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**PERMISSIBLE LEVELS
OF OCCUPATIONAL EXPOSURE
TO AIRBORNE
TOXIC SUBSTANCES**

**Sixth Report of the Joint ILO/WHO Committee
on Occupational Health**

WORLD HEALTH ORGANIZATION

GENEVA

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CONTENTS

	Page
1. Introduction	5
2. Principles for defining permissible limits and suggestions for a common approach	7
3. Biological indicators of environmental exposure	10
4. Assessment of occupational exposure	12
5. Conclusions	13
Acknowledgements	14
Annex 1. Safe concentration zones recommended for inter- national adoption	15
Annex 2. Criteria that have been used to determine permissible limits	16

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Geneva, 4-10 June 1968

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PERMISSIBLE LEVELS OF OCCUPATIONAL EXPOSURE TO AIRBORNE TOXIC SUBSTANCES

Sixth Report of the Joint ILO/WHO Committee on Occupational Health

The Joint ILO/WHO Committee on Occupational Health met in Geneva from 4 to 10 June 1968 to discuss permissible limits of occupational exposure to airborne toxic substances. Dr J. Karefa-Smart, Assistant Director-General of WHO, opened the meeting on behalf of the Directors-General of both ILO and WHO. Referring to the dangers created by certain manufacturing processes, particularly those that involve a toxicity hazard, he stated that if international agreement on the basic principles for defining permissible limits could be reached, this might make possible wider agreement on specific values. Such agreement would lead to better protection of the health of many employed persons.

Professor E. C. Vigliani was elected Chairman, Dr C. R. Harihara Iyer Vice-Chairman, and Mr E. King Rapporteur.

The Committee had before it the following agenda :

- (1) Criteria and procedures for assessing occupational exposure to toxic substances.
- (2) Present approaches to permissible limits of toxic substances in the working environment, and criteria for their establishment.
- (3) Suggestions for the adoption of a common approach to the problem of defining permissible limits.
- (4) The relationship between environmental exposures and biological values.

1. INTRODUCTION

The development and modernization of industry and agriculture often create occupational hazards, such as damage to health from the use of radioactive isotopes, injuries from machinery, and the entry of harmful substances into the body. In numerous industries, workers must handle potentially toxic chemicals. Chemical reactions involved in certain

manufacturing processes result in the liberation of toxic substances. Acute poisoning, or more insidious damage to the health of the individual, his family, and perhaps the community, may occur with resultant adverse effects on productivity. However, the degree of risk of handling a given substance is not necessarily directly related to its known toxicity.

Removal of a hazard at its source, which gives complete safety to the worker, is one of the control methods commonly used. However, it is not always possible totally to enclose a process or to replace a potentially toxic substance by a harmless one. Consequently, where exposure to toxic substances is unavoidable, there has for many years been increasing reliance on the use of permissible limits.¹ As further data have been accumulated, some of the recommended limits for given substances have been raised, and many others have been lowered. This is a continuing process.

The limits recommended for given chemicals often vary from one country to another. Some such differences arise from different concepts of what constitutes damage to health, and others result from the different experimental and epidemiological methods used to establish the limits. Resolution of such differences would be assisted by greater international co-operation and by dissemination of information on the criteria and procedures used in establishing permissible limits. Much useful work has been carried out by the International Union of Pure and Applied Chemistry (IUPAC) and by the Permanent Commission and International Association on Occupational Health (IAOH),² and the activities of such bodies should be extended.

Although the usefulness of permissible limits has been adequately demonstrated, difficulties may arise in their practical application. Such difficulties are sometimes apparent only to technically well-informed personnel — e.g., occupational health physicians and hygienists — who continually deal with problems of industrial hygiene. The concept of permissible limits must be well understood, and the limits themselves must be properly applied; otherwise, health may be affected or, on the other hand, workers and employers may be unnecessarily inconvenienced or penalized. Furthermore, industrialization and the modernization of agriculture may be retarded. Consequently, more detailed information on permissible limits is urgently required. The observance of

¹ The terms "maximum allowable (or acceptable) concentration" (MAC) and "threshold limit value" (TLV) are also used.

