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Medical Problems Encountered in the Manufacture of American—Made Rubber

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THE manufacture of synthetic rubber, preferably called American-made rubber, on an extensive scale is a recently developed United States industrial enterprise brought about by necessity during World War II. Since much of the early research and development prior to World War II was done in the Research Laboratories of The B. F. Goodrich Company, under the direction of Dr. Waldo Semon, the potential health hazards were brought to the attention of the Medical Division at an early date.

Manufacture of American-made rubber progressed to the extent that during the recent war the vital rubber needs of our allies as well as our own were largely supplied by American-made rubber.

Since the war practically every product previously made with crude rubber can be, or is, made with American-made rubber from synthetic plants scattered over the United States. In 1947, for example, half of this nation's record rubber consumption was American-made. In the production of American-made rubber, many chemical compounds are utilized. Some of these have been used in rubber manufacturing processes for a long period of time, and their chemical and toxicological properties are well known. Other compounds are new and very little has been written concerning them.

Mallette[2] in 1943 discussed industrial hygiene problems encountered in synthetic rubber manufacture, while a previous description of the health hazards encountered in the manufacture of synthetic rubber was made by Wilson[1] in 1944.

This paper deals with medical experiences encountered in the manufacture of the butadiene type American-made rubber. The ingredients known or suspected of causing health problems are discussed in some detail. The chemistry of certain compounds used as various catalysts and modifiers in the manufacturing processes is familiar, and since they are used either in small amounts or are not particularly toxic, they will not be discussed in this paper. Specific examples of these are: Dodecylmercaptan, rosin acid soap, hydrochloric acid, sodium sulfite, diisopropyl dixanthogen disulfide, soap, sulphuric acid, Glaubers salt, ferric sulfate, potassium persulfate, sodium chloride, phenyl beta naphthylamine.

The principal basic chemicals used in the manufacture of butadiene type American-made rubber are:

1. Acrylonitrile with a chemical formula of CH_2: CH CN.
2. Styrene with a chemical formula of C_6H_5 CH:CH_2.
3. Butadiene with a chemical formula of CH_2: CH CH:CH_2.

Acrylonitrile

CHEMICAL *and Physical Properties:*[23]

Acrylonitrile (vinyl cyanide), with a structural formula of $CH_2{=}\overset{\overset{H}{|}}{C}{-}C{\equiv}N$, is a colorless volatile liquid boiling at 77.3°C. It has an ethereal odor, and is partially soluble in water. It has a molecular weight of 53.06 and specific gravity of 0.806 (20°C).

Mode of Action and Symptomatology:

Exposure of various laboratory animals, including monkeys, to acrylonitrile[15] in amounts varying from 90 to 635 p.p.m. (parts of vapor or gas per million parts of air) demonstrates that the symptomatology of all animals, except guinea pigs, is that of a typical nitrile exposure. These symptoms include initial respiratory stimulation followed by rapid shallow breathing, slow gasping spasmodic abdominal type respirations, generalized convulsions, coma and finally death. Biochemical studies[16] in this same group of animals showed that sodium nitrite in doses of 50 mg/kg of body weight exhibited a protective and antidotal effect when administered before and immediately after the animal's exposure. No signs of cumulative action were found in laboratory animals exposed to concentrations of 56 p.p.m.

Our own observations, on workmen handling cleaning operations in polymerizers with exposures varying from 16-100 p.p.m. for 20 to 45 minutes, show that the most frequent symptoms include dull headache, fullness in the chest, irritation of all mucous membranes including the eyes, nose and throat, a feeling of apprehension and nervous irritability. Some workmen complain of intolerable itching of the skin with no demonstrable dermatitis. When direct skin con-

tact occurs, it causes a direct irritation and erythema followed by bleb formation, desquamation and slow healing. Wilson[1] reported several cases of acrylonitrile poisoning that developed mild jaundice and low grade anemia and leukocytosis. Given orally the minimal fatal dose in laboratory rats is stated[14] to be 150 mg/kilo body weight. Symptoms in these animals included respiratory changes, cyanosis, convulsions and death.

