For discussion
Assessment of risk by biological monitoring*

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ABSTRACT Variability between workers is reflected in differences in uptake, metabolism, and excretion of toxic substances, and thus individual response to toxic hazards. It is argued that biological monitoring takes account of these differences enabling individual risk assessments to be made. Risk, however, must be seen in terms of clinical and pathological changes—that is, estimated from morbidity and mortality rates—and so laboratory measurements need to be linked to epidemiological studies before they can be used to indicate acceptable or unacceptable uptake of toxic materials.

Industrial workers differ from each other in size, fitness, work practices, smoking habits, alcohol and drug usage, and nutritional state. There is also a significant genetic variability in the way they can metabolise toxic compounds. In considering the response of a group of workers to exposure to toxic material it is clear that they cannot be thought of as a group of genetically homogeneous rats from a well-designed toxicology study. Thus at a specified level of exposure to a toxic material any group of workers will show great differences in their uptake, absorption, metabolism, and excretion of that material. It should also be recognised that even if two workers have the same tissue level of a toxic material they could show differing responses because of either genetically different sensitivity to the material or because of antagonism or synergism by drugs, dietary constituents, and social poisons. Dietary habits affect the activity of hepatic enzymes concerned in the metabolism of foreign substances. Biological monitoring has the specific advantage that it can take account of these differences in uptake, metabolism, and response and therefore reflect the risk for an individual worker.

Blood lead measurements

At present there are few chemical hazards for which a risk assessment may be made from biological measurements. For most toxic materials insufficient data have been collected to relate laboratory measurements directly to disease presentations. There are, however, several studies relating blood lead measurements to clinical and laboratory findings. The relation between increasing concentration of lead in blood and physiological and pathological events is presented schematically in fig 1. The central block in this diagram indicates a spectrum of events applicable to any hazard—exposure, absorption, effect, harm, and disease. Under "effect" is listed inhibition of the enzyme δ-aminolaevulinic acid dehydratase. Although there has been speculation that accumulation of the substrate of this enzyme (δ-aminolaevulinic acid) may affect neurochemical systems, there is little evidence that the inhibition of the red-cell enzyme seen early in

Fig 1 Schematic representation of relation between concentration of lead in blood and onset of biochemical and clinical effects. From various sources.

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Lead absorption has any clinical effect. Similarly, initial increases in free erythrocyte protoporphyrin concentrations are thought to be without pathophysiological effect. Constipation and low grade abdominal pain, however, even if not contributing to mortality statistics, are not acceptable results of occupational exposure. Early and minor falls in haemoglobin (say, for example, from 15 to 14 g/dl of blood) are of little significance, but the chronic anaemia of lead poisoning is not acceptable. The lower scale is an attempt to indicate the concentration of lead in blood associated with the appearance of these changes. This simple model allows risk statements to be made for specific blood lead concentrations. Thus at a blood lead value of 3·7 μmol/l a worker has the risk of having a minor degree of anaemia, low grade abdominal pain, and some preclinical neurological changes.

It is important to emphasise here that a specific blood lead concentration (say 3·7 μmol/l—used in the example given in the preceding paragraph) cannot be equated directly with a specific atmospheric exposure. A worker may achieve a blood lead concentration of 3·7 μmol/l at relatively low air concentrations by disregard of personal cleanliness, and the raised blood lead concentration may reflect ingestion rather than inhalation. The lack of a direct relation between air levels and biological measurements has been taken as a criticism of biological measurement or as evidence that studies comparing the two sets of data have been inadequately performed. Neither of these criticisms is reasonable as will be shown in the succeeding paragraphs.

Inter-individual variation

Many studies have been reported in which the authors measure both personal exposure and a biological marker in an attempt to correlate these measurements. A typical study is presented in fig 2. Here Norseth² has presented measurements of exposure to styrene in the glass-reinforced plastic boat industry and the concentration of the major metabolite of styrene (mandelic acid) in the urine of the workers he studied. The range of values for mandelic acid excretion at any specific exposure level is such that it is impossible to make any judgments concerning exposure from individual biological measurements. Although better relationships than this have been reported, the spread of this data is typical for this type of study. If it is accepted, however, that biological monitoring data should allow for inter-individual differences in uptake, distribution, metabolism, and excretion, then this degree of variability is to be expected.

A measure of the degree of inter-individual variation in the overall process of absorption, distribution, metabolism, and excretion may be gained from studies in clinical pharmacology. In fig 3 the results of a study³ to show the relation between dosage of the drug propranolol and the concentration of propranolol in the plasma are presented. This particular study has been selected for discussion because the conditions of dosage and sampling were so well controlled—in total contrast to the conditions imposed on investigators studying exposure/metabolite relations in industrial settings. In the propranolol study exposure (dosage) was continuous, seven days a week, and measurements were not taken until the subjects were under pharmacokinetic steady-state conditions. There was a totally accurate measure of exposure; the nursing staff monitored the subjects while they were taking the tablets, and sampling was performed at a defined sampling time after the preceding dose. The residual variation is remarkably less than in the styrene/mandelic acid study of Norseth² but is still considerable. At a dose of 500 mg/day of propranolol plasma concentrations still range from 300 to 550 ng/ml. This is to be expected from various twin studies that have been reported. These have shown that there is a large genetic component contributing to individual plasma differences after administration of the same amount of drug (for instance, Vessell⁴). These genetically controlled mechanisms affecting plasma concentration of drugs are the same mechanisms as those controlling plasma concentrations of toxic chemicals and their metabolites.

