31 / Other Important and Widely Used Chemicals

Halogenated Hydrocarbons

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DAILY, we, as individuals, are made aware through the various avenues of communication of the numerous chemicals to which we are exposed in our lives in the form of consumer products, pollutants and raw materials. A brief reflection will reveal that all chemical substances are found in the working environment as materials to be processed into usable products, as waste products or as undesirable cohabitants of that environment. As is the awareness of finding all substances in the working environment, also is found there experience in the diagnosis of intoxication, control of exposure and treatment of people who have been occupationally exposed to noxious substances. The number of such substances that have been identified is indefinite, although an ongoing attempt by the U. S. National Institute for Occupational Safety and Health has been manifested in the publication of The Toxic Substances List.[12] This list is revised annually for input of newly found data describing the noxious characteristics of these substances. Currently there are about 17,000 substances on the list, with the dose or concentration that has been demonstrated to cause toxic effects.

In this section there will be no attempt to discuss all of the known hazardous chemicals in the working environment, the coverage being limited to those substances that are most widely found and which have produced known occupationally associated illness. While reviewing the noxious characteristics of these chemicals, it is important that the reader be aware of what may constitute a toxic effect. It is this definition that dictates the level of control that must be provided for workers working in the proximity of a chemical that may cause these toxic effects. For example, if the toxic effect to be prevented from exposure to carbon monoxide were considered to be the death of a healthy individual, the level, including whatever margin is considered necessary to protect particularly susceptible healthy people, would be between 50 and 100 ppm. On the other hand, if the toxic effect were considered to be the increased susceptibility of people with myocardial disease, it would be the time-weighted average (TWA) of 35 ppm, the level of which was recommended by the NIOSH recently to the U. S. Department of Labor.[39] Similarly, if the toxic effect from exposure to sulfur dioxide to be prevented were selected to be the irritation of the mucosa of the nose or eyes of adapted workers, the level would be a TWA of 5 ppm. However, if the toxic effect is selected to be the increased resistance to the passage of air in the respiratory tract of adapted or nonadapted workers, the level would be a TWA of 2 ppm, the level recently recommended by NIOSH.[40] A toxic effect, therefore, can be defined as any bodily injury—reversible or irreversible; any tumor—benign or

malignant; any mutagenic or teratogenic effect; irritation or allergic effect; a lessening of mental alertness or motivation; or death of a normal or disabled person who has been exposed to a substance via the respiratory tract, skin, eye, mouth or any other route. This definition thus responds to the directive offered by the Occupational Safety and Health Act of 1970, Public Law 91-596, which established a policy of ensuring every working man and woman a safe and healthful working condition in which none will suffer diminished health, functional capacity or life expectancy as a result of his work experience.

Another important aspect that must be kept in mind is that a toxic material seldom is found in the work environment as a single pure chemical substance and that a worker seldom is exposed to a single hazard. Thus, a welder may be working in an occupational environment in which he could be exposed to several oxides of nitrogen, to fumes of cadmium, zinc and beryllium, to ultraviolet light as well as to the stress of a hot, cold or hyperbaric environment in the course of his daily activity, simultaneously or sequentially. It is this multiplicity of exposure that has complicated the investigation and identification of noxious effects produced by chemical substances. Another complication in identifying toxic effects from chemical exposure is the increased mobility of the working population, which prevents accurate identification of the population at risk. And, last, as we shift our attention of the past from the dramatic effects of immediate primary irritation and disabling or lethal immediate effects, we are discovering toxic effects that have latent periods after exposure of as much as 50 years, with recorded exposures of as short duration as 7 months, as is the case with asbestos exposure reported by Knox *et al.*[30]

The bases of accepted standards and occupational exposures are undergoing rigorous re-evaluation in the United States to determine whether there may be different effects that have been presenting themselves and which need to be considered to ensure safe working conditions.

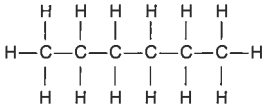
ORGANIC SOLVENTS

In discussing organic solvents as a class of substances used in the working environment (Fig. 31–1), one toxic effect that is common to all solvents but seldom discussed as a toxic effect is the effect caused by the property of "dissolving." Although the number of substances and their combinations that are dissolved by solvents approaches the infinite, the components of the skin generally are not listed among that number. With the exception of the keratolytic agents used for medicinal purposes or those industrial solvents that are overtly corrosive irritants, acids, alkalis, reducers or oxidizers, little attention is directed to the prevention of skin injury due to defatting of the skin by solvents used in the occupations. According to Schwartz,[50] in a survey of more than 40,000 cases of occupational dermatoses, 7.8% were caused by solvents that did not include petroleum products, alkalis and acids.

The defatting of the skin breaks down the barriers to the absorption of substances through the intact stratum granulosum and stratum lucidum and to contact dermatitis, infection and epidermal sensitization. This likely is due to the extraction of hydrophilic material from the skin, which is necessary to retain water moisture in the skin[8] and improve the resistance to absorption.[46]

Chronic eczematous dermatosis often follows the acute eczematous dermatitis in those patients who fail to improve. Dry, fissured, chronic dermatitis frequently is the result of reckless contact with solvents of this nature.[6]

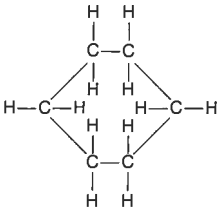
Aliphatic Hydrocarbons (Paraffins)
Straight or branched chains saturated with hydrogen.



Hexane–

Benzine–
Mineral spirits–

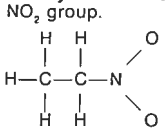
Cyclic Hydrocarbons (Cycloparaffins, naphthenes)
Ring structure saturated and unsaturated with hydrogen.



Cyclohexane–

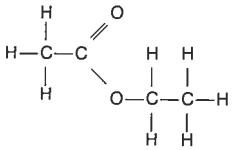
Turpentine–
(Turpentines are mixtures primarily of the unsaturated cyclic hydrocarbons and pinene.)

Nitro-hydrocarbons
Contain an NO_2 group.



Nitroethane–

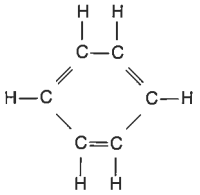
Esters
Formed by interaction of an organic acid with an alcohol.



Ethyl acetate

Amyl acetate

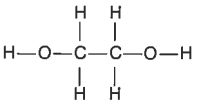
Aromatic Hydrocarbons
Contain a 6-carbon ring structure with one hydrogen per carbon bound by energy from several resonant forms.



Benzene–

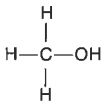
Toluene–
Xylene–

Glycols
Contain double —OH groups.



Ethylene glycol
(1,2-ethanediol)–

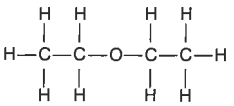
Alcohols
Contain a single —OH group.



Methanol

Ethanol (ethyl alcohol, grain alcohol).
Propanol

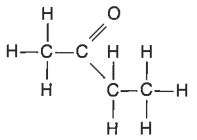
Ethers
Contain the C—O—C linkage.



Ethyl ether

Isopropyl ether
Ethylene glycol monomethyl ether
(methyl Cellosolve).
Ethylene glycol monoethyl ether
(Cellosolve).

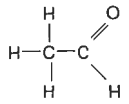
Ketones
Contain the double-bonded carbonyl group, C=O, with 2 hydrocarbon groups on the carbon.



Methyl ethyl ketone–

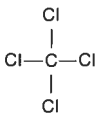
Acetone–

Aldehydes
Contain the double-bonded carbonyl group, C=O, with only one hydrocarbon group on the carbon.



Acetaldehyde–

Halogenated Hydrocarbons
A halogen atom has replaced one or more of hydrogen atoms on the hydrocarbon.



Tetrachloromethane

Trichloroethylene
1,1,1-trichloroethane
(methyl chloroform)
Trichlorotrifluoroethane
(fluorocarbon No. 113)

Fig. 31–1.—Major classes of common organic solvents, with some typical examples. (Modified from *Fundamentals of Industrial Hygiene*, edited by Julian Olishifski, National Safety Council, Chicago, 1971.)

There is no attempt here to describe further the dermatologic phenomenon, which is presented in greater detail in Chapter 12.

HALOGENATED HYDROCARBONS

Although the grouping of chemical substances according to atomic components and their structural arrangement must be arbitrary, particularly when a correlation of biologic effects must be considered also, certain of the halogenated alkyl compounds have similar characteristics. One group includes the di-, tri- and tetrachloro methanes, ethanes, ethylenes and propane. Another, the chlorobenzenes, has importance, as has epichlorhydrin. However, for these solvents, the group is made up principally of chlorinated aliphatic compounds and, of these, the principal economically important members are closely related. Essentially, the group is made up of chloroform, carbon tetrachloride, ethylene dichloride, tetrachlorethane, trichloroethylene, methylene chloride, dichloropropane, tetrachloroethylene, methyl chloride, isopropyl chloride, chlorobenzene, o-dichlorobenzene and trichloroethane.

Trichloroethylene

Trichloroethylene probably is the most widely used of the halogenated hydrocarbon solvents. NIOSH estimates that there are 200,000 workers in the United States exposed to trichloroethylene routinely in their work.[41] These exposures are due, by far, to its use as a degreasing agent in metal-fabricating operations. It is used also in organic chemical processing and production and for vermin extermination.[49] It was first used commercially in the United States in 1935—25 years after its introduction and use in Europe. It has been used as a general anesthetic since early in the 1930s and, as such, claims have been made about its safety[22] and hazards.[25]

Chemical exposures to "nonindustrial" workers, such as those in clinics and hospitals often are overlooked.

Trichloroethylene is a chlorinated unsaturated hydrocarbon, $CHCl{:}CCl_2$, having a formula weight of 131.40; a boiling point of 87.1° C at 760 mm Hg; a melting point of −73° C; a vapor pressure at 25° C of 0.1 part per 100 parts of water and at ambient temperatures is completely miscible with alcohols, ethers and many other organic solvents; a vapor density of 4.5; and an ignition temperature of 463° C. No flash point has been established by any of the standard methods. It is a clear, colorless, noncorrosive liquid with a sweet odor and is generally inert for most of the processes in which it is used.

OCCUPATIONAL EXPOSURES.—Approximately 90% of the total of trichloroethylene is used as a solvent in degreasing operations.[7] Its use may vary in quantity of amounts used in a "bucket" operation in which the solvent is used to clean parts and tools to large quantities used in major sophisticated operations in assembly lines that are well controlled against loss. The remaining 10% is used in dry cleaning operations for fabrics and in extractive processes. Consequently, the major—and possibly the only—occupationally important route of exposure to trichloroethylene has been through inhalation and absorption through the lung. No reports have been found of occupational intoxication brought about through absorption of toxic amounts through the skin. Such effects as have been reported for contact of the substance with the skin were burns,[36] generalized dermatitis[37] and possibly scleroderma.[44] Although no toxic effects were found reported due to absorption of trichloroethylene through

the skin, a report was found suggesting that absorption of any trichloroethylene through the skin would be inconsequential as a source of toxic amounts in the body.[54] First-degree chemical burns of the eyes resulting from hot vapors arising from a degreasing tank were reported by Maloof.[36]

TOXICITY.—The major occupational health problems from the exposure of workers to trichloroethylene are the results of its depressant action on the central nervous system. Although the presence of the chlorine atoms in the molecule would suggest an effect on the liver similar to that produced by chloroform on carbon tetrachloride, such has not been found to be the case. Reports of liver damage have been associated with massive doses that have been at or near lethal quantities, and these doses have been absorbed either from accidental ingestion or by massive inhalation. Suspected liver damage from exposure to high concentrations of inhaled trichloroethylene has been associated with alcohol abuse[34] or with contaminants, such as 1,2-dichloropropane and 1,2-dichloroethane.[51] However, liver damage from lethal concentrations has been reported where those factors were not contributory.[27, 28]

Other studies of workers with high, nonlethal exposures to trichloroethylene revealed some evidence of liver damage as demonstrated by hyperglobulinemia, hypercalcemia,[13] abnormality of cephalin flocculation[3, 21] and total lipids and unsaturated fatty acids.[3] However, many studies have been reported in which no liver effects were found in workers regularly exposed in degreasing operations.[1, 59] Essentially, it can be concluded that trichloroethylene has a low order of toxic effect against the liver. Such a conclusion can be supported by numerous studies of the effects of relatively large exposures of experimental animals. Rabbits were exposed for periods of time ranging up to 8 months in duration at a concentration of 6900 ppm for a 4-hour exposure daily.[2] Mice exposed to 1600 ppm for 4 hours daily for as long as 24 hours a week for 8 weeks were found to have a slight degeneration of the liver.[33] Guinea pigs exposed for more than 1100 hours to levels of 1200 ppm showed no significant changes in the lungs, spleen, heart, adrenals or brain but showed some minor degenerative changes in the liver.[4] Taylor[57] found no effects in dogs exposed to 2000 ppm of trichloroethylene for 6 months, but Seifter[52] found liver changes in dogs exposed to 750 ppm for as little as 3 weeks.

The most commonly reported effects caused by trichloroethylene have been those of central nervous system origin. The first extensive medical study, which involved 284 cases, of occupational exposure was reported by Stuber in 1932.[56] The predominant signs and symptoms were headache, dizziness, vertigo, tremors, nausea, vomiting, fatigue, symptoms similar to alcoholic intoxication and unconsciousness preceding death, Andersson[2] reported much the same 25 years later in another survey of 104 workers. These central nervous system effects can be the result of either an immediate acute toxic exposure or a longer-term exposure of lesser concentration. Andersson found that two-thirds of the people in her survey showed signs of central nervous system effects. Some of the people who had exhibited these signs of intoxication from long and excessive exposure reported that their symptoms of intoxication subsided within 4 or 5 months after their exposure had ceased. Other manifestations of central nervous system effects were reported. McBirney[37] reported loss of tactile sense, loss of motion and dexterity and Fra *et al.*[17] demonstrated by

electromyography that the brainstem structures that supplied facial muscles had been affected. Deafness was reported by Tomasini and Sartorelli[60] and visual effects, such as diplopia and blurring, were reported by Maloof,[36] St. Hill[48] and McBirney[37] and blindness by Kunz and Isenschmid.[32] Visual hallucination was reported by Todd.[58]

Death has resulted from progressive paralysis resulting from and following 20 hours of inhalation exposure[48]; however, the usual cause of death appears to be cardiovascular failure, which can occur during exposure or shortly after.[5, 27, 29] Of course, death can occur from massive acutely inhaled anesthetic concentrations or from ingestion causing an immediate depression of the central nervous system.[56] Andersson[2] reported that 77 trichlorethylene workers of her study population of 104 showed abnormal electrocardiographic tracings, which, she believes, may precede permanent heart damage.

The mechanism of this action is not understood. Lilis *et al.*[35] however, suggested that epinephrine secretion during periods of physical exertion or stress associated with hypersympathicotonia could explain such a sudden death association with trichloroethylene exposure. Butler[11] found that trichloroethylene was converted to trichloroethanol, conjugated with glucuronic acid and free, and concluded that the initial conversion of trichloroethylene was to chloral hydrate. Trichloroacetic acid and monochloroacetic acid and trichloroethanol[53] were found in the urine as well.

Two effects associated with exposure to trichloroethylene must be considered in the occupational environment. Although not caused directly by trichloroethylene, they cannot be ignored as a hazard to the health of the worker. The first is that which is common to most chlorinated alkyls—the formation of phosgene and hydrogen chloride by decomposition in the presence of hot metals, open flames, ultraviolet radiation—all of which may occur in welding operations.[45] The second is the formation of dichloroacetylene by the reaction of trichloroethylene with alkalis, such as those that may be found in rebreathing canisters of respiratory equipment.[9] In addition to the explosive potential of the dichloroacetylene formed, there is a toxic effect—that of trigeminal palsy, long associated with the use of trichloroethylene as an anesthetic.

MEDICAL AND HYGIENIC CONTROLS.—The current standard of the Occupational Safety and Health Administration of the United States as promulgated in 1972 was based on the American National Standards Institute Z-37 limits. The standard established that a time-weighted average concentration in the work place for an 8-hour day, 40-hour workweek shall be 100 ppm, that an acceptable ceiling concentration shall be 200 ppm and that an acceptable maximal peak above the acceptable ceiling 5 minutes during any 2 hours shall be 300 ppm.[47] Recently, the National Institute for Occupational Safety and Health recommended that the occupational exposure to trichloroethylene shall be controlled so that workers will not be exposed to trichloroethylene at a concentration in excess of 100 ppm determined as a time-weighted average exposure for an 8-hour workday, as measured by a minimal sampling time of 10 minutes. Further, no worker shall be exposed to a peak concentration of trichloroethylene in excess of 150 ppm, as measured by a maximal sampling time of 10 minutes.[41] Acceptable concentrations for other countries as published by the ILO are as follows: 100 ppm for Finland, Germany, Japan and

Yugoslavia; 10 ppm for Bulgaria, Hungary, Poland and Rumania; 46 ppm for Czechoslovakia; and 2 ppm for USSR.[26]

Methylene Chloride

Methylene chloride, although perhaps not the most hazardous chlorinated hydrocarbon, is unique in this series of solvents. NIOSH estimates that 70,000 workers are exposed to methylene dichloride and that number does not include hobbyists. Methylene chloride is used industrially as a paint stripper, a degreasing solvent, as an aerosol propellant, as a solvent in the textile, plastic and paint industries, in the manufacture of photographic film and in the preparation of heat-sensitive oils and waxes.[18] It has been used as a general anesthetic, particularly for those patients whose muscle tone is to be advantageously maintained during an operation.[20]

Methylene chloride is one of the chlorinated methane series of solvents, CH_2I_2, having a formula weight of 84.94; a boiling point of 40.4° C at 760 mm Hg; a melting point of −96.7° C; a vapor pressure at 25° C of 440 mm Hg; a solubility at 20° C of 2 parts per 100 parts of water, and at ambient temperatures is completely miscible with alcohols, ethers and acetone; has a vapor density of 2.93; and an ignition temperature of 662° C. No flash point has been established by any of the standard methods. It is a clear, colorless liquid with a sweet, pleasant odor and is inert under the conditions in which it is commonly used.

OCCUPATIONAL EXPOSURES. — Because methylene chloride volatilizes very rapidly, its use capitalizes on this property. Thus, its use as a solvent for degreasing, paints and paint stripping most likely causes exposure by inhalation. Of lesser occupational health importance would be the absorption of the substance through the skin. Absorption through the skin, however, can occur only when methylene chloride is in direct contact with the skin.[25] Therefore, protective equipment should be used to prevent this contact. No report of intoxication from methylene chloride absorption through the skin was found, however.

TOXICITY. — As with other halogenated solvents, the principal hazardous effect is the depressant action on the central nervous system. The range of effects can extend from a decreased performance in psychomotor testing to narcosis and death of the individuals exposed.[10, 16, 23, 55, 62] Although there is experimental evidence that methylene chloride produces the characteristic effects on the liver and kidney reported for other chlorinated alkyl compounds, no reports were found of liver and kidney injury to humans from occupational exposure.[61] Irritation to the respiratory passages and eyes has been reported resulting from exposure to both humans and experimental animals to the vapor.[24, 38] Equivocal findings suggesting that effects similar to those caused by phosgene were reported for methylene chloride, which may have been changed by a kerosene flame.[14, 19]

Within the past few years, an additional unique effect was reported in which it was ascertained that carbon monoxide was produced in the body from methylene chloride.[15, 31, 43, 55] The amount of conversion to carbon monoxide is significant as measured by the concentration of carboxyhemoglobin, up to 12% measured in the blood following occupational exposure of up to 610 ppm methylene chloride.[43]

As has been reported for other halogenated hydrocarbons, methylene chloride will decompose from contact with hot metal and fire.[42]

MEDICAL AND HYGIENIC CONTROLS.—The current standard of the Occupational Safety and Health Administration of the United States as promulgated in 1972 was based on the American National Standards Institute Z-37 limits. That standard established that a time-weighted average concentration in the work place for an 8-hour day, 40-hour workweek shall be 500 ppm, that an acceptable ceiling concentration shall be 1000 ppm and that an acceptable maximal peak above the acceptable ceiling for 5 minutes during any 2 hours shall be 2000 ppm.[60] Maximal acceptable concentrations for other countries as published by the ILO are as follows: 707 ppm for Czechoslovakia; 500 ppm for Finland, The Federal Republic of Germany and Yugoslavia; 57 ppm for Rumania; and 14 ppm for USSR.[51]

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Aromatic Hydrocarbons

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THE INDUSTRIAL HYGIENIST may choose to broadly classify hydrocarbon solvents as *aromatic* and *aliphatic*. The trademark of the aromatic hydrocarbons is the presence of at least one benzene ring. Gerarde[5] has emphasized from an industrial hygiene standpoint that of the three principal groups of aromatic hydrocarbons, benzene and its aliphatic and alicyclic derivatives are the most important. Neither the polyphenyls nor the polynuclear groups have been used as extensively and perhaps, as a result, have not been studied as extensively as benzene and its homologs.