Pathology and Laboratory Findings:

Pathological changes reported[16] in laboratory animals include hemosiderosis, indicating blood destruction, which was found to be proportional to the amount of exposure, renal irritation with hyaline casts in the straight collecting tubules, subacute interstitial nephritis and occasionally a subacute bronchopneumonia. Medical observations in industries where acrylonitrile is used have noted some evidence of liver and kidney irritation in employees, which cleared up promptly on removal from exposure. The probable range of exposure in these cases varied between 15 to 100 p.p.m. Cephalin flocculation, blood cholesterol, urinalysis, blood pressure, and the blood non-protein-nitrogen content are valuable tests in determination of liver and kidney damage associated with nitrile exposure. Four workmen exposed to acrylonitrile in cleaning operations of polymerizers in our plant were checked to determine blood thiocyanate levels in relation to nitrile exposure. The concentration of acrylonitrile in these polymerizers ranged from 16 to 109 p.p.m. With exposure to concentrations of acrylonitrile up to 22 p.p.m. for 30 minutes, the blood thiocyanate level was normal when determined 2½ hours after exposure. When the exposure was 50 p.p.m. for 30 minutes, the blood thiocyanate level had not returned to normal after 12 hours removal from exposure. These findings suggest that the amount of nitrile accumulated in the body even in minimal exposures is not easily eliminated and the detoxification capacity of the body is easily exceeded. These findings correlate with animal experimentation in which it was found that only one-third of the lethal dose of acrylonitrile is destroyed in the following 24-hour period after exposure.

Determinations in Small Amounts in Air:[14,19]

This can be carried out by exercising the principle that acrylonitrile under proper conditions can be converted to ammonia and acrylic acid. The reaction proceeds stoichiometrically so that one molecule of acrylonitrile yields one molecule of ammonia. Ammonia is determined either by titration[19] or colorimetrically.[14]

Treatment:

Because of its mode of action, patients with acrylonitrile poisoning should receive immediately the following routine treatment for cyanide poisoning:

1. Break an amyl nitrate ampule in a handkerchief and hold it directly under patient's nose for 20 seconds every three minutes.

2. In cases where poisoning is induced by oral ingestion, lavage stomach with a solution composed of 52 gm. of sodium thiosulphate dissolved in a liter of water.

3. Inject intravenously 10 cc. of 3% aqueous solution of sodium nitrite at rate of 2-5 cc. per minute, then 50 cc. of 36% solution of sodium thiosulphate

4. Give artificial respiration if necessary

5. Oxygen may be given by mask or nasal catheter.

When signs of poisoning persist or reappear, the sodium nitrite and thiosulphate may be repeated, using half the quantity originally used In any case a second injection of the antidotal solutions (using ½ the original quantities) may be given two hours later for prophylactic purposes.

Vitamins B_1 and C have been beneficial in preventing weight loss to laboratory animals exposed to acrylonitrile over long periods of time.

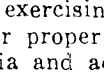
Prophylaxis:

Atmospheric concentrations should not exceed 20 p.p.m. This necessitates enclosure of processes to the maximum degree possible and the effective use of mechanical exhaust ventilation Skin contact should be avoided, not only because of the compound's vesicant action, but also because of possible toxic systemic effects. In the case of skin contact with the concentrated compound, immediate washing with copious quantities of soap and water is necessary. If spilled on the clothing, the clothes should be immediately removed and a shower taken by the individual. The effect of chronic low-grade atmospheric or skin exposures on humans is still undetermined. It is, therefore, advisable that working personnel be given periodic physical examinations, with special emphasis on hematology and liver and kidney functions. The determination of the thiocyanate level in both blood and urine has been sugested as an index of overexposure.

