irritation++	1.098 (0.995 to 1.212)	1.003 (0.936 to 1.075)	0.958 (0.911 to 1.007)
Nasal secretion++	0.931 (0.871 to 1.111)	1.148* (1.090 to 9.324)	0.977 (0.914 to 1.045)
Dry nose++	0.946 (0.834 to 1.074)	1.037* (1.010 to 5.146)	0.975 (0.901 to 1.054)
Nasal bleeding++	0.970 (0.862 to 1.091)	0.970 (0.883 to 1.065)	1.004 (0.936 to 1.079)
Headache++	1.005 (0.920 to 1.099)	1.048* (1.010 to 1.122)	0.987 (0.943 to 1.033)

OR = odds ratio
CI = confidence interval
**P<0.01 or P<0.05*
+chronic symptoms
++acute symptoms

(service) while none was significantly related to smoking (Table 6).

DISCUSSION

Fish processing workers are exposed to several occupational health and safety risks, and fish aerosols in the working environment present a risk for the development of respiratory diseases. Other agents that can cause respiratory diseases or allergic sensitisation include fish enzymes, proteins or skin.

Sherson et al. (10) demonstrated occupational respiratory or rhinitis symptoms, caused by inhalation of fish aerosols, in trout-processing factory workers who worked next to an automatic gutting machine. Shiryaeva et al. (11) recently established impaired lung function in fishermen. Bang et al. (12) reported high prevalence of work-related airway symptoms (42.8 %) in sea food industry workers. In their study, FVC and FEV_1 were lower than the predicted values

Table 5 *Ventilatory capacity in 98 female fish processing workers by smoking habit*

Ventilatory capacity		No. of subjects	
		Smokers* (n=32)	Non-smokers† (n=66)
FVC	Measured (L)	3.2±0.6	3.1±0.6
	Predicted (L)	3.6±0.3	3.5±0.3
	Difference measured-predicted %	89.2±14.0	88.9±12.3
	P	<0.01	<0.01
FEV_1	Measured (L)	2.8±0.4	2.7±0.5
	Predicted (L)	2.9±0.2	2.8±0.3
	Difference measured-predicted %	97.7±13.0	98.7±14.1
	P	<0.01	<0.01
FEF_{50}	Measured (L)	3,9±0.9	3.8±0.9
	Predicted (L)	4.2±0.1	4.2±0.2
	Difference measured-predicted %	91.2±18.7	91.4±22.9
	P	<0.01	<0.01
FEF_{25}	Measured (L)	1.7±0.4	1.8±0.5
	Predicted (L)	2.1±0.1	2.0±0.1
	Difference measured-predicted %	80.7±17.5	87.5±25.9
	P	<0.01	<0.01

The measured date are presented as mean ±SD
** Mean age (42.3±6.6) years; mean years of service (19.0±7.3) years*
† Mean age (44.4±5.4) years; mean years of service (20.9±7.9) years

Table 6 *Regression analysis of ventilatory capacity tests in 98 female fish processing workers*

Test	Variable	DF	Parameter Estimate	Standard Error	T for HO: Parameter=0	Prob>(T)	F	P	R^2
FVC	intercept	1	3.74365	0.15282	24.37	<0.0001			
	exposure	1	-0.02994	0.00706	-4.24	<0.0001			
	smoking	1	0.00645	0.00603	1.07	0.2873	9.18	0.0002	0.1443
FEV_1	intercept	1	3.11190	0.12392	25.11	<0.0001			
	exposure	1	-0.01804	0.00573	-3.15	0.0022			
	smoking	1	0.00313	0.00489	0.64	0.5240	5.01	0.0086	0.0763
FEF_{50}	intercept	1	4.15705	0.26216	15.86	<0.0001			
	exposure	1	-0.01486	0.01211	-1.23	0.2228			
	smoking	1	-0.00364	0.01035	-0.35	0.7258	0.87	0.4216	-0.0027
FEF_{25}	intercept	1	1.84040	0.14036	13.11	<0.0001			
	exposure	1	-0.00212	0.00649	-0.33	0.7450			
	smoking	1	-0.01056	0.00554	-1.91	0.0596	1.96	0.1463	0.0194

T - t-statistics for the null hypothesis
H0 - the parameter is 0
Exposure - length of service

in all exposed nonsmokers. This supports our findings of lower ventilatory capacity tests. In addition, sick-leave rate was higher among our fish-processing workers than controls (data not shown).

Pre-employment and periodic medical examination of workers in fish processing plant as well as improved ventilation in the processing areas should help to prevent the development of acute and chronic

respiratory changes. Early symptom recognition and prompt action to reduce aerosol exposure should further help to avoid chronic changes in pulmonary function, often associated with occupational asthma. In that respect symptoms of the upper airways can be a reliable risk marker for workers exposed to high-molecular-weight agents such as seafood. Lung function tests can help to determine which workers have hyper-responsive airways.

The association between respiratory health effects and environmental concentrations of seafood aerosols helps to identify who is at a higher risk of developing occupational asthma. In addition, the preventive measures should include anti-smoking programmes.

Currently there are no occupational exposure limits for seafood aerosols, local or international, and setting them would definitely contribute to health protection of workers in the seafood industry.

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Sažetak

RESPIRATORNI SIMPTOMI U RADNICA NA PRERADI RIBA NA OBALI JADRANA U HRVATSKOJ

Cilj je ovoga istraživanja bio ispitati respiratorne simptome i plućnu funkciju radnica zaposlenih na preradi riba u industriji na obali Jadranskog mora u Hrvatskoj. U istraživanje je uključeno 98 radnica zaposlenih na preradi riba i 95 žena neizložene kontrolne skupine. Ispitivani su kronični i akutni respiratorni simptomi koji se razvijaju tijekom radne smjene. Mjerena je plućna funkcija registriranjem forsiranoga vitalnog kapaciteta (FVC), forsiranoga ekspiracijskog volumena u prvoj sekundi (FEV_1) te maksimalnoga ekspiracijskog protoka pri 50 % i zadnjih 25 % forsiranoga vitalnog kapaciteta (FEF_{50}, FEF_{25}) na krivulji maksimalni ekspiracijski protok-volumen (MEPV). Učestalost većine kroničnih respiracijskih simptoma bila je značajno viša u eksponiranih u usporedbi s kontrolnom skupinom. U eksponiranih radnica utvrđena je i visoka prevalencija akutnih simptoma koji se razvijaju tijekom radne smjene, posebno za promuklost (57,1 %) i katar nosa (51 %), potom slijedi kronični kašalj (42,9 %), kronični iskašljaj (34,7 %), upale sinusa (32 %) i česte prehlade (35,7 %). S obzirom na naviku pušenja pušači i nepušači imali su sličnu prevalenciju kroničnih respiratornih simptoma. Izložene radnice imale su visoku prevalenciju akutnih simptoma tijekom radne smjene i to naročito za glavobolju (pušači 62,5 %; nepušači 56,1 %). Ventilacijska funkcija pluća bila je značajno smanjena u usporedbi s predviđenim normalnim vrijednostima posebice za FEF25 % upućujući na opstruktivne promjene pretežno u manjim dišnim putovima. Naši podaci upućuju na opasnost razvoja kroničnih i akutnih respiracijskih simptoma i promjena plućne funkcije u radnika koji rade u industriji na preradi riba. Medicinske i tehničke preventivne mjere u radnom okolišu treba preporučiti u industriji prerade riba.

KLJUČNE RIJEČI: *bioaerosoli, prevencija, profesionalne respiratorne bolesti*

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DOI: 10.2478/10004-1254-63-2012-2150

Professional Paper

SMOKING AMONG MACEDONIAN WORKERS FIVE YEARS AFTER THE ANTI-SMOKING CAMPAIGN

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Received in September 2011
CrossChecked in September 2011
Accepted in May 2012

To assess the efficacy of nationwide anti-smoking campaign, we compared the findings of a study on worker smoking performed in 2005 with our latest cross-sectional study completed in 2010. It included 753 randomly selected workers, of whom 126 office, 108 construction, 93 agricultural, 97 petroleum refinery, 114 textile, 117 food processing workers, and 98 cleaners. Information was collected with a self-administered questionnaire. The prevalence of current smokers among all workers was 35.4 %, ranging from 30.2 % in office workers to 43.5 % in construction workers. It did not significantly differ from the prevalence recorded in 2005 (35.4 % *vs.* 36.8 %, respectively; P=0.441). Mean pack-years smoked among all smokers was 12.4±2.3, ranging from 10.9 in administrative workers to 13.7 in agricultural workers. We did not find any significant difference in the prevalence of current smokers between male and female workers and between workers aged less or more than 40 years, as well as between workers of higher and lower education. The prevalence of ex-smokers was 10.5 %, ranging from 8.4 % in construction workers to 12.1 % in administrative workers, whereas the prevalence of passive smokers was 29.1 %, ranging from 26.2 % in food processing workers to 32.9 % in agricultural workers.
Our findings indicate that the prevalence of current and passive smokers has remained high regardless of the anti-smoking campaign and call for stricter implementation of anti-smoking regulations.

KEY WORDS: *current smoker, ex-smoker, occupation, passive smoker, prevalence, tobacco smoke*

Tobacco smoking takes an enormous toll on the global burden of disease (1-3). Its adverse health effects are attributable to approximately 2,500 toxins in the tobacco plant and approximately 4,000 substances in the tobacco smoke. At least 250 of these are harmful and more than 60 are known or suspected to cause cancer (4, 5).

As many epidemiological and clinical studies indicate, the adverse health effects related to tobacco smoke include heart disease, lung cancer, chronic obstructive pulmonary disease, as well as an increase in the number and severity of asthma attacks, increased susceptibility to lung infections (such as pneumonia and bronchitis), other breathing problems including cough, mucus production, chest discomfort, and reduced lung function (4, 6, 7). In addition, despite controversial results of the studies that investigated joint effects of tobacco smoke and specific workplace exposure, the role of such interaction in health impairment could not be excluded (8-10). To prevent adverse health effects, governments worldwide increase tobacco taxes, regulate tobacco content, control tobacco import, issue tobacco warning labels, promote anti-tobacco education, programmes to quit smoking and smokeless life-style, encourage the use of stop-smoking drugs, restrict or ban tobacco

advertising, sponsorships and promotions, ban smokeless tobacco products (such as chewing tobacco and snuff), and restrict or ban smoking in work and public places (11, 12). The Republic of Macedonia has adopted many of these anti-smoking activities such as the 2005 law restricting indoor smoking to separated rooms (13) and the 2008 law banning indoor smoking in all public buildings, workplaces, and public transportation (14).

The aim of our study was to see whether these activities had an effect on smoking among Macedonian workers by comparing the latest findings with a study performed in 2005.

SUBJECTS AND METHODS

This cross-sectional study was performed at the Institute for Occupational Health of the Republic of Macedonia, Skopje - WHO Collaborating Center and GA^{2}LEN Collaborating Center from May to November 2010.

It included 753 randomly selected workers who completed the questionnaire (96.1 % of all invited) from public administration, construction, agriculture, petroleum refining, textile industry, food processing, and cleaning). Three hundred eighty-nine were men and 364 women, aged 19 to 64 years (Table 1). All subjects gave informed consent to participate in the study.

Table 1 *Demographics of the study subjects*

Sex, age, occupation, and level of education	Study subjects (n=753)
Men to women ratio	1:1
Age in years: Mean (range)	38.7±12.9 (19 to 64)
Subjects aged ≤40 years	346 (45.9)
Occupation	
Public administration	126 (16.7)
Construction	108 (14.3)
Agriculture	93 (12.4)
Petroleum refining	97 (12.9)
Textile industry	114 (15.1)
Food processing	117 (15.5)
Cleaning	98 (13.0)
Level of education	
High (University degree)	216 (28.7)
Primary and secondary education	537 (71.3)

Numbers (%) are given, unless indicated otherwise.

Questionnaire

Information on smoking was collected using a self-administered questionnaire. Smoking was classified according to the World Health Organization (WHO) Guidelines for Controlling and Monitoring the Tobacco Epidemic (5). Current smoker was defined as a subject who smoked any tobacco product at the time of the survey. Daily smoker was defined as a current smoker who smoked at least once a day, except on days of religious fasting, while occasional smoker was defined as a current smoker who did not smoke every day. Daily smokers provided information on years of smoking and daily mean cigarettes smoked. From this information we calculated pack-years smoked (one pack-year denotes one year of smoking 20 cigarettes a day) using a website calculator designed by Masters and Tutt (16).

Ex-smoker was defined as a subject who used to smoke, but now does not smoke at all. Ex-smokers were divided in those who quit smoking less than or more than two years ago).

Passive smoker was defined as a subject exposed to environmental tobacco smoke (ETS), that is, with at least one smoker in the household and/or the workplace (17, 18). In addition, passive smokers were divided in those who were exposed to ETS for less than or more than four hours per day.

Statistical analysis

For data description and analysis we used the Statistical Package for the Social Sciences (SPSS) version 11.0 for Windows. Continuous variables were expressed as mean values with standard deviation (SD) and nominal variables as numbers and percentages. The chi-square test was used for testing differences in prevalence. Pack-years smoked were compared using the independent-samples *t*-test. P-value below 0.05 was considered statistically significant.

RESULTS

The prevalence of the current smokers among all subjects was 35.4 % (267 of 753), 94.4 % (252 of 267) of whom were daily smokers. The prevalence of

