Biological monitoring: Future prospects –

The role of biomarkers in monitoring exposure to chemicals

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Introduction

The objective of bio-monitoring is to prevent excessive exposure to chemicals that may cause acute or chronic adverse health effects. Bio-monitoring can be subdivided into (i) biological monitoring of exposure, (ii) biological monitoring of early effects and (iii) the biological monitoring of susceptibility. All three measurements are an integral part of the diagnosis process and should be considered when compiling a health risk assessment.[1] Depending on the characteristics of the selected biological parameters and the condition under which it is measured, the biological monitoring may be subdivided into two groups:

i) biological monitoring of internal dose; and
ii) biological monitoring of the target or biological effective dose.

The latter part relies on the determination of the chemical or its metabolites in body fluids and assesses the exposure of the whole organism. Biological effect monitoring has been the primary focus point for many years and relies on markers (enzyme or functional capacity of the body or organ system) that can be related to the biological effect of the chemical exposed to. Biological monitoring of susceptibility is a more recent approach, which enables verification of whether an individual is particularly sensitive to the effect of a xenobiotic or to the effects of a group of compounds.

Biomarkers are becoming increasingly more important in toxicology and human health. They are exogenous substances, metabolites, and the product of an interaction between a xenobiotic and a target molecule or cell measured within a compartment of an organism.[2] However, the true target is usually not accessible and biomarkers of exposure are surrogate measures of something impossible to measure. Most biomarkers reflect primarily exposure or the effect of the exposure. However, there can be a continuous relationship between biomarker exposure and biomarker of effect. In Figure 1 the relation of events and biomarker classification as demonstrated by Albertini[3] illustrates clearly the importance of the progressive order of chemical exposure.

Bio-research over the years has concentrated on the development and validation of biomarkers that reflect specific exposures and permit the prediction of the risk of the disease in individuals and groups. Recent developments have concentrated on the identification of individual susceptibility to both cancer and non-cancer health effects as the result of certain chemical exposures on a long and short-term basis. Long-term or short-term toxic exposure to mercury and its alkyl constituents may lead to a

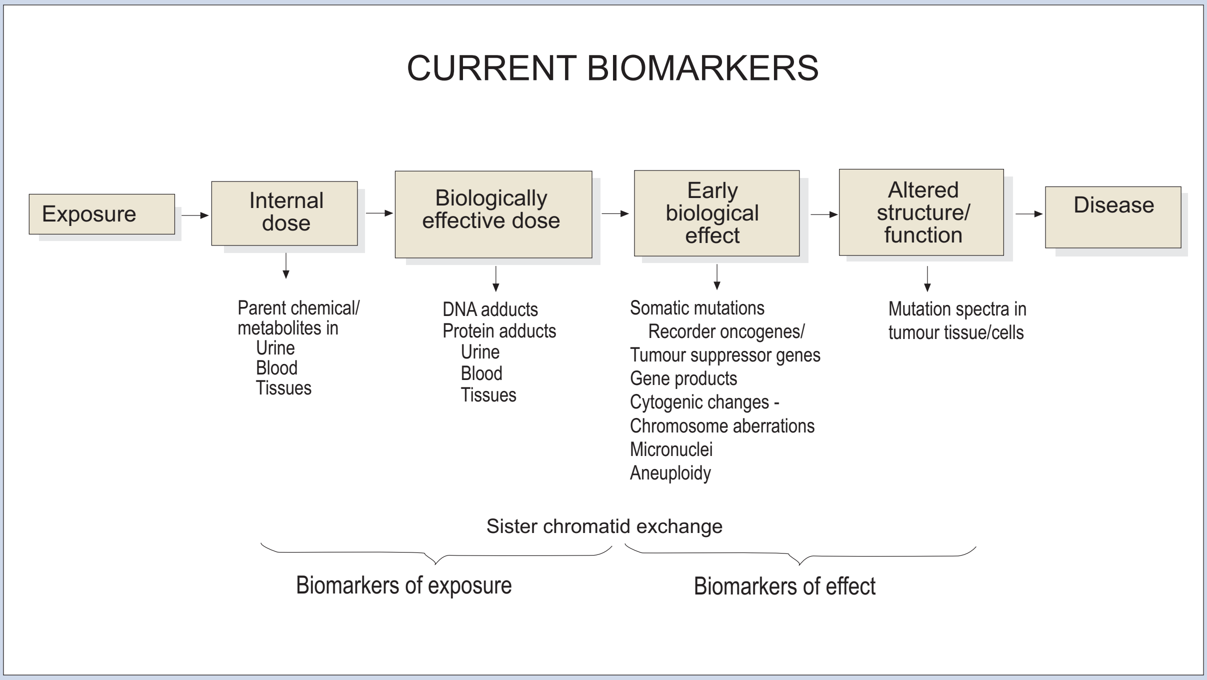

Figure 1. Relation of events and biomarker classification[3]

