

in the urine, but extent of activation was not highly correlated with any single urinary PAH-OH marker.

**Conclusion** Among firefighters, urinary PAH-OH concentrations increase in both entry teams and engineers. The route and extent of dermal and inhalation exposure vary with the specific job task at the fireground. AhR and p53 *in vitro* bioassays demonstrate activation of cancer pathways following occupational exposure in firefighters.

### 53 HUMAN BIO-MONITORING OF EPOXY RESINS AND HARDENERS IN THE PRODUCTION OF ROTOR BLADES

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**Introduction** In a small company producing rotor blades for aviation from carbon composites, epoxy resins based on Novolac and isophorone diamine as hardener are used. Both compounds can be absorbed via skin contact and were shown to be strong skin sensitizers. As a part of risk assessment, the industrial physician prompted a biological monitoring to determine the internal exposure of the workers.

**Methods** 6 workers were identified with potential contact to the hardener and resin. We have collected pre- and post-shift urine samples at the beginning and mid of the work week and analysed them for the concentration of isophoronediamine and bisphenol-f-diglycidylethermetabolites as biomarker for the hardener and Novolac via specific mass spectrometric methods.

**Results** We detected isophoronediamine in almost all urine samples with post-shift-values significantly higher than pre-shift. Median urinary excretion of isophoronediamine over the workweek was 195 µg/g crea. (Monday pre-shift), 709 µg/g crea. (Monday post-shift), 573 µg/g crea. (Wednesday pre-shift) and 1319 µg/g crea. (Wednesday post-shift). Results for urinary bisphenol-f-diglycidylether-metabolites were several orders of magnitude lower and near the limit of detection (0.5 µg/L).

**Conclusion** We found considerable internal exposures to isophoronediamine in workers producing carbon composite rotor blades. Our results indicate a cumulating internal exposure over the work-week. One of the workers showed clinical symptoms of allergic contact dermatitis in the skin examination. Use of inappropriate gloves was determined to be the cause for these high exposures. Biological monitoring should be part of risk assessment of workers handling epoxy resins.

### 684 EXPOSURE FROM GUN SMOKE ACTIVATES SEVERAL SYSTEMIC INFLAMMATORY PATHWAYS

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**Introduction** Norwegian Armed Forces reported episodes of acute respiratory symptoms after exposure to fumes from firing small arms weapon HK416 (Heckler and Koch) using unleaded ammunition. These fumes contain a mixture of gases and solid particles, that may be capable of inducing inflammatory immune responses. The aim of the present study was to find out if exposure to fumes from small arms could induce systemic and airway inflammation, and whether there were any differences between the ammunition types (leaded, and two types of unleaded).

**Methods** Fifty-five healthy men (age 19–62) were recruited and randomised to three groups using HK416 and one of the three types of ammunition. Spirometry and collection of blood and sputum samples were performed 2–4 days before shooting, and 1.5 hour (spirometry), 24 hour (blood and spirometry) and 48 hour (sputum) after shooting under standardised conditions. Exposure was monitored.

**Results** All subjects had a significant increase in median sputum and blood neutrophils (sputum: 46% to 73%,  $p < 0.001$ ; blood:  $2.9 \times 10^6/\text{mL}$  to  $7.1 \times 10^6/\text{mL}$ ,  $p < 0.001$ ). CRP was significantly elevated from 1.3 mg/L to 18.5 mg/L ( $p < 0.001$ ) along with other markers of systemic inflammation (PTX3, YKL-40, SpD, CC16, CXCL16, vWF, MPO, CD25, CD14). CRP and number of neutrophils in blood had a larger increase with unleaded as compared to leaded ammunition. For the whole group, mean FEV<sub>1</sub> and FVC decreased 290 mL ( $p < 0.001$ ) and 130 mL ( $p < 0.001$ ), respectively.

**Discussion** All subjects displayed elevated airway and in particular systemic inflammation following the use of small arms. The changes in systemic markers were enhanced acute stress response (CRP, PTX3), immune cell upregulation (sCD25, sCD14) and increased vascular inflammation (MPO, vWF, CXL16, YKL40). Increased airway inflammation was present at 48 hour post exposure and was accompanied by reduced spirometry that appeared <1.5 hour and lasted >24 hour after exposure. These results suggest that soldiers may be at increased risk to inflammation-based disorders when repeatedly using small arms.

### 753 COMBINATION OF CELLULAR ASSAYS WITH METABOLOMICS REVEALED MECHANISTIC INSIGHTS ON DOSE-RESPONSE RELATIONSHIP OF 3-NITROBENZANTHRONE IN HUMAN UROTHELIAL CANCER CELLS

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**Introduction** A product of incomplete combustion of diesel fuel, 3-nitrobenzanthrone (3-NBA), has been classified as a cancer-causing substance. It gained attention as a potential urinary bladder carcinogen due to the presence of its metabolite in urine and formation of DNA adducts.

The aim of this study was to characterise the dose-response relationship starting from environmentally relevant to high concentrations by utilising toxicological and metabolomic approaches to determine the toxic potential of 3-NBA in bladder cells.