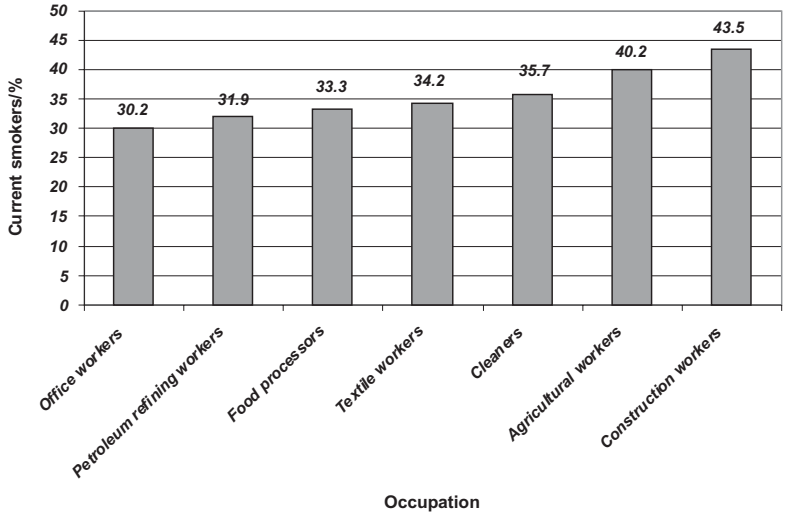

Figure 1 *Distribution of current smokers by occupation*

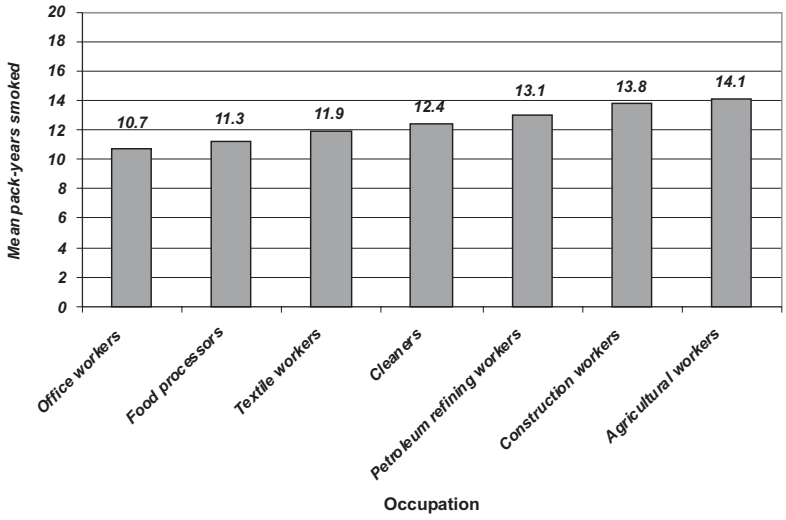

Figure 2 *Distribution of daily smokers by pack-years smoked*

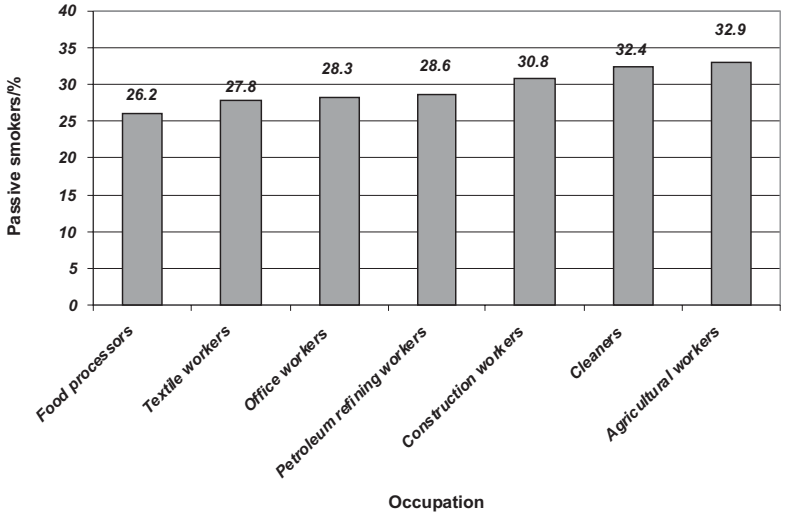

Figure 3 *Distribution of ex-smokers by occupation*

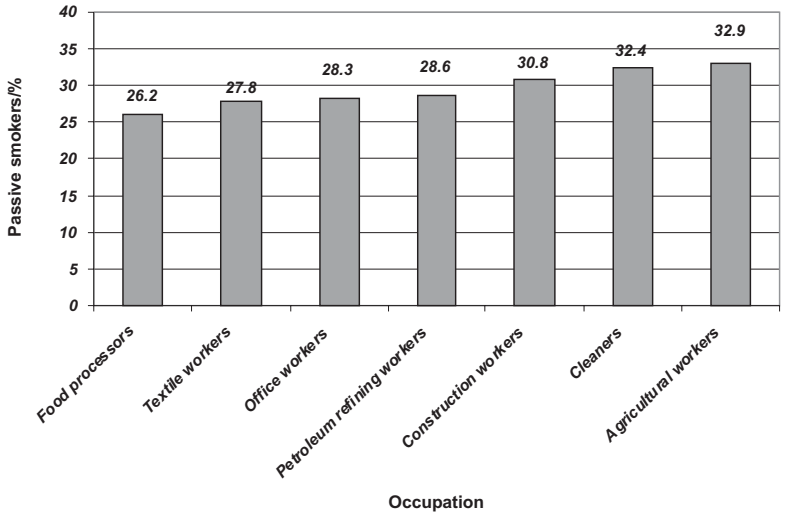

Figure 4 *Distribution of passive smokers by occupation*

current smokers ranged from 30.2 % in office workers to 43.5 % in construction workers. We found no significant difference between occupations (Figure 1).

This prevalence of current smokers is similar to the prevalence established in our study performed in 2005 (35.4 % *vs.* 36.8 %, respectively, P=0.441; chi-square test) (19).

Mean pack-years smoked in all daily smokers was 12.4±2.3 (12.9±1.8 in men and 11.3±3.7 in women), ranging from 10.7 in office workers to 14.1 in agricultural workers. Again, there was no significant difference between occupations (Figure 2).

Men and women did not differ significantly in the prevalence of current smokers (38.6 % *vs.* 33.7 %, respectively, P=0.344; chi square test) and neither did subjects below 40 from those above 40 years of age (37.9 % *vs.* 34.1 %, respectively, P=0.294; chi square test). The prevalence of current smokers was lower in subjects with high (university) education than in subjects with lower education, but not significantly (29.6 % vs. 40.8 %, respectively, P>0.05, chi square test).

The prevalence of ex-smokers among all subjects was 10.5 % (79 of 753), ranging from 8.4 % in construction workers to 12.1 % in office workers (Figure 3). Differences in the distribution of ex-smokers by sex, age, and education level were not significant either.

The prevalence of passive smokers was 29.1 % (219 of 753) among all subjects, ranging from 26.2 % in food processing to 32.9 % in agricultural workers (Figure 4). Differences in the distribution of passive smokers by occupation sex, age, education level, and years of exposure to ETS were not significant.

DISCUSSION

Between the studies performed in 2005 (19) and this one in 2010, the Macedonian government launched a broad anti-smoking campaign that included indoor smoking restriction and ban laws, educational programmes, promotion of smokeless life-style, tobacco warning labels, etc.. However, the comparison among the same occupations between these two years showed no decline in smoking.

As the prevalence of current smokers in this study is similar to its prevalence in the general Macedonian population (34.2 %) (20), we can compare our results with the US New Jersey Adult Tobacco Survey of the general population (21) and with the Australian National Health Survey in workers (22). These countries have come up with more effective anti-smoking strategies and achieved a significant decline in the prevalence of current smokers in both general population and worker populations over the last decade. Similarly effective have been the Slovenian tobacco control measures (23).

In our study, the prevalence of current smokers was the highest in construction and agricultural workers. Similar prevalence was reported for

construction workers in the US study by Bang & Kim (24), by the Centers for Disease Control (CDC) report for May 2003 (25), and by the Australian Bureau of Statistics Report for 2007-2008 (22). Unlike our study, these reports found a significant difference between construction workers and office workers.

Another indication of the success of anti-smoking campaigns is the prevalence of ex-smokers, which in our study (10.5 %) showed a minor increase with respect to 2005 (8.1 %) (19), whereas the CDC reported a much higher prevalence in certain occupations (e.g. public administration) reaching up to 20 % (25).

The prevalence of passive or second-hand smokers in our study (29.1 %) remained similar to 2005 (31.5 %) (19) and 2007 (27.4 %) (26). Most passive smokers of all occupations were exposed to ETS for less than four hours. In a longitudinal study in 12 European countries, Australia and the USA, Janson et al. (27) reported a drop in passive smoking between 1990 and 1994. They also found that people with lower education were more than twice as likely to be exposed to ETS and suggested that anti-smoking strategies should primarily target people with lower education. Our study has not confirmed these findings, as we found a similar prevalence of passive smokers across all occupations and educational levels.

There were some limitations to our study, which should be taken into account when interpreting the results. First, this survey is designed as a cross-sectional study, instead of longitudinal, which renders comparison between this and the 2005 study somewhat imprecise. We could not perform a longitudinal study because of high worker turnover, construction and agriculture in particular. Second, five years is not long enough to evaluate the effects of an anti-smoking campaign, but may provide preliminary information. However, continuous monitoring of smoking in the working population may provide guidelines to better targeting and modifying anti-smoking programmes.

The strength of the study, on the other hand, is that it included all aspects of smoking (current, ex-, and passive smoking) in a large sample across several occupations.

In conclusion, our findings suggest that the anti-smoking campaign in Macedonia has left much to be desired and call for stricter enforcement of the adopted anti-smoking regulations and for additional activities that would target all workers and occupations to prevent adverse health effects of tobacco smoking.

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Sažetak

PUŠENJE MEĐU MAKEDONSKIM RADNICIMA PET GODINA NAKON KAMPANJE PROTIV PUŠENJA

Želeći utvrditi djelotvornost kampanje protiv pušenja u Makedoniji, usporedili smo rezultate istraživanja o pušenju u radničkoj populaciji provedenog 2005. s rezultatima našega najnovijega presječnoga randomiziranog ispitivanja koje je dovršeno 2010. Ispitivanje je obuhvatilo 753 radnika, od kojih je 126 uredskih, 108 građevinskih, 93 poljoprivrednih, 97 u rafineriji nafte, 114 tekstilnih, 117 prehrambenih te 98 čistač(ic)a. Podaci su prikupljeni s pomoću upitnika koji su ispunjavali ispitanici. Prevalencija aktivnih pušača među svim radnicima bila je 35,4 %, od 30,2 % u uredskih radnika do 43,5 % u građevinskih. Nije se značajno razlikovala od prevalencije zabilježene 2005. (35,4 % odnosno 36,8 %, P=0,441). Srednja vrijednost kutija/godina u pušača bila je 12,4±2,3, od 10,9 u uredskih do 13,7 u poljoprivrednih radnika. Značajnih razlika u aktivnome pušenju nije bilo među ženama i muškarcima, radnicima starijim i mlađima od 40 godina, niti među radnicima višeg i nižeg obrazovanja. Prevalencija bivših pušača bila je 10,5 %, od 8,4 % u građevinskih do 12,1 % u uredskih radnika, dok je prevalencija pasivnih pušača bila 29,1 %, od 26,2 % u radnika u preradi hrane do 32,9 % u poljoprivrednih radnika.

Naši rezultati pokazuju da je prevalencija aktivnih i pasivnih pušača ostala visoka bez obzira na kampanju protiv pušenja te pozivaju na strožu provedbu propisa koji ograničavaju pušenje.

KLJUČNE RIJEČI: *aktivni pušač, bivši pušač, duhanski dim, pasivni pušač, prevalencija, zanimanje*

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DOI: 10.2478/10004-1254-63-2012-2197

Professional paper

FREQUENCY OF MUSCULOSKELETAL AND EYE SYMPTOMS AMONG COMPUTER USERS AT WORK*

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Received in January 2012
CrossChecked in February 2012
Accepted in April 2012

Computer users most often complain of the eye and locomotor system disorders. The goal of this paper was to find out the frequency and relation between musculoskeletal and eye symptoms among computer workers.

The data on musculoskeletal and eye symptoms were provided by two questionnaires.

Forty-nine workers were included in the study. Their mean age was 41 years and average length of service 16 years. The average amount of time they spent in front of computers was 6.73 hours per day. Women spent more time working at a computer per day than men (P=0.025). The most frequent complaint in the past year referred to the upper back pain (30.6 % of the workers). Every fourth worker, i.e. 24.5 % of them experienced neck pain in the past year; women more often than men (P=0.024). A health problem which reduced the range of motion and prompted the workers to ask for sick leave was lower back pain. The relation between eye symptoms and the upper back pain experienced in the past year (P=0.004), and in the last week (P=0.031) was statistically significant.

Proper exercises for stretching musculoskeletal system, ergonomic computer equipment, and artificial tears could decrease muscular and eye problems, which in turn could enhance productivity and reduce sick leaves.

KEY WORDS: *computer, locomotor system disorders, video display, vision*

Research shows that workers at video display terminals (VDT) mostly suffer from neck problems and upper and lower back pain but ergonomic interventions can reduce these difficulties (1, 2). Improper display height leads to faster and more pronounced trapezius muscle strain (3). To achieve the best ergonomic solutions, it is necessary to have a detailed analysis of worker's movements, which is nowadays provided by video technology (4).

Persons working with computers, who spend four or more hours on average in front of a computer screen, must have previous preventive tests according to the legislative provisions (5). Eye problems and vision disorders related to working with computers are accompanied by the locomotor system-related diseases (6) and the goal of this paper was to find out the frequency and relation between the two.

METHODS AND SUBJECTS

The data on musculoskeletal disorders were provided by the Nordic Musculoskeletal Questionnaire (7). Eye problems related to work with computers, such as red eye, itching, excessive tearing, scratchiness,

* Partly presented at the 5th Croatian Congress on Occupational Health with International Participation "Healt, Work, and Community", Hvar, Croatia, 28 September to 2 October 2011

and eye burning, were provided by a previously used questionnaire (8). Ten percent of workers working in a factory were tested. All of them were administration workers who worked on computers for more than four hours per day. Statistical analysis was made using SPSS program, Version 8.0 for Windows. (1997, SPSS inc. Chicago, IL, USA). P<0.05 was the statistically significant value for *t*- test and chi-square tests (9).

RESULTS

Forty-nine middle aged workers (27 women and 22 men) were included in this study. Their average age was (41.1±10.87) years and length of service (16.37±11.29) years. The average amount of time they spent in front of computers was (6.73±2.05) hours per day (Table 1). Statistically, there were no substantial differences in age and length of service between women and men. However, women worked longer hours at a computer per day than men (P=0.025). Table 2 shows that in the past year, workers mostly complained about pain and discomfort in the upper back (30.6 % of the subjects) and neck (every fourth worker or 24.5 % of them; women more frequently than men) (P=0.024). Where last week's symptoms are concerned, 12.2 % of women experienced neck pain. Pain in the neck and upper back did not significantly limit the range of motion. However, a health problem which reduced the range of motion and prompted the workers to ask for sick leave was lower back pain. Two workers experienced wrist pain with a limited range of motion indicative of the carpal tunnel syndrome. Eye symptoms like red eye, itching, excessive tearing, scratchiness, and burning were associated with 24 workers (49 %). Those with eye symptoms experienced significantly more pain and discomfort in the upper back in the past year (P=0.004), and in the last week (P=0.031) compared to other workers.

DISCUSSION

Our results showed that computer workers had frequent eye (49 %), upper back (31 %) and neck (24.5 %) symptoms. Lower back pain appeared in about 16 % of subjects, which is less than in recent research (10). However, in our study, back pain was often a cause for sick leave, which was not the case with upper back or neck pain. Female computer users at work have their neck more often and longer exposed

Table 1 *Data on subjects*

	Mean ± SD		
	Men (N=22)	**Women (N=27)**	**Total (N=49)**
Age / years	41.0±11.1	41.2±10.9	41.1±10.87
Length of service / years	15.0±10.5	17.5±12.0	16.37 ±11.29
Daily working at computer / h	5.9 ±2.5*	7.4±1.3*	6.73 ±2.05

** P=0.025, t-test*

Table 2 *Frequency of musculoskeletal symptoms*

	Men (N=22) n (%)	**Women (N=27) n (%)**	**Total (N=49) n (%)**
Neck			
Symptoms in the last year	2 (9.1)*	10 (37.0)*	12 (24.5)
Symptoms in the last week	0	6 (22.2)**	6 (12.2)
Upper back			
Symptoms in the last year	4 (18.2)	11 (40.7)	15 (30.6)
Symptoms in the last week	4 (18.2)	6 (22.2)	10 (20.4)
Lower back			
Symptoms in the last year	3 (13.6)	5 (185)	8 (163)
Symptoms in the last week	2 (91)	4 (148)	6 (122)

**P=0.024, chi-square test*
***P=0.018, chi-square test*

to strain than men (11), which was also pointed out in this paper. Troubles with the wrist and forearm appear to be less frequent musculoskeletal problems for computer users at work than neck and shoulder difficulties (1); the carpal tunnel syndrome was noticed only in two workers in our study.

Troubles in the upper back and neck were significantly associated with eye symptoms, which is indicative of the worker's job strain. Working at a computer for more than 36 hours per week is associated with increased anxiety, and with musculoskeletal and eye symptoms (12). Stress and mental strain increase the frequency of musculoskeletal problems. A recently published study showed that the workers sorting mail, who suffered from eyestrain, had a higher prevalence of musculoskeletal disorders (13).

In the past 20 to 25 years, the costs of sick leaves due to musculoskeletal problems have increased 3.5 times (14). Training workers, encouraging proper exercising, using artificial tears for relieving dry eye symptoms, and reducing the strain of musculoskeletal system with ergonomic equipment may reduce the frequency of eye and muscular troubles (15), which, as a result, could enhance productivity and reduce sick leaves.

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Sažetak

UČESTALOST MIŠIĆNO-KOŠTANIH I OČNIH SIMPTOMA KOD RADA S RAČUNALOM

Kod rada s računalom javljaju se tegobe vezane uz oči i lokomotorni sustav. Cilj je rada utvrditi učestalost tegoba očiju i mišićno-koštanoga sustava kod radnika koji rade s računalom i njihovu povezanost. Pomoću upitnika uzeti su podaci o mišićno-koštanim i očnim simptomima kod rada s računalom. U ispitivanju je sudjelovalo 49 radnika (27 žena i 22 muškarca) prosječne životne dobi od 41 godina i prosječnog trajanja radnog staža od 16 godina koji dnevno rade za računalom u prosjeku 6,73 sata. Žene su značajno duže dnevno radile na računalu od muškaraca (P=0,025). Najviše se radnika žalilo na bolove u gornjem dijelu leđa u zadnjih godinu dana (30,6 %). Svaki četvrti radnik, tj. 24,5 % radnika imalo je bol u vratu u zadnjoj godini i to statistički značajno češće žene (P=0,024). Tegobe koje ograničavaju aktivnost i mogu zahtijevati bolovanje bili su bolovi u donjem dijelu leđa. Statistički je bila značajna povezanost pojave očnih simptoma i bolova u gornjim leđima u zadnjoj godini (P=0,004) i u zadnjem tjednu (P=0,031). Odgovarajuće vježbe rasterećenja mišićno-koštanoga sustava uz ergonomsku opremu za rad s računalom te smanjenje očnih tegoba upotrebom umjetnih suza potrebno je provoditi radi smanjenja mišićnih i očnih tegoba, što zajedno povećava produktivnost i smanjuje bolovanja.

