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Metabolic polymorphisms and biomarkers of effect in the biomonitoring of occupational exposure to low-levels of benzene: State of the art

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HIGHLIGHTS

- At low levels of exposure to benzene, biological effects may be higher than expected, particularly in susceptible individuals.
- The genetic polymorphism of *NQO1* is a metabolic susceptibility factor, whereas the polymorphisms of glutathione S-transferases (*GSTM1*,*GSTT1*, *GSTA1*) may modulate the levels of *S*-phenylmercapturic acid in urine, a very sensitive and specific biomarker of exposure to benzene.
- Among the available biomarkers of effect, only the periodical blood cell count seems validated enough to be applied in the longitudinal monitoring of effects from occupational benzene exposure.

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ABSTRACT

Current levels of occupational exposure to benzene, a genotoxic human carcinogen, in Western countries are reduced by two–three orders of magnitude (from ppm to ppb) as compared to the past. However, as benzene toxicity is strongly dependent on biotransformation and recent evidence underlines a higher efficiency of bio-activation pathways at lower levels of exposure, toxic effects at low doses could be higher than expected, particularly in susceptible individuals. Currently, biological monitoring can allow accurate exposure assessment, relying on sensitive and specific enough biomarkers of internal dose. The availability of similarly reliable biomarkers of early effect or susceptibility could greatly improve the risk assessment process to such an extent that risk could even be assessed at the individual level. As to susceptibility biomarkers, functional genetic polymorphisms of relevant biotransformation enzymes may modulate the risk of adverse effects (*NQO1*) and the levels of biomarkers of internal dose, in particular *S*-phenylmercapturic acid (*GSTM1*, *GSTT1*, *GSTA1*). Among biomarkers of early effect, genotoxicity indicators, although sensitive in some cases, are too aspecific for routine use in occupational health surveillance programmes. Currently only the periodical blood cell count seems suitable enough to be applied in the longitudinal monitoring of effects from benzene exposure. Novel biomarkers of early effect are expected from higher collaboration among toxicologists and clinicians, also using advanced "omics" techniques.

Abbreviations: ADH, alcohol dehydrogenase; ALDH, aldehyde dehydrogenase; BDE, benzene diol-epoxide; BDHD, benzene dihydrodiol; BO, benzene oxide; BQ, benzoquinone; BT, benzenetriol; BZ, benzene; CAT, catechol; CSG, cysteynylglicinase; CYP, cytochrome P-450; DHDH, dihydrodiol dehydrogenase; EPHX1, microsomal epoxide hydrolase; GGT, gamma-glutamyl transferase; GST, glutathione S-transferase; HQ, hydroquinone; MCA, muconaldehyde; MPO, myeloperoxidase; NAT, *N*-acetyltransferase; NQO1, NAD(P)H; PH, phenol; SPMA, *S*-phenylmercapturic acid; SQ, semiquinone; TTMA, *t*,*t*-muconic acid.

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1. Introduction

It is long known that occupational exposure to benzene (BZ) is associated with a higher risk of toxic and carcinogenic effects, in particular on the lympho-haematopoietic system (Sacca, 1948; Paterni et al., 1954). The solvent may induce bone marrow suppression causing leukopenia, anemia, thrombocytopenia, aplastic anemia, and pancytopenia (ATSDR, 2007). In China, where BZ has been used extensively resulting in very high air concentrations, a haematotoxic syndrome called chronic benzene poisoning has been even nosologically recognized by the Ministry of Health (GBZ 68-2013).

In its more recent re-evaluation of the carcinogenicity of BZ, the International Agency for Research on Cancer (IARC, 2012) has concluded that there is sufficient evidence in humans for a causal role in inducing acute myeloid leukemia/acute non-lymphocytic leukemia and limited evidence in humans for a causal association of BZ with acute and chronic lymphocytic leukemia and multiple myeloma. A recent study has estimated that occupational exposure to BZ is responsible for as much as 0.19% and 0.34% of the overall incidence of non-lymphocytic leukemia in men and women, respectively (Rushton et al., 2010).

