Methods for Estimating Risk of Chemical Injury: Human and Non-human Biota and Ecosystems
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Individual Exposure and Biological Monitoring

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ABSTRACT

Estimation of individual or collective exposure by biological monitoring is discussed with particular reference to multi-media pollutants. Examples are given of organic substances, metals and metal-like elements amenable to biological monitoring. Quantitative estimation of exposure requires knowledge of the relationship between the level of a chemical in biological media ('biological levels') and the magnitude of exposure. For single-medium pollutants with short biological half-life, adequate knowledge of these relationships can be obtained from short-term controlled exposure studies on humans, but the number of chemicals for which such data exist is limited. For long-lived substances, the feasibility of such studies may be enhanced by toxicokinetic modelling; this approach, however, requires an extensive verification. For multi-media pollutants, the levels of chemicals in biological media are functions of several variables which can only be estimated if adequate measurements in the appropriate media are at hand and transfer coefficients known. The experience with quantitative interpretation of biological monitoring data for multi-media pollutants is still very limited.

Biological monitoring is also used as a tool in predicting the likelihood of health effects, either in an individual or in a population. In this case the exact knowledge of exposure is not needed but instead adequate dose–effect and dose–response studies are required. The two ways of using biological monitoring data are based on different assumptions and may require different types of methodological developments.

1 INTRODUCTION

Since the beginning of modern environmental toxicology it has been understood that the likelihood of adverse health effects of chemicals depends on the magnitude of exposure. Measures of exposure and the permissible levels have been developed independently in various areas of environmental toxicology.

Thus, industrial toxicologists have developed methods for measuring and guidelines for interpreting the concentrations of chemicals in the air of working premises. Public health scientists have developed similar procedures for concentrations of some chemicals in the ambient air of inhabited areas and in drinking water. Food hygienists have concentrated on the levels of toxic substances in various foodstuffs.

In each of these areas, acceptable limits for the levels of chemicals in the respective media have been set on the assumptions that (1) there is no appreciable risk at levels below the limit values, and (2) at levels significantly exceeding the limit values, the risk may be great enough to justify action. Studies in industrial toxicology soon demonstrated that neither of these assumptions was entirely correct. Examples were found where sufficiently low concentrations of chemicals in the air of working premises did not secure the health of workers if chemicals could be absorbed through the skin (for example, aniline or benzidine) and if other exposure routes, such as drinking water or food, contributed appreciably to the total exposure (for example, lead). On the other hand, high concentrations in the air of working premises did not necessarily increase the risk, especially if the effective exposure time of the workers was short, or if personal protection had been instituted satisfactorily.

It became clear that the relevant factor to be monitored is the 'real' or 'effective' exposure, quantified in terms of doses absorbed daily through various routes, and possibly from various sources. In response to these findings, industrial toxicologists developed a practice called in the past 'exposure tests', and more recently referred to as 'biological monitoring'. Biological monitoring methods have been described in several manuals and monographs (see Teisinger *et al.*, 1956; Elkins, 1959; Dutkiewicz *et al.*, 1964; Gadaskina and Filov, 1971; Piotrowski, 1977; Baselt, 1980; Bardodej *et al.*, 1980).

More recently, environmental toxicologists have developed biological monitoring as a means for estimating 'real exposure' of the general population. Although this has been so far limited to only a few persistent chemicals such as lead, cadmium, methylmercury, DDT and others (see Friberg *et al.*, 1974; WHO 1976, 1977, 1979a), biological monitoring may become a new approach in preventive toxicology.

2 EXPOSURE: INDIVIDUAL, COLLECTIVE, INTEGRATED

Exposure may be estimated either on a collective or individual basis. The exposure of an individual can often be estimated from the general data on environmental contamination (such as air or food contamination) if other relevant conditions of exposure are known (such as the pattern of food consumption or physical activity). Biological monitoring can provide verification of such estimates by measuring the level of pollutants in the individual. Whether the results obtained can be finally interpreted in terms of exposure of any given

individual or have to be used for group or 'collective' exposure estimation, depends on the relationship between the attainable and the required precision of the whole test procedure. The same limitation applies to biological monitoring.

