SECTION IV

ASSESSMENT AND EVALUATION

ASSESSMENT OF HEALTH IMPACT OF ENVIRONMENTAL CHEMICALS

by
J. Parizek, E. Somers
and
V.B. Vouk

Controlling the Chemical Environment

Two main reasons exist for the growing concern about the effects of chemicals on human health. One is a profound quantitative and qualitative change in the exposure of human populations to naturally occurring substances and to new compounds synthesized by intention or as the unintended by-products of new technologies. Recent estimates of the number of chemicals used in daily life exceed several tens of thousands, including several thousand compounds in drugs, several thousand substances as various food additives and more than one thousand chemicals as active ingredients in different pesticides. In addition, industrial technology, power production and transport produce wastes that may be eventually found as pollutants in the air, water, soil and food. Before reaching the environment, many of these chemicals escape into the workplace. Homes are exposed to a variety of consumer chemicals, some of which may be contaminated with impurities of toxicological importance.

The second reason for the growing concern with the health effects of chemicals is the increasing knowledge of their adverse health effects. Episodes of intoxications affecting populations exposed to such chemicals as alkylmercury compounds or chlorinated organic compounds have been reported recently in Japan, Iraq and Turkey. Several thousand people were seriously affected in these outbreaks, with permanent disability and even death resulting in many cases. However, these episodes, as well as instances of occupational or acute accidental intoxications, represent only a part of the problem. Growing evidence, based on animal experiments and epidemiological studies, indicates that chemicals can play an important role in the etiopathogenesis of certain chronic diseases, either by being a major causative factor or by modifying the effects of other pathogens. The course and outcome of other diseases may be changed by exposure to chemicals. Increasing incidence of some

noncommunicable diseases in various parts of the world indicates that further analysis of changes in the chemical environment deserves particular attention.

Environmental pollution by chemicals is not an entirely new phenomenon. In certain areas of the world, it can be traced many years back in association with such processes as exploitation of mineral deposits. However, several factors have recently emerged which have changed the dimensions of the environmental pollution problem. These factors include:

- increases in the scale of fossil fuel combustion and exploitation of mineral deposits and other natural resources;

- rapid development of the chemical industry and increasing use of synthetic chemicals in everyday life; and

- growth and urbanization of population, resulting in localized high concentrations of waste.

Of importance is the recognition that the increase in the exposure to chemicals is not limited to industrialized countries. Rapid development of industry, growing use of mineral resources and fossil fuels and increasing use of chemicals in agriculture, food production and industry, medicine and in public health are connected with profound changes in the exposure to chemicals. They affect, or will affect, the populations living both in industrialized and developing countries. Industrialization and increased use of chemicals are important components of development highly beneficial to mankind; however, they must be accompanied by the corresponding development of environmental health control measures.

Some measures of general technological character are directed at the reduction of discharges from power plants and industry or at safer disposal of industrial or human waste. Other measures are concerned with the production, use or disposal of specific chemicals or groups of chemicals. Regulatory action can limit the presence of certain chemicals in environmental media or define the mode of their use, thus limiting human exposure and health hazards. Decisions aimed at the prevention of chemical hazards are based on risk assessment, i.e. on the assessment of whether or not a chemical may cause an

adverse health effect and, if so, at what level of exposure and with what frequency or probability. Risk assessment must be based, therefore, on specific knowledge regarding, in principle, three components:

- character of the biological effects of the chemical;
- intensity of the effects in the affected individual as dependent on the dose (sometimes called the dose-effect relationship); and
- frequency or probability of occurrence of an effect in a given population as a function of the dose, i.e. the dose-incidence, or dose-response, relationship.

Health Effects of Chemicals

Chemicals present in the environment can influence, both directly and indirectly, human health and wellbeing. The indirect effects include effects on other biota, with possible changes in food production and preservation, or in the occurrence and type of various pests and vectors of diseases. Some of these indirect effects may require regulatory action. The present concern with DDT can serve as an example of a problem where the assessment of a direct effect on humans has not been the decisive issue in the consideration of regulatory action. On the other hand, the beneficial effects of certain chemicals in the environment can be of such importance that in the risk-benefit evaluation, the risk of adverse health effects must be balanced with the risk of not using these chemicals. This situation applies particularly to pesticides or food preservatives.