**Method** Cells of RT4 cells were exposed against 0.3 nM to 80 µM 3-NBA for 24 hour. Both activity of enzymes involved in the metabolism of 3-NBA as well as cytotoxicity were

determined using specific assays. Finally, the potential of 3-NBA to alter the cellular metabolism was assessed by gas chromatography-mass spectrometry.

**Result** RT4 cells were capable of bioactivation of 3-NBA within 30 min, whereas the main contributor for bioactivation of 3-NBA was NAD(P)H:quinone oxidoreductase (NQO1). Cytotoxicity assessment revealed an activation of adaptive mechanisms at low dosages, which diminished at higher doses.

The metabolomic analysis of the cells showed elevated levels of various antioxidants at low concentrations of 3-NBA. At higher exposure concentrations, it appeared that the cells reprogrammed their metabolism to maintain the pentose phosphate pathway (PPP) aiding in cell protection.

**Discussion** Starting from a relevant environmental dose of 0.0003  $\mu\text{M}$  up to 80  $\mu\text{M}$ , we described the driving mechanism behind the different cellular states – in particular an activation of adaptive mechanisms at low dosages, which diminished at higher doses. The metabolomic data suggested that the PPP and the folate metabolism play a leading role in this transition. Moreover, there was evidence for an additional carbon flux into PPP via the gluconate metabolism to support the formation of NADPH, which in term is an important determinant of the defence system against oxidative stress.

#### 771 HEART RATE VARIABILITY IN SMELTER FURNACE WORKERS

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**Introduction** Exposure to fine particulate matter in urban air has been associated with increased risk of hospitalisation and death from cardiovascular diseases. One hypothesis suggests a direct influence of particles on the autonomic nervous system. Some studies have shown an association between particle exposure and reduced heart rate variability (HRV). Furnace workers in metal smelters are occupationally exposed to fine and ultrafine particles. The aim of this study was to examine the association between exposure to particulate matter in metal smelters and HRV.

**Methods** We examined 64 workers in three Norwegian metal smelters on a working day, and on a day off after at least two days since last exposure. On the working day, exposure to different particle size fractions was assessed by personal sampling, using respirable cyclones and five-stage Sioutas cascade impactors. The workers carried Holter monitors for 24 hours' heart rate registration during the working day and the day off. HRV indices were analysed by exposure for each hour of the day, using mixed model regression, adjusted for relevant covariates.

**Results** There were 58 male and 6 female workers. Their mean age was 34 years (range 19–64). The mean exposure to respirable particulate matter was 2.36  $\text{mg}/\text{m}^3$ , while 0.88  $\text{mg}/\text{m}^3$  was below 250 nm. Standard deviation of normal-to-normal intervals (SDNN) was reduced during working hours on the working day relative to the day off, whereas in the afternoon and night hours there were no significant differences. Low frequency/high frequency (LF/HF) ratio was higher during working hours on the working day, but in the afternoon and evening hours the LF/HF ratio was significantly higher on the day off compared to the working day.

**Conclusion** HRV indices differ between working day and day off. Analyses are in progression, and further results on the effects of particle exposure will be presented.

#### 780 CONTRIBUTIONS OF DERMAL VS AIR EXPOSURE TO BIOMONITORING FOR SOLVENT EXPOSURE

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**Introduction** Dermal exposure assessment is becoming increasingly important in occupational settings, but its contribution to the overall body burden is not yet well-established. Therefore, we evaluated the contribution of dermal exposure to the total body burden as reflected by biomonitoring, by simultaneous quantitative assessment of dermal, and air exposure in combination with bio-monitoring, in workers exposed to solvent.

**Methods** Exposure to the volatile organic compounds, styrene, acetone and toluene on the skin was evaluated using activated charcoal cloth patches; inhalation exposure was measured using passive organic vapour monitors, and systemic exposure was assessed by quantification of mandelic acid, acetone and hippuric acid in urine, as biomarkers for styrene, acetone and toluene, respectively. Exposure was measured in 40 workers performing different tasks: hydraulic press (HP) workers, sheet moulding composite (SMC) workers, mechanics and office workers in a thermoplastic panels factory.

**Results** For styrene, the dermal exposure levels found were higher for HP workers ( $1532 \pm 450 \mu\text{g}/\text{cm}^2$ ) than for the other workers (e.g. SMC  $179 \pm 50$ ). Inhalation exposure levels for HP and SMC workers were similar ( $58 \pm 11 \text{ mg}/\text{m}^3$  and  $60 \pm 8 \text{ mg}/\text{m}^3$ , about 70% TLV), but urinary concentrations of mandelic acid were higher for HP ( $549 \pm 85 \mu\text{g}/\text{mL}$ ) than SMC ( $331 \pm 21 \mu\text{g}/\text{mL}$ ) workers. In addition, a good correlation between dermal, air and urinary levels of acetone was found. Unlike for styrene and acetone, toluene levels in air were less than 1% TLV, regardless of the tasks performed by the workers. No relevant dermal or inhalation exposure was found for mechanics and office workers.

**Discussion** This study shows that for solvents, high dermal exposure substantially contributed to the increased concentrations of urinary metabolites. Therefore, the contribution of dermal exposure to the overall body burden is as important as the respiratory exposure, especially for less-volatile solvents, such as styrene.

#### 832 ORGANOPHOSPHATES IN THE WORKPLACE: A 20-YEAR PROSPECTIVE STUDY

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