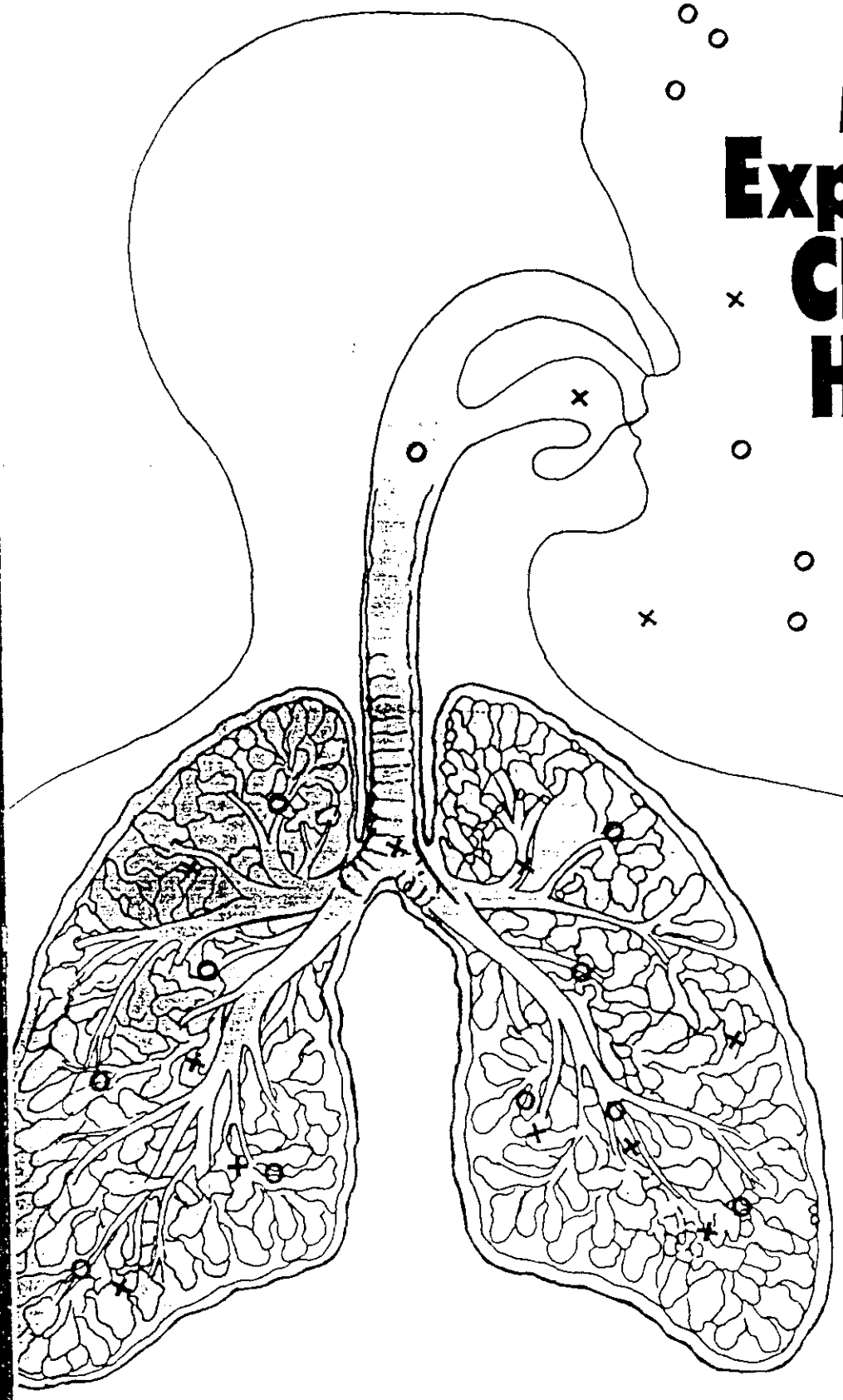
Assessments of health risks in the chemical industry must acknowledge mutual interference between worksite pollutants

Mixed Exposures to Chemical Hazards



In occupational health practice, the elucidation of health effects following exposure to worksite chemicals is of vital importance. Unfortunately, current research frequently focuses on the investigation of only a single substance which toxicologically plays a leading role in the work process under study, and this may lead to misinterpretation. Likewise, controlled studies with model substances are usually concerned with the adverse effect exerted by a single substance.