KLJUČNE RIJEČI: *mišićno-koštani poremećaji, računalo, vid, videoterminal*

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DOI: 10.2478/10004-1254-63-2012-2193

Professional paper

NOVA RADNA ZADAĆA LJEKARNIKA: RAD S RAČUNALOM*

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Primljeno u siječnju 2012.
CrossCheck u svibnju 2012.
Prihvaćeno u travnju 2012.

Cilj je ovog rada bio utvrditi koliko rad s računalom utječe na promjene vidnih funkcija ljekarnika te na pojavu smetnji na vratnom dijelu kralježnice. U presječnom istraživanju ispitane su vidne funkcije i subjektivne smetnje pri radu 50 ljekarnika (srednja dob 41,8±11 godina), te 56 službenika (srednja dob 36,2±8,6 godina), koji 40 sati tjedno rade na računalu. Pri tome, ljekarnici pretežno stoje, a službenici sjede.

Od subjektivnih smetnji pri radu, suzenje očiju i bolovi u vratnoj kralježnici bili su značajno češći u skupini ljekarnika ($P<0,01$). Rezultati ispitivanja vidnih funkcija nisu se razlikovali između ispitivanih skupina. Poremećaj vida (miopija ili hipermetropija) utvrđen je kod 22 (44 %) ljekarnika i 23 (41 %) službenika ($P>0,05$).

Rezultati potkrepljuju odredbu Pravilnika o sigurnosti i zaštiti zdravlja pri radu s računalom (1) prema kojoj poslodavac mora planirati aktivnosti radnika na osobnom računalu tako da se rad periodički izmjenjuje s drugim aktivnostima. To se upravo događa pri obavljanju posla ljekarnika. Njegov rad s računalom se neprekidno izmjenjuje s obraćanjem klijentu, odnosno s izdavanjem lijeka. Za rješavanje poteškoća s kralježnicom treba tijekom svakog sata rada osigurati odmore u trajanju od najmanje 5 minuta te organizirati vježbe rasterećenja radi smanjenja statodinamičnoga napora.

KLJUČNE RIJEČI: *smetnje vida, statičko opterećenje kralježnice, suzenje očiju*

Sukladno odredbama Pravilnika o sigurnosti i zaštiti zdravlja pri radu s računalom (1) zaposlenici na radnom mjestu ljekarnika obvezni su svake druge godine obaviti pregled vida s obzirom na to da su među izloženosti opasnostima na radnom mjestu navedene i opasnosti pri radu s računalom.

Računala se koriste u raznim djelatnostima već tridesetak godina a danas je njihova upotreba svakodnevna. Među opisanim oštećenjima zdravlja u osoba koje rade na računalu navodi se astenopija, brzo umaranje oka, bolovi u očima, glavobolja, zamagljen vid te smetnje mišićno-koštanog sustava (2).

Cilj je ovoga rada bio utvrditi koliko rad s računalom utječe na promjene vidnih funkcija ljekarnika, te na pojavu smetnji na vratnom dijelu kralježnice.

ISPITANICI I METODE

U sklopu ovoga istraživanja tijekom 2009. godine izvršeni su pregledi 50 ljekarnika, 48 žena i 2 muškarca, te 56 službenika, 46 žena i 10 muškaraca, koji 40 sati tjedno rade na računalu. Ispitani ljekarnici zaposleni su na radnim mjestima na kojima većinu poslova obavljaju u stojećem položaju rabeći računalo

* Djelomično predstavljen na 5. hrvatskome kongresu medicine rada s međunarodnim sudjelovanjem "Zdravlje, rad i zajednica", Hvar, 28. rujna do 2. listopada 2011.

za svaki traženi lijek. Druga se skupina ispitanika sastojala od službenika, ekonomista srednje, više i visoke stručne spreme koji uglavnom rade sjedeći ispred računala.

Ispitanicima obiju skupina utvrđena je duljina izloženosti radu na računalima koja je izražena u mjesecima, sve ispitanike se pri liječničkom pregledu pitalo imaju li pri radu na računalu bolove u vratnoj kralježnici, te suzenje očiju. Ispitane su vidne funkcije svih ispitanika uključujući pregled vida ortoreterom te pregled pozadine oka.

Statistička značajnost razlika između ispitivanih skupina testirana je t-testom te hi-kvadrat testom na razini značajnosti $P<0,05$.

REZULTATI

Srednja dob skupine ljekarnika (41,8±11) godina bila je statistički značajno viša od srednje dobi skupine službenika (36,2±8,6) godina; ($P<0,01$), a ista razlika utvrđena je i za duljinu radnog staža uz računala [(147±76,4) mjeseci: (101±74,7) mjeseci; $P<0,01$)].

Nije utvrđena značajna statistička razlika s obzirom na stanje vida utvrđeno ortoreterom između skupine ljekarnika i službenika. Poremećaj vida (miopija ili hipermetropija) utvrđen je kod 22 (44 %) ljekarnika i 23 (41 %) službenika ($P>0,05$). Rezultati ispitivanja stereovida nisu se razlikovali između ispitivanih skupina. Ispitanici obiju skupina nisu imali smetnje u razlikovanju boja. Nalaz očne pozadine odstupao je od normale kod 4 (8 %) ljekarnika i 2 (4 %) službenika ($P>0,05$).

Od subjektivnih smetnji pri radu ljekarnici su se značajno više tužili na suzenje očiju pri radu u odnosu na službenike (78 %: 5,4 %; $\chi^2 = 58,28$; $P<0,01$). Utvrđeno je da je bol u vratnoj kralježnici statistički značajno učestalija kod ljekarnika nego u službenika (84 %: 1,8 %; $\chi^2= 70,41$; $P<0,01$).

RASPRAVA

U literaturi se ističe da je nužan medicinski nadzor radnika koji rade s računalom (3, 4). Goldoni (3) i La Dou (4) navode da su smetnje vida mnogo češće u radnika na računalu koji rade najmanje 10 godina. Smetnje pripisuju titranju slike na ekranu računala kojem su radnici izloženi svakodnevno cijelo radno vrijeme. Dodig (5) tvrdi da s time u vezi treba posebnu pozornost posvetiti pregledima očiju i obaviti selekciju radnika za rad na računalu. Proučavajući djelatnost ljekarnika, Portolan (6) upozorava na česte smetnje suzenja očiju i smetnje s vratnom i slabinskom kralježnicom. Rezultati ovoga istraživanja potvrđuju da su suzenje očiju i vratobolja česti problemi pri radu ljekarnika koji se mogu pripisati radu s računalima. Ne treba zanemariti niti podatak da je gotovo polovina ispitanih ljekarnika i službenika imala poremećaj vida u obliku kratkovidnosti ili dalekovidnosti. Suzenje očiju i vratobolja bili su značajno češće izraženi u skupini ljekarnika u odnosu na skupinu službenika. Međutim, dobivene razlike u učestalosti ovih simptoma između ljekarnika i službenika u ovom ispitivanju treba razmatrati s oprezom jer su se ispitivane skupine razlikovale po dobi, što može utjecati na veću učestalost suzenja očiju i vratobolje u skupini ljekarnika koji su bili prosječno 5 godina stariji od ispitivanih službenika. Pri liječničkom pregledu službenici, koji rade sjedeći, više su se žalili na bolove u slabinskom dijelu kralježnice, ali ovi simptomi nisu statistički obrađeni u ovom ispitivanju.

Ovi rezultati potkrepljuju odredbu Pravilnika o sigurnosti i zaštiti zdravlja pri radu s računalom (1) prema kojoj poslodavac mora planirati aktivnosti radnika na osobnom računalu tako da se rad periodički izmjenjuje s drugim aktivnostima. To se upravo događa pri obavljanju posla ljekarnika. Naime, njegov rad s računalom se neprekidno izmjenjuje s obraćanjem klijentu, odnosno s izdavanjem lijekova. Međutim, za rješavanje poteškoća s kralježnicom treba tijekom svakog sata rada s računalom osigurati odmore u trajanju od najmanje 5 minuta, a treba i organizirati vježbe rasterećenja radi smanjenja statodinamičnoga napora.

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Summary

A NEW TASK FOR PHARMACISTS: WORKING AT A COMPUTER

The aim of this study was to establish the effect of working at personal computers (PC) on vision and neck-pain in pharmacists. In this cross-sectional study, vision and subjective disturbances at work were examined in 50 pharmacists [mean age (41.8±11) years] and 56 office workers [mean age (36.2±8.6) years] using PCs at work for 40 hours per week. Pharmacists work mostly in the standing position and office workers in the sitting position.

Excessive lacrimation and neck-pain during work were more pronounced in pharmacists than in office workers ($P<0.01$). Vision tests did not differ between the two groups. Disturbances such as myopia or hypermetropia were found in 22 (44 %) pharmacists and in 23 (41 %) office workers ($P>0.05$).

Our results support the recommendations set by the Ordinance on Safety and Health Protection when Working with Personal Computers (1), that employer should make sure that work with screen interchanges regularly with other activities in order to diminish vision load at work. This also refers to the work of pharmacists because their activities involve continuous interchanges between serving customers, looking at PC screen, and issuing medicines. In addition, the pharmacists should take at least 5-minute breaks every hour and take relaxation exercises to diminish the strain for the spine.

KEY WORDS: *lacrimation, spine, static load, vision disturbances*

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DOI: 10.2478/10004-1254-63-2012-2169

Case Report

RECOVERY FROM AN EIGHTY-PERCENT TOTAL BODY SURFACE AREA BURN INJURY SUSTAINED AT WORK*

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Received in November 2011
Cross Checked in January 2012
Accepted in May 2012

This article presents a case of severe burn injury at work involving 80 % of body surface area and patient treatment and rehabilitation, which resulted in preserved working ability. The worker was injured by hot water and steam. After initial treatment in the intensive care unit, he underwent comprehensive clinical and outpatient rehabilitation that took 92 weeks, after which he returned to work. His working disability was 100 % after the initial treatment in the intensive care unit, but rehabilitation improved it to 50 %. It should always be kept in mind that even patients with serious or life-threatening injuries can be reintegrated into the workforce if patients, physicians, occupational physicians, and employers all work together.

KEY WORDS: *occupational physician, rehabilitation, working ability*

The outcome of a severe burn trauma depends on the age of the patient and the percentage of the affected total body surface area (TBSA) (1). In developed countries, modern therapy and rehabilitation have significantly cut down burn mortality over the last four decades, making survival possible even after 100 % TBSA burn (2, 3). However, the working ability of patients who survived severe burns is rarely discussed, and the aim of this case report is to address this topic.

Case report

On 6 November 2000, two workers were involved in an accident with hot water steam at a large power plant. The worker described in this report was a 40 year old plumber servicing long-distance hot water pipes. The accident happened during replacement of a special hot water pump for long distance heating. The workers were injured by hot water and hot steam. Fifty-six litres of 130 °C hot water expanded into approximately 1500 m^3 of steam. Two colleagues took the injured workers out of the accident area. Narrow space, no cold water supply in the vicinity, and grid staircases hampered swift first aid. It took about 20 minutes for the colleagues to start cooling the patients down with cold water. Paramedics and a rescue doctor arrived to take the accident victims to the nearest hospital intensive burns unit. This case report focuses on the patient who suffered greater burn injury and was diagnosed with an 80 % TBSA burn. As complications ensued, he was later diagnosed with drug induced colorectal bleeding, colitis, and posttraumatic tinnitus. Treatment, including

* Partly presented at the 5th Croatian Congress on Occupational Health with International Participation "Health, Work, and Community", Hvar, Croatia, 28 September to 2 October 2011

rehabilitation, took 92 weeks, 10 of whom in intensive care (see chronology in Table 1).

Initial hospital treatment

As approximately 80 % of the TBSA was destroyed by mostly superficial and deep second-degree burns, an escheratomy plus fasciectomy on both arms and legs was performed shortly after hospital admission. Over time, several tangential necrotomies and mesh grafts were also necessary. The rest of the burns were treated with dexpanthenol, a fat-based ointment twice a day in combination with a special pressure suit (with socks and gloves). The little finger on his left hand was treated with proximal interphalangeal (PIP) joint arthrodesis for three weeks. Because colitis lowered haemoglobin, he was also receiving two concentrates of red blood cells a day. The bleeding stopped after coloscopic injections and special oral medication. The second right toe was amputated on 12 January 2001, and on 21 January the patient also received a free flap deficiency cover for the middle joint of his left little finger.

He began psychotherapy while in the intensive care unit, a few days after extubation. It consisted of 25 90-minute sessions, three sessions a week.

Outpatient treatment and rehabilitation

When the patient was discharged from hospital on 23 January 2001, most body surface areas were epithelised. However, some areas still needed daily treatment with yellow paraffin, a mixture of cloxiquine, fluprednidene acetate and gentamicin sulphate, and Arachidis oleum. Additionally, a wide range of oral medication was necessary for several weeks (caroverine, paroxetine, flunitrazepam, omeprazole, enoxaparin sodium, vitamins A, B and E, magnesium, *Lactobacillus rhamnosus*). On the inside and outside of both thighs, areas with hypertrophic granulation tissue were cauterised with silver nitrate.

Upon discharge from the hospital the patient was assessed with a 100 % reduction in working ability. Table 2 shows his subjective symptoms recorded in February 2001. At the same time, the patient experienced mobility problems such as difficulties bending and stretching knees, ankles, elbows, and wrists, a 3 cm deficiency in stretching fingers 2 to 5 of the left hand, inability to make a fist with either hand, reduced mobility of both shoulders and hip joints, and a 50 % reduction in the mobility of the remaining nine toes. Clinical rehabilitation included bandage change, general fitness training and training with weights, single ergotherapy, single physiotherapy, lymph drainage, work therapy, breathing exercises, and weekly psychotherapy sessions lasting 90 minutes (Table 1). However, on discharge from the rehabilitation clinic, the patient still suffered from decubitus ulcers on both heels (2 cm x 1 cm and 1 cm x 1 cm).

All other special treatment and patient assessment was conducted by occupational health office in an outpatient clinic. From 15 January 2001 to 29 January 2002, the patient wore a special compression suit with socks and gloves 24 hours a day. From 23 January to 5 February 2001 he had breathing exercises and ergotherapy one hour a day. This was repeated from January to April 2002. He developed tinnitus in May 2001, which was treated with *Ginkgo biloba* leaves and his paraesthesia with piracetam for six weeks. He was continuously receiving caroverin, paroxetin and vitamin B. At the same time, he had 14 hourly sessions of physiotherapy, which was repeated. This was combined with special gymnastics for the big joints plus 20 massage sessions lasting one hour each in order to stretch the skin. The patient was subjected to 245 soft 250 mW laser treatments from May 2001 to December 2004, each session lasting three to four hours. Every 10 cm^2 of skin was treated for 15 minutes to relieve itching and contractions. One-hour special skin treatment with collagen patches under a plaster occlusive dressing was administered 14 times,

Table 1 *Chronology of treatment and rehabilitation*

6 November 2000: Accident, first aid by colleagues, transport to general hospital intensive care unit.
23 January 2001: Discharge from hospital and the beginning of outpatient treatment for two weeks.
6 February 2001: Beginning of treatment in a rehabilitation clinic for 11 weeks.
24April 2001: Discharge from rehabilitation clinic.
25 April 2001: Beginning of further outpatient treatment for another 57 weeks.
1 June 2002: Patient returns to work.

