Methods used in establishing permissible levels in occupational exposure to harmful agents

Glaser

Report of a WHO Expert Committee with the participation of ILO

Technical Report Series
601

World Health Organization, Geneva 1977

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WHO EXPERT COMMITTEE ON METHODS USED IN ESTABLISHING PERMISSIBLE LEVELS IN OCCUPATIONAL EXPOSURE TO HARMFUL AGENTS

WITH THE PARTICIPATION OF ILO

Geneva, 24–30 August 1976

Members

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Dr J. F. Finklea, Director, National Institute for Occupational Safety and Health, Rockville, MD, USA (*Rapporteur*)

Professor Ju. I. Kundiev, Director, Kiev Institute of Industrial Hygiene and Occupational Diseases, Kiev, Ukrainian SSR (*Vice-Chairman*)

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Dr D. Djordjevic, Occupational Safety and Health Branch, Working Conditions and Environment Department, ILO, Geneva, Switzerland

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Professor R. Zielhuis, Coronel Laboratory for Occupational Health, University of Amsterdam, Netherlands (*Temporary Adviser*)

METHODS USED IN ESTABLISHING PERMISSIBLE LEVELS IN OCCUPATIONAL EXPOSURE TO HARMFUL AGENTS

Report of a WHO Expert Committee with the participation of ILO

A WHO Expert Committee on methods used in establishing permissible levels in occupational exposure to harmful agents met in Geneva from 24 to 30 August 1976. Dr A. S. Pavlov, Assistant Director-General, opened the meeting on behalf of the Director-General. He called attention to recent developments in WHO's programme in occupational health and referred to the Sixth General Programme of Work covering the specific period 1978–83, in which the promotion of workers' health is given a high priority. A recent resolution of the World Health Assembly (resolution WHA29.57) also emphasized the need of countries undergoing rapid industrialization to develop adequate occupational health programmes.

The main objectives of the meeting were to review the information available on methods used in different parts of the world in establishing permissible levels in occupational exposure to harmful agents, to identify areas of agreement on the methods used in experimental and epidemiological studies as a basis for recommending permissible levels, to provide advice to developing countries on appropriate approaches in establishing and using permissible levels, and to identify gaps in knowledge.

1. INTRODUCTION

The usefulness of the concept of permissible levels of harmful agents in the working environment has been adequately demonstrated in many practical situations in which there has been a significant reduction or disappearance of occupational diseases following the adequate application of these levels. The main object of the application of permissible levels should be to maintain an optimum state of physical, mental, and social wellbeing in the working population. " Permissible level " has

been defined in previous ILO and WHO documents ; [1, 2] it is a quantitative hygienic standard for a level considered to be safe, expressed as a concentration with a defined average time. The term " permissible level for occupational exposure " can also be taken to mean " maximum allowable concentration ", " threshold limit value ", and " maximum permissible limit or dose ".

Although the main emphasis in this report is given to methods used in establishing permissible levels of airborne toxic agents, the Expert Committee agreed to include a brief reference to the methods used in establishing permissible levels for certain physical agents, namely heat and noise. This was done in order to demonstrate the differences in approach necessary when dealing with chemical and physical agents and to prepare for future consideration of permissible levels of different harmful physical agents that may be encountered in the working environment.

The Expert Committee also considered the fact that workers may often be exposed to more than one harmful agent and thus to a potentiation or synergism of harmful effects. Workers may also be exposed to occupational hazards for periods longer than 8–10 hours per day, and those exposed may include vulnerable people who may not have the advantage of preplacement medical examinations and who may be affected by endemic or chronic diseases. Permissible levels therefore should not be rigidly fixed but should allow for adjustment, depending on the type of exposure, its complexity, the general environmental and living conditions, and other variables.

For a number of years permissible levels have been developed in an increasing number of countries so that today they are a basic factor in the protection of workers' health. Values for several hundred substances in occupational use have been established in Member States. However, recommendations and requirements by different national authorities for the control of the same agent appear to diverge much more than one would expect from the available scientific information. This disagreement has been a matter of concern for international organizations such as WHO, ILO, and the Permanent Commission and International Association on Occupational Health. These organizations have jointly and independently attempted to promote an international exchange of

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[1] WHO Technical Report Series, No. 415, 1969 (*Permissible levels of occupational exposure to airborne toxic substances* : sixth report of the Joint ILO/WHO Committee on Occupational Health).

[2] HATCH, T. F. *Bulletin of the World Health Organization*, **47** : 151–159, 1972.

information among specialists to discover the main reasons for these differences and to promote closer agreement.[1, 2, 3]

Not only is terminology nonstandard, but there are differences even in the approach to the problem—in, for example, the development of toxicological and epidemiological information, the choice and evaluation of data, the setting of standards, and monitoring. These differences will be resolved only when more complete information is made available.

Permissible levels of airborne toxic chemical agents assume that for each substance there is a concentration in the air of the working environment at which (and below which) the worker does not incur any health impairment. To establish such levels requires a large amount of scientific information. There is increasing agreement on recommendations for permissible levels that are based on medical and other scientific data, but the translation of these recommendations into workplace regulations is a complex task that can be accomplished in various ways. In this area closer cooperation is needed. A better knowledge of the methods used in different research centres would be advantageous, and the research methods used should be refined and extended to cover the widest possible range of potentially harmful effects of a given agent. The goal is to promote the use of essentially equivalent research and monitoring techniques, which will lead to comparable results.

When a standard is urgently required to control a severe hazard it is often possible to derive a temporary permissible level from an uptake/response relationship based on available scientific data.

Both developed and developing countries would benefit from a full exchange of information on how permissible levels are established. Everyone should understand research methods, the interpretation of the results obtained, and the application of the permissible levels. In this way developing countries could make their own independent critical appraisals of permissible levels and adapt them for the protection of their workers. In addition, scattered and isolated efforts could be better

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[1] TRUHAUT, R. Le problème des limites tolérables pour les substances toxiques dans les ambiances professionnelles : divergences et points d'accord à l'échelle internationale : essai d'établissement d'un nucleus d'entente [The problem of permissible levels of toxic substances in the working environment: differences and agreements on the international level : attempt to establish a basis for understanding]. In : *Comptes rendus du deuxième symposium international sur les limites tolérables pour les substances toxiques dans l'industrie, Paris, 1-6 avril 1963*. Paris, Institut national de Sécurité, 1966, pp. 103–117.

[2] TRUHAUT, R. *Archives des maladies professionnelles de médecine du travail et de sécurité sociale*, **32** : 353 (1971).

[3] WHO Technical Report Series, No. 415, 1969.

coordinated and the overall efficiency of efforts aimed at protecting workers' health improved.

2. UPTAKE/RESPONSE RELATIONSHIP

2.1 " Uptake" compared with " concentration "

Permissible levels of occupational exposure usually refer to the concentrations of harmful agents in the air in relation to duration of exposure. However, health effects are more likely to be related to the amount of the agent taken up per unit time over a period of time. " Uptake " is preferred in this report to the usual term " dose " because the precise dose administered is very difficult to measure and because " uptake " indicates effective exposure.

The uptake of a given compound also depends on factors that are not taken into account when one relies only on concentration level —factors such as (*a*) body size, (*b*) respiratory minute volume as determined by the energy expenditure required by the workload [1] and by the barometric pressure, (*c*) the compound's physicochemical characteristics, which determine its pharmacokinetic fate, (*d*) circulatory rate depending on physiological (and perhaps pathological) conditions and on environmental temperature, (*e*) duration of exposure, which is never easily measured in practice, (*f*) respirable fraction, and (*g*) individual or group differences in pharmacokinetics due to such factors as genetic traits and nutritional status. In addition, absorption through the skin (which depends on skin temperature, sweating rate, and the physicochemical characteristics of the agent) [2] and through the gastrointestinal tract also increases the uptake, and this is not apparent from simple concentration data.

Because many of the factors mentioned depend on individual or group characteristics of the people exposed, the measurement of uptake gives a better idea of the actual health risks than does the measurement solely of concentration in air. Therefore the basing of permissible levels on the uptake of a substance should be encouraged. Biological monitoring may also permit the estimation of the dose actually taken up by the body, and this approach can provide valuable data for evaluating the dose (or uptake)/response relationship (see section 5.6.3).

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[1] It has been assessed that for equal concentrations the amount taken up by the body could easily vary from one work situation to another by a factor of up to 5.

[2] KUNDIEV, JU. J. [*Absorption of pesticides through the skin and prevention of poisoning*], Kiev, Zdorov'e, 1975.

2.2 Uptake/effect and uptake/response relationships

In recent years, more and more publications distinguish between the two terms :

(1) *uptake/effect relationship*, indicating the relationship between the uptake of a chemical and the magnitude of a qualitatively specified biological effect in an individual, and

(2) *uptake/response relationship*, indicating the relationship between the uptake of a chemical and the proportion of individuals with a quantitatively specified magnitude of a qualitatively specified effect in a group of subjects.

Uptake/effect and uptake/response relationships are shown very effectively as curves on graph paper.

Although both terms (" uptake/effect " and " uptake/response ") are still being used in toxicological and pharmacological literature for the same type of events, it is wise to distinguish between the two because permissible limits are ultimately based on uptake/response relationships, i.e., on the proportion of individuals in a population exhibiting a specific measured response at a given uptake.

In the ideal case one distinguishes in an uptake/response curve, the following data :

— effect under consideration (quality), e.g., decrease of haemoglobin, impaired psychomotor performance ;
— the intensity under consideration (quantity) e.g., 10% decrease of haemoglobin, 80% of performance maintained ;
— the proportion of subjects affected ;
— the variability in response at each dose level ;
— the chosen group at risk, e.g., adolescents, pregnant women, groups with nutritional deficiency ;
— the dose (uptake) at which the response is not observed under defined conditions, i.e., the " no-response " level.

Uptake/response or uptake/effect relationships display a range of variability at each dose level. This variability tends to increase at lower and at higher dose levels. Unless mathematically transformed the relationship is not usually linear over all dose levels but is usually linear in the middle exposure or dose ranges. However, in many cases the uptake/response curves are not fully established. Experts must then make a judgement based on the information available.

Health experts do not set the ultimate standard ; they provide the basic health-related facts on which a policy decision can be based, together with a recommendation regarding permissible levels. Only they can provide an insight into actual health risks at various levels of uptake in terms that can be understood by the policy-making authorities.

2.3 Models of uptake/response relationships

All theoretical models of human response to a chemical stimulus are derived directly or indirectly from the underlying mechanism involved. If the health response is of the " all or none " type, then the mechanism is assumed to contain one or more rate-limiting stochastic processes. Neoplasms and inheritable changes are examples of occupational risks believed to result from unique molecular events and they may therefore be theoretically simulated by stochastic mathematical models. Such uptake/response models predict the existence of a health risk at all levels of uptake, although the degree of risk decreases with decreasing uptake. However, stochastic processes are rare ; almost all occupational health problems are described by deterministic uptake/response models.

Both stochastic (quantal) and deterministic (graded) models are usually based on the assumption of linear response mechanisms, which is a serious theoretical limitation for complex nonlinear biological systems. In order, for a given chemical, to determine the airborne concentration that causes no detectable harm to the worker, it is necessary to determine the nature of the relationship between the human response and the length of time for a given exposure. The exact nature of this relationship is determined by the underlying mechanism, which may be only poorly understood and is always assumed to be a continuous function of the uptake unless specific evidence to the contrary exists. In view of : (1) the variable structure of the exposed population, (2) the large number of different responses that may be induced in humans and animals, and (3) the nonlinearity of biological systems, a number of different uptake/response relationships will exist for each chemical.

3. METHODS USED IN SETTING HEALTH-BASED PERMISSIBLE LEVELS

Industrialized countries are moving towards a greater degree of uniformity in their scientific requirements for establishing or revising permissible levels of occupational exposure. In making their recom-

mendations all countries are moving towards a far more adequate protection of workers' health. The Expert Committee agreed that increasingly standardized toxicological and epidemiological studies are required to provide basic scientific information for establishing or revising permissible levels of occupational exposure. As a minimum the Committee agreed that the following technical information should be available.

3.1 Minimum requirements

In developing the following recommendations for minimum procedures to be used in establishing permissible levels it was recognized that very detailed guidelines would be inappropriate in the light of the wide variation in properties, modes of action and use of toxic substances. There is general agreement on basic prerequisites for developing permissible levels for a given substance. These are :

(1) the physical and chemical properties of the substance, including the nature and amount of any impurities ;

(2) toxicological investigations involving acute, subacute, short-term, and chronic testing (such tests covering the respiratory, alimentary, and dermal routes of entry) ;

(3) the careful consideration of any available human data.

In acute studies both LC_{50} and LD_{50} determinations [1] should be made in at least two species of animals—one rodent and the other non-rodent. The aim of acute studies is to determine the magnitude of action, the signs and symptoms of response, and the local effects on the skin and mucosa, especially the eye. When chronic effects are suspected, chronic toxicity testing should be performed. Basic biochemical information on comparative metabolism in man and animal species is very helpful when selecting a suitable species for toxicity testing. At each stage of the investigation it is necessary to re-evaluate the results obtained in previous steps in order to determine the necessity for and appropriate direction of subsequent investigations.

