

*2 Methods for Estimating Exposure to Chemicals**

2.1 INTRODUCTION

Exposure is a basic concept in toxicology. Without adequate exposure data it is virtually impossible to make a reliable estimate of potential damage to human health and non-human biota attributable to the presence of chemicals in the environment.

For regulatory purposes, exposure is usually defined as the concentration of a chemical at the external surface of the target organism. This definition has the advantage of simplicity. However, the contact between a chemical and the target organism, which determines the effects, is far more complex than this definition might suggest. As exposure always involves time, either explicitly or implicitly, the following definition seems more appropriate (UNEP/WHO, 1977; see also WHO, 1982; Miller, 1983):

'The exposure to a given pollutant is a measure of the contact between the pollutant and the outer or inner (e.g. alveolar surface or gut) surface of the human body. It is usually expressed in terms of concentrations of the pollutant in the medium (e.g. ambient air and food) interfacing with the body surfaces. Once absorbed through body surfaces, the pollutant gives rise to doses in various organs or tissues. Doses are measured in terms of concentrations in the tissues. Records of exposure and dose should include an indication of the time and frequency at which an individual is subjected to them.'

For man and terrestrial mammals, the important interfaces between the organism and the environment are the skin and the epithelial linings of the respiratory and digestive tracts; for fish, the digestive tract and the gills; for terrestrial plants, the stomata, the leaf surface and the root; for aquatic plants, the stems and the leaves (see Butler, 1978). These interfaces are often called routes of exposure. Since it may be difficult to measure the concentrations at all the pertinent interfaces, interface concentrations are usually estimated from the

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average mass concentration of the chemical in the relevant compartments of the environment such as air, water and food.

When exposure occurs at an internal interface such as the epithelial lining of the respiratory or digestive tract, it has to be estimated from the intake (or rate of intake), i.e. the amount of a substance inhaled and/or ingested. Intake depends both on environmental and physiological variables.

Biological effects of chemicals are better correlated with 'dose' than they are with exposure or intake. 'Dose' has been defined as the amount or concentration of a substance at the site of effect, that is, where its presence causes a given effect (whole organism, organ or tissue) (see for example, Nordberg, 1976, or Butler, 1978). The level of exposure (or dose) determines the effect but the way in which exposure or dose is distributed may also determine the type and magnitude of the effect. There is a whole spectrum of concentration-time-effect relationships, which depend on the physical and chemical properties and toxicity of the chemical involved (see, for example, Piotrowski and Buchanan, 1982). For some chemicals, the instantaneous or peak concentration in the target organ determines the likelihood and the type of effect which may be immediate and of short duration; immediate but of long duration (chronic); delayed and of short duration; or delayed and chronic. For other chemicals some effects may result from repeated or continued delivery of the agent to the target organ or tissue. These effects may again be either of short or long duration, occurring after short or long delay and reversible or irreversible.

In some cases, the magnitude of the effect is related to the level of exposure or dose (graded effects). Some effects do not show gradation; they either do occur or do not occur (quantal effects) and their incidence (called 'response' by some authors, see Nordberg, 1976; WHO, 1978) and not their magnitude is a function of the exposure or dose.

When assessing the effects of releasing chemicals into the environment, the possibility of their continued presence in the environment and potential risk for future as well as present generations have to be considered. Modelling (see Miller, 1978) and exposure commitment analysis (see Barry, 1979; O'Brien, 1979; Bennett, 1981) are useful approaches to estimating future exposures and their consequences. Exposure commitment is defined as the integral of concentration in a compartment over infinite time:

$$E_i = \int_0^{\infty} c_i(t) dt \quad (2.1)$$

where c_i is the average mass concentration in compartment i at time t . Exposure commitment is measured in units of mass concentration multiplied by time, for example, $\text{mg} \cdot \text{m}^{-3} \cdot \text{years}$.

2.2 IDENTIFICATION AND ASSESSMENT OF SOURCES OF ENVIRONMENTAL CHEMICALS

Exposure assessment begins with the examination of the total input of a chemical into the environment, and this involves identification and qualitative and quantitative description of sources of chemicals. For local problems, the actual amount involved in a given activity is important. If pollution is more widespread, the analysis requires consideration of the chemical and physical form of the substance, total amounts, patterns of distribution, use and disposal (including the possibility of spills, dissipative uses, and recycling) and routes of entry into the environment (Butler, 1978).

The total amount of a substance produced, either in a particular geographic region or globally, is in many cases not easy to obtain. In addition, some highly toxic organic synthetic compounds are not produced deliberately but occur as impurities in more or less innocuous products (see Holdgate, 1979). Natural sources may dominate for certain substances, especially metals. Some environmental pollutants may also originate in natural sources from which they may be released when such sources are exploited. For example, the main source of environmental pollution by mercury related to human activity is now the combustion of fossil fuels which generally contain mercury as an impurity in concentrations of less than one part per million (WHO, 1976). The same is true for some other elements, for example, vanadium (NAS/NRC, 1974).

