

Occupational Experience of Exposure to Mixtures of Chemicals

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ABSTRACT

Occupational diseases are associated with complex sets of causes of both environmental and personal origin. The problems of dealing with mixtures of chemicals in the work environment are identified and limitations of currently used methods are stressed. Exposures to more than one metal and more than one solvent are used as typical examples to point out deficiencies in methods and to suggest some unified approaches based on the effects. Factors contributing to occupational cancer are discussed in relation to multievent and multifactor models. The importance of identifying confounding factors in the interpretation of results of epidemiological studies is pointed out. The need for biological models for elucidating the mechanism of action of mixtures of chemicals is stressed in relation to the design of epidemiological studies.

1 INTRODUCTION

Occupational diseases are associated with complex 'webs of causations' of both environmental and personal origin (Siemiatycki and Thomas, 1981). Well-designed health monitoring studies have led to the identification of specific risks but the methods used have been of only limited usefulness in exploring the mechanisms by which multiple factors give rise to health risks in the work environment. Due to this inadequacy of methodology, our existing knowledge of the interaction of combined factors, especially those attributable to inheritance or acquired by habit, with those risk factors present in the work environment is incomplete (WHO, 1981; WHO EURO, 1982).

The study of health effects elicited by the combined action of more than one factor in the work environment poses many conceptual and methodological challenges (WHO, 1975). Any job in the chemical industry, for example, presents a situation where a worker is likely to be exposed to a mixture of chemicals.

As it is, to obtain accurate estimates of the exposures themselves is not easy. Technological changes, rotation of jobs done by an individual within the same

industry, exposure to a different set of chemicals when he moves to another industry, and lacunae in the maintenance of and accessibility to the past health records, all tend to complicate the issues further. Above all, we cannot overlook the fact that quantitation of the health outcome or the exposure to even a single chemical is also subject to 'confounding factors' (Gamble and Battigelli, 1977).

2 STATEMENT OF THE PROBLEM

A network that attempts to interconnect the many causative factors of occupational diseases is shown in Figure 1. The two main variables to be considered are those presented by the individual and those arising out of the work environment. The factors presented by the individual include those he has inherited which determine proneness or susceptibility to diseases and those personal habits like smoking or drinking which he has acquired. The environmental factors consist of single physical or chemical stresses or their combinations. The health status of the worker may be considered as the outcome of the interaction of these factors in a given socioeconomic milieu. One cannot overemphasize the relevance of the latter to any meaningful study of the health status of industrial workers in the developing countries where undernutrition, endemic parasitic infestations and unsanitary living conditions constitute the background for the low status of health.

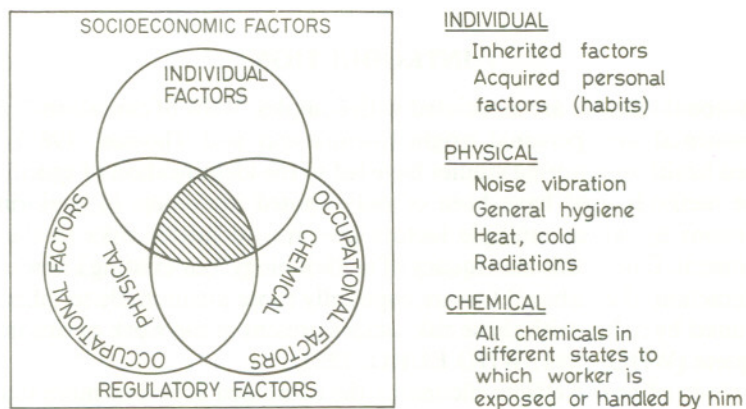


Figure 1 Interaction of risk factors in the work environment. Individual: inherited factors, acquired personal factors (habits). Physical: noise vibration, general hygiene, heat, cold, radiations. Chemical: all chemicals in different states to which worker is exposed or handled by him. The hatched area is the grey region where there is need for greater understanding and hence data

2.1 Limitations of Currently Used Methods

Health records of workers are usually kept on the basis of history taking, physical examination, and laboratory tests which, when supplemented with industrial hygiene data, form the base for identifying risk factors (Hampton *et al.*, 1975). Standard mortality rate is calculated from the retrospective analysis of the health records of the exposed group by a comparison with health records of a non-exposed population (Symons and Taulbee, 1981). When the relationship between the disease of a specific organ (e.g. lung) and the death rate has to be deduced, the risk assessment involves a functional analysis of the biological effects of exposure to the implicated chemicals along with the risk factors, if any, associated with personal habits such as smoking (Nurimen *et al.*, 1982). The additivity of attributable risks is also used as the basis of a technique for assessing combined effects (Walker, 1981).