Benzene is obtained from two sources—as an alternative product of the petroleum industry or as a by-product of the coke industry. In the former, either the naphthene fractions are dehydrogenated or the paraffin fractions are aromatized. In the latter, benzene is recovered in the light oil resulting from the destructive distillation of coal tar.

Because of its excellent solvent properties, benzene was used extensively as a vehicle in paints, lacquers, printing inks and as a major component of industrial solvents used for various other purposes. Its prolific use in certain industrial operations resulted in what would be considered today gross chronic exposures. After its toxic properties were recognized, toluene and xylene were suggested and generally used as substitutes. This substitution now results in only a small fraction of the presently available benzene being used in the paint industry.

Approximately 85% of the benzene produced now is used in converting it to intermediate products where the hazard is more likely to be recognized and controlled. Benzene still is a major component in some paint-remover products and is found in varying amounts in gasoline and petroleum naphtha. It probably is in some of the smaller industries where the health hazards associated with excessive exposure to benzene go unrecognized and uncontrolled.

Toluene and xylene are obtained from coal and petroleum in the processes associated with benzene production. They are used extensively as paint, lacquer and printing ink solvents and as a constituent of many solvent mixtures as well as motor fuels. They, like benzene, are also used

as starting materials and intermediates in the synthesis of many chemicals.

PHYSICAL AND CHEMICAL PROPERTIES

Benzene, toluene and xylene are clear, colorless liquids having a somewhat sweet, pungent odor that, relatively speaking, is not particularly offensive. These flammable solvents have lower and upper explosive limits (per cent of volume in air) of 1.35–7.9, 1.17–7.1 and 1.09–6.4 respectively. Respective closed cup flash points are 12° F, 40° F and 63° F to 77° F for the xylene isomers.

The vapor pressure is more than 3 times as great for benzene (100 m at 26° C) as for toluene and approximately 10 times as great as the vapor pressure of xylene. Since vapor pressure has a bearing on the rate of vaporization of a solvent into the surrounding air, it is seen that benzene evaporates more rapidly than both toluene and xylene. The evaporation rate of benzene is about 1.5 times as rapid as toluene. Toluene evaporates about twice as rapidly as xylene. Solvent evaporation rates have an important bearing on the ability and time necessary to reach a given atmospheric concentration during operations involving open-surface tanks or workroom air drying.

ABSORPTION AND EXCRETION

As in the case of most industrial exposures, the main route of entrance of solvents into the body is through the respiratory system. Ingestion of solvents is rare, occurring mainly as accidental swallowing due to mistaken identity. It is worthy of note that the primary purpose of poison control centers throughout the United States is to provide information for prompt emergency treatment for victims of accidental swallowing of toxic substances in the home, where ingestion is indeed the most common route of entrance.

In the case of certain specific solvents, absorption through the skin can be appreciable and it is essential to consider this route concurrently with the inhalation of the vapors in the evaluation of exposures. It is generally believed that the absorption of benzene, toluene and xylene through the skin is minimal and probably not enough to cause systemic poisoning.[5]

Analysis of biologic samples is of value in evaluating exposures to solvent vapors for a variety of reasons where the exposures vary considerably in both length and intensity, where these actual exposures are difficult to measure accurately, where it is desirable to measure the effectiveness of respiratory protection against these exposures and where the intensity of physical work varies with these exposures.

A portion of the benzene vapors inhaled during exposure are eliminated unchanged in the expired air. Some are excreted unchanged in the urine. Metabolic processes oxidize some of the benzene to phenols and diphenols.

Ethereal sulfates are formed from the conjugation of phenols and sulfate ions in the liver. The ratio of organic sulfates to total sulfates in the urine collected at or near the end of the day is a means of determining the daily exposure. Gerarde[5] states that this ratio normally is 85% or above and exposures to benzene decrease this ratio. Ratios of 60% or less indicate dangerous exposures warranting immediate correction.

Wakely, Pagnatto and Elkins[12, 17] have investigated the measurement of urinary phenol as a means of evaluating benzene exposure. Their conclusions were that this index of exposure has greater sensitivity than the use of the sulfate ratio, particularly where exposure to relatively low concentrations of benzene is involved and interpretation of atmospheric exposure is difficult or unreliable, but that it should not be used as an exclusive

measure of exposure. Good correlation was found for benzene exposures ranging from 5 to 68 ppm and corresponding phenol concentrations ranging from 68 to 570 mg/liter respectively. A urinary phenol concentration of 200 mg/liter was considered to be indicative of exposure to a 25-ppm atmospheric concentration of benzene.

As in the case of benzene, part of inhaled toluene vapors is exhaled unchanged. A small amount may be detected unchanged in the urine, with approximately 80% being oxidized to benzoic acid and excreted as hippuric acid. Pagnatto and Lieberman[11] studied this relationship and found good correlation between hippuric acid content of urine specimens collected at the end of the work shift (adjusted to specific gravity of 1.024) and industrial exposures to toluene in leather-finishing and rubber-coating plants. They reported a 7.0 gm/liter of hippuric acid for workers exposed to 200 ppm of toluene. The average value of 0.8 gm/liter for unexposed persons was considered due to eating of food containing benzoate or from naturally occurring benzoic acid in certain fruits and vegetables.

Ikeda and Ohtsuji[9] reported 3.5 gm/liter of urine (adjusted to a specific gravity of 1.016) for workers exposed to 200 ppm of toluene. This value, if adjusted to 1.024, as reported in the preceding study, would result in a value of 5.3 gm/liter. This lower value reportedly is due to the analytic specificity for hippuric acid and did not include methylhippuric and uric acids.

Capellini and Alessio[4] determined that exposures of 18 workers to average toluene concentrations of 110 ppm resulted in a mean urinary output of 2.1 gm/liter. A level of 9 gm/liter was found in a worker exposed to 250 ppm. A control group of 17 non-exposed workers had a mean urinary output of 0.95 gm/liter.

Few studies have been made clarifying quantitative differences in the effect of solvent exposure *at rest* and *during increased physical activity*. In 1970, Zenz and Berg[18] performed such a study using trichloroethylene and simulated submaximal work on a treadmill. They showed that the concentration of trichloroethylene in expiratory air after constant exposure increased in proportion to exercise intensity. They pointed out that it is not enough to state the concentration of a substance in inspiratory air and the duration of exposure. Attention must also be paid to the biologic reaction to physical exercise, i.e., to increased pulmonary ventilation and blood circulation.

Since metabolic products of toluene found in the urine are principally a result of toluene vapors being absorbed in the lungs during exposure, the study by Åstrand *et al.*[3] further supported the view that biologic limit values are important and a necessary complement to measurement of atmospheric vapor concentrations. In this case, the authors determined the toluene concentration in alveolar air and arterial and venous blood during and after exposure to 200 ppm at rest and to 100 ppm during light exercise (on a bicycle ergometer for generally 30 minutes). They state, "The concentration in alveolar air and arterial blood was of the same magnitude in exposure to 200 ppm at rest as to 100 ppm during light exercise. Exposure at rest to 100 ppm in air containing 4 percent CO_2 produced an increase in alveolar air and arterial blood concentration corresponding to the increase obtained during exercise with a corresponding increase in alveolar ventilation."

The metabolic products of xylene have not been studied nearly as extensively as those of benzene or toluene. Gerarde[5] indicates that "the urine could be analyzed for toluric acid or other xylene metabolites." The publication *Occupational*

Diseases[16] indicates that there are no specific diagnostic tests associated with xylene exposures. Mikulski *et al.*[10] indicate that it is possible to use a joint determination of hippuric and methylhippuric acids for the assessment of mixed exposure to atmospheric toluene and xylene vapors. It was also stated that these exposures impaired the excretion of uric acid.

TOXIC RESPONSES

In humans, acute high exposures to benzene, toluene or xylene have a dramatic narcotic effect associated with central nervous system depression. Initial symptoms associated with these types of exposures include drowsiness, fatigue, headache and loss of equilibrium. Loss of consciousness, convulsions and death may result when relatively high concentrations or long exposure times are involved. Gerarde[5] states that toluene is a more powerful narcotic than benzene and that the acute toxicity of xylene appears to be greater than that of either benzene or toluene.

The chronic low-level exposures to benzene have gained considerable attention, since these exposures have been shown to produce demonstrable changes in the peripheral blood system. Anemia, leukopenia and thrombocytopenia have been associated with long-term exposures involving relatively low atmospheric concentrations of vapors.

In the early 1930s, benzene was chosen as the ideal solvent with the advent of high-speed presses in the rotogravure printing industry. A fast-drying ink was required, and benzene, with its dual properties of a good ink solvent and a fast evaporation rate, was found superior to others studied. A case of fatal benzene poisoning in a rotogravure plant in Philadelphia prompted the Division of Industrial Hygiene, New York Department of Labor, to start an investigation of the existing problem in their state. A total of 332 workers were examined in the 3 plants investigated where atmospheric benzene concentrations ranged from 11 to 1060 ppm. Greenburg *et al.*[7] arrived at several important conclusions following blood studies of the exposed employees. Significant conclusions included the following.

1. Too great reliance should not be placed on the leukocyte count alone as a rapid means of detecting cases of benzene poisoning.
2. A reduction in number and an increase in size of the red blood cells would appear to be more sensitive and earlier signs of intoxication.
3. Various combinations of tests were suggested, which, it is believed, would reveal a majority of the positive cases with the least expenditure of time. The incidence of these blood abnormalities, in the order of frequency, were found to be: (a) diminution of erythrocytes; (b) increase in mean corpuscular volume of the erythrocytes; (c) a reduction in blood platelets; (d) a reduction in hemoglobin; (e) a reduction in white blood cells.
4. Serious abnormalities in the blood picture were found in the complete absence of symptoms or physical signs, and vice versa. A clinical picture suggestive of benzene poisoning was found in persons whose blood appeared to be perfectly normal.

As a result, control measures were instituted, including the substitution of less toxic solvents and improved exhaust ventilation.

Acute and chronic leukemia has been observed in workers and reported in the literature. Girard *et al.*[6] conducted a survey among 401 hospital patients with serious blood diseases together with controls who were free from any blood disorders. Those who showed a history of previous exposure to benzene and toluene had a significantly higher occurrence of acute leukemia (13.6%), aplastic (20%)

and chronic lymphatic leukemia (14.7%) than did the control group (4%).

Aksoy *et al.*[2] studied 32 pancytopenic patients who had long-term exposures to benzene in concentrations varying from 150 ppm to 650 ppm and exposures of from 4 months to 15 years. Apart from 4, in whom the platelet count was normal, all had pancytopenia. Aksoy *et al.*[1] also describe the development of acute leukemia in 4 shoemakers using adhesives containing benzene.

Chromosome studies have indicated that aberrations may occur in a significant number of workers exposed to benzene. Hartwich and Schwanitz[8] reported a mean aberration rate of 10.4% in 9 seemingly healthy refinery workers, 3–7 years after exposure to benzol. A comparable group had a mean aberration rate of 5.1%, leading the authors to conclude that the rate of the exposed group was at the upper limit of normal. A relatively low degree and duration of exposure was also indicated. In a NIOSH criteria document,[14] Forni *et al.* were quoted concerning chromosome studies carried out on peripheral blood lymphocytes of 34 workers in a rotogravure plant. Toluene had been substituted for benzene in 1953, with 10 of the workers exposed prior to and after the substitution and 24 exposed to toluene only. They reported that the proportions of unstable and stable chromosome aberrations were significantly higher statistically in the benzene group compared to the toluene group. No significant differences were found between the toluene and control groups.

The main effect of excessive exposures to both toluene and xylene is that of narcosis. Slight loss of coordination and sense of timing can result in increased accident proneness. Other reported effects include headache, lassitude and loss of appetite. Higher exposures may result in dizziness, nausea and definite loss of coordination.

Many of the early studies reporting effects of toluene and xylene on the blood system are believed to be due to the fact that consideration was not given to the benzene content of these solvents. In reporting on the effects of human exposure to toluene, the National Institute for Occupational Safety and Health's Criteria Document on Toluene[15] states that "Although studies in experimental animals show rather convincingly that toluene is not myelotoxic, there has been some persistent controversy concerning the effects of toluene on human bone marrow. This is probably due to investigations of groups of industrial workers exposed to toluene derived from coal tar which was contaminated with considerable benzene, frequently as much as 15%."

MEDICAL AND HYGIENIC CONTROLS

The majority of industrial hygiene studies have been conducted in the past by industrial hygienists from federal and state agencies, insurance companies, industrial plants and private consultants. The basis of the industrial hygienist's evaluation of health hazards has been primarily the comparison of their findings with recommended threshold limit values (TLVs) for airborne atmospheric contaminants established by the American Conference of Governmental Industrial Hygienists (ACGIH). With the advent of the Occupational Safety and Health Act of December 1970, two federal agencies, the Department of Labor and the Department of Health, Education, and Welfare, were given separate and explicit responsibilities. Enforcement of safety and health regulations was assigned to the labor department's Occupational Safety and Health Administration (OSHA). One of HEW's National Institute for Occupational Safety and Health's (NIOSH) responsibilities is to prepare criteria documents of recom-

mended exposures for toxic substances. The documents then are presented to OSHA for consideration as a basis of adoption as a regulation with subsequent enforcement.

These documents are comprehensive in nature, not only containing methods for evaluation of the environment but also recommending that comprehensive preplacement and biennial medical examinations should be provided for all workers exposed to the specific contaminant involved.

One such document published in 1973 was for the occupational exposure to toluene.[15] It indicates that the medical examinations "be directed toward but not limited to the incidence of headaches, nausea, and dizziness; particular attention should be focused on complaints and evidence of eye, mucous membrane, and skin irritation. Laboratory tests recommended at the time of the biennial examination include complete blood count and urinalysis."

As documents for benzene and xylene ultimately are developed, they undoubtedly will include similar recommendations concerned with medical examinations of exposed employees.

Of additional significance are the requirements concerned with periodic industrial hygiene air monitoring of the working environment to determine the degree of exposure. Where it is determined that these environmental levels do not exceed one-half of the environmental standard (TLV), the employee is not considered to be "exposed." As a consequence, the preponderance of industrial hygiene surveys will be relegated to two categories—periodic monitoring by the employer by whatever means available and surveys by federal or state industrial hygienists to determine compliance with existing regulations.

The American National Standards Institute's recommendations for benzene (Z37.4-1969) and toluene (Z37.12-1967) and the ACGIH's recommended TLV for xylene were officially adopted by OSHA and published by the Department of Labor in the *Federal Register*, Volume 37, No. 202, Part II, October 18, 1972. They are shown in Table 31-1.

Industrial hygiene surveys should be conducted regardless of the motivative reason, to minimize and control exposures to toxic substances to a point at which all available medical evidence indicates that the resulting environment is an assurance to the employee that he is indeed working in a healthful environment. Providing such protection against long-term chronic exposures should be through the installation of effective local exhaust ventilation controls or, when this is not possible, with sufficient and effective amounts of dilution ventilation. In the case of benzene, with its extremely low TLV, control by dilution ventilation is not sufficient.

Indeed, wherever benzene is being used, a concerted effort should be made to find a less toxic substitute for this solvent. Invariably, its ordinary use as a sol-

TABLE 31-1.—RECOMMENDED ANSI AND ACGIH TLV'S FOR BENZENE, TOLUENE AND XYLENE ATMOSPHERIC INDUSTRIAL SOLVENT VAPOR EXPOSURES

MATERIAL	8-HOUR, TIME-WEIGHTED AVERAGE	ACCEPTABLE CEILING CONCENTRATION	ACCEPTABLE MAXIMAL PEAK ABOVE THE ACCEPTABLE CEILING CONCENTRATION FOR AN 8-HOUR SHIFT	
			Concentration	Maximal Duration
Benzene*	10 ppm	25 ppm	50 ppm	10 minutes
Toluene	200 ppm	300 ppm	500 ppm	10 minutes
Xylene	100 ppm	–	–	–

*Emergency standard of 1 ppm proposed, 1977.

vent presents a very definite health hazard to those exposed.

Respiratory protection should be the last resort when ventilation control measures are impossible to institute. Proper protection, such as air-supplied respirators, *always* should be provided when the worker enters confined spaces that have contained solvents and have not been ventilated adequately. It is in these cases that acute massive exposures and fatalities occur.

Considerable emphasis should be placed on avoiding prolonged or repeated skin contact with these aromatic hydrocarbons. Their degreasing properties remove the natural oils and fats and are a potential cause of dermatitis.

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Occupational Health Aspects of Plastics and Rubber Manufacturing

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CHEMICALS and materials used and manufactured in the rubber and plastics industries constitute an incredible array; only a few typical, widely used and most hazardous are described. Some of the most important are alcohols, antioxidants, ketones, plasticizers and certain solvents,

including carbon disulfide, chlorinated hydrocarbons, certain petroleum distillates, polyester and polyvinyl resins.

The alcohols used in the manufacture of rubber are primarily amyl alcohol, butyl alcohol, ethyl alcohol, isopropyl and methyl alcohol. Acetates commonly in use are butyl, isoamyl, ethyl, methyl, isopropyl and propyl. The alcohols and acetates used as solvents have similar actions and are recognized as upper respiratory irritants; to some degree, all are irritating to the eyes and, with prolonged concentrated exposures, may cause narcosis.

AROMATIC HYDROCARBONS

The aromatic hydrocarbons, such as benzene, xylene and toluene, described elsewhere in this book, are excellent solvents and are used extensively in the production of plastic and rubber products (see contribution by Otterson). The commonly used halogenated hydrocarbons are discussed by Christensen.

KETONES

Typically, these are acetone (dimethyl ketone), methyl ethyl ketone (butanone), methyl amyl ketone and methyl isobutyl ketone. These are not especially toxic, but they do have a known narcotic action during high concentrations with prolonged exposure. Environmental concentrations must not exceed the threshold limit values shown in Table 31-2. As emphasized elsewhere, skin contact must be avoided because of rapid defatting action, often leading to dermatitis. Proper control of work-place exposures depends on adequate ventilation to prevent unnecessary inhalation and to minimize skin contact. Control relies on work-place atmospheric sampling to determine concentrations encountered. Blood cell counts, including differentials, cannot be relied on as an indicator of worker exposure control. Abnormal blood findings, when demonstrated, may be too late to be of value in the consideration of health protection for the worker.

In a special communication, McDonough[36] reported that following the receipt of reports indicating a possible relationship between exposure of personnel in certain types of industrial operations to methyl *n*-butyl ketone (MBK) and the development of peripheral neuropathy, the Health and Safety Laboratory of Eastman Kodak Company, Rochester, New York, has carried out preliminary tests involving different species of animals exposed to several levels of MBK by various routes of exposure. Rats exposed to inhalation of MBK at an atmospheric level of 1300 ppm for 6 hours a day, 5 days a week for 4 months have developed nerve changes characteristic of peripheral neuropathy. In this rat inhalation study, the concentration was many times the threshold limit value established by the ACGIH. Eastman plans further studies to establish the upper levels of exposure where peripheral neuropathy does not occur in animals.