Global release rates are notoriously hard to estimate (Miller and Buchanan, 1979). Thus, for many substances even the total amounts available for possible environmental discharge are not accurately known. Since several thousand substances exist in amounts adequate to produce widespread environmental pollution (Korte, 1977), it is surprising that such a level of uncertainty exists in regard to this basic information. Some of it is now being accumulated (IRPTC, 1978, 1979; Ott *et al.*, 1978); however, additional data are still required for a large number of natural and manufactured substances.

Another problem is to predict the physical and chemical form in which a substance would be released and whether it would be released at all. If the release is a vapour or a compound bound to very fine particles, environmental transport over long distances is likely to occur (Whelpdale, 1978). If the release is an organic compound or an element chelated to organic substances, bioaccumulation and food-chain magnification are to be expected (Jaworski, 1979).

2.3 APPROACHES TO EXPOSURE ESTIMATION

Exposure estimation is based on a variety of techniques which, in order to be effective, must be well coordinated. Modelling and monitoring are two of the main techniques used; in addition, such techniques as laboratory and field testing, examination of human activity patterns and methods based on chemical characteristics may be involved.

Two different approaches to exposure estimation are in general use. For major environmental pollutants of concern, such as metals (for example, Pb, Cd, Hg), common atmospheric pollutants such as SO₂, CO, NO_x, pesticides and some persistent organic compounds (for instance, polychlorinated biphenyls) exposure estimations have largely been carried out through a combination of environmental and biological monitoring and modelling. Even for these widely studied pollution problems, exposure estimates are usually far from reliable. For example, for lead there is still considerable controversy about the relative contribution of emissions from motor vehicles. The environmental fate of even well-studied pollutants is often poorly understood. Yet this is vital for the establishment of emission controls to achieve acceptable exposure levels.

As far as the actual measurement or estimation of exposure is concerned, the situation is uneven. For substances such as Pb, Cd, Hg and some organochlorine compounds, analysis of biological samples (bioanalysis) may provide a good measure of exposure. However, bioanalysis cannot be used to estimate exposure to pollutants such as SO₂ or NO_x. It is also recognized that for these airborne substances ambient monitoring provides a poor measure of individual exposure. Several pilot projects are now under way to measure actual individual exposure to air pollutants and its dependence on human activity patterns, and to correlate the results of these measurements with the results of ambient monitoring (WHO, 1982).

Numerous chemical notification schemes now in operation are another more recent approach to exposure estimation. As these schemes deal mainly with new chemicals, the approach is of necessity predictive. Such exposure estimations rely mainly on laboratory determination of physicochemical properties and degradation and accumulation processes, and on knowledge of the use, emission and disposal patterns and characteristics of populations likely to be exposed.

In practice, the actual estimation procedure will depend on a large number of factors and there can be no detailed prescribed procedures: each estimation must be geared to the specific situation. Thus, the estimation is either carried out at the premarketing stage or after the chemical has been released or used. For premarketing decisions, predictive estimations are required. These are largely based on laboratory and microcosm tests, on basic physicochemical properties and on the study of similar chemicals.

The required precision of exposure estimates depends on the amount produced and released, the likely size of the exposed population and the type of biological effects that may occur. A major factor in deciding on the required precision of exposure estimation is the 'potential for exposure' which increases in the following order:

- chemicals used only as process intermediates
- chemicals used in closed systems
- chemicals in consumer products
- chemicals dispersed in the environment.

Exposure estimation for chemicals mainly used in consumer products relies primarily on the knowledge of use patterns and consumer habits. Estimation for dispersed substances requires evaluation of environmental pathways and transfers between environmental compartments. In many cases, the chemical of interest may fit into more than one of these categories (for example, lead is both used in consumer products and emitted into the environment).

The characteristics of the population exposed have a major influence on the type of exposure estimate required. As regards human targets, we are generally concerned with one or more of the following types of populations:

- occupationally exposed groups
- consumers
- the most highly exposed groups in the general population
- groups of susceptible individuals
- general population.

While in many cases the problem of estimating or measuring population exposure is similar for the various groups, the difficulties in establishing the essential links between all sources and exposures becomes progressively more difficult as one goes down the list.

The other main consideration is whether one tries to estimate individual or population exposure. Predictive exposure estimates deal primarily with average population exposure. Environmental monitoring and modelling are used for estimating population exposures, whereas different forms of biological monitoring deal with individuals or groups of individuals.

One important task in the development of exposure estimates will be to link the population to be assessed with individual exposure estimates. In many cases population averaged estimates may pinpoint groups from which individuals can be selected for the more expensive biological monitoring programmes.