Table 2 *Patient's symptoms on arrival to the rehabilitation clinic on 2 February 2001*

Itching
Reduced flexibility of all fingers
Reduced muscular strength
General oedema and oedema of both ankles
Inability to lift either foot
Limping and slow gait
Inability to walk or stand on toes and heels
Inability to squat and kneel
Various scars on all limbs after several operations
Various more or less secreting wounds
Decubitus ulcers on both heels (4 cm x 2 cm, and 2 cm x 2 cm)
Hyper- and depigmentation
Circular scars reaching from the abdomen to the back
Defective hearing and tinnitus
Reduced sensibility of both arms
Reduced sensibility of both legs from the knee down

followed by 74 treatments with hyaluronic acid lotion applied by massage and treatments with epidermal growth factor activator. On 4 December 2001, a plastic surgeon declared that plastic surgery was not necessary at that point unless joint dysfunction should develop. Until the writing of this article no operation was necessary.

In April 2002, the patient was assessed a 50 % reduction of working ability and returned to work on 1 June 2002. In the beginning, he mostly did office work and was also allowed to take breaks or stop working whenever he felt necessary. In 2003, he gradually started doing manual work such as installation of measuring devices and even began to install three to six meters long pipes. Because of his experience, he no longer works shifts and cannot work in small rooms, on scaffoldings, beneath grids, or in areas where he is unable to leave immediately.

My conclusion is that cooperation between patient's employers and occupational physicians is vital and should receive due attention. In addition, every plant should have an adequate number of first aid assistants. We should always keep in mind that even patients with serious or life-threatening injuries can be reintegrated in the workforce if patients, physicians, occupational physicians, and employers all work together.

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Sažetak

OPORAVAK OD OPEKLINE NA RADU KOJA JE ZAHVATILA OSAMDESET POSTO UKUPNE POVRŠINE TIJELA

Ovaj članak prikazuje slučaj teške ozljede na radu uslijed opekline koja je zahvatila 80 % površine tijela bolesnika, njegovo liječenje i rehabilitaciju, kojima se uspio očuvati dio radne sposobnosti. Opeklinu je izazvala vrela voda i para. Nakon početnoga liječenja u jedinici intenzivne skrbi, bolesnik je bio na kliničkoj i ambulantnoj rehabilitaciji od 92 tjedna, nakon koje se vratio na posao. Nakon početnoga liječenja bolesnik je bio potpuno nesposoban za rad, da bi se nakon rehabilitacije radna sposobnost vratila na 50 %. Uvijek valja imati na umu da se čak i bolesnici s teškim i po život opasnim ozljedama mogu vratiti u radnu zajednicu ako surađuju zajedno s liječnicima, specijalistima medicine rada i poslodavcima.

KLJUČNE RIJEČI: *specijalist medicine rada, rehabilitacija, radna sposobnost*

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DOI: 10.2478/10004-1254-63-2012-2201

Review

THE MARGIN OF EXPOSURE TO FORMALDEHYDE IN ALCOHOLIC BEVERAGES

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Received in January 2012
CrossChecked in June 2012
Accepted in June 2012

Formaldehyde has been classified as carcinogenic to humans (WHO IARC group 1). It causes leukaemia and nasopharyngeal cancer, and was described to regularly occur in alcoholic beverages. However, its risk associated with consumption of alcohol has not been systematically studied, so this study will provide the first risk assessment of formaldehyde for consumers of alcoholic beverages.

Human dietary intake of formaldehyde via alcoholic beverages in the European Union was estimated based on WHO alcohol consumption data and literature on formaldehyde contents of different beverage groups (beer, wine, spirits, and unrecorded alcohol). The risk assessment was conducted using the margin of exposure (MOE) approach with benchmark doses (BMD) for 10 % effect obtained from dose-response modelling of animal experiments.

For tumours in male rats, a BMD of 30 mg kg^{-1} body weight per day and a "BMD lower confidence limit" (BMDL) of 23 mg kg^{-1} d^{-1} were calculated from available long-term animal experiments. The average human exposure to formaldehyde from alcoholic beverages was estimated at $8 \cdot 10^{-5}$ mg kg^{-1} d^{-1}. Comparing the human exposure with BMDL, the resulting MOE was above 200,000 for average scenarios. Even in the worst-case scenarios, the MOE was never below 10,000, which is considered to be the threshold for public health concerns.

The risk assessment shows that the cancer risk from formaldehyde to the alcohol-consuming population is negligible and the priority for risk management (e.g. to reduce the contamination) is very low. The major risk in alcoholic beverages derives from ethanol and acetaldehyde.

KEY WORDS: *alcohol, alcohol consumption, aldehydes, cancer, risk assessment*

Formaldehyde (methanal, CH_2O, CAS # 50-00-0) is a colourless substance, which is widely present in foods, industry, and in the environment (1, 2) and may also be endogenously produced in humans and animals (3). The industrial use includes mainly the production of various types of resin, the use as intermediate in the manufacture of industrial chemicals, and the direct use in aqueous solutions (formalin) as a disinfectant and preservative (1-3). Epidemiological studies have demonstrated a causal relationship between formaldehyde and cancer in humans (3). Causality is indicated by consistent findings of increased risks of nasopharyngeal cancer, sinonasal cancer, and myeloid leukaemia among individuals with high exposure to formaldehyde. The findings are based on case-control studies of industrial workers and other professional groups in inhalatory contact with formaldehyde such as pathologists, funeral directors or embalmers (3). Biological mechanisms associated with formaldehyde-induced cancer are not completely understood, but potential carcinogenic modes of actions for formaldehyde include DNA reactivity (covalent

binding), gene mutation, chromosomal breakage, aneuploidy, and epigenetic effects (3). However, the biological plausibility of an association between formaldehyde exposure and leukaemia was questioned, because formaldehyde is rapidly metabolised, and it would not be expected to enter the systemic circulation (3). No studies in humans are available for the oral route of exposure, but animal feeding experiments have demonstrated that formaldehyde may also be carcinogenic after ingestion (4, 5).

The hazard of formaldehyde has been confirmed by the International Agency for Research on Cancer (IARC), which found sufficient evidence for the carcinogenicity of formaldehyde both for humans and experimental animals. The IARC cancer classification was upgraded in 2006 and formaldehyde was assigned to group 1 ("carcinogenic to humans") with clear evidence for cancer in humans (5, 6).

Formaldehyde is a natural constituent in a variety of fruits, vegetables, meat, milk products, and fish (1). Feron et al. (1) estimated that the formaldehyde intake from food ranges between 1.5 mg and 14 mg per person per day, which may already reach the reference dose (RfD) for chronic oral exposure of 0.2 mg kg^{-1} d^{-1} (approximately 12 mg d^{-1} for a 60-kg adult) postulated by the US Environmental Protection Agency (EPA) (7). Relatively high concentrations of formaldehyde were found in alcoholic beverages; for example, in sugar cane spirits (mean 4.13 mg L^{-1}, maximum 10.90 mg L^{-1}) (8) and rum (mean 2.42 mg L^{-1}, maximum 10.07 mg L^{-1}) (9). In our on-going investigation of the composition and global public health impact of alcoholic beverages, including unrecorded alcohol (10), we have also detected high formaldehyde concentrations in a number of products (11). Thus, the natural occurrence of formaldehyde from methanol oxidation in alcohol products, together with contamination from other sources (e.g. the usage of formaldehyde-containing or formaldehyde-releasing disinfectants), could therefore be a potential problem on a worldwide scale.

In contrast to other constituents of alcoholic beverages (e.g. methanol, higher alcohols, acetaldehyde or ethyl carbamate), for which excellent risk assessments are available in the literature (12-15), we found a major knowledge gap regarding information about the potential public health impact of formaldehyde, resulting in an inability to adequately ascertain the risk for consumers of the alcoholic beverages researched. In this study, applying the harmonised approach of the European Food Safety Authority (EFSA) (16), we present for the first time, a quantitative risk assessment for formaldehyde in alcoholic beverages.

METHODS

Data on formaldehyde were obtained by a computer-assisted literature search. Searches were carried out in the following databases: PubMed, Toxnet, and ChemIDplus (US National Library of Medicine, Bethesda, MD), Web of Science (Thomson Scientific, Philadelphia, PA), and IPCS/INCHEM (International Programme on Chemical Safety/ Chemical Safety Information from Intergovernmental Organizations, WHO, Geneva, Switzerland). We specifically aimed to identify long-term animal studies that would be usable for dose-response modelling as well as studies on the occurrence of formaldehyde in alcoholic beverages.

Analysis was conducted according to the harmonised approach of EFSA (16) and similar to our previous acetaldehyde cancer risk assessment (14). This includes an approach known as the margin of exposure (MOE). MOE is defined as the ratio between the benchmark dose (BMD) and the estimated human intake of the same compound. MOE can be used to compare the health risk of different compounds and prioritise risk management actions. By definition, the lower the MOE, the larger the risk for humans; generally a value under 10,000 is used to define public health risks (16). The benchmark dose (BMD), derived from animal data by mathematical modelling within the observed range of experimental data, was used as a reference point. To obtain MOE, the Benchmark Dose Lower Confidence Limit (BMDL) for a 10 % effect was taken (MOE = BMDL / Exposure). BMDL is an estimate of the lowest dose that is 95 % certain to cause no more than a 10 % effect (e.g. cancer incidence) in rodents. The BMD and BMDL values were calculated using the US EPA's BMDS 2.2 software (available at the US Environmental Protection Agency website: http://www.epa.gov/ncea/bmds/index.html).

RESULTS

Toxicity of orally ingested formaldehyde in animal studies

There is adequate evidence for the carcinogenicity of formaldehyde in animal experimental studies (6).

Several studies have proved that long-term inhalation exposure to formaldehyde causes both benign and malignant nasal tumours in male and female rats (17-19). As the focus on the specific effects of orally administered formaldehyde is relatively new, there are not many studies on this subject. The following two are considered to be the most significant ones: Soffriti et al. (4) conducted a long-term study of rat groups exposed to formaldehyde that resulted in a carcinogenic effect; Til et al. (20) observed severe damage to the gastric mucosa, renal papillary necrosis, and irregular mucosal thickening in the forestomach and/or glandular stomach in rats given top doses of formaldehyde. These studies are discussed in more detail in the section "dose response analysis".

Besides these two pivotal studies, some further studies were identified. In the paper of Tobe et al. (21), groups of 20 male and 20 female Wistar rats were given formaldehyde in their drinking water at four concentrations (0.50, 0.10, 0.02, and 0) % for 24 months. Various non-neoplastic lesions, erosions, and ulcers were found both in the forestomach and glandular stomach mostly in the 0.50 % group. There were no significant differences in the incidence of any tumours among groups of both sexes. Based on their results, the no observable effect level of formaldehyde was 0.02 % in drinking water (10 mg kg^{-1} d^{-1}). Another valuable oral study is that of Takahasi et al. (22), in which Wistar rats were given formaldehyde during a 32-week period at a single concentration level (0.5 % - about 300 mg kg^{-1} bw per day). Due to the single dose level and/or limited number of animals, these studies were not included in our dose-response-modelling. However, it is important to mention that although no tumours were observed, papillomas in the forestomach and non-neoplastic changes in glandular stomach were reported (22). The finding suggests that formaldehyde could exert pre-carcinogenic activity in the rat glandular stomach. Long-term or lifetime studies above certain concentration threshold are necessary for detecting tumours (4).

Dose-response analysis

There is no adequate human study available for a dose-response analysis. From the animal experiments mentioned above, two long-term studies of the oral route of exposure to formaldehyde appear to be suitable for dose-response modelling.

Til et al. (20) examined the oral toxicity of formaldehyde in rats in a two-year drinking-water study at dose levels of (0, 1.2, 15, and 82) mg kg^{-1} d^{-1} for males and (0, 1.8, 21, and 109) mg kg^{-1} d^{-1} for females. The study did not provide any evidence of carcinogenicity of formaldehyde after oral consumption. Thickening and raising of the limiting ridge of the forestomach, irregular mucosal thickenings, histopathological gastric changes (papillary epithelial hyperplasia, hyperkeratosis, focal ulceration, and focal chronic atrophic gastritis) were observed mostly in the high-dose group. In a more recent 104-week study of carcinogenicity by Soffritti et al. (4), male and female Sprague-Dawley rats were given drinking water containing formaldehyde at concentrations of about (0, 1, 5, 10, 51, 102, and 153) mg kg^{-1} d^{-1} [own calculations based on formaldehyde concentrations in drinking water (0, 10, 50, 100, 500, 1000, and 1500) mg L^{-1} and data about average body weight and drinking volume]. Treatment with formaldehyde resulted in an increase in total malignant tumours and showed specific carcinogenic effects on various organs and tissues.

Due to the lower number of animal subjects and smaller doses, Til et al. (20) provided only limited applicable evidence for dose-response assessments, especially as carcinogenic effects were not detectable. However, we modelled this study for comparison purposes, as irregular thickenings in the forestomach and glandular stomach, chronic atrophic gastritis, and histopathological changes (papillary epithelial hyperplasia accompanied by hyperkeratosis) could be pre-carcinogenic lesions. A large number of oncological lesions of the intestine and the stomach were detected in the study of Soffritti et al. (4), especially at the highest doses (which were higher than the ones used in Til et al. (20)). The study by Soffritti et al. (4) is, therefore, the only study adequately designed to be used for a dose-response assessment of carcinogenic effects of orally administered formaldehyde.

The best-fitting models for different end-points are listed in Table 1. It can be seen that the values for different end-points calculated from the Til et al. (20) study are consistent: the BMD and BMDL values are in the range of (22 to 50) mg kg^{-1} d^{-1} and (12 to 45) mg kg^{-1} d^{-1}, respectively. Regarding the Soffritti et al. data (4), significant models were reached for both sexes when the total number of tumour-bearing animals was modelled. An adequate model for hemolymphoreticular neoplasias (females) was also observed (Table 1). Overall, BMDs and BMDLs of models from both studies (4, 20) are in the same order of magnitude, which is indicative of an overall adequacy of the calculated values, as even between

Table 1 *Summary of own dose response modelling results for formaldehyde in different animal experiments conducted by Til et al. (20) and Soffritti et al. (4)*

End-point		Model[a]	p-value[b]	BMD[c] / mg kg^{1} d^{-1}	BMDL[d] / mg kg^{1} d^{-1}
Til et al. (20)					
Focal papillary epithelial hyperplasia	Male	Gamma	0.77	41	18
	Female	Multistage	0.42	29	22
	Combined	Dichotomous-Hill	0.49	25	21
Focal hyperkeratosis	Male	Multistage-Cancer	0.28	34	12
	Female	Multistage-Cancer	0.43	34	21
	Combined	Multistage	0.55	45	26
Chronic atrophic gastritis	Male	Gamma	(1)[e]	(38)	(21)
	Female	Gamma	(1)[e]	(38)	(24)
	Combined	Gamma	(1)[e]	(38)	(28)
Focal ulceration	Male	Gamma	(1)[e]	(70)	(38)
	Female	Gamma	(1)[e]	(95)	(55)
	Combined	LogProbit	0.85	62	45
Gradular hyperplasia	Male	Multistage-Cancer	0.24	37	25
	Female	Gamma	(1)[e]	(90)	(49)
	Combined	Dichotomous-Hill	0.78	41	23
Papillary necrosis	Male	Logistic	0.38	36	29
	Female	Multistage-Cancer	0.24	50	36
	Combined	Quantal Linear	0.11	22	17
Soffritti et al. (4)					
Tumour-bearing animals	Male	Probit	0.13	30	23
	Female	Logistic	0.59	67	38
Hemolymphoreticular neoplasias	Male	Quantal Linear	(0.036)[f]	(40)	(28)
	Female	Multistage-Cancer	0.63	111	61

[a] *Data from best-fitting models selected with BMDS 2.2-software according to US EPA criteria are presented*
[b] *A p-value greater than 0.1 indicates that the model fits the data (p-value 1.0 = perfect fit).*
[c] *BMD: benchmark dose for a 10% incidence of health effect*
[d] *BMDL: lower one-sided confidence limit of the BMD*
[e] *Only the highest dose-level exhibited effects. No clear dose-response established. Values are shown in brackets for information*
[f] *Not significant dose-response. Values are shown in brackets for information*

different models differences up to factors of five are accepted as typical and would allow for an averaging of the values (23). To be conservative, we decided to take the model for male tumour-bearing animals with a BMD of 30 mg kg^{-1} d^{-1} and a BMDL of 23 mg kg^{-1} d^{-1} for our further calculations (Figure 1). Notably, these values are expectedly smaller than what we calculated for acetaldehyde from the same Soffritti et al. (4) study (BMD=114 mg kg^{-1} d^{-1} and BMDL=56 mg kg^{-1} d^{-1}) (14). This is consistent with previous assumptions that the toxicity of aldehydes decreases with chain length (24).