Styrene (Monomeric)

Chemical and Physical Properties:

Styrene (phenyl ethylene, vinyl benzene) is a colorless liquid with a boiling point of 144.7°C and a melting point of —31°C. with a characteristic disagreeable odor. Its structural formula is



Mode of Action and Symptomatology:

In man, concentrations of 1,300 p.p.m. cause extreme eye and nose irritation. This symptom complex in itself, affords a definite safeguard against voluntary exposure to acutely hazardous concentrations. Laboratory animals[13] exposed for 12-hour periods to vapor concentrations of approximately 5,000 p.p.m. had symptoms of local irritation in the eyes, nose and mucous membranes, followed by primary effects on the central nervous system with incoordination, tremors, loss of equilibrium and finally loss of consciousness. No other significant changes are

noted in laboratory animals given repeated exposures for periods varying up to six months with 650 p.p.m. In man, however, eye and nose irritation is marked at this concentration and could not be tolerated except for brief periods. A study of exposure of humans[17] indicated that in an atmosphere of 800 p.p.m. eye and mucous membrane irritation resulted, immediately followed by listlessness and sleepiness. After three hours exposure to this concentration, lack of muscular coordination and interference of equilibrium, depression, and weakness resulted. A metallic taste continued in most of the subjects long after interruption of exposure.

In experimental animals ingestion produces local irritation of the gastro-intestinal tract directly proportional to the amount ingested.

When styrene comes in contact with the skin directly, it produces an irritation and its dermatitis-producing qualities are comparable to that of the other hydrocarbons, such as benzene and toluene.

Pathological Changes and Laboratory Findings:

The outstanding pathological lesions encountered in tissue examination of animals exposed to styrene in varying concentrations are found to be pulmonary congestion, hemorrhage, edema and exudation. The degree of pathological involvement appears to vary directly with the amount of exposure. The kidneys and liver are affected as in any acute intoxication. Acute deaths in laboratory animals are central nervous system in origin. Delayed deaths are from pneumonia resulting because of initial lung irritation. Workmen exposed to 500 p.p.m. for varying periods of time presented no significant pathological changes and had no variation from the normal limits in chest x-rays or in laboratory examinations of urine and blood. A marked rise of total benzoic acid ranging from two to six times the normal (Quick method) has been reported[13] to have appeared in the urine of laboratory animals proportionate to the amount of styrene exposure. No hematological changes were noted in this same series.

Determination of Styrene in Air:[22]

Monomeric styrene can be quantitatively determined in the atmosphere by absorbing the vapors in a solvent (such as carbon disulfide, methyl alcohol, or ethyl alcohol). The amount of styrene present can be determined by either ultra-violet spectrophotometry, infra-red spectrophotometry, or nitration.

Treatment of Exposure:

Bed rest with general supportive and symptomatic treatment is indicated. A complete physical examination should be made with special emphasis on investigation of the respiratory system.

Prophylaxis:

The enclosure of all manufacturing processes, accompanied by necessary mechanical exhaust ventilation should be used wherever styrene is handled. Atmospheric concentrations should never exceed 400 p.p.m. and should be preferably maintained below 200 p.p.m. The former value has been tentatively established by the American Standards Association. However, there is good evidence to believe that concentrations at this level are too irritating to operating personnel for prolonged exposures. If skin contact occurs, with the concentrated compound, immediate washing with copious quantities of soap and water is necessary. If spilled on the clothing, the clothes should be immediately removed and a shower taken. Individuals working with styrene should be examined periodically. Hematological studies are of questionable value in low grade exposures.

Butadiene (erythrene, divinyl)

CHEMICAL and Physical Characteristics:

Butadiene is a colorless gas with an aromatic odor. It has a molecular weight of 54.09 and a boiling point of —4.7°C. The structural formula is $CH_2=CH—CH=CH_2$.