In the work environment, where exposure to mixtures of chemicals is the general rule, one usually encounters a cluster of diseases or symptoms. There is a need for evolving reliable quantitative approaches to assess the outcome and trace the cause-effect relationship in such clusters (Baumgarten and Oseahorn, 1980). The inadequacy of the currently used methods is reflected in the rather unsatisfactory state of the art in regard to the interpretation of results, the classification of diseases, and most significantly in the arbitrariness of establishing threshold limit values or maximum allowable/permissible concentrations for regulatory purposes (Glindmeyer, 1981; Pepys, 1982; Tockman, 1982).

3 CURRENTLY USED METHODS

Two main approaches are currently used to gather information on the health effects of toxic chemicals in the work environment: (1) health surveillance by medical examination, and (2) industrial hygiene by measuring exposure levels.

An effective health surveillance system includes a comprehensive medical registry or repository of records of observations on mortality and morbidity. Retrospective analysis of the data stored in such banks provides valuable information leading to the identification of risk factors.

A highly sophisticated information system is an essential prerequisite in industries for storing the data of routine examinations, periodic check-ups, pre- and post-employment health records, death records, etc. Representatives of 21 major chemical companies of the USA met in Chicago in February 1981 to survey the medical information system currently used in the chemical industry and to devise more effective means of using the wealth of information hidden in such records. The lacunae in the data processing and referral systems were identified (Joiner, 1982). In the context of a documentation base for occupational health, one cannot ignore the need for evolving information systems appropriate to medium- or small-scale industries where the (health) hazards of

exposure to combinations of chemicals could be equally potent. The higher incidence of bladder cancer among workers engaged in the cottage dyestuff manufacturing units of India is a classic example. A survey conducted on the health conditions of agate stone cutters in Khambhat, Gujarat, India, an industry which is still practised as it was centuries ago, suggested the combined effect of background tubercular infection and exposure to respirable-size silica particles in causing extensive silicosis (ITRC, 1980). The need for more detailed studies of combined effects in other less-developed countries has been emphasized by El-Batawi (1974) and Asgowa (1981).

4 EXPOSURE TO MIXTURES OF CHEMICALS

A relatively recent WHO (1981) publication gives in tabular form examples from industry of human exposure to mixtures of solvents, metals, gases, and vapours. In welding, for example, welders are likely to be exposed to three major groups of toxicants as given in Table 1. It must be remembered that welding is a ubiquitous operation in industry, workshops, and even wayside repair shops.

4.1 Solvents

Mixtures of solvents are used in the painting, degreasing, and solvent extraction processes employed in many industries. Besides synergism in the well-known narcotic action of solvents, potentiation of the action of one solvent on another can occur. Behavioural effects due to exposure to a mixture of organic solvents have been reported to occur in a study conducted in Finland where tests for intelligence, memory, psychomotor performance, and personality were carried out and a potentiating effect of solvents identified (Hanninen *et al.*, 1976). Limited studies on gasoline handlers in Lucknow and Kanpur in India in the hot summer months (ambient day temperature 35–43°C) have also suggested the possible involvement of behavioural changes due to the mixture of aromatics and aliphatics in the gasoline (Dr K. P. Pandya and Dr S. H. Clerk, Industrial Toxicology Research Centre, Lucknow, India, personal communication).

Table 1 Environmental exposures encountered by welders

Metals

Iron, lead, manganese, zinc, cadmium, chromium, mercury, copper, aluminium, and nickel

Gases

Carbon monoxide, nitrogen oxide, ozone, and phosgene

Miscellaneous

Fluorides, hydrocarbons, silica, and ultraviolet radiation

After Beaumont and Weiss (1981).