The prerequisite for a direct effect of a chemical is that the chemical compound reaches the organism. Exposure to chemicals can be direct, as in skin contact or accidental ingestion, or indirect, through environmental media such as air, water and food. The chemical composition, biological availability and concentration in environmental media may change in the passage of chemicals through the environment. Chemicals may be degraded to less toxic substances or transformed into more toxic forms. They may accumulate, particularly in aquatic organisms, and build up concentrations which are many thousand times higher than those found in polluted water. In this fashion, methylmercury enters the food chain, and substantial

concentrations can build up in fish. On the other hand, other pollutants may be eliminated from water by physical processes such as sedimentation and adsorption. In the air, secondary pollutants may be formed from photochemical reactions involving oxides of nitrogen and hydrocarbons emitted from motor exhausts.

Some pollutants are chemically very stable and almost nonbiodegradable. This stability can result in high persistence in the environment, especially when chemicals are released repeatedly or continuously, resulting in a gradual accumulation, for instance, in soil. An example of a fairly persistent compound is TCDD (2,3,7, 8-tetrachlorodibenzo-p-dioxin), one of the most toxic substances prepared by man. TCDD may escape from industry as a pollutant or be present as an impurity in some herbicides based on 2,4,5-trichlorophenoxyacetic acid.

Although chemicals may reach humans through different pathways (e.g. food, air, water or consumer products), one of them is usually the major contributor. This pathway is called the "critical pathway". Its identification enables the most efficient and the least costly monitoring and control of exposure. In other cases, the quality and quantity of total exposure through multiple routes must be carefully investigated. The lack of such knowledge is one of the principal obstacles in the assessment of the health impact of environmental chemicals.

Chemicals taken up by the organism may act in their original form or be metabolized so that toxicity is different from that of the parent chemical. Knowledge of the kinetics of chemicals in the organism, organ distribution, biotransformation and excretion is an important prerequisite for the assessment of adverse health effects.

In extreme cases, changes induced by a chemical in the body may be incompatible with survival of the organism and exposure may result in death. Where exposure is lower, lesions may be confined to certain organs as a result of selective vulnerability of target tissues. Such selection occurs, for example, in the case of neurotoxic effects of chemicals acting on cholinesterase. It may also result from selective accumulation of the chemical (or its metabolites) in certain target tissues (e.g. inorganic mercury (II) compounds in the kidney). At very low exposure levels, some of the changes can be detected only

by special investigations and might not manifest themselves by a noticeable impairment of some functions of the body. This situation applies, for instance, to some changes in enzyme activities not resulting in significant metabolic alterations.

Depending on the level of exposure, the nature of the effect and the biological characteristics of the affected organ, the induced changes may be transient (as, for example, some metabolic or behavioural changes detectable only during or shortly after exposure) or permanent (e.g. the destruction of an organ by necrosis). Depending on the degree of lesion and on biological characteristics of the affected tissues, the resulting damage may be irreparable or may be compensated by regenerative processes. The transient changes can serve in some cases as important "early warning" signs and also, when a dose-effect relationship is established, as indications of the exposure level. The detection of those effects which are irreversible and which represent a permanent, irreparable impairment of functional capacity of the organism could be too late to serve as an efficient "early warning".

Several categories of effects deserve particular attention. Included are those which may alter genetic information and thus affect the health of future generations, disturb further development of the exposed organism by acting during a specific critical period of prenatal life, induce transformations of somatic cells which may result in carcinogenesis, or induce such damage in organs and tissues that regeneration is limited or nonexistent (the neurotoxic effects connected with irreparable damage to neuronal cells).