Any data that may be available on human experience are of the utmost importance in establishing or revising permissible levels. Validation mainly depends on human observations, and every effort must be made to obtain relevant clinical and epidemiological information.

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[1] The lethal concentration (LC) or the lethal dose (LD) that causes death in 50% of experimental animals under defined conditions of exposure and observation.

It is the role of national health programmes and institutions to determine more detailed requirements, and scientific investigators should be allowed to exercise a reasonable amount of discretion and judgement in the design and interpretation of their studies.

3.2 Preliminary studies

" Toxicity " is the relative capacity of a compound to cause harm by means of adverse biological effects. " Hazard " is the likelihood of its doing so.

Toxicity is one of the factors determining hazard, which also involves such factors as intensity and extent of exposure, volatility, and particle size. " Toxicity " refers to the biological effects after the compound has been introduced into the body ; " hazard " also refers to the likelihood of the compound's being so introduced.

The first step, where necessary, is the chemical identification of the compound, because the level of exposure and the biological activity of a substance are determined by its chemical composition. Modification of the chemical formula alters the toxicity owing to changes in chemical activity, absorption, distribution, accumulation, or metabolic transformation and elimination of the substance.

Non-electrolytes provide the best-known examples of correlation between structure and activity. Several procedures have been proposed to predict toxicity from the compound's physicochemical properties, such as its thermodynamic activity.

Distribution coefficients (e.g., water/oil, air/water, and air/oil) have been used to predict narcotic activity, because a positive correlation has been shown to exist between such coefficients and narcotic activity within homologous series of hydrocarbons. High liposolubility increases the uptake by, and decreases the rate of elimination from, organs containing much lipid, e.g., the brain in the case of narcotics, subcutaneous fat in the case of organochlorine insecticides.

Chemical bonds have also been studied to ascertain their significance for biological activity. A close correlation has been shown to exist between hazard and molecular weight, specific gravity, refractive index, boiling point, melting point, and saturated vapour pressure, particularly for volatile organic compounds.

For a preliminary evaluation of toxicity it is therefore necessary to collect information on : chemical formula ; molecular weight ; specific gravity ; refractive index ; boiling point and melting point ; saturated vapour pressure at relevant temperature ; solubility in water, fats and

other substances; coefficient of vapour solubility in water at relevant temperature ; state of aggregation and particle size stability in various conditions of hydrolysis, oxidation and so on ; degradation products and possible products of transformation in the atmosphere ; and impurities and composition as encountered in practice.

Preliminary information is also needed on current conditions of occupational exposure to the substance concerned. This information should provide an understanding of the characteristics of the hazardous agent as it is used, manufactured, or stored and of any toxic by-product, the physical makeup of the production system (i.e., the equipment involved and the points in the system where release of the hazardous agent may occur), and the expected levels of airborne exposure in the workplace. These data will provide indications as to how the agent will behave if released into the atmosphere and in what state it will exist (i.e., solid, liquid, or gas). It should be determined whether the agent is an ingredient, by-product or end-product of the production process. If the agent is an ingredient, information should be obtained on the stage in the production process at which it is introduced, its function, and whether it reacts or combines with other substances. If the agent is an end-product or by-product, the total processes of production and application should be understood.

Permissible levels refer not only to mining and production processes in industry, but also to agriculture and to those workplaces where end-products are being stored, purchased, or utilized. A notable example is the application of pesticides by means of spraying, dusting, or dipping. Although the toxicity of the compound will remain the same, the hazard may largely differ from that occurring during production, involving such factors as inhalation of aerosols, contamination of the skin, high environmental temperature and humidity, long working days, and seasonal peaks of exposure. Therefore for special types of activity special tests may have to be carried out.

3.3 Animal experiments

Animal experimentation is the basic step in research because it provides an opportunity to :

(1) evaluate the control exposure parameters by enabling the intensity and duration of exposure to be kept as regular as possible, by permitting the avoidance of mixed exposure, and by permitting the standardization of environmental and living conditions ;

(2) ascertain the toxic effects through biopsy, alterations in gross anatomy, and histopathological evaluation ;

(3) predict serious health risk (such as cancer, mutation, and reproductive disorders) which may follow the introduction of new or existing products or processes that have not been or cannot be studied epidemiologically.

On the other hand the main constraints of animal experiments in industrial toxicology are :

(1) difficulties in interpretation caused by differences in sensitivity to noxious agents attributable to variations in age, sex, species, and strain ;

(2) the different life-span of man and animals ;

(3) the different biological responsiveness of man and animals ;

(4) the difficulty of obtaining information on sensory responses ;

(5) the much less extensive experience in toxicity evaluation following inhalation than in toxicity evaluation following oral administration (e.g., food additives and pesticide residues).

In particular, LD_{50} values have shown that sensitivity to toxic substances of the different species of laboratory animals varies by one or two orders of magnitude. This implies the need for experiments involving more than one animal species and a number of exposure levels. The choice of species and strains depends on the objectives of the test, the agent under consideration, and the effects to be examined.

Susceptibility to chemical compounds may be affected by sex ; sometimes females appear to be more susceptible than males (same response at lower dosage), and in other cases the reverse is true. There are no general rules for predicting sex differences in susceptibility, which may amount to a factor of 2 to 3 in certain chronic exposures. Differences between individuals may cause toxicity to vary by factors of as much as 4 to 6.[1] This makes it necessary to carry out experiments on groups of animals sufficiently large to attain significant differences (usually $P = 0.05$) for a given estimated end-point between exposed and control groups.

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[1] KRASOVSKIJ, G. N. Species and sex differences in sensitivity to toxic substances. In : *Methods used in the USSR for establishing biologically safe levels of toxic substances*. Geneva, World Health Organization, 1975, pp. 109–125.

The conditions under which the animals are kept, their diet, and circadian and seasonal biological rhythms, together with meteorological factors, also induce variations in toxicity indices by a factor of 2 to 3.

To reduce these variations as much as possible the conditions in which animals are kept should meet with agreed international requirements, and the experimental conditions should be clearly defined with regard to species and strain, age, sex, weight, diet, doses and dilution factors, solvent used, and method of administration of toxic agent. The control group should always receive the vehicle in which the toxic agent is administered in order to confirm that the vehicle itself is not toxic to the animal.

3.3.1 *Exposure experiments*

Toxicological tests should be carried out with :

— the pure substance,

— the technical material that will be used in practice, and

— the formulation, if the chemical is used dispersed in other chemicals.

In some circumstances, comparison of the toxicity of different batches may be considered.

Animal experiments involve three different lengths of exposure : acute toxicity experiments with exposures lasting up to 24 hours, short-term [1] and subacute toxicity experiments with exposures lasting up to a tenth of the life-span of the experimental species, and chronic toxicity experiments with exposures sometimes lasting as long as the whole life-span of the animals concerned. Since the respiratory tract and the skin are the main routes of entry of workplace chemicals, knowledge of the toxic effects by inhalation and skin contact is certainly the most useful.

During inhalation experiments, conditions in the working environment should be reproduced as far as possible. The concentrations existing in the breathing zone should be systematically monitored. However, inhalation experiments have not yet been standardized. The most troublesome problem is that of generating and monitoring the size distribution of aerosols. Deposition, the absorbed dose, and the resulting effects are all functions of aerosol size. Particle size should be adapted to the physiological characteristics of the particular animal

[1] Some research groups reserve the designation " short-term toxicity testing " for 90-day exposures in the rat and one-year exposures in the dog. For the purpose of this report subacute and short-term exposure testing are considered together.

species used. The dose depends not only on the concentration in air and the duration of exposure but also on the minute volume and percentage retention. It is therefore essential to understand the factors affecting absorption, such as solubility in water or in blood and adipose tissue.

Acute toxicity experiments. Acute toxicity refers to a single, repeated or continuous exposure to a chemical for 24 hours or less. This definition covers single oral or parenteral administration of the chemical as well as the longer exposure periods (up to 24 hours) usually selected for inhalation or dermal procedures. Animals should be observed for not less than 14 days so that delayed effects can be discovered.

By and large, there is agreement on the methods used in various countries for determining acute toxicity by oral and parenteral administration. The procedures described by the Standing Committee for the Establishment of Maximum Allowable Concentrations of Toxic Substances in the Atmosphere of Industrial Premises of the Committee on the Scientific Problems of Occupational Hygiene and Pathology of the Academy of Medical Sciences of the USSR [1] and those recommended by the US National Academy of Sciences [2] are examples of standardized tests.

Because the lethal level can be established objectively and easily and the dose causing the death of half the experimental animals is unaffected by the presence of hypersusceptible or resistent animals, the LC_{50} and the LD_{50} appear to be the most important and reliable indices for acute toxicity.[3, 4, 5]

Subacute and short-term toxicity experiments. Forecasts of long-term effects of a toxic substance that cannot be obtained from acute exposure experiments may be more reliably predicted from subacute and short-term exposure experiments. Such exposures, usually lasting up to a tenth of the life-span of the experimental animal, have three main objectives :

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[1] *Permissible levels of toxic substances in the working environment.* Geneva, International Labour Office, 1970, pp. 163–170.

[2] *Principles for evaluating chemicals in the environment.* Washington DC, National Academy of Sciences, 1975.

[3] PRAVDIN, N. S. *Metodika maloj toksikologii promyslennyh jadov* [Methods for the toxicology of low concentrations of industrial poisons]. Moscow, Medgiz, 1947.

[4] BLISS, C. I. *Science*, **79** : 38 (1934).

[5] MILLER, L. C. & TAINTER, M. L. *Proceedings of the Society for Experimental Biology and Medicine*, **57** : 261 (1944).

(1) to define in one or more animal species the level of exposure that, on the basis of the morphological, physiological, and biological parameters selected, has no adverse effect on the animal repeatedly exposed to the chemical ;

(2) to discover in a relatively short period of time the possible cumulative effects [1] of the substance under consideration ; and

(3) to detect the organs and systems that are affected by such cumulation in order to be able to conduct later chronic experiments in a proper manner.

Substances with low toxicity in acute exposure may prove to be very dangerous in subacute experiments because of cumulation.

The assessment of cumulation by the use of lethal doses or strong single exposure does not always provide sufficient information on those cumulative effects of very small doses that may occur in prolonged industrial exposure. Repeated exposures over a relatively short time-span allow study of the kinetics of the substance and the rate of recovery of functions that have been impaired.

Chronic toxicity experiments. Chronic toxicity experiments, in which animals are exposed for the major portion of their life-span, forecast the effects of prolonged occupational exposure more precisely. Three specific objectives of these experiments are :

(1) to determine the uptake/response relationship ;

(2) to estimate the no-effect level and the no-adverse-response level within the limitations posed by a specific experimental design ; and

(3) to determine the mechanism of action.

Since there are often considerable differences between species, chronic toxicity experiments should be carried out on no fewer than two species. It has often been stressed that, if possible, one or more of the species selected should be of a kind in which the pharmacodynamics of the compound is similar qualitatively and/or quantitatively to that in man. In practice, however, the choice of species for testing may have to be made before information on the metabolism of the compound in man is available.

[1] The effects of repeated exposure to a toxic substance. Cumulative effects may take two different but not mutually exclusive forms : *material cumulation* due to the growing dose of the toxic substance deposited in the organism and *functional cumulation* due to a progressive summation of changes resulting from the effects of the substance. In occupational exposure cumulation may occur with very small amounts of substance acting for a long time, perhaps throughout the lifetime of the worker.

Investigations on the effects of at least two concentrations of the substance, differing by a factor of between 5 and 10, are carried out on two equal experimental groups with the necessary controls, the investigations being made repeatedly throughout the period of exposure. At the end of the exposure some of the experimental and control animals are sacrified for biological examination. Observations are made on the others during their period of recovery (up to one month) to determine the reversibility of the effects on withdrawal of the chemical.

Concentration levels should be chosen according to the results of the acute and intermediate experiments, the known properties of compounds similar in structure and action, and the level expected in occupational exposure. Special note must be taken of cumulative effects. The highest dose level should not markedly shorten the life-span of the animals but should be sufficiently elevated to produce slight effects.

3.3.2 *The effects of exposure*

Animal experiments may focus on a variety of different toxicological effects. For any period of exposure the adverse effects may be local or systemic and clinically acute or clinically chronic. Toxicological effects include (but are not limited to) irritation, skin sensitization, functional changes in the nervous system, carcinogenesis and mutagenesis, and harmful effects on the reproductive system. Animal experiments also help to trace metabolic pathways and elucidate mechanisms of action.

In acute toxicity experiments a rough estimate of the LC_{50} and LD_{50} is sufficient. A precise determination of LD_{50} is not required since a threefold difference in oral LD_{50} obtained by different laboratories is not unusual, and this difference may be higher when the compound is administered by inhalation. It is more important to collect basic information on signs of intoxication, cause of death, latency period for onset of symptoms and recovery, and slope of the dose/response curve (although the uncertainty in the estimate of this slope is very large).

An example of an arbitrary classification of toxicity is given in Annex 1.

Macroscopic (autopsy) and sometimes microscopic examination should be performed in order to determine the target organ. This may help in indicating previous disease states that might make exposed persons more susceptible to the chemical.