Exposure estimations often require considerable financial and manpower resources. It is, therefore, vital to specify clearly the purpose for which the estimation is to be made. Within the risk estimation process itself, exposure estimations may be required in support of one or more of the following objectives:

- hazard* identification
- hazard ranking
- hazard estimation.

However, exposure estimates are also required for other purposes which include:

- demonstration of compliance with regulations

* There is no generally agreed definition of 'hazard' associated with a chemical. The term is sometimes used to indicate the likelihood that a chemical will cause harm under the conditions in which it is produced, used or disposed (see WHO, 1978).

- support of research programmes, in particular epidemiological investigations
- support of modelling activities.

2.4 ENVIRONMENTAL TRANSPORT AND DISTRIBUTION

2.4.1 Environmental Modelling

The basic concepts and processes of cycling of trace substances in the environment are reasonably well understood, and relevant models have been developed to describe their environmental behaviour. Many models have been formulated to describe the movement of radionuclides released from nuclear installations or from atmospheric nuclear tests. These methods are generally applicable to airborne substances present in particulates or as gaseous pollutants. There are atmospheric dispersion models, aquatic transport models, and food-chain and ecosystem models (see Miller, 1978).

More than one model may be required in conducting an exposure estimation for a chemical. For example, air dispersion or aquatic transport models may be applied to the initial movement of the chemical from the sources to the point of interest. Food-chain and other more local transport models may then be used to determine further transfer of the chemical to the receptor.

Modelling begins with the specification of the compartmental arrangement which reflects the system components. Only as much detail as may be essential is introduced. Simplified models have advantages, and increasing the complexity is justified only for substantial improvements in reliability of results.

Models can be broadly classified either as time-dependent or time-independent. Time-dependent models outline the short-term kinetic behaviour of a chemical substance in the environment. First-order kinetics is generally assumed, and a system of differential equations describes the changes in compartment contents. Many parameter values are required for this type of model, but the output evaluation is most complete with amounts and transfer rates given for all points and at all times (Drake and Barrager, 1979).

A time-independent description of the behaviour of a chemical can be based on more limited data. In this case, the objectives are to determine the partitioning of the chemical in pathway compartments and to estimate the total amounts which ultimately reach the receptor. The relationships between compartmental amounts are expressed as the ratios at steady state, called concentration factors. The time-independent approach is often referred to as the concentration factor method.

An expression which is useful in describing the environmental behaviour of chemicals is the time integral of concentration. For transfers of trace substances between environmental reservoirs which can be described by linear first-order kinetics, the integrated concentrations in successive compartments, and also integrated fluxes (cumulative intakes to compartments), maintain constant

relationships. The ratios of integrated concentrations per unit release of a chemical substance define the transfer factors for movement between successive compartments. The integrated concentrations reflect the accumulation in the compartment or transfer of the substance through a compartment. The integral covering the entire period of the presence of the substance in the final compartment is termed exposure commitment (Barry, 1979; see equation 2.1). For a given release, this is a useful measure of the possible long-term transfer of a chemical through an environmental region.

In applying general models to specific chemicals, appropriate values must be assigned to the various parameters, and this is the major difficulty. The physical, chemical, biological and interaction factors must be selected from a wide range of possible values. Due to inherent variabilities and incomplete data bases, particularly for new chemicals, uncertainties in exposure evaluations cannot be avoided.

2.4.1.1 Air Dispersion Models

In the local region of release, dispersion models based on the Gaussian diffusion equation are most commonly used. Dispersion estimates can be made for a variety of meteorological conditions such as windspeeds (Pasquill, 1974). A particular result depends on constant wind and stability conditions and, therefore, there are limits on time and distance validity. Generally, predictions are considered reliable only within a few tens of kilometres from the source.

Trajectory models may be used to estimate the dispersion of substances to greater distances (Nordo *et al.*, 1974). These models may be quite complex, requiring large computer capacity and must be backed by detailed wind data. However, account can be taken of a wide variety of changing conditions and of complex terrain.

It is also necessary to account for various removal processes from the plumes and for chemical transformations which may occur during transport. This may be done by estimating effective source strengths or by estimating depletion at various stages of the transport. Knowledge of chemical kinetics is required for reactive gases and aerosols. Deposition of particulates occurs by precipitation and by impaction on the underlying surfaces.

2.4.1.2 Aquatic Transport Models

Aquatic transport of chemical substances is governed by general water movements and by sedimentation processes. Models are categorized according to the type of water bodies into which chemicals are released (rivers, lakes, estuaries or coastal areas) (see, for example, UNSCEAR, 1982). It may be assumed that relatively rapid mixing occurs in the receiving water volume or that equilibrium is

achieved. Otherwise, flow characteristics can be modelled if hydrological information is available (see Imboden and Gächter, 1979).