Biological monitoring and metabolic transformations of solvents have been discussed in relation to their uptake, tissue storage, and pathophysiological impact (Gomperiz, 1980). Exposure to organic solvents has also been suggested as a possible contributory factor in occupational Hodgkin's disease (Olsson and Brandt, 1980). The renal excretion pattern of hippuric acid, mandelic acid, and phenylglyoxylic acid was found to be a useful index in assessing the combined occupational exposure to toluene and styrene (Bieniek *et al.*, 1982). Incidence of fatty changes in liver has been correlated with the exposure to a mixture of chlorinated and non-chlorinated solvents (Edling, 1982). Evidence of non-interaction may also be obtained, for example, by using changes in the levels of free erythrocyte protoporphyrins. Toriumi and Kawai (1981) concluded that, in a combined exposure to lead fumes and organic solvents, the latter did not cause any additive effects.

4.2 Metals

Combined effects are likely to occur in workers handling metals, welding operations, etc. Thus, urinary output of lead was found to be a good indicator to evaluate the combined effects of mixed exposure to lead, zinc, and cadmium (Dutkiewicz and Chodon, 1979). The combined exposure to nickel and chromium leads to neuropathic effects (Perbillini and Debrandis, 1979). Multiple exposures invariably occur during welding, electroplating, and general handling of metals (Cant and Legendre, 1982; Lengard *et al.*, 1980; Suzuki *et al.*, 1981). There have been attempts to link respiratory symptoms to multiple metal exposures (Akbarhazadeh, 1980) or renal function disturbances with combined exposures to lead, cadmium, and/or mercury (Buchet *et al.*, 1980, 1981; Kallowicki *et al.*, 1981; Schaller *et al.*, 1980). The polishing, electroplating, and coating of metals involve hazardous exposure to chromium, nickel, copper, iron, lead, and zinc, to corrosive acids and alkalies, and to trichloroethylene and tetrachloroethylene. The results obtained from studies of cause-specific disease rates in such situations have been used with proportionate mortality ratio (PMR) analysis to derive risk estimates (Blair, 1980). Multiple exposures to metals, nitric oxides, and hydrocarbons have also been related to diverse ailments including lung cancer and dermatoses (Beaumont and Weiss, 1981; Satoh *et al.*, 1981).

4.3 Miscellaneous Studies

Combined exposure to dust, cyanide fumes, and solvents in electroplating shops led to detectable changes in lung function as well as in the response of the workers to standard psychological tests (ITRC, 1982). Mortality data of workers exposed to a mixture of chlorinated pesticides have been analysed to identify specific risk factors (Ditraglia *et al.*, 1981; Riihimaki *et al.*, 1982).

5 OUTCOMES OF COMBINED EXPOSURES

Respiratory disorders, impact on reproductive function, and cancer are three of the many outcomes of exposure to chemicals in the occupational environment. Respiratory disorders account for a good proportion of causative factors of mortality and have been associated with exposure to multiple factors (Fish, 1982). The diverse pathological base for this group of disorders includes bronchoconstriction, airway inflammation and oedema, toxic or inflammatory alveolitis/bronchitis, and non-cardiogenic pulmonary oedema.

5.1 Reproductive Effects

With the thalidomide episode in the background, the increased concern with teratogens is understandable. Epidemiological approaches to this group of chemicals in the general population as well as subgroups of industrial workers have been presented (Klingberg and Weatherall, 1979). The necessity of using a battery of surveillance techniques and screening tests has been highlighted and elaborate protocols have been designed for surveys involving mixtures of chemicals in industries (Buffler, 1979). Guidelines for conducting studies on humans exposed to mutagenic and reproductive hazards are available (Bloom, 1981).