However, in practice there are multiple commercial, agricultural or industrial operations which in-

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volve exposure of workers to more than one chemical. It should also be realized that workers, in addition to being exposed occupationally, absorb other foreign compounds (such as alcohol, tobacco smoke and its combustion products, miscellaneous drugs) outside the working area. It is imperative that an assessment of the work-related health risks in the chemical industry should invariably allow for such factors because the various materials may produce mutual interference, thereby appreciably modifying the concept of a single-substance risk.

It is the purpose of the present review to call attention to this particular situation. A selection of well-substantiated topical examples may serve to illustrate which materials are most liable to cause impairment to health by means of their combined action. It is further attempted to provide some guidelines to stimulate further research on work-related combined exposures. The results obtained should be considered, where indicated, in the establishment of hygienic threshold limit values (TLVs, MACs). The observation that asbestos-induced bronchial carcinoma is potentiated by cigarette-smoking is appalling evidence of the urgent need for such tests. Reports indicating that the hazardous effects of other combined exposures, such as the cleaner's flush observed when trichloroethylene workers imbibed alcohol, or the effects of drugs such as Phenobarbital on toxic substances detoxification, reaffirm this need.

TYPES OF EFFECTS The following terms are used to designate types of combined effects: "synergism" and "antagonism" which refer to enhanced and reduced effect, respectively, and "additive" or "summation" which imply simply adding or summing of the combined action of substances. In those instances when the total effect is considerably stronger than the additive, the term "potentiation" or "multiplicative" is used. Occasionally, an enhanced effect is referred to as "sensibilization" to indicate that an agent by itself produces little effect, whereas in combination with others it elicits an unusually high response.

There are essentially four possible types of action[1] when a mixture of toxic or harmful pollutants is encountered; to represent these four types, the terms below are suggested for use in industrial toxicology. They are indicated mathematically as follows: where C and c_n indicate concentrations of mixtures and individual components respectively, M and m_n the corresponding permissible levels of exposure (MACs or equivalent), and f a function of the nature of which will vary for different combinations.

1. Addition:

$$\frac{C}{M} = \frac{c_1}{m_1} + \frac{c_2}{m_2}$$

2. Independence:

$$\frac{C}{M} = \frac{c_1}{m_1} < \frac{c_1}{m_1} + \frac{c_2}{m_2}$$

3. Synergism:

$$\frac{C}{M} = \frac{c_1 + f(c_2)}{m_1} > \frac{c_1}{m_1} + \frac{c_2}{m_2}$$

4. Antagonism:

$$\frac{C}{M} = \frac{c_1 - f(c_2)}{m_1} < \frac{c_1}{m_1}$$

Cases of synergistic or antagonistic effects appear in practice, but this aspect of industrial toxicology is extremely diverse, encompassing innumerable interactions between chemical agents in the work environment.

Exposure to a combination of several industrial chemicals does not always produce clearly distinguishable interactions which are synergistic or antagonistic in character. Accordingly, the four types of combined effects outlined above fail to provide an adequate explanation for the causal mechanism that underlies a large number of pathological symptoms. This is exemplified below by several observations in workers exposed to a combination of agents.

EFFECT MECHANISMS Interferences of foreign chemicals in the organism follow the concept of "toxicodynamic" (pharmacodynamic) or "toxicokinetic" (pharmacokinetic) interactions. In the first case the phenomenon takes place at the receptor site, e.g., competitive removal of one substance by another. On the other hand, the mechanism of chemical effects is determined by changes in the organism as a consequence of spread in the biological media (penetration, distribution), their metabolism and their elimination.

Each step in the metabolic pathway of a chemical in the organism can be influenced by another foreign compound or its metabolites to produce a toxicokinetic interaction. As the toxicity of a chemical agent largely depends on how effectively the body is able to accomplish its biotransformation, any interference with metabolism is likely to be reflected in a reduction or enhancement of its toxic potential. Thus, the hypothesis as to how such alterations in toxicity result from multiple exposures mainly relies on changes at the detoxication level.

The role of the liver is of exceptional importance for enzyme detoxication of bound chemicals. There are many foreign substances which induce microsomal hepatic enzymes, thereby enhancing metabolic conversion and detoxication of chemicals. Some chemical materials, however, inhibit microsomal enzymes, and thus produce a prolongation of the toxic action.

