A critical review of current biological monitoring techniques for the assessment of exposure to low levels of benzene

2nd edition

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A CRITICAL REVIEW OF CURRENT BIOLOGICAL MONITORING TECHNIQUES FOR THE ASSESSMENT OF EXPOSURE TO LOW LEVELS OF BENZENE

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EXECUTIVE SUMMARY

EI *Guidance on health surveillance and biological monitoring for occupational exposure to benzene* was first published in 1993. This document was updated in 2000, in particular to reflect lower levels of exposure. This report contains an update to the 2000 review.

Approaches to assess chemical exposure can be classified into: biological monitoring (where a chemical or a metabolite is measured in an appropriate sample), and biological-effect monitoring (where an endpoint related to a specific health effect is monitored). The biological markers S-phenyl mercapturic acid (SPMA) and trans, trans-muconic acid (ttMA) were recommended for benzene exposure in the 2000 update. More recent evidence shows that ttMA may be less appropriate for low level exposure as it is also produced as a metabolite of dietary sorbate. SPMA remains a useful marker; however, the quantification of benzene itself has become more popular as instrument detection limits have improved. Methods to measure adducts in either blood or urine have not developed sufficiently to be considered suitable for routine monitoring.

A wide array of biological-effect markers continues to be proposed and used in studies of occupationally exposed individuals. However, while some associations with benzene exposure have been reported, these studies have typically included relatively highly exposed individuals. No clear examples of biological-effect monitoring that would be suitable for the routine monitoring of workers exposed to low levels of benzene are currently available.

This report has outlined recent advances in biological monitoring techniques for benzene and guidance is given to determine the most appropriate biomarker for use. Clearly, as occupational exposures continue to be better controlled, then non-occupational sources of benzene (particularly smoking, but also other environmental sources) will become potential confounders. Some strategies to help assess occupational exposure to benzene above background environmental levels are discussed.

1 INTRODUCTION

The EI has previously published guidance on biological monitoring to assess benzene exposure in 1993 and 2000. At the time of the 2000 review, it was found that for benzene exposures down to 5 ppm, phenol was an acceptable measure; between 1 ppm and 0,1 ppm both SPMA and ttMA were acceptable measures. Below 0,1 ppm it was 'not appropriate' to recommend any measure at that time. Biological-effect monitoring was also discussed.

This document provides an updated review of currently available biological monitoring techniques, focusing on the suitability for measuring exposure to low occupational levels of benzene.

Since the publication of the last review in 2000, biological monitoring for benzene has continued to develop, particularly in response to lower occupational exposure levels (below 1 ppm [approximately 3,2 mg/m^3 at 1 atm and 25°C] in air); however, there have been no radical step-changes in methodology. Consequently, available methods tend to fall into one of two categories, either: determination of fairly recent exposure by measuring benzene and its metabolites, or attempting to quantify longer-term exposure using adducts. Little progress has been made in the field of adducts. DNA adducts remain unproven and while haemoglobin or plasma albumin adducts are still used, it is questionable whether available methods are sufficiently sensitive to be useful at low exposure levels. In contrast, the measurement of un-metabolised benzene in either blood, urine or exhaled breath has seen some increase in use. The urinary metabolites SPMA and ttMA remain useful, although the continued use of ttMA for monitoring low-level exposure may become increasingly difficult to justify due to interference from dietary sorbate. The use of some other urinary metabolites, such as phenol, is not appropriate as they are not specific for benzene.

The continued development of computational modelling, particularly physiologically-based pharmacokinetic (PBPK) modelling, has the potential to aid the interpretation of biological monitoring data. However, while several PBPK models are available for benzene in blood, there has only been very limited extension to include urinary benzene or its metabolites (Knutsen et al. 2013). Generally, urine is preferred over blood for biological monitoring due to the ease of collection; therefore, un-metabolised benzene or SPMA in urine is recommended as the best currently available biomarker for benzene exposure at low levels. Both candidates have strengths and weaknesses and these will be discussed in detail. However, when analysed by a competent laboratory using recent instrumentation, either analyte will satisfactorily determine benzene exposure down to environmental levels and the choice may be determined largely by the instrumentation available in a given laboratory.

Biological-effect monitoring is a complementary approach where the aim is to monitor actual or surrogate markers of early effects. Ideally, these effects should be reversible upon removal or reduction of exposure. Most of the candidate effect markers outlined in the 2000 review have continued to be used in studies of benzene exposure. However, while the analytical capability has progressed, none of these published studies presents strong evidence that biological-effect monitoring would be useful for the routine monitoring of workers exposed to low levels of benzene.