Methods for Assessing the Effects of Mixtures of Chemicals
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Epidemiology of Occupational Exposures with Special Reference to Mixtures of Chemicals

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ABSTRACT

Exposures to mixtures of chemicals are common events. They occur in manufacturing and service industries, mining, agriculture, and laboratories. Epidemiology has made a relatively small contribution to the identification and evaluation of combined exposures and to understanding their mechanisms.

The methods used are general or descriptive studies, experimental investigations on human volunteers and specially designed surveys to test interactions between the various components of exposure. The latter method has had a strictly limited use for studying the combined effects of smoking and asbestos exposure.

General studies have been made of workers exposed to solvents, pesticides, occupational carcinogens, plastics, metals, dusts, and products of combustion. An important need is to develop methods for investigating interactions of combined exposures in working people.

Experimental studies of human volunteers have several limitations as a method of investigation, but they may help to define mechanisms.

Identification of adverse effects from combined exposures comes from several sources such as case histories, descriptive epidemiological studies, and routine health surveillance programmes undertaken by occupational health services. More systematic methods using regional or state records and job exposure matrices should be developed.

1 INTRODUCTION

Exposures to mixtures of chemicals are common daily events. They can occur in manufacturing industries, mines, agriculture, and laboratories. A survey of over 500 manufacturing industries in the USA revealed that 75% had exposures to

more than one potentially hazardous chemical (Finklea, 1981). One-fifth of these factories had airborne concentrations which exceeded the appropriate permissible limit of more than one chemical. Potentially hazardous exposures were frequently multiple. One-tenth of the plants had exposures to 10 or more hazardous substances. A larger representative sample of several thousand workplaces in the USA confirmed the frequency of combined exposures (WHO, 1981). Such mixed exposures are without doubt commonplace in both developed and developing countries.

2 USES OF EPIDEMIOLOGY

The epidemiology of multiple exposures is a relatively unexplored field in occupational and environmental health. It can help to identify and evaluate health risks, clarify mechanisms and modes of action, and establish exposure–response relationships from which meaningful permissible levels can be derived.

2.1 Permissible Levels

While the ultimate aim is to set and enforce permissible levels, governmental agencies are only able to give definitive guidance with respect to combined exposures that have additive or independent effects.

The ACGIH (1982) recommends that when there are exposures to two or more hazardous substances which act upon the same organ system, in the absence of information to the contrary, their combined effects should be considered as additive. The control limit (threshold limit value, TLV) is exceeded if the sum of the following fractions exceeds unity:

$$\frac{C_1}{T_1}+\frac{C_2}{T_2}+\ \ldots\ +\frac{C_n}{T_n}$$

where C_1, C_2, and C_n indicate observed atmospheric concentrations and T_1, T_2, and T_n corresponding control limits.

When there is reason to believe that the chief effects of the different harmful substances are not additive but independent, having local effects on different organs of the body, the control limit is exceeded only when at least one member of the series $\left(\frac{C_1}{T_1}+\text{ or }+\frac{C_2}{T_2}, \text{ etc.}\right)$ itself has a value exceeding unity.

Elkins (1962) has proposed mathematical terms to indicate combined effects that are more than additive (potentiated) or less than additive (antagonistic). They contain a variable function (f) which has to be calculated separately for different combinations.

Epidemiological and experimental studies indicate that potentiation or antagonism may occur from exposures to mixtures of solvents and gases,

mixtures of pesticides, and mixtures of metal compounds (WHO, 1981). There is no simple method of assessing such effects. They have to be determined individually for each type of mixture.

While evidence of combined effects from simultaneous or sequential exposures may emerge from observing groups of working people, the mechanisms of such effects need to be understood before control limits can be set with any degree of confidence. Understanding mechanisms is more likely to follow from animal experiments than from human studies. Animal experiments or toxicity screening tests may reveal dangerous potentiating effects from combined exposures, which should preclude their use except under strict control measures. It may, however, be precarious to extrapolate from animal studies to man.

3 EPIDEMIOLOGICAL METHODS

Epidemiological surveys of work groups are costly and time consuming. They are seldom done without evidence to suggest that a particular health hazard exists. This may come from theoretical considerations of the chemical interaction of mixtures, from animal experiments, from case studies, and from routinely collected epidemiological data based on deaths, episodes of sickness, prevalence of symptoms, or the routine function tests of organ systems, such as lung, liver, blood, or kidney.