In subacute (short-term) and chronic exposure tests the quantities that are usually measured or noted, either at regular intervals in the course of the exposure period or at its termination, are as follows :

(1) growth rate and food consumption (weekly records) ;

(2) clinical signs of toxicity or cause of death ;

(3) physiological activity according to the type of toxic action of the chemical investigated (e.g., lung function, liver function, kidney function, electrocardiography, electroencephalography, peripheral nerve functions, and electromyography) ;

(4) organ weight, morphological appearance, and histopathological features ;

(5) concentration levels of the agent (or its metabolites) in blood and organs.

Other biochemical tests may be suggested by the study of the mechanism of action of the chemical. These may include immunological tests and assays and the determination of enzyme activity (e.g., cholinesterase activity) and microsomal enzyme induction or inhibition.

Unfortunately, when new chemicals are involved, the mechanism of action and the target organ are not necessarily known before long-term studies are undertaken, and in this case only routine biological tests are performed on blood and urine.

3.3.3 *Studies on metabolism and mechanism of action*

The metabolic pathway (absorption, distribution, biotransformation, elimination) of the chemical and its mechanism of action are of major interest. Knowledge of these factors is a prerequisite for rational biological monitoring. Studies must first be carried out on animals. Usually they are performed in the rat and one non-rodent species. If significant differences in toxicity are found between species it is of interest to determine whether they correlate with differences in metabolism. The radioactive labelling of chemicals is now widely used in investigations on animals because it permits the determination of the total recovery balance (urine, faeces, carcass). Identification of the metabolites in biological materials calls for various analytical methods.

3.3.4 *Local toxicity and irritation*

The term " local toxicity " is usually restricted to the direct local irritant action of a compound on the skin and the eye. The irritant action on the respiratory mucosa is normally evaluated during systemic toxicity tests by inhalation. The albino rabbit is often used for these investigations, but some investigators recommend experiments on the skin of pigs, which is anatomically and physiologically similar to the

skin of man. The results of the animal experiments have to be compared with the results of epidemiological investigations. Only in this way is it possible to obtain better knowledge about the relationship between the physical properties of chemicals and the irritant effects. Many substances in the industrial environment possess irritant properties and can cause inflammatory reaction when they come into direct contact with living tissue. An example of a classification based on irritant effects is given in Annex 2.

3.3.5 *Sensitization*

Sensitization diseases are frequent in exposed workers, and it is of the utmost importance to discover potential sensitizers before their large-scale use. However, sensitization tests are difficult because of the high variability of individual response and of the low level of contamination at which sensitization appears. The likelihood of sensitization being induced in workers probably descreases with decreasing exposure levels. However, if sensitization has already taken place, extremely low levels of exposure may cause sensitization diseases. Permissible levels may therefore prevent the induction of sensitization but can hardly prevent disease once sensitization has been established.

Recent research carried out by cutaneous, intracutaneous, subcutaneous and respiratory routes in laboratory animals (mainly guinea-pigs and sometimes rats or rabbits) has shown that in principle small doses reduce the risk of becoming sensitized. As the dose increases, the effect increases rapidly, then gradually reaches a maximum and finally diminishes and disappears. Usually the curve begins to fall when the dose has already reached toxic levels.

While in the past sensitization has been studied almost exclusively by the cutaneous route, at the present time the inhalation route is also used when studying the sensitization potential of industrial contaminants, because the risk must be assessed through experimental conditions that are as far as possible realistic. This consideration leads to the frequent use of simultaneous exposure combining inhalation with cutaneous contact. If necessary, exposure should simulate the usual mode of contact in the workplace.

For an initial screening of sensitization properties several methods have been worked out.[1, 2, 3] In view of the shortcomings of *in vivo*

[1] ALEKSEEVA, O. G. & PEMKEVIČ, A. I. *Gigiena i sanitariya*, No. 3 : 64 (1972).

[2] KLIGMAN, A. M. *Journal of investigative dermatology*, **47** : 393–409 (1966).

[3] MAGNUSSON, B. & KLIGMAN, A. M. *Journal of investigative dermatology*, **52** : 268–276 (1969).

methods (e.g., the interference of allergic and irritant reactions, the difficulties of assessing the degree of sensitization objectively, and the lack of specificity) special efforts are being made to improve *in vitro* methods.

To evaluate the severity and the course of the process of sensitization in animal experiments, use is made of non-specific methods based on changes in cellular elements of the blood, activation of biogenic amines, modification of blood serum proteins, and alterations in coagulation.

3.3.6 *Functional studies of the nervous system*

Subtle functional changes in the central and peripheral nervous systems and in behaviour are being increasingly recognized as important effects of relatively low levels of exposure to toxic substances. The scientific approach to this problem is largely based on Pavlov's assumption that the central nervous system is the functionally integrating unit of the organism. A detailed review of the research methods utilized in the USSR for establishing permissible levels for toxic substances was recently published by WHO.[1] Research approaches for behaviour toxicology were also summarized at a behavioural toxicology workshop for the early detection of occupational hazards held in Cincinnati, Ohio, USA, in 1973.[2] The paper presented by Stokinger[3] was of particular interest.

The changes caused by a toxic substance in the functions of the higher nervous system may be studied in three ways:

(1) initial appraisal of the effect of the substance on the whole organism;

(2) evaluation of the changes in the central nervous system on prolonged exposure to small amounts of the substance in order to establish the dose/response relationship;

(3) investigation of functional changes in order to study the mechanism of action of the substance.

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[1] PAVLENKO, S. M. Methods for the study of the central nervous system in toxicological tests. In: *Methods used in the USSR for establishing biologically safe levels of toxic substances*. Geneva, World Health Organization, 1975, pp. 86–105.

[2] XINTARAS, C. ET AL., ed., *Behavioural toxicology: early detection of occupational hazards*. Washington, DC, National Institute for Occupational Safety and Health, 1974 (HEW Publication No. 74–126).

[3] STOKINGER, H. E. (1974) Behavioral toxicology in threshold limit values. In: Xintaras, C. et al., ed., *op. cit.*

An initial appraisal of the effects on the central nervous system is necessary when studying an unknown substance. After administration of a single dose and without preparation of the animal, it may be possible to ascertain changes in orienting and defensive reflexes showing cortex and subcortex involvement. In these experiments use is made of stereotyped sets of stimuli, such as auditory, tactile, and pain stimuli.

For substances with central neurotropic activity, the behaviour of animals under exposure is studied with a set of more sensitive methods focusing mainly on the evaluation of motor activity, thus making it possible to detect any specific effect that the substance may have on higher nervous system function and to determine whether behavioural effects are likely to develop on industrial exposure. The evaluation of changes in the central nervous system during long-term exposures to small concentrations of toxic substances requires precise and sensitive methods based on conditioned reflexes in a variety of laboratory animals.

Such exposures may result in the elimination of internal inhibition processes ; there may even be loss of the conditioned reflex or an alteration of the stimulatory process with reduction of the strength of the response and disturbance of its pattern. The severity of the change and the time taken for it to develop depend on the concentration or the dose to which the animal has been exposed. In chronic inhalation experiments, phases of depression and activation of various functions may occur, showing the interaction between the toxic effect and the adaptive mechanisms, which may lead to an apparent normalization of higher nervous system functions.

A simpler but still sensitive method involving the determination of the latent period of the response to an electrical stimulus has also been used to evaluate toxic effects.

Stress tests are very useful in carrying out investigations on subtle functional changes owing to their high sensitivity to the latent effects produced by subthreshold doses of toxic substances.

3.3.7 *Carcinogenesis and mutagenesis*

Perhaps the most difficult and specialized field in the establishment of permissible limits involves carcinogenic and mutagenic agents. Industrial toxicologists and cancer research specialists must cooperate in the planning, execution, and interpretation of these studies. Many studies have been carried out in the past 20 years in this area but the fundamental question is still under discussion : whether there is or is not a threshold of effect. Many scientists are inclined to believe that the initial biological effect of the carcinogen is at molecular level, inducing irreversible changes

in the cell, and in this case there may be no threshold. Other scientists feel that the process of transformation of precancerous cells into malignant cells or clones of cells may have a quantitative threshold.

One point of departure in proposing permissible levels for carcinogenic agents is to choose a dose that would not be expected to increase the risk of cancer during the natural lifetime of a given animal species. Such an approach requires the extrapolation to humans of the results obtained from animal experiments (see Annex 3 for USSR application involving benzopyrene). Specific guidelines for carcinogenic and/or mutagenic testing have been developed by WHO,[1] the International Agency for Research on Cancer,[2] a number of governments, and individual research workers. Testing of this kind should be carried out in close cooperation with specialists in the field of carcinogenesis and mutagenesis.

Short-term tests for identifying potential carcinogens. In the past 10–15 years, short-term tests have been developed for assessing the carcinogenic potential of chemicals in the hope of replacing lengthy and expensive animal studies. Among such tests are :

(1) implantation of embryonic tissues following exposure to the chemical, and the use of newborn or pregnant animals (transplacental carcinogenesis) in an attempt to reduce the latent period for the induction of malignancies ;

(2) tests for chromosomal aberrations ;

(3) tests of mutagenesis based on the hypothesis that chemical carcinogenesis is a process involving two or more steps of which the first is a mutation detectable by tests such as those involving DNA repair synthesis, cell transformation *in vitro*, reaction with nucleic acid, and sebaceous gland suppression.

Selection of the most appropriate short-term tests for the detection of potential carcinogens is determined by the pharmacokinetic properties of the agent and the expected pathways of metabolic conversion. The results obtained from a single assay, particularly if they are negative, should be confirmed by testing with a battery of other short-term procedures in order to minimize the risk of not detecting a carcinogen. At

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[1] WHO Technical Report Series, No. 574, 1974 (*Assessment of the carcinogenicity and mutagenicity of chemicals*).

[2] *Screening tests in chemical carcinogenesis*. Lyons, International Agency for Research on Cancer, 1976 (IARC Scientific Publications, No. 12).

present, the mutagenicity tests that appear most promising are those that include a biochemical activating system for the chemical tested (e.g., an *in vitro* metabolic activation system derived from mammalian tissues).[1] However, until short-term assays have been properly validated they must be considered as only suggestive of a compound's carcinogenic potential, the indication being viewed in conjunction with the agent's expected biochemical reactivity (e.g., the presence of reactive groups).

Thus, structure-activity relationships to predict a possible carcinogenic hazard can be used in conjunction with the results of short-term tests to give a preliminary risk evaluation. Consideration must also be given to other criteria such as the likelihood of large-scale production, the likelihood of release and/or persistence in the environment, the expected exposure (duration, number of people, vulnerable groups), the socioeconomic need and, the routes of entry into and degree of absorption in the human body.

Studies of this kind lead to a preliminary risk/benefit evaluation and can help to establish whether a long-term test for carcinogenicity is necessary. As short-term tests cannot identify all chemical carcinogens, negative results in such tests do not necessarily imply lack of carcinogenicity. The opposite is also true. A positive response in a short-term test in animals does not imply that the chemical will invariably exhibit a carcinogenic activity in man, but this finding constitutes an alarm signal justifying further investigations (i.e., long-term tests) if a large-scale use of the chemical is foreseen.

Long-term tests for carcinogenicity. The main stages in long-term experiments are as follows.

(1) Study of the animals for the whole duration of life (i.e., until only 20% of the starting group is still alive) under administration of a range of doses varying from those certainly carcinogenic to the least effective postulated dose. Macroscopic and microscopic examinations of tissues at autopsy are the definitive methods of detecting potential carcinogenicity. Autopsies should be performed on all animals including those that die during the course of the study.

(2) Mathematical evaluation of the relationship between the dose and the carcinogenic effect, including the time of appearance of the effect.

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[1] *Screening tests in chemical carcinogenesis.* Lyons, International Agency for Research on Cancer, 1976 (IARC Scientific Publications, No. 12).

(3) Assessment of the risk of appearance of the effect following exposure to very small doses of the carcinogen for a time exceeding the natural longevity of the animal.

(4) Extrapolation of resulting data to man and calculation of the permissible level with appropriate safety margin (see section 4.2).

The main disadvantage of extrapolation on animals in research on maximum permissible levels for carcinogenic substances is the limited number of animals available. The usual experimental groups not exceeding 50 rats are far from the impracticable number of more than 900 statistically required for substances causing 0.1% tumour development. Therefore, in addition to including sizable safety factors in the final calculation, great caution is necessary in the methods used for the tests. At least one rodent species with known spontaneous tumour formation should be tested; carcinogenic additives may be used to enhance the activity of the test agent; and a positive control group receiving a known carcinogen should be included.

Mutagenicity tests. Various mutagenicity tests are currently used (dominant lethal test, host-mediated assay, cytogenetic analysis, specific locus test, etc.) but interpretation of the results in terms of mutation risk for man remains difficult.

3.3.8 *Effects on reproductive function*

In recent years special attention has been given to the harmful effects of toxic agents on the reproductive functions in men and women (gonadotoxic effect), on the development of the fetus in the uterus (embryotoxic effect), on the production of malformations or deviations from normal structure of offspring (teratogenic effect), and on the postnatal development and health of offspring of exposed male and female workers.

Evidence of these dangers to man can be obtained from medical examination and epidemiological investigation. However, for preventive purposes it is essential to have adequate experimental models to permit the extrapolation of data from animals to man. Appropriate animal models for the study of embryotoxic, gonadotoxic, and mutagenic agents are not well established, and it has therefore been necessary to study the problem by collating the results of epidemiological studies and of animal experiments. It should be realized that an embryotoxic effect can be exhibited by almost any chemical if the administered dose is high enough.

