Methods for Assessing the Effects of Mixtures of Chemicals
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Combined, Complex, and Joint Effect of Chemical Compounds

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ABSTRACT

This paper deals with a few selected problems encountered in setting the sanitary standards for mixtures of chemicals. It concentrates on definitions, calculations of exposure limits for mixtures, and practical examples.

1 INTRODUCTION

It is well known that in working environments people are exposed to chemicals not singly but in combination with other chemicals and a variety of physical agents. The interactions between these agents and their biological effects should not be forgotten in our efforts to simplify the problem of interpretation.

2 DEFINITIONS

In the English literature on the subject of toxic effects all types of simultaneous effects may be called *combined* effects but these are further classified in toxicological documents published by COMECON, the Soviet Toxicological Centre, the USSR Ministry of Public Health and some international scientific groups. The following are some of their definitions and concepts:

(a) *Combined effect* results from the simultaneous action of substances on the organism that is exposed to them by the same route, such as inhalation.
(b) *Complex (integrated) effect* results from the simultaneous action of substances on the organism by different routes of uptake.
(c) *Joint effect* results from the simultaneous action of various agents in diverse media, e.g. chemical plus physical or chemical plus psychic stresses.
(d) *Successive effect* may result from exposures occurring at different times as a result of changing occupations.

The biological expression of these four types of combined effects are usually classified into the following four types:

(1) *Summation* is an effect equal to the sum of the effects of the individual agents.
(2) *Potentiation* is an effect greater than that of summation.
(3) *Antagonism* is an effect less than that of summation.
(4) *Independence* results when the agents have actions that do not influence each other.

3 GENERAL DISCUSSION OF COMBINED EFFECTS

Many authors consider that in many cases of combined, complex, and joint effects of exposure to environmental chemicals an estimate of the total effect can be arrived at by a simple summation of the effects of the exposure to each component of the mixture. But experience shows that the total effect depends on the intensity of the exposure to each component, on exposure time, and on the pattern of exposure with time. The famous Soviet toxicologist and pharmacologist N. V. Lazarev published dose–effect curves illustrating the different effects of joint chemical exposures which he classified as synergo-summation and -antagonism, antagonism–summation, etc. (Lazarev and Levina, 1976). Examples of these curves are given in section 5 of the Joint Report.

Another example of the effects of the relative concentrations of two components of a mixture is illustrated in Figure 1, reproduced from the *Guide to Industrial Toxicology* by Pravdin (1934). The plot in Figure 1 shows a sort of cyclical variation of effect which was described by Biurgy at the beginning of the 20th century as 'effect return'.

For these reasons it is seldom justified to extrapolate from effects at high levels of doses or concentrations to those at low levels in the neighbourhood of threshold levels for chronic exposure or safe concentrations. Some authors propose the use of correction factors for such extrapolations. Examples of the use of these correction factors are given in the book by Kustov *et al.* (1975). The same book deals also with the joint effect of chemical and physical factors. Our experience with the joint action of mercury and γ-rays has shown that the character of the dose–effect relationship changes with the level of exposure.

It was reaffirmed at the All Union Congress of Hygienists in 1965 that potentiation, displayed at lethal exposure levels, usually becomes summation at low levels, and that if summation is observed at lethal levels it becomes independent effects at low levels. This kind of behaviour was displayed by mixtures of the industrial solvents ethyl acetate and toluene. With these, there was a summation of effects at high exposure levels whereas the effect of low-level chronic exposures to the mixture was not appreciably different from that of exposure to toluene alone. Another example of this behaviour was observed by Burykina *et al.* (1982) in their studies of the combined effects of noise with carbon disulphide and noise with acetone.