Spontaneous abortion rates have been used as indicators for assessing the effect of chemicals in a selected population of women, mainly wives of employees exposed to chemical teratogens (Roberts and Lowe, 1975; Stein *et al.*, 1975). Methods based on sperm motility have been used to assess the direct effect of chemicals on the reproductive ability of male workers (Levine *et al.*, 1981). Reproduction malfunction has been studied in persons occupationally exposed to dibromochloropropane, ethylene oxide, epichlorhydrin, α -chlorhydrin and carbamyl; these chemicals all interfere with spermatogenesis (Whorton *et al.*, 1977, 1979). When the exposures are properly classified according to the nature of the chemicals, sperm studies on groups of individuals provide a very simple and straightforward epidemiological approach (Milby and Whorton, 1980). A list of reproduction outcomes associated with parental exposure to chemicals in the work environment is given in Table 2, based on a survey by Sever (1981). The need for accurate toxicological information on the chemicals or combination of chemicals, the degree of exposure, and dose-response and threshold exposure levels in assessing the risk of exposure to embryo/foetotoxic chemicals has been emphasized (Karrh *et al.*, 1981).

5.2 Occupational Cancer

Continuing discovery of new cases of occupational cancer, the increasing realization that many substances in common use can cause cancer in laboratory

Table 2 Outcome associated with parental exposure to toxic chemicals

Altered fertility
Single gene defects
Chromosomal abnormalities
Spontaneous abortions
Late foetal deaths
Congenital malformations
Altered sex ratio
Altered gestation length
Intrauterine growth retardation
Neonatal deaths
Infant deaths
Developmental disabilities
Behavioural disorders
Chronic diseases
Malignancies

After Sever (1981).

animals or have been proved to be putative carcinogens in short-term tests (Purchase, 1980) and, above all, the explosive growth of the chemical industry, have contributed to the global concern with environmental/occupational carcinogens (Doll, 1981). The need for more detailed epidemiological studies in the chemical industry has been stressed so that the effects which have been presumably overlooked or only tentatively suggested by laboratory tests could be uncovered and levels of exposure estimated. Some essential requirements, as outlined by Doll (1981), to establish carcinogenicity from epidemiological evidence are: (a) a positive incidence of cancer in groups of individuals and its association with occupational exposure by case-control or cohort studies; (b) the cases are not attributable to bias in recording observations or in the use of detection techniques; (c) the cases are not attributable to confounding factors; (d) the cases are not attributable to chance; (e) the case histories show variations appropriately with dose; (f) the case histories show variations appropriately with period of exposure; and (g) the cases are observed repeatedly in different situations but with similar exposures.

A matrix method has been used to evaluate the contribution of 19 industrial chemicals to the risk of liver angiosarcoma associated with the exposure to vinyl chloride (Waxweiler, 1981). Exposure indices have been suggested for evaluating the combined action of sulphur dioxide and arsenic (Lubin *et al.*, 1981). PMRs for leukaemia, multiple myeloma, and other lymphomas were found to be elevated in a study of health data of workers engaged in three Texas oil refineries (Thomas *et al.*, 1980, 1982). On the basis of the existing knowledge that many chemicals in industry are already recognized as human carcinogens, attempts have been made to evolve statistical models for quantitative risk assessment in chemical industries

(Greenberg and Tamburro, 1981; Ryzin, 1980). Models for linking exposure levels to cancer incidence have also been suggested for workers engaged in the newspaper industry with potential for exposure to mixtures of hazardous chemicals (Hoar *et al.*, 1980).

Mortality studies of cancer depend mostly on the examination of site-specific cancers in different occupational groups. Studies based on cell types have been confined to rare tumours such as angiosarcoma of the liver, mesothelioma, or adenocarcinoma of the nasal sinus. Wegman and Pieters (1978) have drawn attention to the fact that 'oat cell' or small cell carcinoma is prevalent in the range of 38–64% in workers exposed to asbestos, arsenic, chromium, or uranium, in contrast to the 20% US national average of all lung tumours classified histologically in the Third National Cancer Survey.

