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.

First part of the present study was focused on evaluating the role of various biomarkers to assess genotoxic effects of above mentioned xenobiotics. Biomarkers reflecting styrene- and BD-induced genotoxicity and mutagenicity: O^6-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 (Publications No. II, III, V, VI).

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 (Publications No. II, III, VI). DNA samples of exposed workers and controls were subjected to genotype analysis for *EPHX1* (Tyr113His and His139Arg), *GSTM1* (deletion), *GSTP1* (Ile105Val) and *GSTT1* (deletion) polymorphisms. Hand-lamination workers exhibited a significantly higher proportion of low *EPHX1* activity genotype. Styrene-exposed individuals with *GSTP1* genotype Ile/Ile exhibit significantly lower MF at the *HPRT* locus as compared to those with heterozygous *GSTP1* genotype.

Third part of the study was focused on assessing the role of DNA repair capacities (DRC) in styrene- and BD-exposed workers (Publications No. II-VII). 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 analyzed. The only positive correlation was found between DRC and DNA damage in females. An increased capacity to incise 8-oxoguanine, which represents oxidative damage in lymphocytes, was recorded among highly exposed workers. Significant association between both internal and external exposure parameters and repair capacity to remove oxidative DNA damage suggests a possible role of oxidative stress in styrene-related genotoxicity.

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. Genetic polymorphisms in DNA repair genes and possible links with DNA repair rates, CAs and SSBs in DNA are summarized in Publications No. IV, VI, VII. Among all analyzed polymorphisms, *XPD* Lys751Gln polymorphism was a major factor influencing the frequencies of CAs. SSBs and CAs frequencies were the highest in individuals with common *AA* genotype and the lowest in those with variant *CC* genotype for this polymorphism. Tire workers with a combination of low *EPHX1* activity genotypes and the *AA* (wild type) and *AC* (heterozygous) *XPD* alleles exhibited higher levels of CAs than individuals with combined high *EPHX1* activity genotypes and variant allele *CC* genotype for *XPD*. This observation suggests an increased risk of genotoxic effects in individuals with particular genotype combinations.

Finally, analysis of immune markers and their relationship with various genetic polymorphisms has been performed for the first time in the present study (Publications No. I, IV). An increase number of leukocytes and lymphocyte was observed in individuals with *GA* and *AA* genotypes of *Cyclin D1* Pro242Pro polymorphism as compared with those with common *GG* genotype. The number of eosinophiles was positively associated with variant *C* allele for *XPD* Lys751Gln. Immunoglobulin IgA was positively associated with variant *T* allele *XRCC3* Thr241Met and negatively with *AC* and *CC* genotypes of *XPC* Lys939Gln. 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.