Handling precautions for MBK stated in Eastman Technical Bulletins are as follows: The threshold limit value is 100 ppm (410 mg/m^3). Local exhaust ventilation should be used to maintain concentrations in the air below the TLV. Contact with the skin and eyes should be avoided by the use of appropriate protective clothing and eye protection. In case of spills, persons exposed to MBK should have respiratory protection. The skin should be thoroughly washed with water after contact with MBK.

An extensive review article on the health hazards of plastics has been published by Eckardt and Hindin.[15] They discuss virtually all occupational exposures, including the use of fillers, often compounded with plastics. They mention the apparent health hazards encoun-

TABLE 31-2.—TYPICAL SUBSTANCES USED IN PLASTICS AND RUBBER INDUSTRIES
(Modified from ACGIH Documentation of TLVs for Substances in Workroom Air, 1974[4])

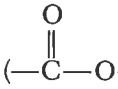
SUBSTANCE	PPM OF AIR	MG/M³
Acetone	1000	2400
Acrylonitrile	20	45
Amyl acetate	100	525
Amyl (iso) alcohol	100	360
Benzene (see footnote, Table 31-1)	10	30
Butadiene 1,3	1000	2200
Butyl acetate	150	710
Butyl alcohol	100	300
Carbon tetrachloride	10	65
Ethyl acetate	400	1400
Ethyl alcohol	1000	1900
Ethylene dichloride	50	200
Gasoline	*See below	
Heptane	400	1600
Hexane	100	360
Propyl (iso) alcohol	200	500
Methyl alcohol	200	260
Methyl ethyl ketone	200	590
Methyl isocyanate	0.02	0.05
Naphtha (coal tar)	100	400
Perchlorethylene (tetrachlorethylene)	100	670
Propyl acetate	200	840
Stoddard solvent	100	575
Styrene	100	420
Toluene	100	375
Toluene diisocyanate	0.02	0.12
Trichloroethylene	100	535
Xylene	100	435
Vinyl chloride	1	3

*The composition of gasoline varies greatly and thus a single TLV for all types of these materials no longer is applicable. In general, the aromatic hydrocarbon content will determine what TLV applies. Consequently, the content of benzene, other aromatics and additives should be determined to arrive at the appropriate TLV (Elkins *et al.*, Am. Ind. Hyg. Assoc. J. 24:99, 1963).

tered in the use of fillers and plastics (fiberglass-reinforced polyester plastic with calcium sulfate or calcium carbonate).

Asbestos is another material used as a filler, resulting in generation of dust from sawing and grinding in finishing processes. The writers of this review also discuss the use of plastics in medicine, including tissue reactivity to the various plastics. Hazards associated with ethylene oxide as a sterilizing agent through the formation of ethylene chlorohydrin are noted. Silicones are discussed also.

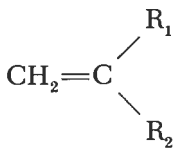
Polyester resins are polymeric substances, having ester groups in chains



with catalyzers, and harden or cure at room temperature. Commercial products are alkyds used in paints and enamels, and unsaturated polyesters or unsaturated alkyds are used with fiberglass for some boat hulls, wall panels and films.

POLYVINYL RESINS

"Polyvinyl resins" generally include polymers derived from monomers having a structure



R_1 and R_2 represent hydrogen, alkyl, halogen or other groups. Some of the polymers, such as polyvinyl chloride, polyvinyl acetate, polyvinyl acetals, polyvinyl alcohol, polyvinyl ethers and polyvinylidene chloride, have been used for many years. Others are polyvinyl fluoride, polyvinyl pyrrolidone and polyvinyl carbazole. These monomers are prepared by the addition of an appropriate compound combined with acetylene. Reactions of acetylene with HCl, HF and CH_3OOH are used to form vinyl chloride, vinyl fluoride, vinyl acetate and vinyl methyl ether. Polyvinyl acetates are used in adhesives, coatings for paper and in the leather and textile industries.

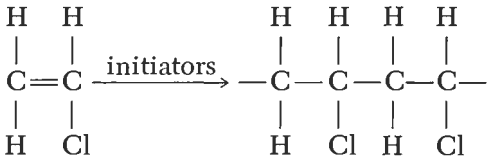
World production of vinyl chloride in 1973 was more than 10 billion kg, with U. S. production about 25% of that amount. In 1973, the Environmental Protection Agency estimated that as much as 90 million kg escapes into the atmosphere in the United States per year. Polyvinyl chloride, commonly known as PVC, is an exceedingly widely used material.

PVC may be blended with fillers and pigments, stabilizers and other materials, such as plasticizers, which then may be made into sheets or extruded into various shapes. These include insulation for cables and wires, packaging, tubing, pipefittings, as well as phonograph record blanks, tape cassettes, house siding, gutters and drainspouts, garden hose, furniture, upholstery, mats and tops for automobiles, footwear, raincoats, films, sheets, bottles, tools, medical equipment, etc., including acrylic resins, butadiene, styrene copolymer, polypropylene and others. Vinyl chloride polymerized with other vinyl monomers generally carried out in closed systems is used to produce blends or alloys of polyvinyl chlorides to form rubbery materials intended for applications in panels, other covers, including floors, and pipes with high-impact resistance. Films of polyvinylidene chloride and the copolymer containing about 15% vinyl chloride are considered resistant to moisture and many gases. These have the property of being heat sealable and shrinking on heating. Many floor products are coated with this tough and resistant cover. Vinyl chloride is present in many aerosol consumer products as a propellant, especially in certain pesticides and hair sprays.

Polyvinyl ethers, soluble in organic solvents, are used in some adhesives. Vinyl stearate, a waxy material, is used for treating leather and in wax formulations.

Manufacturing Processes and Toxicologic Factors of Polyvinyl Chloride (PVC)

PVC resin is formed from the vinyl chloride (a colorless gas) monomer (VC) by addition polymerization (simple addition of monomer molecules without loss of atoms from the original molecule):



Vinyl chloride Polyvinyl chloride

Vinyl chloride:
m.p. = 160° C
b.p. = 13.9° C
v.p. = 760 mm Hg (13.8° C)
vapor density = 2.15
flash point = 78° C
TLV = 1 ppm (1974—see Table 31-2)

Manufacture of VC Monomer

$HgCl_2$—Catalyst; metallic mercury (reduced from $HgCl_2$ in acetylene process).

Acetylene (colorless gas, sp.gr. = 0.91, highly flammable; relatively nontoxic).

Phosphine ([impurity in acetylene]; CNS depressant and lung irritant; no evidence of cumulative effects); TLV 0.3 ppm.

Ethylene—density = 0.97; colorless gas. (Asphyxiant displacing content of air; low order of systemic toxicity.)

1,2 Dichloroethane—intermediate; clear colorless liquid; TLV 50 ppm. Skin and eye irritant; acute poisoning by inhalation has resulted in liver and kidney damage. Liver damage is more permanent and assessed by increased liver weights, changes in liver function tests and fatty liver changes in animals.

Cl_2—an intermediate; density (gas) 32; TLV 1 ppm. Mucous membrane and respiratory tract irritant; chronic effects primarily on respiratory system (bronchitis, possibly decreased pulmonary function).

HCl—an intermediate; TLV 5 ppm (corrosive; vapors are irritants to entire respiratory tract).

Vinyl Chloride Polymerization

The starting point of PVC resin may be either VC monomer or production of the VC monomer from either acetylene and/or ethylene.

1. Acetylene process: $CH \equiv CH + HCl \xrightarrow{HgCl_2} CH_2 = CClH$
   (acetylene)
2. Ethylene process: $CH_2 = CH_2 + Cl_2 \rightarrow CH_2Cl - CH_2Cl$ pyrolysis $\rightarrow$
   (ethylene)
   $CH_2 = CHCl + HCl$ (1,2 dichloroethane)
3. Combination methods to utilize HCl for:
   (a) $CH_2 = CH_2 + CH \equiv CH + Cl_2 \rightarrow 2\,CH_2 = CHCl$
   (ethylene) (acetylene) (VC)
   (b) $CH_2 = CH_2 + 2HCl + 1/2O_2 \rightarrow CH_2Cl - CH_2Cl + H_2 \rightarrow CH_2 = CHCl$
   (1,2 dichloroethane)

There are four major types of polymerization of VC to PVC.

1. Suspension (pearl, bead, granular) polymerization is used in the majority of general-purpose PVC manufacturing processes for the production of general-purpose resins. The VC monomer plus water is agitated to form tiny droplets, which are stabilized by "suspending agents" mixed in the water phase before agitation and introduction of monomer. VC-soluble initiating agents are added to the monomer to polymerize PVC. The compounds involved include the following: Vinyl chloride and initiating agents (lauryl peroxide, isopropyl peroxydicarbonate [IPP] [dissolved in hexane], azobisisobutyronitrile, diethylperoxydicarbonate—produced by adding ethyl chloroformate [VC phase], H_2O_2 + NaHCO [H_2O phase] and benzoyl peroxide). Suspending agents (protective colloid): gelatin, polyvinyl alcohol and methyl cellulose. Other chemical additives: inorganic salts, buffers and surface-active agents.

2. Bulk polymerization is carried out in the fluid monomer; no water or suspending agent is used. The monomer and initiating agent are liquefied under high pressure. After about 70% polymerization has taken place, additional monomer and initiator are added and the reaction allowed to go to 70–85% polymerization. Thereupon, the remaining monomer is recycled and the polymer resin is pneumatically conveyed to the finishing operation for screening and storage. PVC resin produced by this process is free from

polymerization residue, with excellent clarity and fusion characteristics. This resin is especially suited for blown bottles, clear films, rigid pipe and fluidized bed coatings. The initiating compounds are the same as in suspension polymers.

3. Emulsion polymerization is used to produce fine particle size dispersion resin of about 1 micron. The monomer is emulsified in water by a surfactant (soap) and polymerized with a water-soluble initiator to form a polymer latex. The latex is degassed and then dried. The chemical compounds are monomer—VC, surfactant—0.2—0.5%. Initiator (water soluble): potassium persulfate.

4. Solution polymerization is bulk polymerization with the monomer dissolved in a solvent. This process produces resins of good clarity and purity useful in the manufacture of fibers and is used to produce high-quality copolymers (e.g., vinyl chloride-vinyl acetate). The chemicals used include the following: monomer, initiators (monomer soluble)—same as for suspension polymerization—and solvents (benzene, cyclohexane, *n*-butane, chlorinated aliphatics).

Copolymers of VC with vinyl acetate, vinylidene chloride, maleic esters, vinyl ethers and propylene are most commonly made with suspension and solution polymerization.

A summary of some properties of chemicals used in PVC production is as follows.

Initiating agents. Monomer-soluble lauryl peroxide (C_{11}, $H_{23}CO)_2O_2$, a white, coarse powder, is highly toxic by ingestion and inhalation and is a strong skin irritant and an oxidizing material.

Benzoyl peroxide $(C_6H_5CO)_2O_2$, a white granular crystalline solid, is moderately toxic and relatively safe when mixed with 25–33% water.

Aminoethanols. 2-*N*-alkyl-substituted aminoethanols are widely used as curing agents, flotation agents, dispersants and emulsifiers. Cornish *et al.*[10] exposed rats to 2-*N*-dibutyl-aminoethanol (DBAE) by ingestion and inhalation, finding an acute oral LD_{50} of 1.78 gm/kg for neutralized DBAE. The rats experienced periods of depression followed by tremors, incoordination, clonicotonic convulsions and death.

Sodium peroxide (Na_2O_2) is a yellowish white powder (highly toxic by ingestion; strong oxidizing agent).

Ethylchloroformate ($ClCOOC_2H_5$) is a colorless liquid (highly toxic; strong eye and skin irritant; chronic and acute systemic effects not known).

Azobisisobutyronitrile $(CH_3)C(CN)NNC(CN)(CH_3)_2$ is a white powder; may be toxic by ingestion; nitrile group suggests toxicity similar to other nitriles (e.g., acrylonitrile) and cyanides.

Water-soluble initiating agent. Potassium persulfate ($K_2S_2O_8$), consists of white crystals; decomposes at <100° C (liberates sulfur oxides), moderately toxic, strong irritant and oxidizing agent.

Suspending agents. Polyvinyl alcohol $(-CH_2CHOH-)_x$ is a white to cream-colored powder; low toxicity; possible carcinogen (fibrosarcomas when embedded in abdominal wall of animals).

Methyl cellulose is a grayish white, fibrous powder (nontoxic).

Solvents. Benzene (C_6H_6); TLV 10 ppm; strong irritant; anesthetic; toxic to blood-forming tissues (anemia, leukopenia, macrocytosis, reticulocytosis, thrombocytopenia, increased bleeding time; leukemia). (See Aromatic Hydrocarbons by Otterson.)

Cyclohexane (C_6H_{12}); TLV 300 ppm (skin irritant, anesthetic).

n-Butane ($CH_3CH_2CH_2CH_3$) is a colorless gas (slight to moderate systemic effects from inhalation).

This is a partial list, since there are more than 227 monomers, polymers, catalysts, dispersants, inorganic compounds for coalescence regulation, emulsifying

agents, surfactants and organic solvents as well as copolymers and polymers used or produced.

POLYVINYL CHLORIDE FABRICATION (PVC Resin to Final Product)

PVC plastics have hundreds of uses. They may be rolled into sheets and used as imitation leather or as floor covering or they may be molded into such products as electric insulators, water pipes, drug bottles, syringes, medical tubing, etc. They may be used as copolymers for such things as films or synthetic fibers or, after immersion in acetone and carbon disulfide, spun and used as "textile yarn."

Whatever the use, fabrication processes involve "compounding" the resin with other chemicals (plasticizers, stabilizers, fillers, pigments, lubricants and modifiers) to produce the desired properties. The compounding often is done in a Banbury mixer. After mixing, the compound continues to follow a production flow similar to rubber. It may be milled, then calendered or extruded or, if a molded product, go into a mold. Compression, injection and extrusion molding are the common processes used.

PVC powder or solution is also used for coatings, such as for kitchen appliances, fabrics, metal articles and food-wrapping films, or the liquid "plastisol" may be poured directly into molds.

PVC is tough and brittle with poor heat stability, so that stabilizers, antioxidants, plasticizers, etc. must be added to make the desired product. These additives may constitute up to 60% in some plastics and may produce adverse health effects in the fabrication processes and even finished articles. Potential adverse health effects in the finished product may be a result of leaching out, as has been shown, for example, in transfusion tubing. Considerable investigation has been concerned with the migration of these additives out of biologic systems (implants, cell culture studies) as well as solvent extracts evaluated by intraperitoneal and intradermal injections, cell culture and hemolysis of red blood cells.

A listing of the different types of additives with a brief summary of the toxicity of individual chemicals follows.

PLASTICIZERS.—These are high boiling point, chemically stable liquids that reduce the intermolecular forces and lower the transition temperature of the PVC polymer. The resulting compound has decreased tensile strength but increased flexibility, softness and elongation and is more easily processed at a lower temperature. Better than half of the plasticizers used are phthalates (diethylhexylphthalate [DOP], butyl benzyl and diisoctyl phthalates), with phthalic acid esters comprising 20–40% by weight in most flexible PVC plastics. The phosphoric esters also act as flame retarders.

Phthalates, e.g., DOP (diethylhexylphthalate), $C_6H_4(COOCH_2CH[C_2H_5]C_2H_{52})$; TLV 5 mg/m³. The phthalates used are moderately volatile, liquid soluble and stable, and have been found in human tissue (lung, liver, spleen). Practically nontoxic (based on short-term oral toxicity) and poorly absorbed via skin.

Dibutyl and dioctyl phthalates. Phthalate esters are of low level toxicity. Many of the phthalate esters have high oral lethal doses and can be tolerated in relatively high levels in the diet. Rats have tolerated 0.25% dibutyl phthalate and some animals have tolerated 1.25% for a year. Oral LD_{50} for rats was 8.0 gm/kg dibutyl phthalate and, for mice, greater than 13.0 gm/kg dioctyl phthalate. The inhalation toxicity of dibutyl phthalate for cats that caused nasal irritation was 1000 mg/m³ for 5.5 hours.[42]

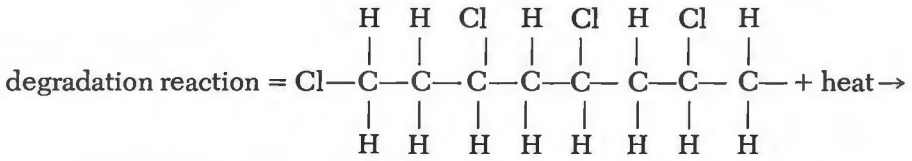
The degree of toxicity of phthalate esters is said to be related inversely to the molecular weight and water solubility.[8]

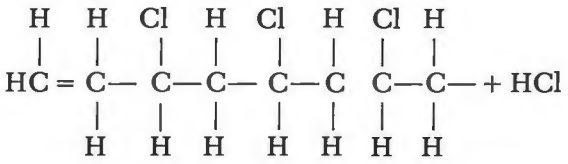
The ester of adipic acid ($COOH[CH_2]_4COOH$) has low toxicity, but may cause eye and skin irritation.

Phosphoric acid esters, e.g., tricresyl phosphate; TLV 0.1 mg/m³; GI upset (nausea, vomiting, diarrhea, abdominal pain); soreness of lower leg muscles, numbness of toes and fingers, weakness of toes; polyneuritis, CNS degeneration; allergen. Tri (2-ethyl hexyl) phosphate; toxicity not known (low?), possibly slightly irritant.

Citrate esters, e.g., triethyl citrate, acetyl tributyl citrate; relatively toxic (soluble compounds) to nontoxic (nonsoluble).

STABILIZERS.—These are metal salts or soaps that react with HCl degradation product of the heat-sensitive PVC,





thereby providing good long-term heat stability. Organo-tin compounds are used for higher heat processing or for high-clarity objects such as clear, rigid products. Organo-phosphite chelators sequester the metal chloride formed from the metal salt. Finally, epoxidized resins or oils react with acid, thereby adding to over-all compound stability.

In polymers for medical use, the toxic organo-tin compounds often are replaced with epoxidized soya oil as the primary stabilizer. The soya oil is a complex mixture containing different contaminants (e.g., peroxides, decomposition products of soya oil). In translucent compounds, light stabilizers provide protection from ultraviolet light.

Stabilizers as a group may contain other agents as contaminants.

1. Metal salts or soaps; e.g., (a) lead compounds (see Chapter 30); (b) cadmium compounds or organic acids (see Chapter 29); (c) barium salts or organic acids; (d) calcium and zinc salts—used especially when nontoxic compounds are required, Cd, Ba and Zn compounds are preferred in general processing; (e) organo-tin compounds (up to 1% of the formulation).

2. Epoxidized resins or oils; e.g., soya oil (variable composition with many contaminants), linseed oil, epoxy stearates (toxic to cells in culture and on intracutaneous and intraperitoneal injection).

3. Light stabilizers; e.g., benzophenones ($C_6H_5COC_6H_5$), benzotriazoles (C_6H_4NHNN); toxicity not known; animal experiments suggest moderate toxicity by ingestion.

FILLERS.—These materials are added to produce opacity and hardness and to reduce costs. They also improve electrical properties, ultraviolet light resistance and impact resistance as well as improving processing characteristics and dimensional stability by reducing elasticity. Because of their higher specific gravity (2–3 times greater than unfilled com-

pound), they increase the density of the finished product. Unlike fillers used in rubber, which have a reinforcing effect, fillers normally lower tensile strength, elongation and tear strength in PVC.