3.1 General Studies

Most epidemiological surveys of workers exposed to mixtures of chemicals have been made without attempting to evaluate interactions. For example, observations on the effects of exposure in car painting to low concentrations (below permissible levels) of solvents revealed various adverse effects that were unexpected from single exposures (Hanninen *et al.*, 1976; Husman, 1980; Seppalainen *et al.*, 1978). These investigations did not show the extent to which these effects were due to interactions between solvents. Nevertheless, exposure–response curves may indicate the extent of the risk and levels for control limits. Such data are scarce, largely because of difficulties in obtaining data on exposure and the difficulties of integrating variables of time and concentration. These types of inquiry are the main source of epidemiological information on combined effects. They will be reviewed in more detail in section 4.

3.2 Experimental Epidemiology

Investigations have been undertaken on groups of healthy human volunteers. Under experimental conditions it is possible to evaluate effects by comparing single and combined exposures. Volunteer studies have limitations in that the

numbers exposed are small and exposures are short-term and have to be below permissible levels. Examples of such studies will be reviewed later in section 4.2.

3.3 Specially Designed Surveys

Few investigations of work groups have been designed to evaluate the separate contribution of exposures and their interactions. While this can be done with relative ease in animal studies, it is much more difficult in human studies. Priority has been given to the type of general investigation described in section 3.1, which measures overall effects without quantifying interactions.

3.3.1 The Case–Control (or Referent) Study

This study is a method which could be used to investigate the significance of combined exposures in diseases such as cancers or chronic obstructive pulmonary disease in which details of work exposures, rather than occupations, are recorded. The recording of exposures is a more sensitive indication than a listing of occupations and should make it possible to determine increased health risk related to combined exposures. This type of investigation has been made possible by the relatively recent development of the job exposure matrix which may be defined as a list of job titles with a list of agents to which persons carrying out these jobs are exposed (MRC, 1983).

A carpenter in the construction industry has a variety of exposures which can cause adverse health effects (Table 1). A jobbing carpenter who would normally be included under the same job title of carpenter will have fewer exposures.

3.3.2 The Cohort Study

The interaction between two different factors having long-term effects has been determined for asbestos and smoking (Sarraci, 1981). It is a good example of using statistical models to find out which suits the epidemiological data best. The models that can be tested are (1) additive with no interaction, (2) multiplicative,

Table 1 Exposures of a carpenter in the construction industry

Azo compounds
Phenols (creosote)
Aromatic hydrocarbons (coal tar and pitch)
Metals (chromium)
Minerals (asbestos)
Wood dust
Ultraviolet light

Adapted from MRC (1983).

Table 2 Death rates for lung cancer per 100 000 person-years

Exposure group*	Death rate	Relative risk
A− S−	11	1.0
A+ S−	58	5.2
A− S+	123	10.8
A+ S+	602	53.2

*A = asbestos exposure, S = smoking.
Adapted from Hammond *et al.* (1979).

and (3) additive with interaction but no effect of asbestos alone. The investigation by Hammond *et al.* (1979) is an example of the kind of data necessary for this type of epidemiological investigation (Table 2).

It supports the multiplicative model since the relative risk of the group who smoked and were exposed to asbestos is 53.2. This approximates the product of the relative risks of the groups who were only exposed to asbestos (5.2) and who only smoked (10.8). Unfortunately, such data which allow this type of analysis are seldom available for combined exposures to chemicals under normal working conditions.

4 EXAMPLES OF EPIDEMIOLOGICAL STUDIES

4.1 General Studies

4.1.1 Solvent Mixtures

Organic solvent mixtures are widely used in modern industry in making shoes, furniture, synthetic plastics and fibres, pharmaceuticals, and in metal work. Thus, there are numerous opportunities for studying the effects of such combined exposures. Most investigations have been made of persons exposed to mixtures with each agent below the permissible level.

An example of a well-planned study is that of 102 car painters in Finland exposed to mixtures of solvents (Hanninen *et al.*, 1976; Husman, 1980; Seppalainen *et al.*, 1978). Loco engineers and assistants were used as a matched control group. They were unaware that they were the control group and believed that they were also being investigated for effects of work exposures.