The term 'integrated exposure' is used here in its broadest sense. In industrial toxicology, the term 'integrated exposure' refers to the amounts of a chemical absorbed by various routes, such as lungs, skin and the gastrointestinal tract. In general environmental toxicology, it refers to the total amount of a chemical absorbed under occupational conditions by all routes and from ambient air, food, water and any other source. Procedures for estimating integrated exposure are difficult for a variety of reasons. When based solely on levels of environmental contamination (air, water, food), estimation may be unreliable when skin absorption or absorption from unmeasured sources plays a major role. For this reason, biological monitoring has become an important tool in estimating integrated exposure.

3 BIOLOGICAL MONITORING

Biological monitoring of chemicals was first developed in industrial toxicology as a method for estimating exposure of individuals. It was first applied to estimation of exposure to chemicals for which the routes of entry other than lungs, or sources of exposure other than the workplace, were not important, for example, benzene and trichloroethylene (Teisinger *et al.*, 1956). Some difficulties arose when Teisinger and his collaborators in Prague realized that these measurements, although using samples of biological media from individuals, cannot be interpreted in terms of individual exposure because of great individual variations of results at the same exposure level (air concentration). The concept of 'collective exposure test' was then proposed (Teisinger, 1969). On the other hand, there are examples where individual exposure can be measured by biological monitoring with sufficient precision (see Piotrowski, 1977).

In industrial toxicology, biological monitoring encountered the problem of estimating integrated exposure when substances could be easily absorbed through the skin, such as aniline, nitrobenzene, benzidine, parathion, dimethylformamide and others (Piotrowski, 1977; Lauwerys *et al.*, 1980). Obviously, the common denominator in biological monitoring of exposure by inhalation and through the skin are the doses absorbed by each route. The same may apply to any type of environmental exposure, provided that several conditions discussed in section 4.3 are fulfilled. The availability of procedures for biological monitoring is discussed below separately for organic chemicals and for metals and metal-like elements.

3.1 Organic Chemicals

Of thousands of organic chemicals produced in quantities that warrant toxicological interest, only a few hundred have been evaluated toxicologically to

the extent allowing industrial threshold limit values (TLVs) or maximum allowable concentrations (MACs) to be proposed. For about 10 % of these (some 50–60 substances) data exist on methods for biological monitoring (Table 1). The number of such chemicals has much increased over the past 15 years because of methodological developments, particularly in gas chromatography. Gas chromatography is applicable to a wide variety of organic chemicals, and it is both specific and sensitive. Whereas the older tests were mainly based on the analysis of metabolites in urine, more recent procedures often recommend the analysis of blood (or expired air for volatile compounds), and the original unchanged substance is usually determined. For several organic chemicals alternative procedures are now available, based on the determination of either the unchanged substance or its metabolites in the appropriate media (urine, blood, expired air). The degree to which results of such monitoring can be quantitatively interpreted

Table 1 Organic chemicals† for which methods of biological monitoring are available

Group	Chemical
Aliphatic	
hydrocarbons	2-methylpentane, 3-methylpentane, *n*-hexane
alcohols	methanol, ethanol, isopropanol
aldehydes	formaldehyde, acetaldehyde
ketones	acetone, butanone
chloroderivatives	methyl chloride, methylene dichloride, chloroform, carbon tetrachloride, 1,1,1-trichloroethane, vinyl chloride, trichloroethylene, tetrachloroethylene
others	*N*-methylformamide, dimethylformamide, hydrogen cyanide, acetonitrile, acrylonitrile, carbon disulphide
Cyclic and aromatic	
hydrocarbons	methyl-cyclopentane, cyclohexane, benzene*, toluene*, xylenes*, mesitylene, ethylbenzene*, isopropylbenzene, styrene, methylstyrene
chloroderivatives and phenols	phenol, chlorophenols, pentachlorophenol, chlorobenzene, *p*-dichlorobenzene, HCH, HCB, PCBs, DDT, 2,4-D, 2,4,5-T, aldrin, dieldrin, endrin, chlordane, chlordecone, hexachlorophene
nitro- and amino-derivatives	nitrobenzene, aniline, benzidine*, dinitro-*o*-cresol
organophosphorus compounds	parathion, fenitrothion, diazinon
Others	furfural, carbaryl, paraquat

* One asterisk (*) denotes a substance for which adequate metabolic studies in man are available.