Any consideration of combined exposures to chemical agents must at least make mention of tolerance phenomena. Tolerance is a state in which the organism adapts itself to an alien chemical environment. Tolerance connotes a reduction in sensitivity and thereby in the

duration of toxic effects. Target organs are thus rendered resistant to otherwise severe damage by toxic insult, and in this manner an agent protects against its own toxic action. Cross-tolerance is that phenomenon whereby prior exposure to one agent confers protection against subsequent challenge with toxic amounts of a similar-acting agent. Tolerance requires pre-exposure in order to confer subsequent protection against acute effects. Pretreatment with a combination of agents of similar action will confer protection against the challenge of one or both.

Results of controlled laboratory exposure studies on human beings are scarce. However the following examples, observed on worksites during recent years, characterize the environmental stress found in some workplaces and the possible influence on human health.

METALS In ore mines and foundries and in the production of different types of cast-iron, steel, nonferrous metals (e.g., zinc, copper, lead) and their alloys, evolvement of dust, fume or mist of metals and their compounds (e.g., oxides, complex salts) presents risk of combined exposures to workers. In addition, machine manufacturing and welding operations can generate multi-component oxide mixtures which are hazardous to health, like handling of metal compounds containing pigments. Background information on the health status of workers encountering mixed exposure to metals or their compounds is available. But there is a wide gap in knowledge in terms of fundamental epidemiological research at the worksite.

Fourteen steelworkers, exposed for approximately five hours per work shift during periods of up to 16 years to fume concentrations ranging from 1.3 to 294.1 mg^3 made up mainly of iron oxide with varying proportions of chromium oxide and nickel oxide, were clinically investigated. Four of them, with 14 to 16 years' exposure, showed radiological evidence of pneumoconiosis classified as ILO categories 2 or 3; two of these had measurable loss of pulmonary function.[2]

Compared to the controls, the analysis of lung tissue from 19 bituminous coal miners indicated no correlation between pneumoconiosis and the observed amounts of chromium, copper, iron, manganese, nickel, titanium, zinc, and non-coal dust.[3]

Twenty automechanics with raised whole blood levels of chromium, copper, lead, manganese and nickel, single or mixed, were investigated for peripheral nerve disorders by means of electromyography. Of the workers with evidence of peripheral neuropathy, three showed increased levels of lead, nickel and chromium, four workers showed enhanced lead, nickel and chromium, and one of lead, chromium and manganese.[4]

The widespread use of multicomponent solvents points to the importance of studying combined exposures to these agents.

High copper levels in the whole blood of 216 employees in carworkshops (service stations and repair shops) with simultaneous high lead amount were slightly related to decreasing ALA-D activity.[5]

In a cohort of 97 male subjects occupationally exposed to lead and zinc for 1 to 9 years, a decrease of delta-aminolevulinic acid levels in the urine of workers undergoing mixed exposure appeared in comparison with single exposure to lead alone. The zinc amount in serum beside the lead level in whole blood should be taken into account, apart from the ALA-level in urine, in the evaluation of occupational hazards under combined exposure to the two metals.[6]

GASES The work environment can often be polluted by irritant gases which are elicited in varying combinations by several work processes. Because of the attack on the respiratory system, corresponding signs of damage increase, e.g., reduction of lung function or enhanced predisposition to viral- and bacterial-linked diseases.

A controlled two-hour inhalation study on eight male subjects revealed a decrease in pulmonary function (maximal mid-expiratory flow rate) after application of sulfur dioxide and ozone together. The combination of both gases had a much greater effect than did either individually.[7]

Eleven male volunteers were exposed to mixed gases, each at the maximum permissible concentration level. The combination of NO_2 (5 ppm) + SO_2 (5 ppm) + 0_3 (0.1 ppm), $N0_2$ + 0_3, or $N0_2$ + $S0_2$ did not exceed the effect of $N0_2$ alone, thereby causing a decrease of the respiratory oxygen exchange and an increase in airway resistance. However, in the triple series the airway resistance even augmented in the post-exposure period.[8]

SOLVENTS The widespread use of different multicomponent mixtures of organic solvents in industry points to the importance of studying the effects of combined exposures to these agents which occur not only in industries (where large quantities of solvents may be used in manufacturing and processing operations) but also in handicraft workshops (with the use of substances such as paint removers or floor and tile cleaners). Several recent studies draw attention to the severity of worker health effects linked to combined exposure to solvents, and this can be considered one of the most important areas for study and prevention of combined effects in industry.