Exposure assessment

In this study we used the EFSA guidelines (16), which recommend that risk assessments provide different exposure scenarios (e.g. for entire, or specific groups of populations) along with their inherent uncertainties. Other than the mean and median, intakes from highly exposed individuals (due to high consumption of average contaminated foods or to average consumption of highly contaminated foods) should be considered as represented by the 90th, 95th, 97.5th, and 99th percentiles.

To provide estimates on the dietary intake of formaldehyde, data on the consumption of alcoholic

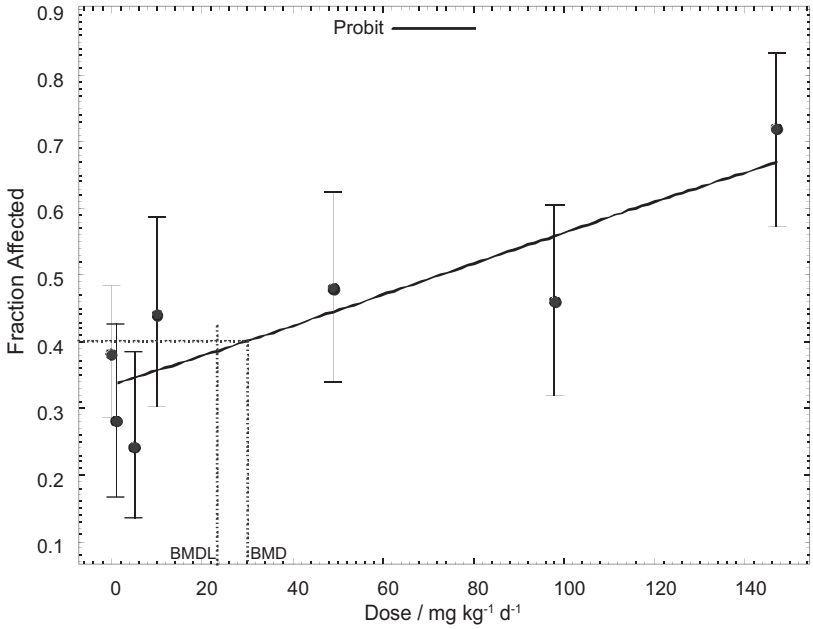

Figure 1 *Benchmark dose modelling for oral formaldehyde administration with male tumour-bearing animals as endpoint. Probit model with 0.95 confidence level. BMD: benchmark dose for a 10 % incidence of health effect; BMDL: lower one-side confidence limit of the BMD. Original data from Soffritti et al. (4).*

beverages and their content of formaldehyde is needed. Currently, there are not enough systematic data on formaldehyde content of alcoholic beverages or indeed of most foods in general. Although formaldehyde is a natural component of a variety of foodstuffs (1), with the highest concentrations in fruits (25), vegetables (25), and fish (26-28), monitoring has generally been sporadic and inconsistent.

Nevertheless, there are some studies where the actual formaldehyde content in different alcoholic beverages was determined (8, 9, 11, 29-48). The investigation of alcoholic beverages for formaldehyde

Table 2 *Formaldehyde concentration in alcoholic beverages*

Category [a]	Sample size	Formaldehyde / mg L^{-1} (data summarised from Refs. 8, 9, 11, 29-48)							>2.6 mg L^{-1} [b] / %
		Mean	Median	90th percentile	95th percentile	97.5th percentile	99th percentile	Maximum	
Rum/cane	86	0.42	0.06	0.48	2.20	3.08	7.33	10.90	6.98
Whiskey	29	0.26	0.08	0.72	1.19	1.43	1.54	1.62	0.00
White spirits	139	0.01	0.00	0.01	0.01	0.06	0.11	0.80	0.00
White spirits incl. tequila	177	0.27	0.00	0.83	1.72	2.69	3.24	6.06	5.08
Flavoured spirits	106	0.24	0.00	0.45	0.95	1.43	2.70	5.39	1.89
Asian products	43	1.23	0.03	1.54	9.75	13.44	14.06	14.37	9.30
Brandy	19	0.69	0.18	2.06	2.24	2.62	2.86	3.01	15.79
Beer	93	0.02	0.00	0.05	0.17	0.21	0.23	0.27	0.00
Wine	39	0.2	0.02	0.72	0.82	0.89	1.05	1.15	0.00
Unrecorded and others	116	0.32	0.00	1.04	1.53	3.05	3.47	6.71	4.31
Total spirits	417	0.31	0.01	0.82	1.70	2.84	3.32	10.90	4.80
Total all alcoholic beverages	708	0.32	0	0.74	1.54	2.93	6.01	14.37	4.10

[a] *The categories were chosen based on available consumption data (see Lachenmeier et al. (14) for details)*
[b] *A tolerable concentration of 2.6 mg L^{-1} was suggested by WHO IPCS (2) based on non-cancer endpoints*

content started as early as in 1983 with the measurement of a limited number (n=9) of beer samples (29). From then, formaldehyde has also been detected in wine, spirits, and unrecorded alcohol. However, most of the studies evaluated only a limited number of samples. Up to now, the only study on a large sample of alcoholic beverages was provided by Jendral et al. (n=488) (11). The formaldehyde concentrations of the corresponding beverage groups for all mentioned studies are summarised in Table 2. Mean concentrations of formaldehyde in a variety of alcoholic beverages ranged from 0.01 mg L^{-1} in white spirits to 0.69 mg L^{-1} in brandies. The highest concentrations were typically detected in spirits from Asia (mean 1.23 mg L^{-1}).

Annual consumption of different types of alcoholic beverages for the population older than 15 can be easily obtained from the WHO databases. This can be done for most countries around the world. However, as studies about formaldehyde concentrations in alcoholic beverages other than European-style beverages are unavailable (especially the knowledge about Asian beverages is based on only very few analytical results), we decided to limit the whole population dietary intake estimate to the European Union (EU). The formaldehyde exposure due to alcoholic beverage consumption was calculated from Table 2 combined with values of annual per capita consumption of alcoholic beverages in the EU (see Lachenmeier et al. (14) for details on annual consumption of different beverage groups). Table 3 summarises the exposure for different scenarios.

Risk characterisation

The exposure data from Table 3 was used to characterise the risk using the margin of exposure (MOE) calculated from BMDL (Table 4). MOEs can be used by risk managers for setting priorities; small MOE represents a higher risk and vice versa. In general, an MOE of 10,000 or higher, if based on a BMDL from an animal study, would be considered a low public health concern and subsequently a low priority for risk management actions (16). In the case of formaldehyde, MOEs were in all scenarios above this 10,000 threshold, demonstrating that, in general, formaldehyde in alcoholic beverages appears not to be a public health concern.

This evaluation is in line with previous risk assessments that have considered only non-cancer end-points. For example, the WHO IPCS (2) has established a tolerable concentration (TC) of 2.6 mg L^{-1} in ingested products based on the experiments of Til et al. (20). In this respect, some brandies, rum, and Asian spirits are problematic, as these products can contain formaldehyde concentrations above the threshold of 2.6 mg L^{-1} (see Table 2). However, a 60 kg person would need to daily consume 0.8 L of alcohol at 14.37 mg L^{-1} (the highest concentration found in alcoholic beverages so far) (11) to exceed the US EPA RfD of 0.2 mg kg^{-1} d^{-1} (7), which is extremely unlikely even in this worst-case scenario. None of our population-based exposure estimations exceed the US EPA RfD.

Table 3 *Population-based exposure scenarios for the European Union. The table shows the formaldehyde exposure due to all types of alcoholic beverages (beer, wine, spirits, unrecorded) calculated as mg kg^{-1} d^{-1} (calculated for a 60 kg person)*

Formaldehyde exposure / mg kg^{-1} d^{-1}		**Exposure scenarios for different formaldehyde concentrations in the beverages**					
		Mean	**Median**	**90th percentile**	**95th percentile**	**97.5th percentile**	**99th percentile**
Exposure scenarios for different amounts of alcoholic beverage consumption in Europe	Mean	8.0E-05	7.8E-06	2.6E-04	3.6E-04	4.3E-04	5.3E-04
	Median	5.3E-05	4.9E-06	1.7E-04	2.4E-04	2.9E-04	3.5E-04
	90th percentile	1.7E-04	1.7E-05	5.5E-04	7.7E-04	9.2E-04	1.1E-03
	95th percentile	2.0E-04	2.1E-05	6.5E-04	9.1E-04	1.1E-03	1.3E-03
	97.5th percentile	2.5E-04	2.5E-05	7.7E-04	1.1E-03	1.3E-03	1.6E-03
	99th percentile	2.8E-04	2.8E-05	8.7E-04	1.2E-03	1.5E-03	1.8E-03

Table 4 *Margin of exposure (MOE) for formaldehyde in different exposure scenarios. Calculated with BMDL of 23 mg kg^{-1} d^{-1} (MOE = BMDL / exposure)*

MOE		Exposure scenarios for different formaldehyde concentrations in the beverages					
		Mean	Median	90th percentile	95th percentile	97.5th percentile	99th percentile
Exposure scenarios for different amounts of alcoholic beverage consumption in Europe	Mean	287,500	2,948,718	88,462	63,889	53,488	43,396
	Median	433,962	4,693,878	135,294	95,833	79,310	65,714
	90th percentile	135,294	1,352,941	41,818	29,870	25,000	20,909
	95th percentile	115,000	1,095,238	35,385	25,275	20,909	17,692
	97.5th percentile	92,000	920,000	29,870	20,909	17,692	14,375
	99th percentile	82,143	821,429	26,437	19,167	15,333	12,778

DISCUSSION

In contrast to the risk assessment of another carcinogenic aldehyde - acetaldehyde - for which a considerably lager database about human carcinogenicity and genetic epidemiology exists (14, 49), our formaldehyde assessment contains several limitations:

1. The assessment is based on only one oral animal study where formaldehyde showed specific carcinogenic effects on various tissues and organs. Some problems with the modelling of these data existed. In particular, the modelling of the data was complicated, as the background levels were relatively high. In addition, the incidence of certain carcinomas was increased in the treated groups, but the statistical power was insufficient to allow the modelling of any specific cancer site besides hemolymphoreticular neoplasias in females (see also (14) about discussion of the same problems in dose-response modelling of acetaldehyde). Additionally, there are no other estimates for BMDL and BMD values in the literature. However, as the values obtained for different end-points corresponded well to each other and also to non-cancer endpoints from another study, we believe that the chosen BMDL value is certainly in the right order of magnitude and could be used for quantitative risk assessment.

2. The second important limitation is the fact that we assumed a uniform distribution of formaldehyde in the whole body. However, the tissues that are in direct contact with an alcoholic beverage are exposed at considerably higher levels than other organs. For example, the risk for gastrointestinal tract cancer could be higher, as stomach and intestine lesions have been reported in the animal experiments (4). On the other hand, some recent research has suggested that formaldehyde might enter the systemic circulation of humans exposed to formaldehyde (3), which would justify the application of this assumption to provide a conservative assessment until the mechanism of action has been fully elucidated.

3. The whole population evaluation may under-estimate the risk for heavy drinkers and the risk for drinkers that drink predominantly formaldehyde-rich beverages.

Besides alcoholic beverages, humans could be exposed to formaldehyde from other sources. However, the current data only allow rough estimations. Formaldehyde appears in almost all common foods at (1 to 100) mg kg^{-1} (1) and adult dietary intake is estimated in the range from (1.5 to 14) mg per person per day [(0.022 to 0.23) mg kg^{-1} d^{-1}] (1). Drinking water is expected to contain less than 0.1 mg L^{-1} (2), resulting in a daily intake of less than 0.2 mg per person (0.003 mg kg^{-1} d^{-1}) (2). The endogenous levels in human blood were estimated at about 2 mg L^{-1} to 3 mg L^{-1} (6). However, all of these estimates are comparably old and possibly outdated (due to regulatory changes and inadequate analytical methodologies in older studies). Migration of formaldehyde monomers from tableware was pointed

out as a further source of food contamination with formaldehyde (50-52). This migration was estimated at ppm (mg kg^{-1}) levels.

An important source of formaldehyde intake is cigarette smoke (2). Formaldehyde levels in mainstream smoke were reported at 45 μg to 283 μg per cigarette (2, 53). This equals a maximum exposure of 0.094 mg kg^{-1} d^{-1} for a 60 kg person smoking 20 cigarettes per day.

Compared with these other exposures, the average exposure via alcoholic beverages of $8 \cdot 10^{-5}$ mg kg^{-1} d^{-1} appears to be negligible. Nevertheless, data on cumulative formaldehyde exposure (especially for foods and beverages) are sparse and should be updated in the future.

CONCLUSIONS

The overall conclusion is that the occurrence of trace levels of formaldehyde in alcoholic beverages does not constitute an additional cancer risk for humans. Our data showed that even in worst-case scenarios, the exposure (0.0018 mg kg^{-1} d^{-1}) is lower than thresholds of toxicity (if a threshold-based mechanism is assumed for this carcinogen, which is still a matter of debate) (54).

Our calculation has revealed that formaldehyde in alcoholic beverages shows MOEs in a magnitude that is not considered a high priority for regulatory measures. For other compounds of alcoholic beverages, such as acetaldehyde or ethyl carbamate, MOEs have been found in considerably lower ranges (below 1000) according to EFSA and Lachenmeier et al. (14, 15). The major risk, however, certainly comes from ethanol with a MOE of 1 or even smaller (55). Ethanol was also identified as the most important carcinogen in alcoholic beverages in a comparative quantitative assessment of 15 carcinogenic compounds (56). This study fully confirms this finding and suggests prioritising general alcohol policy measures over more specific measures such as mitigative efforts to reduce the content of trace contaminants such as formaldehyde.

Conflicts of interest statement

All authors declare that they have no direct financial interest in the subject matter or materials discussed that could inappropriately influence the manuscript.

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Sažetak

GRANICA IZLAGANJA FORMALDEHIDU U ALKOHOLNIM PIĆIMA

Formaldehid je kancerogen za ljude te je klasificiran u skupinu 1 prema WHO IARC-u. Uzrokuje leukemiju i nazofaringealni karcinom, a navodi se i kao redoviti sastojak alkoholnih pića. Međutim, rizik od izlaganja formaldehidu konzumacijom alkoholnih pića nije sustavno istražen pa će ovo istraživanje pružiti prvu takvu procjenu rizika. Količina formaldehida koju ljudi unose alkoholnim pićima u Europskoj je uniji procijenjena temeljem podataka Svjetske zdravstvene organizacije o konzumaciji alkohola i literature o sadržaju formaldehida u različitim skupinama alkoholnih pića (pivo, vino, jaka alkoholna pića i neregistrirani alkohol). Procjena rizika obavljena je korištenjem pristupa granice izlaganja (eng. *margin of exposure*, MOE) i graničnih doza (eng. *benchmark doses*, BMD) za 10 %-tni učinak koji se postiže modeliranjem odnosa doza-odgovor u ispitivanjima provedenima na životinjama. BMD od 30 mg kg^{-1} tjelesne težine na dan i BMD s nižom granicom pouzdanosti (BMDL) od 23 mg kg^{-1} d^{-1} izračunati su za tumore kod mužjaka štakora temeljem raspoloživih dugotrajnih ispitivanja provedenih na životinjama. Prosječno izlaganje ljudi formaldehidu u alkoholnim pićima procijenjeno je na $8 \cdot 10^{-5}$ mg kg^{-1} d^{-1}. U usporedbi s BMDL vrijednošću krajnji MOE je iznosio više od 200.000 u prosječnim situacijama. Čak i u najlošijim situacijama MOE nije nikada bio niži od 10.000, što se smatra graničnom vrijednošću za zdravlje ljudi. Procjena rizika pokazuje da je rizik od nastanka karcinoma uslijed izlaganja formaldehidu iz alkoholnih pića zanemariv te da je prioritet upravljanja rizikom u takvim slučajevima (npr. kako bi se smanjila kontaminacija) vrlo nizak. Najveći rizik proizlazi iz etanola i acetaldehida koji se također nalaze u alkoholnim pićima.