An important input of chemicals to aquatic systems is provided by the surface run-off from soils to lakes and streams and the downward penetration through soils to groundwater (Freeze and Cherry, 1979). Downward migration of chemicals in soils is due to leaching with rainfall or irrigation water. Factors affecting the movement comprise solubility, soil properties, including potential for adsorption to soil minerals or organic material, and water influx (see, for example, Lester *et al.*, 1975; Cameron and Klute, 1977). Chemicals soluble in water and poorly adsorbed by soil components are the most mobile. Downward movement occurs in preference to surface run-off until the surface layer is saturated.

Modelling of migration of chemicals in groundwater (Mihram, 1973; Duguid and Reeves, 1976) depends on acquiring hydrographic information for the specific location. It may be particularly important to determine migration times, dilution effects and amounts returned to drinking water sources.

2.4.1.3 Food-chain and Ecosystem Models

Transfers along terrestrial and aquatic food chains are represented as compartmental sequences with transfer factors or concentration ratios expressing the relationships at steady state. Several stages in the modelling may be identified, for example, soil-pasture grass-cow-milk-man. An overall transfer in a single step may also be evaluated, such as in aquatic models in which the concentration factor from water to aquatic organisms is used. Linear models may also be formulated to describe food-chain transfers. The interlinking transfer rate constants must be evaluated; the solution then gives concentration variations as a function of time (see Miller, 1978).

Ecosystem theory, involving examination of aspects such as stress, stability, energy fluxes, nutrient cycles, carbon metabolism and trophic structure, is being applied in models to describe chemical pollutant behaviour in specific environments. Availability of information is the major limiting factor in direct applications of large-scale ecosystem models.

2.4.1.4 Chemical Transformation and Speciation

Models for the behaviour of chemicals in the environment may not be sufficient if only one set of rate constants and transfer processes is included. More often than not, chemical transformations take place in the environment, and the models must deal simultaneously with more than one chemical species, the parameters governing their behaviour being often quite different. In such cases, the danger is of having to set up a model of overpowering complexity. The number of possible chemical forms of any element is endless, and the attempt to deal with all possible

interconversions will destroy any hope of incorporating the details into a manageable picture of overall dynamics.

Thus a 'trade-off' between simplicity and relevance has to be made. If a small number of chemical species of the element in question which are of particular environmental significance can be identified, then a manageable model of overall dynamics may be achieved.

The differences in environmental behaviour of, for example, organic species of metals as opposed to their inorganic forms are profound. In the now well-studied case of mercury, the conversion of a quite small fraction of the inorganic form to the lipophilic methylated form results in the accumulation in a food chain of the organic form, and a significant health hazard may result (see Wood, 1974; Jensen and Jernelöv, 1969). This hazard could never have been predicted (and was not foreseen) on the basis of chemical properties of the parent substance. However, now that the transformation is understood, the situation can be described with more accuracy by simple partition coefficients (Miller, 1978). The case of mercury is relatively simple, for there are only two chemical species accounting for the bulk of the material and also the bulk of toxicity. In other cases, we may need to think of a larger number of parallel models. Each of them describes the environmental behaviour of one species and a coupling of the models has to be made in each compartment where chemical transformation takes place. There is as yet little experience with such multiple models; this is a part of the modelling art which is in need of further development.

2.4.1.5 Validation and Credibility of Models

For years, computer applications have been open to criticisms in all areas and environmental modelling is no exception. These criticisms refer to uncritical acceptance of computer-generated data on the one hand and to unreasonable rejection on the other, as well as to the possibility that models are irrelevant in the first place.

The acceptance by some decision-makers of conclusions based on environmental modelling has been less than enthusiastic. This may to a great extent be blamed on the modellers themselves who sometimes make unsupported claims based on poorly formulated models and expect authorities to act upon such statements in exclusion of other considerations (Frankiel and Goodall, 1978). Even today, it is quite typical to see conclusions of modelling studies presented without an accompanying statement of error bounds or uncertainty levels in the results obtained (Miller *et al.*, 1976). This need not have happened, since techniques for model validation have been available as long as modelling itself (Naylor *et al.*, 1966). While this is not the place to present a survey of model validation techniques, it might be pointed out that validation need not be restricted to a comparison of model output with field observations (Mihram, 1973).

Other approaches to validation and error estimation are available, such as the assignment of a reasonable error range for each parameter and running a Monte-Carlo simulation to find the error distribution of the result. Such techniques have been available for some time (Miller, 1974; Burns, 1975) and are being incorporated into recent modelling studies (O'Neill and Rust, 1979). Nevertheless, in many modelling studies such techniques are often omitted.