Mode of Action:

The passage of butadiene into the blood in vivo following inhalation is a process of simple diffusion of the gas from the alveoli of the lungs. It is rapidly eliminated in exhaled air without causing any significant pathological changes in the body, outside of its narcotic effect at very high concentrations.

Symptoms of Over Exposure:

Butadiene is practically innocuous aside from its narcotizing and anethetizing effect at very high concentrations. Human subjects exposed to 8,000 p.p.m. complained of eye irritation, blurring of vision, coughing, nasal congestion, and drowsiness.[17] Subsequent repeated exposures gave no indication of cumulative action. A complete examination of the chest including an x-ray, blood examination and urinalysis were not informative. Subsequent follow-up examinations were also negative. In laboratory animals[17] subjected to high exposures, irritation of all of the mucous membranes and the respiratory tract occurs along with varying degrees of narcosis. Acute deaths are due to pulmonary edema. Delayed deaths are due to chemical pneumonia following pulmonary irritation. Experimentation with butadiene in laboratory animals indicates that butadiene is not a safe general anesthetic because there is not complete muscular relaxation even in the fourth stage. Death ensues rapidly when the laboratory animal is kept in deep anesthesia for any length of time.

Pathology and Laboratory Findings:

No pathological changes or laboratory findings in the exposures of humans. No progressive changes have been reported in laboratory animals exposed to butadiene in concentrations of 600 to 6,700 p.p.m. for a period of 7½ hours per day, six days per week for eight months.[17] At the higher levels of exposure (6,700 p.p.m. or more) for the same period of time, some cloudy swelling was found in the livers of these animals. No significant changes in blood or urine

were found in any of the studies made on laboratory animals.

Method of Detection in Atmosphere:

Under proper conditions iodine pentoxide oxidizes butadiene completely with the liberation of 2.2 molecules of iodine. The amount of liberated iodine can be determined by titration with sodium thiosulfate.

Treatment:

Workmen anesthetized with or suffering from exposure to butadiene should recover completely, providing they are removed from exposure while respiration and heart action are still strong. Oxygen by inhalation should be administered until the pulse and blood pressure remain normal and the color is good. Symptomatic treatment in indicated.

Prophylaxis:

Of the three basic materials used in the manufacture of butadiene type American-made rubber, butadiene is the least toxic. Special precautions need to be observed in handling the compound from a fire and explosive standpoint. These include enclosure and mechanical exhaust ventilation and will in most cases automatically control the health hazard. There is no apparent systemic injury to humans in concentrations below 5,000 p.p.m. Any complaints which include eye and respiratory irritation, headache and vertigo might be considered as indicative of excessive exposure.

IN THE processing of butadiene-type American-made rubber into products, a number of chemicals are used. These include aromatic hydrocarbons, chlorinated hydrocarbons, petroleum distillates, ketones, acetates, alcohols and carbon disulfide. These compounds are all toxic in varying degrees and present certain medical problems in their handling. Specific methods for determining the atmospheric concentrations of these chemicals can be found in Jacob's[20] text.

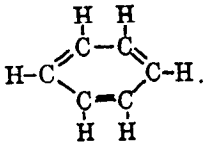
Aromatic Hydrocarbons

THE aromatic hydrocarbons are used extensively in the processing of American-made rubber. Of these, benzene (benzol, C_6H_6); toluene (toluol, $C_6H_5CH_3$); and xylene (xylol, $C_6H_4(CH_3)_2$) are the principal ones. These compounds are of value because of the fact that they are excellent solvents.

Benzene

CHEMICAL *and Physical Properties:*

Benzene is one of the most dangerous of the industrial solvents. It is a colorless coal tar distillate with a rather pleasant characteristic odor. It boils at 80.2°C and has a specific gravity of 0.879. The commercial varieties usually used in industry may contain from 2 to 10% toluene, xylene, olefine, paraffin, and carbon disulfide.

The structural formula is .