KLJUČNE RIJEČI: *alkohol, aldehidi, karcinom, konzumacija alkohola, procjena rizika*

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DOI: 10.2478/10004-1254-63-2012-2170

Review

PLES KAO ČIMBENIK RIZIKA ZA OZLJEDE I RAZVOJ PROFESIONALNIH BOLESTI

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Primljen u studenom 2011.
CrossCheck u lipnju 2012.
Prihvaćeno u svibnju 2012.

Ozljede i bolesti mogu znatno utjecati na stvaralačku sposobnost, kreativnost i dostignuća umjetnika. Povezanost uvjeta i načina rada s pojavom bolesti u umjetnika prepoznata je već u srednjem vijeku. Tjelesna zahtjevnost izvedbe, gdje se tijelo koristi kao instrument izražavanja, može uzrokovati ozljede i razvoj profesionalnih bolesti koje mogu dovesti do nemogućnosti umjetničke interpretacije na očekivanoj razini, prekinuti aktivnosti i onemogućiti nastavak profesionalne karijere. Plesači su jedna od skupina umjetnika-izvođača koji su izloženi specifičnim rizicima i kojima treba specifična zdravstvena zaštita, što nije moguće ostvariti bez poznavanja mehanizama nastajanja ozljeda i uvažavanja posebnosti potreba plesača. Mnogi plesači teže visokim umjetničkim i estetskim kriterijima izvedbe, pri čemu često protežu svoje tjelesne mogućnosti i izdržljivost i zanemaruju vlastita tjelesna ograničenja. Zdravstveni problemi plesača obuhvaćaju čitav niz ozljeda, profesionalnih bolesti i bolesti vezanih uz rad koji se kreću od stresa i straha od nastupa sve do poremećaja u prehrambenim navikama. Također obuhvaćaju ozljede mišićno-koštanoga sustava, sindrome prenaprezanja i trenažnoga preopterećenja koje može uzrokovati karakterističnu topološku pojavu boli, koja je često početak kroničnih zdravstvenih problema kod plesača. Navedeni zdravstveni problemi plesača sve su češće područje zanimanja liječnika različitih specijalizacija, unaprjeđenja i provođenja preventivnih programa, dijagnostičkih metoda i liječenja u tom djelu populacije.

KLJUČNE RIJEČI: *evidencija ozljeda, plesači, preventivni i dijagnostički postupci, profesionalne bolesti*

Plesom se još od prethistorijskog doba obilježavalo različite događaje u ljudskom društvu. S vremenom su pokreti, uzastopnim ponavljanjem poprimili određene ritmički uobličene obrasce i pretvorili se u ples, koji se izvodi radi iskazivanja emocija i ostavljanja određenoga dojma na publiku. Plesanje je ritmično kretanje tijela prema zvucima glazbe koje objedinjuje plesne pokrete tijela i zvuk, glumu, pantomimu, prikazuje ideje i priče, a izvodi se pojedinačno, u parovima ili u skupinama (1). Ples obuhvaća razne plesne tehnike i stilove kao što su balet, *jazz dance*, suvremeni ples, standardni plesovi (*engleski i bečki valcer, tango, slowfox, quickstep*) i latinoamerički plesovi (*samba, rumba, paso doble, jive, cha-cha-cha*), folklorni plesovi, *street dance* (*breakdance, house, hip hop*), a novi plesni stilovi se i nadalje razvijaju. Svaki od plesova ima svoje specifičnosti izvođenja pokreta. Sa zdravstvenoga stajališta ples ima višestruke pozitivne učinke na zdravlje jer doprinosi razvoju motoričkih sposobnosti (koordinacije, ravnoteže, frekvencije pokreta, izdržljivosti, fleksibilnosti), a koristi i kao pomoć u liječenju somatskih, neuroloških i psihijatrijskih poremećaja (2, 3). Plesačima tijelo predstavlja osnovno sredstvo umjetničkog izražavanja i komunikacije. Kako se tijekom vremena umjetnička

izvedba razvijala, plesači su težili višim estetskim kriterijima i što savršenijoj izvedbi. Pri tome kroz intenzivne treninge protežu svoje tjelesne sposobnosti i izdržljivost često zanemarujući vlastita tjelesna ograničenja, što može dovesti do prenaprezanja i ozljeda. Intenzivni plesni trening može uzrokovati karakterističnu topološku pojavu boli, koja je često početak kroničnih zdravstvenih problema kod plesača.

Prve prikaze profesionalnih bolesti umjetnika-izvođača naveo je Ramazzini već u srednjem vijeku u "Diseases of Workers". Prva rasprava o oštećenjima zdravlja u umjetnika-izvođača zabilježena je još 1713. godine, a djelomično zanimanje se nastavio i u 19. stoljeću, no tek se od 1970-tih počinju izraženije razvijati specifični pristupi i prilagođeni zdravstveni programi. Plesači su jedna od skupina umjetnika-izvođača koji su izloženi specifičnim rizicima i kojima treba specifična zdravstvena zaštita, što nije moguće ostvariti bez poznavanja mehanizama nastajanja ozljeda i uvažavanja afiniteta i potreba plesača. Osim profesionalnih plesača u svijetu i u Hrvatskoj se sve veći broj ljudi (učenika, studenata, trenera, pojedinaca rekreativaca) aktivno bavi plesom u amaterskim društvima. Amatersko plesanje i plesna rekreacija imaju gotovo istovjetne tjelesne aktivnosti kao i aktivnosti profesionalnih plesača. Razlika je u tome što rekreativci izvode manje komplicirane elemente koliko to dopuštaju individualne prirodne predispozicije tijela. Profesionalni plesači imaju odgovarajuće treninge i kondicijske pripreme koji osim tehničke izvedbe obuhvaćaju i fizičku pripremu plesača za specifična plesna opterećenja, dok kod amaterskih plesača to često izostaje, treninzi mogu biti nestručni ili neodgovarajući što je razlog da se pri istraživanjima sve češće prate i te skupine. Rastući broj plesača svih stilova i ozljede koje plesne aktivnosti mogu uzrokovati dovode do potrebe postojanja specijalizirane medicinske zaštite i preventivnih mjera koje će smanjiti mogućnosti ozljeda. Sve veći broj liječnika različitih specijalizacija bavi se specifičnim zdravstvenim problemima plesača, prateći uzroke ozljeda i provodeći liječenje (4, 5). Prepoznavanje umjetnika kao posebne skupine koja je izložena specifičnim problemima, suvremena praćenja, dijagnostika i liječenje te uspostavljanje interdisciplinarnih zdravstvenih programa za umjetnike rezultiralo je razvojem medicine umjetnosti (4-7).

Najveći broj istraživanja zdravstvenih problema usmjeren je na profesionalne plesače baleta (8). Balet je jedna od najstarijih plesnih tehnika koja je temelj svim ostalim plesnim stilovima, a danas ga najčešće izvode profesionalni baletni plesači te učenici baleta tijekom školovanja. Baletna umjetnost je scenska umjetnost izuzetno teških tjelesnih i psihičkih napora zbog elemenata napornih i složenih pokreta, ali i stalne prisutnosti straha od ozljeda koje mogu uzrokovati prekid njihovih karijera (9). Za uspješno izvođenje tih pokreta potrebno je stalno uvježbavanje i usavršavanje, a sukladno tome organizam plesača zahtijeva i posebnu medicinsku skrb.

Plesači kao profesionalna skupina nisu značajno zastupljeni u zdravstvenoj literaturi. Pregledom literature o zdravstvenim problemima plesača utvrđeno je da prevladavaju istraživanja o pojavama boli, oštećenjima mišićnoga i koštanoga sustava te metabolički i prehrambeni poremećaji (10).

RIZIČNI ČIMBENICI OZLJEDA I PLESNE OZLJEDE

Uzroci plesnih su ozljeda mnogobrojni i različiti, a kreću se od nepravilnoga zagrijavanja prije treninga, loše tehnike pri izvedbi do neodgovarajućega poda. Rizični čimbenici mogu značajno povećati rizik od ozljeda. Vanjski rizični čimbenici obuhvaćaju vrstu plesnih aktivnosti, nedostatak vještine i tehnike, pogreške pri treningu, neodgovarajući radni okoliš (temperatura, skliski i neravni pod, predmeti u plesnom području), plesnu opremu (baletne "špice") ili intenzivno radno opterećenje plesanjem u velikom broju predstava. Unutarnji čimbenici su dob, spol, vještina, kondicija, motoričke sposobnosti, umor plesača, pretreniranost i psihološki utjecaji (strah od nastupa, ozljeda, socijalni status) (5-7).

Na povrede lokomotornoga sustava kod baletnih plesača utječu nagli nekontrolirani pokreti, repetitivne kretnje, naprezanja individualnih mišićno-koštanih struktura, izraziti intenziteti fizičkoga stresa tijekom pojedinih napora te nefiziološki položaj pojedinih dijelova tijela kroz dulje vremenske periode, a te povrede su čimbenici rizika za razvoj povreda perifernoga živčanog sustava. Baletni plesači su zbog toga visoko rizična skupina za pojavu oštećenja perifernoga živčanog sustava (11). Ta se oštećenja u plesača ne mogu rješavati kao iste ozljede u općoj populaciji zbog potrebe za brzim prepoznavanjem vrste ozljede, hitnim dijagnostičkim postupkom i odlukom o tijeku liječenja. Ozlijeđenim baletanima se ne može preporučiti dugotrajno mirovanje, privremena pošteda

ili promjena radnog mjesta, jer se baletni plesači trebaju što prije vratiti na svoje radno mjesto u ansamblu i utvrđenim rasporedima predstava (12).

Posebnu pažnju treba usmjeriti na mlade plesače koji već u ranoj, dječjoj dobi započinju s intenzivnm učenjem baletne tehnike što ih svrstava u visoko rizičnu skupinu izloženosti ozljedama i pojave profesionalnih bolesti koji mogu značajno utjecati na njihovo buduće zdravlje (10, 13, 14). Za razvoj dobroga plesača karakterističan je dug razvoj, stalno vježbanje koje može kod pojedinaca prijeći i u pretjerano vježbanje te uzrokovati ozljede i oštećenja mišićnoga i koštanoga sustava, mentalne i emocionalne probleme.

Praćenjem 476 učenika švedske baletne škole u dobi od 10 do 21 godine, zamijećene su ozljede prvenstveno nastale kao rezultat preopterećenja. Najviše ozljeda, 76 % zabilježeno je u donjim ekstremitetima, a primijećene su i razlike u ozljedama po spolu, što upućuje na potrebu prevencije ozljeda i u tim dobnim skupinama (13). I u drugim istraživanjima mlađih dobnih skupina plesača dobi od 9 do 20 godina zabilježeni su slični rezultati i potreba za uvođenjem preventivnih pregleda i stalnih praćenja zdravstvenoga stanja (14). Zbog svega toga baletna umjetnost zahtjeva od plesača posebne fizičke i psihičke sposobnosti, redovite preglede lokomotornoga sustava uz antropometrijska mjerenja radi kontrole tijekom cijeloga školovanja, tijekom profesionalnoga bavljenja plesom pa sve do umirovljenja (1).

Učestalost ozljeda određenih dijelova tijela baletnih plesača je 41,2 % na plesnim probama, 38,5 % na nastupima i 19,1 % na satima baleta. Najveći broj ozljeda javlja se u mišićima, zatim slijede ozljede tetiva i ligamenata, a najugroženiji dijelovi tijela su gležanj, stopalo, koljeno, kralježnica i kuk. Kod muškaraca baletnih plesača, često dolazi do ozljeda ramena prilikom dizanja i nošenja partnerice. I istraživanja u Sjedinjenim Američkim Državama i Velikoj Britaniji također upozoravaju na učestalost tih ozljeda u plesača, a mnogi imaju kronične ozljede, koje su djelom i posljedice neodgovarajućega i nepravovremenoga liječenja (15, 16). Anketno istraživanje o kroničnim i nedavnim ozljedama provedeno u sedam profesionalnih ansambla baleta i modernoga plesa u Velikoj Britaniji pokazalo je da od 141 obuhvaćenoga plesača u dobi od 18 do 37 godina, njih 84 % ima barem jednu ozljedu uzrokovanu plesom koja utječe na njihovu izvedbu. Nadalje, 42 % plesača bilo je ozlijeđeno tijekom zadnjih 6 mjeseci, a 53 % plesača iznosi barem jednu kroničnu ozljedu koja uzrokuje bol (17).

Provedeno istraživanje na 54 plesačice u dvije baletne skupine pokazalo je ukupno 27 prijeloma kod njih 17. Najčešći su bili prijelomi metatarzalnih kosti (63 %), zatim prijelomi tibije (22 %) i kralježnice (7 %). Plesačice koje su plesale više od 5 sati dnevno imale su znatno veću vjerojatnost prijeloma od onih koje su plesale manje od 5 sati. Plesačice u skupini izloženijih prijelomima također su imale značajnije dulja razdoblja trajanja amenoreje, što pokazuje da produljena razdoblja amenoreje uz intenzivne treninge pridonose češćim prijelomima u balerina (18).

Najviše ozljeda, od 65 % do 80 % odnosi se na ozljede donjih ekstremiteta, od čega je oko 50 % ozljeda stopala i gležnja. U određenim slučajevima, kada ozljede nije moguće zaliječiti tretmanima koji podrazumijevaju kontrolu upale, istezanje, a kasnije vježbe s progresivnim otporom uz elektroprocedure s ciljem smanjena boli i natečenosti, potrebna je i kirurška intervencija (5).

Manji broj istraživanja je bio usmjeren na ostale plesne stilove. Istraživanja ozljeda u plesača *breakdance*-a uglavnom su bila usmjerena na prikaze pojedinih slučajeva (19). Praćenjem 40 profesionalnih i 104 amaterska plesača *breakdance*-a pokazalo se da profesionalni plesači zbog izvođenja složenijih plesnih elemenata imaju više ozljeda (posebice ručnoga zgloba, koljena, kukova, gležnja i lakta) te sindrome prenaprezanja. No, i kod ozbiljnih ozljeda, plesači su kratko vrijeme prestajali s treninzima. *Breakdance* treba smatrati sportskim plesom koji je potencijalno visoko rizičan zbog izvođenja elemenata akrobatskih figura, a liječnici trebaju biti svjesni rizika ovoga plesa i ozljeda koji uzrokuje (19). Ograničeni podaci o ozljedama postoje i za ples *hip hop* koji je sve popularnija umjetnička forma. Istraživanjem učestalosti ozljeda u skupini od 312 plesača srednjeg, naprednog i ekspertnog stupnja, čak 232 plesača prijavila su ukupno 738 ozljeda, od čega je 52 % bilo ozljeda donjih i 32 % gornjih ekstremiteta. *Hip hop* plesači prijavljuju stope ozljeda koje su više od ozljeda u ostalim plesnim stilovima, a usporedive su s ozljedama u gimnastici, što upućuje na važnost njihove edukacije o prevenciji ozljeda, biomehanici plesnih pokreta i potrebi korištenja zaštitne opreme (20).

Ni istraživanja plesača modernih i suvremenih plesova također nisu previše zastupljena u literaturi. Anketno istraživanje 204 studenata plesa, profesionalaca i bivših plesača u Velikoj Britaniji pokazalo je da, iako ozljede sami plesači nisu ni prijavljivali, 90 % svih ispitanika imalo je određene

ozljede i pojave boli, najčešće u leđnom području i koljenima (21).

Promjene intenziteta fizičkih aktivnosti zbog bolovanja, trudnoće, promjene koreografije, stila i tehnike plesa, loše izvedene plesne podloge, pa čak i druge plesne cipele uzrokuju još veću osjetljivost plesača i podložnost ozljedama (4). Zdravstveni problemi obuhvaćaju osim navedenih poremećaja i stres, strah od nastupa, umor, socijalni pritisak i financijsku nesigurnost zbog ograničenoga trajanja aktivnoga radnog staža, jer su i njihov socijalni i društveni status okolnosti koje mogu značajno utjecati na njihovo zdravlje. Zbog ozljeda, mnogi plesači ne mogu više nastupati već u dobi od 30 godina, a prijevremeno umirovljenje dodatno otežava karijere profesionalnih plesača (5).