Cohort studies have been conducted to identify an increase, if any, of cause-specific mortality in cancer of the pancreas among workers exposed to toxic chemicals in the paints and coating industry (Morgan *et al.*, 1981). Attempts have also been made to correlate lymphatic leukaemia and myeloid leukaemia with exposure to more than one organic solvent used in the rubber industry (Williams *et al.*, 1980; Wolf *et al.*, 1981). Chemists working in analytical and research laboratories are recognized to be vulnerable to diverse cancers. A retrospective study conducted in E.I. du Pont on 3686 men and 75 women employed as chemists showed that this professional group was at higher risk of death from malignancies of the colon and from cerebrovascular diseases. Incidence rates among chemists of melanoma and of cancer of the prostate were slightly higher than among the other subgroups (Hoar and Pell, 1981). Interaction of multiple factors in precipitating endemic mesothelioma in the asbestos mining industry of Turkey has been highlighted by Lilis (1981). The spectrum of pleural and pulmonary effects includes non-malignant changes such as diffuse pleural fibrosis (thickening), localized pleural fibrosis (pleural plaques), pleural calcification, benign pleural effusions, and interstitial pulmonary fibrosis.

5.3 Genotoxicity

Genotoxic effects of chemicals have assumed a sombre significance as a result of the extensive information available today on the mutagenic potential of a wide variety of chemicals or their possible interactions with physical agents such as radiation. Along with the global interest in developing reliable *in vitro* screening tests, attention is being increasingly devoted to conducting genetic monitoring in the workplace as well as instituting genetic counselling among industrial workers and their family members. A WHO report (WHO, 1980) calls our attention to the fact that about 2500 hereditary diseases have been detected in man by careful diagnosis and investigations. Some of these diseases are rare and perhaps can be considered more as medical curiosities than real threats. Nonetheless, several genotypic variations are likely to be of relevance to occupational medical practice.

Illustrative examples include haemoglobinopathies and allied disorders, serum α_1 -antitrypsin deficiency, and pseudocholinesterase abnormalities. How far genetic variation is reflected in the susceptibility to occupational toxins is illustrated by the few examples of interactions with known genetic disorders enumerated in Table 3.

Table 3 Genetic variation in human susceptibility to occupational toxins and other agents of daily or occasional use

Inhaled pollutants	α_1 -Antitrypsin deficiency Aryl hydrocarbon hydroxylase inducibility Metabolic conversion of nicotine Plasma paraoxanase activity Pseudoesterase activity
Physical agents	Cold weather Motion sickness Metal poisoning Colour vision Ultraviolet X-rays
Drugs (could arise out of chemicals of related structure in industry)	Metabolism: <i>N</i> -Acetyltransferase Plasma pseudocholinesterase Co-oxidation Glucose-6-phosphate dehydrogenase deficiency Sensitivity: Methaemoglobin reductase deficiency
Infectious agents/ autoimmune disorders	Malaria, Duffy blood group Sickle cell Thalassemia Glucose-6-phosphate dehydrogenase deficiency Predisposition due to impaired antibody production or cellular immunity Predisposition associated with histocompatibility antigens

After Omenn (1982).

Genetic traits that may predispose individuals to occupational diseases include variations in blood groups, erythrocyte enzyme profiles, plasma protein profiles, and the occurrence of the histocompatibility antigens, etc. (Omenn, 1982). The role of genetic counselling and monitoring in detecting such abnormalities and work placement according to susceptibility to chemical hazards has been emphasized (Dabney, 1981; Fabricant and Legator, 1981). Standard techniques used for monitoring cytogenetic changes have helped in identifying individuals who were excessively exposed to particulate pollutants in the welding industry (Knudson, 1980). The utility of the sister chromatid exchange technique in

monitoring human populations for exposure to industrial toxicants and environmental pollutants has been evaluated by Lambert *et al.* (1982).

6 CONFOUNDING FACTORS

The impact of confounding factors underscores the urgent need for evolving reliable methods for examining the health effects of the combination of causative agents. Using death rates prevalent in the general population as a reference point, epidemiologists generally use the standardized mortality ratio as a parameter to evaluate the impact of diverse factors leading to illness in industrial workers. However, the unique feature of each occupational cohort imposes certain limitations on such a generalized approach (Gilbert, 1982). When confounding factors related to personal habits are considered, analysis of the events arising out of exposure to toxic chemicals in the work environment becomes obviously more complex.

