METHODS USED IN THE USSR FOR ESTABLISHING BIOLOGICALLY SAFE LEVELS OF TOXIC SUBSTANCES

World Health Organization Geneva 1975

METHODS USED IN THE USSR FOR ESTABLISHING BIOLOGICALLY SAFE LEVELS OF TOXIC SUBSTANCES

Papers presented at a WHO meeting held in Moscow
from 12 to 19 December 1972

WORLD HEALTH ORGANIZATION
GENEVA
1975

ISBN 92 4 156043 6

PRINTED IN BELGIUM

CONTENTS

METHODS USED IN THE USSR FOR ESTABLISHING BIOLOGICALLY SAFE LEVELS OF TOXIC SUBSTANCES

METHODS USED IN THE USSR FOR ESTABLISHING BIOLOGICALLY SAFE LEVELS OF TOXIC SUBSTANCES

Papers presented at a WHO meeting held in Moscow
from 12 to 19 December 1972

WORLD HEALTH ORGANIZATION
GENEVA
1975

ISBN 92 4 156043 6

PRINTED IN BELGIUM

CONTENTS

PREFACE

The expansion of the chemical industry and the intrusion of chemical technology into practically all branches of the economy and into everyday life has led to the appearance of new substances in the biosphere.

Chemical pollution of the environment has resulted in serious impairment of health and in enormous ecological losses. To prevent further damage to the biosphere there is a need for collective international action aimed at the protection of nature and the rational utilization of its resources.

A solution to the problem of protecting the biosphere is impossible without a knowledge of the initial criteria for determining the toxicity and health hazard of chemical compounds. From a practical point of view the establishment of hygiene standards for harmful substances in the environment is of primary importance. There are considerable differences between maximum allowable concentrations, the criteria adopted in the USSR, and threshold limit values, which are used in the USA. These differences are due to different methodological approaches. Fruitful international cooperation demands the elaboration of uniform approaches to the establishment of hygienic limits for the levels of harmful substances in the environment.

A meeting to discuss these problems was organized by the World Health Organization at the Industrial Hygiene and Occupational Diseases of the USSR Academy of Medical Sciences in Moscow from 12-19 December 1972. A list of the participants will be found in page 169.

One of the main principles used by scientists in the USSR in establishing limits for the level of harmful substances in the air of places of work is that the health aspects must have priority over all others, including technological feasibility and economic considerations. Soviet toxicologists accept the concept that there is a threshold for all types of harmful action, including carcinogenic and mutagenic effects. They also believe that in all countries, irrespective of their level of economic development, hygiene standards should have the force of law and should not be mere recommendations.

It is hoped that the publication of the papers presented at the meeting will promote the development of common principles and methods for establishing permissible levels of harmful substances in the environment and will contribute to international agreement in this field.

Investigation of new substances: permissible limits and threshold of harmful action

I. V. SANOCKIJ[a]

The middle of the twentieth century has seen a rapid increase in the chemical pollution of the environment in which man lives : his place of work, his home, the atmosphere, water and soil, i.e., to all intents and purposes the biosphere as a whole. The term "ecocide" is being used more and more frequently outside the USSR, and with good justification.

The state of the environment is a matter of general concern, but different solutions to the problem of protecting it against chemical pollution have been adopted in different countries.

Procedure adopted in the USSR

In the USSR, the activities of the State Sanitary Inspectorate rest on the solid legal basis of the appropriate items of legislation : the law on the protection of nature, the fundamental legislation of the USSR and the Union Republics on health, the law relating to land use, the law on the use of water, etc. Additional laws are at present being prepared : a law on the safeguarding of mineral resources, a law on the protection of the environment, etc.

These laws prohibit the production and use of new substances *until they have been subjected to compulsory preliminary toxicological evaluation.* The scope of this evalution differs, depending on the stage of development of the new compound.

In the planned economy of the USSR, it is possible to initiate investigations at a time when the substance is still at the testing stage, and thereby to prevent not only any hazard to the health of the population but also the considerable material losses associated with a delay in the introduction of hygiene measures. A further advantage of this proper timing of the investigations is that they can be distributed among scientific institutions of various categories, from the toxicological departments of the sanitation

[a] Institute of Industrial Hygiene and Occupational Diseases, Academy of Medical Sciences of the USSR, Moscow, USSR.

and epidemiological centres to the leading institutes concerned with particular hygiene problems.