For the time being the most effective available procedure for estimating the reproductive hazard of a substance to man appears to be a complex investigation on warm-blooded animals by the method of dominant lethal mutations, the analysis of chromosomal aberrations (particularly during the metaphase) in somatic tissues and sex cells, and the study of the progeny for several generations.

The teratogenic risk may best be evaluated in short-term experiments in which the pregnant animal is exposed to the test material at certain periods of organogenesis. At least two mammalian species are used —one rodent and one non-rodent.

3.4 Observations on humans

Animal experiments are a basic, but not the most definitive step in describing the uptake/response relationship. Observation of effects in humans is of the utmost importance in establishing permissible levels for occupational exposure. The purpose of collecting human data is twofold—to supplement animal experiments as a basis for the establishment of adequate permissible levels of occupational exposure, and to provide the most appropriate information for determining the adequacy of previously established permissible limits. The following approaches can be used.

(1) Studies of human case histories, morbidity data, and vital records involving individuals exposed to the toxic substance of concern. Great care should be taken in evaluation of the validity of such data in that morbidity and mortality classification systems are not always comparable.

(2) Studies of the results of regular occupational health programmes including pre-employment and periodical examinations of workers.

(3) Studies of data derived from questionnaires to workers on their state of health as related to their work. In such an approach, great care must be given to the design and implementation of the study in order to avoid bias in the questionnaire, the interviewer and the interviewed.

(4) Studies of the results of special medical surveys and in-depth functional, biological, and clinical investigations.

(5) Studies of the effects of laboratory exposure of humans.

In any of these studies it is important to record the environmental concentrations of the hazardous substances to which workers are

exposed. The use of protective equipment, such as respirators or special clothing to prevent skin absorption, and any other safety measure should be reported along with the observations on health effects. In many cases reported studies seldom provide all the desired information. They must therefore be thoroughly evaluated and reinforced with other studies on animal or human exposure.

Annex 4 gives examples of the different types of scientific data available for assessing permissible levels of occupational exposure.

3.4.1 *Investigations involving human subjects*

Although satisfactory evidence of irritant effects and other types of discomfort can be obtained from current methods of studying local toxicity and higher nervous system functions in animals, it is not yet feasible to extrapolate these results to man in the sense of defining permissible levels of exposure. Studies of the metabolism of chemical substances in man may be needed in order to evaluate man's comparability (qualitative and quantitative) with animals. Therefore short-term tests in human volunteers may become necessary. These experiments and tests are governed by ethical and legal principles, set forth internationally in 1964 by the Declaration of Helsinki of the World Medical Association and revised in 1975.[1] The basic requirements to be fulfilled are :

(1) that the experiment shall be strictly voluntary ;

(2) that preliminary experiments shall be carried out on laboratory animals to determine the threshold for irritant and/or other acute effects (so as to avoid human experiments with substances having small irritating effect and high systemic toxicity) ;

(3) that the level of risk involved shall be known to be insignificant ;

(4) that the investigators shall carry out a careful preliminary medical examination and shall keep the subjects under observation for some time after the experiment.

Observations in man may also provide an opportunity to study the human metabolism of toxic substances. A typical example of the need for experiments in humans is found with odours. Here it should be

[1] World Medical Association. Declaration of Helsinki. Recommendations guiding doctors in clinical research, adopted by the 18th World Medical Assembly, Helsinki, Finland, 1964, and revised by the 29th World Medical Assembly, Tokyo, Japan, 1975. The revised text was published in *WHO Chronicle*, **30** : 360–362 (1976).

remembered that repeated exposure may create a reduction of sensation (e.g., workers become accustomed to the smell of sulfur dioxide). The threshold of smell is determined by the short-term exposure of humans under laboratory conditions. One approach involves the use of EEG recordings. In view of the varying sensitivity of the sense of smell, these investigations should be repeated over a period of time in order to assess the degree and limits of acquired tolerance.

The threshold of irritating effects on man can usually be determined by short-term exposure. Sophisticated techniques using objective indices enable investigators to record irritation effects at levels lower than the subjective threshold. Changes in the speed of the motion of mucus in the nose and EEG changes during inhalation of very small concentrations of some irritant substances have been shown to be much more sensitive than the subjective response.

In studying sensitization responses, inhalation tests are usually conducted only in specialized clinics. Patch and other skin tests are widely used in medical examination of workers.

Non-specific methods can also provide valuable information on the severity and nature of human toxicity. Non-specific effects may be detected early by functional tests carried out on small groups of volunteers of the same age and sex and in apparent good health, or on groups occupationally exposed to the given substance. These groups and a control group are studied using the tests that have given the most significant results in animal experiments. Depending on the type of effect anticipated, the following sensitive but non-specific methods may be utilized : psychophysiological tests (alertness, performance, reaction time, flicker fusion), ECG and EEG, measurements of peripheral nerve conduction velocity, measurements of the speed of the oculomotor reflex, adaptometry, olfactometry, serum proteins, liver functions, enzymatic activity, immunological response of the organism, and the phagocytic activity of leucocytes. In functional studies, the results are compared with the initial indices in the exposed and control groups, and the statistical significance is then assessed.

3.4.2 *Epidemiological studies*

The purpose of epidemiological investigations is to correlate environmental conditions with the state of health of exposed workers. They must therefore be designed in such a way as to provide as complete a picture as possible of the presence (or absence) of the effects of exposure to a harmful chemical substance. Such studies must provide quantitative

information that is statistically reliable and must cover a sufficiently long period of time to provide useful results.

The investigations may take the form of retrospective and case control studies or cross-sectional and prospective studies. The latter are difficult to carry out but give the most valuable information.

When lifetime records of health and occupational exposure are available for large numbers of workers exposed to various concentrations of a chemical, comprehensive epidemiological studies may effectively establish the uptake/response relationship in humans. Such epidemiological studies can then provide a firm practical basis for assessing the effects of exposure in humans. Unfortunately, such comprehensive lifetime records are seldom available, and consequently the majority of recommended permissible levels are theoretical extrapolations from more limited human data and from the evidence accumulated from animal models.

The selection of the working places in which clinical and hygienic studies will be conducted is complicated by a number of factors. The most important are the exposure to multiple hazards in the workplace and the presence of many stressors acting on the working community in their non-occupational environment. Any attempt to focus only on the substance under consideration as the cause of a detectable health effect may therefore lead to an overestimate of the seriousness of the hazard under study. The proper use of epidemiological methods can help to avoid this problem. Therefore the following requirements [1] should be considered as far as possible in epidemiological investigations.

(1) The toxic substance to be studied should be the only chemical agent present or at least the predominant one.

(2) The other substances present should be identified and their concentrations and permissible levels known ; their concentrations should not exceed their permissible levels, and their toxic effects should differ from those of the substance under consideration.

(3) The concentration of the substance under consideration in the working atmosphere should remain relatively constant, preferably within one order of magnitude of the tentative permissible level ; however, significant fluctuation and intermittent exposure must be anticipated in view of changes in production processes, and such fluctuations

[1] VOLKOVA, Z. A. Use of data on human health and environmental conditions. In : *Methods used in the USSR for establishing biologically safe levels of toxic substances*, Geneva, World Health Organization, 1975, pp. 160–168.

should be taken into account in planning epidemiological studies and in evaluating combined exposure.

(4) Uptake of the substance under consideration by other routes (particularly through skin contamination) should be precluded.

(5) The number of workers to be tested should be sufficiently large to allow consideration in the statistical analysis of such factors as age, sex, and living conditions.

(6) If possible, two or three factories of the same type but with different exposure concentrations should be studied.

The study design should be developed in detail before the start of the investigation, due consideration being given to such factors as raw materials, intermediates, end-products, by-products, routes of exposure, workload, and control measures.

Sampling strategy and analytical methods should be adapted to the actual conditions. Sampling plays a significant role, perhaps even more so than that of analysis, because air must be sampled in a manner that preserves the contaminants and permits an accurate quantitative analysis of the constituents that were actually present in the air at the time of sampling. Difficulties involve the large variability of airborne concentrations of industrial substances and the discontinuity of worker exposure. Sampling and analytical methods must be accurate and reliable over the whole range of concentrations likely to be encountered. The specific effects on man of the contaminant under study influence the type of sampling to be used. Substances that cause adverse effects in a short time should be monitored continuously.

On the other hand, the pharmacokinetics and effects of certain contaminants may call for time-weighted averaging over a workshift. Whether the air in the room or the breathing zone should be sampled and whether personal samplers should be used may be determined by the type of hazard. Certainly, careful consideration must be given to the simplicity of the sampling device and the degree to which it may interfere with an employee's performance. Other factors such as specificity of sampling, collecting efficiency, and sensitivity must similarly be taken into account.

A complicating factor that often hampers the development of reasonable uptake/response relationships is the instability of airborne contaminants. If a substance reacts with other airborne constituents, it is often difficult to ascertain whether the substance itself or a reaction product should be sampled. These reactions may occur after collection in the sampling device and produce misleading results.

Analysis is usually more straightforward, but the usual problems of interferences and variables, interlaboratory variations, calibration, and data reduction are to be faced. Moreover, sampling and analytical systems that are not completely comparable must be tested for reliability and reproducibility.

Where data are available on previously existing conditions, they may not always go back in time sufficiently far to allow for the proper establishment of uptake/response relationships. This is of special importance where cumulative, chronic, or latent effects are of concern.

Current exposure conditions may be useful in estimating prior exposures, especially where process changes have not taken place. In some instances, it may also be possible to duplicate conditions temporarily in order to estimate earlier exposures. However, it is recognized that the estimation of environmental conditions existing at the onset of toxicological response is necessary in establishing or validating permissible levels.[1] The recent experience of unexpected and very severe chronic effects of exposure to substances considered to be only moderately toxic, such as vinyl chloride, demonstrates the need for continuous monitoring of the health status of exposed workers and where necessary the revision of permissible levels of exposure.

4. INTERPRETING DATA ON UPTAKE/RESPONSE RELATIONSHIPS

4.1 Effects and responses considered

While the concepts of health and of adverse effects may differ from country to country, uptake/response relationships are, to a large extent, similar. Regardless of the criteria used in determining health impairment there will always be three types of effects or responses to be considered : [2]

— those generally agreed to be adverse ;

— those that may be adverse, although epidemiological or experimental evidence is not yet conclusive ;

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[1] STOKINGER, H. E. Criteria and procedures for assessing the toxic responses to industrial chemicals. In : *Permissible levels of toxic substances in the working environment*. Geneva, International Labour Office, 1970, p. 36.

[2] WHO Technical Report Series, No. 571, 1975 (*Early detection of health impairment in occupational exposure to health hazards*).

— those possibly related to exposure and to health impairment but about which there is no consensus.

The first two categories of effects should be considered most relevant ; the last category is still the subject of scientific research and is not necessarily taken into account in recommending permissible limits.

Once toxicity test results, human data, and epidemiological findings have been obtained, the next step is the interpretation of the available information. Except when new agents or substances very rarely used are being evaluated, the difficulty is usually that there is an excess of sometimes contradictory information rather than a paucity of data. The interpretation of this information is therefore a crucial step that requires a wise critical approach and extensive experience. It is inevitable that the conclusions must be influenced by individual professional judgement. Although it is impossible to prevent any degree of bias from entering at this step, certain basic criteria can be suggested that will help in identifying the main areas of agreement and disagreement.

Not all changes in experimental animals or in humans should be regarded as health effects. For instance, the presence of an agent or its metabolites in blood, urine, hair, organs, or exhaled breath is a biological effect not necessarily associated with health impairment. These changes may be highly important for estimation of uptake and of health risks, but they are not usually considered as constituting direct health effects.

Biological effects are due to the action of an agent on animal or man. Whether an effect is observed depends not only on the dose but also on :

— whether the effect was considered in the study design ;
— whether the method of examination is sensitive enough ; and
— whether the species exposed could respond with this type of effect.

With increasing uptake, the intensity of an effect and/or magnitude of a response (proportion of subjects affected) increases. With decreasing level of uptake there comes a point at which the response is no longer observed, but this does not mean that it no longer exists. One has reached the " no-effect " (or no-response) level. It is seldom possible to read off this level from the study data ; usually it is necessary carefully to review the design of the study, the existing data, and the statistical analysis. The establishment of a no-effect or no-response level is a matter of scientific judgement by health experts, not of mathematics.

Many effects are non-specific, i.e., the cause cannot be deduced from the effect itself because exposure to a chemical may merely be only

one of several possible causes. The experts then have to make a careful review of all the possible exposures that could produce the particular effect. As was pointed out by a WHO Study Group in 1974, " a statistically significant effect as such is not the same as impairment of health ; one should therefore distinguish between effects as such and adverse effects, i.e., unacceptable effects. What is regarded as unacceptable (not permissible) is a matter of interpretation and ultimately of choice ".[1] Health experts therefore consider those dose-related changes that are potentially relevant to health impairment. Whether the observed changes are really relevant cannot be stated *a priori* but only after all data have been considered, i.e., after the study has been completed. If one considers an effect or response as adverse, then the corresponding dose or level of concentration in air has to be considered not permissible.