Where individuals may be exposed to mixtures, as in the manu-

facturing processes for shoes, furniture, synthetic plastics and fibres, pharmaceuticals and in metal cleaning machine building, the combined effect may be additive, antagonistic or potentiating, depending upon the mechanism of toxicity. Interactions can result predominantly from both processes, i.e., those at the receptor level or those with the toxicokinetic processing of the agents. Where the toxic response to two or more chemicals may be similar (i.e., anesthesia), the effects are generally considered additive and suitable calculations can be made to estimate safe levels of exposure.

Since there are many organic solvents, the possibilities for combined exposures in the work environment are numerous. This applies not only to solvent combinations, but also to solvents in mixture with other chemicals.

The individual concentrations of organic solvents in the work environment can indicate that each agent is within the permissible level, yet the combined effect of these solvents has been shown to promote changes in workers' health. One hundred workers of both sexes in two handicraft workshops were exposed to a mixture containing low concentrations of acetone, butylacetate and toluene (each below the maximum permissible level). Ninety-four percent of the individuals registered subjective complaints attributable, by order of frequency, to numerous symptoms (e.g., headache, sleeplessness), digestive disturbance and signs of irritation. No characteristic objective findings during clinical examination have been noted. In a relatively large number of the investigated women spontaneous abortion and premature birth, as well as disturbances of the menstrual cycle, were recorded.[9]

Eight male subjects showed a prolonged mental reaction time and a probable impaired short-term memory during psychological testing after 50-minute exposure under controlled conditions to 400 mg/m^3 of white spirit, which is a common solvent containing a mixture of 83 percent aliphatic and 17 percent aromatic hydrocarbon components varying in number and mutual proportion.[10]

A male worker complained of a changed sense of smell and suffered from hyposmia and parosmia attributable to exposure to a solvent mixture (tetrahydrofurane, cyclohexanone, acetone).[11]

One hundred and two car painters underwent long-term exposure to a mixture of low concentrated solvents and thinners such as aromatic hydrocarbons, alcohols, esters, ketons, and terpenes. In comparison with a reference control group, the exposed cohort showed a high prevalence of impaired psychological performance as well as personality changes. Impairments in visual intelligence and verbal memory and a reduction of emotional reactivity were the central features of the adverse effects of solvent exposure.[12]

All plastic production and manufacturing processes bear a risk to health by attack of liberated volatile monomeric materials.

In a group of 92 car painters who had occupational contact with the same organic solvent mixtures mentioned above, there was a high incidence of ocular lens changes compared with age-matched controls. Pathological signs consisted mainly of nuclear sclerosis, clefts, lamellar separation or cortical and subcortical opacities not effecting visual activity.[13]

Membranous nephropathy occurred in four male employees following exposure at work (photographic film research laboratory, plastics industry, hygroscope assembly plant) to 24 organic solvents. The occupational inhalation lasted for periods of 2, 11, 18 and 20 years, respectively. The mechanism of production of membranous nephropathy is not known: an indirect immunological process mediated by endogenous tubular antigen is suggested. Proteinuria for long periods before onset of overt manifestations was observed.[14]

A very high prevalence of polyneuropathy was observed in 350 male and female shoe and leather workers exposed to different volatile solvents containg glues which were composed of n-hexane, aliphatic branched or linear low boiling point hydrocarbons, ethyl acetate, trichloroethylene, n-heptane, and traces below 1 percent of benzene, toluol and xylol. There was a relationship between the daily duration of glue use and intensity of nerve disturbances. The subjective symptoms were muscle spasms, leg weakness and pains, and arm paresthesia. A linear decrease of nerve motor conduction velocity was observed as a function of the length of exposure to solvents.[15]

In four male technicians exposed to a mixture of (m p)-xylene (56-65 ppm) and ethylbenzene (34-41 ppm) in a histology laboratory, a little more than 1 percent of the retained ethylbenzene was metabolized to urinary 2-ethylphenol. The compound 2, 4-dimethylphenol as a metabolite of m-xylene was not found. A competitive reaction mechanism between xylenes and ethylbenzene is actually believed to prevent m-xylene oxidation at the aromatic nucleus.[16]

PLASTICS Synthetic polymer plastics derive from simple structured monomers by a process of polymerization.[17] The polymers used in plastics generally are not regarded as markedly harmful. However, in almost all commercial plastics, they are "compounded"

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Where individuals may be exposed to mixtures, as in the manu-

with ingredients to ameliorate their processing and end-use performance. These monomeric additives comprise such compounds as reinforcing fibers (e.g., asbestos), fillers, coupling agents, plasticizers (e.g., phthalates), colorants, stabilizers, processing aids (lubricants), flame retardants, peroxides, and antistats.[18,19] During finalizing operations, foaming, or mechanical packaging, high temperatures are applied which can decompose plastics and lead to formation of numerous pyrolysis products.[20] All production and manufacturing processes bear a risk to health by attack of liberated volatile monomeric materials. Hazardous situations are illustrated by the following examples.