Compared with the control group, the car painters had significantly more acute symptoms of prenarcosis and irritation and long-term effects such as fatigue and loss of memory. They also had a greater reduction in nerve velocities than the loco engineers. Each exposure was below the recommended threshold limit value (TLV). When added together the concentrations expressed as a fraction of the relevant TLV are less than unity (Table 3) and thus are well below

Table 3 Organic solvent exposures of 102 car painters

Solvent	C/T
Toluene	0.15
Xylene	0.06
Butyl acetate	0.05
White spirit	0.03
Other solvents	0.04
Total additive exposure	0.33

C = concentration of each solvent,
T = corresponding TLV.

Adapted from Hanninen *et al.* (1976).

the TLV for additive effects. The TLVs may have been too high, but the more likely explanation is that there was a potentiating effect of these solvents.

Another study of workers exposed to acetone, butyl acetate, and toluene, each under the recommended maximum allowable concentration values, recorded a high prevalence of acute symptoms with headaches and insomnia (Postolache, 1974). A relative risk of 1.8 for neuropsychiatric disorders among workers exposed to solvents indicated an increased risk from mixtures (Axelson *et al.*, 1976).

Thus, the evidence of a potentiating effect with solvents is too strong to be dismissed and indicates a need for studies in which separate and combined effects can be evaluated.

4.1.2 Plastics

The thermal destruction of plastics such as polyurethane is accompanied by the emission of carbon monoxide, di-isocyanates, and nitric acid vapours (Kimmerle, 1976). Similarly, thermal cutting of PVC (polyvinyl chloride) sheets emits pyrolysis products, causing asthma and other acute respiratory effects (Wooley and Palmer, 1976). PVC produces hydrogen chloride, carbon monoxide, nitrocellulose, nitric oxides, and polyacrylonitrile and hydrogen cyanide. Some of these separate components have an irritant effect on the respiratory system which, it is suggested, is potentiated during combined exposure (Furon *et al.*, 1973) (see section 4.1.7 for other effects of pyrolysis).

4.1.3 Metals

Generally, few epidemiological studies have been made of the effects of combined exposures to metals. There is one study of 97 workers exposed to low

concentrations of lead and zinc. ALA (δ-aminolaevulinic acid) levels in urine are a recognized test for the destructive action of lead on haemoglobin synthesis. This group had decreased levels of ALA in urine, indicating that zinc is a direct antagonist to lead (Dutkiewicz *et al.*, 1979).

4.1.4 Pesticides

The application of pesticide mixtures overcomes the problem of increased resistance of pests to individual compounds. The rightly chosen combination of various components increases the overall pesticide activity and reduces the number of applications and human exposures (WHO, 1976). Experiments with insects have demonstrated the synergism of insecticides in their combined application with herbicides (Lichtenstein *et al.*, 1973). The increased toxicity of parathion, DDT, carbofuran, and diasinon in combination with triasin depends on the type of soil, the quantity of pesticide residues in the soil, and the water content of the soil. The effect of the combined action of pesticides depends also on the character of their metabolism in the organism and mode of action in the biotransforming chains in the liver. As many factors influence these combined effects, studies under experimental and industrial conditions are needed.

An epidemiological study by Kaloyanova-Simeonova (1977) of 200 agricultural workers in contact with different groups of pesticides showed, by comparison with a control group, significant increases in respiratory, nervous, and gastrointestinal symptoms. More of the agricultural workers than the controls had leucopenia, raised total bilirubin, and albuminuria. None of these findings had any serious clinical significance for the individual, but, epidemiologically, they are indicative of early adverse effects of combined exposures.

Dimitrieva (1974) studied 133 agricultural workers exposed to combinations of organic phosphorus and organic mercury pesticides. Comparison of test results made before the beginning of the season and seven months later showed a considerable decrease in the activity of thiol enzymes, cholinesterase, lactate dehydrogenase, and phosphomonooxidase. The addition of fungicides to the insecticides provoked even more significant changes.

Michail (1974) studied 256 workers who had used combinations of organophosphorus, chlororganic, and carbamate insecticides. The study revealed a decreased activity of serum cholinesterase, decreased values of the sulphydryl groups and an increase of 17-ketosteroids in the urine. These abnormalities increased with the level of exposure. Ensbert *et al.* (1974) reported changes in the nervous system and in serum glutamic–oxaloacetic transaminase, serum glutamic–pyruvic transaminase and alkaline phosphatase levels in the blood of agricultural and industrial workers exposed to the combined effects of insecticides, fungicides, and fumigants.

