(rs11640851 and rs8052394) and two MT2A SNPs (rs10636 and rs28366003). The MT1A2A SNPs combination was divided into 16 groups. Data were treated for descriptive analysis, one-way ANOVA, and multiple linear regressions by SPSS.

Results Urine uric acid had significantly negative association with time-weighted index of cumulative blood lead (TWICL) after adjusting other potential confounders except 16 groups of MT1A2A SNPs combination. Moreover, the association was modified by 16 groups of SNPs combination. For urine uric acid, group 6th and group 12th were more susceptible to lead toxicity, while group 5th was less susceptible to lead toxicity. On the other hand, urinary NAG was positively associated with TWICL no matter whether the 16 groups were adjusted or not.

Conclusion Urinary uric acid and urinary NAG might be considered as proper indicators of lead nephrotoxicity. Moreover, MT1A2A combination 16 groups were modifiers in the relationship between urinary uric acid and TWICL. The group 5th was positive association while group 6th and 12th were negative association with TWICL on urinary uric acid

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BONE EFFECT UNDER CAUSED BY CO-EXPOSURE TO FLUORIDE AND ARSENIC

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Introduction Chronic exposure to combined fluoride and arsenic continue to be a major public health problem worldwide. Although there have been reports in the literature about the toxicity of arsenic and fluoride individually, there is very little known about the combined effects of these two elements. In this study, based on the population and *in vivo*, the aim is to explore the combined bone toxicity of fluorine and arsenic and provides a scientific basis for the mechanism, prevention and control of endemic combined fluorine-arsenic poisoning on bone toxicity.

Methods The population-based study group was selected from people living in fluoride-arsenic polluted areas due to burning coal in China. The total number of participants was 196 to observing the changes in gene and protein expression of PTH/PKA/AP1 signalling pathway. A total of 90 weaned specific pathogen-free SD rats were randomly assigned to a group to explore the role of PTH-cAMP-PKA signalling pathway on bone toxicity of rats exposed to fluoride and arsenic.

Results Fluoride can increase the expression levels of PTH, PKA, and AP1, but arsenic can only affect the expression of AP1; fluoride and arsenic have an interaction on the expression of AP1, c-fos and Runx2. Fluoride exposure can affect the metabolism of collagen and bone resorption, and arsenic exposure main affect bone resorption, fluoride and arsenic co-exposure have a more significant effect on bone resorption.

Conclusion PTH-PKA-AP1 and PTH-cAMP-PKA signalling pathway may play an important role in bone toxicity of fluoride. Arsenic can affect the expression of c-fos and Runx2, thereby affecting the expression of transcription factor AP1, MMP-9, RANKL and Osterix, indirectly involved in fluoride induced bone toxicity. The main sign of bone damage under the exposure level of the study is osteosclerosis and main combined bone toxicity of fluoride and arsenic showed antagonistic effects

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LOW LEVEL URINE ARSENIC CONCENTRATION AND OBSTRUCTIVE PULMONARY DISEASE AMONG U.S. WORKERS

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Introduction Arsenic (As) is a known carcinogen commonly found in drinking water. An emerging body of evidence suggests that exposure to inorganic arsenic may be associated with non-malignant respiratory disease. The aim of this study was to determine whether there is an association between As exposure at levels seen among workers in the United States and prevalence of asthma, emphysema, chronic bronchitis, and respiratory symptoms.

Methods Urinary As was collected from 5365 participants from the combined 2003–2006 National Health and Nutrition Examination Survey (NHANES) cohorts. Two methods to adjust for organic As component were incorporated into the statistical model. Linear and logistic regression models compared urinary As adjusted for organic As with diagnoses of obstructive pulmonary disease and respiratory symptoms.

Results Geometric mean concentration of urinary As were not significantly different between participants with and those without asthma, chronic bronchitis, and emphysema. Odds of having asthma was 0.71 for participants with the highest quintile of urinary As ($\geq 17.23 \mu\text{g/dl}$) when compared to the lowest quintile ($\leq 3.52 \mu\text{g/dl}$). A significant association was found between increasing urinary As concentration and decreasing age, male gender, and non-'white' race.

Conclusion A significant association between urinary As and obstructive pulmonary disease and symptoms was not demonstrated in the U.S. working population

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BONE METABOLISM ABNORMALITY AND RENAL DYSFUNCTION IN CADMIUM EXPOSED FARMER FROM THAILAND

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Introduction Paddy fields in Mae Sot, Tak province of Thailand are polluted with cadmium (Cd) over safe level. Farmers exposed Cd from contaminated rice consumption and the high prevalence of kidney dysfunction was shown in the exposed population. Bone fracture is another Cd related pathology which shown in elderly with high exposure level. The identification of high risk individuals will be advantageous to provide suitable health promotion and to prevent severe pathology. This study was done to compare bone fracture risk between glomerular dysfunction, proximal tubular dysfunction and Calcium (Ca) handling abnormality.