Both toxic and carcinogenic effects caused in the past by exposures to tens of ppm (1 ppm = 3.25 mg/m^3) (Pliofilm cohort; Infante et al., 1977), have been demonstrated more recently also for exposures in the ppb (μg/m^3) range (Health Watch study: Glass et al., 2003, 2014; Lan et al., 2004, 2006; UK Petrol Cohort: Rushton et al., 2014; Pooled analysis of the Health Watch, Canadian and UK Petrol cohorts: Schnatter et al., 2012), i.e. lower than the 8 h occupational exposure limit (1 ppm) recommended by both the European Scientific Committee for Occupational Exposure Limit (SCOEL; EC, 1991) and the U.S. Occupational Safety and Health Administration (OSHA; OSHA, 1987). Beside the occupational settings, the risk assessment of BZ has also environmental

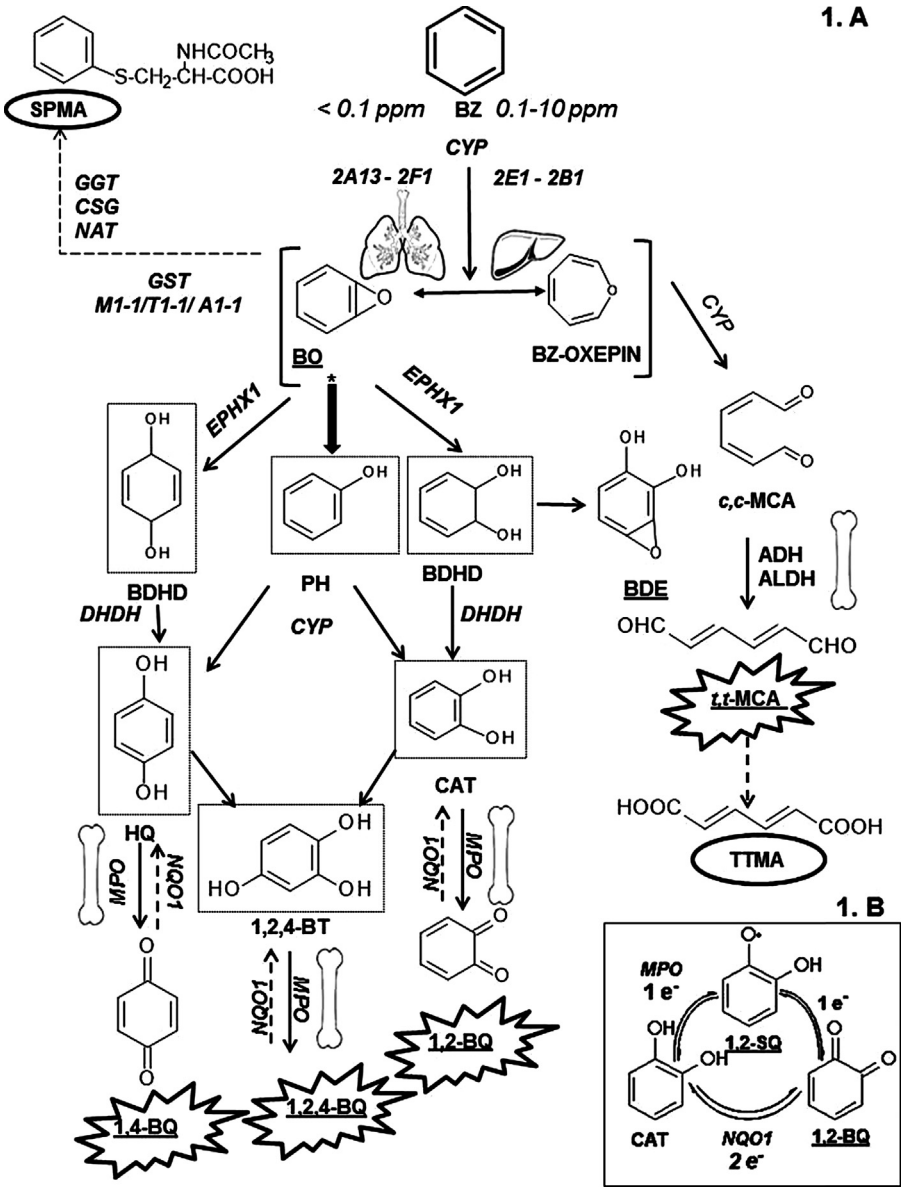

Fig. 1. Simplified scheme of benzene metabolism. 1. A The main pathways of benzene bioactivation and detoxication. The first step of benzene oxidation involves different enzymes (and organs), depending on exposure levels. The thickness of the lines indicates the relative amount of the corresponding metabolic reaction. The asterisk indicates a spontaneous reaction. Continuous lines indicate bioactivation pathways; dashed lines indicate detoxication pathways. The square framed compounds can be excreted as a glucuronide or a sulphate; oval framed compounds are biomarkers of internal dose; pointed framed compounds are electrophilic reactive metabolites. 1. B Redox-cycling of 1,2-Benzoquinone (valid also for 1,4- and 1,2,4-Benzoquinones). The free electrons released by oxidation reactions react with molecular oxygen producing superoxide anion.