A female molding machine operator and other employees suffered from paroxysmal nausea, tightness in the throat, chest discomfort, dyspnea and light-headedness followed by fever, chills, and malaise. The complaints were caused by the thermal (320° C) degradation products of polyurethane plastic material during the molding operation. When removed from the working environment, symptoms generally subsided within 24 to 36 hours.[21] The syndrome described is called polymer-fume fever and is closely related to metal-fume fever. During a nine-month period a female employee suffered more than 40 typical polymer-fume fever attacks which were due to the thermal degradation products of polytetrafluoroethylene (Teflon). Eighteen months later, pulmonary function tests demonstrated alveolar-capillary block due to pulmonary fibrosis, as was seen on the subsequent autopsy.[22]

Urinary fluoride levels of 77 workers at a polytetrafluoroethylene fabricating plant were significantly elevated, mostly after more than one year of exposure to the pyrolysis products, expecially carbonyl fluoride, and mostly with episodes of polymer-fume fever.[23]

A group of 17 meat wrappers exposed to pyrolysis products of polyvinyl chloride (following thermal decomposition of the wrapping film by cutting with a hot wire) demonstrated a higher prevalence of cough, phlegm, hay fever, and asthma and relative decreases in forced expiratory volume, as forced expiratory flow, after one shift of work than did 21 control subjects.[24]

Pesticides can affect both workers who mix and apply the formulations and field workers who are exposed to residues on crop foliage.

Fifteen female meatpacking plant workers exposed to pyrolysis products of polyvinyl chloride produced by a thermocutting and sealing machine suffered from breathlessness, chest pain, fatigue, drowsiness, vertigo, headache, nausea and fever. There was a close coincidence between the occupational generation of pyrolysis fume (containing a variety of miscellaneous aliphatic and aromatic compounds, hydrogen chloride and perhaps trace amounts of phosgene) and the rising incidence of harmful attacks and complaints.[25]

One hundred twenty-one men who were exposed to tire-curing fumes for several years showed increased morbidity of the respiratory system, as manifested by chronic bronchitis and chronic obstructive pulmonary diseases, compared with 189 nonexposed workers. Gaseous and particulate materials exposures were released by the heated curing press at about 130° C.[26]

Two women exposed at work (reinforced plastic industry) to a combination of styrene, polyester resin, organic peroxides and acetone, each gave birth to a child with central nervous system defects. Statistical evaluations based on the general population design pointed to a correlation between congenital malformation and occupational exposure.[27]

PESTICIDES General concern about the possible adverse effects of pesticides on human health has led investigators to continue to search for evidence of health impairment in employees with long-term exposure to pesticide combinations. Health hazards can affect both pesticide workers who mix and apply pesticide formulations, and field workers who are exposed to pesticide residues by contact of treated crop foliage and soil, respectively. This latter category is the one on which controversy centers because of the impact of low expected pesticide yields.

Negative findings in 45 subjects (structural pest control operators and agricultural chemical workers) offer substantial assurance of the absence of strong porphyrinogenic or sympathotonic effects by daily exposure to one or more of many pesticides (chlorinated hydrocarbons, organophosphates, pyrethins, propoxur, dursban), predominantly to a combination of parathion and toxaphene.[28]

Investigators failed to detect any effect of the common chlorinated hydrocarbon pesticides, which are stored in the tissues, on the urinary keto- or ketogenic steroids of 133 subjects, or on the serum cortisol of 257 subjects, all with an average occupational exposure of six or eleven years to numerous pesticides (organophosphates, chlorinated hydrocarbons, defoliants, fungicides) in changing rates.[29]