† A tentative list based on data from Piotrowski (1977) and Baselt (1980) and on a survey of individual reports not listed in the list of references.

differs considerably for the various chemicals listed in Table 1. A few substances, such as benzene, toluene, trichloroethylene and styrene, have received most attention and the number of reports on individual substances ranges from about 100 to one or two. For many substances metabolic studies in man have never been performed. The applicability of many procedures at low exposure levels (such as occur in non-occupational exposure) is dubious.

3.2 Metals, Metal-like Elements and their Compounds

Industrial toxicologists were the first to develop methods for biological monitoring, most extensively for lead. Much effort has also been devoted to the monitoring of mercury, chromium, arsenic and vanadium. More recently, in non-occupational toxicology, biological monitoring has been developed for lead (WHO, 1977; Friberg and Vahter, 1983), methylmercury, cadmium (Friberg *et al.*, 1974; Friberg and Vahter, 1983) and to a lesser degree for arsenic (WHO, 1981). Other metals have been monitored only sporadically (Table 2).

Table 2 Metals and metal-like elements for which methods of biological monitoring are available; based mostly on data of Baselt (1980)

antimony (U); arsenic (U, H); beryllium (U); cadmium (B, U); chromium (U); cobalt (U); copper (B, U); lead (B, U); lithium (B); manganese (U); mercury (B, U); methylmercury (B, H); selenium (U); thallium (B, U); tin (U); uranium (U); zinc (U)

Symbols: B, blood; U, urine; H, hair

A variety of media and procedures have been used in biological monitoring of metals and metal-like elements. The early data refer mostly to urine; apart from other advantages, urine monitoring may be related in a relatively simple fashion to exposure. Assuming a steady-state condition, the average daily dose can be computed from the daily excretion in urine, if the ratio urine/faeces is known.

Blood analysis has recently replaced urine analysis in routine monitoring. There seem to be two principal reasons for this change:

(1) modern analytical techniques, particularly atomic absorption spectrophotometry, make such determinations possible with small blood samples, and
(2) the concentration of an element in blood seems to be a better basis for the evaluation of health risk.

The usefulness of hair monitoring has been examined (Jenkins, 1979). The analysis of hair has gained recognition only in a few cases where the analytical determination is sufficiently reliable. One advantage of hair analysis is the possibility of estimating not only the average dose rate, but in some cases to derive a dose rate–time function which may be used in more sophisticated approaches to exposure estimation, as for methylmercury (see Piotrowski and Inskip, 1981;

Piotrowski and Buchanan, 1982). A special case is the analysis of tissues not routinely available for analysis, which may be obtained as autopsy samples. An example from the Global Environmental Monitoring System (GEMS) programme is cadmium (WHO, 1979b), for which the most reliable estimate of lifelong exposure may be obtained from its level in the kidneys. Monitoring of autopsy samples is used as a measure of exposure of groups of individuals and population segments (Friberg *et al.*, 1974; Friberg and Vahter, 1983).

4 BIOLOGICAL MONITORING AND EXPOSURE ESTIMATION

The need for estimating integrated exposure to chemicals has resulted in a high demand for biological monitoring methods. In response to this demand, the number of chemicals amenable to biological monitoring has increased, and so have the difficulties in interpreting the results. The three problems of biological monitoring discussed below throw some light on inherent difficulties.

4.1 Biokinetic Properties of Chemicals

In general, the application and interpretation of biological monitoring depend on the biokinetic properties of the substance. The two extreme cases are as follows.

(1) The half-life of the chemical in the body is sufficiently short for the biological level to reflect the actual exposure of a given day. In this case, biological monitoring is useful in industrial toxicology even if the measured levels fluctuate largely from day to day, depending on the days of exposure and time of sample collection. The use of biological monitoring in environments other than industry, where the source of exposure has not been identified, could give misleading results.
(2) The half-life of the chemical is very long, allowing for substantial accumulation of the substance. Here, the fluctuations of levels from day to day and within the day are small and, therefore, the exact location of the source of exposure is not necessary. For this reason, biological monitoring is used for exposure estimation in the general environment mainly for persistent chemicals.