The first stage of the investigations (corresponding to the development of the compound in the laboratory) is the screening of potentially hazardous substances in order to replace the more harmful substances by other that are less harmful but possess the same technological properties. This stage can be divided into two sections: (i) the pre-experimental (theoretical); and (ii) the experimental.

Considerable information has been accumulated on the relationships between the structure, physicochemical properties and biological action of certain series of compounds. On the basis of these relationships, an approximate forecast can be made of the lethal quantities of the poison, the general nature of its effects, and the safe level of exposure, i.e., the maximum allowable concentration (MAC).

As regards the experimental section, the first stage of the investigation is devoted to the preliminary toxicological evaluation of the compounds (expert hygienic examination): their toxicity (LD_{50}, LC_{50}) is determined in animals, the nature of their general effects on the living organism is investigated, the possibility of specific effects (including late effects, which are discussed on p. 75) is considered, and special attention is paid to the study of their local and sensitizing effects.

Most laboratories are now equipped to carry out at least a minimum series of suitable functional, morphological and other investigations of biological materials at various levels, including the cellular and molecular.

The practical results of the first stage of the investigations are as follows: partial development of hygiene standards for the raw materials and products; hygienic screening of the technological process; design and construction of the apparatus; and determination of the type of protection required and of the MAC of the substance in the working area, the calculations being based on analogy, on the physicochemical properties of the substance, and on its lethal concentration.

The second stage of the investigations (coinciding with pilot-plant scale tests and planning) calls for the extension of the scope of the investigation to subacute (repeated) experiments on animals in order to determine the cumulative properties of the poison, and also the more precise determination of the threshold indices of its acute effects ($Lim_{ac\ int}$ and $Lim_{ac\ sp}$ in animals and Lim_{ch}, Lim_{ref}, and Lim_{ir} in man).[a] The ratios between the various toxicometric indices are of great value in the objective assessment of the hazards that the substances present; they can also be used for predicting any possible late effects and for the establisment of safe levels of exposure.

[a] The suffixes have the following significance: ac int: acute integrated effect; ac sp: acute specific effect; ch: chronic action; ref: reflex; ir: irritant action.

It has been shown, in particular, that the specificity of an effect (irritant, gonadotropic, carcinogenic, etc.) may be expressed as the ratio between the threshold of action for a single exposure, based on integral indices (i.e., reactions at the level of the entire organism—mental and physical working capacity, motor activity, resistance to additional chemical, physical, and biological and mental stress, etc) and the corresponding threshold based on specific indices, such as chromosomal aberrations or the state of the mucous membrane of the upper respiratory tract and lungs, as determined by biophysical and biochemical tests.

The greater the zone of specific action:

$$Z_{sp} = \frac{\text{Lim}_{ac\ sp}}{\text{Lim}_{ac\ int}}$$

the more marked the specific properties of the poison and the closer the threshold of its acute specific effects to that of its chronic effects, on which the allowable concentration of the chemical compound in the environment is based (examples will be given later). Unfortunately, in some branches of prophylactic toxicology the threshold of acute action based on integral indices is disregarded (a procedure often adopted outside the USSR), with the result that the informative value of the results of the investigations is greatly reduced.

The second stage of the investigations can be considered essentially as filling in the details of the "common toxicological certificate" [a] of the substance.

The third stage of the investigations (which also coincides with the planning of factory production or of the use of a new substance) involves chronic experiments on animals; it is the most laborious but most valuable stage, from the point of view of hygiene. The duration of chronic experiments for various purposes in prophylactic toxicology may vary considerably—from three months of continuous inhalation to 1–2 years of intermittent exposure. At the present time, experiments are carried out simultaneously on different species of laboratory animals, for the conclusions drawn from them are of great importance: if the permissible levels of concentration (in other words, the MACs) are set too high, this will lead to a hazard to health of unknown extent, while if they are set too low, this will result in unjustified economic losses.