These negative results are in contrast to reports from other authors who indicated sensitivity of different parameters to various pesticides. A close relationship was found to exist between the lung fibroses (confirmed by X-ray) of three structural pest control operators and occupational inhalation of

carrier materials of the pesticide formulations (slate-meal, kaolin, talcum) and their ingredients which led to bronchial irritation (organophosphates, chlorinated hydrocarbons, chloral hydrate, arsenates, thiurams and ethers).[30]

The serum activity of the thiol enzymes, cholinesterase, lactate dehydrogenase and phosphomonoxidase was considerably decreased following a seven-month exposure of 133 agricultural workers to combinations of phosphororganic and mercuroorganic pesticides. An additional simultaneous application of fungicides led to even more significant changes.[31]

In 69 pesticide workers predominantly exposed to chlorophenoxy herbicides in addition to chlorinated hydrocarbons, organophosphates or other (unclassified) pesticides, there was no difference in mean systolic and diastolic blood pressure values, but a modest excess of hypertension prevailed, which was largely explained by a constitutional predisposition, as suggested by a positive family history.[32]

In an epidemiological study among 316 pesticide workers who had long-term exposure, 30 cases of malignant tumors of various organs were discovered, 11 of which were lung cancers. In contrast to the age-specific population, the incidence of lung cancer was twenty times higher. The average duration of pesticide exposure was 14 years (range: 6-23). The average latency period between the start of the exposure and tumor manifestation was 18 years. Exposures occurred consecutively or simultaneously to phenoxyacetic acid derivatives (2,4-D and MCPA), chlorinated hydrocarbons (DDT, HCH, toxaphen), organic phosphorus compounds (parathion), organic nitro derivatives (DNOC), thiocarbamates and copper- or arsenic-containing agents.

The electromyographic voltage of six men occupationally exposed to organophosphorus pesticides (chemically not defined) varied in a manner which reflected the pattern of exposure over the investigation period of 7-9 months.[34]

Six of 22 male subjects exposed at work to a mixture of chlorinated pesticides, mainly lindane and DDT, had hypertriglyceridemia (type IV pattern) and one had hypercholesterolemia (type II A) in comparison to 19 controls who had no changes. Forty per cent of the subjects with pesticide exposure and none of the control subjects had hyperlipoproteinemia of the high density (alpha)-lipoprotein type, which normally occurs very rarely.[35]

Combined effects of dusts occur in mining, building material production, glass manufacturing, and the textile industry.

DUSTS There are numerous chemical mixtures at the work-site which cannot be classified in the above categories. Mainly, it should be mentioned that combined effects of different types of dust occur in mining, in the production of building materials, in glass manufacturing and the textile industry. A few examples may serve to characterize the health risks involved.

In 8047 male smelter workers, a threefold increase in respiratory cancer was diagnosed in relation to the length of employment and the degree of exposure to arsenic, sulfur dioxide and other materials (elements). An additional aggravating influence of sulfur dioxide and other unidentified chemicals, varying concomitantly with arsenic exposure, cannot be discounted.[36]

The prevalence rates of characteristic respiratory symptoms of chronic nonspecific lung diseases were significantly higher in cement workers than in adequate controls. The higher prevalence rates were found in workers with longer, rather than shorter, cement work experience.[37]

After a mean exposure of no more than 13 years to mixtures of hemp and flax, a high prevalence of byssinosis was found in 124 textile mill workers. There was no difference in the acute respiratory response between subjects exposed to similar concentrations of flax and mixtures of two different proportions of flax and hemp dust.[38]

DRUGS Worksite chemicals and drugs can interact. Depending on the dose of the individual chemical, a mutual influence of metabolic pathways, (mainly the oxidative conversion) may arise. Phenytoin (anticonvulsant) and phenobarbitone (anticonvulsant, hypnotic) induce hepatic microsomal metabolizing enzymes which result, for example, in a lower DDE (metabolite of DDT) level in the fat tissue of patients receiving both anticonvulsants, compared with the general untreated population.[39] This leads to the assumption of a lower body-load of DDT and related metabolites in DDT workers, under treatment with phenytoin or phenobarbitone, due to an accelerated metabolic DDT conversion.