One may distinguish the following broad overlapping categories of potentially relevant effects : [1]

— changes in biological and morphological parameters ;
— changes in the physical state and the function of physiological systems ;
— changes in wellbeing to be evaluated by medical history records and questionnaires ;
— integrative changes that may result from effects on several physiological systems.

In any event identification of what is, or is not, determined to be an unacceptable effect for the substance being evaluated is of the utmost importance.

The effect or no-effect level is intimately tied to the criteria used for its determination and it is preferable to work with the " no-adverse-effect level ".

In a recent report by the USA's National Academy of Sciences [2] non-adverse effects are defined as :

(1) changes that occur with continued exposure and do not result in impairment of functional capacity or the ability to compensate for additional stress ;

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[1] WHO Technical Report Series, No. 571, 1975 (*Early detection of health impairment in occupational exposure to health hazards*).

[2] COMMITTEE FOR THE WORKING CONFERENCE ON PRINCIPLES OF PROTOCOLS FOR EVALUATING CHEMICALS IN THE ENVIRONMENT. *Report*. Washington DC, National Academy of Sciences, 1975.

(2) changes that are reversible following cessation of exposure if such changes occur without detectable decrements in the ability of the organisms to maintain homeostasis ;

(3) changes that do not enhance the susceptibility of the organism to the deleterious effects of other environmental influences—whether chemical, physical, microbiological, or social.

The problem that the expert must face is therefore the choice of effects to be taken into consideration with a view to constructing the uptake/response curve on which the permissible level will be decided. Four categories of choice have been identified : [1]

(1) the choice of parameter that is thought to be relevant and type of effect considered to be decisive (qualitative choice) ;

(2) the intensity that is to be permitted for the chosen parameter (quantitative choice) ;

(3) the variation that is to be permitted in the vulnerability of individuals or subgroups within the working population ; and

(4) the extent to which an effect of uncertain health importance should be allowed to continue—in both duration and frequency of occurrence.

It is in these areas of choice that large differences of opinion have occurred in the past. The approach of medical research in Western Europe and the USA has traditionally been oriented towards cell and organ alterations and biochemical changes as early indicators of diseases. In the USSR attention has been directed more towards the integrated functional response of the organism, taking into account specific and non-specific effects as well as some changes in the function of the higher nervous system and regarding them as a signal of biological interaction between organism and noxious factor.

In conclusion only the combined use of a comprehensive set of integral and specific indices is considered to provide reliable data with a view to assessing permissible levels. As a consequence of the use of such sensitive methods, the boundary line between health and disease tends to be blurred.

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[1] ZIELHUIS, R. L. Permissible limits. In : Zenz, C., ed. *Occupational medicine : principles and practical applications*. New York, Year Book Medical Publishers, 1975.

4.2 Extrapolation from basic information to permissible levels

A large amount of information for the establishing of permissible levels comes from results of animal experimentation, epidemiological studies, case histories, and studies on human volunteers. A necessary step in the interpretation of this rather heterogeneous material is the extrapolation of data from animals to man. While food toxicologists have a great deal of experience of this step, in inhalation and skin toxicology there is not yet an agreed approach, although some guidance is given in section 3 of this report in carrying out experiments on animals in such a way as to smooth as much as possible the variability involved in the choice of animals.

Extrapolation may necessitate the introduction of a safety margin, safety coefficient, or safety factor to allow for differences within and between species, for the number of animals used in relation to the human population at risk, and for the great difference between strictly controlled experimental conditions and those encountered in real life. Furthermore, safety margins recognize the substantial area of uncertainty in postulated uptake/response relationships.

The size of the safety margin depends on many considerations including:

— type of effect (e.g., a much larger margin is required for carcinogenicity and, indeed, for liver toxicity than for eye irritation);

— numbers of experimental animals or subjects in human volunteer studies in relation to population at risk;

— weight to be given to a particular non-adverse-effect level;

— existence of human data, particularly from well conducted epidemiological studies, the margin in this case being much smaller;

— gradient of the dose/effect or dose/response curve (a steep curve calls for a wider safety margin).

The size of the animal is a basic factor. A number of substances may obey the body-weight rule; others may require permissible levels to be related to body surface rather than to body weight. Until now there has been no internationally agreed rule for establishing a safety margin. In the approach adopted in many countries [1] the ultimate margin is based

[1] SANOCKIJ, I. V. *Metody opredelenija toksičnosti i opasnosti himičeskih večšestv* [Methods for determining the toxicity and hazard associated with chemical compounds]. Moscow, Medicina, 1970.

on the scientific judgement of an expert group whose duty it is to state explicitly why and how they arrived at their decision.

4.3 Detection and evaluation of harmful agents in the workplace

Placing limits on the concentration of harmful airborne contaminants in the workplace is widely accepted and promoted as a means of ensuring workers' health. Yet it is too infrequently recognized that the health efficacy of permissible levels depends on the sensitivity and reliability of sampling and analytical methods. Both the maintenance of environmental air standards and the means of assuring compliance with them depend on the integrity of the means of sampling and analysis of airborne contaminants.

When reviewing the data in order to develop the criteria for recommended permissible levels, it is necessary to examine the validity with which measurements of airborne contaminants were made. In evaluating epidemiological studies, inhalation chamber studies, and reports of occupational accidents, it is necessary to scrutinize the methods of sampling and analysing contaminants in order to derive the most accurate uptake/response relationship.

If, after the results of these and other studies have been evaluated and interrelated, it appears that the degree of exposure is related to the occurrence of an effect, then the uptake/response relationship leads to the derivation of the most appropriate workplace permissible level. At this point, sampling and analytical methods must be available for determining the concentration of a particular contaminant.

On the other hand, if the data available do not allow for the estimation of the degree of exposure that will result in the occurrence of an effect, then criteria other than the uptake/response relationship may be used as a basis for the environmental limit. In some instances, in the absence of sufficient data to quantify the no-response level for an effect such as carcinogenesis, it has been reasonable to recommend that workplace environmental limits be set at concentrations dictated by certain aspects of sampling and analytical methods. This may involve the setting of permissible levels that can be reliably detected but at the same time are close to the limit of sensitivity of a particular sampling and analysis system.

In any case, criteria for the selection of these sampling and analytical methods should be developed after scrutinizing the available methods and assessing their reproducibility and accuracy. Many criteria must be considered in selecting sampling and analytical methods to be recom-

mended as the most appropriate. Clearly, as the limit of detection of a substance is approached, the reliability with which one can establish the presence or absence of a substance decreases. It is reasonable to define acceptable reliability as that which has been found to occur in laboratory conditions while analysing the smallest possible quantities of the substance. As soon as this quantity is established as the least quantity that can be reliably detected, the type of sampling device and the duration of sampling that seem most appropriate may be specified.

5. HEALTH RECOMMENDATIONS AND NATIONAL DECISION-MAKING

5.1 Concepts of health

One of the objectives of occupational health is the prevention of health impairment, and setting up permissible levels is one of the means of achieving this goal. Therefore, in deciding on permissible levels from the uptake/response relationship, the concept of health is fundamental.

Between optimal health and health impairment resulting from occupational exposure to potentially hazardous substances there is no clear-cut borderline but a continuum of effects progressing from no observed response through a stage of apparently acquired tolerance to early observable effects of dubious health significance and then to a stage of unequivocal health impairment with manifest disablement and overt disease. National health authorities may differ in their choice of the point on the continuum that constitutes health impairment. Thus national health authorities may not always agree on what is not acceptable. It is obvious that these differences of interpretation play a role of paramount importance in the ultimate weight accorded the same scientific information and in the subsequent establishment of official national standards.

A major disagreement has in the past existed between values of permissible concentrations recommended in the USA and the USSR, particularly in regard to volatile substances and metals. In 1968, only 5% of the substances taken into consideration were close enough in agreement for common international permissible levels to be recommended by the Joint ILO/WHO Committee on Occupational Health.[1]

[1] WHO Technical Report Series, No. 415, 1969 (*Permissible levels of occupational exposure to airborne toxic substances*).

These differences resulted from the interaction of a number of factors, including the definition of what constitutes an adverse health effect. However, the basic objectives in establishing permissible levels are now very similar in both countries. In the USA the goal is to ensure that " no employee will suffer impaired health or functional capacities or diminished life expectancy as a result of his work experience ",[1] while in the USSR it is to achieve the safe level that " in the case of daily exposure at work for 8 hours throughout the entire working life will not cause any disease or disorders from a normal state of health detectable by current methods of investigation, either during the work itself or in the long term ".[2]

In the USA proposed permissible levels are based solely on health considerations. In practice, however, in the standard-setting process, technological and economic factors are taken into consideration. Recommendations based solely on preventing adverse health effects then serve as goals for the development of improved control technology and later revision of official standards. In the USSR it is also recognized that technological and economic factors may affect exposure situations, but official levels are still based solely on health considerations.

It is anticipated that future official standards originating from the USA, the USSR, and other parts of the world may be more in agreement, and international organizations such as WHO and ILO will be more able to make international recommendations based on a broad consensus among health scientists.

In their evaluation of the state of health in their countries, health planners are guided by the status of medical science and by national cultural values. Official standards are therefore the result of several criteria that may not be explicitly stated. Authorities in different countries make decisions on the basis of these criteria according to their own concept of health, and according to their interpretation of priorities and the need for applying permissible levels. National authorities also may consider the costs and economic factors involved and the resource demands of other health programmes.

At the international level there can be no mechanism for incorporating social, cultural, economic, and priority factors into decision-

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[1] UNITED STATES CONGRESS. *Occupational Safety and Health Act of 1970.* Washington DC, US Government Printing Office (Public Law 91–596. Ninety-first Congress, S.2193. December 29, 1970).

[2] SANOCKIJ, I. V. Investigation of new substances: permissible limits and threshold of harmful action. In : *Methods used in the USSR for establishing biologically safe levels of toxic substances.* Geneva, World Health Organization, 1975, pp. 9–18.

making. However, WHO can develop health-based recommendations for international consideration, leaving to national health authorities the responsibility of determining how best to implement them. Important activities such as the exchange of information on basic data and the improvement and standardization of test procedures allow nations to share a common pool of biological information to promote the setting of similar permissible levels and ultimately similar official standards in various countries. In addition, the further refinement of analytical techniques would facilitate decision-making.

Epidemiological findings may indicate factors requiring special attention in setting permissible levels, e.g., variations in the vulnerability of the working population, the effect of work exertion, and the effect of exposure to a number of contaminants. In developing countries, where the nutritional status is often poor and the general level of health may be affected by endemic diseases, the increased vulnerability of the working population to chemical exposures is of special concern. Genetic differences in individuals or ethnic groups may also increase vulnerability to certain substances. Permissible levels should be revised as necessary to take account of the reproductive vulnerability of young people and women exposed to toxic chemicals.

5.2 Technical factors

The main technical factors to be considered in the adoption of an official standard for a substance relate not only to the feasibility of implementing control measures to meet the stated standard but also to the sampling and analytical techniques available.

Sampling and analytical techniques play a definite role in establishing standards because their sensitivity can prove to be a limiting factor for the most stringent permissible levels. Insensitive analytical methods require prolonged if not continuous air sampling, the minimum volume of the sample of air being :

$$\frac{10 \times \text{analytical sensitivity (in milligrams)}}{\text{official standard (in mg/m}^3\text{)}}$$

When sampling and analytical methods are of limited sensitivity it is difficult to measure peak concentrations. Thus only long-term average concentrations can be considered. Sampling and analytical methods should be standardized and standards should refer to specific methods because there may be substantial differences between one method and another in precision, accuracy, and sensitivity.

In the past, technical feasibility has been a real obstacle to the implementation of health recommendations in the working environment, especially in factories already in existence, but the great progress made recently in industrial design, artificial ventilation, and process enclosure has changed the situation. There are few remaining technical difficulties that can hinder the adoption of permissible levels (except for carcinogens) provided that there are no economic restrictions.

5.3 Economic factors

Capital investment, operational costs, and other economic factors are often taken into consideration when setting national standards. There is clearly some conflict between a productive industrial economy and the maintenance of workers' health, job satisfaction, and environmental protection. In setting national standards the authorities sometimes attempt to balance these goals.

The adoption of industrial hygiene measures at the design stage is relatively less expensive than the capital and maintenance costs for large modifications in existing factories. The modification of existing plants may prove a severe handicap for established small and medium industries. These difficulties are further compounded by changes in the business cycle and uncertainties about other operating costs.

5.4 Current mechanisms in decision-making

Translating health recommendations into national standards often requires that one or more national groups perform the following tasks : collection of information ; preparation of criteria documents based on a review of the literature ; study of methods for biological and environmental monitoring ; and study of social, economic, and feasibility factors. These committees often comprise, in addition to experts, representatives of the responsible government authorities, representatives of employers, and representatives of workers' associations. Tripartite agreement is often considered to be an essential prerequisite because consensus standards having the support of workers, employers, and government representatives are more likely to be achieved in practice in the factories.

5.5 Re-examination of permissible levels

It is essential to carry out a periodic re-examination of permissible levels in the light of new scientific findings and general progress of

knowledge in toxicology and hygiene, and such re-examination and revision is a current practice in the USA, the USSR, and other countries. It is important to ensure that permissible exposure levels are not being exceeded, and, from a health point of view, it is important to know the actual extent of exposure to particular harmful substances. The collection and assessment of data on exposures and corresponding biological effects are essential for validating recommended permissible levels or for redefining those levels if necessary. These data are also needed for epidemiological studies. The monitoring of workplace exposures also permits an assessment of the effectiveness of the engineering and medical control programme.