In occupational medicine the most precise studies that have been performed are probably those using volunteers exposed to organic solvents in carefully controlled environments. Figure 4 shows the results from a study relating exposure to methylene chloride...
and its concentration in exhaled air. Although in this type of study the concentration of the organic solvent atmosphere is known precisely (measured continuously by gas chromatography and infrared spectroscopy), blood and breath concentrations still vary considerably at each dose level. This precision of exposure data cannot be obtained in industrial surveys, making exposure chamber data essential for defining inter-individual variation in response to organic solvent exposure.

The degree of biological variability in measurements taken from industrial, experimental, and pharmacological surveys does not invalidate the use of this type of measurement in protecting the workforce and in assessing the exposure of individuals.

For many drugs, measurement of the plasma concentration is the best indicator of the concentration of the drug at the site of pharmacological action and also of its toxicity.6 Apparently the spread of biological monitoring measurements at any fixed exposure gives a measure of the range of abilities of individuals to absorb, metabolise, and excrete the foreign chemical and, conversely, the likely toxicity in any individual.

Although plasma concentrations may relate directly to acute toxic effects, measurement of a foreign material or its metabolites in urine can give an integrated measure of exposure and uptake. For example, the measurement of trichloroacetic acid excretion on the fourth or fifth day of the working week provides a useful measure of trichloroethylene exposure.7 The relative value of any particular biological indicator—for instance, blood measurements, urine concentrations, and motor nerve conduction velocity—finally depends on its value as an indicator of risk. This cannot be determined by laboratory measurements alone; risk can only be estimated from clinical investigations and morbidity and mortality surveys. It was possible to use lead exposure as an example of a hazard where there is enough data to link laboratory measurement with risk assessment because of a wealth of studies in publications. Similar data are only rarely available for other chemical hazards.

An example of a laboratory measurement that cannot be related directly to risk is the determination of β2-microglobulin in the urine of cadmium workers.8 This protein is normally present in urine in small amounts, and an increasing excretion is evidence of early kidney dysfunction. There are,
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However, insufficient data to indicate whether an increased excretion of β2-microglobulin indicates risk of clinically significant renal damage. If it is assumed that any change in function after industrial exposure is not acceptable, then β2-microglobulin excretion may be a good indicator of excessive exposure. It would seem appropriate to collect prospective data to establish at what level a raised β2-microglobulin excretion has prognostic significance before using this measurement routinely as an early indicator of damage to kidney tissue.

The measurement of potentially carcinogenic chemicals and their metabolites can be used to indicate exposure and perhaps estimate dose; however, these measurements cannot be used to estimate risk. The role of biological monitoring here is to confirm that protective measures are functioning; individual workers do ignore safety procedures and resist the use of protective clothing. The appearance of the potential carcinogen or its metabolite in the urine of an individual worker indicates a change in work or personal practices.

Genetic differences

Genetic differences in chemical and drug metabolism may make a subpopulation of workers more at risk from a specific chemical hazard. There are several examples of genetically determined deficiencies in enzyme activity that increase susceptibility to toxic action. Recently it has been suggested that genetic differences in aromatic amine metabolism may be related to the incidence of bladder cancer. In all populations there is a proportion of people known as slow acetylators. This is a genetically determined trait, and the slow acetylators may be identified by their reduced ability to acetylate sulphamides. Studies from Denmark show that there is an excess of slow acetylators within the urban group of patients with cancer of the bladder. The authors suggest that this is related to an increased exposure to aromatic amines in the urban environment interacting with the slow-acetylator phenotype. Demonstrations of a slow acetylator state may therefore indicate a worker with an increased risk under certain conditions of exposure.

In any population certain individuals are at much higher risk from allergic sensitisation from either small molecular weight haptens or protein allergens. A detailed history of allergic disease at a pre-employment medical examination can indicate some individuals at high risk—for example, atopic individuals. Possibly immunological and genetic markers will be established to identify the worker who will become so highly sensitised to trace amounts of material that he has to leave that particular industry.

In the preceding discussion it has been argued that the variability among workers is such that for any controlled exposure individual workers will show great differences in uptake, metabolism, and excretion of a toxic substance. Differences in uptake, elimination, and response are reflected in differences in individual risk and the function of biological monitoring is to indicate risk on an individual basis. There is, however, another conclusion that needs to be drawn from this variability and it is that measurements made on workers cannot be used to monitor the environment quantitatively. Obviously, excessive absorption by a group of workers in one part of a plant can indicate a local problem, but in general biological measurements are not suitable for assessing environmental levels or the degree of compliance with specific limits. It has not been emphasised enough that environmental and biological monitoring are ways of investigating different problems and should be seen as complementary and not mutually exclusive procedures.

References

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