A single therapeutic oral dose (as small as 5 mg/kg) of disulfiram (alcohol aversant) caused a temporary but significant reduction in the formation of 4-amino-antipyrine from amidopyrine (analgesic, single oral dose: 7 mg/kg) by oxidative N-demethylation.[40] Since disulfiram is widely used in industry as a rubber cross-linking agent and fungicide, occupational absorption and a subsequent effect on drug metabolism are to be expected. Due to the induction of microsomal drug metabolism by a mixture of insecticides, mainly lindane and DDT, the mean antipyrine (p. o. dose: 10 or 15 mg/kg) plasma half-life (7.7 hrs) was signifi-

cantly shorter in 26 male workers handling the commercial insecticide mixture, compared with 33 controls (13.1 hrs). This effect is explained by an accelerated oxidative metabolization of antipyrine.[41]

The serum half-life of phenylbutazone (antirheumatic, single oral dose: 400 mg/person) was 19 percent lower (p 0.01) in 18 DDT factory workers than in 18 controls without occupational exposure to DDT. The amounts of DDT-related substances in the serum and fat of DDT workers exceeded those in the control population 20 to 30 times.[42]

During a controlled six-hour exposure to concentrations of not more than 10 ppm (permissible work and environment level) of carbon disulfide, the oxidative N-demethylation of amidopyrine (given orally in a therapeutic dose of 7mg/kg at the beginning of inhalation) was significantly inhibited in 19 male volunteers (intraindividual study). The inhibition, measured by the urinary 4-amino-antipyrine excretion, was enhanced by graded higher concentrations of carbon disulfide. All effects were reversible shortly after maximal eliciting.[43]

Five workers exposed to polychlorinated biphenyls (PCBs) in a capacitor-manufacturing plant showed a significantly lower mean antipyrine half-life (10.8 hrs) in blood plasma after oral administration (18 mg/kg) than the non-PCBs-exposed controls (15.6 hrs). This difference in half-life was accompanied by increased metabolic clearance rates in the PCBs workers.[44]

Five male volunteers were pretreated for 11 days with phenobarbital (2 mg/kg daily p.o.) and on the 12th day exposed to 400 mg/m³ of m-xylene for 8 hrs. Phenobarbital treatment had no influence on the retention of xylene vapors nor on the amount of urinary conjugated m-methylbenzoic acid.[45]

SMOKING The use of tobacco is a widespread habit among workers exposed to industrial chemicals. The additional ill-effects of smoking on the respiratory tract of workers in different occupations has been amply demonstrated by numerous papers. They conclude that habitual smoking may aggravate occupational respiratory diseases caused by industrial chemicals. This is illustrated by the following well-documented and striking examples.

Tobacco smoking may potentiate the effects of cotton dust inhalation. Among (female) workers exposed to cotton dust, smokers had a significantly greater prevalence of byssinosis than nonsmokers.[46] The prevalence of symptoms and the fall in the forced respiratory volume was greater among the heavy smokers than in light smokers or nonsmokers;[46] this led to a smoking frequency-response relationship in the outspread of the phenomenon. Pulmonary function data confirmed that in all smoking categories (cigarette, cigar or pipe smokers) white male and female cotton textile workers were at much greater risk of developing chronic lung disease with loss of function, than were the controls.[47]

Often, field studies lack precise data regarding the exposure profile or the substance concentrations prevailing at the worksite.

Asbestos insulation workers with a history of regular cigarette smoking had an about 92-fold higher risk of dying of bronchogenic carcinoma in comparison with men who neither smoked cigarettes nor had occupational contact with asbestos.[48] Exposure to one of the two agents (asbestos and tobacco smoke) produced an effect (augmented lung cancer incidence) which was proportional to the effect of the other, a phenomenon which was regarded as a multiplicative mode of action.[49] In contrast to workers in contact with chrysolite only, employees exposed to amosite as well as chrysolite during asbestos manufacturing revealed a definite relationship between smoking and the prevalence of pulmonary disease detected by chest roentgenograms.[50]

Other combined actions of industrial chemicals and tobacco smoking are under active discussion. In part such observations represent more case histories, the validity of which should be further clarified. Some examples may illustrate this situation. The possibility that, in combination with smoking, the herbicide 3-amino-triazole might cause lung cancer could not be ruled out.[51] Lung cancer has appeared predominantly among cigarette-smoking uranium miners, and the cigarette smoking habit slightly reduced the induction-latency period of this type of cancer by cocarcinogenesis or tumor promotion rather than by synergism.[52]