Animal experiments with combined exposures to pesticides have shown a variety of different effects. Some have been additive and potentiating, others

antagonistic or protective. Responses have varied according to animal species. Some of the toxicity effects were unpredictable. Animal investigations emphasize a need for epidemiological studies of combined effects of pesticides in humans.

4.1.5 Occupational Carcinogens

In theory, combined exposure to chemical carcinogens, including carcinogenic modifiers, may have an additive, potentiating, or antagonistic effect on carcinogenic response. While there is good epidemiological evidence that cigarette smoking potentiates the effects of asbestos (see above) and uranium ores (Archer *et al.*, 1973), there is no generally accepted evidence of an enhanced occupational cancer risk from a combined exposure to two or more chemical substances used in industry. There are two investigations where combined effects are suspected. The use of copper sulphate in combination with copper hydroxide as a fungicide in vineyards appeared to cause an increase in lung cancer in exposed vineyard workers. Experiments with guinea-pigs indicated that the combined effect of both copper fungicides might be a factor in the increased cancer risk (Villar and De Menezes, 1973). In a Swedish company producing ethylene oxide, a cohort study of workers exposed to a combination of ethylene oxide, ethylene dichloride, ethylene hydrin, and ethylene showed a significant mortality excess from cancer (9 observed against 3.4 expected). The excess cancer incidence cannot be attributed to any particular chemical. There may have been a combined effect which is not possible to detect from the available data, although ethylene oxide and ethylene dichloride are the prime suspects (Hogstedt *et al.*, 1979).

There is no known epidemiological study of humans that has shown a modified carcinogenic effect from combined exposures.

4.1.6 Dusts Causing Pneumoconiosis

Pneumoconiosis in general, and silicosis in particular, have been the source of early investigations into combined exposures because of the usual complex chemical composition of mineral dusts which could be inhaled by workers in the mining and milling of various ores (metals and coal), or the drilling or quarrying of rocks and stones such as granite, slate, basalt, pumice, marble, and talc (Parkes, 1982). Mixed dust exposures also occur in pottery, abrasives, glass, and cement industries, in metal foundries and in iron and steel production. The fibrogenic properties of such dusts have been attributed to their various amounts of silica, silicates, metal oxides, and carbonates. Some silicates such as sericite have been credited with a potentiating action on the fibrogenic properties of silica, while calcium carbonate has been thought to inhibit this effect (WHO, 1976).

Exposure to different gases may alter the response of the lungs to inhaled dust. Combined exposures to carbon monoxide or nitrogen dioxide are said to

accelerate the development of pneumoconiosis (Sevcenko and Caganz, 1967) and exposure to sulphur dioxide with quartz seemed to increase the risk of silicosis (Kacnelson, 1974). Sweet *et al.* (1974) studied the lungs of bituminous coal miners and determined the content of total dust, free silica, and residues of chrome, carbon, iron, manganese, nickel, titanium, and zinc. There was no correlation between the content of these residues and the degree of pneumoconiosis or other respiratory disease.

4.1.7 Pyrolysis Effects

The burning of any substance produces a variety of combustion products such as carbon monoxide, nitrogen oxide, and hydrocarbons. Unexpected responses have been described in firemen fighting a polyurethane fire (LeQuesne *et al.*, 1976). The firemen developed neurological signs and symptoms that could not be explained by exposure to any known product of combustion. Firemen, as a group, may be exposed for short periods to high concentrations of gases and vapours, without adequate respiratory protection. Several investigations have been made of effects on the respiratory system of groups of firefighting workers (Musk *et al.*, 1977; Tashkin *et al.*, 1977).

A follow-up study of respiratory symptoms and lung function has been undertaken in over 1000 London firemen. Symptoms and decrements in lung function will be related to work histories of exposures (Douglas, personal communication).

4.2 Experimental Studies on Human Volunteers

4.2.1 Gases and Vapours

Tests have been made of the synergistic effects of combined exposures to sulphur dioxide and ozone in view of the possibility that these two gases, present in the polluted atmosphere, may combine in the warm moist surfaces of the respiratory tract to form sulphuric acid.