mechanism of action for neurotoxicity. These processes are complex and multifaceted and are demonstrated in Figure 2.

Knowledge of the mechanism of the different chemicals has become more relevant when completing occupational exposure assessment to chemicals. Moreover, the persistence of chemicals and their metabolites depends on the individual repair rate and the capability of subdivided cells to repair the impact of the exposure.[5] The kinetics of the description of the exposure chemical is thus of importance in respect to possible biological variability relative to exposure.[6] The examples in Figure 3 illustrate the metabolic path of different organic solvents (alcohol) and the preferred metabolite of measurement. Observe the different organic acid (formic and acetic acid formation) and the formation of additional solvent (acetone) when exposed to ethanol, methanol and isopropanol.

There are four main categories of biomarkers of exposure based on their biological half-life that should be remembered before rushing

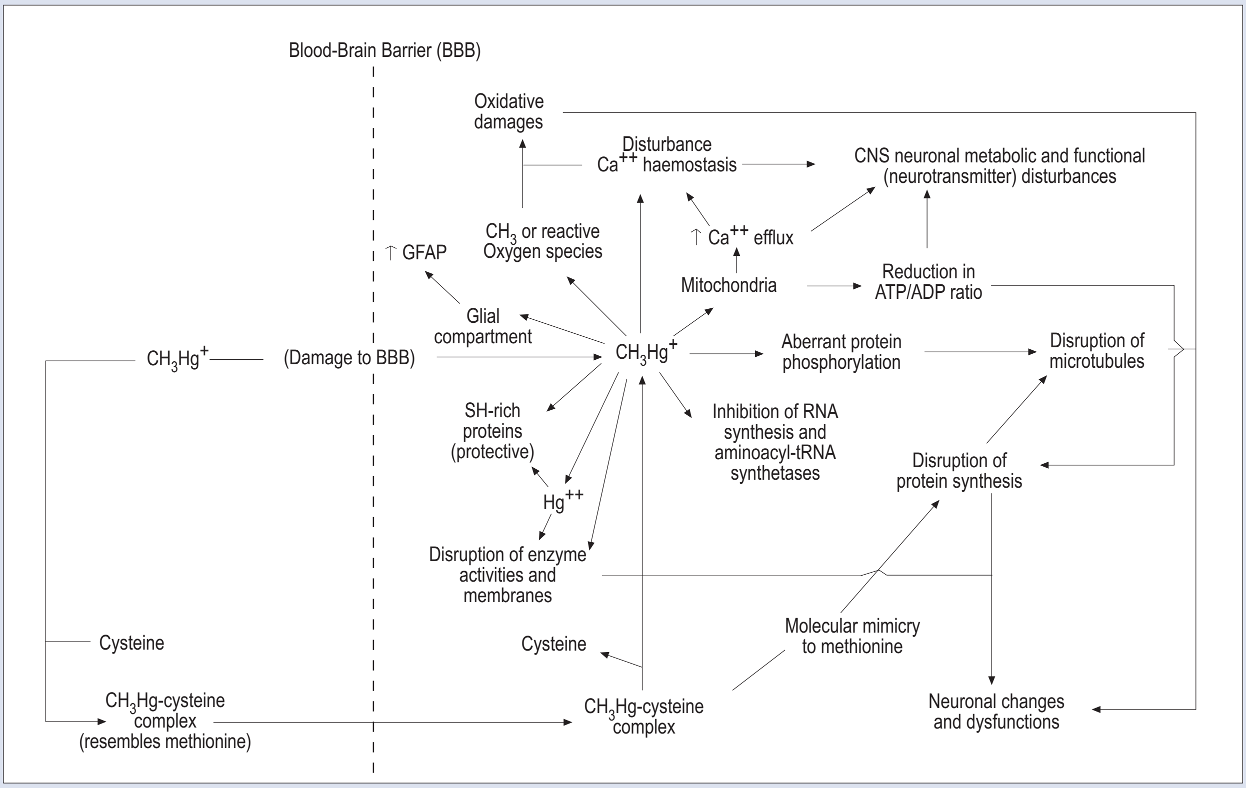

Figure 2. Neurotoxic mechanism of action of methylmercury[4]