² Much useful background information on permissible limits will be found in the following publications: IUPAC and IAOH (1961) *Proceedings of the International Symposium on Maximum Allowable Concentrations of Toxic Substances in Industry, Prague, Czechoslovakia, April 1959*, London, Butterworth; and IUPAC, IAOH, & ILO (1965) *Proceedings of the Second International Symposium on Maximum Allowable Concentrations of Toxic Substances in Industry, Paris, 1963*, Paris, Institut national de Sécurité.

permissible limits may involve major financial and technical difficulties. Future developments, however, may permit such difficulties to be overcome.

2. PRINCIPLES FOR DEFINING PERMISSIBLE LIMITS AND SUGGESTIONS FOR A COMMON APPROACH

Any permissible limits related to occupational air pollution should safeguard health as defined in the Constitution of the World Health Organization as "a state of complete physical, mental, and social well-being and not merely the absence of disease or infirmity".

The use of permissible limits has played an important role in reducing occupational exposures to toxic substances. It is important, therefore, that for practical purposes the use of such limits be retained. However, every effort must be made to improve their validity and widen their use. In this way, greater understanding might be brought about between national authorities, and greater conformity in the use of limits might result.

Biological effects

For scientific purposes, a classification based on the biological effects of toxic substances might be of value. The use of such a classification might stimulate further research on biological effects and lead to improved understanding of the exposure-response relationship, so that valid predictions could be made of the effects of different concentrations of a given substance in the air. A four-level classification of biological effects, somewhat similar to that used by a 1963 WHO Inter-Regional Symposium¹ for classifying the effects of atmospheric pollution, has therefore been developed (see p. 8).

The biological response to a toxic substance in the environment is affected by several factors, such as the degree and duration of exposure and the health of the exposed person. Furthermore, many of the toxic substances used in industry and agriculture differ in their mode of action. Some cause acute and others chronic effects; however, the majority can be dangerous in both ways. Exposure to different concentrations of toxic agents does not always produce readily distinguishable signs and symptoms, and medical assessment is not always easy. Further research is needed on methods of evaluating the acute and chronic effects of toxic substances on man. The evaluation of long-term effects is particularly difficult and due consideration should be given to genetic effects, carcino-

¹ See *Wld Hlth Org. techn. Rep. Ser.*, 1964, No. 271, p. 13.

genesis, and effects on reproduction and life expectancy, as well as to the possibility that long-term exposure may be a contributory cause of death. Further epidemiological studies are clearly needed. Practical difficulties also arise from the inadequacy of long-term sampling procedures and analytical techniques.

Special medical and/or biological procedures are necessary to detect persons for whom a given exposure is contraindicated. This is particularly important for hypersensitive individuals and those with certain genetic deficiencies. A few tests for the detection of such persons have already been developed.

Occupational exposure to toxic substances differs considerably from exposure to atmospheric pollution. In occupational exposure, the concentration of contaminants is usually greater, the daily duration of exposure is comparatively short, the exposed population is highly selected, and the overall number of air contaminants is potentially much greater. In addition, when establishing levels for occupational exposure, it is unnecessary to consider adverse environmental effects such as reduction in visibility and damage to vegetation. For these reasons, a classification of occupational exposure levels will inevitably involve concentration ranges different from those used in classifying atmospheric pollution levels.

The Committee agreed that, for scientific reasons, the proposed guides should cover a wide range of exposures and effects, from a level of contamination at which no adverse effects can be detected to one at which severe effects occur. However, under no circumstances should this be taken as even an indirect authorization for the maintenance of any level that can cause ill health. If the permissible limits are exceeded for any reason, additional protective measures must be introduced.

The following classification of the biological effects of occupational exposure to airborne toxic substances was accepted by many Committee members :

Category A (safe exposure zones) :

Exposures that do not, as far as is known, induce any detectable change in the health and fitness of exposed persons during their lifetime.

Category B :

Exposures that may induce rapidly reversible effects on health or fitness, but that do not cause a definite state of disease.

Category C :

Exposures that may induce a reversible disease.

Category D :

Exposures that may induce irreversible disease or death.

The categories listed above are based on exposure for 8 hours daily, 5 days per week. However, short-term exposures to high concentrations of certain substances may lead to acute irritation, poisoning, or death, and different considerations must be used in establishing permissible limits of such substances. Similarly, when working periods are shorter or longer than those noted above, where there is abnormal heat stress, where workers suffer from poor nutrition, or where other special conditions obtain, an informed judgement must be made as to the applicability of the four categories given above.