Dose-effect and Dose-incidence Relationships

As already mentioned, knowledge of the dependence of the effects on the dose is essential for the assessment of health risks of environmental chemicals. The fact that the effect and/or its incidence is determined not only by the quality of the chemical, i.e. its physical and chemical characteristics, but also by the amount of the compound or dose has been recognized since the time of Paracelsus (1493-1541).

In some instances a gradual increase of the intensity of the effect can be observed with increasing exposure (dose); for example, the effects of lead on enzyme systems connected with haem biosynthesis. One of the enzymes affected is δ-aminolevulinic acid dehydratase (ALAD), the activity of which is known to decrease with an increasing dose of lead. Using the blood lead levels as a measure of the dose, a negative linear relationship can be established between the logarithm of the activity of ALAD in the erythrocytes and the levels of lead in blood. Almost complete inhibition of ALAD can be observed at blood lead levels exceeding 60 µg/100 ml. Usually demonstrable ALAD inhibition can be observed at blood lead levels below 10 µg/100 ml. When plotting the intensity of an effect against the dose, an observable effect cannot usually be demonstrated until a threshold dose is reached. However, a difference must be made between this no-observed-effect level established for a certain individual or a limited defined group and the threshold for general populations for which this value must be understood in statistical terms.

Some of the effects in the individual cannot be measured on a graded scale of intensity and can be considered only as "occurring" or "not occurring". A typical example of such a "quantal" effect is death. The relation between the dose and the proportion of individuals responding with a quantal effect is expressed by the dose-incidence curve (or dose-response curve). In contrast to the dose-effect curves which may have various forms, the dose-incidence curves, in general, are S-shaped with upper and lower asymptotes.

In principle, a high dose should exist to which all individuals will respond and a low dose to which none will respond. However, as will be discussed later, the dose-response relationship is usually based on observations established within a certain range of doses, and the extrapolation to low levels is one of the most difficult problems of quantitative toxicology.

Several investigators have assumed that one single molecule may be sufficient to initiate the process which may lead to cancer development, i.e. no threshold exists. A similar assumption has been made for some other effects, mutagenicity in particular. However, the general validity of such an assumption has been questioned, particularly in view of the fact that some environmental carcinogens are

precarcinogens which have to be metabolized into the ultimate carcinogens in the organism. Such biotransformation may depend on the dose and the existing DNA repair processes.

The dose-incidence relationship can be established for other effects. For lead and ALAD, for instance, one can plot the proportion of those individuals in a given population who show an inhibition of ALAD higher than 40% against the dose.

Factors Modifying the Effects of Environmental Chemicals and the Dose-effect and Dose-incidence Relationships

The existence of a dose-incidence relationship is per se a good illustration of the fact that not all individuals in the population react in the same way. The capacity of an organism to react to, or to resist, the presence of a dose of a certain chemical as well as to metabolize the chemical is dependent on inherited and acquired morphological and functional properties of the organism. These properties are sometimes called host factors and include species characteristics, sex-linked differences, age and the general functional state of the organism, as determined both genetically and by the previous life history. Thus, the interindividual and interspecies variations of metabolic capacity of certain enzymatic systems can influence the kinetics and biotransformation of chemicals in the body and may also modify the reaction of target systems to a given dose of these chemicals. For instance, the capacity of enzyme systems to convert certain compounds to electrophilic substances that act as ultimate carcinogens can determine the outcome of exposure to such chemicals.

When unhealthy individuals are present in the exposed population, the response can be even more variable and the dose-incidence relationship skewed. Thus, impairment of the functional capacity of the excretory systems, e.g. a renal disorder, can change the rate of clearance of chemicals and their toxic metabolites from the organism. Thus, by changing their retention in the organism, such impairment can modify the effects. Impaired liver function can change metabolic conversion, particularly detoxication of certain chemicals or their biliary excretion.

SECTION IV

The metabolism and effects of environmental chemicals are influenced not only by host factors but also by exposure to other environmental factors. These influences can be chemical, including nutritional factors, drugs or other pollutants, or physical, such as ionizing radiation. Of special importance is the fact that repeated exposure to the same chemical may in some instances change its metabolism or its effects. This consideration is relevant in evaluating the effects of long-term exposure.