1. Organic fillers. Carbon black is used commonly. When mice were fed massive quantities of carbon black over 12–18 months, there was no detectable change.[40] A case of carbon black pneumoconiosis was reported in an individual who worked 32 years in carbon black storage and in the calender department of the same factory.[38]

Hamsters, mice, guinea pigs, rabbits and monkeys were exposed by inhalation for prolonged periods to high concentrations of channel or furnace black without significant effect other than the accumulation of the dust in the pulmonary system. No malignancies were observed.[41] A threshold limit value for carbon black of 3.5 mg/m³ has been recommended in the United States.[1]

Wood fibers: (allergenic and inhalation hazard). (See Chapter 10.)

2. Inorganic fillers (<1% silicon dioxide). Clay, along with carbonates, the most widely used; average particle size >3μ. Calcium carbonate, mica—TLV 20 mppcf (>1%SiO_2), antimony oxide (see Antimony, Chapter 29).

Asbestos. Talc; diatomaceous earth; titanium dioxide. (For talcosis, see Chapter 10.)

COLORANTS.—A wide range of colorants is used, selection being on the basis of cost, processing temperature, service requirements and color effect. Inorganic pigments do not produce a bright color but give excellent heat stability and good hiding power and are inexpensive. Organic pigments provide brightness and transparency, have a low specific gravity and high tinting strength. They are, however, more expensive and have a poorer heat stability. Normally, only small quantities are used and, therefore, probably do not pose a hazard.

1. Inorganic colorants. Titanium oxide (most commonly used) (similar to TiO_2), chromium oxide (toxic by inhalation or ingestion, see Norseth, Chapter 29), molybdate orange (lead chromate, molybdate and sulfate) and ultramarine blue.

2. Organic colorants. Phthalocyanines, with a structural unit of $4(C_6H_4)C_2N$ groups; blue-green is metal free, blue contains Cu, green contains chlorinated Cu, water-soluble green contains H_2SO_3. Benzidines (a family of pigments) (see Chapter 33). Quinacridones. Oxynaphthoic reds; moderately toxic, irritant.

LUBRICANTS.—Usually less than 1% is incorporated into a compound to reduce internal friction and the tendency of the stock to adhere to the surfaces of the processing equipment; these are the stearic, palmitic and oleic acids.

Metallic stearates, waxes, oils and low molecular weight polyethylene (a polymer of ethylene [C_2H_4]; molecular weight 2000–5000).

MODIFIERS.—These are other polymers added to the PVC polymer to either reduce the melt viscosity or increase the impact strength.

1. Processing aids (5–10%); acrylic polymers (the monomer methyl methacrylate has a TLV of 100 ppm; acrylic acid monomer is highly toxic, an irritant and corrosive). Styrene—acrylonitrite resins, chlorinated polyethylene (nontoxic).

2. Impact modifiers (10–20%); acrylic polymers; acrylonitrile-butadiene-styrene resins ("ABS") (see separate sections); chlorinated polyethylene.

PVC, as a product (resin plus additives), is more or less inert as measured by oral LD_{50}s. Inhalation of PVC dust has resulted in at least one reported case of pneumoconiosis; PVC film (as well as a num-

ber of other plastics, metals, glass, polyvinyl alcohol sponges, polyurethane, acrylic) has been shown to produce malignant tumors in rats and/or mice.

Aware of the considerable number of rubber-fabricating plants in Ohio, Bourne *et al.*,[6] from the Ohio State Division of Occupational Health, conducted a statewide survey of the industry in order to assess potential hazards. They surveyed 140 plants employing 19,400 workers, noting that the main problem areas were mixing or milling of rubber stocks with the additives, curing or vulcanizing and dusting of finished and semifinished products. They discovered that the number of additives encountered (mainly according to their trade names) was very high—in excess of 580. Generically, they were able to group these into less than a dozen chemical classifications. Among these are the thiurams, dithiocarbamates, thiazoles, guanidines, amines, amides, quinolines and phenols. Decomposition products evolving from curing and vulcanizing were considered but not investigated. Their survey disclosed more than 30 substances most frequently used as ingredients (Table 31-3).

Rubber processing may be divided into two phases: (1) masterbatching and (2) addition of a curing agent and preparation for operations to follow. Masterbatching involves breakdown of the raw elastomer in an open-roll mill or closed mixer (Banbury) to soften the elastomer and increase plasticity. To speed the softening operation and to aid in the addition of pigments, plasticizers may be added during breakdown. When softening is complete, resins and pigments are added and mixed together until homogeneous. The batch then is extruded or formed into sheets to cool and an antitack agent is applied to the surface to prevent sticking in storage. Many of the plants included in this study purchased their rubber already masterbatched, ready for the second stage of processing in their own plants.

In the second phase, the masterbatch is added to an open-roll mill or Banbury

TABLE 31-3.—COMMON RUBBER ADDITIVES

Accelerators	Dusting or Dipping Agents
Tetramethylthiuram disulfide	Zinc stearate°
Diphenylguanidine	Talc
Benzothiazyl disulfide	Soap solution
Zinc dimethyldithiocarbamate	
Activators	"Inert" Fillers
Zinc oxide	Kaolin
Stearic acid	Whiting
Magnesium oxide	Silica
Lead monoxide	Pigments
Antioxidants	Plasticizers
N-isopropyl-*N*′phenyl-*P*-phenyldiamine	Dibutyl phthalate
N-phenyl-beta-naphthylamine	Dioctyl phthalate
1,2-dihydro-2,2,4-trimethyl quinoline	Reinforcing Agents
2,2-methylene-bis (4-methyl-6-tertiary butyl phenol)	Carbon black
Blowing Agents	Retarders
Sodium bicarbonate	Salicylic acid
Stearic acid (used in combination with sodium bicarbonate)	*N*-nitroso diphenylamine
	Vulcanizers
Dinitrosopentamethylene tetramine	Sulfur
Azodicarbonamide	

°See Fishburn, Chapter 29.

TABLE 31-4.—RUBBER FORMULATIONS

TYPE OF INGREDIENT	BLACK MOLDING RUBBER		BLACK CHLOROPRENE SPONGE	
	Specific Agent	Wt (%)	Specific Agent	Wt (%)
Elastomer	Styrene-butadiene rubber	59.00	Chloroprene	68.0
			Zinc oxide	2.0
Vulcanizer	Sulfur	1.00	Calcined magnesia (MgO)	3.0
Accelerator				
Primary	Benzothiazyl disulfide	0.09	–	–
Secondary	Copper dimethyl-dithiocarbamate	0.06	–	–
Antioxidant	Octylated diphenyl-amines	0.06	P-(p-toluene-sulfonylamido)-diphenylamine	0.3
Activator	Stearic acid	0.60	–	–
	Zinc oxide	3.00	–	–
Processing aid	–	–	Petrolatum	2.0
Plasticizer	Mix of paraffin oil & sol. sulfonic acid	6.00	Aromatic light oil	10.0
Reinforcing agent	Thermal carbon black	18.00	Thermal carbon black	13.0
	Furnace carbon black	12.00		
Blowing agent	–	–	P,p'-oxybis-(benzene-sul-fonyl hydrazide)	2.0

mixer to warm up. Then the curing agent, antioxidant, plasticizer and other ingredients called for in the formula are added and mechanically worked. This process must be carefully regulated, since both the mixing time and the heat generated govern the chemical reactions that take place within the batch.

Various pigments are added to rubbers; for example, chromium compounds are used to impart the bright green colors, with generation of much dust during the milling operation.

When ready, the batch is removed and formed into shapes for vulcanizing, i.e., strips, tubes, sheets or slabs. Many articles, such as hose, belts, rolls and footwear, are built to approximately finished form before vulcanization.

The well-known vulcanization stage is the conversion of the plastic material to impart strength and also elasticity. This reaction is completed by the addition of sulfur or sulfur compounds at temperatures above 140° C with open steam autoclaves, heated dry air ovens or heated platen press molds, and a lubricant is necessary to ensure easy removal of the cured article from the mold. Finally, a dusting or dipping agent is supplied to eliminate surface tackiness. To add other special characteristics to rubber products, a number of aromatic amines are used, these being chiefly the "accelerators" in the vulcanization process to speed vulcanization and to make this a more efficient process. To combat the effects of aging (by sunlight and oxygen), the antioxidants used in rubber processing are of three groups: the acetone-amino condensation products, aromatic amines or hydroquinolines and phenolic substances.

Bourne and his co-investigators[6] con-

cluded "that the manufacturers of rubber chemicals have an obligation to know the total health effects from worker exposure to their products and to disseminate such information to their customers." (Ed. note: Also to the employees!)

There are several major types of synthetic rubber. Some are known as "butyl," "ethylene propylene," "neoprene," "nitrile," "polyurethane," "stereoregular" and "styrene-butadiene" rubbers. The materials used and the occupational and hygienic aspects of importance are described separately, some in considerable depth, such as acrylonitrile, butadiene, styrene and the polyurethanes.

Butyl rubber is made by copolymerization of isobutylene and isoprene (primarily exerting a physiologic effect as an anesthetic on inhalation) in the presence of boron trifluoride and methyl chloride. Usually, these processes are closed systems, containing the hazardous materials. Boron trifluoride, highly toxic, with a TLV of only 1 ppm, has shown marked respiratory irritation in animals. Methyl chloride is described elsewhere in this book.

Ethylene-propylene rubbers result from copolymerization of ethylene and propylene, using a hydrocarbon solvent method, along with titanium, vanadium and alkyl aluminum compounds as catalysts. The aluminum alkyls are especially dangerous because they can ignite spontaneously in air, and extreme precautions are needed; spillage on skin results in severe or fatal burns. Ethylene and propylene display some health risks, both having anesthetic properties, and are highly flammable.

Polymerization of chloroprene (2-chloro-l,3-butadiene) produces the polymer polychloroprene, best known by its trade name, Neoprene. The monomer is easily absorbed percutaneously or by inhalation, is capable of inducing central nervous system depression and may be toxic to the liver. Alopecia has been noted among workers with the polymerization process, accompanied by atrophy and disappearance of the follicles and fatty glands.

Khachatryan[25] reported a massive study of the population in the industrial region of Yerevan, USSR from 1956 to 1970, stating that 24,989 persons of both sexes over 25 years of age were examined; 137 cases of primary skin cancer were diagnosed. The persons examined were divided into groups according to their occupational exposures (presence or absence of extended contact with chloroprene, with its derivatives and with other chemical compounds): first group: those who never worked in industry; second group: those with lengthy experience in nonchemical industries; third group: those with extended work experience in chloroprene production only; fourth group: those having worked only in plants utilizing chloroprene derivatives exclusively; fifth group: those working for a long time with other chemicals (unrelated to chloroprene). Data on the number of people examined and the incidence of skin cancer in each of these groups as well as their average age and average work experience were described.

The greatest frequency of skin cancer (3%) was found among workers in chloroprene plants. In the first group, i.e., among persons who never worked in industry, and in the second group, i.e., among persons working in nonchemical industries, the frequency of skin cancer occurrence was 0.12% and 0.40%, respectively. The first, and partly the second, group thus were regarded as controls with reference to the other groups. On this basis, Khachatryan reported that among people who had an extended contact with chloroprene, the frequency of skin cancer occurrence increased 25-fold as compared with the control, and among workers who had contact with various

chloroprene derivatives (latexes, adhesives, rubber, etc.) there were increases of 13.3-fold. Among workers in other branches of the chemical industry (fifth group) who had extended contact with lacquers, acetone, gasoline and acids, the frequency of skin cancer occurrence exceeded that of the control by a factor of only 5.5.

Khachatryan revealed some definite differences in the location of skin cancer among patients working in the chemical industry and patients from the first control group. Among the latter, neoplasm formation was found most frequently on the face, neck or hands and often (18 ± 12%) also occurrences of various birth defects on the skin. Among the patients who had extended contact with chloroprene, cancer developed most frequently on the skin of the nose and ears, and in 90 ± 7% of the patients it was preceded by a chronic dystrophic or inflammatory skin condition (eczema, fissures, dyskeratoses). In 91 ± 5% of the patients from the fifth group (extended contact with lacquers, acetone, gasoline, acids), cancer was also preceded by chronic dystrophic or inflammatory skin conditions (eczema, scars as a result of chemical burns). Khachatryan noted that these observations were in agreement with data of other investigators, asserting that chloroprene is a carcinogen or cocarcinogen toward human skin. In the development of skin cancer under the influence of chloroprene, as with other occupationally related similar cancers, a definite role is played by the chronic dystrophic and inflammatory skin ailments, which precede the cancer. These pathologic changes are believed to be caused by the bonding of chloroprene to the free SH groups in the cells, with the formation of RS-CH compound types.

Khachatryan[26] has studied the occurrence of lung cancer among people who have worked for extended periods with chloroprene and its various derivatives (these were workers from the chloroprene production plant, from plants manufacturing technical rubber products, footwear, artificial leather, as well as from other factories). His data covered the period from 1956 to 1970 and are based on materials from the oncology department of the greater industrial Yerevan region.

Among the sample studied, 87 cases (82 men and 5 women) were identified. The career progression of the patient, age at which he started to work, his work experience, the working conditions, evidence of contagious lung diseases prior to and after starting to work, detrimental habits (smoking), etc. were studied. To assess the damaging effect of the various compounds, a control study on three population samples was run: in the first group were workers exposed to prolonged contact with various chemicals *unrelated* to chloroprene (gasoline, lacquers, acetone, benzene, acids, etc.); the second group consisted of workers from nonchemical industries; finally, the third control group consisted of workers from cultural and civic institutions.

Among 2934 workers and employees over 25 years of age who were examined and who had extended contact with chloroprene and its derivatives, 34 cases (1.16%) were found. The average age of these workers was 44.5 years, the average work experience 8.7 years. Among these 34 workers, 18 cases of primary lung cancer were found among occupations involving very prolonged contact with chloroprene. These were operators, cleaners, foremen, packers, weighers, pressers and others. Seventeen of the patients had work entailing extended contact with chloroprene latexes: shoemakers, cutters, gluers, foremen, chemists, janitors and others.

In the first control group, i.e., among 4780 persons examined, 22 cases (0.46%) of lung cancer were found with average age of 54.9 years and average work experience of 10.3 years. By occupation, these were truck drivers, polishers, cabinet makers, stokers, gasoline station attendants, typesetters, painters and others.

In the second control group, among 6045 workers examined, 11 cases (0.18%) were diagnosed, with average age of 59.3 years and average work experience of 14.9 years. They were mainly electricians, carpenters, joiners, arc welders, tinsmiths, furnace workers and others.

In the third group (those with a history of occupational chemical exposure), among 6220 persons over 25 years of age, Khachatryan's study uncovered only 5 cases of illness, i.e., 0.064% with average age of 60.2 years and average work experience of 18.5 years. In addition, 16 patients who were diagnosed as having primary lung cancer formerly were employed by the "Khrompik" plant, a plant using chromium compounds in their processes. Basically, these workers were calciners, cleaning women, scrubbers, foremen, operators and others. (All 16 patients were found to have perforations of the nasal septum, which occurred during their work.)

Khachatryan stressed the fact that among his 87 workers having primary lung cancer, 66 (75.8%) suffered from chronic bronchitis, 3 of them (3.4%) developed tuberculosis of the lungs after starting to work, 1 (1.1%) had bronchial asthma and 4 (4.5%) had "focal" pneumonia. He noted that of the 87 patients, 57 (65.5%) were heavy or long-term smokers. Khachatryan found it noteworthy that almost 78% of the patients suffered from chronic bronchitis and other respiratory ailments (asthma, pneumonia, tuberculosis) and ultimately developed primary lung cancer, which was detected after they started to work.

Thus, Khachatryan's investigations showed that in the first control group, the frequency of primary lung cancer occurrence was 2.67 times lower than among workers having contact with chloroprene and its derivatives; the second control group indicator was 6.3 times lower and, finally, in the third group, it was even lower yet—17.5 times!

According to this investigator, the data indicate that extended occupational contact with chloroprene and chloroprene derivatives leads to a significant (over 1 order of magnitude) increase in contracting primary lung cancer. Those workers who had contact with chromium compounds had apparent susceptibility to lung cancer of 4.2% (21 times higher than in the control group). The increase in lung cancer occurrence among workers who had extended contact with chloroprene and its derivatives is quite comparable to the increase in lung cancer occurrence caused by contact with chromium, borne out by the coincidence of data on the average age and average work experience of workers from both of these industries.

Khachatryan's summation of his data indicated that the development of lung cancer among people who, through their work, were exposed to chloroprene and its derivatives is directly linked to the harmful effects of chloroprene, believing that the active initiator is chloroprene itself because of its ability to vaporize constantly. He conceded that in the formation of lung cancer among workers involved in contact with chloroprene, a role apparently was played by the presence of chronic inflammatory bronchial ailments among people who had contact with chloroprene and smoking, which increased the carcinogenetic effect of chloroprene and which could also have

contributed to the increase in lung cancer occurrence among workers in the chloroprene industry.

ACRYLAMIDE

The vinyl monomer acrylamide (acrylic amide, $CH_2 = CHCONH_2$) has been found to be neurotoxic. Neurotoxicity was produced in cats, rats, mice, monkeys and dogs. Initial production experience revealed neurologic findings in workers exposed to monomeric acrylamide.

Acrylamide is used for polymer production in paper making, in waterproofing and for soil stabilizing.

Reported human exposures have resulted in such nonspecific symptoms as dizziness, fatique, insomnia and lassitude. Symptoms seemingly of peripheral neuropathy include numbness and tingling of the fingers, sweating of the hands, weakness and unsteadiness of the legs progressing to ataxia, and tremors. Skin absorption appears to be the only mode of entry, and, in all cases, improvement has been noted following cessation of exposure.

Leswing and Ribelin[28] found severe peripheral neuropathy by oral dosage with acrylamide in cats and monkeys, shown by nerve conduction studies and histopathologic examinations:

"It appears clear that acrylamide toxicity in man is due to peripheral neuropathy similar to that seen in animals. The major focus of effect is probably the distal nerve trunk and muscle arborization fibers. Man, as a primate, may be more resistant than non-primates, requiring heavier exposure before symptoms appear. Recovery may be anticipated but may require variable periods of time depending upon severity of involvement and length of exposure. Measurement of conduction velocity is probably of no value for early detection of poisoning or in minimally involved workmen. It is useful to evaluate and follow symptomatic individuals. Industrial hygiene measures and close supervision of workmen are preferable to neurophysiological screening measurements in preventing clinical toxicity."

ACRYLONITRILE

Acrylonitrile, or vinyl cyanide, used in large quantities in the manufacture of synthetic rubber (based on copolymerization with butadiene, resulting in a product known for its resistance to oils and greases), is a colorless, volatile liquid with an ethereal odor, is partly soluble in water, with a boiling point of 77.3° C. This compound, long known for its toxicity, may gain entry into the body by ingestion, inhalation or through the skin.

Acrylonitrile is one of the chemicals belonging to the common group called the cyanides and cyanogen compounds; the best known is hydrogen cyanide (HCN). The cyanides are rapidly absorbed and can prove quickly fatal, whether through the gastrointestinal tract, the lungs or the skin. Cyanides are carried in solution in plasma with little or no direct combination with hemoglobin. However, if methemoglobin is present, cyanide forms a complex with it, cyanmethemoglobin, which is reconverted to hemoglobin at a slow rate with a gradual release of cyanogen. The cyanides undergo relatively rapid decomposition or modification in the body, part combining with sulfur to form thiocyanate, a part of the detoxification mechanism, and probably some cyanide is excreted as such through the lungs and saliva and in the urine.