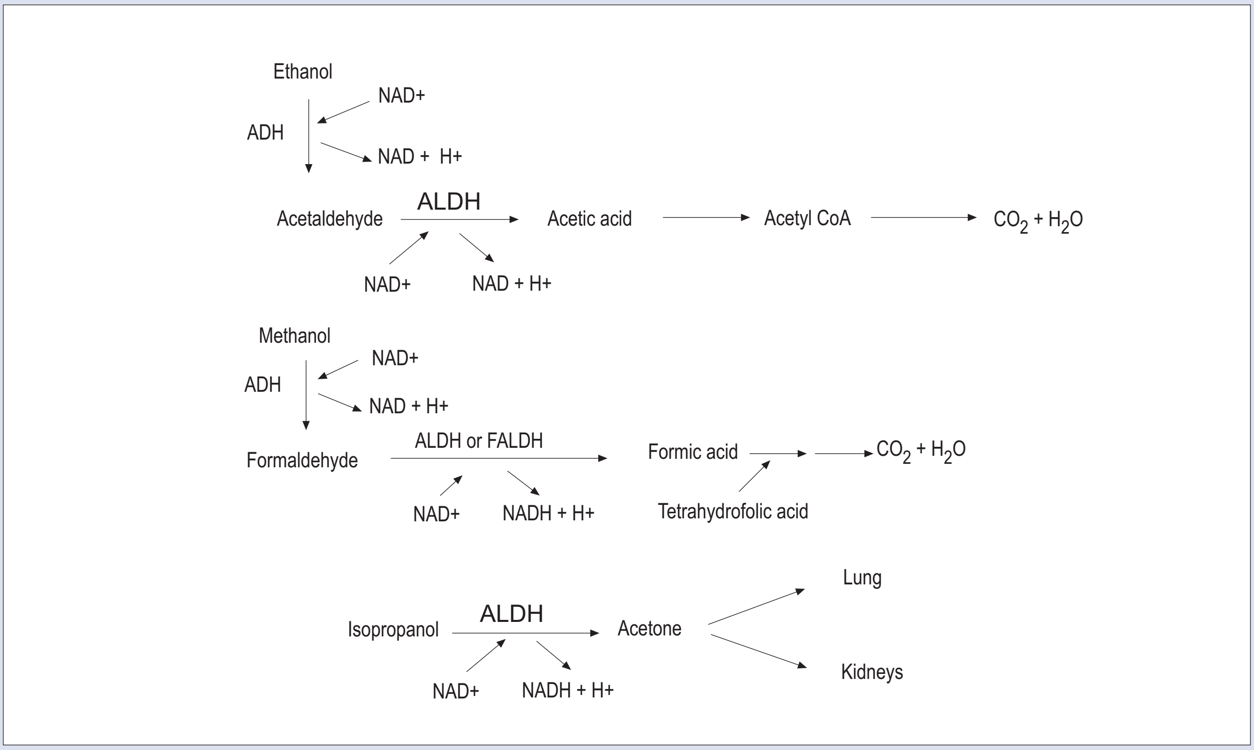

Figure 3. Different pathways of metabolism for the different alcohols

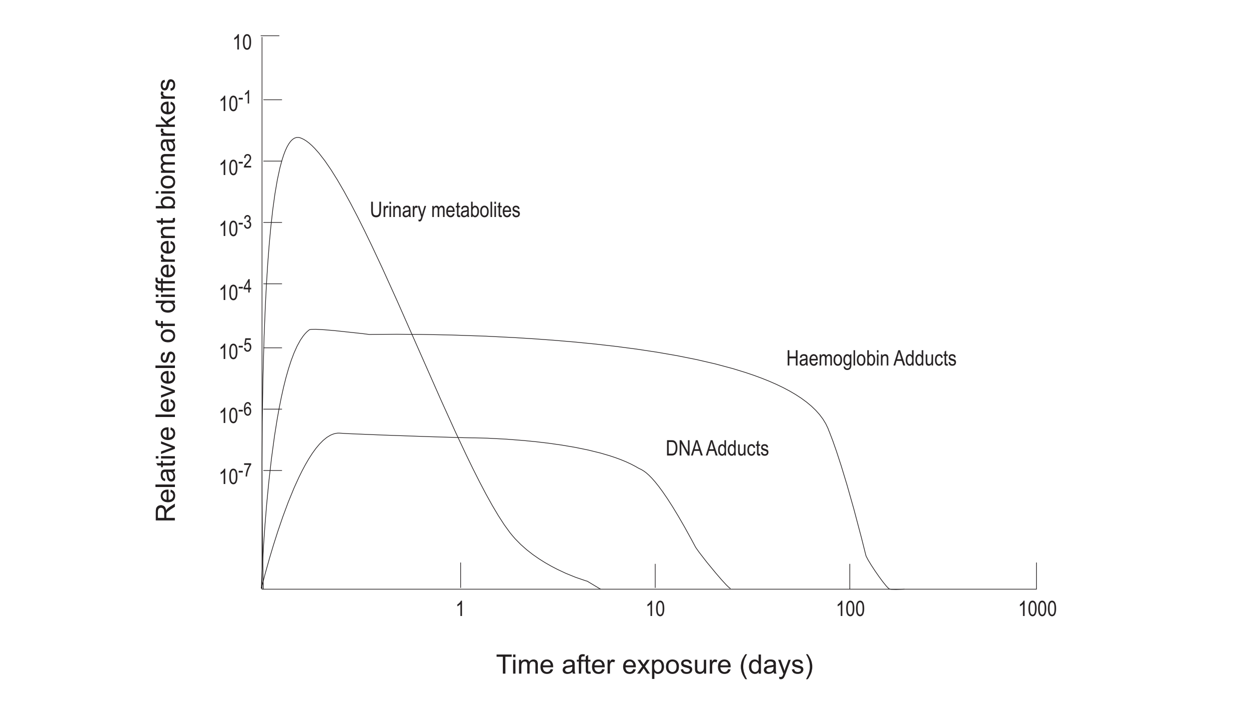

Figure 4. Time range for urinary metabolites, DNA adducts and haemoglobin adducts following a single exposure[9]

into the monitoring of hazardous chemical in bio-samples.

i) Very short: phenol measurement for benzene exposure.

ii) Short: 2,5 hexanedione measurement for hexane exposure.

iii) Long: heavy metal exposure, lead, calcium, mercury, as well as the adducts of DNA and haemoglobin for electrophilic compounds and the metabolites from certain chemicals.

iv) Very long: heavy metals in bone and polycyclic hydrocarbons in fatty tissue.[7]

Figure 4 demonstrates the half-life cycle of urine metabolites, DNA adducts and haemoglobin adduct following a single dose of exposure. Observe the relationship between the time intervals and the impact the different biomarkers have on the metabolic system, but remember that for chronic exposure the time range curve will be an indication of body-burden. Bio-monitoring in particular urinary metabolites may also be used in the risk characterisation phase to assist high-risk exposure groups. Biomarkers of effect can be used as part of health surveillance programmes for early diagnosis of exposure-related disease, but the application of biomarkers of effect is usually aimed at determining whether particular exposure is associated with early effects in the critical organ.[8]

Conclusion

No matter how the toxicologist and physician approaches this subject, the importance of having a good understanding of industrial chemistry, biochemistry, occupational toxicology and clinical toxicology is a prerequisite in determining the short and long-term effect of chemicals in the workplace. Current developments in analytical chemistry have opened new fields of research which allows the measurement of chemical compounds, their metabolites and DNA effects as a tool in the prediction of group or individual short and long-term effect on health as the result of hazardous chemical exposures.

To assist the physician and toxicologist in this process it is important for industry to build a reliable database of biomarkers measured. Historical data is very important as this might be the only way the physician and toxicologist can make certain deductions and recommendations, and prevent or limit health risk which may lead to occupational diseases. Risk assessment in its current state may suffer from shortcomings that may have been overlooked, if we as occupational practitioners do not adopt a more comprehensive and in some cases rational approach that would take all the risk factors of short and long-term exposures into account. The real breakthrough lies in detailed data capture both for exposure and human monitoring, the analysis and the interpretation of individual and group results.

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