5.6 Supplementary actions

5.6.1 *Work practice instructions*

Achieving air concentrations equal to or less than the permissible level requires engineering controls and safe work procedures. Correct operation and maintenance of equipment is also needed to prevent emergency problems from developing. Where skin absorption and/or ingestion are potential problems, it is most important to institute work practices relating to the proper use of protective equipment such as gloves and boots and rules for personal hygiene. Checks should be made to ensure that safety instructions are being followed by the workers concerned.

5.6.2 *Preplacement and periodic medical examinations*

Medical examinations, including where possible appropriate clinical laboratory tests, should be utilized to evaluate the health status of workers before exposure to toxic substances and periodically thereafter. Such examinations will help to identify workers who may be especially vulnerable to specific substances and thus minimize the possibility of unwarranted exposure to such substances. Periodic medical examinations of workers exposed to toxic substances are necessary to ensure that adverse effects are not developing as a result of inadequate control procedures, inappropriate work practices, or insufficiently protective permissible levels.

5.6.3 *Biological monitoring*

A useful technique for monitoring the exposure of workers involves the measurement of toxic substances or their metabolic products in biological samples such as blood, urine, and exhaled air. At times

biological monitoring may be utilized to detect early biochemical changes that precede adverse biological effects. Biological assays are sometimes more reliable indicators of exposure and of health risk than are intermittent measurements of air contaminants. They take into consideration compliance with work practices, use of personal protective equipment, and many other variables including host factors and physical workload. Biological monitoring provides a better estimation of the total exposure to the contaminant of interest, reflecting uptake through the lung, skin, and gastrointestinal tract and the contribution of sources outside the workplace.

Biological monitoring is best perfomed in workplace situations but the range of tests suitable for use in these conditions is limited. The criteria for selection of tests have been discussed by a WHO study group on the early detection of health impairment in occupational exposure to health hazards.[1]

Biological monitoring by itself clearly cannot be used to determine compliance with a standard expressed as a concentration in air, and in any event, employees usually have the right to refuse such tests. However, if the level of exposure does not correlate with blood levels (as may be assumed in exposure to lead, for example) biological monitoring is a much more reliable test. It also has the advantage of providing a reliable estimate of group exposure. Environmental monitoring of workroom air is usually based on representative samples and thus does not necessarily represent the actual exposure of individual workers.

The biological monitoring procedure should be specific for the substance of concern and responsive to the dose received. This implies an understanding of the relationship between time of exposure, time of measurement (often after exposure), and intensity of exposure. Many candidate procedures do not yet meet these requirements.

Development of biological monitoring techniques is necessary to improve our methods of monitoring actual exposure. Such tests should be evaluated only by physicians who can interpret this information with clinical findings to assess the state of workers' health.

5.6.4 *Instructions on the application of standards*

As a final step, the setting up of new hygiene standards for a toxic substance means not only assessing the quantitative value of the standard but also supplementing it with the necessary instructions for its

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[1] WHO Technical Report Series, No. 571, 1975.

application in the workplace. Scientific and practical information should be provided on :

(1) appropriate exposure tests for biological monitoring using the most sensitive techniques available in occupational medicine ;

(2) preventive measures (including diet when appropriate) and other information to be provided to workers ;

(3) criteria for early diagnosis of occupational health impairment ; and

(4) first aid, including antidotes and treatment.

5.7 Presentation of standards

In the USSR, a standard is expressed as a maximum allowable concentration.[1] This concentration must not be exceeded even for short periods. For agents with pronounced cumulative properties, time-weighted average concentrations may be established in addition. Moreover, the maximum allowable concentration is the compulsory basis for the design of industrial buildings, work processes, equipment, and ventilation and is the standard to be observed during regular preventive sanitary supervision.

In the USA many standards are expressed as a time-weighted average,[2] and recently, where appropriate, recommended standards also include a ceiling value synonymous with the concept of maximum allowable concentration.

In other countries the approach may be voluntary or compulsory, and the presentation of permissible levels generally follows the models proposed by the USSR or the USA. Some countries combine aspects of both.

6. HEAT AND NOISE

A brief account of the methods used in establishing permissible levels of exposure to certain physical agents such as heat and noise is given below to demonstrate the differences in approach and experimental

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[1] The maximum allowable concentration is the concentration of a harmful substance in the air of the working area that, by its action on workers for 8 hours a day throughout the entire working life, does not cause any health impairment detectable by current methods of investigation during the work itself or in the long term, in the present or any subsequent generation.

[2] A time-weighted average is a workplace environmental limit designed to protect workers for up to 10 hours a day or 40 hours a week over a working lifetime.

and epidemiological methods that are necessary in dealing with a physical as opposed to a chemical agent.

6.1 Occupational exposure to heat

In setting up permissible levels, no matter what approach is used, the following environmental parameters have been taken into consideration : air temperature, humidity, air velocity, radiant heat, and thermal insulation between environment and body surface.

These five factors, considered simultaneously, describe the thermal environment. However, the heat stress imposed on the individual is not only a result of the thermal environment but also of metabolic heat (i.e., basal metabolism plus the heat generated by working). Depending on the degree of heat stress imposed and time of exposure, physiological strain and subsequent heat disorders may result (e.g., heat stroke, heat syncope, heat cramps, and heat exhaustion).

In adopting standards for heat exposure, a distinction has been made between :

— optimal climatic conditions, which provide thermal comfort (i.e., deep body temperature is maintained in equilibrium without using the mechanisms for active thermoregulation), and

— permissible climatic conditions, which do not ensure thermal comfort (physiological mechanisms are induced) but which do not cause health impairment.

Permissible standards are applied in the so-called " hot " industries, and it should be borne in mind that they may involve thermal discomfort and subsequent changes in work performance.

Physiological strain caused by exposure to heat can be assessed with relative accuracy by measuring certain physiological functions, i.e., those associated closely with thermoregulation. The core temperature of the body provides some indication of the degree of strain to which the thermoregulatory system is being subjected. Similarly, the heart rate is a simple and readily observable indicator of the demands imposed by work and heat load on the circulatory system. Also, the amount of sweat produced reflects the degree of heat strain since the evaporation of sweat constitutes the main way of dissipating heat in hot environments.

Through carefully controlled laboratory experiments and field studies on human beings it has been possible to establish a correlation between the degree of heat stress (environmental plus metabolic heat load) and heat strain (resulting physiological or pathological change).

Practical experience as well as clinical observations in hot occupations has also contributed to a better understanding of the complex interrelationship between heat exposure, the resulting consequences, and associated factors (age, sex, acclimatization, clothing, etc.). Attempts have also been made to correlate chronic heat exposure and certain chronic diseases.

The permissible levels for heat exposure that have been established in different countries have been based on the degree of strain considered acceptable. For example, increase of deep body temperature and increases in heart rate have been used as recommended criteria for heat strain. The corresponding permissible limit for stress would be represented by whatever combinations of environmental conditions, workload, and personal factors would induce such levels of strain.

The standards for permissible exposure to heat are based on several practical measurements defining the thermal environment, with adjustments for workload and personal factors. The evaluation of heat stress has been possible because of the correlation that has been established between thermal factors and resulting physiological strain, which is valid for practical occupational situations. To integrate all these variables into a single evaluation index, several indices have been designed (e.g., effective temperature, corrected effective temperature, Belding and Hatch heat stress index, wet-bulb globe temperature index, and predicted 4-hour sweat rate). The different values that the evaluation index takes for the various sets of environmental conditions and other related factors are then correlated with levels of heat strain.

6.2 Occupational exposure to noise

Setting permissible levels for occupational noise exposure is particularly complex owing to the wide variety of effects that noise gives rise to. In establishing standards for occupational exposure to noise, it is usually only the direct effect on the auditory function that has been considered. Extra-auditory effects such as neurovegetative reactions, psychological effects, and interference with communication have largely been neglected. Even less consideration has been given to the indirect effects of noise such as annoyance, disturbance, and influence on performance.

The criterion which has been used to set up permissible levels of occupational exposure to noise has been hearing loss. It has been widely accepted since ancient times that excessive noise can cause hearing loss and this has been supported by clinical observations during

the past century. At present, data relating to noise and hearing loss are available from controlled experiments and field studies. The former include :

(1) studies of temporary hearing loss in human test subjects ;

(2) studies of temporary hearing loss in animal test subjects ;

(3) studies of permanent hearing loss in animal test subjects ;

(4) anatomical studies of noise-damaged inner ears of animal test subjects.

Field studies include :

(1) cross-sectional studies of hearing loss in persons exposed to known noise levels over periods of years ;

(2) cross-sectional studies of hearing loss in groups of persons exposed to specific types of noise for which noise levels and exposure patterns may not be precisely defined or quantified (e.g., persons living near airports, factory maintenance workers) ;

(3) longitudinal studies of hearing loss in noise-exposed persons, showing the progression of hearing loss in individuals over the course of several years ;

(4) post-mortem anatomical studies of noise-damaged inner ears of individual humans exposed to noise during their lifetimes.

In addition, there is a considerable amount of information resulting from occupational health practice, particularly audiometric examinations of workers exposed to noise.

From this experience almost universal agreement has been reached that repeated exposure for a number of hours each day to excessive noise will in the most sensitive persons, result in gradual, continuing, and irreversible damage to the hearing mechanism, beginning at the higher frequencies. Repeated daily exposures to intense sound for short periods of time are also observed to result in these effects.

Standards adopted in different countries have been generally based on this knowledge and are expressed either by one value in dB(A) or by a combination of sound pressure levels (in energy units) at different bands of frequencies. These permissible levels are meant to prevent occupational hearing loss only, but not to prevent other noise effects (extra-auditory effects, annoyance, etc.). It should also be emphasized that these levels do not take account of impulse noise.

7. APPLICATION OF PERMISSIBLE LEVELS IN DEVELOPING COUNTRIES

The existing differences in recommended permissible levels have been associated with uncertainties in the choice of values to be implemented at the operational level in many developing countries and may sometimes have been instrumental in delaying the protection of workers exposed to harmful agents. This situation will no doubt be ameliorated with the introduction of internationally recommended values accounting for differences in working and health conditions and for priority exposures.

Despite the overwhelming health problems at present receiving attention in developing countries, a complete public health programme should cover the complex health problems that workers may encounter. The working populations in these countries, in addition to being an important sector on which economic development depends, are affected by the general diseases prevailing in the community as well as by many uncontrolled hazardous agents at work. Where it is not feasible to replace toxic substances by harmless ones, to enclose dangerous processes, and to automate and mechanize manual processes, permissible levels are essential for the protection of workers' health. They should also be available in the planning stages of new industrial operations, in order to prevent future health impairment or costly redesign of operations.

It must be recognized, however, that conditions in the developing countries sometimes impose constraints on the application of permissible levels and may even influence the authorities with regard to the adoption of those levels.

7.1 Conditions affecting the adoption and application of permissible levels

Some of the factors involved are obvious. They include the fact that developing countries are undergoing industrialization, which calls for the rapid adaptation of the labour force to mechanization and new industrial processes. A large number of developing countries are in tropical and subtropical areas where temperature and humidity (and sometimes altitude) may play a role in the absorption, metabolism, and elimination of toxic agents. Other factors bearing on the adoption and application of permissible levels are cultural attitudes to health and disease, socioeconomic structure, urbanization, level of education, and degree of skill. It is important to account for these factors in making international recommendations on permissible levels and in communi-

cating these recommendations to developing countries. Three considerations of especial importance are discussed in the following paragraphs.

7.1.1 *Vulnerability*

The recommended permissible levels in use in highly industrialized countries tend to reflect the fact that workers in these countries are generally a selected population with respect to age and health status. In the developing countries this may not always be the case. The overwhelming majority of the working population are employed in agriculture and small industries and are unlikely to have received preemployment medical screening. A large part of the working populations in developing countries, even in large industries, may be affected by endemic diseases, including parasitic infestation, chronic diseases, and malnutrition. The workforce may include young children, elderly people, and partially handicapped workers. In addition, hours of work may not always be strictly regulated, and longer shift periods and longer periods of exposure to potentially harmful agents are encountered. In some instances workers may utilize the workplaces as their own dwellings or undertake certain hazardous operations in their homes. Permissible levels that assume an exposure of 8 hours a day for basically healthy individuals would therefore be inappropriate for more vulnerable workers in the developing countries.