Some difficulty may be experienced in deciding how to classify, in terms of the suggested categories, certain industrially encountered substances. This may well be the case with carcinogenic and mutagenic substances, where dose-response relationships require further clarification.

Further attention should be given to the establishment of internationally acceptable guide levels for emergency exposures. The Committee believe that further research on the proposed four-category classification will provide information that may be useful for this purpose.

Since the sensitivity of analytical procedures is continually being increased, the concept of zero concentration is unreal, and can mean only that a given substance cannot be detected by a procedure of given sensitivity. True zero can be obtained only by complete prohibition of the materials and processes of which a given pollutant is a by-product, a procedure that is often impracticable.

Developing countries

In discussing the problem of permissible limits in developing countries, the Committee gave attention to the Fifth Report of the Joint ILO/WHO Committee on Occupational Health.¹ In such countries, the problem is compounded by many factors, such as (1) rapid industrialization; (2) different attitudes to health matters on the part of workers and employers; (3) possible genetic and biological differences in the populations and probable differences in their absorption of, and susceptibility to, toxic substances; (4) the existence of undernutrition and endemic parasitic diseases; (5) adverse climatic conditions; (6) long hours of work; (7) a lack of detailed knowledge of the degree of exposure; (8) the use of unsuitable manufacturing processes and of old machinery; and (9) the use of unsuitable personal protective equipment.

In establishing permissible limits for universal application, studies of the conditions in developing countries are urgently necessary. Since such countries seldom have the facilities required for this type of study,

¹ *Wld Hlth Org. techn. Rep. Ser.*, 1967, No. 354.

international organizations should devote some of their resources to the task until such time as the developing countries are themselves able to undertake it.

Safe concentration zones recommended for international use

The Committee noted¹ that the threshold limit values of the American Conference of Governmental Industrial Hygienists and the maximum allowable concentrations provided by the health legislation of the USSR are the permissible limits that are most widely accepted in other countries. A comparison of the limits most recently established by the USSR and the ACGIH showed close agreement for 24 industrial and/or agricultural chemicals, the values not differing by more than a factor of 2. Further comparison with several other national values showed a large measure of agreement. Consequently, the Committee adopted, for these 24 substances, a list of safe concentration zones that can be recommended for international use (see Annex 1).

On the other hand, the different lists show considerable variation for a comparatively large number of other toxic substances used in industry and/or agriculture, the permissible limits differing by as much as a factor of 90 in a few instances. It is strongly recommended that further efforts be made to assemble all relevant data and that research be undertaken to explain and possibly eliminate such differences. Such research would also help to bring about wider understanding of the overall problem. It is essential to establish a list of substances for high-priority study; such a list should take into account the extent to which the substances are used industrially and the degree of hazard that they present.

A major effort will be needed if the problems noted above are to be solved. Since the problems have wide international implications, an effort aimed at solving them should involve close collaboration between individuals, national and regional institutes, international organizations such as ILO and WHO, and the Permanent Commission and International Association on Occupational Health.

3. BIOLOGICAL INDICATORS OF ENVIRONMENTAL EXPOSURE

In evaluating the extent to which a toxic agent has been absorbed, factors other than the concentration of the substance in the air and work areas must be considered. This is particularly true of substances of low

¹ ILO (1968) *Survey on legislation and practice concerning permissible limits*, Geneva (Document JCOH/1968/1).

volatility and those that can penetrate the skin. In addition to factors such as individual sensitivity, the biological effects of exposure also depend on the concentration of the chemical in the "target" organs or systems. The route of absorption (e.g., the skin) must also be considered, as must the size of particles, the presence of other active (or activating) substances, and several important features of the work environment, such as heat and humidity.

Since so many factors are involved, there is great interest in the development of tests that could be used for (a) diagnostic purposes and (b) the evaluation — and, if necessary, prevention — of environmental exposure. In developing such tests, it is first necessary to know what can be used as an index of absorption. Exposure to some substances is well correlated to the extent to which they are present in body fluids and expired air. Other substances undergo metabolic transformation within the body, and the choice of indicator will depend on the type of such transformation (e.g., the formation of phenols from benzene and of DDA from DDT). Estimation of exposure to certain substances may involve the measurement of biological changes, such as (1) the inhibition of cholinesterase activity by organophosphorus insecticides, and (2) the accumulation of certain intermediate products of metabolism (e.g., porphyrins and δ -aminolevulinic acid as a result of exposure to inorganic lead compounds).