Mode of Action and Symptomatology:

As pointed out by Wilson[3] benzol poisoning may result from absorption of benzene by either the respiratory tract, the alimentary tract, or probably the skin. Cases of poisoning in human beings have been found with exposures to atmospheric conditions as low as 25 p.p.m. Concentrations of 50 to 100 p.p.m. are considered to be safe for the average person. Individual susceptibility varies. Acute benzol poisoning is rare. The symptoms of an acute case are referable to the central nervous system. There are muscular tremors, salivation, violent twitching, exhaustion, narcosis, paralysis, convulsions, and death from paralysis of the respiratory center.

Patients exposed to concentrations of vapors between 50 and 500 p.p.m., with the average concentration being about 100 p.p.m. show symptoms of lassitude, malaise, nausea, vomiting, dizziness, and headaches.[3] Macular dermatitis may appear. As exposure continues symptoms become more severe. Hemorrhages under the skin and from the body cavities may occur. In one case ecchymosis and petechiae were the first symptoms noted. At the time of appearance the blood count was normal. In five days the white blood cell count was 500. Diplopia, especially for close distances, occurs in some cases. If the person is highly susceptible, or if the exposure has been great and prolonged, he may get physiologic or functional depression of the bone marrow. This varies in degree from a slight hematopoietic suppression to a total bone marrow aplasia.

The symptoms of a total aplasia are usually those of benzol absorption followed by prostration. On the other hand, it is sometimes strange how well the patient may appear. Aside from fatigue there may be no other complaints.

The best index of benzol absorption is the blood count. All components of the blood are affected, being lowered. Most important, the total leucocyte count falls. Special reference should be made to the differential count. The ratio of polymorphonuclear cells to monocytes is changed. The number of monocytes increases and the polymorphonuclear cells decrease. The red blood cell count is lowered. The hemoglobin usually falls. It has been reported by some investigators that the leucocyte count may be elevated at first. However, when this occurs it is quickly followed by a general lowering of the count. The platelet count is lowered, dropping to practically zero in severe cases. The reticulocyte count is also lowered. The prothrombin time is normal. The resulting picture is one of aplastic anemia. One patient exhibited a count of 125 white blood cells, 1,500,000 red blood cells, and 25% hemoglobin. This patient died with bronchopneumonia. The red blood cells exhibit anisocytosis, poikilocytosis, and polychromatophilia. In all patients showing a marked blood reduction, a bone marrow biopsy should be done. The degree of aplasia can be determined, and usually an accurate prognosis can be made. Patients with total aplasia usually die. Patients with

partial aplasia have a prognosis dependent upon the amount of regeneration present. Urine examinations are usually negative. The blood pressure may be lowered.

Aplastic anemia is to be differentiated from agranulocytosis and acute leukemia. The symtoms of all of these diseases are very similar. In agranulocytosis the red blood cell and platelet counts are usually essentially normal. In acute leukemia the white blood cell count may be normal, raised, or lowered with the differential count showing a marked increase in very young white blood cells. The liver and spleen are usually enlarged in acute leukemia and are normal in aplastic anemia and agranulocytosis. The lymph nodes are normal in aplastic anemia and agranulocytosis and are usually enlarged in leukemia. Sore throat is common in leukemia and especially so in agranulocytosis. It must be recognized that the differential diagnosis between these three diseases may be difficult. Bone marrow studies usually reveal the proper diagnosis.

Treatment:

In patients with mild benzene intoxication, with or without a change in the blood count, the treatment is permanent removal from exposure. These patients will return to normal in a few days with no medication.

In patients, where absorption is sufficient to cause a marked change in the blood picture, more active treatment is necessary. These patients are placed at absolute bed rest. Multiple small whole blood transfusions (about 250 cc.) are given as often as once daily. One patient was given 50 transfusions, another 36. The patient may be alkalinized with sodium or potassium citrate. When severe reactions occur, blood plasma may be used in place of whole blood.