The problem of extrapolation of the results of animal experiments to man assumes particular importance in this connexion. It has been shown that a threefold difference in lethal doses and concentrations is within the normal limits of experimental error and cannot therefore serve as a criterion of species differences in sensitivity. Review of the literature

[a] The "common toxicological certificate" is a special form on which the data obtained in the second stage of the investigations are entered.

shows that, when four species of laboratory rodents show closely similar sensitivity to a poison, in two-thirds of cases man will have the same sensitivity. However, more reliable conclusions can be drawn from a comparison of species differences in metabolism (Tijunov, 1967). Allowing for body weight, body surface area and rate of oxidation gives very promising results (Krasovskij, 1970). Nevertheless, the problem of species differences in sensitivity to poisons or, in other words, the problem of the application of the results of animal experiments to the practical problems of hygiene, has still not been completely solved.

This third stage of the investigations is undertaken in well-equipped institutions with highly trained staff. By combining chronic experiments of different duration for the investigation of problems in occupational and communal hygiene, a great economy of time and materials can be achieved. The practical results of these investigations, in addition to those already mentioned, are approximate MACs, programmes of periodic examinations, etc. (Table 1).

The fourth stage of the investigations is undertaken when the substance is being introduced into industry and agriculture, and also into everyday life. The techniques used to study and assess chemical environmental agents at this stage are mainly clinical (toxicological) comparisons and epidemiological (statistical) investigations. Meanwhile, the metabolism of the poison continues to be the subject of intensive experimental investigation, including the study of the pathogenesis of acute and chronic poisoning.

Practical aspects of the fourth stage of the investigation of chemical environmental agents include the approval of a safe level (MAC), and the development of exposure tests, therapeutic and prophylactic measures (e.g., dietary), and methods of early diagnosis, first aid, and treatment (Table 1).

A comprehensive and differential evaluation of chemical factors in the industrial and domestic environment is impossible without the specification of initial statistical indices and without the use of computers and the corresponding mathematical facilities (multifactorial analysis). Laboratories of medical cybernetics have been organized in some institutes.

The main techniques and methods of investigation used to assess chemical compounds in the environment are thus:

(*a*) theoretical prediction, based on the laws relating the chemical structure and physical and chemical properties of a substance to the intensity and character of its biological action;

(*b*) multistage experimental studies (expert toxicological assessment, toxicological certificate, full toxicological investigation); and

(*c*) clinical (toxicological) comparisons and epidemiological (statistical) investigations.

By conducting the investigations in stages, better coordination of research is obtained, both in work on the same problem and on different problems. Successful coordination between investigations of different problems depends, however, not only on good organization but also on the solution of fundamental theoretical problems.

Basic Concepts

In the writer's opinion, a unified approach to the basic concepts of prophylactic toxicology is extremely important. These are:

1. the concept of the MAC, applicable to all media; and
2. the concept of the threshold of harmful action.

Permissible limits

The official definition of the MAC adopted in the USSR reads: "maximum allowable concentrations of harmful substances in the air of the working area are those concentrations that, in the case of daily exposure at work for 8 hours throughout the entire working life, will not cause any diseases or deviations from a normal state of health detectable by current methods of investigation, either during the work itself or in the long term".

For comparison, I give the definition of the threshold limit value (TLV) adopted by the American Conference of Governmental Industrial Hygienists: the TLV defines the conditions to which "nearly all workers can be repeatedly exposed, day after day, without adverse effect. Because of the wide variation in individual susceptibility a small percentage of workers may experience discomfort from some substances at concentrations at or below the "threshold limit"; a smaller percentage may be affected more seriously by aggravation of a pre-existing condition or by development of an occupational disease".

The essential differences between these two definitions call for a closer examination.

The definition of the TLV adopted by the American Conference of Governmental Industrial Hygienists deliberately accepts unfavourable effects and even occupational diseases in individual workers. The definition of the MAC adopted in the USSR is in full agreement with the definition of the concept of health given by the World Health Organization in its Constitution: health is "a state of complete physical, mental and social well-being and not merely the absence of disease or infirmity".

Differences in the values of the permissible limits for individual substances are closely linked with these differences in the understanding of the nature of these limits. In the USSR, these values are lower than those