The chief mode of action is the inhibition of the cellular respiration via the cyanide ion, and death may result due to paralysis of the respiratory center. Symptoms following acute pulmonary absorp-

tion have been reported as headache, fullness in the chest, irritation of all mucous membranes, including the eyes, nose and throat, a feeling of apprehension and nervous irritability. Workmen have complained of intolerable itching of the skin without evidence of dermatitis. Wilson *et al.*[53] reported observations on exposures varying between 16 and 100 ppm for 20–45 minutes with the above symptoms. There may be nosebleeds, nausea and vomiting and, in extreme cases, shortness of breath, cyanosis resulting in collapse and asphyxia. Evidence of kidney and liver irritation has been reported, which cleared rapidly when exposure stopped. Workmen exposed to acrylonitrile in cleaning operations of polymerizers were checked by Wilson and associates to determine blood thiocyanate levels in relation to the nitrile exposure. Atmospheric concentration of the acrylonitrile ranged from 16 to 109 ppm. They found that the thiocyanate level returned to normal 2½ hours after exposure at levels of 22 ppm for 30 minutes. When exposure reached 50 ppm for 30 minutes, blood thiocyanate levels did not return to normal after 12 hours' removal from exposure. These findings were correlated with animal experimentation, revealing that only one-third of the lethal dose of acrylonitrile is destroyed in the following 24-hour period after exposure.

Overexposure to acrylonitrile should be treated as an emergency, with removal from exposure and immediate washing of contaminated areas with copious amounts of soap and water. Oxygen should be administered as well as amyl-nitrite by inhalation every 5 minutes. Sodium nitrite may be given intravenously in 3% concentration (10 ml during a period of 2 minutes), followed by 50 ml of 25% sodium thiosulfate intravenously. These injections may be repeated at hourly intervals if necessary. Artificial respiration may be necessary. *Other diagnostic tests are cyanmethemoglobin levels in blood, cyanide levels in blood and the observation of increased excretion of thiocyanate in urine.

Hygienic measures necessitate adequate exhaust ventilation to prevent atmospheric concentrations above 20 ppm (the present TLV); this is a basic requirement. Avoidance of skin contact also is necessary, along with scrupulous cleanliness; eating and smoking in the work areas are forbidden.

CARBON DISULFIDE

Carbon disulfide is used extensively to manufacture a variety of products noted in the increasing production of this substance in the United States, with 200,000,000 kg produced in 1948 to well over 450,000,000 kg in 1970. In the rubber industry, it is used as a solvent for sulfur, as a solvent for rubber cement and

*Cyanide prevents oxygen exchange between the tissues and the blood. The symptoms of poisoning are dizziness, headache, a feeling of oppression in the chest, dryness and irritation of the throat, palpitation of the heart, difficult breathing and sometimes vomiting, followed by loss of consciousness and convulsions. A lethal dose produces rapid death and, therefore, can be counteracted only by immediate first aid.

A most effective single first aid measure for this type of internal asphyxia is the supplying of oxygen or oxygen-carbon dioxide mixture for breathing. The person administering first aid should also:

1. Send for a physician.
2. Remove the victim to fresh air *without exposing the rescuer to poisoning.*
3. Remove clothing which may contain hydrogen cyanide and wrap the patient in a blanket.
4. Apply artificial respiration if breathing has stopped.
5. Give oxygen by inhalation.
6. Permit inhalation of the contents of an ampule of amyl nitrate; repeat after 15 minutes.
7. If the person has swallowed a cyanide compound and is conscious, induce vomiting by giving him a large quantity of warm water containing an emetic, or better, stimulate vomiting by forcing finger(s) into back of throat. *(Never try to induce vomiting in an unconscious person!)*

First aid supplies, as specified by the physician in charge, should be available in all plants where cyanides are used.

also in the vulcanizing process. Perhaps its greatest use is in the preparation of rayon viscose fibers during spinning and washing of viscose. It has been used as an insecticide and in the chemical industries as a general solvent for such substances as phosphorus, fats and oils, resins and waxes. Other uses include manufacture of lacquers and paints.

Absorption, Metabolism and Excretion

Carbon disulfide is absorbed chiefly through the lungs, entering the bloodstream and being distributed throughout the body. It also can be absorbed through the skin and rapidly absorbed from the gastrointestinal tract if swallowed. Excretion through the lungs and urine is small, with about 92% retained in the tissues and up to 70% metabolized and excreted in the urine mainly as inorganic sulfates and other sulfur compounds; some is eliminated unchanged in the expired air (about 8%), about ½% in the urine and none in the feces.[42] Studies reported by Teisinger[47] revealed that members from his Institute (1956) found that CS_2 forms dithiocarbamic acid and thiazolidone substances, which was corroborated by Scheel[45] in the spectrographic examination of the blood of exposed workers.

Toxic Responses

Toxic responses in humans may be divided into acute effects and chronic effects. The chief effect at very high concentrations (ranging from 200 to 500 ppm) is narcosis, which may result in death because of respiratory failure. Exposures to lower concentrations (under 100 ppm) may have little or no evident effect, but some workers may experience headache, dizziness and some respiratory irritation and gastrointestinal disturbances, such as nausea, vomiting and discomfort. Conjunctivitis and keratitis have been reported. Carbon disulfide has a distinct irritating or vesicant action on skin.

The chronic effects of long-term exposure are of concern in carbon disulfide processes; it is regarded as a very toxic substance. The subtle effects of chronic exposure now are becoming evident.

The now classic study by the Pennsylvania Department of Labor and Industry[19] revealed that poisoning was present even when exposure was low. Chronic carbon disulfide intoxication can involve all parts of the central and peripheral nervous systems. There may be damage to the cranial nerves, a decrease of corneal and pupillary reflexes; a Parkinson-like syndrome can occur, characterized by speech disturbance, muscle spasticity, tremors, loss of memory and even severe mental depression, including marked psychic symptoms. These patients can become permanently disabled. Involvement of the peripheral nerves often is similar to a polyneuritic syndrome. The chief symptoms are loss of strength in the muscles of the upper and lower extremities, unsteady gait and grip weakness and dysphagia; changes of sensation in the extremities may be noted. Severe ocular disturbances have been observed; there may be marked gastrointestinal changes, such as chronic gastritis and even achlorhydria; liver damage has been reported, and there have been reports of individuals exhibiting symptoms similar to those of cerebral arteriosclerosis of a presenile type and found at a fairly early age—from 40 to 55 years—after many years of exposure. Syndromes of cerebral, renal and myocardial sclerosis have been observed.

Brieger[7] reported that actual knowledge of the developmental mechanism of the carbon disulfide atherosclerosis is fragmentary. The blood concentration of lipids, the inhibition of the lipolytic activity of the arterial wall and the cholesterol content of the arterial wall resemble the findings in experimental atherosclerosis.

Teisinger[47] recorded new advances in

the toxicology of carbon disulfide and stated that there is no doubt that the whole organism is affected by chronic poisoning. In addition, he stated that other unfavorable effects have been observed more frequently, even in workers exposed to concentrations lower than the maximum allowable.

Teisinger referred to the work of Goto *et al.*,[18] who showed frequent occurrence of microscopic aneurysms in the retina of exposed humans as revealed by fluorescent angiography, finding such changes in 29% of Japanese workers exposed to carbon disulfide. Hotta and Savic[22] believe that the pathogenesis of these changes may be the same as in cases of diabetes mellitus and that carbon disulfide has a slight diabetogenic effect. Furthermore, they found that carbon disulfide has a toxic effect on the optic nerve, so that a considerable portion of the workers examined had a decreased adaptability to darkness and greater difficulty in discerning colors.

In conclusion, Teisinger stressed that "carbon disulfide, owing to its toxicity, still deserves the attention of research workers; even if the chronic classic poisonings subside, it remains a very dangerous substance."

In an epidemiologic study of viscose rayon workers, Mancuso and Locke[33] reported carbon disulfide as a cause of suicide. Their study was based on the personnel records from a single viscose rayon plant in 1949 of all new employees for each year from 1938 through 1949, in which all essential characteristics were available: name, Social Security number, birth date, sex, chronologic assignment by department, occupation and dates of employment and job changes, height, weight, marital status and reasons for termination. Processing by Social Security number was accomplished through the Social Security Administration using the method developed by Mancuso.[31]

The medical literature has stressed the occupational risk of exposure to carbon disulfide and the development of mental illness among viscose rayon workers. Mancuso and Locke's epidemiologic study has carried this association one step further from mental illness to the ultimate step of suicide as an additional occupational risk. In their longitudinal study of viscose rayon workers employed during 1939–1948 and observed to 1968, a higher rate of suicides was found among 4899 white males and females ages 25–64 in certain departments and occupations. They postulated that in addition to the acute and subacute toxic effects of carbon disulfide, biochemical and pathologic changes initiated by carbon disulfide during occupational exposure may persist over a long span of time and that delayed biologic effects of abnormal mental and social behavior may occur in subsequent years in response to further environmental and social stresses.

In recent years and at present, coronary heart disease (CHD) apparently associated with long-term exposure to carbon disulfide has been the main concern of occupational physicians in both Europe and the United States. Hernberg *et al.*[21] described excess mortality from coronary heart disease in viscose rayon workers exposed to carbon disulfide. In their summary, they state, "In 1967, two cohorts of 343 men each were formed and matched with respect to age, birth district, and similarity of work. One cohort was comprised of viscose rayon workers with at least five years' exposure to carbon disulfide during any period between 1942 and 1967, and the other of workers from a paper mill with no such exposure. On examination in 1967, it could be confirmed that all the relevant coronary risk factors had been controlled except for blood pressure, which was slightly higher in the exposed group. However, this finding was interpreted as a result of exposure rather than an independent risk

factor. A 5.5 year follow-up showed that 16 men had died from CHD in the exposed cohort against three in the control cohort. Other causes of death were evenly distributed. The difference between the risk ratios was statistically significant. Similar results were obtained on comparison of the coronary mortality of the exposed cohort with the national death statistics, although the difference was less. Discriminant function analysis enabled accurate prediction of the deaths or survivals in 88.7% of the exposed group when not only exposure, but also age, smoking habits, diastolic blood pressure, and the serum cholesterol level were taken into account. The risk of death rose with increasing exposure. The results agree with earlier mortality studies, and strongly support the hypothesis of a causal relation between carbon disulfide exposure and CHD."

It was Hernberg and co-workers' opinion that "sufficient evidence has been acquired for significant improvements to be demanded in working conditions. An energetic program was immediately started in the factory when the data became known; this program includes systematic improvement of the ventilation, continuous monitoring of the concentrations of CS_2 in the air, transfer of workers with symptoms and signs of CHD to departments without exposure, more rigid criteria for the pre-employment examination, which will include an exercise electrocardiogram, and restriction of the lifetime exposure to ten years or less.

"On the basis of these data, it was suggested that the Finnish TLV for CS_2 be reduced from 20 to 10 ppm. Naturally, the argument might be raised that our exposure data were too vague for such a decision as we ourselves pointed out in 1970; however, in view of the potentially serious outcome of overexposure, it is prudent to be overcautious rather than the reverse. To find better documentation for the TLV, extreme importance is now attached to establishment of the threshold for the effects of CS_2 on CHD."

Medical and Hygienic Controls

Prevention of exposure is essential; workroom concentrations must not exceed 20 ppm. Proper enclosures with adequate exhaust ventilation must be provided, since carbon disulfide is highly volatile. Regular hygienic surveys should be made in work places to ascertain concentrations and deviations from allowable limits. Periodic physical examinations of workers have been recommended and should be continued, although analytic tests to determine carbon disulfide levels in blood, urine and expired air may be made, as well as liver function tests and electrocardiograms, all of which are desirable but not as a basis for monitoring a work place. Temporary preventive measures are the use of air-supplied respirators and suitable protective equipment for the eyes and skin, e.g., rubber gloves, aprons, etc. If proper engineering controls are instituted and maintained, most persons can work safely with CS_2.

VINYL ACETATE

Deece and Joyner[12] reported the effects of chronic exposures to vinyl acetate in a chemical plant that had produced the substance for 22 years. Twenty-one of a total of 26 employees with long periods of employment were assigned to the vinyl acetate area. The mean age of the 21 workers studied was 45.3 years, with a mean length of service of 15.2 years. (A matching control group was selected that had no history of exposure to the vinyl acetate.)

Their findings revealed exposures to vinyl acetate ranging from 5 to 10 ppm, with intermittent brief exposures as high as 50 ppm and occasionally as high as 300 ppm. Studies of medical records and

physical examinations failed to reveal any chronic effects from long-term exposures to vinyl acetate at the time-weighted levels of from 5 to 10 ppm. No eye or upper respiratory irritation was noted below 10 ppm but were definite at 21 ppm. The present threshold limit value for vinyl acetate is 10 ppm.

TOXICOLOGY OF VINYL CHLORIDE

The earliest studies on vinyl chloride were limited to *acute exposures*. These observations led to its consideration as a surgical anesthetic. About 20–25 years ago, during the earlier work exposures, the chief concern was to keep workroom atmospheric concentrations below the explosive limit (3½% or about 30,000 ppm); men commonly worked at exposure levels of 3000–4000 ppm (near the narcosis level), and it was not at all unusual to have men leave the work place for relief and fresh air outside. Generally, these studies showed vinyl chloride to be low in acute toxicity, to be anesthetic in action and to have little capacity to cause liver injury from exposures of a few hours. Mastromateo *et al.*[35] and Lester *et al.*[27] reported on acute exposures of animals and humans. They reported very little effect until exposure concentrations approached 10,000 ppm, when humans reported dizziness after 5 minutes' exposure.

Torkelson *et al.*[48] conducted animal studies to determine chronic toxicity to assess the hazards to humans. Vinyl chloride was found to have a slight capacity to cause liver and kidney injury on repeated exposures. Male and female rats showed micropathologic changes after repeated 7-hour exposures at 500 ppm for 4.5 months. Repeated 7-hour exposures at 200 ppm for 6 months resulted in micropathologic changes in the livers of rabbits and statistically significant increases in the average weight of the livers of male and female rats but no detectable changes in dogs and guinea pigs. Repeated 7-hour exposures at 100 ppm resulted in slight increases in the average weight of rat livers; the other species were not affected. All species studied tolerated repeated daily 7-hour exposures to 50 ppm for 6 months with no detectable injury.

Repeated daily 1-hour exposures at 200 and 100 ppm of vinyl chloride were without effect; longer exposures caused a slight increase in liver weight.

The standard for evaluating regular daily 7–8-hour exposures may be defined as the concentration below which practically all analytic results must fall. The value of 100 ppm was suggested as the standard for vinyl chloride, with a time-weighted average for all exposures not to exceed 50 ppm (Torkelson, *et al.*[48]).

Lester *et al.*[27] differed with the conclusions of Torkelson *et al.*[48] and recommended 500 ppm as a time-weighted average exposure.

Because of these conflicting reports, the TLV Committee of the ACGIH[2] in 1963 chose to change their TLV from 500 ppm as a maximal time-weighted average for industrial exposure to 500 ppm as a ceiling value.

Harris and Adam[20] studied workers engaged in the polymerization of vinyl chloride, reporting 2 cases in which autoclave cleaners in the vinyl chloride polymerization process were scraping the walls of the autoclave to remove the polyvinyl chloride with considerable hand/skin contact. Acroosteolysis was reported to have occurred in 2 workers.

Of the 588 polyvinyl chloride workers in this plant, including 150 autoclave cleaners, 2 cases were identified based on x-rays of the hands of these workers. The terminal phalanges of the hands, the patella and the phalanges of the feet were involved. Two other workers, also autoclave cleaners, demonstrated early

changes accompanied by Raynaud's phenomenon.

Wilson *et al*[52] studied 31 cases of occupational acroosteolysis of the hands of workers engaged in vinyl chloride polymerization processes, and most of these had worked as cleaners of vessel walls and other equipment in the polymer process. The acroosteolysis was localized to the distal phalanges of hands and frequently was associated with Raynaud symptoms. They reported the disorder to have resulted from a combination of physical insult, chemical insult and personal idiosyncrasy and were unable to name specific causes. Prevalence was reported to be less than 3% among employees performing similar work, and no cases were found in workmen processing the polymer or manufacturing commercial resins. More than 100 workers handled the finished resin; those who processed it into plastic products did not demonstrate findings of acroosteolysis.

In 1970 and 1971, the Institute of Environmental and Industrial Health at The University of Michigan[13] conducted a comprehensive study of acroosteolysis in workers producing and compounding vinyl and polyvinyl chloride. The epidemiologic population represented more than 5000 workers in 32 plants. Thirty-one cases were discovered, of which 25 had a definite diagnosis; there were 16 suspicious diagnoses of acroosteolysis clearly associated with hand cleaning of the polymerizers.

Dodson and co-workers[14] determined that work practices rather than any specific agent or combination of agents appeared to relate to the occurrence of the disease. These investigators thought the disease to be of systemic rather than localized nature, but were unable to define the etiologic agent or portal of entry, suggesting some idiosyncratic "sensitization of susceptibility." An industrial hygiene survey of this epidemiologic investigation[9] revealed vinyl chloride concentrations in the reactor before ventilating to be about 3000 ppm. After aeration of the containers, the vinyl chloride concentra-

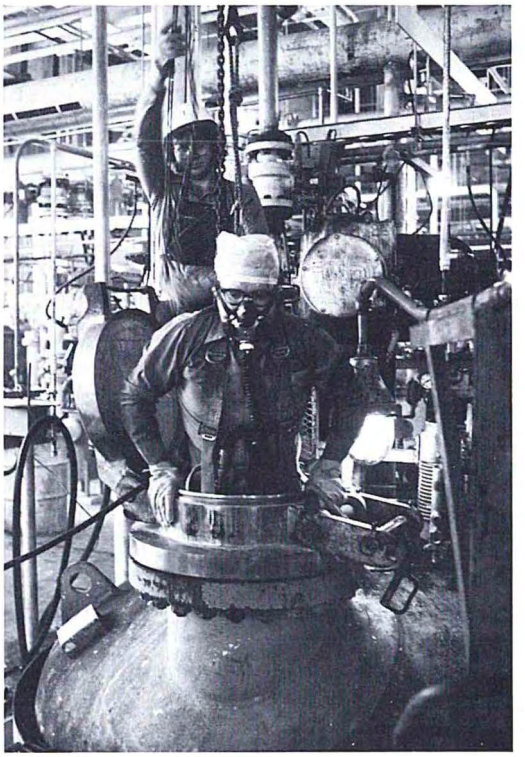


Fig. 31–2.—A worker entering a polyvinyl chloride reactor vessel to clean out caked polymer adhering to the inner surfaces. During the polymerization reaction, sludge from the slurry has a tendency to form a crust on the impeller mechanism as well as the tank inner surfaces. The caked polymer is periodically hand-chipped by workers inside the tank, and this is the operation that subjected workers to the highest concentrations of vinyl chloride. Current practice requires that flexible ducts be used for purging with clean air before the worker enters. In addition, workers in this operation must be provided with positive-pressure air-supplied respirators, preferably the hood type. Demand-type respirators have been used, but may not offer the same protection as the continuous-flow type of hood respirator. (Courtesy of Maurice N. Johnson, M.D., B. F. Goodrich Company, Akron, Ohio. Photographer—H. Groskinski.)