Direct bone marrow transfusions may be given as often as twice weekly. In this procedure 2 to 5 cc. of bone marrow are removed from the sternum of a compatible donor and introduced directly into the sternum of the patient. From the same donor 250 cc. of blood are drawn and transfused into the patient. This is followed by 1,000 cc. of normal saline solution.

Ten milligrams of liver are given intramuscularly daily. Large daily doses of liver, iron, calcium, phosphorus, yellow bone marrow, and multiple vitamins are given by mouth. A total of 400 to 600 mg. of ascorbic acid are given daily by mouth. A full diet is prescribed. The patient's general hygiene is improved as much as possible. Bleeding areas are stopped if at all possible. Pentnucleotide has been used and found to be effective in some cases.

The poor resistance in these patients is due to the lowered leucocyte count. Secondary infection, the most common of which is a Vincent's organism infection of the mouth, is one of the causes of death. For certain types of severe secondary infection sulfadiazine and antibiotics are indicated.

The response to therapy is slow since a considerable time is necessary for the bone marrow to regenerate. One patient was under treatment for twelve months, at which time he still had a low hemoglobin and red blood cell count. Splenectomy may be considered in some refractory cases. Any treatment, at best, is not wholly satisfactory. Extreme caution must be observed in the handling of this compound. In too many patients the disease proves fatal.

Prophylaxis:

Prophylaxsis is discussed at the end of this section on aromatic hydrocarbons.

Toluene

CHEMICAL *and Physical Properties:*

Toluene is a colorless, highly refractive inflammable liquid obtained from tolu and other resins, and from coal tar. It boils at 110.4°C. and has an odor somewhat similar to that of benzene. It is insoluble in water and is miscible with alcohol, ether, chloroform, carbon disulfide and petroleum benzine. Its specific gravity is about 0.865 at 25°C. Its structural formula is .

Toluene constitutes two to 10% of commercial benzene. It is used extensively in the rubber, lacquer, and munition industries.

Mode of Action and Symptomatology:

As pointed out by Wilson[4] the pathologic manifestations of exposure to toluene are a matter of controversy. The conclusions reached by various authors are in decided variance with one another.

Toluene poisoning is probably caused by absorption through the respiratory system, the skin, and the alimentary tract. The absorbed vapors exert a progressive depressant action on the central nervous system and the bone marrow. Toluene is also a pronounced irritant to mucous membranes. A factor to be considered whenever it is employed is individual susceptibility. Exposure to concentrations of toluene from 200 to 500 p.p.m. for six to eight hours will in most persons cause tiredness and lassitude. Concentrations over 500 p.p.m. for one to three hours are definitely dangerous and will cause symptoms attributable to depression of the central nervous system and the bone marrow.

Treatment:

Toluene may be assumed to be a dangerous chemical. Definite precautions should be taken whenever it is used. The treatment of toluene poisoning is the same as that of benzene poisoning.

Prophylaxis:

Prophylaxsis is discussed at the end of this section on aromatic hydrocarbons.

Xylene

CHEMICAL *and Physical Properties:*

Xylene is a colorless liquid with a mildly irritating odor somewhat similar to that of gasoline. It is insoluble in water and miscible with most organic solvents. It boils in a range from 138°C to 144°C. Its specific gravity is approximately

0.870 at 20°C. The commercial grade of xylene is a mixture of the ortho, meta, and para isomers and usually contains as an impurity small quantities of benzene and toluene. The formula of xylene is $C_6H_4(CH_3)_2$.

Mode of Action and Symptomatology:

Xylene is stated to possess more severe narcotic properties than benzene. Xylene poisoning is relatively uncommon because its volatility is lower than that of benzene or toluene. Chronic poisoning does occur. There is some evidence that xylene exerts an action on the blood forming organs similar to that of benzene. Cases of aplastic anemia have been attributed to xylene vapors. There have been some cases reported in German literature of leukopenia and thrombocytopenia with no reduction in red cells.