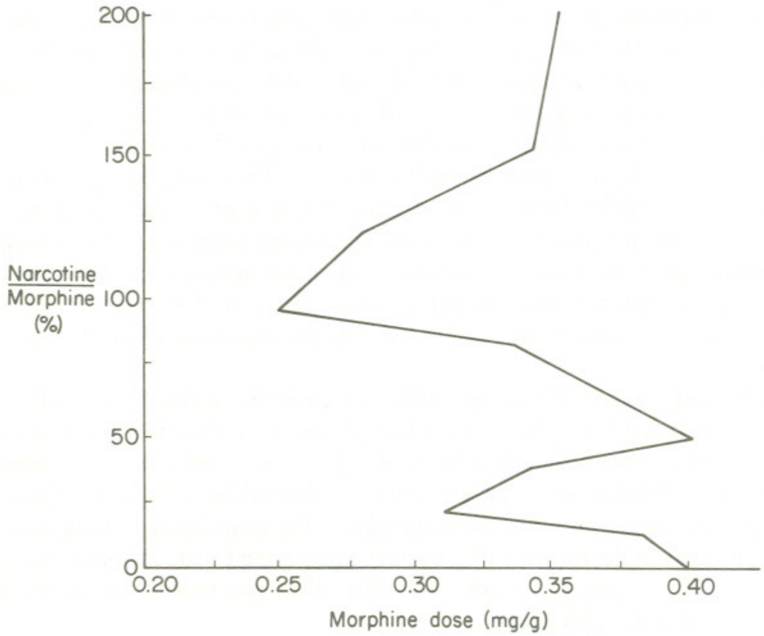

Figure 1 The effects of the relative concentrations of two components of a mixture. From Pravdin (1934)

It may be concluded that at low levels of exposure the most typical behaviour of mixtures is not summation but independence of action. This was foreseen by Academician A. A. Letavet of the Soviet School of Hygiene. He asserted that the effects of chemicals, at the level of standards for environmental quality, would be independent if the standards were valid.

The concept of safe levels of exposure embodies the principle that to be safe a level of exposure should not produce any observable disturbance in the equilibrium between an organism and its environment. Thus, if the pollutant is considered to be a functional stress, the organism must cope with it completely at the level of the maximum acceptable concentration (MAC) and maximum acceptable level (MAL). If the MAC or MAL is determined incorrectly, say by feasible technology or by economic criteria rather than by medical or biological considerations, one may not observe the required independence of effects. This difficulty may arise when standards of environmental quality are set by balancing the costs of risks and benefits.

4 COMBINED EFFECTS OF GASES AND AEROSOLS

From their studies of the effects of 'lethal mists', Tiunov and Kustov (1980) came to the conclusion that the toxicity of gas–aerosol mixtures depends on the following principle: if the aerosol component penetrates more deeply into the respiratory tract than the gas, the toxicity of the mixture is enhanced, but if the depths of penetration are similar the toxic effect does not change. An example of this latter behaviour is given by oil aerosols mixed with acrolein.

The results of their studies show that the toxicity of the mixtures depends not primarily on the depth of penetration but rather on the adsorption–desorption of the gas on the particles. Desorption occurs in deeper areas of the respiratory tract and depends on the properties of both the aerosol (particle size, surface character, etc.) and the gas (molecular size, solubility, etc.); the smaller the gas molecule the more is it adsorbed. Enhancement of adsorption by, for example, capillary penetration or chemosorption will reduce any enhancement of the effects of the mixture.

Another explanation of the joint effects of gases and aerosols can be found in the physical reactions of the exposed organism. For example, Sanotski *et al.* (1965) found that the fibrosing activity of copper oxide aerosols on the lung was reduced when inhalation of the aerosol was followed by inhalation of nitrogen oxide at low concentrations, presumably due to the stimulation of lung clearance by the nitrogen oxide. Another effect was the reduction by the copper oxide of the irritative effect of nitrogen oxide. A similar effect has been observed by B. A. Katznelson and his colleagues.

On the other hand, enhancement is observed in two other cases of combined exposures, viz. coal dust and carbon monoxide (Erman cited by Navrotsky, 1961) and silicon oxide with radon.

5 PROBLEMS IN ESTABLISHING HYGIENIC STANDARDS FOR COMBINED EFFECTS

In national sanitary legislation mixtures of known substances are usually regulated according to the formula

$$\frac{C_1}{\mathrm{MAC}_1}+\frac{C_2}{\mathrm{MAC}_2}+\frac{C_3}{\mathrm{MAC}_3}\cdots\frac{C_n}{\mathrm{MAC}_n}<1$$

This principle and formulation can also be applied to regulate the total intake by different routes (inhalation and ingestion). If it is discovered that exposure by one route predominates, control may be based on that route alone.

The problem of complex mixtures of unknown, or partially known, composition is much more complicated. There are two kinds of incompletely known mixtures: stable and unstable. Most authorities consider that only stable mixtures may be assessed quantitatively for their safety or hygienic rating. Two of the most important descriptors of these mixtures are:

1. the leading component(s), i.e. the substance(s) that governs the toxicity of the mixture; and

2. the characteristic component(s), i.e. the substance(s) that identifies the source of the mixture.

The use of this classification was encountered in a workplace where the air was contaminated with titanium tetrachloride. Hydrogen chloride was the leading component but its MAC was lowered five-fold (from 5 mg/m^3 to 1 mg/m^3) because of the presence of titanium. Since the hydrogen chloride could have come from other sources, titanium ion was the characteristic component.

Another example is provided by the mixture generated in the burning of aluminium alkyls where aluminium oxide is both the leading and characteristic component.

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