Fig. 31–3.—The solid, caked polymer must be removed by chisels, hammers and handpicks. Neither workers nor management may be aware of the hazard involved when a spark is generated by steel on steel. It is not uncommon to open a pocket of the cake lining the vessel. The pocket may contain liquid vinyl chloride monomer. It is very possible that the lower explosive limit for vinyl chloride monomer (33,000 ppm) can be reached during the chipping with steel on steel. Reactor vessels have exploded, leaving nothing but a crater in the ground where the plant once stood. Reactor chipping or cleaning tools should be of the nonsparking type. To minimize worker entry, some companies use high-pressure water guns to remove the caked polymer. These water guns may operate from 9000 to 13,000 pounds of pressure per square inch. This in itself may produce a serious safety hazard. Some attempts in the United States to remove the caked slurry have utilized closed solvent cleaning systems in which solvents such as tetrahydrofuran are used. To date, such solvent cleaning systems have been relatively unsuccessful. Recently completed production systems using 30,000-gallon reactor vessels have been utilizing automatic high-pressure water cleaning guns and solvent systems to minimize or eliminate the need for worker entry into reactor vessels. Older reactor vessels, which contain cooling vanes of heat exchangers, complicate the cleaning process and high-pressure water guns and solvent systems cannot be used in these tanks. (Courtesy of Maurice N. Johnson, M.D., B. F. Goodrich Company, Akron, Ohio. Photographer—H. Groskinski.)

tion inside the reactors during scraping was found to be under 100 ppm and usually around 50 ppm. It was found that scraping released some unpolymerized vinyl chloride so that *levels of 600–1000 ppm* were *found close* to the *hands* during these operations.° Other possible constituents of the scrapings of the reactor vessels were thought to be polymerized resins, unreacted catalysts, additives and, of course, the polymerized vinyl chloride. No serious disability had been reported in any of the above-mentioned cases but a few men had been partially disabled because of hand soreness, with some restriction in manual activity. With proper protective equipment and careful hygienic measures, all these cases are preventable. Vinyl chloride, although thought to be relatively nontoxic and even innocuous, typified by the 1973 threshold limit value of 500 ppm and known mainly as a narcotizing substance when inhaled in high concentrations, recently has caused alarm in occupational health practitioners. Conjunctivitis, corneal burns and dermatitis have been seen, and high concentrations and prolonged exposures cause headaches, dizziness and some irritation of the upper respiratory tract. With extreme exposures, narcosis may occur, and it has been apparent from the acroosteolysis reports mentioned that preventive measures were undertaken lightly.

°Our italics, implying the potentially high worker respiratory inhalation.

Because of the report of acroosteolysis in humans, Viola[50] attempted to produce the disease in animals. He exposed rats 4 hours per day, 5 days per week to 30,000 ppm (3%) vinyl chloride vapor. In his first report on the results of 12 months' exposure, he described metaplastic changes in the bones, which he considered similar to human acroosteolysis. He made no mention of having observed cancer in these animals until the Tenth International Cancer Congress in May, 1970. In the abstracts of this meeting, and subsequently in May, 1971, Viola *et al.*[51] reported tumors of the skin, lungs and bones occurring first after 10 months' exposure, appearing to be the earliest and only publication in which carcinogenic activity had been ascribed to vinyl chloride.

Observing workers of a PVC-producing plant (Germany), Marsteller *et al.*[34] found esophageal varicosities, splenomegaly and nonspecific liver damage. These observations, together with the above-mentioned reports on "subclinical liver damage" initiated an investigation of the pathology of these changes.

Radiologic, biochemical and enzymatic tests, liver scanning, laparoscopy and liver needle biopsy were used in 20 workers (ages 30–56 years) of a PVC-producing plant; length of work exposure was 1½–21 years.

There was a total of 120 workers involved in the production of PVC; 45 of them had been examined at the Department of Dermatology, some because of manifest skin changes, but many were given a preventive examination. In most of these 45 workers, the examination resulted in a clinical and/or biochemical suspicion of liver damage.

Until May, 1973, it was possible to perform laparoscopy in 20 of these 45 workers suspected of having liver damage. The prevalence of liver damage in workers exposed in the PVC-producing plants could not be evaluated on this basis only.

In 13 of 20 cases, the liver was found to be enlarged. Two patients had pain on abdominal palpation in the right upper quadrant; hyperlipidemia had been diagnosed in 1967 (after 6 years of exposure) in another patient, together with "liver damage."

There was a history of jaundice in only 1 patient in 1955, before the onset of exposure; in 1968, a diagnosis of chronic liver dysfunction had been established. There was no history of alcoholism. Splenomegaly was found in 7 of 20 cases (range 1.5–5 cm). Bilirubin (total) exceeded the upper normal limit of 1 mg/100 ml in 3 cases (range 1.1–1.7 mg/100 ml). The bromsulphalein test was abnormal (5% after 45 minutes in 19 cases [range 6.1–21.5]). SGOT exceeded the upper normal limit of 12 mU/ml in 17 cases; in 14 cases, SGPT was elevated (range 15–30). An increased level of alkaline phosphatase was found in 2 patients (48 mU/ml). Hypothrombocythemia (less than $150 \cdot \times 10^3/mm^3$) was found in 19 of 20 patients, at least initially; in 12, the initial level was lower than $100 \times 10^3/mm^3$. Acroosteolysis was present in 4 patients. BSR, CBC, glycemia, urinalysis, LDH, cholinesterase, acid phosphatase, iron and copper serum levels, proteinemia and electrophoretic separation of serum proteins, cholesterol, beta-lipoproteins, triglycerides and plasmatic coagulation factors were not found to be abnormal.

In 3 cases, varicose esophageal veins (and in 2 cases also of the gastric fundus) were visualized.

Laparoscopy showed the following changes: capsular fibrosis in 15 cases, reorganization of the liver architecture in 8 cases, splenomegaly in 7 cases, portal hypertension in 2 cases and hepatomegaly in 4 cases.

The histologic changes encompassed the following: centrilobular collagen

transformation of the walls of sinusoids in 5 cases, focal activation of Kupffer cells in 9 cases, fatty infiltration (focal) in 14 cases, increased collagen deposition in the portal spaces and portal fibrosis, septal fibrosis or intralobular fibrosis in 17 cases, isolated cellular necrosis in a few cases and a low degree of cholestasis in a few instances.

The biochemical changes and the histologic abnormalities were, in most cases, of a low or moderate degree. The similar findings in many cases, all exposed to the same toxic environment, gave more weight to the above-mentioned observations. In workers at PVC-producing plants, thrombocytopenia, chronic toxic liver damage, with splenomegaly and signs of portal hypertension in some of the cases, are more frequent than acroosteolysis.

In January, 1974, a manufacturer of polyvinyl chloride and copolymers notified its employees, the National Institute for Occupational Safety and Health, the Kentucky State Department of Labor and the public that 3 workers had died of angiosarcoma of the liver. These cases had a common denominator—employment in the manufacture of polyvinyl chloride resins. This report by Creech and Johnson[11] has resulted in an enlarged scope of knowledge and eventually uncovered a total of 14 known angiosarcomas connected with vinyl chloride exposures, all within a few months, from other work places.

Two case reports were described by Creech and Johnson. One of these was reported as: Patient One, a 36-year-old white male, was hospitalized January 5, 1970, because of tarry stools. Occupational History: The patient had been employed from November, 1955, until his illness, except for two layoffs of 9 months in 1958 and 6 months in 1959, as a chemical helper and operator in the Louisville plant of a chemical company in the manufacture of polyvinyl chloride resins. Present Illness: At the time of admission, the patient had no complaints except passage of tarry stools. Past history was negative except for an operation for hemorrhoids 4 years earlier. Physical examination showed pallor and black stool on rectal examination. Liver and spleen were not palpable. Although an upper GI series was interpreted as normal, a tentative diagnosis of bleeding duodenal ulcer was made.

On diet and medication, the patient had no recurrence of overt bleeding until May 1, 1970, 4 months later, when he was readmitted for tarry stools. Again, he was found to have marked pallor and tarry stool on rectal examination. At this time, the liver was demonstrably enlarged and the spleen was palpable. Blood chemistry studies ("SMA/12") were not significantly abnormal; total bilirubin, alkaline phosphatase, LDH and SGOT were only slightly elevated. GI series showed only anterior displacement of the stomach, but barium swallow suggested esophageal varices. Intravenous pyelogram was normal; barium enema was normal except for displacement of the splenic flexure by an enlarged spleen. Liver scan on May 4, 1970 was interpreted as being compatible with a large lesion in the left lobe of the liver, extending into the right lobe.

The report of pathologic findings was "liver, biopsy of, angiosarcoma (malignant hemangioendothelioma)." The patient succumbed to the liver tumor on September 27, 1971, 14 months postoperatively, despite cobalt therapy and interarterial infusions of 5 FU.

The authors refer to Viola *et al.*,[51] who had reported in 1971 the oncogenic properties based on experimental use of monomer vinyl chloride. Viola and co-workers performed experiments with pure vinyl chloride on 3-month-old male (albino) rats exposed to vinyl chloride

vapors for 4 hours a day, 5 days a week for 12 months. The animals were kept in airtight cages in which a constant flow of air containing 3% (equal to 30,000 ppm) of vinyl chloride was passed through. They described the lesions found in the experimental animals and demonstrated that almost all of the animals developed tumors of the skin and lungs, skin tumors most frequently accounting for 65–70%.

Maltoni[29] presented his results of unpublished experiments with vinyl chloride in February, 1974, at a U. S. Department of Labor hearing in Washington, D. C. He has observed liver cancer in rats exposed 4 hours a day, 5 days a week to 250 ppm of vinyl chloride for up to 12 months. An investigation under the auspices of the Manufacturing Chemists' Association[23] reported the development of angiosarcoma in mice after 7 months of exposure to 50 ppm 7 hours a day, 5 days a week.

Mancuso[32] testified that although the focus now is on the experimental cancer-causing effect, it is very important to note that other pathologic changes occur in the brain (degeneration of the nerve cells—cerebellum), severe chronic hepatitis (as well as cirrhosis), interstitial pneumonia and damage to the kidneys. Further, the skin tumors frequently developed near the ear and submaxillary or the same areas as the salivary glands. It was postulated by the investigators that vinyl chloride may enter the salivary gland system. If this is confirmed subsequently, it will raise the question whether tumors of the parotid gland can also occur (as has been demonstrated in the rubber industry). (At this writing there have been 31 cases of angiosarcoma of the liver reported associated with vinyl chloride exposures.) Investigators observing and conducting epidemiologic studies of vinyl chloride monomer workers must be aware of other unusual or unique pathologic findings, such as laryngopharyngeal involvement. These cases have been noted in plants in different locations in the United States and as yet have not been officially reported; however, they reinforce the need to correlate pathologic changes in other organ systems with chronic work exposure.

Analytic Methods

Four methods are available for environmental monitoring of air for the presence of vinyl chloride: combustion-conductivity, gas chromatography, infrared spectrophotometry and flame ionization spectrophotometry. Gas chromatography is very specific but requires about 10 minutes per sample. Flame ionization detectors have no specificity—responding to all carbon-carbon or carbon-hydrogen bonds—but are portable and the measurement is instantaneous. Infrared analyzers are very specific, respond quickly and are portable. All these techniques have adequate sensitivity, detecting concentrations of 1 ppm or less.

Worker monitoring is achieved through the use of absorption tubes filled with activated carbon, and the absorbed chlorinated hydrocarbons are determined by gas chromatography.

Most environmental monitoring has been with combustion-conductivity analyzers. These analyzers are used for continuous monitoring with excellent results. NIOSH recommends the gas chromatographic method with known sensitivity of 1 ppm.

Medical and Hygienic Controls

The National Institute for Occupational Safety and Health[39] published detailed medical and hygienic recommendations for the manufacture and processing of polymer from vinyl chloride on March 11, 1974:

"Consultants from industry who worked with NIOSH proposed that the

recommended standard contain the concept of an allowable 'working level' for vinyl chloride gas in the atmosphere, which they identified as a time-weighted average of 50 ppm. They recommended that where workers were exposed to concentrations in excess of this level they should wear air-supplied respirators. This concept of an allowable 'working level' might seem justifiable in that Professor Maltoni[29] found no liver tumors at 50 ppm, but there is the possibility that tumors might have been produced if a larger number of animals had been exposed at that concentration. Based on theoretical considerations, there is probably no threshold for carcinogenesis although it is possible that with very low concentrations, the latency period might be extended beyond the life expectancy. In view of these considerations and NIOSH's inability to describe a safe exposure level as required in section 20(a)(3) of the Occupational Safety and Health Act, the concept of a threshold limit for vinyl chloride gas in the atmosphere was rejected.

"Consequently, the recommendations are such that where any employee is exposed to measurable concentrations of vinyl chloride, as determined by the recommended sampling and analytical method, he shall wear an air-supplied respirator. This recommendation is based on some preliminary information that the standard chemical cartridge respirators are inefficient in protecting against vinyl chloride. NIOSH is implementing a study to evaluate the degree of protection afforded by different types of respirators using vinyl chloride as the test gas. As information becomes available, it will be forwarded to OSHA as recommendations for alternative respirator usage. The employer is also required to develop a Control Plan to reduce airborne concentrations of vinyl chloride to levels not detectable by the recommended method."

Similar recommendations have been made for other toxic substances by the ACGIH: "Recommendations for worker exposure by all routes should be reduced to a minimum in the light of the warning of the potency of the substances to induce tumors in animals. 'Reduced to a minimum' means extraordinary care shall be taken both in manufacture and in handling so that worker exposure by all routes is kept below the limit of sensitivity of the analytic method of determining the exposure concentration."[3]

NIOSH Recommendations for Medical Surveillance

The following recommendations are directed primarily at medical screening to detect liver disease and/or hepatic tumor. They should be considered in the context of routine health screening for any general employee health problems, including nonhepatic health conditions potentially related to vinyl chloride monomer exposure. Routine health screening should include at the time of initial employment the recording of past medical history and the performance both of a general physical examination and certain basic laboratory procedures (e.g., complete blood count, urinalysis, chest x-ray); provisions should also be made for routine periodic health follow-up examinations.

Employees covered by the following specific recommendations shall encompass all persons engaged in vinyl chloride monomer production and polymerization, including personnel peripherally involved, such as in clerical and management assignments. The recommendations shall be applied both as a pre-employment requirement and as part of a periodic health follow-up. Screening priority should be given to current employees with prolonged and close potential exposure to vinyl chloride monomer, whether in present or past work settings.

1. At the time of initial employment, or on institution of screening, a physical examination shall be performed with specific attention to detecting enlargement of liver or spleen by abdominal palpation.

2. At the time of initial employment, or on institution of screening and annually thereafter, a medical history check list shall be completed by the employee. This list shall include questions concerning alcohol intake; past history of hepatitis; past exposure to potential hepatotoxic agents, including drugs and chemicals; past history of blood transfusions; and past history of hospitalizations. The completed medical check list shall be reviewed by a physician and should be acted on as medically indicated for each individual employee.

3. At the time of initial employment, or on institution of screening, a serum specimen shall be obtained for screening with respect to the following 5 biochemical determinations of liver function: total bilirubin, alkaline phosphatase, serum glutamic oxaloacetic transaminase (SGOT), serum glutamic pyruvic transaminase (SGPT) and gamma glutamyl transpeptidase (GGTP, if test is available).

Additional tests that may optionally be considered for use in screening include lactic dehydrogenase (LDH), serum protein determinations, serum protein electrophoresis and platelet count. Laboratory analysis shall be performed in laboratories accredited by the College of American Pathologists or licensed in accordance with the provisions of the Clinical Laboratories Improvement Act of 1967.

4. If the results of laboratory screening are normal, screening shall be repeated on an annual basis. If the person being screened has been employed directly in vinyl chloride monomer production or polymerization for 10 years or longer, screening shall be repeated every 6 months.

5. If one or more liver function tests are abnormal, serum testing shall be repeated as soon as possible, preferably within 2–4 weeks. If no abnormalities are present on rescreening, testing should be repeated in 3 months.

6. If abnormalities persist on rescreening, the employee shall be removed from contact with vinyl chloride monomer operations and an individualized medical work-up shall be instituted. Suggested as initial steps in the medical work-up are a complete physical examination and various special procedures, such as hepatitis B antigen determination and liver scanning.

If liver function abnormalities are determined to be unrelated to liver disease (e.g., elevated alkaline phosphatase in a young, physically active man or elevated bilirubin in Gilbert's syndrome) or to be transient (e.g., due to recent hepatitis or recent alcohol intake), the employee may be permitted to return to vinyl chloride-related employment, subject to individual medical evaluation.

7. In view of the preliminary results of animal toxicology studies, it is recommended that no woman who is pregnant or who expects to become pregnant should be employed directly in vinyl chloride monomer operations. [See chapter 30, Lead, by Hernberg, on women of reproductive age who are exposed to toxic threshold limits.]

In summary, these new regulations state that until exposures to vinyl chloride are reduced below detectable levels, employees entering any regulated area shall be provided with and required to wear and use a full-face supplied-air respirator with a continuous flow or a pressure-demand type. In addition, employees are to be provided with and required to wear clean full-body protective clothing and gloves prior to entering the regulated area.

At the Second International Symposium on Cancer Detection and Preven-

tion, Maltoni[30] concluded his presentation on Occupational Carcinogenesis by stating, "We may diagnose some tumors quite early, but on the basis of 15 years' experience with periodic checks of workers exposed to high risk, I doubt that periodic medical examination has a real bearing in saving people with occupational cancer although detected early, or in prolonging their life span. Thus, my position is in sharp contrast with those who claim to 'protect' (!) workers exposed to carcinogenic risk with medical examinations. I do believe that the potentialities of medical examinations should be evaluated at an international level. In conclusion, I would like to emphasize the need for a close collaboration among scientists, public health services, workers' unions and industries, to evaluate the risks and to devise preventive measures for avoiding or minimizing occupational tumors."

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Butadiene

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THE PRODUCTION AND UTILIZATION of butadiene emerged as a necessity to make synthetic rubber during World War II because the sources of natural latex no longer were available to the United States. In 1960, synthetic rubber production accounted for 67% of rubber produced (1,436,000 long tons) and 71% in 1969 (2,250,000 long tons).[4] Butadiene is only partly involved, since it usually is polymerized with other monomers of the butyl series, acrylonitrile, silicones, etc. Approximately one-third of a million workers are employed in the manufacture of rubber products, yet only a few intoxications have been reported among butadiene workers, organic chemical synthesizers, rocket fuel handlers and makers and rubber makers who work with butadiene.[5] Human exposures may elicit confusing clinical features because workers are exposed to other monomers used with butadiene. The accrued medical experience in humans and animals attests to its relatively benign toxicity even at excessive concentrations. The dominant effect is one of narcosis without cumulation.

ABSORPTION, METABOLISM AND EXCRETION

Human experience and animal data readily attest to absorption of butadiene gas by inhalation. Few data are available for other portals of entry. Distribution is ubiquitous but by no means uniform. Fat tissues are favored. Shugaev and Yaroslavl[3] determined the LD_{50} to be 270 and 285 mg/liter in mice and rats respectively. As an example of comparative tissue concentrations to controlled exposure of rats, they presented the figures shown in Table 31-5.

TABLE 31-5.—CONTROLLED TISSUE CONCENTRATIONS OF BUTADIENE

BRAIN	LIVER	KIDNEY	SPLEEN	PERINEPHRIC FAT	HYPODERMIC FAT
50.8*	51.4	36.3	45.0	152.1	–

*Mg/100 ml.

Narcosis effects paralleled brain concentrations. Animals in deep narcosis returned to normal coordination 1 hour after removal from butadiene exposure. No cumulative effects were demonstrated.

Carpenter *et al.*[1] reported that the toxicity is not very great for man. Two humans exposed to 8000 ppm displayed no greater narcosis than when exposed to 200 ppm of toluene. At high concentrations, humans note burning of the eyes and coughing. As the exposure continues, narcosis begins and is accompanied by headache, drowsiness, fatigue and vertigo. Ultimately, loss of consciousness, respiratory paralysis and death can occur, paralleling the effects observed in rats and mice. Physical examination reveals a lethargic, somewhat ataxic person with normal vital signs. There are no specific laboratory tests.

DIAGNOSIS

Diagnosis hinges on a recognition that the individual has been exposed to butadiene and that his clinical features are compatible. Differential diagnosis includes such other intoxications as acetylene, ethanol, benzene, many hydrocarbons, halogenated hydrocarbons, antihistamines, some narcotic drugs and tranquilizing neuroplegics.

TREATMENT

Treatment involves removal of the worker from the exposure and symptomatic and supportive therapy. When he has recovered, he may return to his job provided that the hazardous concentrations have been reduced to acceptable limits.