A recent publication (Frankiel and Goodall, 1978) reported that many problems of model use and acceptance were not due to the technical aspects of model structure and performance, but were shortcomings resulting from the lack of involvement in the working design and initial construction (Holcomb Research Institute, 1976). Models and conclusions from modelling studies were unlikely to be given much weight by those responsible for environmental decisions unless these models had been developed with specific needs of the decision-maker in mind. In fact, the model specialist was rarely able to foresee these needs on his own (Holcomb Research Institute, 1976) and the success normally depended on the actual involvement of the user or his representative early in the process.

Another aspect of user acceptance of models might be termed accessibility, or what in recent computer parlance is termed 'friendliness'. 'Friendliness' is the ease with which a non-specialist in computer procedures and modelling techniques can understand model performance and interact with it. Attempts by modelling specialists to increase the sophistication of their models may be self-defeating, for the models become less accessible to the user (Holling, 1973). Those responsible for decisions in the public sector are adverse to accepting information the development of which they do not understand (Holcomb Research Institute, 1976). In this connection, we note that user-oriented models with video graphics and simple programming are gaining wider acceptance than more sophisticated models that only a specialist can understand (Holling, 1973).

The continued development of environmental models in the direction of improved validation, error specification and user orientation may be seen as essential if such models are to be useful in the safety evaluation of chemicals.

2.4.2 Environmental Monitoring

Exposures of animal and plant organisms and man to chemicals in the environment can be evaluated with most certainty by direct measurement of concentrations and fluxes, provided that the sampling and analytical procedures are adequate. Extensive and comprehensive measurements are desirable but limited resources usually require that selective measurements be made to provide essential information. Monitoring and modelling programmes are mutually supportive in that modelling studies suggest the most important measurements

and extend the relevance of the results of measurement. Monitoring programmes provide basic data for input to and validation of modelling efforts.

Essential features of monitoring programmes include site selection, sampling methods, measurements to be undertaken, frequency of measurements and procedures for reporting and interpretation of results. Measurements included in monitoring programmes must be appropriate to the purpose of the programme, reflect spatial and temporal variations, provide details of physical and chemical forms and be reported with relevant data on environmental conditions. An integrated approach to monitoring, i.e. multi-media and multi-substance analyses at specific locations, is required to evaluate the behaviour of chemicals and their interactions in the environment.

Monitoring sites are generally chosen because they are considered as representative, but in some cases sites may be selected randomly. This occurs usually in more limited programmes for specific purposes, for example, to determine the extent of ground contamination following an accidental release. A representative site for ambient measurements should be related to the exposure estimate. For example, outdoor measurements may be available but the population in question resides primarily indoors. Relationships between outdoor and indoor concentrations of pollutants in air must then be found, and more measurements must be made in the relevant locations. More attention is now being paid to the distribution of monitoring sites and to indoor exposures (see WHO, 1982).

Monitoring data should indicate changes with time of chemical concentrations and media properties to establish whether equilibrium conditions have been reached or to reflect trends in accumulation or diminution of the amounts of chemicals or degradation products. Analysis of stored specimens, so-called historical monitoring, is undertaken to determine retrospective, long-term trends in background levels. It is important that not only present and past exposures be determined, but the build-up of chemical substances in soil, sediments or other sinks be monitored, and the long-term potential transfer to different organisms and man be evaluated.

When the objective is the estimation of human exposure, ambient monitoring has to be closely linked to individual activity patterns. Alternatively, personal monitors may be worn to obtain a more direct estimate of exposure from airborne chemicals (see WHO, 1982). Personal monitors are usually passive filtering devices which have demonstrated usefulness for some chemicals but have limitations for others.

Monitoring programmes may be conducted to study the mechanisms of transfer of chemicals. The results of measurements may serve as data bases for the formulation of models that describe environmental behaviour.

Monitoring for exposures of effects in ecosystems may often be conducted by sampling and analysis of representative exposed species (see, for example, Cairns, 1981). In some cases, this may be a particularly available species or one which has accumulated high levels of a chemical. Monitoring in remote areas,

such as in biosphere reserves, may be conducted to study relevant changes in the global background of pollutant levels.

2.5 BEHAVIOUR OF CHEMICALS IN THE ORGANISM

2.5.1 Metabolic Models

Metabolic models are used to describe the relations between intake of chemical substances and their absorption (uptake), distribution, retention, transformation and excretion by the organism. These models may be useful in relating intakes to measured levels in body fluids, such as blood and urine. On the other hand, they may be used to calculate doses and integrated doses to target organs.

As in environmental modelling, either time-independent or time-dependent metabolic models may be appropriate. At steady state, the concentration factors give a simple expression of the final disposition of chemicals taken in at constant rate. It may be difficult to assume that there is a steady state, particularly if there are long-term transfers or wide variations. The values of concentration factors apply to particular environmental conditions, but wider applicability can usually be assumed for reasonably comparable circumstances.

