

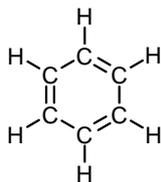
Biomarkers of exposure to environmental and endogenous leukaemogens

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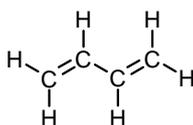
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Genomic DNA is under continuous assault by various reactive chemical species produced by normal cellular metabolism. In addition, exposure to exogenous chemical agents adds further insult. Modification of DNA by chemical carcinogens has long been recognised as an early event in carcinogenesis and many DNA adducts have been characterised. There appears to be great value in using DNA adducts as markers of exposure to genotoxic (i.e. DNA-damaging) agents and some may be even more useful as indicators of risk of disease (Shuker, 2002).

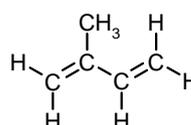
Among the chemicals that are known to cause leukaemia the DNA damaging properties of benzene and 1,3-butadiene are perhaps the best characterised (Scheme). Both benzene and 1,3-butadiene have been identified as potential leukaemogens through studies of occupational groups. However, environmental exposures could also arise as both compounds occur in tobacco smoke and automobile emissions.



Benzene



1,3-Butadiene



**2-Methylbuta-1,3-diene
(Isoprene)**

Scheme. Structures of the chemicals discussed in this abstract

Several groups have developed methods for the analysis of protein and DNA adducts of 1,3-butadiene. Analysis of haemoglobin in both animals and occupationally exposed humans has revealed the presence of characteristic reaction products between 1,3-butadiene metabolites and the terminal amino acid, valine, of this protein. 2,3,4-Trihydroxybutyl adducts, which are derived from 3,4-epoxy-1,2-butanediol, are several orders of magnitude higher than N-(2-hydroxy-3-butenyl) adducts, which are derived from 1,2-epoxy-3-butene. Studies have demonstrated higher levels of either, or both, of these adducts in workers exposed to 1,3-butadiene (several thousand ppb) compared to controls (Perez et al., 1997). However, at low levels (less than 10 ppb) there were no correlations between exposure and levels of excreted mercapturic acids (Fustinoni et al., 2004). In one study of 1,3-butadiene-DNA adducts in humans, levels of N-1-(2,3,4-trihydroxybutyl)adenine adducts were significantly higher in lymphocyte DNA of workers occupationally exposed to 1,3-butadiene compared to control subjects (Zhao et al., 2001). Isoprene (2-methylbuta-1,3-diene) is structurally very similar to 1,3-butadiene and is a ubiquitous natural product as it is a key intermediate in plant and animal biochemistry. Humans, in fact, exhale isoprene. Isoprene is also used as an industrial chemical. It undergoes similar metabolism to 1,3-butadiene and forms DNA adducts (Begemann et al., 2004).

There is still great uncertainty about the mechanism of leukaemogenicity of benzene and several discrete metabolic pathways can lead to DNA and protein damage (Snyder, 2002). In

one pathway, benzene is converted into *trans,trans*-muconic acid which is excreted in the urine. It has been used as a biomarker of low level exposures, such as environmental tobacco smoke (Hecht, 2003). In fact, a recent study in Italy showed that levels of urinary *trans,trans*-muconic acid were more heavily influenced by exposure to tobacco smoke than other source of environmental pollution (Saieva et al., 2003). DNA adducts from benzene appear to be derived from oxidised metabolites such as 1,4- and 1,2-benzoquinone (Gaskell et al., 2002) and studies on this pathway are progressively yielding further knowledge of the genotoxicity of benzene.

In summary, there are a number of possibilities for using biomarkers to characterise low-level exposures to environmental and endogenous leukaemogens. It remains to be seen whether these biomarkers will shed any light on the role, if any, of chemicals such as benzene, 1,3-butadiene and isoprene in childhood leukaemia.

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