Psihološki stres zbog stalnoga pritiska na plesače da moraju izgledati lijepo i biti vitki, može utjecati na razvoj problema s prehranom, pojavu anoreksije ili bulimije (4). Psihološka priprema i koncentracija prije javnih predstava te emocionalni pritisci kojima su plesači izloženi zbog nemogućnosti ostvarenja svojih plesnih ciljeva, očekivane popularnosti i uspjeha ili nemogućnosti nastupanja zbog ozljeda, bolesti ili starenja može uzrokovati i depresivna stanja (1, 5).

Iako je ozljede pri plesnim aktivnostima nemoguće u potpunosti izbjeći, na njihovu učestalost i težinu moguće je djelovati nizom preventivnih i intervencijskih mjera, čime će se čimbenike rizika smanjiti na najmanju moguću mjeru (22). Analiza učinaka sveobuhvatnoga upravljanja i intervencija na učestalost ozljeda, mehanizme nastanka ozljeda te izgubljenih radnih dana zbog ozljeda obuhvatila je 42 plesača u jednoj skupini modernoga plesa. Uspoređivani su podaci prikupljeni tijekom 2 godine bez provođenja intervencija i kroz tri godine provođenja intervencija. Rezultati dobiveni u tom 5-godišnjem razdoblju primjenom faktorijalnog dizajna, pokazali su učinkovitost provođenja intervencija i značajno smanjenje izgubljenih radnih dana za 60 %, te smanjenje učestalosti novih ozljeda. Većina novih ozljeda koja se dogodila mladim plesačima zbog prekomjernoga korištenja donjih ekstremiteta bila je prije provedbe programa intervencija (23).

ZDRAVSTVENI POREMEĆAJI PLESAČA U HRVATSKOJ

Istraživanja u Hrvatskoj najvećim su djelom bila usmjerena na profesionalne baletne plesače. Istraživanja učestalosti pojave boli i lokaliteta na mišićno-koštanom sustavu pri opterećenju u 36 profesionalnih folklornih plesača ansambla "Lado" pokazala su da se kod žena bol češće javlja u području koljena, kod muškaraca kod skočnog zgloba, dok je za oba spola bol bila značajna za područje lumbalnog djela kralježnice. Rezultati upućuju na potrebu stalnih praćenja kondicijskoga trenera i fizioterapeuta radi povećanja izdržljivosti i prevencije ozljeda u plesača (24).

Na uzorku od 30 plesačica Hrvatskoga državnog baleta i 21 plesačice Hrvatskog državnog ansambla narodnih plesova "Lado" iste dobi, provedeno je anketno istraživanje te mjerenje morfoloških karakteristika, motoričkih i funkcionalnih sposobnosti. Zabilježena je značajna korelacija u postocima masnog tkiva, broju poroda te trajanju menstrualnog krvarenja i nepravilnosti ciklusa u obje grupe. Značajna razlika zabilježena je i u indeksu tjelesna mase (ITM) (19,52 u balerina i 22,65 u folklorašica) između tih skupina. Pozitivno je što je u obje skupine ITM bio iznad 19, jer vrijednosti od 19 i niže, predstavljaju veći rizik za ozljede. Balerine su bile fleksibilnije, nježnije konstitucije, manje težine od plesačica narodnih plesova, a relativni maksimalni primitak kisika je bio značajno viši kod njih što je povezano s težinom (25). Radi odgovora nosi li profesija balerine veći rizik za oboljenje od osteopenije i osteoporoze uspoređivana je kontrolna skupina od 17 žena i 17 balerina rođenih u razdoblju od 1945. do 1959. godine. Dobiveni su rezultati upućivali da niža tjelesna masa, nedovoljan unos kalcija, nedostatak spolnih hormona, amenoreja zbog intenzivne tjelovježbe i zakašnjeli pubertet mogu utjecati na veći broj osteopenija i osteoporoza već u ranijoj životnoj dobi balerina (26).

Istraživanje specifičnih razlika u pojavi boli u 32 plesačice i 24 plesača, natjecatelja u standardnim i latinoameričkim plesovima, pokazalo je da plesačice češće prijavljuju bol tijekom treninga i nakon njega u području prstiju nogu (59,4 %), listova (59,4 %), gornjeg djela leđa (43,8 %), a plesači u području listova (75 %), koljena (54,1 %), kukova (50 %) i leđa (45,8 %). Rezultati upućuju da intenzitet treninga i tjedno trenažno opterećenje pri treningu mogu utjecati na frekvenciju pojave i topologiju boli kod plesača i plesačica (27). Ostala istraživanja uključivala su utvrđivanje odnosa između morfoloških dimenzija studenata i uspješnosti u savladavanju plesnih struktura te povezanosti motoričkih i morfoloških obilježja s uspjehom u društvenim i narodnim plesovima (28-30).

U Hrvatskoj je 1997. godine bio osnovan "Zdravstveni centar za umjetnike" sa svrhom organiziranoga ostvarenja zdravstvene zaštite za umjetnike-izvođače. Centar je bio utemeljen međusobnim sporazumom Kliničke bolnice Dubrava i Hrvatske udruge za zaštitu izvođačkih prava (HUZIP), dok su supotpisnici bile strukovne udruge umjetnika izvođača u Hrvatskoj, no centar kao djelatnost nije zaživio. Ipak, u Hrvatskoj djeluje odbor Europskoga udruženja medicine umjetnosti (HOEUMU) koji okuplja eminentne hrvatske stručnjake raznih područja koji provode međunarodni, interdisciplinarni program "Medicina, znanost i umjetnost". Udruga djeluje s ciljevima istraživanja položaja umjetnika-izvođača u Hrvatskoj prateći njihove zdravstvene, obrazovne, pravne i socijalne probleme, izrade programa prevencije i liječenja i baze podataka o umjetnicima, kao i pripreme programa edukacije liječnika i samih umjetnika, a od 2000. godine održavaju godišnje znanstvene skupove.

Popularnost plesa kao tjelesne i umjetničke aktivnosti u Hrvatskoj i dalje raste i sve veći broj ljudi se profesionalno, ali i amaterski i rekreativno bavi plesom. Prema podacima Sremca (1990.) u Hrvatskoj su postojala dva profesionalna baletna i dva folklorna ansambla i dvije grupe suvremenog plesa, s oko 200 profesionalnih plesača. Pored toga je bilo evidentirano oko 680 amaterskih grupa folklornoga plesa, baleta te suvremenoga, društvenoga i sportskoga plesa, ne uključujući dječje i školske grupe, što je oko 20 000 amaterskih, najviše folklornih plesača (31).

U Hrvatskoj se ovisno o registriranoj djelatnosti plesnih organizacija podaci nalaze u sklopu Ministarstva znanosti, obrazovanja i sporta, Ministarstva kulture, u Registru udruga Republike Hrvatske ili različitih stručnih udruženja i udruga građana koje samostalno prikupljaju podatke o određenim plesnim skupinama.

Telefonskim istraživanjem provedenim tijekom travnja i svibnja 2012. godine prikupljeni su podaci o registriranim udrugama, kulturno-umjetničkim društvima, skupinama, plesnim centrima, profesionalnim te amaterskim i rekreativnim plesačima na području Hrvatske. Uz 361 profesionalnog plesača, što obuhvaća plesače klasičnoga baleta, baletne majstore, plesače suvremenoga plesa i plesače-pjevače u profesionalnim ansamblima narodnih plesova, pribrajamo i učenike osnovnih i jedne srednje škole baleta, suvremenoga i narodnoga plesa. Uz procjenu da u svakoj plesnoj skupini ima oko 20 amaterskih i rekreativnih plesača, proizlazi da se u Hrvatskoj plesom bavi oko 50 000 pojedinaca. Dok balet i suvremeni ples imaju razrađene treninge koji su važni zbog tehničkih i kondicijskih priprema plesača, u amaterskom je plesu češći izostanak pravilnih priprema, što može uzrokovati veće mogućnosti ozljeda.

EVIDENCIJA PLESNIH OZLJEDA U HRVATSKOJ

U Republici Hrvatskoj ne postoji sustavno i metodički ujednačeno evidentiranje ozljeda profesionalnih plesača, amatera i rekreativaca. Evidencija ozljeda se svodi na bolničku dokumentaciju ozlijeđenih plesača, zdravstvene kartone obiteljskih liječnika i pojedinačne slučajeve gdje plesne organizacije vode evidenciju o ozlijeđenim članovima.

Za zaposlene osobe u radnom odnosu Hrvatski zavod za zaštitu zdravlja i sigurnost na radu objavljuje analize ozljeda na radu i registar profesionalnih bolesti po pojedinim godinama. Ozljede i profesionalne bolesti klasificiraju se prema Nacionalnoj klasifikaciji zanimanja koja u skupinu umjetnika i srodnih stručnjaka uključuje pored plesnih umjetnika i likovne, glazbene, dramske umjetnike, filmske i kazališne redatelje i producente, spikere, produktivne i reproduktivne umjetnike. Ukupan broj ozljeda na radu i profesionalnih bolesti se iskazuje za cijelu skupinu umjetnika i srodnih stručnjaka, a ne iskazuje se koliki je broj bio unutar pojedine podskupine, tako da iz tih podataka ne možemo vidjeti broj ozlijeđenih plesača.

Ozljede na radu u djelatnosti poslodavca koji se u Nacionalnoj klasifikaciji zanimanja vodi pod umjetnost, zabava i rekreacija zabilježene su u 2010. godini kod 206 osoba, što iznosi 1,52 %, a u 2011. je broj ozlijeđenih osoba bio 222 (1,61 %) (32, 33).

U registru profesionalnih bolesti od 2006. do 2010. godine nije bilo evidentirano niti jedno profesionalno oboljenje u skupini u umjetnika, dok je u 2011. bilo samo jedno, što predstavlja stopu od 4,99 na 100 000 zaposlenika u djelatnosti, a uzrok bolesti je bio sindrom prenaprezanja uzrokovan kumulativnom traumom (32).

Kvalitetan nadzorni sustav ozljeda uzrokovanih plesom trebao bi sadržavati sljedeće odrednice: identifikaciju (prepoznavanje problema u okvirima incidencije i težine ozljeda), evaluaciju (utvrđivanje

etiologije i mehanizma plesne ozljede) i prevenciju (uvođenje preventivnih mjera).

Nakon uspostavljanja kvalitetnoga sustava nadzora plesnih ozljeda, treba osvijestiti važnost kontinuiranoga i sustavnoga prikupljanja podataka. Samo će takav pristup omogućiti da se i u Hrvatskoj u budućem razdoblju stvori baza podataka iz koje će se vrlo lako moći utvrditi uzročno-posljedične veze koje povećavaju mogućnost ozljeđivanja u profesionalnom, amaterskom i rekreativnom plesu.

Z AKLJUČAK

Zdravstveni problemi plesača, obuhvaćaju čitav niz zdravstvenih poteškoća, specifičnih ozljeda i profesionalnih bolesti te zahtijevaju multidisciplinarni pristup zdravstvenih djelatnika različitih specijalizacija u dijagnostici, liječenju i provođenju preventivnih mjera u svrhu smanjivanja broja ozlijeđenih. U Hrvatskoj je potrebno razviti metodologiju prikupljanja podataka o ozljedama profesionalnih i amaterskih plesača i rekreativaca, kako bi se sustavno pratile i evidentirale ozljede i kako bi se uopće mogao započeti proces stvaranja sigurnijega okruženja. Takav bi pristup dugoročno omogućio stvaranje sveobuhvatnoga nadzornog sustava na razini Republike Hrvatske kao ključnog ishodišta za planiranje i provođenje prevencije te odgovarajućeg stručnog i zdravstvenog pristupa.

Najveći broj istraživanja u svijetu usmjeren je plesnim pripremama i prevenciji od ozljeda, a pravovremene intervencije i tretmani plesnih ozljeda postaju uobičajene. Plesni ansambli, institucije i druge plesne organizacije sve više uključuju fizikalne terapeute i medicinske stručnjake zbog praćenja zdravstvenoga stanja plesača, što može doprinijeti smanjenu troškova zdravstvene skrbi i liječenja, smanjenju vremena liječenja, unapređenju kvalitete života plesača i brži nastavak karijere, a upravo to je u Hrvatskoj područje koje može znatno napredovati.

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Summary

DANCE AS A RISK FACTOR FOR INJURIES AND DEVELOPMENT OF OCCUPATIONAL DISEASES

Injuries and diseases can significantly affect the creativity and artistic performance. The link between working conditions and artistic performance had been recognised as early as the medieval age. Physically demanding performance arts such as dance can sometimes result in injuries, illnesses, inability to perform, and even end artist's career.
Dancers are exposed to specific risks and in need of specific medical care. Many dancers often stretch their physical capabilities and endurance and neglect their physical limitations. Their health problems include a number of work-related illnesses that range from stress and stage fright to metabolic and nutritional disorders. They also include musculoskeletal injuries due to overload training that are often the beginning of chronic health problems.

KEY WORDS: *dancers, preventive and diagnostic procedures*

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REPORT

39th International MEDICHEM Congress on Occupational and Environmental Health in the Production and Use of Chemicals "Occupational Health in a Changing World", Heidelberg, Germany, 2 - 5 June 2011

REPORT OF THE CHAIR OF THE ORGANISING AND SCIENTIFIC COMMITTEES OF MEDICHEM 2011 CONGRESS

International MEDICHEM Congresses have been held since 1972. From 1974, they have been organised continuously each year, either as a sole event or a separate session within a Congress of the International Committee of Occupational Health (ICOH) where MEDICHEM Board acts as the Scientific Committee on Occupational Health in the Chemical Industry.

The 39th international MEDICHEM Congress was held in Heidelberg, Germany, between 2nd and 5th June 2011 under the motto "Occupational Health in a Changing World". This exceptional event brought together 165 experts from 30 countries for 56 oral and 11 poster presentations. The Congress provided occupational medicine specialists, scientists, and young researchers in the chemical and pharmaceutical industry, as well as epidemiologists, toxicologists, and experts on environmental protection, occupational health and safety regulations with a forum to exchange their experiences and cutting-edge scientific findings. This was the second time in 25 years that the MEDICHEM Congress was held in Germany. It was organised by the German Social Accident Insurance Institution for the Raw Materials and Chemical Industry (Berufsgenossenschaft Rohstoffe und chemische Industrie, BG RCI) in Heidelberg. The Marriott Hotel turned out to be the ideal venue for a congress that attracted a total of 218 participants, 165 congress participants, and 53 accompanying persons. The official language during the Congress and accompanying events was English.

The Congress began on Thursday with an optional field trip of 75 participants to the "Cradle of MEDICHEM", that is, the world's leading chemical company BASF (Badische Anilin und Soda Fabrik) in Ludwigshafen. The former BASF Physician-in-Chief and current Honorary President of MEDICHEM, who established MEDICHEM in 1972 (39 years ago to be precise), almost 90-year old Prof. Dr. med. Dr. h.c. Alfred Michael Thiess not only guided the participants through the trip but also delivered an impassioned welcome address with visible pride. The latter occasion was the opening ceremony on the evening of 2nd June 2011, at the behest of Dr. med. Maren Beth-Hübner, the organiser and facilitator of the Congress, Dr. Thiess passed then the floor to other speakers delivering a welcome address on the evening: the Mayor of the city of Heidelberg, Dr. Joachim Gerner, the Chairman of the Supervisory Board of BASF SE, Dr. Eggert Voscherau, who also stepped in for the President of the Industrial Union of Mining, Chemical and Energy (IG BCE), Hanover, Michael Vassiliadis, who was unable to attend owing to illness, the Executive Director of the German Chemical Industry Association (VCI), Dr. Gerd Romanowski, the spokesman of the Board of Management of BG RCI, Thomas Köhler, and other dignitaries, the representatives of WHO, and guests from all over the world, welcoming into his "MEDICHEM family fold" the 23 new MEDICHEM members from 13 countries gained from the Congress.

During the following two and a half days, the Congress participants keenly followed the welcome address delivered by the Chairman of MEDICHEM, Dr. Thirumalai Rajgopal, Vice President, Medical and Occupational Health, Hindustan Unilever Limited & Head of Occupational Health, Unilever Asia, India, the introduction to the event's hosting organisation, the BG RCI, given by the spokesman of the BG RCI's Board of Management, Thomas Köhler, and the introduction to the ambitious scientific program by the Director of

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the Institute of Environmental Toxicology from Martin-Luther University Halle-Wittenberg, Halle/Saale, Professor Heidi Foth, who is also a member of the board of EUROTOX and ICOH. Seven highly acclaimed keynote speakers, 11 invited experts, and 27 submitted oral presentations provided a detailed insight into the latest findings on the link between shift work and cancer, the opportunities and risks of nanotechnology, new findings in biomarker research and toxicology, trends, case reports, regulation in industrial medicine, as well as the initiatives of Strategic Approach to International Chemicals Management (SAICM) and the European Community Regulation on chemicals and their safe use (REACH).