Much data from animal experiments indicate the factors modifying the character of the effects and the dose-effect and the dose-incidence relationships for chemicals. However, growing evidence confirms the validity of these interactions for humans, as shown, for instance, by the potentiation of carcinogenesis in smokers exposed to asbestos or ionizing radiations. A better understanding of factors which can modify the kinetics and action of chemicals in humans is important for test protocols and for the identification of individuals or segments of population at particular risk. The knowledge of critical groups for a given chemical and of individuals at a particular risk is important for preventive measures.

Approaches to and Limitations of Health Impact Assessment

Substantial and complex knowledge is required for the assessment of health risks which, in principle, should be based on a comparison of exposure levels with established dose-effect and dose-incidence relationships. Several limitations make this process highly demanding on the scientific skill and experience of the investigator.

In many cases, data on existing exposure levels are extremely scarce, and the evaluation must be done on a basis of rough estimates. Data on dose-effect and dose-incidence relationships in humans are available only rarely and usually only for more immediate effects of high-level exposures to chemicals produced and used in the past. The most complete information can usually be obtained from data on occupational exposure, However, in addition to usually higher levels of exposure, the situation is different from the exposure of the general population in another important aspect: the occupationally exposed population is usually highly selected and may not include the more sensitive groups or individuals at particular risk.

Information obtained from the surveillance of health effects in humans is limited in another respect. For chemicals introduced even several years ago, the time period may be too short to observe all the effects, and the available results of follow-up studies could be misleading. The period of latency (the period of time between the beginning of exposure and the first manifestation of effects) may be very long: for some known human chemical carcinogens, it may exceed 30 years.

Developing gradually and undetected for some time, pathophysiological processes induced by exposure to chemicals in the environment may be very complex. This factor played an important role in epidemics of alkylmercury intoxications. However, a similar period of latency is also characteristic for other environmental chemicals, including extremely toxic ones.

For newly introduced chemicals, it is ethically unacceptable to wait for human effects before proceeding with the evaluation of their health impact. In most cases, therefore, the evaluation of health risk will depend on data from animal experiments. Clearly, these studies should simulate as closely as possible the condition of exposure in humans regarding the length of exposure and the levels of chemicals in environmental media. However, the information obtainable through animal experiments is necessarily limited. In addition to well-recognized species differences, at least three other problems should be mentioned:

- extrapolating results obtained in animal experiments, usually at high exposure levels, to long-term, very low-level human exposure;

- the limited number of animals which can be used for testing (usually not more than 50 to 100 per group) with the size of human populations that may be exposed and the range of changes in the response to be assessed; and

- foreseeing and modelling host factors and environmental interactions which may modify the effects in human populations.

Different mathematical models have been developed for low-dose extrapolation. However, all these methods represent an approximation based on a number of

assumptions. Better understanding of the mechanisms of action of chemicals could improve the reliability of extrapolations across species and from the large doses used in experimental animals to the exposures experienced by humans.

WHO Activities

The evaluation of the health effects of environmental agents is one of the essential bases for planning and implementing national environmental health programmes, and the World Health Organization has given considerable attention to this subject during the last two decades. Annual meetings of the Joint FAO/WHO Expert Committee on Food Additives have been held regularly since 1956. Joint FAO/WHO meetings on pesticide residues in food have been held regularly since 1961. A programme is also in progress on the evaluation of new insecticides for the control of vectors of disease and, jointly with the FAO, on the preparation of data sheets providing basic information on the safe use of pesticides. A classification of pesticides by hazard was adopted by the 28th World Health Assembly in 1975. In its sixth Report (1969), the Joint ILO/WHO Expert Committee on Occupational Health evaluated recommendations and standards for occupational exposure to airborne toxic substances. In 1977 a programme was initiated to develop internationally recommended, health-based permissible levels for occupational exposure to chemical agents. This programme is being implemented in close cooperation with the International Labour Office (ILO). The International Standards for Drinking-Water were first published in 1958 and revised in 1963 and 1970. A new edition was published in 1980 in which the international and European standards (1961, 1970) were merged. Several expert committees on air pollution were convened between 1957 and 1972.

