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ABSTRACT

The evaluation of individual health risk in workers occupationally exposed to industrial xenobiotics requires the use of a large number of parameters reflecting external exposure, internal exposure, biological effects and individual susceptibility. Environmental, occupational and life style-related exposure to mutagenic agents may contribute to cancer risk in humans. To prevent the potentially hazardous effects of such agents it is important to understand their mechanisms of action. Styrene is one of the most important monomer for

producing polymers and copolymers in plastics, latex paints and together with 1,3-butadiene (BD) in the manufacture of synthetic rubbers. In this thesis, a large set of parameters, including markers of external and internal exposure and biomarkers of biological effects and susceptibility have been studied in relation to the occupational exposure to both styrene and BD.

Biomarkers reflecting styrene- and BD-induced genotoxicity and mutagenicity: O6-styrene guanine DNA adducts, haemoglobin adducts, single-strand breaks (SSBs), SSB Endo III sites, chromosomal aberrations (CA), hypoxanthine-guanine phosphoribosyltransferase gene mutation freguencies (HPRT MF), from the aspects of their accumulation over time and of the role of adaptation and/or selection in the genotoxic risk of styrene exposure have been analyzed.

Second topic of the study was to investigate the possible modulating role of genetic polymorphisms of genes encoding for metabolizing and detoxifying enzymes in individuals occupationally exposed to styrene and BD. DNA samples of exposed workers and controls were subjected to genotype analysis for EPHX1 (Tyr113His and His139Arg), GSTM1 (deletion), GSTP1 (exon 5) and GSTT1 (deletion) polymorphisms.

Third part of the study was focused on assessing the role of DNA repair capacities (DRC) in styrene- and BD-exposed workers. Individual DRC in styrene-exposed workers was significantly higher in comparison with controls. The stimulation of DNA repair in laminators could explain their enhanced capacity to repair DNA damage, which is assumed to be repaired mainly by base excision repair pathway. Possible relationships between the capacity to repair oxidative DNA damage, parameters of exposure and parameters of genotoxic effects have been also analyzed.

In the next part of the study, modulating effect of DNA repair gene polymorphisms in the context of styrene and BD exposure has been investigated. Among all analyzed polymorphisms, XPD Lys751Gln polymorphism was a major factor influencing the frequencies of CAs.

Finally, analysis of immune markers and their relationship with various genetic polymorphisms has been performed for the first time in the present study. The relationships between various DNA repair polymorphisms and immune parameters are even more difficult to explain at the moment, due to the lack of knowledge on functional aspects of the genetic polymorphisms analyzed and due to the complexity of the immune system.

It is important to use many biomarkers in large population and consider altogether all aspects of genotxicity. A comprehensive approach may provide fundamental information about the suitability of the biomarkers and may contribute to the understanding of the mechanisms of genotoxic effects of industrial xenobiotics and their metabolites in humans.

1. INTRODUCTION

Exposure to a potential chemical carcinogen involves a continuum of events starting from absorption, continuing through activation to reactive metabolites and binding to DNA and resulting into mutations. In the worst case, the above process may result in cancer development. (Perera *et al.* 2000; Au and Salama 2005) Various biomarkers can be used to follow these events to elucidate the mechanisms of the genotoxic/carcinogenic process as well as the individual response to carcinogens. DNA damage is probably best regarded as a marker of exposure, and the level of DNA damage represents a steady state between induction of damage and its repair. As a biomarker, DNA damage in lymphocytes probably reflects exposure over the previous few weeks, but if some damage is resistant to repair, a cumulative increase in the steady state level might appear with time. (Somorovska et al. 1999)

Responsiveness to exogenous and endogenous genotoxins may be due to genetic polymorphisms of xenobiotic-metabolizing enzymes (XMEs), resulting in increased or decreased efficiency of metabolic activation. Another group of genetic susceptibility factors that could influence the level of chromosome