Compartment models of more or less detail and complexity may be used to describe metabolic behaviour of chemicals. Compartments may represent a physical structure of the organism, such as main organs and tissues, or they may represent various components of retention. Retention equations consisting of a sum of exponential terms are often used to reflect overall metabolism (Butler, 1978).

Models have been developed which reflect physiological processes following intake in humans and animals. These include a lung model (ICRP, 1966b) and a model for the gastrointestinal tract (Eve, 1966). Summaries of absorption values and other metabolic data for chemical elements are given by ICRP (1979).

Multicompartment models have been formulated to represent the metabolism of specific chemical substances, for example, an eight-compartment metabolic model for cadmium (Kjellström and Nordberg, 1978) or a five-compartment model for lead (Bernard, 1977). Reviews of this and other aspects of the modelling procedures are given by Gehring *et al.* (1976), Butler (1978), WHO (1978) and Camner *et al.* (1979).

In designing a model for any particular chemical, one has to consider several aspects of metabolic behaviour, each of which calls for a specific treatment. Such aspects may be that:

- (1) chemicals, and organic compounds in particular, may undergo a biotransformation as a result of which several new chemical entities emerge, each with different kinetic properties and toxicities. Combining the overall process into one model may be a task of excessive complexity, and therefore, reasonable simplifications of the system may be sought;

- (2) substances may become chemically or physically bound at specific sites, resulting in semi-irreversible deposits the behaviour of which cannot be described by the kinetics of first-order processes. A specific example is lead and other osteophilic elements, where the partial kinetic coefficients are time-dependent. One of the solutions to such situations may be the use of a power-function model. Other solutions may be sought by limiting the scope of modelling to a purely empirical description of the behaviour in a given organ or tissue, in isolation from the overall fate in the organism;
- (3) the assumptions underlying, in general, the kinetic modelling of the behaviour of chemicals by using first-order processes, may not be valid for high doses of chemicals. This, however, rarely represents a problem in environmental toxicology where low concentrations of chemicals are normally encountered in biological media.

2.5.2 Biological Monitoring

The term 'biological monitoring' has been used in two different ways:

- (1) Chemical analysis of biological specimens, such as blood or excreta samples, to determine the concentration of pollutants (or their metabolites) (bioanalysis).
- (2) Biological response: measurement of biological alterations in an organism, population, community or ecosystem resulting from exposure.

In some instances the term biological monitoring is also applied to the procedure of exposing selected test species to a polluted medium of unknown composition and recording short-term effects. Only one aspect of biological monitoring (chemical analysis of biological specimens) will be discussed in this section.

The results of chemical analysis of biological specimens (bioanalysis) may be used with metabolic models which describe the processing of substances by the organism, such as the absorption resulting from specific intake modes and forms, and the distribution and retention of the chemicals in the body. Both dynamic and steady-state models are available.

As is well known, special precautions must be taken in sampling and analysis of biological specimens. The levels of chemicals may be quite low, and care must be taken to avoid contamination from sampling equipment. The difficulties of obtaining accurate analytical results in biological specimens have stimulated an interest in collaborative studies. Interlaboratory comparisons have been undertaken, but the results of these studies are often disappointing, showing wide differences even for quite common measurements. The need for strict analytical quality control has been frequently pointed out (cf. WHO/UNEP, 1979; Friberg and Vahter, 1983).

2.5.2.1 *Health-related Biological Monitoring*

Chemical analysis of biological specimens (bioanalysis) was developed first in industrial toxicology as a method for estimating exposure of individuals. However, although human biological specimens are used, the data cannot be always interpreted in terms of individual exposure because the results obtained with different individuals may be very different for the same exposure. For this reason, bioanalysis is sometimes used only for estimating collective or group exposure (Teisinger, 1969).

Bioanalysis has also been used as a method of measuring total exposure to substances which are easily absorbed through skin and lungs, such as aniline, nitrobenzene, benzidine, parathion, dimethylformamide and others (Piotrowski, 1977; Lauwerys *et al.*, 1980).

An international programme of biological monitoring (bioanalysis) has been initiated by WHO and UNEP to estimate human exposures to selected pollutants. In this project, the levels of lead and cadmium in blood, cadmium in kidney cortex and certain organochlorine compounds in breast milk are being determined in selected population segments in 10–12 countries in different parts of the world (WHO, 1980; Friberg and Vahter, 1983). Information on methods for bioanalysis exists for about 50–60 organic substances. This number has increased greatly over the past 15 years due to methodological developments, particularly in gas chromatography.

It should be pointed out that it does not suffice to be able to detect and quantify a chemical substance. For a meaningful bioanalysis programme, it is necessary to have standardized or agreed-upon sampling procedures and adequate inter-laboratory comparison programmes. The number of substances for which these conditions are satisfied is rather small.