In fact, most chemicals do not belong to either of these two extreme classes, having neither very short nor very long half-lives. For substances such as nitrobenzene, biological levels depend on both the actual exposure during the data and on the past exposure over the last week or so (Piotrowski, 1971).

None of the situations is usually clear enough to allow proper interpretation of the data without adequate knowledge of the biokinetic properties of the substance. Even with substances having essentially a short half-life (such as toluene), the deposition and accumulation of a small fraction in lipoid tissues may

still occur and this may be revealed better by some monitoring procedures than by others (for example, toluene in blood as opposed to hippuric acid in urine) (see Piotrowski, 1977; Konietzko *et al.*, 1980). On the other hand, with substances having long half-lives there are cases where a 'fresh' dose influences temporarily the blood level to an unexpected degree, for instance, methylmercury (Kershaw *et al.*, 1980).

4.2 Biological Level as a Function of Exposure

The analysis of biological samples provides the biological level of a chemical (B); however, the quantity of interest may be the level of exposure (E) which is the independent variable in the equation:

$$B = f_o(E) \tag{1}$$

In its general form, equation (1) applies to all situations, whether in steady state or not. Depending on the use of monitoring data, exposure may be defined in a variety of ways. For instance, in industrial toxicology, for substances absorbed by one route only (airways), exposure may simply be the concentration of the chemical in the air. In measuring the integrated exposure, however, exposure must be defined in terms of dose rate, i.e. the dose absorbed by the body in unit time. In exposures by way of the gastrointestinal tract, the dose rate must be defined even more strictly in terms of intake rate (I) and uptake rate (U).

In biological monitoring, two stages must be clearly distinguished: (1) when equation (1) is being established, and (2) when exposure is being estimated from the monitoring data and equation (1).

If equation (1) is to be used for single-route exposure, the form of f_o may be determined either under conditions of controlled exposure of volunteers, or by using properly selected field data. Some controlled exposure studies are usually necessary in any case in order to obtain information on biokinetic properties of the chemical. Investigations of this type have been performed in several laboratories, especially for application in industrial toxicology, and for short-lived organic chemicals. Similar studies with long-lived chemicals are much more difficult, as they have to continue until a steady state is achieved. Such trials have been performed in the past for lead (Kehoe, 1961), DDT and aldrin (for a review see Piotrowski, 1977). Of necessity, long-term studies involve several problems, both ethical and technical.

Difficulties inherent in the long-term studies justify attempts to determine the form of equation (1) by computation, using data from short-term tests. This is fairly easy if B is directly proportional to E but examples are known where the best fit is obtained by using some power function, as for DDT (Durham *et al.*, 1965) and lead (WHO, 1977).

Assuming direct proportionality and expressing exposure in terms of intake

rate (I), equation (1) takes the form:

$$B = f \cdot I \tag{1a}$$

where f is a coefficient of proportionality, which may be the product of several fractional coefficients that may be either determined or computed from data obtained from short-term tests. In the most general case

$$f = \alpha \cdot \delta \cdot \mu \cdot \varepsilon \tag{2}$$

where the individual fractional coefficients express properties with regard to accumulation (α), body distribution (δ), metabolic yield (μ), and fractional uptake (ε). So far, examples can be given where the procedure has been much simplified by using only one or two of these fractional coefficients. An interesting example is methylmercury. Using data from single dose experiments with labelled mercury, coefficients α and δ could be computed. For this compound uptake equals intake, and the equation refers to unchanged substance, i.e. $\varepsilon = 1, \mu = 1$ (see WHO, 1976; Piotrowski and Inskip, 1981). It has to be emphasized that the computational techniques for establishing the form of equation (1) for steady-state conditions of long-lived chemicals are now in very early stages of development. The assumptions made in such computations require extensive study.

Whatever the outcome of these studies, one has to realize that biological monitoring alone, if not combined with information on exposure, leads only to comparative data, the usefulness of which is limited.