The programme of the International Agency for Research on Cancer on the evaluation of the carcinogenic risk of chemicals to humans has been in progress since 1971. The Regional Office for Europe has issued a number of reports on toxic substances in the environment and is also in charge of a WHO programme on accident prevention which includes chemical accidents.

In most of these activities, however, total exposure to a given toxic agent from various media or environments (air,

water, food, work and home) was not considered. The inadequacy of this approach is evident for substances that are distributed through several media or used for several different purposes. For this reason, an integrated programme on health risk evaluation was initiated in 1973 in collaboration with more than 20 Member States and with the support of the United Nations Environment Programme (UNEP). The aim of this "environmental health criteria" programme is to assess existing information on the relationship between exposure to environmental agents, including chemicals, and human health. The programme also provides guidelines for setting exposure limits consistent with health protection. Furthermore, it will identify new or potential chemical hazards by making preliminary reviews of chemicals and other agents likely to be used increasingly in industry, agriculture or at home. Other objectives of the programme are to identify gaps in knowledge and to promote research and the harmonization of toxicological and epidemiological methods.

Eighteen monographs, including those dealing with physical factors, have been, or are in the process of being, published:

1. Mercury
2. Polychlorinated biphenyls and terphenyls
3. Lead
4. Oxides of nitrogen
5. Nitrates, nitrites and N-nitroso compounds
6. Principles and methods for evaluating the toxicity of chemicals, Part I
7. Photochemical oxidants
8. Sulfur oxides and suspended particulate matter
9. DDT and its derivatives
10. Carbon disulfide
11. Mycotoxins
12. Noise
13. Carbon monoxide
14. Ultraviolet radiation
15. Tin and organotin compounds
16. Radiofrequency and microwaves
17. Manganese
18. Arsenic

An interim document on cadmium and an interim re-evaluation of methylmercury have been issued. Other evaluations being prepared include hydrogen sulfide, selenium and chlorinated dibenzodioxins. In view of the

extremely large number of environmental agents which may have a negative impact on human health, the choice of substances for comprehensive evaluation must be selective. In addition to the availability of necessary information, the following points have been considered in setting priorities in this programme:

- severity and frequency of observed or suspected adverse effects on human health;
- ubiquity and abundance of the agent in the human environment;
- persistence in the environment and possible environmental transformations or metabolic alterations important from the point of health risk; and
- size of population exposed and/or selective exposures of critical groups of population.

The list of chemicals selected for the review is periodically amended by a group of international experts.

Each of the volumes dealing with environmental chemicals follows the same format. First, the relevant information on chemical and physical properties and analytical methods is reviewed. Following chapters deal with sources of chemicals in the environment, environmental transport, distribution, transformation and metabolism of the compound in the organism including uptake from the environment, biokinetics and metabolic transformations within the organisms. Then experimental studies on the effects are reviewed, and epidemiological and clinical studies of the effects in humans described. The document concludes with the assessment of health risks to humans, expressing the opinion of an international task group of experts convened to examine the findings reported in the document. However, knowledge of the effects of chemicals on health is very limited: for only a small proportion of the existing chemicals is the state of knowledge sufficient to prepare a criteria document.

The promotion of appropriate methods for health effects evaluation has been an essential component of most WHO activities mentioned above. In the last 20 years, this focus has resulted in a number of technical reports and guidelines on the general principles and methods for testing and evaluating food additives and contaminants,

drugs and chemicals for carcinogenicity, mutagenicity and teratogenicity. More recently, emphasis has been on identification of new or potential environmental pollutants, early detection of health impairment in occupational exposure, chemical and biochemical methods for assessing the hazard of pesticides to humans and on the methods used in establishing permissible levels of occupational exposure. Methods used in some Member States have also been reviewed. In connection with the environmental health criteria programme, a monograph on the principles and methods for evaluating the toxicity of chemicals is now being finalized. A similar monograph on epidemiological methods for investigating the health effects of environmental agents is being prepared in collaboration with the International Epidemiological Association.