ENVIRONMENTAL CONTROL

Air samples are analyzed by gas chromatography, although other methods are available as for other aliphatic hydrocarbons.[2] Current OSHA standards are set at 1000 ppm (2200 mg/m^3) on an 8-hour workshift, 40-hour week time-weighted average.[6] Controlling the generating source and providing adequate exhaust ventilation correct these exposures.

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Styrene

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DURING RECENT YEARS there has been an increasing use for styrene, particularly

in the plastics and rubber industries. Styrene, or vinylbenzene (with formula C_8H_8), has a molecular weight of 104.14, boils at 145.2° C (293.4° F) and has a vapor pressure of 6.45 mm Hg at 25° C (77.0° F). From the hygienic point of view, styrene might be considered a solvent, although it is used as starting material for polystyrene and as a modifier of polyester plastic. It is also used in the manufacturing of synthetic rubber.

OCCUPATIONAL EXPOSURES

Particularly spraying and hand-rolling of styrene-modified polyester plastic, as used with fiberglass reinforcement in sport boats, swimming pools and acid-resisting steeping baths and similar products of large size, may imply very high exposures to the workers by inhalation. Thus, 8-hour time-weighted average (TWA) concentrations of 235–292 ppm have been reported to occur in small shops.[14] Because of the small size of these shops, they often have difficulty in solving ventilation problems for economic and technical reasons. In addition to inhalation, considerable absorption may also take place through the skin.[10]

TOXICITY

Styrene causes irritation to the eyes and mucous membranes of the nose at about 200–400 ppm, but some adaptation seems to occur among workers exposed daily.[14] Signs indicating systemic intoxication have been reported by different authors. Drowsiness, listlessness, muscle weakness and unsteadiness[7] have been found to occur in human subjects exposed to 800 ppm. Transient nausea, vomiting, loss of appetite and general weakness also have been described in a group of plastics workers.[22] Impaired night vision, slight gastric irritation and also slight leukopenia with relative lymphocytosis were reported in Italian polystyrene workers with an assumed exposure of about 25–50 ppm.[6] A report from Czechoslovakia, describing exposure to styrene in 35 workers, indicates different neurologic disorders, mostly of a vegetative type but also lesions of peripheral nerves.[17] More or less abnormal EEGs were found in about 70% in 18 determinations from 17 of these workers. Episodic activities occurred in 39%. The injuries to the peripheral nerves were supposed to be caused by styrene penetrating the skin of the unprotected hands, whereas inhalation of styrene vapors was accused for the disturbances of the central nervous system. Total work exposure time amounted to about 2 years and concentrations were estimated not to exceed 150 ppm. The evaluation of this report is difficult and it is not referred to in the documentation of TLVs either in Czechoslovakia[8] or in the United States (ACGIH[1]) but was considered important by the Japanese Association of Industrial Health,[16] also mentioning another report about central and peripheral nervous disturbances. Also, 2 cases of disabling psychiatric symptoms have been reported as possibly caused by styrene.[3] Common to all these observations are fairly short-time exposures to high concentrations over work spans of 2–5 years at levels of 150–600 ppm, although 60 ppm is mentioned as the lower bond in one of the reports. The causal association between styrene exposure and reported symptoms and signs in these studies cannot be ruled out.

Increased simple reaction time was found, particularly in the morning, among styrene workers exposed to more than 150 ppm TWA of 8 hours, but no significant difference from the control group was observed among those exposed to less than 150 ppm TWA of 8 hours.[14] In an experimental investigation, an exposure to 200 ppm TWA of 2 hours (with 350 ppm during the last half hour) also resulted in a prolonged simple reaction time.[13] These findings may be taken

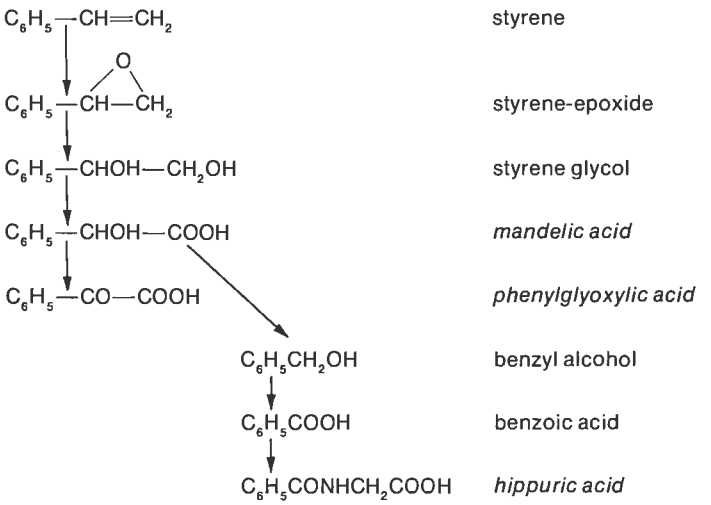
as indicative of an interaction of styrene in the synapses of the central nervous system, also with some lasting effect.

METABOLISM AND EXCRETION

The toxicity of styrene by oral administration to animals is similar to that of xylene, the LD_{50} being 4920 and 4322 mg/kg, respectively. Styrene is metabolized with formation of hippuric acid as a main metabolite in the rabbit but also styrene glycol and mandelic acid are found in the urine.[11] Experiments with subcutaneous injections of radioactive styrene in rats showed styrene to be rapidly metabolized and, to the greater extent, recovered as follows: 71% of the radioactivity appeared in the urine, 12% as respiratory CO_2 and 3% was exhaled unchanged through the lungs.[9] Based on studies in rats, a principal biotransformation as shown in Figure 31–4 has been proposed.[19]

In man, however, styrene metabolism seems to be somewhat different, at least from a quantitative point of view. Thus, human studies have revealed mandelic acid and phenylglyoxylic acid to be the major metabolites, whereas hippuric acid has not been found to increase,[4] and similar results have been obtained in several investigations.[5, 18, 23] At high exposure levels, however, some formation of hippuric acid also seems to occur in man,[15] as also was proposed early,[7] although the "hippuric acid branch" seems to be of minor importance in man. This is also indicated in inhalation studies,[4] as 60% of inspired styrene (at 22 ppm) was found to be retained in the respiratory tract. Of this amount, 85% was metabolized to mandelic acid and some 10% to phenylglyoxylic acid. These metabolites may be used for surveillance of styrene exposure, as proposed by several authors.[4, 18] Although Bardodej and Bardodejova[5] proposed 1500 ppm of mandelic acid to correspond to exposures of work-place levels of 50 ppm of styrene and 3000 ppm to correspond to 100 ppm, studies on workers by others[14] have suggested 1000 ppm of mandelic acid in urine in the afternoon to correspond to an 8-hour TWA exposure of 50 ppm styrene and 2000 ppm to correspond to 100 ppm of styrene in the air. (These values for mandelic acid refer to urine adjusted to a specific gravity of 1.024.) At exposures above 150 ppm TWA for 8 hours there seem to be uncertain relationships between concentration of

Fig. 31–4. – Metabolism of styrene.



styrene in the air and mandelic acid as well as phenylglyoxylic acid in the urine; i.e., the metabolites perhaps should be considered in the light of the possible range of exposure.[14] Similar experiences have been encountered in animal studies (rats), as mandelic acid shows a good correlation with styrene exposure up to about 100 ppm in the air during 8 hours.[15] Above this styrene concentration, however, the excretion of mandelic acid forms a plateau, whereas hippuric acid continues to increase with increasing styrene exposure. As work load increases, the absorption of styrene and (possibly the excretion of mandelic acid) will vary with performance of the worker.[2] The relationship between styrene exposure and mandelic acid excretion given above[14] refers to moderate or light work.

Methods for the routine determination of metabolites of styrene* have been described by different authors.[18, 22] For monitoring of styrene in air, sampling on activated charcoal tubes[20, 24] in connection with gas chromatography seems to be the method of choice.[14]

MEDICAL AND HYGIENIC CONTROLS

The difficulties in evaluating the risks of chronic styrene exposure may to some extent be reflected in the different TLVs proposed throughout the world, most often ranging from 50 to 100 ppm but also as low as 1.2 ppm (USSR, 1967). Although the validity of the reports referred to above may be doubted, in certain respects they imply careful precautions to be undertaken to avoid undue exposures. Central and peripheral nervous system disturbances should be kept in mind in monitoring workers exposed to styrene.

Control of work exposures demands adequate ventilation at all times. Because of the large sizes and shapes of objects fabricated in styrene-modified polyester plastic, difficulties in providing and construction of adequate exhaust systems are encountered. Some type of air-supplied helmet or face mask should be used where there is insufficient ventilation, with medical monitoring of the workers as a backup measure to detect individual worker sensitivity and as a control of the efficacy of the plant hygienic engineering methods installed.

*The discussion on mandelic acid refers to a nonspecific method of analysis; a new simple and specific method has just been published.[12]

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Isocyanates

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ISOCYANATES have been used for many years as chemical couplers to form polymerized resins. The isocyanate radical reacts readily at ambient temperatures with the hydrogen atoms of water; hydroxyl, sulfhydryl, carboxyl groups; amines and polyhydric compounds such as: alcohols, cresols and glycols. These reactions produce polyurethanes, polyamides, polyureas, biurets and allophonates. The most common isocyanate used is toluene (or toluyl) 2,4 diisocyanate, which occurs as two isomers: 2,4 and 2,6 toluene diisocyanate. Commercially, it is available in three isomeric ratios: (1) 100% 2,4; (2) 80% 2,4:20% 2,6; and (3) 65% 2,4 and 35% 2,6 diisocyanates. This group is commonly called TDI. Other isocyanates commonly used are diphenyl methane diisocyanate (MDI), naphthalene diisocyanate (NDI), hexamethylene diisocyanate (HDI), and diisocyanatodicyclohexyl urethan.[13]

The Society of Plastic Industries reported USA production of one-half billion kg of polyurethane in 1972.[12] In 1970, 57 million kg of polyurethane and diisocyanate resins were produced, excluding foam and elastomers (USA). Taken together, in the two different years this amounts to a large utilization of such materials. Reliable estimates of the number of workers or those with potential exposures are not available. These prod-

TABLE 31-6.—OCCUPATIONS IN WHICH POTENTIAL EXPOSURES TO ISOCYANATES EXIST

Abrasion-resistant rubber makers	Polyurethane sprayers
Adhesive workers	Polyurethane foam makers
Aircraft builders	Ship burners
Insulation workers	Ship welders
Lacquer workers	Spray painters
Mine tunnel coaters	Textile processors
Organic chemical synthesizers	TDI workers
Plastic foam makers	Upholstery makers
Plasticizer workers	Wire coating workers

ucts are used by small numbers of employees most often. Gafafer[4] lists some of the occupations in which potential exposures to isocyanates exist (Table 31-6).

Incidence and prevalence statistics are meager because large-scale epidemiologic studies have not been made, the surveillance of smaller numbers have been made in the past and are continuing, the manner in which the exposures occur varies and the nature of industrial hygiene control practices are inconsistent. Nonetheless, the over-all prevalence of TDI toxicity in the work force ranges from 1.5% to 5%, depending on the nature of the isocyanate used, the hygienic control employed and the criteria utilized in establishing toxicity.[11] The very property of high chemical reactivity possessed by isocyanates that renders its great industrial utility also accounts for its irritant nature and its sensitization potential.

BIOLOGIC INTERACTIONS

Isocyanates readily react with a variety of radicals, most of which are available at man's interface with his environment, i.e., his respiratory tract. These reactions occur without the addition of external energy and therefore are exothermic. The most common reaction occurs between isocyanate and water, forming unstable carbamic acid (a) which dissociates to a primary amine (b) and which, in turn, may itself react with isocyanate (c).

(a) $R\text{-}NCO + HOH \longrightarrow RNH\text{-}COOH$

(b) $RNH\text{-}COOH \longrightarrow RNH_2 + CO_2$

(c) $R\text{-}NH_2 + RNCO \longrightarrow RHN\text{-}CO\text{-}NHR$

Isocyanates also react readily with hydroxyl (-OH), amino (NH) and sulfhydryl (SH) radicals of carbohydrates, lipids, proteins and their complexes. Such reactions may modify or inactivate functions of such molecules, e.g., enzymes, or render such molecules antigenic with the isocyanate group acting as a haptene. These "host" molecules need not be freely soluble, e.g., soluble albumin or mucopolysaccharides, but may be part of insoluble cell membranes.

As anyone who has worked with isocyanates in the chemical laboratory will attest, they are most irritating to mucous membranes. This property accounts for several biologic effects: bronchitis, bronchospasm, rhinitis, pharyngitis and conjunctivitis. This irritating property of isocyanates produces "asthmatic bronchitis," a "pharmacodynamic action," not related to an allergic reaction.[1] All individuals are susceptible to the irritating property. An allergic reaction to isocyanates appears to require genetic predisposition and sensitization to the isocyanates. Such genetic programming presumably explains the restricted prevalence (5–15%) and incidence of those sensitized to TDI.

Skin sensitization to isocyanates is rare. Irritative dermatitis from skin contact with liquid or vapor is encountered more frequently. A thickening of the

palmar surfaces occurs in workers handling recently synthesized urethans, e.g., urethan sand molding cores. This appears as a translucent, dirty thickening of the epidermis, a "plastication" of the skin.

As mentioned before, irritative conjunctivitis is not uncommon. Thus far, vapor exposure to the eyes has not produced permanent effects. Even liquid TDI splashes have only produced acute responses. Conjunctival reactions to isocyanate vapors do not appear to be a predictor of sensitization.

To date, there are no reported medical data to suggest that environmental exposure to isocyanates relates to mutagenesis, teratogenesis or carcinogenesis.[13]

CLINICAL ASPECTS

Respiratory considerations are the dominant concern in isocyanate exposures. Exposures to concentrations of isocyanates greater than the threshold limit values (e.g., of the order of 0.1 ppm or more) produce smarting discomfort to the mucous membranes and coughing. Hours following such an incident, spasms of coughing, sometimes with wheezing dyspnea, lasting several hours may occur. Concomitantly, chest tightness, a feeling of "lung congestion," anxiety and discomfort are not infrequent. Usually there is no fever or chills. Unless the exposure was massive and prolonged, conservative symptomatic treatment, sometimes as modest as humidification, is followed by recovery in 24–48 hours. Such workers may resume work in an environment containing isocyanates controlled at 0.02 ppm without symptoms. This is a classic description of a typical "pharmacologic-overdose reaction." The hallmarks of this response are: excessive exposure to isocyanate, progressive development of bronchitis and wheezing dyspnea over many hours, subsidence with conservative treatment in a day or so and the ability to remain asymptomatic when exposed to acceptable levels of isocyanate subsequently.[8] Commonly, several employees in the same work area usually will be affected.

Contrast the circumstances and symptoms of an isocyanate-sensitized worker.[9] He usually is a person with an exudative or allergic diathesis, a family history of allergies and has sustained several pharmacodynamic reactions in the past. Eventually, he develops typical bronchial asthma even on exposure to isocyanate levels less than 0.02 ppm. His clinical history is very important! The clues to look for are: decreases in exposure-response intervals, increases in the intensity of asthmatic responses and increases in the duration and recovery from the bronchospastic attack. Much more aggressive treatment measures are required. Subsequently, infinitesimal exposures can provoke an exacerbation.

Physical findings in the asthmatic syndrome include: rhonchi, a prolonged expiratory phase proportionate to the degree of bronchospasm and musical rales.

During the asthmatic syndrome, whether a pharmacodynamic type or an allergic reaction, leukocytosis occurs. Eosinophilia has been observed with some frequency in workers who are sensitized. Circulating antibodies to TDI or TDI-protein conjugates have been reported in the blood of workers exposed to isocyanates. The conventional allergy tests usually fail to distinguish between sensitized and nonsensitized isocyanate-exposed persons. The lymphocyte transformation test utilizing TDI-albumin antigen appears to distinguish between sensitized and nonsensitized workers.[1]

As might be anticipated in pulmonary ventilation tests, FEV_1 and VC are compromised in workers during bronchospastic reactions. The magnitude of the pulmonary function abnormality is greater in individuals whose wheezing dyspnea is of allergic origin. Peters[8-10] has

shown attenuation of ventilatory parameters even in workers experiencing no symptoms when exposed to TDI levels of 0.02 ppm or lower. Furthermore, this attenuation progresses significantly during a Monday workshift, during the workweek and at 6 months and 2 years of such exposures. Others have found conflicting results on this point, however.

Chest x-rays taken during asthmatic syndrome attacks usually are negative or reveal fairly nonspecific changes unless pneumonia or pulmonary edema supervenes. Reversible consolidation and radiopacities have been reported, which clear on removal from further TDI exposure.

SAMPLING AND ANALYSIS

The criteria document on TDI recommends the Grim-Lynch and Larkin-Kupel modifications of the Marcali method for measuring isocyanates in air. In this method, isocyanate is hydrolyzed to a diamine, diazotized by sodium nitrite-bromide solution, then coupled with *N*-l-naphtha-ethylene diamine to form a colored complex readily calibrated by absorbance spectroscopy at 500 mm. This test has a sensitivity to 0.0035 ppm.[13] Other methods are available.

ENVIRONMENTAL CONTROL

The standards for control under the Occupational Safety and Health criteria now state that no worker shall be exposed to a time-weighted average (TWA) of more than 0.005 ppm (0.036 mg/m^3) for any 8-hour workday or for any 20-minute period to more than 0.02 ppm (0.14 mg/m^3). Details for the protection and evaluation of exposed workers are discussed in the NIOSH Criteria Document on TDI.[14]

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Pyrolysis Products of Plastics

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TOXICITY resulting from the massive use of plastics in our modern society is not restricted to exposures sustained by workers during synthesis, formulation or manufacture. Rapid and nearly complete oxidation of plastic products occurs with the application of extreme heat during a conflagration, resulting in carbon diox-

TABLE 31-7.—COMBUSTION PRODUCTS OF POLYURETHANE FOAM AT SEVERAL COMBUSTION CONDITIONS

AIR FLOW, CC/MIN	100	100	100
OXYGEN FLOW, CC/MIN	0	40	0
HEATING RATE, C/MIN	5	5	50
Carbon dioxide	591.0	836.0	480.0
Carbon monoxide	165.0	235.0	241.0
Cyanide ion (as HCN)	34.7	32.5	11.6
Ammonia	0.23	0.09	0.01
Methane	2.40	2.41	27.3
Ethylene	1.57	3.08	15.5
Ethane	0.27	0.32	3.5
Propylene	3.58	10.60	61.1
Propane	0.37	0.68	8.3
Methanol	26.4	19.7	26.0
Acetaldehyde	27.1	32.5	53.9
Propionaldehyde	2.4	3.1	16.2
Acetone	12.4	11.1	39.8
% Nitrogen accounted for	32.3	30.3	10.8
% Plastic accounted for	34.3	44.5	49.8

TABLE 31-8.—COMBUSTION PRODUCTS IDENTIFIED BY GAS CHROMATOGRAPHY

POLYPHENYLENE OXIDE	POLYPROPYLENE	POLYCARBONATE
Benzene	Carbon dioxide	Carbon dioxide
Toluene	Carbon monoxide	Carbon monoxide
Ethylbenzene or xylene	Methane	Methane
Styrene	Ethylene	Ethylene
Trimethylbenzene°	Ethane	Ethane
Indan	Propylene	Propylene
Indene	Propane	Propane
Unidentified	1-Butene	Methanol
Unidentified	Butane	Acetaldehyde
Phenyl propynyl ether°	trans-2-Butene	1-Butene
o-Cymene°	cis-2-Butene	Butane
Naphthalene	1-Pentene	Benzene
o-Cresyl ethyl ether°	Pentane	Toluene
Dimethylindan	1,3-Pentadiene?	Ethylbenzene
Unidentified	1-Hexene	Styrene
Unidentified		
Methylnaphthalene		
2,6-Dimethylphenol		
o-Cresol		
Trimethylphenol		
2,4-Dimethylphenol		
2-(x-Xylyloxy) ethanol?		
Trimethylphenol		
Unidentified		

°Or isomer.

ide, water and oxides of nitrogen. Even so, partially degraded molecules result and these may recombine to form new molecular species. The application of lower heat results in a host of compounds, as depicted in Tables 31-7–31-10.[1,5] Thermal degradation often begins at relatively low temperatures (200–400° C), producing hydrogen chloride, carbon dioxide, carbon monoxide and some hydrocarbons. Neoprenes release sulfur dioxide and hydrogen sulfide.[5] Rigid urethans and isocyanates also produce CO_2, CO and small amounts of $CFCl_3$, HCN, HCl and hydrocarbons.[5]

Although the expected toxicity results from those compounds released in greater amounts, those emitted in smaller quantities cannot be disregarded, for three major reasons: (1) they are very toxic, e.g., benzene and hydrogen cyanide; (2) certain workers are hypersusceptible for some reason, e.g., allergy to isocyanates and pharmaco-biochemical sensitivity as encountered occasionally with amines and certain halogenated hydrocarbons; and (3) the toxicity of some substances is not yet recognized and therefore not studied. Not only should the

TABLE 31-9.–IDENTIFICATION OF POLYSULFONE RESIDUE CHROMATOGRAM PEAKS

PEAK NUMBER	MOLECULAR WEIGHT	SUBSTANCE DETECTED
1	92	Toluene
2	106	Ethylbenzene (or xylene)
3	104	Styrene
4	120	Methyl ethylbenzene°
	126	Chlorotoluene?
5	106	Benzaldehyde
	118	Benzofuran
	116	Indene
6	132	Methylbenzofuran
	130	Methylindene
	120	Trimethylbenzene°
7	128	Naphthalene
	142	Methylnaphthalene
8	94	Phenol†
	154	Biphenyl
9	170	Diphenyl ether (or phenyl phenol)
10	108	Cresol
11	168	Dibenzofuran
	184	Phenyl-p-tolyl ether†
	156	Dimethylnaphthalene
	122	Ethylphenol
12	198	aryl-Ethylphenyl phenyl ether°
13	212	2-Hydroxyphenyl-2-phenyl propane
14	226	Unidentified
15	224	Unidentified

°Or isomer.
†Major component.