Hazucha and Bates (1975) exposed a group of eight healthy male volunteers to a mixture of ozone and sulphur dioxide each at concentrations of 0.37 ppm for 2 hours. They used the maximum expiratory flow rate at 50 % vital capacity. This is a sensitive index of bronchospasm. The combination of gases resulted in more severe decrements in lung function than the gases on their own. Similar investigations on male volunteers by Bell *et al.* (1977), Horvath and Folinsbee (1977), and Bedi *et al.* (1979) did not confirm that ozone and sulphur dioxide have a synergistic effect.

Von Nieding *et al.* (1979) exposed 11 male volunteers to single and combined exposures of nitrogen dioxide, ozone, and sulphur dioxide. They used gas exchange (PaO_2) and airways resistance (Raw) to measure response. Combined

exposures had no stronger immediate effect than single exposures. After the combined exposures, recovery of gas exchange was delayed and there was some increase in airways resistance and increased reactivity to acetylcholine. In this experiment there was no obvious potentiating effect from combined exposure.

Such studies have serious defects which limit their value quite apart from the need to keep exposures below permissible levels and for short durations. First the number of subjects that can be exposed is too small to deal statistically with the large differences which may occur in individual susceptibility. Secondly, variables such as temperature, humidity, and the particle size of aerosols may influence the response and need to be taken into account and controlled. Examination of the methods used by Bell *et al.* (1977) and Hazucha and Bates (1975) show that the acid sulphate particles could have been 10- to 100-fold higher in the exposure chamber used by Hazucha and Bates than in the exposure chamber used by Bell *et al.* This may explain why one investigation showed a synergistic effect and the other did not.

4.2.2 Other Experiments

There have been other experiments using human volunteers to investigate the combined effects of alcohol intake and trichloroethylene and alcohol and xylene. These do not come within the scope of this report.

5 FUTURE DEVELOPMENTS

Epidemiology has made a relatively small contribution to our understanding of the extent, severity, and nature of the effects of occupational exposures to multiple chemicals. Knowledge is derived mainly from descriptive epidemiological studies and speculations based on animal experiments.

In the laboratory, using animals or human volunteers, responses to separate and combined exposures can be measured and the type of effect, whether it be additive, potentiated, independent, or antagonistic, can be identified. Human volunteer studies may help to clarify both the type of combined effect and mechanisms. However, they have serious shortcomings which have been discussed and can only make a limited contribution to our understanding of combined exposures.

In the workplace it is much more difficult to undertake controlled studies. The models for investigating combined effects of asbestos exposure and cigarette smoking have not been applied to the study of multiple exposures to chemicals under industrial conditions. This is due to the fact that data are lacking on the response to combined and separate exposures. For example, the tentative conclusion drawn from the study of behavioural effects in car painters exposed to mixed solvents well below control limits (Hanninen *et al.*, 1976) was that the combined effects were more hazardous than the summated effects of the

components. However, it was not possible to obtain better evidence of a potentiated effect because there were no data on the effects on the central nervous system of the separate solvents to which the car painters were exposed. Similar problems occur in studying workers exposed to pesticides.

Specially designed studies should be possible in industries with experienced occupational health staff. However, they could only be undertaken with the full cooperation of management and workers and would be justified only where there was strong evidence from clinical studies or animal or *in vitro* experiments of a potentiating effect.

Although combined exposures are common events, synergism adversely affecting health is probably rare (Elkins, 1962). Clues which indicate these more adverse responses come from case histories, descriptive epidemiological studies, routine health surveillance programmes and experimental studies on animals and *in vitro* tests. There may be a case for more systematic methods of clue finding through regional records or job exposure matrices.

The case–control study should be exploited using job exposure matrices to determine the significance of combined exposures in cancers and other diseases related to work.

Routine health surveillance of groups with combined exposures, together with environmental measurements, could be an important preliminary step in identifying synergism. In sampling and analysing air in workplaces for combined exposures, the specificity of the methods used has to be considered. Specificity is the degree to which methods produce a response to only one component of a sample and not to any other components that may be present. In this way occupational health services, working in collaboration with research organizations, may be able to contribute to the identification of adverse health effects of combined exposures.

On the limited evidence available, the more fruitful areas for epidemiological research into combined exposures appear to be pesticides, organic solvents, mixed gases, and carcinogens.

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