Much further research is necessary in this area, and it should as far as possible be co-ordinated at the international level.

The ideal method of measuring exposure would be analysis at the site of the "target" organ or systems, but this is possible only in exceptional cases. Consequently, reliance must be placed on the analysis of biological materials that are easy to collect, such as urine, blood, and expired air. The selection of material for analysis depends on several factors, including the volatility of the chemical and the rapidity and periodicity of its elimination from the body. If the results are to be valid and comparable, methods of sampling and analysis should be standardized and should be appropriately specific, sensitive, and accurate. In this connexion, the Committee recommends that closer co-operation be developed between WHO, ILO, IUPAC, the Permanent Commission and International Association on Occupational Health, and other international organizations.

The use of personal sampling apparatus to collect representative "breathing zone" samples (i.e., samples of the air actually breathed) might make it possible to establish better correlation between biological indices and levels of exposure.

The establishment of reference centres and laboratories to develop methods for biological and environmental analysis would offer a greater guarantee of acceptable accuracy in determining safe work zones.

Several difficulties are involved in the establishment of permissible levels of toxic substances in biological materials. For example, certain chemicals (e.g., arsenic and lead) and/or their metabolites may be present in specimens of blood, urine, etc., obtained from persons who are not abnormally exposed, occupationally or otherwise, to such substances. Knowledge of the "normal" limits of such substances in the body and its fluids is essential if occupational exposure to them is to be correctly evaluated. WHO has already sponsored studies of the normal limits of arsenic, lead and mercury,¹ and further studies of this nature should be carried out.

Since the results of certain biological tests vary widely from one individual to another, it is necessary to determine the range for a group of employees.

Levels of some substances in biological specimens have shown varying degrees of correlation with the extent of exposure to such substances, and provide an index that makes it possible to achieve a greater degree of protection than that given by environmental monitoring alone. For other substances, however, there seems at present to be no hope of achieving such correlation, since they are stored in certain body tissues and excreted only slowly and irregularly. Useful correlation is also impossible (at least, at present) for chemicals — e.g., phosgene — that react rapidly with the tissues and produce a serious adverse effect even in extremely low concentrations. Indeed, biological indices do not exist for many substances.

Adequate protection of persons exposed to toxic materials usually depends on environmental control and on biological sampling, rather than on observation of adverse effects on health. When an adverse biological change, no matter at that level, is observed, it is clearly too late to prevent that change. Although biological indices of exposure are important, they should not usually replace the sampling and analysis of environmental air.

4. ASSESSMENT OF OCCUPATIONAL EXPOSURE

Although certain advances have recently been made in the development of criteria and procedures for the toxicological evaluation of occupationally encountered substances, some difference of opinion exists on the most appropriate procedures to be used and on the interpretation of the results. However, the Committee agreed that in evaluating new substances and validating existing guides, testing must be preceded by detailed

¹ World Health Organization (1966) *Report of a Meeting of Investigators for the International Study of Normal Values for Toxic Substances in the Human Body*, mimeographed document WHO/Occ.Health/66.39, available on request.

consideration of the chemical and physical properties of the substances and of their modes of action. New substances should also be compared with chemicals of known toxicity that are absorbed into the body in similar ways.

Acute and subacute toxicity hazards that may arise from the use of such substances should then be tested, and long-term toxicity studies should be undertaken subsequently. In planning long-term studies, due consideration should be given to biochemical data obtained from studies of acute toxicity. At least two species of animal should be used; the animal strains should be specified, and one of them should react as similarly as possible to man. The studies should cover modes and routes of absorption (including, where applicable, the skin), metabolism, and excretion. The necessary biochemical measurements should be made, together with observation of organic and functional changes, including effects on the "target" organs. The effects of single and repeated exposure—including, if appropriate, exposure to the vapour phase—should be investigated. It is also desirable to determine the threshold level for the development of acute toxic effects. Further and more detailed testing in other animal species will often be necessary, and the animals should again be selected on the basis of reacting as similarly as possible to man.

It must be realized that tests such as those outlined above, no matter how detailed, may not fully reveal the embryotropic, mutagenic, and carcinogenic potentialities of certain substances, even when the physical and chemical properties of such substances strongly suggest that they have such potentialities.