International Programme on Chemical Safety

The principal objectives of the International Programme on Chemical Safety (IPCS) are the following:

- evaluate the effects of chemicals on human health and the environment;
- develop guidelines on exposure limits of chemicals in air, food, water and the working environment;
- develop methodology for toxicity testing, epidemiological and clinical studies, and risk assessment;
- coordinate laboratory testing and epidemiological studies when an international approach is appropriate and to promote research on dose-response relations and on mechanisms of biological action of chemicals; and
- develop information for coping with chemical accidents, to promote technical cooperation on control of toxic substances in Member States and to promote training and development of manpower.

This programme is based on existing activities of WHO and the other cooperating organizations concerned with evaluation of the health effects of chemicals. The aims of IPCS are to strengthen and expand ongoing programmes and to increase international collaboration in this area.

In this respect two characteristics of IPCS deserve special attention. First, executive heads of UNEP, ILO and WHO signed a Memorandum of Understanding in April 1980 whereby the IPCS became a cooperative venture of the three organizations. Negotiations are currently in progress with FAO concerning the involvement of this organization; existing joint FAO/WHO activities in the field of food additives or pesticides were mentioned in the previous section. Second, the programme has to rely on active participation of Member States, and the necessary resources, both financial and human, being provided by them. IPCS has been conceived as an international collaborative activity based on a network of lead and participating institutions, each of which is responsible for, or involved in, a specific component of the programme. Institutions could be involved, for example, by evaluating the health risks of certain chemicals or classes of chemicals or by leading or participating in such activities as manpower development, emergency response or testing for certain specific effects (e.g. mutagenicity). In addition to the national institutions, two international bodies have accepted the role of lead institutions. The International Agency for Research on Cancer (IARC) will be the lead institution for chemical carcinogenesis. UNEP has agreed that the International Register of Potentially Toxic Chemicals (IRPTC), with the assistance of the International Referral Service (INFOTERRA) and the computerized data base of the Industry and Environment Office (IEO), should operate as the lead institution for the collection, retrieval and dissemination of information within the IPCS.

The WHO regional offices have an important role in IPCS, including the dissemination and application of results of the programme, technical cooperation and manpower development. The WHO Regional Office for Europe is particularly involved in developing programmes on manpower training, emergency response to contingencies and environmental health impact assessment.

The organizational structure of IPCS has several key components, which include:

- the Intersecretariat Coordinating Committee, providing the managerial link between the cooperating organizations and the Central Unit (CU);

- the Programme Advisory Committee (PAC), advising on the policies and priorities, the work plan and budget of the IPCS;

- the Technical Committee, comprised of directors of lead institutions or their designates and concerned with developing the work of the lead and participating institutions;

- the (CU), responsible for the management and implementation of the Programme on behalf of the cooperating organizations and providing links and support to the programme elements (CU is located at WHO headquarters and operates under WHO procedures);

- the network of lead institutions with the subnetwork of participating institutions, dealing with specific components of IPCS; and

- the focal points for IPCS, representing the link of the participating Member State with IPCS and its CU.

The main outputs of IPCS, both present and future, include:

- evaluations of the health and environmental effects of new and existing chemicals, ranging from extensive monographs and criteria documents to single-sheet reports;

- evaluations of specific effects, such as carcinogenicity, mutagenicity and teratogenicity, or of effects on specific organs;

- guidelines on exposure limits which can be ADIs for food additives and pesticides or recommended levels for the working environment;

- guidelines on methodology for exposure measurement, risk assessment, toxicity and epidemiological studies;

- information on chemical accidents and regulatory control;

- responses to chemical emergencies;

- advisory services for technical cooperation; and

- trained manpower.

Hopefully, this programme will receive the necessary support - both financial and human resources - required by all Member States to provide a comprehensive and integrated evaluation of the health and environmental effects and risks of chemicals.