6.1 Personal Factors

It is known that persons who consume alcohol and also smoke cigarettes run the relative risk of oesophageal cancer approximately equal to the product of the relative risks associated individually with cigarettes or alcohol. If an occupational stress such as exposure to ionizing radiations or asbestos particles is superimposed on such an individual, relative risks approximating the multiple of the risks related to respective pairs of individual factors are produced. Interpretation of the results of such studies has led to much controversy, generating more heat than light (Archer *et al.*, 1976; Blot and Day, 1979; Dayal, 1980; Greenland, 1979; Kupfer and Hogan, 1978; Murphy, 1978; Rothman, 1974; Rothman and Killer, 1974; Rothman *et al.*, 1980; Saracci, 1977, 1980; Shore *et al.*, 1980; Wahrendorf *et al.*, 1981; Walter and Halford, 1978).

In this context, the NIOSH summary (Blackwell *et al.*, 1979) of the existing information on the interaction of smoking with chemical pollutants of the work environment is relevant:

- (1) Certain toxic agents in the workplace also occur in tobacco products or smoke, thus increasing the exposure levels. Examples are carbon monoxide, cadmium, and polycyclic hydrocarbons.
- (2) Workplace chemicals may be pyrolysed into more harmful agents by the temperatures generated in a burning cigarette (approx. 875°C). A disease known as polymer fume fever has received some attention.
- (3) Tobacco products serve as vectors by becoming contaminated with workplace agents, facilitating their absorption by inhalation, ingestion, or skin contact. Toxicants of concern in this group are tetrafluoroethylene polymers, lead, and pesticides.

- (4) Effects of smoking may be additive with workplace agents such as chloride, cotton dust, coal dust, or γ -radiation.
- (5) Effects of smoking may be synergistic with asbestos, gold mine dust, silicates, or products of the rubber industry.
- (6) Smoking influences proneness to accidents.

Using case referent techniques, Pershagen *et al.* (1981) has studied the interaction between tobacco smoke and occupational arsenic exposure in precipitating lung cancer in copper smelters. It was evident that, by decreasing either one of the exposures or by disaggregating them, a preventive effect could be achieved. Increased ambient air temperature and humidity, noise, and physical work load were the main physical factors which were found to influence the toxic consequences of occupational exposure to carbon disulphide in viscose plants in Yugoslavia (Dojurk, 1981). By applying multivariate statistical models to mortality data, the effects of combined exposure to asbestos and cigarette smoke were found to be more additive than synergistic (Samet *et al.*, 1979). Analysis of mortality data of workers exposed to amosite indicated a relatively high risk among smokers although smoking did not influence the mortality from mesothelial tumours or from cancer of the stomach, colon, or rectum. Cigarette smoking was, however, associated with a marked excess of death from asbestosis (Selikoff *et al.*, 1980). An inverse relationship to cigarette smoking has been reported, in contrast to the above observation, in regard to the effect of chloromethyl exposure (Weiss, 1980; Weiss and Boucot, 1975). The effect of carbon monoxide on the aggravation of cardiovascular disease induced by occupational factors has also been indicated (Weir and Fabiano, 1982).

6.2 Individual Susceptibility

There has been increasing awareness of individual susceptibilities to the toxic effects of chemicals due to specific immune or non-immune causes or genetic factors. Indeed all these observations have collectively led to the emergence of immunotoxicology as a distinct discipline. A list (not exhaustive) of common environmental agents known to elicit sensitization reactions in industrial workers is given in Table 4.

A list of high-risk occupations for chromium-induced dermatoses is given in Table 5 to enable a more critical search for other additive, synergistic, or antagonistic factors in individual susceptibilities (Adams, 1981).