The exposure of human volunteers is commonly used to define threshold levels of certain substances that may affect the sensory organs (e.g., ability to detect odours). However, human exposures must not entail a risk to health, and should not be made until the limits of response have been precisely defined by animal experiments.

When any substance is used in industry, particularly when it is used for the first time, persons exposed to it must be observed for long periods by means of the most refined techniques, so as to establish valid figures for the levels likely to be encountered in occupational exposure.

Some of the criteria that have been used to determine permissible limits for occupationally encountered toxic substances are listed in Annex 2.

5. CONCLUSIONS

(1) The recording of information on the permissible limits adopted in different countries should be improved, and such information should be summarized in a uniform manner for international dissemination.

(2) Many Committee members believed that a four-category classification of biological responses to occupational exposure to airborne substances would, to a considerable extent, stimulate experimental and epidemiological research and assist in reaching greater understanding of the over-all problem.

(3) Due attention should be given to the establishment of guide levels for emergency exposures and to the additional protective measures that would be necessary in the event of such exposures.

(4) The establishment of permissible limits for many developing countries presents a particular problem to which the Committee recommended that ILO and WHO give appropriate attention.

(5) Permissible limits for 24 industrial and agricultural chemicals, on which there is a significant degree of national agreement, are recommended for international adoption.

(6) More up-to-date information is needed on the permissible limits adopted in different countries, and especially on the validity of the reasons for differences in such values. Consideration should be given to the establishment of international reference centres.

(7) When the permissible limits used in different countries are in agreement, consideration should be given to extending the list in Annex 1.

(8) Further study of the levels of toxic substances in biological specimens is necessary, with particular attention to (a) the normal range in different countries and local variations within a given country; (b) the range that is indicative of greater than normal absorption of given substances; and (c) the range that is indicative of dangerous levels of absorption of given substances.

(9) Close collaboration is essential between ILO and WHO, other international organizations, national bodies, and research institutes, to ensure the development of analytical and biological procedures necessary for the establishment of permissible limits.

ACKNOWLEDGEMENTS

The Committee acknowledges the special contributions made to its deliberations by the following members of the WHO Secretariat : Mr R. Pavanello, Chief, and Dr V. B. Vouk, Consultant, Environmental Pollution.

Annex 1

SAFE CONCENTRATION ZONES RECOMMENDED
FOR INTERNATIONAL ADOPTION

Substance	Safe concentration zone ^a (mg/m ³)
Hydrogen chloride (hydrochloric acid)	5 - 7
Phosgene	0.4 - 0.5
Hydrogen sulfide	10 - 15
Sulfur dioxide	10 - 13
Sulfuric acid and sulfuric anhydride	1
Ozone	0.1 - 0.2
Ammonia	20 - 35
Arsine	0.2 - 0.3
Ethanol	1000 - 2000
Methyl acrylate	20 - 35
Nitrobenzene	3 - 5
Dinitrobenzene	1
Dinitrotoluene	1 - 1.5
Trinitrotoluene	1 - 1.5
Parathion	0.05 - 0.1
Iodine	1
Beryllium and compounds (as Be)	0.001 - 0.002
Molybdenum, soluble compounds, dust (as Mo)	4 - 5
Vanadium (as V ₂ O ₅)	
dust	0.5
fume	0.1
Ferrovanadium	1
Zinc oxides (fumes)	5
Zirconium and compounds (as Zr)	5
Chlorinated derivatives of diphenyl	1
Chlorinated derivatives of diphenyloxide.	0.5

^a The figures given are used by some authorities as maximum values, and by others as time-weighted average values.

Annex 2**CRITERIA THAT HAVE BEEN USED TO DETERMINE
PERMISSIBLE LIMITS***Organic effects*

Effects on different systems or organs; roentgenographic changes; carcinogenesis; effects on fertility and reproduction; mutagenesis; embryological effects.

Functional effects

Irritation; changes in the function of organs; behavioural changes (changes in sensory and higher nervous functions or in conditioned and unconditioned reflexes); changes in food consumption and body weight.

Biochemical effects

Changes in the amounts of the constituents of body fluids and excretions; changes in enzyme or isoenzyme activity; immunochemical effects; metabolism of toxic substances.

Miscellaneous effects

Nuisance; odour; unaesthetic effects; discomfort; allergy; narcosis; addiction.