Smoking of cigarettes contaminated with a fluorocarbon polymer by the workmen's fingers during the manufacturing process liberated pyrolysis products (in the 875° C cigarette burning zone), which caused polymer fume fever with cough, chills, aching and weakness.[53] Acute reductions in pulmonary function were observed more frequently in heavy cigarette smokers over 40 years of age working in the vinyl chloride, polyvinyl chloride, and rubber industries.[54] In manganese alloy workers, subjective symptoms of subclinical manganism occurred more frequently in heavy smokers than in light smokers or nonsmokers.[55] Smokers occupationally exposed to lead had statistically significantly higher blood lead levels than nonsmokers, probably due to finger contamination of the used cigarettes.[56] The induction-latency

time of lung cancer among metal and iron ore miners which was probably caused by exposure to radon and its daughters, was several years shorter for the smokers in comparison to nonsmokers.[57]

Tobacco combustion products contain distinct concentrations of CO, and frequently lead to carboxyhemoglobin levels above 8 percent in the blood.[58] CO exposure from smoking has been shown to be harmful in persons with a diseased arterial system (intermittent coronary heart disease). Following inhalation of CO from smoking additional to occupational-linked CO exposure, health hazards can be expected in persons who already have an arterial disease, but not in those with normal arteries. Inhaled solvents of the halogenated methane type (e.g., dichloromethane) are converted metabolically in the organism to yield considerable amounts of CO.[59-61] A simultaneous pulmonary absorption of CO by active smoking can contribute to adverse long-term health effects.

Pulmonary microsomal aryl hydrocarbon hydroxylase, which is present in human alveolar macrophages,[62] and bronchi,[63,64] but not in lung tissue,[65] metabolizes carcinogenic polycyclic aromatic hydrocarbons to active electrophilic intermediate epoxides and diolepoxides which both react covalently with nucleoproteins and probably are responsible for carcinogenic effects. Cigarette smoke[65] and cigarette tars,[66] both consisting of aromatic polycyclic hydrocarbons (e.g., benzo(a)pyrene), increase the aryl hydrocarbon hydrolase activity in human alveolar macrophages. A deleterious rise of this inductive process can be expected during concomitant occupational inhalation of other aromatic polycyclic hydrocarbons or on industrial exposure to chemicals with microsomal enzyme inducing properties.

CONCLUSIONS The above examples of combined exposures to foreign compounds reveal that insults of this type can be grouped according to the individual exposures encountered. Such classification leads to the emergence of certain key groups, such as combined exposure to solvent mixtures or exposure of smokers to chemical agents.

It is not always possible to identify the action that results from exposure to at least two substances in a consistent manner. On the other hand, the causal relationships that underlie a combined effect are often highly complex or cannot be clearly differentiated. It has also been seen that the mechanism producing an interaction cannot be identified in all instances. For methodological reasons, controlled exposure experiments using model substances such as carbon disulfide and simultaneous alcohol consumption are performed rarely, although they may contribute appreciably toward assessing a potential health risk.

Consideration of quantitative situations will have a positive bearing on establishment of hygienic threshold limit values.

Very frequently, published field studies show a lack of precise data in regard to the exposure profile or the substance concentrations actually prevailing at the worksite. Analytical data on possible concentrations of foreign materials in the body (urine, blood) after combined exposure and the relation of such chemicals to disease manifestations would likewise be of value.

Similarly, there is a paucity of epidemiological surveys on the correlation existing between the combined effects of hazardous industrial materials and toxic factors unrelated to work (alcohol, drugs, smoking). The case reports and controlled human model experiments that have been published on these aspects are inadequate, and it is desirable that the knowledge derived therefrom be extended and updated.

Efforts at elucidating occupational combined exposures that take into consideration quantitative situations should be intensified and will not fail to have a positive bearing on the establishment of hygienic threshold limit values at the workplace (TLVs, MACs). Taking into account that for pharmacodynamic and pharmacokinetic reasons it is impossible to set hygienic thresholds for fixed combinations of chemicals, this aspect becomes particularly important.

Numerous animal experiments have been performed to elucidate adverse health effects that are attributable to the combined effects of chemical agents. They also provide in part important new leads as to potential patterns of health impairment in man. However, it is only too often that the experimental conditions chosen in these studies are not related to the prevailing occupational setting. Quite frequently, the dosage range of the occupational materials was too high and failed to correspond to that encountered in the occupational environment. It should also be noted that the selected exposure conditions were comparable to those found on occupational exposure only in a few instances. Nevertheless, investigations in workers under occupational conditions are imperative and indispensable for discriminant elucidation of chemical interactions in model animal experiments. OH&S

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References available upon request.