Treatment:

The treatment of xylene poisoning is comparable to that of benzene poisoning.

Prophylaxis of Aromatic Hydrocarbons:

Atmospheric concentrations should not exceed the values shown in Table I. In order to accomplish this, mechanical exhaust ventilation will, in most cases, be necessary. Skin contact should be avoided. Blood counts, including hemoglobin, red and white cell, and differential determinations should be made on all exposed personnel at least every three months. Sternal bone marrow examinations should be done on suspicious cases. Individuals with blood or bone marrow abnormalities should be considered for immediate and permanent transfer away from these solvents. Wherever possible, an attempt should be made to substitute less toxic solvents for the aromatic hydrocarbons.

TABLE I.
SUGGESTED MAXIMUM ALLOWABLE CONCENTRATIONS
(Parts per million parts of air)

Acetone	500
Acrylonitrile	20
Amyl (iso) acetate	200
Amyl alcohol	100
Benzene	100
Butadiene	5000
Butyl acetate	200
Butyl alcohol	100
Carbon tetrachloride	100
Carbon disulfide	20
Ethyl acetate	400
Ethyl alcohol	1000
Ethylene dichloride	100
Gasoline	500
Heptane	500
Hexane	1000
Propyl (iso) acetate	200
Propyl (iso) alcohol	400
Methyl alcohol	200
Methyl amyl ketone	200
Methyl ethyl ketone	200
Methyl isobutyl ketone	200
Naphtha (petroleum)	500
Perchlorethylene (tetrachlorethylene)	200
Propyl acetate	200
Stoddard solvent	500
Styrene	200
Tetrachlorethane	10
Tetrachlorethylene	200
Toluene	200
Trichlorethylene	200
Varsol	500
Xylene	200

Chlorinated Hydrocarbons

THE chlorinated hydrocarbons used in the manufacture of American-made rubber are:

1. Carbon tetrachloride (tetrachlormethane) CCl_4.
2. Ethylene dichloride (dichlorethane) $C_2H_4Cl_2$.
3. Tetrachlorethane (acetylene tetrachloride) $C_2H_2Cl_4$.
4. Trichlorethylene (ethylene trichloride) C_2HCl_3.
5. Perchlorethylene (tetrachlorethylene) C_2Cl_4.

Chemical and Physical Properties:

These compounds have varying uses. Some are used as solvents, others are used in fire extinguishers, as dry cleaners, degreasers, lacquer thinners, in the production of photographic film, and as anthelmintics. Their many uses are chiefly based upon their solvent properties and because some are non-inflammable.

Mode of Action and Symptomatology:

Most physicians are thoroughly familiar with the action of carbon tetrachloride on the human system and do not realize that the other members of the chlorinated hydrocarbon group are also extensively used in manufacturing processes.

The most toxic of the group is tetrachlorethane, having, according to Matruchot,[5] a comparative toxicity of 6.0. Carbon tetrachloride is listed by the same author as having a comparative toxicity of 2.6, trichlorethylene of 1.0, perchlorethylene of 1.4, and ethylene dichloride of 1.6. According to Davis[6] and the U. S. Public Health Service,[21] the maximum allowable concentration of carbon tetrachloride is 100 parts per million. According to Elkins[7] this level is too high and should be reduced to 50 parts per million.