Methods Serum osteocalcin and cross-linked N-telopeptide of type I collagen to detect bone metabolism abnormalities, whereas glomerular filtration rate, serum cystatin C, urinary β_2 -microglobulin (β_2 -MG) and fractional excretion of calcium

(FECa) were used to indicate renal dysfunction. Urinary Cd was used as exposure marker.

Results We found that high FECa was related to high bone fracture risk in both genders. Proximal tubular dysfunction and glomerular dysfunction did not relate to bone fracture risk.

Conclusion Abnormal Cd handling was a key risk factor for bone fracture in Cd exposed people. Men was at risk of bone fracture risk as similar as women. FECa was a specific indicator of Ca wasting and its determination cost was cheaper compare to β_2 -MG and serum cystatin C. We recommended to use FECa to monitor abnormal Ca metabolism and individual who showed high FECa should have a special health promotion to reduce bone fracture risk. Reduced renal toxicant exposure, and Ca supplementation were suggested as a health promotion for this Cd exposed farmer.

1654 GENETICS AND EPIGENETICS IN TOXICOLOGY OF METALS

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Aim of special session To provide current knowledge on genetic and epigenetic effect of metal exposure in different population.

1654a EPIGENETIC ALTERATIONS AS AN UNDERLYING MECHANISM OF THE TOXICITY OF METALS

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Introduction Toxic metals are present at many workplaces as well as in food and drinking water, causing life-long daily exposure. In the last decade, epigenetic alterations have gained attention as underlying mechanisms of the adverse health effects observed in relation to exposure to metals. Epigenetic marks, broadly defined as dynamic changes to the genome other than changes in the DNA sequence itself, can lead to persistent changes in the regulation of gene expression. Epigenetic mechanisms have key functions in regulating cellular homeostasis, and lineage-specific gene expression, and perturbations may have long-lasting influence on future health, including risk of cancer.

Methods Epigenetic changes in candidate genes and in the epigenome (pyrosequencing, MS-HRM, target-enrichment next-generation sequencing, RNA sequencing, histone modifications, and microRNA) have been measured in different tissues in relation to exposure to toxic metals (arsenic, cadmium, lead, welding particles) in samples collected from humans occupationally and/or environmentally exposed to metals.

Result We have shown that exposure to particularly arsenic, but also cadmium and metal-containing particles, are significantly associated with changes of epigenetic marks, and some of these marks are linked to carcinogenesis, cardiovascular and

immune function. The epigenetic changes seem to persist over several years and for arsenic and cadmium sex differences were found.

Discussion Research during the last decade have shown that metals common at workplaces and in the general environment are associated with epigenetic alterations that in turn may have long-lasting effects on the gene regulation and risk of disease. Experimental and animal studies support that epigenetic perturbations are underlying mechanism for metal toxicity. Similar to what has been shown for smoking-related epigenetic marks, metal-related epigenetic marks may be promising exposure and effect biomarkers.

1654b MANGANESE TOXICITY ACROSS THE LIFESPAN FROM PRENATAL EXPOSURE TO THE OLD AGE

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Introduction Manganese exposure causes neurotoxicity from prenatal life to the old age. An extended body of literature is now available on:

- different exposure sources and routes of absorption;
- mechanistic aspects provided also by imaging assessment;
- dose-response relationship from epidemiological and animal studies;
- gender differences;
- genetic predisposition.

Methods New evidence was reviewed from the scientific literature and the studies presented during the world conference held in 2016 at the Icahn School of Medicine at Mount Sinai, New York, USA.

Results Current manganese research offers a wide spectrum of observations within a continuum of exposure from early life to old age, with new evidence of neurotoxicity at low exposure levels in occupational settings and operations including welding. Gender differences are consistently shown by human studies and toxicity vs beneficial effects are reported to varying as a function of the exposure windows. Brain imaging studies through structural and functional MRI provide new information about differences and similarities between occupational, environmental exposure and parkinsonian conditions. Genetic studies focused on genes regulating specific transporters, such as SLC30A10, offer new prospective in understanding the regulation of metabolic pathway and toxicodynamic properties of manganese.

Conclusion Manganese exposure is increasingly common through a variety of industrial and agricultural products. Current research offers consistent evidence of potential links from neurodevelopment to neurodegeneration. The enhanced vulnerability of specific exposure windows and the cumulative mechanism of toxicity require further studies to identify the critical windows of susceptibility and the exposure levels suitable to protect the brain throughout the lifetime exposure. Understanding these aspects is of outmost relevance in view of the potential role of manganese as determinant of both neurodevelopmental disorders and neurodegenerative diseases.