Whereas the older procedures were mainly based on the analysis of metabolites in urine, the more recent methods often recommend the analysis of blood (or expired air for volatile compounds) and the original substance is usually determined. For several organic chemicals alternative procedures are now available, based on the determination of either the original substance or its metabolites in different specimens (urine, blood, expired air). For lipophilic compounds which have a long half-time in the organism, such as DDT and other chlorinated hydrocarbons, fat tissue is often used as the monitoring medium (WHO, 1979).

The degree to which results of such monitoring can be interpreted in relation to exposure differs considerably for various chemicals. A few substances, such as benzene, toluene, trichloroethylene and styrene, have consumed most of the effort whereas for many other chemicals metabolic studies in man have never been performed. The applicability of many of the available procedures to low level, non-occupational exposures is doubtful.

Much effort has been devoted to the bioanalysis of elements such as lead,

mercury, cadmium, arsenic and others. The bioanalysis of metals and metal-like elements has been performed in a variety of specimens using many procedures. The early data refer mostly to urine, but blood analysis has recently replaced much of the routine analysis of urine. The analysis of hair has gained recognition only in a few cases, where the determination is sufficiently reliable and biologically meaningful.

Tissues not routinely available for analysis may be sometimes obtained from autopsy. An example from the WHO/UNEP international programme (WHO/UNEP, 1979) is cadmium, for which the most reliable estimate of life-long exposure may be obtained from its level in the kidneys (Friberg and Vahter, 1983).

If applicable, bioanalysis may provide a dose rate-time function which may be used for more sophisticated approaches of risk estimation, as is the case with methylmercury (Piotrowski and Inskip, 1981; Piotrowski and Buchanan, 1982).

2.5.2.2 Use of Biological Monitoring (Bioanalysis) for Estimating Exposure

Although bioanalysis yields the concentration of a chemical in tissues or body fluids (B), the real object may be the estimation of exposure (E) which is the independent variable in the equation:

$$B = f(E) \quad (2.2)$$

Depending on the use of monitoring data, exposure may be estimated in a variety of ways. For single route exposures the concentration in the relevant type of environmental specimen may be used as a measure of exposure. For multiroute exposures, however, exposure should be considered in terms of the total intake or uptake rate, i.e. as the total amount taken into the body or absorbed in a unit of time.

When bioanalysis is used for exposure estimation, three stages should be clearly distinguished:

- (1) elaboration of a procedure whereby the function $f(E)$ in equation (2.2) is established (calibration),
- (2) sample analysis and
- (3) calculation of exposure from equation (2.2).

Calibration of exposure function may be achieved either by controlled exposure studies with volunteers, or by using properly selected data from field studies. Controlled exposure studies have been performed in several laboratories with organic chemicals of short biological half-time, especially for use in industrial toxicology. Similar studies with chemicals which have a long biological half-time are much more difficult. Long-term studies were performed in the past

for lead, DDT, and aldrin (for a review see Piotrowski, 1977). Of necessity, such long-term studies involve several problems, both ethical and technical. These difficulties justify attempts to establish the form of the function $f(E)$ in equation (2.2) computationally by using data from single-exposure studies. It has to be emphasized, however, that such modelling techniques are still under development.

Although it has not been explicitly stated, estimation from bioanalysis data of the total exposure contributed to by various routes is based on the assumed additivity of absorbed doses expressed as functions of exposure:

$$B = f_a(E_a) + f_b(E_b) + f_c(E_c) + \dots \quad (2.3)$$

where the biological level B integrates absorbed doses $f_i(E_i)$ via routes $i = a, b, c, \dots$. To solve equation (2.3), a set of equations should be constructed using additional data. The procedure may raise several problems both computational and technical.

Simplified situations exist in which exposures, expressed as intake rates, are equal to uptake rates (absorption rates), and the functions are linear and additive, as may be the case with some organic compounds absorbed through the lungs and skin simultaneously. However, even in such simple systems the estimation of total dose involves several assumptions which have been rarely verified experimentally. These procedures, when used for multimedia pollutants, clearly require further experimental and theoretical support and development.

2.5.2.3 *Use of Biological Monitoring (Bioanalysis) for Predicting Health Effects*

The levels of a chemical in organs or tissues reflect the exposure of the individual (or population) and in turn determine adverse effects which may be manifested in the same individual (or population). Therefore, if dose-effect or exposure-effect relationships are available, bioanalysis data can be used for predicting health effects directly, i.e. not involving estimates of exposure as discussed above. Depending on the intended use of monitoring data, the methodology of bioanalysis should be developed along different lines.