TABLE 31-10.–IDENTIFICATION OF POLYVINYL CHLORIDE CHROMATOGRAM PEAKS

PEAK NO.	SUBSTANCE DETECTED
1	Methane
2	Ethylene
3	Ethane
4	Propylene
5	Propane, methyl chloride
6	Vinyl chloride
7	1-Butene, isobutane, butadiene
8	Butane
9, 10	trans-2-Butene, cis-2-Butene
11	3-Methyl-1-butene
12	Isopentane, 1,4-Pentadiene
13	1-Pentene
14	Pentane
15, 16	trans-2-Pentene, cis-2-Pentene
17	2-Methyl-2-butene
18	cis or trans-1,3-Pentadiene
19	cis or trans-2-Pentadiene
20	Cyclopentene
21	Cyclopentane
22	2-Methylpentane
23	1-Hexene, 3-methylpentane
24	Hexane
25	2-Hexene
26	Methylcyclopentane
27	1-Methylcyclopentene
28	Benzene
29	Cyclohexane
30	1-Heptene
31	1,4-Dimethylcyclopentene
32	Heptane
32	Unidentified
34	3-Ethylcyclopentene
35	Methylcyclohexane
36	Ethylcyclopentane
37	1,2-Dimethylcyclopentene
38	1-or 4-Ethylcyclopentene
39	1-Methylcyclohexene
40	Toluene
41, 42	Unidentified
43	Octane
44–47	Unidentified
48	Ethylbenzene
49–51	o-, m-, p-Xylene

major parent compounds be considered but also additives, such as accelerators, catalysts, copolymers, dyes, fillers, mold lubricants, pigments, plasticizers, solvents, stabilizers and ultraviolet absorbers.

There are a number of syndromes being reported that appear to result from thermal degradation products of plastics. *Teflon fume fever* has been reported, especially in smokers exposed to Teflon fume generated by temperatures far in excess of those achieved during cooking with Teflon-coated utensils.[2, 4, 6, 8] *Meat-wrapper's asthma* is another alleged syndrome that appears to be associated with exposures to the products of heated plastics, in this instance, hot wire cutting of polyvinyl chloride film.[7] There are instances of adverse reactions when urethan foams, polystyrene and other plastics are thermally degraded. It is likely that the last has not been heard from this category of hazard.

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Effects of Nitroglycerin and Nitroglycol Exposure

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SINCE 1847, when Herning studied and introduced nitroglycerin in medicine, this substance has been subject to a great number of investigations from the pharmacologic and toxicologic points of view. Early chronic toxicity studies were undertaken by Nobel and associates, followed by others,[4] who emphasized common features in effects to nitrous and nitric acid esters and sodium nitrite. During the 1930s, the serious effect of the nitric ester compounds on man seems to have been observed, i.e., sudden death, which strikes isolated workers in the explosives industry about 2 or 3 days after cessation of exposure. Gross *et al.*,[7] aware of these sudden deaths during the 1930s, started experimental investigations concerning the effects of nitric esters on cats and rabbits. Their findings indicated nitroglycol to be about twice as toxic as nitroglycerin to these animals. In 1952, Symanski[21] reported 3 cases of sudden death in workers exposed to mixtures of nitroglycerin and nitroglycol and briefly mentioned another 37 fatal cases from the United States, assuming nitroglycol to be mainly responsible. Further reports appeared and were summarized by Hilbert in 1966.[9] Common to all these cases seems to be a predominant exposure to nitroglycol and less contact with nitroglycerin with most of these workers engaged in dynamite patroneering (cartridge manufacturing). Another few reports on this matter exist[1, 12, 14] and a number of other cases have been mentioned[9, 21] but not in detail.

Moreover, unverified rumors in different countries indicate additional cases to have occurred in explosives industries throughout the world. Nitroglycerin was first synthesized in 1846, but due to its highly explosive characteristics, the substance did not come into general use until development of the Nobel process (1860s) of adsorbing nitroglycerin with diatomaceous earth. This classic type of dynamite turned out to be risky in the winter because the nitroglycerin froze to crystals, resulting in unexpected and severe accidents. Therefore, nitroglycol was introduced as a modifier of dynamite in the 1930s. This new type of dynamite, a mixture of nitroglycerin and nitroglycol, was advantageous from the technical and economic points of view. Different relations between nitroglycol and nitroglycerin in dynamite have been used during the past years, and, presently, a ratio of about 8:2 is used.

OCCUPATIONAL EXPOSURES

Manufacturing of dynamite involves both skin contact and inhalation exposure to the workers. Automatic procedures presently established may contribute to the elimination of exposure; nevertheless, serious hygienic risks probably will persist for the near future. Furthermore, not only explosives workers but also other groups of workers, such as rock blasters and miners, might be exposed. In the explosives industry, heavy exposure usually strikes patroneers, packers, knead-house workers and nitrifying workers. In 1942, Gross[7] pointed out that skin contact might be an essential route of exposure, which he confirmed later in animal experiments.[8] Nitroglycol was shown to be more readily absorbed through the skin than nitroglycerin by a factor of about 10. These findings were confirmed later by others[27] in experiments on rabbits. Williams and Murray[26] found nitroglycol to be rapidly absorbed into human skin. So far, no comprehensive experimental study on the absorption of nitroglycol and nitroglycerin through the skin seems to exist.

Exposure by inhalation was considered by Trainor and Jones,[22] who exposed volunteers to an atmosphere of 0.5 and 0.7 mg/m³ of nitroglycerin and found these subjects to develop headache and fall in blood pressure. A close relationship between nitroglycol in the air and in blood can be shown if no contemporary skin contact occurs, as discussed by Götell.[6] As shown in Figure 31-5, a closely controlled inhalation exposure to atmospheres of a nitroglycol concentration in the range of 1.2–7.8 mg/m³ will result in a blood level of 0.9–8.0 ng/ml. However, venous blood samples from 333 workers in two different explosives plants revealed very different blood levels of nitroglycol, i.e., ranging from less than 1 ng/ml to as much as 1160 ng/ml *without any apparent relation to the air concentrations of nitroglycol* (Table 31-11). These findings suggest that the skin absorption of nitroglycol probably is by far the *most important route* of absorption.

Fig. 31–5.—Inhalation chamber exposure to nitroglycol.

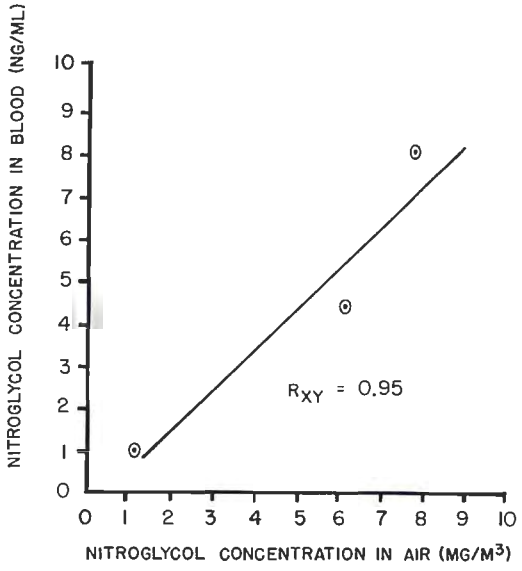

TABLE 31-11.—NITROGLYCOL IN BLOOD FROM WORKERS IN EXPLOSIVES INDUSTRY. THE BLOOD SAMPLES WERE TAKEN 3–5 HOURS AFTER START OF WORK

NUMBER OF PERSONS	NITROGLYCOL IN AIR (MG/M³)	NITROGLYCOL IN BLOOD (NG/ML)		
		Mean	S.D.	Range
192	<0.5	43	121	<1–920
93	>0.5–1.0	55	123	<1–675
22	>1.0–2.0	99	250	1–1160
26	>2.0–10	88	138	2–450
TOTAL 333				

No significant difference between any of the four groups was found, meaning that judging exposure from the air concentration is irrelevant.

TABLE 31-12.—NITROGLYCOL CONCENTRATIONS IN BLOOD DURING THE WORKDAY IN DIFFERENT CATEGORIES OF WORKERS

CATEGORY	NUMBER	NITROGLYCOL IN BLOOD (NG/ML)		
		Mean	S.D.	Range
Knead-house workers	44	8	8	1–30
Patroneers	182	89	176	1–1160
Nitrifying workers	24	8	11	0.5–39
Supervisors, truck drivers, etc.	28	4	4	0.5–16

Particularly the patroneers, a risk group for sudden death as mentioned before, have shown very high blood levels (Table 31-12). Therefore, the handling of dynamite in the manufacturing process should be given special attention to avoid skin contact whereas inhalation exposure probably is of minor importance. This also suggests an irrelevancy in controlling exposure to the workers by measuring airborne nitroglycol and nitroglycerin if skin contact occurs.

CLINICAL PICTURE

The clinical picture in the explosives workers exposed to nitroglycerin and nitroglycol sometimes is characterized by severe headache, flushing and gastrointestinal complaints, often in the beginning of the exposure period and readmission to work after vacations. Experienced workers seem to suffer comparatively little from these symptoms, either because of adaptation or due to self-selection to this type of job. Fainting because of fall in blood pressure is another acute effect of exposure to nitrate esters, and a decreased pulse pressure has been reported.[20, 25] Symptoms simulating angina pectoris are known to occur, particularly after a few days off exposure, i.e., in the same period as the sudden deaths most frequently reported.[14] It is also emphasized that the withdrawal symptoms after exposure to nitroglycol seem to be more frequent or apparent than those observed after exposure to nitroglycerin alone. Although some of the exposed workers have died from attacks clinically resembling heart attack, at necropsy, no signs of atherosclerotic changes or myocardial

damage have been found. In some of the cases presented by Hilbert, a right ventricular dilatation was a common feature in the necropsy protocols and, besides the chest pain often preceding death, abdominal pain and a terminal cyanosis have been reported. The findings by Lange *et al.*[12] in 5 of 9 munitions workers manifesting ischemic symptoms revealed normal coronary arteriography and abnormal exercise hemodynamics in this group. One patient, studied 64 hours after removal from exposure, demonstrated severe and diffuse spasm of the coronary arteries; he also showed significant peripheral arteriospasm. Sublingual nitroglycerin administration resulted in a marked improvement in the angiographic findings. In this study, 3 patients were reported to have ST–T changes in the ECG and serum enzyme changes consistent with nontransmural myocardial infarction. Removal from exposure resulted in relief from the ischemic symptoms in these patients occupationally exposed to nitroglycerin.

TOXICOLOGY

The toxicity of nitroglycerin and nitroglycol should be regarded as comparatively high, lethal doses being about 200–500 mg/kg and 100–400 mg/kg respectively in experiments on cats and rabbits.[7] Similar toxicity was revealed in investigations by von Oettingen in 1946.[24] In a review on human toxicity data by Munch and Friedland,[15] some early experiences from the nineteenth century and the first decades of the twentieth century seem to imply that the lethal oral dose of nitroglycerin to man is in the order of 100–125 mg. Nitroglycerin and nitroglycol are also recognized to produce methemoglobinemia, and 1–6% has been observed in explosives workers.[19] Similar findings have been made in exposed animals, with formation of Heinz bodies.[7, 11]

Much work has been done in pharmacologic studies in nitroglycerin; since these experiences are summarized elsewhere,[13] only brief comments are given here on this point. There has been much controversy as to the effect of nitroglycerin in angina pectoris, and the action of nitroglycerin has been thought not exclusively to depend on a dilatation of the coronary arteries but on a dilatation of the peripheral vessels, resulting in a decrease in vascular resistance, lowering of blood pressure and diminished strain on the left side of the heart. Consequently, myocardial oxygen consumption is reduced, being particularly dependent on blood pressure. Relaxation of the venous capacity vessels also results in a lowered central venous pressure and tachycardia. The effect on blood pressure by nitroglycerin is well known and has been observed in exposure chamber experiments.[22] In explosives workers, a somewhat decreased pulse pressure has been reported, which might be a more or less chronic effect of the exposure.[5, 21, 25]

An interaction between effects exerted by nitrate esters and monoamines has been indicated in some investigations. Thus, an inhibition of monoamine oxidase (MAO) was reported in rats (tyramine as substrate) at concentrations corresponding to therapeutic doses of nitroglycerin in man.[17] However, these results are not agreed on by others[10] who found nitroglycerin and also nitroglycol to reduce the MAO activity in rabbit liver in vitro. No inhibition was found in vivo, but differences exist between the methods used in these investigations.

Concerning the possible mechanisms behind the sudden deaths of explosives workers, some unpublished data from animal experiences attract a good deal of interest.[20] It was found that rats became desensitized to norepinephrine 4–5 hours after an injection of nitroglycol. About 10–15 hours after injection, the

animals again had a "normal sensitivity" to norepinephrine whereas they showed doubly increased sensitivity to this monoamine some 40–48 hours after the injection. Attacks of transient ventricular fibrillation with a duration of a few seconds were also observed by the same investigator during these animal experiments. Perhaps these observed interactions between the nitrate esters and the monoamines bear on parts of the explanation about the sudden deaths in these workers, although a clear-cut hypothesis cannot be put forward at present.

BIOTRANSFORMATION

The metabolism of the nitrate esters is partially known. Needleman and Krantz[16] found nitroglycerin to be metabolized to 1,3 and 1,2 glyceryl dinitrate and inorganic nitrite in the presence of a specific liver enzyme and reduced glutathione. Clark and Litchfield[3] and Tsuruta and Hasegawa[23] have studied the decomposition of nitroglycol but do not agree about the metabolic pathways. The Japanese investigators proposed nitroglycol to break down to ethylene glycol and nitrates, under the action of a nitrite-forming enzyme and reduced glutathione, excreted in urine. This biotransformation was suggested to occur in erythrocytes and the liver, partly verified in subsequent studies on nitroglycol metabolism in erythrocytes.[6] Thus, it can be shown by in-vitro tests that nitroglycol is broken down in erythrocytes of unexposed men according to an exponential curve with a half-life of 0.4 hour (Table 31-13), whereas the erythrocytes from exposed men in the explosives industry exert a decreased decomposition activity with an increased half-life to about twice that in the unexposed men. In women, there seems to be no difference between exposed and unexposed individuals, whereas the decomposition half-life is longer than in men, or about 0.6 hour.

MEDICAL AND HYGIENIC CONTROLS

From the medical preventive point of view, a pre-employment examination should exclude cardiac diseases of different types (CHD, arrhythmias and signs of valvular dysfunction). Individuals suffering from incipient or manifest hypertension or those complaining about migraine or showing different vegetative symptoms, such as hypertonia, should not be accepted in exposed jobs. Regular surveillance might be of value to protect workers, and indications of unfitness revealed in the history or in ECG findings should result in removal of the worker from exposure.

Hygienic prevention should focus on

TABLE 31-13.—THE BIOLOGIC HALF-LIFE FOR NITROGLYCOL IN ERYTHROCYTES IN VITRO (37° C)

NUMBER OF PERSONS INVESTIGATED	SUBJECT	HALF-LIFE HR°		REMARKS
		Mean	Range	
28	♀ Controls	0.6	0.4–0.8	$p < 0.005$ compared to ♂ controls
30	♀ Exp. >2 yrs	0.7	0.4–1.3	No significance compared to ♀ controls No significance compared to ♂ exp.
22	♂ Controls	0.4	0.3–0.6	$p < 0.005$ compared to ♀ controls
26	♂ Exp. >2 yrs	0.8	0.4–1.4	$p < 0.005$ compared to ♂ controls

°Time in hours after adding nitroglycol, equivalent to 100 ng/ml of whole blood (adjusted to ml:s of erythrocytes) passed until the initial concentration has decayed to the half.

TABLE 31-14.—TLVs FOR NITROGLYCOL AND NITROGLYCERIN IN DIFFERENT COUNTRIES (ILO 1970)

COUNTRY	EFFECTIVE YEAR	NITROGLYCOL (MG/M³)	NITROGLYCERIN (MG/M³)
Finland	1962	–	5
Japan	1967	1.2	–
Poland	1967	–	3
Rumania	1966	–	2
Germany	1972	1.6	5
Hungary	1965	–	5
USA (ACGIH)	1972	1.2	1.9
USA (FL)	1960	–	4.7
USA (Mi)	1958	–	4.7
USA (Pa)	1966	1.2	1.9
USA (S.C.)	1958	–	4.7
Sweden	1974	1	2

eliminating skin contact (clean gloves, resistant to nitrate esters, are necessary and the hygienic routines should be vigorous). Again, it must be pointed out that the exposure level of the workers is not reflected in measurements of the air concentrations of nitrate esters unless skin contact is completely eliminated. However, control of the air concentrations might be of some significance in protecting against headache in individuals without skin contact with the compounds. Headache seems to be induced in sensitive individuals already at air concentrations of about 0.1 mg/m³, whereas the TLVs proposed in different countries[18] are about 1–2 mg/m³ for nitroglycol and 2–5 mg/m³ for nitroglycerin, as shown in Table 31-14. The most suitable method for controlling over-all exposure (skin and inhalation), therefore, seems to be the determination of nitrate esters in venous blood samples taken at random times during the workday. A blood level of nitroglycol should not exceed 2 ng/ml to correspond with an 8-hour time-weighted average exposure of 1 mg/m³ in the air and, concerning nitroglycerin, a maximal blood concentration of 2 ng/ml seems to be consistent with proposed TLVs of about 2 mg/m.³ Thus, blood levels exceeding these figures indicate that skin absorption has taken place, or reveal that the air concentrations are not under control.

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Occupational Medicine

PRINCIPLES AND PRACTICAL APPLICATIONS

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