6.3 Environmental Factors Unrelated to Occupation

Residential accommodation in urban clusters with high automobile traffic and proximity to coal- or oil-based power generation stations is generally associated with a high incidence of lung cancer. It is, however, not clear whether this

Table 4 Occupational pollutants which cause sensitization reactions

Toxic reactions	Immediate allergic hypersensitivity (known mechanism)	Immediate allergic hypersensitivity (unknown mechanism)	Irritation
Ammonia	Dander	Grain dust	Non-specified
Hydrochloric acid	Ethylene diamine		Inhaled products
Chlorine	Enzyme detergents	Toluene diisothiocyanate	Flavours
Phosgene	Platinum salts	Vegetable fibre	Proteins
Nitric oxide	Trimellitic anhydride	Soldering fumes	
Sulphur dioxide	Phthalic anhydride	Formalin	
Ozone			
Hydrogen fluoride	Gums		
Cadmium oxide			
Chromates			
Zinc chloride			
Formaldehyde			

After Fish (1982).

Table 5 High-risk occupations for chromium-induced dermatoses

Cement workers (including load carriers, bricklayers, plasterers)
 Tannery workers
 Diesel engine repair shop attendants
 Radiator repair shop attendants
 Painters
 Textile dyers
 Foundry workers
 Electroplaters
 Galvanized steel workers
 Welders
 Glass polishers
 Glazers

Parameters to be looked for:
 Atopic dermatitis
 Psoriasis
 Specific contact allergens
 Chronic hand eczema

After Adams (1981).

association is attributable to any single risk factor or to a multiplicity of factors (Vena, 1982). Comprehensive reviews of epidemiological evidence of urban versus rural distribution of lung cancer would implicate cigarette smoking, occupational exposures, and air pollution for the differences in rates of lung cancer morbidity between rural and urban populations (Doll, 1981). In the urban occupational situations one encounters particulate pollutants which can act as carriers of the lung carcinogen benzo[*a*]pyrene. Out of the wide range (0.0001–10.0 mm diameter) of particulates, the size range 0.25–5 mm diameter is significant in regard to retention in the alveoli. These carriers adsorb, transport, and retain carcinogens in the respiratory tract and modify their action on the lung.

7 BIOLOGICAL MODELS

Extensive animal experiments or simulated models have furnished valuable data out of which have emerged biological models for occupational diseases. The basic assumption is that a cell must accumulate a number of distinct heritable changes or stages before becoming cancerous. At each stage, there is a possibility of background incidence of end-results independent of exogenous causative factors.

Moolgavkar (1978) has postulated that the probability of a tumour developing in an organ at a point in time t , on the above assumptions, is approximately equal to

$$\lambda_1 \lambda_2 \dots \lambda_s S \frac{1}{(S-i)} t^{(S-1)} N$$

where N = number of cells in the organ, S = number of stages in the multistage process, and λ = spontaneous rate of transformation from stage $i-1$ to stage i .

Data from cohort studies or from retrospective analysis of mortality data can be fitted into this model. Siemiatycki and Thomas (1981) have used this model to analyse the outcome of interaction of binary factors in occupational carcinogenesis with very useful suggestive conclusions, one of which is reproduced as follows:

The most scientific approach is to postulate biological mechanisms, infer a statistical model, see how the data fit the model and interactively repeat the process using both inductive and deductive reasoning. A plausible and widely accepted biological model of carcinogenesis can give rise to additive, multiplicative or other statistical relations between pairs of risk factors which are biologically independent of each other.

8 CONCLUSIONS

- (1) Occupational diseases are associated with complex 'webs of causations' attributable to both environmental and genetic factors.
- (2) Epidemiological studies in industries have led to the identification of specific risk factors but have not helped in unravelling the mechanism by which combined effects are produced.

- (3) Animal experiments provide basic information out of which mechanisms can be postulated. However, even with animal models, very few studies have been conducted to analyse the outcome of the effects of more than one toxicant.
- (4) Confounding factors add a distinct dimension to the complexity of the problem of interpreting data collected from health surveillance programmes in industries.
- (5) Major outcomes of the impact of toxic chemicals like neurotoxicity, behavioural changes, genotoxicity, cancer, etc., should be viewed as end-results of combined effects and appropriate statistical approaches devised to evaluate them.
- (6) Biological models for end-results of the outcome of long-term exposures to chemicals are urgently needed. It is only on these models one can hope to construct appropriate statistical models.

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