Congress sessions started on Friday morning. The first session was Shift work and cancer - Current discussion (chaired by Dr. Michael Nasterlack and Dr. Abed bin Onn). The results on the carcinogenicity of shift work were interpreted quite differently by the three speakers and fuelled highly controversial discussions. Professor Kurt Straif, Head of the Section of the IARC Monographs, official publication of International Agency for Research on Cancer (IARC), Lyon, France, presented the very latest findings gleaned from epidemiological studies in 2007. These, in the opinion of IARC, confirm the view that shift work, which causes disruption of the circadian rhythm, is "probably carcinogenic to humans" and thus could be classified by IARC as Group 2A. Professor Thomas Erren, Director and Chair of the Institute and Policlinic for Occupational Medicine, Environmental Medicine and Prevention Research at the University of Cologne, Germany, considered the results achieved from observations of human beings to be inconclusive. He underlined that additional studies with a specific epidemiological design were needed before any statements could be made on the carcinogenic effect on humans of shift work that involves disruption of the circadian rhythm. In a major study conducted over a ten-year period with 13,000 BASF employees who were employed in BASF's special shift work system, Dr. Michael Nasterlack, Vice-President of the Occupational Medicine & Health Protection in BASF, said that he was unable to detect a higher rate of breast cancer or any other cancer among shift workers compared to 17,000 BASF employees who only worked the day shift, nor could he detect a higher mortality rate. It is possible that shift work, similar to the BASF model that avoids disruption of the "internal", approx. 24-hour day/night rhythm, can actually prevent an increased risk of cancer.

Other sessions held on Friday were: Case Reports - Interesting observations in the occupational health world (chaired by Dr. Andreas Flückiger and Dr. Diane J. Mundt); Toxicology - New results, emerging risks (chaired by Prof. Dr. Günter Oberdörster and Dr. Kenneth A. Mundt); Regulation in occupational health - Recent developments and REACH - Impact on occupational and environmental health (chaired by Prof. Dr. Andrea Hartwig and Prof. Dr. Heidi Foth); Strategic Approach to International Chemicals Management (SAICM) - Status and developments (chaired by Prof. Dr. Maged Younes and Prof. Dr. Helmut Greim).

There is no doubt that Saturday, which opened with theme Nanotechnology - Challenges and Solutions (chaired by Prof. Dr. Uwe Heinrich and Dr. Maren Beth-Hübner) was the most eagerly anticipated day of the Congress. It brought together leading international scientists in the field of nanotechnology: Professor Günter Oberdörster, USA, Professor Uwe Heinrich, Germany, Professor Ken Donaldson, Scotland, and Professor Vincent Castranova, USA. Although they were unable to give the all-clear, the researchers were able to highlight specific features that can pose a risk to human health and others that can help to avoid them. For example, long and thin carbon nanotubes (CNTs), which resemble asbestos fibres in appearance and exhibit a needle-like shape, can also have similar effects. Professor Vincent Castranova used an electron micrograph to demonstrate in a most impressive way that these inhaled fibres are too bulky to be further transported and absorbed by the body's own cells. Instead, they are trapped in the pleural cavity where they cause persistent inflammation that can ultimately lead to pleural mesothelioma, the well-known cancer of the lining of the lungs that is caused by exposure to asbestos. The Chairpersons of the eight presentations on the subject of nanotechnology proclaimed this image "Photo of the year" since it visualised the underlying mechanisms of injury more clearly and immediately than any other image (see the photo attached). The Chairperson of the MAK Commission, that is, the Senate Commission for the Investigation of Health Hazards of Chemical Compounds in the Work Area, Professor Andrea Hartwig, suggested classifying various nanomaterials according to their hazard potential. Nanofibres and metal-based nanoparticles would need to be researched individually and assessed in a differentiated manner. Speakers from industry, the VCI, and the BG RCI presented technical and organisational occupational

safety and health measures that can prevent exposure and safeguard safety at work.

Another session held on Saturday was Adverse effects on employees, customers and the general public - Preventive measures (chaired by Dr. Michael Nasterlack and Dr. William Murray Coombs). This Congress day was closed by MEDICHEM General Assembly.

Although Sunday was the last Congress day, it was just as busy as all previous ones. Based on the number of contributions submitted, Sunday morning opened with session Biomarkers - Progress in research and practical application (chaired by Dr. Heiko U. Käfferlein and Dr. Martina Piasek). The session dealt with one of the thematic focal points of the Congress and contained nine presentations on human biomonitoring of occupational and/or environmental exposures.

Session that closed the Congress was Occupational health - Trends and evolution (chaired by Dr. Steffen Hitzeroth and Dr. Andreas Flückiger). It began with an impressive keynote lecture on psychosocial risks at the workplace delivered by Dipl. Psych. Roland Portuné, an occupational psychologist with the BG RCI. Today there is no longer any doubt about the causal relationship between growing psychosocial stress at the workplace and damage to employees' health such as cardiovascular disease, affective disorders, and back pain. These disorders are becoming a growing challenge for occupational health and safety regulations. The final presentation, which dealt with unconventional threats to corporate leadership and was a highlight of the Congress, was delivered by Dr. William Lang, the former Medical Director at the White House, Washington DC, USA, where he was responsible for medical care services for the White House members of staff and the President. In accordance with the theme of the Congress "Occupational Health in a Changing World", Dr. Lang explained that weapons of mass destruction (chemical, biological, radiological, and nuclear weapons that have the potential to kill and bring significant harm to a large number of humans) are nowadays aimed more at disrupting basic functions of critical infrastructures and destroying economic power. This means the management echelons of multinational groups and regional business enterprises have become the target of potential attacks. A large number of photographs from the world of politics and industry, which document examples of potential targets, highlight the explosive nature of the theme in our ever-changing world for the large number of senior company physicians in the numerous chemical and pharmaceutical multinationals in attendance. The Congress ended at around 2:00 pm after promotion of next MEDICHEM Congresses in 2012 and 2013.

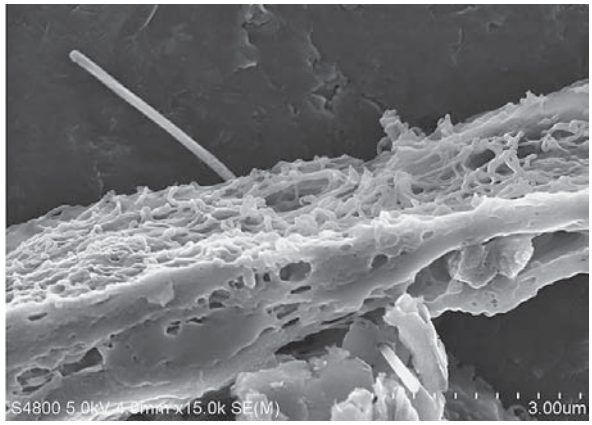

Image: Multi-walled carbon nanotube penetrating the pleura (electron micrograph by Vincent Castranova)

Poster presentations covered almost all Congress themes and were exhibited during the entire period of Congress sessions. Two winners of the MEDICHEM Scholarship Award 2011 were Dr. Martina Piasek, Croatia and Dr. Caihong Xing, China. Three participants granted the MEDICHEM Young Professionals Award 2011 were Dr. Keiichi Fujimoto, Japan; Prof. Dr. Ehsan Habibi, Iran; and Dr. Amir Radfar, Iran.

The varied social program, ranging from performances by the Heidelberg Brass Orchestra on the opening evening, and an organ concert featuring internationally recognised organist Wenzel Hübner, to a reception at the Palais Prinz Carl hosted by the City Mayor on Friday, culminated with a gala dinner at the world-famous Heidelberg Castle. The icing on the cake was a spectacular fireworks display over the city and River Neckar on Saturday evening. These events inspired not just maximum concentration during the keynote addresses but will ensure that the early summer stay in Heidelberg remains an unforgettable experience with nice memories for the 218 Congress participants from 30 countries all over the world.

Entire Congress brochure with abstracts was available to the Congress participants in printed version and it is now available at the following link: www.medichem2011.org.

Maren Beth-Hübner

CURRICULUM VITAE
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CURRICULUM VITAE

FABIJAN KNEŽEVIĆ, autor grafike na naslovnici

Fabijan Knežević rođen je 1953. godine u Zagrebu. Osnovno školovanje i gimnaziju završio je u Zagrebu. Polazio je nižu i srednju glazbenu školu "Vatroslav Lisinski" u Zagrebu. Pod vodstvom poznatih glazbenih pedagoga Mirjane Čakmak Despot i Rudolfa Matza učio je violončelo, glasovir kod Margite Matz i Stele Raukar, tonski slog kod Huberta Petana, komorno muziciranje kod Zvonka Pomikala, a orkestralno muziciranje kod Vladimira Kranjčevića. Kao istaknuti učenik - čelist sudjelovao je na V. glazbenom natjecanju učenika glazbenih škola Hrvatske. Tom prilikom je 1969. dobio diplomu, a na VII. natjecanju učenika srednjih muzičkih škola Hrvatske 1971. kao čelist osvaja treću nagradu. Maturirao je 1971., a 1978. diplomirao na Medicinskom fakultetu Sveučilišta u Zagrebu. Specijalistički ispit iz patološke anatomije položio je 1985. godine. Godine 1991. magistrirao je, a 2002. stekao naslov doktora medicinskih znanosti. Od 2004. radi kao voditelj Službe za patologiju Klinike za tumore Zagreb. Odlukom Fakultetskoga vijeća Medicinskoga fakulteta u Zagrebu 2005. godine izabran u znanstveno-nastavno zvanje naslovni docent, a 2011. u znanstveno-nastavno zvanje izvanrednoga profesora na Katedri za patologiju i patološku anatomiju Medicinskoga fakulteta Sveučilišta u Zagrebu. Danas je predavač kolegija *Patologija* na Katedri za patologiju i patološku anatomiju Medicinskoga fakulteta Sveučilišta u Zagrebu i voditelj kolegija *Molekularna patologija* na Biološkome odsjeku Prirodoslovno-matematičkoga fakulteta. Član je Hrvatske liječničke komore i Hrvatskog liječničkog zbora.

Slika od studentskih dana. Bavi se štafelajnim slikarstvom, grafikom i skulpturom. Unatrag pet godina izlagao je računalnu grafiku. Istovremeno je radio i na vlastitoj zbirci umjetničkih tepiha. Zadnje dvije godine izlaže reljefe, objekte i skulpture. Član je Hrvatskoga društva likovnih umjetnika.

Do danas je imao četrnaest samostalnih i dvije skupne izložbe.

1982. Brdovec, Narodno sveučilište Zaprešić Muzej Brdovec, Skupna izložba - XI. izložba likovne sekcije zbora liječnika Hrvatske

2005. Zagreb, Muzej Mimara, Izložba računalnih grafika

2006. Zagreb, Galerija AZ, Hrvatska kulturna zaklada Izložba računalnih grafika

2006. Karlovac, Galerija Studentskog centra Karlovac, Izložba računalnih grafika

2007. Zagreb, Caffe kulturno središte "Zeus Faber", Izložba računalnih grafika

2007. Zagreb, Sajam "Ambijenta", Regeneracija d.d. Zabok, Izložba tepiha

2007. Karlovac, Galerija Studentskog centra Karlovac, Izložba računalnih grafika

2008. Zagreb, Sajam "Ambijenta", Regeneracija d.d. Zabok, Izložba tepiha

2008. Zagreb, Galerija NOVA, Izložba reljefa i objekata

2009. Slavonski Brod, Galerija umjetnina grada Slavonskog Broda, Galerija Ružić i suvremenici, Izložba reljefa, objekata i skulptura

2009. Karlovac, Galerija Studentskog centra Karlovac, Izložba reljefa, objekata i skulptura

2009. Zagreb, Galerija Filakovac, Izložba računalne grafike: Varijacije u kvadratu

2010. Zagreb, Galerija Filakovac, Skupna izložba - Izbor iz fundusa galerije Vladimir Filakovac

2010. Pećuh, Galerija Chopor(t) Horda, Izložba reljefa, objekata i skulptura

2011. Zagreb, Muzej Mimara, Ritmovi i forme, Izložba tepiha i skulptura

2011. Zagreb, Galerija Nova, Muzičke minijature, Izložba grafika

ABOUT THE AUTHOR of graphic on the cover page

Fabijan Knežević was born in 1953 in Zagreb. He completed his elementary and secondary school education in Zagreb. In parallel to his formal education, he attended elementary and secondary music schools "Vatroslav Lisinski" in Zagreb. Headed by famous music pedagogues, Mirjana Čakmak Despot and Rudolf Matz, he studied cello and piano with Margita Matz and Stela Raukar, music theory with Hubert Petan, chamber music with Zvonko Pomikalo, and orchestral music with Vladimir Kranjčević. He proved to be an extremely talented student, which is why he participated in the 5th Music Competition of Croatian music school students. On this occasion, in 1969, he was conferred his degree, while on the 7th Competition of Croatian secondary music schools he won third place as a cello player. He graduated from high school in 1971, and in 1978 received a degree from the School of Medicine at the University of Zagreb. He passed his anatomical pathology board exam in 1985. Thereafter, he received his master's degree in 2002 and was conferred the title of Doctor of Medical Science in 2002. Since 2004, he has been holding the position of the Head of Pathology Service within the Clinic for Tumours in Zagreb. Following a decision rendered by the Faculty Council of the School of Medicine in Zagreb in 2005, he was appointed adjunct assistant professor, and in 2011 was awarded the title of associate professor in the Department of Pathology and Anatomical Pathology of the School of Medicine at the University of Zagreb. Today, he is a lecturer at the School of Medicine at the University of Zagreb where he teaches Pathology in the Department of Pathology and Anatomical Pathology. He is also heading the module Molecular Pathology in the Department of Biology at the Faculty of Science. He is a member of the Croatian Medical Chamber and Croatian Medical Association.

He has been painting since early adulthood. His areas of interest are easel painting, graphics, and sculpture. Five years ago, he held an exhibition of computer graphic artwork. At the same time, he worked on his own collection of artistic rugs. In the past two years, he has had several exhibitions of reliefs, objects, and sculptures. He is a member of the Croatian Association of Artists.

Up to this day, he has had fourteen solo and two combined exhibitions.

1982 Brdovec, Open University Zaprešić, Museum Brdovec, Combined exhibition - 11th exhibition of art section of Croatian Medical association

2005 Zagreb, Museum Mimara, Exhibition of computer art graphics

2006 Zagreb, Gallery AZ, Croatian Cultural Foundation, Exhibition of computer art graphics

2006 Karlovac, Gallery of the Student Centre in Karlovac, Exhibition of computer art graphics

2007 Zagreb, Café Cultural Meeting Point "Zeus Faber", Exhibition of computer art graphics

2007 Zagreb, Trade Fair "Ambijenta", Regeneracija d.d. Zabok, Rug exhibition

2007 Karlovac, Gallery of the Student Centre in Karlovac, Exhibition of computer art graphics

2008 Zagreb, Trade Fair "Ambijenta", Regeneracija d.d. Zabok, Rug exhibition

2008 Zagreb, Gallery NOVA, exhibition of reliefs and objects

2009 Slavonski Brod, Art Gallery of the Town of Slavonski Brod, Gallery Ružić and contemporaries, Exhibition of reliefs, objects, and sculptures

2009 Karlovac, Gallery of the Student Centre in Karlovac, Exhibition of reliefs, objects, and sculptures

2009 Zagreb, Gallery Filakovac, Exhibition of computer art graphics: Square variations

2010 Zagreb, Gallery Filakovac, Combined exhibition - A selection of the gallery Vladimir Filakovac collection

2010 Pećuh, Gallery Chopor(t) Horda, Exhibition of reliefs, objects, and sculptures

2011 Zagreb, Museum Mimara, Rhythms and forms, Rug and sculpture exhibition

2011 Zagreb, Gallery Nova, Musical miniatures, Exhibition of computer art graphics