4.3 Integrated Exposure*

Biological monitoring for estimating integrated exposure by various routes of entry is based on an assumed equation:

$$B = f_a(E_a) + f_b(E_b) + f_c(E_c) \tag{3}$$

where 'the biological level' (B) integrates exposures (E_i) by routes i = a, b, c. In this general form, exposures E_a, E_b, E_c represent different variables and therefore a solution can be found if a set of three equations can be established using additional data. Still, difficulties may be encountered if the fractional functions f_a, f_b, f_c are not constants (for an example see WHO, 1977).

The equation becomes much simpler if there are only two routes of entry (f_a, f_b are constants), and if we do not need to distinguish between the intake and uptake, i.e. if intake is equal to uptake, $\varepsilon_a = \varepsilon_b = 1$. Assuming that the other

* Exposure by all routes

fractional coefficients in equation (2) are independent of the route of entry,

$$B = f(I_a + I_b) \tag{4}$$

where the sum $(I_a + I_b)$, which is equal to $(U_a + U_b)$, is a measure of integrated exposure.

The simplified situation expressed by equation (4) may be typical of industrial exposures for some organic chemicals, where the two routes of entry are commonly the airways and the skin. Here for each of the routes, the uptake rate may be equal to the intake rate, and the three fractional coefficients α, δ, μ are independent of the route of entry. At least one example can be given where this hypothesis has been verified by controlled exposure studies with volunteers either by inhalation or by dermal application of aniline (see Piotrowski, 1977). In most cases, however, where the above principle is applied, the coefficients are determined by using one route of exposure (inhalation), and it is assumed that they are valid for the other route as well. In certain cases, some indirect indicators point to the correctness of this assumption. However, it is not certain that the assumption of equal fractional coefficients for two routes of entry is valid universally; in particular, it is disputable if the metabolic rates and metabolic products of organic chemicals are always independent of the route of entry: each site (lungs, skin, intestine) has mechanisms of biotransformation which are independent of the processes that occur in the liver (see Bend and Hook, 1977). The more general situation, where the fractional coefficients differ depending on the route of entry, may be illustrated by a case, where $U \neq I$, and $\varepsilon_a \neq \varepsilon_b$; equation (4) then takes the form:

$$B = \alpha\delta\mu\,(\varepsilon_a I_a + \varepsilon_b I_b) \tag{5}$$

which can be, in principle, solved for both independent variables I_a and I_b if one of the two terms can be estimated separately; however the variability of uptake coefficients may introduce an additional difficulty. The above reasoning shows that the interpretation of biological monitoring data for multi-media pollutants is not a simple task. The situation calls for extensive studies addressed to selected key questions. It still remains to be decided whether exposure of a subject to multi-media pollutants can be adequately evaluated by biological monitoring.

5 BIOLOGICAL MONITORING FOR HEALTH EFFECTS

The 'biological level' of a chemical reflects the exposure of an individual (or a population), and it is in turn reflected in adverse effects which may appear in the same individual (or population). The interpretation of biological monitoring data may, therefore, aim at predicting health effects directly, i.e. not involving

estimates of exposure as discussed in section 4. The predictions can be made either for individuals or populations.

Such estimations for individuals use the so-called 'dose–effect relationships' that are established from studies of several individuals in whom both the 'biological level' of the chemical and the selected quantifiable health effects are measured simultaneously. Although the concept is theoretically sound (see WHO, 1978), there are few data to confirm it.

The predictive value of biological monitoring for health effects in populations is based on the so-called 'dose–response relationship'. This concept, derived from studies of acute toxicity, was first used for chronic toxicity in humans of methylmercury (WHO, 1976) and was then adopted for metals (Nordberg, 1976). The concept, however, has not yet been generally accepted.

A detailed discussion of the use of biological monitoring for the prediction of health effects is beyond the scope of this paper. Attention has only been drawn to the two possible applications of biological monitoring, for evaluating exposure on the one hand and for predicting health effects on the other.

The 'biological levels' of chemicals represent the logical link between external exposure and health effects in the population. The two ways of interpreting the results of biological monitoring are, therefore, not exclusive. On the contrary, they complement each other in the process of environmental assessment. However, depending on the intended use of monitoring data, the methodology of biological monitoring may be developed along different lines. If resources are limited, the priorities have to be determined; these may be different in various sectors of environmental toxicology.

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