7.1.2 *Combined exposures*

In highly industrialized countries combined exposure to multiple stresses in certain industrial operations is presenting a genuine problem with respect to recommendations for permissible levels of individual agents. The questions of synergism and potentiation of harmful effects and of adjusting permissible levels to account for these factors represent a gap in knowledge and experience. In the developing countries the likelihood of simultaneous exposure to physical and chemical hazards appears to be greater, since work may involve a good deal of physical labour in adverse climatic conditions, thus imposing additional stresses that may influence the uptake of toxic chemicals. Furthermore, the situation becomes even more complex when vulnerable workers are employed in industrial processes such as foundry work, glass manufacturing, pottery industries, agriculture, and mining in which they may be subject to many potentially harmful exposures. It is suspected that even minimal exposure to harmful agents for a short period of

time, may produce a rapid aggravation of health problems.[1] Such situations may require emergency intervention by health planners, for they not only lead to a rapid deterioration in the health of very many people but also reflect on overall socioeconomic development. The Expert Committee therefore fully appreciated the World Health Assembly's expression of alarm at the fact that there are large numbers of working populations throughout the world that are left without preventive occupational health care.[2]

7.1.3 *Unknown biological effects of certain agents*

Industrialized countries have naturally dealt with priority substances encountered in various industrial, mining, and agricultural operations existing in these countries. A wide variety of potentially harmful agents have not received adequate attention in research in industrialized countries because exposure to them is minimal or nonexistent; in the developing countries, however, they may present important potential health risks. For example, thousands of workers in the developing countries are exposed to organic dusts such as textile dusts (cotton, flax, jute, hemp, kapok, and artificial fibres), wood dusts, grain dusts (rice, wheat, cocoa, and coffee), and other dusts of vegetable and animal origin (paprika, tea, tobacco, bagasse, bone, feathers, and leather). Moreover, certain products of plant origin that are produced and processed in developing countries expose workers to sensitizing agents such as the fluids contained in wood pulp, rubber latex, and gum.

Preliminary observations made in the course of the WHO research programme in occupational health have shown that there are definite health problems of workers exposed to many of these substances. The information available, however, does not yet allow a fair description of biological effects or the recommendation of safe levels of exposure. In only a few instances (e.g., cotton, flax, rice, and tea dusts) have some recommendations been made following epidemiological studies in developing countries.[3, 4] Exposure to such agents is an area requiring investigation and a crash programme aiming at the recommendation of

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[1] El Batawi, M. A. Occupational exposure and control in the production and use of pesticides. In: *Proceedings of the Third International Congress on Pesticide Chemistry, Helsinki, July 1974*. Washington, DC, International Union of Pure and Applied Chemistry, 1975.

[2] WHO Official Records, No. 233, 1976, p. 37 (Resolution WHA29.57).

[3] Pinnagoda, P. V. C. *Study of exposure to tea dust in Sri Lanka and United Kingdom*. London (Thesis), 1973.

[4] Noweir, M. H. Private communication.

tentative values that would at least ameliorate the health problems of workers and prevent irreversible respiratory or other functional disabilities.

7.2 Administrative constraints

The constraints in developing countries in the application of permissible levels include a lack of awareness of the importance of permissible levels, ignorance of methods of applying them, and the imposition of legislative measures without adequate machinery for their administration. A complete lack of awareness can be countered by better communication of information associated with exploration of the real needs in developing countries. Legislative measures should be avoided until such time as the authorities have acquired the capacity to carry out a reasonably effective supervision programme. Many of these constraints also exist in highly industrialized countries.

7.3 Foreign industries in developing countries

Large corporations in developed countries have established industrial enterprises in many developing countries in Africa, Asia, and Latin America, thereby realizing a number of advantages both to those corporations and to the developing countries. The corporation saves on the transport of raw materials and the cost of labour, while the developing country benefits from the creation of employment opportunities and from the contribution made to economic and technological progress. While these are recognized advantages of multinational corporations, there may be a tendency for some of these corporations to overlook health and safety standards, particularly where there is inadequate administrative supervision by governments. In addition, there is a tendency by some multinational corporations to subcontract certain hazardous operations to local firms employing temporary and largely unregistered labour. This may result in health problems among the workers concerned, and the government of a developing country may not be in the best position to control them.

As these foreign industries have the economic ability to institute health services and organize safe conditions at work, they are in a position to provide a model of occupational health practice in the real preventive sense. They may also be able to contribute to the overall health effort in developing countries by carrying out comprehensive preventive health measures among workers and, wherever possible, their families, including immunization, health education, and nutritional

programmes. Until such time as foreign industries in developing countries comply with practices of this kind, they will represent a real constraint in the establishment and operation of adequate occupational health programmes.

7.4 Need for the early application of permissible levels

Mention has already been made of the rather alarming situation of workers exposed to harmful agents while at the same time suffering from general debilitating diseases. The absence of a mechanism for identifying these diseases at an early stage renders the application of safe standards in workplaces even more important, and the continual establishment of new industries and introduction of new substances requires the institution of safeguards at the earliest possible opportunity in the process of industrialization. Moreover, it is at this early stage that the introduction of preventive measures is most feasible and least costly.

Permissible levels should never, even at the very early stage of industrialization, be regarded as a second priority that cannot be afforded. They are in fact a necessity that must be accounted for and introduced together with a basic infrastructure of health services for working populations. In WHO's Sixth General Programme of Work, covering the period 1978–83, which was approved by the World Health Assembly in 1976, it is stated that WHO will collaborate with countries, even during the early stages of industrialization, in developing comprehensive occupational health programmes and services.[1]

7.4.1 *Preliminary measures*

In view of the present constraints and the wide variety of technical problems unresolved as yet, the Committee considered certain preliminary measures that might be taken pending a genuine opportunity for international recommendation of permissible levels :

(1) the use of the recommended permissible levels now available as a guide in establishing and operating different work processes ;

(2) the advisability of widening the safety margin so that lower levels are used than those recommended, particularly when dealing with such agents as hepatotoxic substances ;

[1] WHO Official Records, No. 233, 1976 (Annex 7, p. 88).

(3) the use of arbitrary " permissible levels " based on rapid preliminary surveys of workers exposed to synthetic and organic dusts and other substances of unknown biological effects ;

(4) the strengthening of administrative supervision of workplaces and the education of workers and employers in the use of permissible levels ;

(5) the compliance of foreign industries in developing countries with strict occupational health and safety standards and the possible contribution of these industries to national occupational health programmes ;

(6) the carrying out of systematic epidemiological investigations (with WHO assistance) to enable international standing committees to recommend appropriate permissible levels.

8. AREAS IN WHICH FURTHER KNOWLEDGE IS NEEDED

The following paragraphs call attention to several areas that deserve special attention and further research to provide a scientifically sound basis for permissible levels of occupational exposure.

(1) The Expert Committee felt that it was important to understand more completely the relationships between concentrations of chemicals in air, duration of exposure, and actual uptake by the worker. When studies are performed in the workplace, it is important to ascertain the contribution both of air levels and of work practices to biological uptake. Major influences on uptake that must be better understood include physical workload, size distribution of aerosols and dusts with particular emphasis on the respirable fraction, absorption through the skin, absorption from the gastrointestinal tract, exposures to combinations of noxious agents, heat stress, nutritional status, and health status.

(2) The relationships between exposure, uptake and biological response are not well defined even for many commonly encountered workplace chemicals and dusts. This applies to industrialized countries and even more to developing countries. Our understanding of these relationships can be greatly improved by well designed epidemiological studies. The efficacy of recently instituted workplace controls meeting the permissible levels of occupational exposure can best be evaluated by prospective epidemiological studies. Special attention should be given to metals, organic solvents, organic dusts, and fibrous mineral dusts.

(3) Understanding the pharmacokinetics (including biotransformation) of the more important workplace agents would be most helpful in improving the effectiveness of biological monitoring and health surveillance programmes.

(4) Establishing and revising permissible limits of occupational exposure will require an international programme to improve the comparability of methods of sampling and analysing chemical and physical agents. This will facilitate the interpretation of experimental and epidemiological studies and the establishment of firm uptake/response relationships. Special attention should be given to the development of sampling and analytical methods appropriate to the problems faced in developing countries.

(5) There is insufficient knowledge about the most appropriate methods of extrapolating from animal data to actual human situations. Extrapolation problems are also encountered when workers must be protected from the effects of exposure involving a combination of noxious chemical and physical agents. Even when both animal experiments and epidemiological data are available, there is a need for a greater degree of international agreement on the most appropriate approach for establishing safety margins.

(6) The effects of combined exposures in processes that involve a number of chemical agents (or of chemical and physical agents) are poorly understood. Appropriately designed animal experiments and epidemiological investigations of actual work processes would greatly increase our knowledge of the effects of the most important and commonly encountered combinations of noxious agents. Such investigations are necessary to help select the most appropriate methods of extrapolation and of establishing safety margins. Studies of combined exposures should also consider the effect of climatic factors and physical and mental activity on health, behaviour, and productive capacity.

(7) Groups of workers who may be particularly vulnerable to occupational exposures are not sufficiently characterized. Increased vulnerability may be associated with nutritional status, age, sex, parasitic infestations, specific genetic traits, and the presence of risk factors for chronic diseases.

(8) There is limited information on the effects of occupational exposures on the reproductive system. Although both sexes may be affected by chemical agents, the susceptibility of an unborn child through the exposure of the mother is a matter of particular concern. Existing

permissible levels of occupational exposure do not generally consider the potentially harmful effects of workplace exposures on reproduction. The continued introduction of new chemicals for which permissible levels have not been established complicates the problem further. Both experimental and epidemiological studies of potentially harmful effects on reproduction are required to ensure that existing and proposed permissible levels and work practices are adequately protective.

(9) There is need to evaluate short-term tests for carcinogenesis and for mutagenesis. Such tests are rapidly becoming accepted as a basis for setting priorities for long-term testing and for epidemiological studies and as a reason for reassessing optimal work practices. Short-term tests can be validated if non-mammalian tests using agents found in the workplace are combined with *in vitro* tests of biological fluids from workers exposed to the same agents, with the assessment of cytological abnormalities in exposed workers, and with epidemiological studies of workers already exposed.

(10) There is a need to improve the toxicological testing system for the evaluation of new chemicals before significant exposures occur. A hierarchical system for testing new chemicals, beginning with short-term tests and progressing where necessary to chronic toxicity testing, should be developed and validated. Such testing permits the establishment of preliminary permissible levels and the definition of good work practices for occupational exposures.

9. CONCLUSIONS

(1) Occupational toxicologists, physicians and hygienists have reached a broad agreement on the approaches and the methods to be used for providing the basic scientific information needed to recommend, establish, evaluate, and revise permissible levels for occupational exposure. This is a major step towards developing international recommendations for permissible levels.

(2) Differences exist in the way that Member States translate health-based permissible levels for occupational exposure into educational, technical, compliance and enforcement measures directed towards protecting workers' health.

(3) There are many potentially harmful agents for which permissible levels of occupational exposure have not been established and the number of such agents is continually increasing. In some industrialized

countries, large numbers of chemical agents have been and are being introduced into the working environment without appropriate toxicological evaluation. In developing countries permissible levels for occupational exposure have not been established for well recognized work hazards associated with organic and mineral dusts or for occupational conditions not commonly encountered in industrialized countries. Clearly there is a great need to accelerate, coordinate and extend scientific efforts directed towards recommending permissible levels for many of these agents.

(4) The scientific community and Member States have not always developed and established the research and regulatory approaches necessary to ensure that the health of workers will not be impaired by exposure to new chemicals or new combinations of chemicals introduced into the working environment.

(5) Member States have not always encouraged the research necessary to ascertain whether or not existing permissible levels are adequate to protect the health of workers. Epidemiological studies and health surveillance programmes are most useful in evaluating the adequacy of health recommendations and compliance efforts.

(6) Biological monitoring programmes may provide valuable information for improving estimates of actual uptake and for evaluating the adequacy of permissible levels.

(7) Occupational cancer, respiratory diseases, cardiovascular diseases, mutations, and health impairments due to gonadotoxic, embryotoxic, and teratogenic agents are areas where major research efforts are required. Occupational exposures may act alone or in concert with other risk factors to induce, aggravate, or retard recovery from health problems.

(8) A common scientific basis for evaluating the harmful effects of physical agents exists but there are major differences between physical and chemical agents in the methods used to establish permissible levels.

(9) There is no generally accepted approach to the problem of extrapolating from animal or human data to permissible levels for occupational exposure. An approach for establishing a safety margin has been developed for acceptable daily intakes of ingested agents, but no agreed approach exists for inhalation exposures.

(10) Economic, industrial, and health planners in developing countries have not usually given occupational health early consideration or accorded it the necessary high priority in their development plans.

Many developing countries do not utilize as well as they might their substantial existing competence in occupational health. Scarce national resources can be more efficiently allocated by early attention to working conditions and the health of workers. Initial capital expenditures necessary to control exposures to organic dusts, mineral dusts, and chemical agents are much less than the cost of modifications of industrial facilities at a later date.

(11) There is a need for an exchange of information on the revisions of existing permissible levels that are being considered in different countries and on the new permissible limits that are actually being proposed. There is a need to exchange key research reports and scientific summaries dealing with specific noxious agents or industrial processes.

(12) It is necessary to summarize and evaluate the effectiveness of the different approaches used in different countries in translating health recommendations into effective occupational health programmes. It would be an advantage to share experience with and information on different approaches to health surveillance, workplace monitoring, the education of workers and employers, engineering controls, work practices, labelling, record keeping, and compliance and enforcement.

(13) Foreign interests fostering the establishment of industrial facilities or mechanized agriculture in developing countries have not always shared their available information on occupational health programmes and on the control of workplace exposures to chemical and physical agents.

(14) Both industrialized and developing countries have encountered major problems in translating health recommendations into effective programmes of medical surveillance, workplace monitoring, worker education, employer education, technical services, and compliance and enforcement. Such programmes must be administratively strengthened and carefully aimed at priority problems if limited resources are to be most efficiently allocated.