As pointed out elsewhere (Nordberg, 1976), adverse effects show first in some tissues or organs which are the critical organs. In this context the 'critical organ' is defined as that particular organ which first attains the critical concentration of a chemical under specified circumstances of exposure and for a given population. Critical organ concentration is defined as the mean concentration in the organ at the time the concentration in any of its cells reaches a critical concentration. The critical concentration for a cell is the concentration at which undesirable functional changes, reversible or irreversible, occur in the cell, (TGMA, 1973). This definition of the critical organ differs from the definition given by the

International Commission on Radiological Protection (ICRP, 1966a). The word 'critical' was used by the Commission to describe the organ of the body whose irradiation was likely to be of greatest importance either because of the dose it receives, its sensitivity, or the importance to health of any damage that may result. The Commission now considers that it is necessary to specify several organs and tissues that have to be considered because of their susceptibility to damage, the seriousness of such damage and the extent to which it could be treatable (ICRP, 1977). The definition of critical organ given in the report of the Subcommittee on the Toxicology of Metals of the Permanent Commission and International Association on Occupational Health (Nordberg, 1976) implies that no effects adverse to the whole organism will occur if critical effects in the critical organs are identified and can be prevented. Thus, the best way of estimating the likelihood of effects would be to obtain the level of the chemical in the critical organs directly (for example, in brain, liver or kidneys). This is usually not possible and, therefore, a substitute biological medium is selected which is easily available (such as blood or hair) under the assumption that there is a high correlation between the concentrations in the two media. In this case, the monitoring by bioanalysis is based on an assumed function:

$$B = \phi(D_{\text{crit}}) \quad (2.4)$$

where D_{crit} is the concentration in the critical organ and ϕ is some function. If a linear relationship applies, ϕ is simply a coefficient of proportionality. In contrast to the estimation of exposure by bioanalysis, the validity of function (2.4) can only rarely be proved on human subjects directly and the exact form of the function is never known with certainty. Instead, animal experiments are used to ascertain if (1) a high correlation exists and (2) some characteristics of the function (such as linearity and range of partition coefficients) can be established. The most relevant factor seems to be the correlation coefficient; it determines the degree of association between the level of the chemical in the biological medium selected and the concentration in the critical organ(s).

Since blood transports chemicals to tissues, it is often assumed that it is the most suitable biological medium for monitoring if the aim of monitoring is to provide support data for risk assessment. However, any other medium can also be used (such as expired air for volatile compounds, hair or nails for elements accumulating in these tissues), provided the relation (2.4) is valid.

2.6 CONCLUSIONS

(1) Exposure assessments require, in addition to the estimation of concentrations at targets, information of environmental sources and pathways. These data are often used in the regulatory process. Assessment of human exposures

also requires much detailed information about the life-styles of the exposed people.

(2) Methods for estimating exposure of non-human targets to environmental chemicals are not sufficiently developed.

(3) Methodology for relating environmental behaviour of chemicals to exposure is in a state of development. Several different techniques are in use and they must be adequately coordinated. Environmental transport models are useful for relating exposures to rates of release but they require improvement as regards groundwater modelling, identification of chemical species involved and validation.

(4) Much environmental monitoring has been carried out. It has been increasingly recognized that it should be more closely related to exposure estimation. In addition to the continuing need to improve sampling procedures and analytical techniques, special attention should be directed to characterizing chemical species involved. Multi-media and multi-substance measurements are important for understanding the transfers and reactions of environmental chemicals.

(5) Environmental monitoring is needed to validate exposure predictions for new chemicals based on laboratory testing.

(6) Metabolic models are required to design the most informative biological monitoring methods and to assess the results. These models must be related to the routes of intake and to the toxicological properties of the chemical. They are also needed for estimating the total intake resulting from exposures by multiple routes.

(7) For toxicological interpretation, biological monitoring should provide information from which the dose to the target can be estimated.

2.7 RECOMMENDATIONS

(1) Procedures should be developed for obtaining better information about the release of natural and man-made chemicals to the environment.

(2) For assessing human exposures, especially in the home environment, more information is needed about the use of consumer products and about human activity patterns.

(3) Better methods should be developed for estimating exposure of non-human targets and ecosystems.

(4) Groundwater transport and dispersion models should be further developed and improved.

(5) The existing models for environmental transport should be modified to take into account chemical transformations that take place during the movement of chemicals through the environment.

(6) Environmental transport modelling procedures should be improved

particularly as regards validation, error specification and user orientation of models.

(7) Where possible, environmental monitoring should be oriented to exposure estimation. To improve exposure estimates, testing and evaluation of chemicals should include metabolic studies following single, repeated and long-term exposures and intakes by all routes should be considered.

(8) Environmental monitoring should include identification and analysis of all chemical forms of a pollutant.

(9) Environmental monitoring should cover as many media and contaminated materials at the same site as possible.

(10) The levels of chemicals most closely related to the adverse effect should be measured to define effective exposure.

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