10. RECOMMENDATIONS

10.1 Recommendations to governments

(1) Governments should accelerate, support, and enhance their efforts to develop and, when necessary, revise scientific summaries or criteria documents that provide the background for health-based permissible levels for occupational exposure. Governments should cooperate in international efforts to establish health-based permissible levels.

(2) Governments should examine their legal, administrative, technical cooperation, compliance and enforcement programmes to ensure that health-based recommendations for permissible limits of exposure are translated, with high priority, into effective action programmes in industrial and agricultural workplaces.

(3) Official standards for occupational exposures should have as their primary consideration the protection of the health of workers and their families.

(4) Industrial nations should ensure that multinational corporations and national aid programmes fulfil their ethical responsibility to consider occupational health needs. Industrial development should be planned to prevent and not repeat the lamentable mistakes of the past that caused serious occupational health problems. Multinational companies have a responsibility to ensure that permissible levels accepted by these companies in developed nations are not ignored in developing nations. Specific attention must be paid to worker and supervisor education and to medical and industrial hygiene surveillance programmes.

(5) Developing nations should utilize their own practical experience and their existing occupational health capabilities to set provisional permissible levels and establish safe work practices for organic and mineral dusts that pose special problems for them. Developing nations alone or in cooperation with WHO should conduct research (especially epidemiological research) on these problems. Industrialized nations and international organizations should play a role by providing consultation and technical cooperation. Assistance should be given to help developing countries adopt and where necessary modify permissible levels already recommended.

(6) Governments of developing nations and private or governmental organizations (including multinational corporations participating in industrialization or agricultural projects in developing nations) should give priority attention to occupational health matters in long-range planning and in the development of specific projects. Early attention and preventive action, apart from ethical considerations, protect the investment made in the training of workers and prevent disruptions caused by outbreaks of occupational illness.

10.2 Recommendations to occupational health institutions

(1) Institutions should make every effort to accelerate the assembly and collation of the scientific information required for the recommen-

dation of permissible levels. They should exchange with other institutions the documentation for their scientific reviews that form the basis for establishing or revising permissible limits of occupational exposure. In addition, the detailed documentation of key toxicological and epidemiological studies should be made available for exchange on request from WHO or collaborating institutions.

(2) Institutions in industrialized countries should request government agencies and the headquarters of private corporations to summarize the engineering controls, the industrial hygiene efforts, and the occupational health programmes that they require for each process in each country in which they operate.

(3) Institutions should accelerate their efforts to validate short-term testing for potentially carcinogenic and mutagenic agents in the workplace and to conduct epidemiological studies to define existing occupational cancer and mutation hazards. Industrial toxicologists and specialists in cancer and genetic research should cooperate closely in planning, conducting, and interpreting these studies.

(4) Institutions should conduct research to ensure that existing and new permissible levels allow for the potential reproductive hazards of occupational exposures.

(5) Institutions should conduct research to establish or revise permissible limits for agents inducing or increasing the risks of chronic respiratory diseases. Research should particularly consider organic dusts such as plastics, cocoa, latex, tea, tobacco, bagasse, wood, kapok, cotton, flax, and grain and fibrous and non-fibrous mineral dusts. Institutions in developing countries should emphasize applied research necessary to answer the country's specific problems.

(6) Institutions should conduct research to elucidate the cumulative contribution of occupational conditions and exposures to cardiovascular diseases. Of particular concern is the effect of solvents and metals.

(7) Studies sponsored by private industry and worker groups should be encouraged and technical assistance provided to ensure that they can be appropriately documented and utilized by the international community (together with other information) in establishing or revising permissible levels. Every effort should be made to ensure that such studies do not remain proprietary information and therefore partially hidden.

(8) Institutions should try to obtain more accurate data on the relationship between exposure and uptake and to devise biological monitoring procedures that can more effectively monitor actual work-

place exposures and form an integral part of health surveillance systems.

(9) Institutions should reserve a portion of their research efforts for toxicological and epidemiological studies on the effects of exposure to combinations of chemical and physical agents as actually found in work processes.

(10) Integrated research programmes should combine inhalation experiments in animals (using exposures chosen to approximate the industrial setting), carefully controlled exposures of human volunteers, and epidemiological studies. Such programmes are necessary to improve safety margins and to better define the most appropriate techniques for extrapolating from animal experiments to man.

(11) Institutions should conduct epidemiological research to evaluate new hazards and confirm or revise existing permissible levels.

(12) Institutions should conduct training programmes for occupational health personnel to ensure efficient practical workplace monitoring and health surveillance programmes. Workers should also be trained to recognize hazards in the workplace and to work with occupational health personnel in efforts to reduce these hazards.

10.3 Recommendations to WHO

(1) A joint WHO/ILO standing committee should be established to develop additional health-based recommended permissible levels for occupational exposure to chemical agents. International, regional, and national institutions should be invited to participate in this effort. Where agreement is not immediately possible the standing committee would state clearly the reasons for the differences.

(2) WHO should obtain plans of research programmes from institutions and arrange meetings to improve the coordination of research projects on specific classes of noxious agents or on industrial processes of common interest to Member States. These efforts should be closely coordinated with the WHO programme on early detection of health impairment in occupational exposure to health hazards. Such coordination will ensure the most efficient allocation of limited resources.

(3) WHO and ILO, through an expert committee or in collaboration with research institutions, should continue their efforts to recommend internationally agreed health-based permissible levels for exposures to physical agents. As a sequel to their work on noise and heat, they

should consider impulse noise, vibration, laser emission, and non-ionizing radiation.

(4) WHO should continue and strengthen its collaboration with institutions and Member States to ensure that sampling and analysis procedures utilized by different countries produce comparable and, where possible, equivalent results.

(5) WHO should strengthen collaboration with institutions to improve the reliability and comparability of toxicological tests, epidemiological studies, and detailed medical investigations involving human volunteers and small groups of workers exposed to specific hazardous agents.

(6) WHO, in collaboration with international, regional and national institutions, should assemble an expert committee or study group to set priorities for research on combinations of chemical and/or physical agents encountered in the most important industrial or agricultural activities. The committee should also produce work practice guidelines for situations in which workers are exposed to combined agents and advise on control technology.

(7) WHO should sponsor collaborative efforts to facilitate the translation of health recommendations into effective control programmes. As a first step WHO and its collaborative research institutions should identify and describe the best available control technology for the most important industrial and agricultural activities that involve significant health hazards. In this way, it will be possible to better assess the feasibility of health recommendations and identify priorities for the development of new cost-effective engineering controls.

Annex 1

ARBITRARY CLASSIFICATION OF TOXICITY

As a result of investigations carried out by means of toxicity testing in animals, it is possible to work out a classification of harmful substances based on classes of toxicity. Two examples are reported here, one of four categories adopted in the USSR (Table 1) and the other of five categories proposed by Deichmann & Gerarde (Table 2).

TABLE 1. CLASSIFICATION OF TOXICITY, USSR

Indices	Extremely toxic	Highly toxic	Moderately toxic	Slightly toxic
LD_{50}, oral (mg/kg)	15	15– 150	151– 1 500	1 500
LC_{50} (mg/m³)	500	500–5 000	5 001–50 000	50 000
LD_{50}, skin (mg/kg)	100	100– 500	500– 2 500	2 500

From : Ulanova, P. I. Toxicometry and prophylactic toxicology. In : *Methods used in the USSR for establishing biologically safe levels of toxic substances.* Geneva, World Health Organization, 1975, pp. 45–55.

TABLE 2. CLASSIFICATION OF TOXICITY, DEICHMANN & GERARDE

Indices	Extremely toxic	Highly toxic	Moderately toxic	Slightly toxic	Practically non-toxic or Relatively harmless
LD_{50}, oral (mg/kg)	1	50	500	5 000	15 000
LC_{50} (mg/m³)	10	100	1 000	10 000	100 000
LD_{50}, skin (mg/kg)	5	43	340	2 810	22 590

From : Deichmann, W. B. & Gerarde, H. W. *Toxicology of drugs and chemicals.* New York, Academic Press, 1969.

The definition of each degree of toxicity differs between the groups of investigators and thus semantic differences rather than substantive differences are encountered. In general, investigators in the USSR are more stringent in their classification of toxicity.

A classification of pesticides by hazard was adopted by the Twenty-eighth World Health Assembly.[1]

[1] WHO Official Records, No. 226, 1975, p. 84 (Annex 11, Appendix 1).

Annex 2

CLASSIFICATION OF IRRITANT EFFECTS

Because the individual sensation of irritation increases with increase in airborne concentration of the irritant, it has been possible to work out a classification of the severity of irritant effects taking as a yardstick the threshold of irritant effects on the respiratory tract and eyes in man. An example is given below :

CLASSIFICATION OF IRRITANT EFFECTS

	Concentration of agent (mg/m³) required to produce following effects :			
	Subjective sensation in man	Accelerated breathing in rabbits	Changes in the respiratory system in rats	Increase in salivation in cats
Extremely irritating agent	⩽20	⩽500	⩽50	⩽900
Very irritating agent	21– 200	501– 5 000	51– 500	901– 9 000
Moderately irritating agent	201–2 000	5 001–50 000	501–5 000	9 001–90 000
Slightly irritating agent	>2 000	>50 000	>5 000	>90 000

From : Golubev, A. A. *Voprosy toksikologii legko gidrolizujuščijsja veščestv i himičeskih soedinenij, obladajuščih razdražajuščimi svojstvami* [Problems of toxicology of easily hydrolysed substances and chemical compounds possessing irritant properties]. Leningrad (Thesis) 1968.

Annex 3

EXTRAPOLATION FROM A CHRONIC EXPOSURE TEST FOR CARCINOGENICITY

The example given here is from a research project on the permissible level of benzopyrene in air. The study involved repeated intratracheal injections in rats, using doses ranging from 0.005 mg to 25 mg. After 10 injections of 25 mg each, at monthly intervals, 80% of the animals presented lung tumours, 42.5% of which were malignant. The lowest effective dose was 0.1 mg, which produced only benign tumours in 14.4% of the animals. Doses of 0.02 and 0.005 mg were ineffective.

TABLE 1. APPEARANCE OF LUNG TUMOURS IN RATS INJECTED WITH BENZOPYRENE

Dose (mg)	25.0	2.5	0.5	0.1	0.02	0.005	Control
Percentage of animals with tumours	80.0	42.8	28.2	14.1	—	—	—
Percentage of these with malignant tumours	42.5	28.5	15.7	0	—	—	—
Time of appearance of first tumour (months)	12	17	19	27	—	—	—
Maximum life-span (months)	28	31	34	37	33	33	34

From : Janyseva, N. Ja. *Gigiena i sanitariya*, No. 7 : 87 (1972).

After 25 mg of benzopyrene the first tumours appeared after 12 months, while at the minimum effective dose of 0.1 mg it took 27 months for the tumour to appear. At high doses flat epithelial cancers were observed, at small doses adenocarcinomas. Further investigations were then carried out with the simultaneous introduction

TABLE 2. CALCULATED RISK OF LUNG TUMOURS IN RATS AFTER INTRATRACHEAL INTRODUCTION OF VARIOUS DOSES OF BENZOPYRENE COMBINED WITH OTHER SUBSTANCES

Dose (mg)	0.1	0.02	0.05	0.002	0.0005
Percentage of animals with tumours	17.9	6.9	2.23	0.95	0.24

of benzopyrene with other substances and mixtures by the intratracheal route, in order to reproduce the multiple exposure of real industrial conditions.

The uptake/response relationship was mathematically modelled according to the following equation :

$$Y = 10\left[\log_n\left(\frac{X_n}{X}\right) + 1\right]$$

where Y is the percentage of animals with tumours, X_n the dose of the carcinogen in milligrams, and X the maximum ineffective dose of the carcinogen in milligrams. Further calculations made it possible to establish that the carcinogenic effect of a 0.05 mg dose becomes apparent by the thirty-seventh month, thus coinciding with the natural longevity of the animals, while the time required by lower doses (0.02 mg : 68 months ; 0.1 mg : 119 months) to have apparent effect exceeds the natural life-span.

Annex 4

TYPES OF SCIENTIFIC INFORMATION UTILIZED IN ONE COUNTRY IN THE DEVELOPMENT OF PERMISSIBLE LEVELS, WITH EXAMPLES OF SUBSTANCES

A. Experiments on human beings alone :

ammonia
trichloroethylene

B. Experiments on man and animals :

carbon monoxide
methylene chloride
ultraviolet radiation

C. Epidemiology :

chromic acid
coke oven emissions
cotton dust
ethylene chloride
inorganic fluorides
inorganic lead
inorganic mercury
noise
toluene diisocyanate

D. Epidemiology and human case histories (mortality studies) :

inorganic arsenic
asbestos

E. Epidemiology and human experimentation :

hot environments
isopropyl alcohol
toluene
oxides of nitrogen

F. Epidemiology and animal experimentation :

benzene
beryllium
carbon tetrachloride
chloroform
chromium (VI)
ketone
silica (crystalline)

G. Epidemiology and human and animal experimentation :

hydrogen fluoride
sulfur dioxide
sulfuric acid
zinc oxide
vinyl chloride

H. Case history (plus) :

methyl alcohol (plus animal experimentation)
nitric acid (plus epidemiology and experimental animals)
phosgene (plus experimental animals)
sodium hydroxide (plus case history, animal and human experimentation)

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