The symptoms of over-exposure to the chlorinated hydrocarbons usually start with a feeling of drowsiness which, if exposure continues, is accompanied by anorexia, nausea, vomiting, abdominal pain, diarrhea, headache, and dizziness. Jaundice may develop. Oliguria progressing into anuria may also develop. In some cases bronchitis or bronchial pneumonia occurs, especially if free Cl or HCl is present. Some cases present hypertension. A constriction of the visual color fields has also been noted. Polyneuritis has been described. The mode of action is that of a narcotic with direct or indirect effects on the central nervous system. The chlorinated hydrocarbons also act as hepato-toxics, probably causing cirrhosis of the liver. This is especially noted when the diet has been deficient in calcium or there has been a depletion of body protein. The kidneys may be affected, the lesion being described as destruction of the epithelium with the stroma left intact. Hypertension and azotemia may accompany the kidney involvement. Clinton states[8] "that the renal injury is usually the predominant result of exposure to carbon tetrachloride. The lungs may be involved with either a bronchitis or bronchial pneumonia resulting, especially if free Cl or HCl is present." Acute

exposure to the chlorinated hydrocarbons is usually manifested by narcotic intoxication, with liver and kidney damage in six to 24 hours. The symptoms of chronic poisoning usually simulate those of portal cirrhosis.

Treatment:

A careful evaluation of the patient should be made including liver function tests, kidney function tests, electrocardiogram, and x-ray of the chest. Intravenous glucose should be given either in saline and distilled water. A high carbohydrate, high protein diet with a normal fat content is recommended. Methionine has been reported to be of benefit by some investigators. Others state that it is of no value. Choline has also been used. The patient should be kept under observation until all signs of liver and kidney damage have disappeared.

Prophylaxis of Chlorinated Hydrocarbons:

Workers should be carefully selected. The obese and the under nourished individual, nephritics, diabetics, individuals with lung and liver pathology and those having an enlarged thymus or thyroid should be rejected. Frequent physical inspections of exposed individuals should be made with particular attention being paid to kidney and liver function. Atmospheric concentrations should not exceed those listed in Table I. Mechanical exhaust ventilation is usually required to maintain these levels. Skin contact should be avoided.

Petroleum Distillates

Chemical and Physical Properties:

Gasoline (unleaded), hexane, heptane, Stoddard solvent, Varsol, and naphtha are mixtures of hydrocarbons, paraffins, olefins, cycloparaffins (naphthenes), aromatics, and other impurities including sulphur. Cracked gasoline may also carry a fairly high percentage of benzol. These substances are frequently referred to by the general name of benzine. This is to be distinguished from benzene (benzol). They are colorless liquids with gasoline-like odors. They have varying boiling points ranging from approximately 70°C upwards. They are inflammable. The specific gravity varies from approximately 0.65 to 0.78. The volatility of these distillates is a factor in determining their toxicity for industrial use. The chemical formula of hexane is $CH_3 \cdot (CH_2)_4 \cdot CH_3$. The formula of heptane is $CH_3 \cdot (CH_2)_5 \cdot CH_3$. The others are mixtures with no single formula.

Mode of Action and Symptoms:

These distillates are narcotics, and it is possible to produce complete anesthesia with heavy doses. However, their anesthetic properties are much less than those of the aromatic and chlorinated hydrocarbons. For this reason they may be more desirable for commercial use.

Drinker and associates, in studying the effects of gasoline vapors,[9] found that concentrations from 270 to 500 p.p.m. were tolerable. Neuromuscular symptoms began at about 900 p.p.m. Mild intoxication at 2,600 p.p.m.

The susceptibility of humans varies greatly. Acute poisoning produces the symptoms of a narcotic. There is fullness of the head, headache, blurred vision, dizziness, unsteady gate, and nausea. The patient becomes irritable. Burning of the eyes, dimness of vision are common complaints. It is of interest to note that on exposure to air the symptoms become increased. Massive exposures may cause sudden collapse, coma, and death. In fatal cases there is usually some blood vessel damage with small hemorrhages into the organs. Bronchitis, lung edema, cellular damage of the kidneys, liver and the spleen have been described. The symptoms of chronic poisoning are usually central nervous system in origin. Epileptiform seizures, unconsciousness, tonic muscular spasms, lancinating pains in the limbs, coldness and numbness in the hands, loss of strength, loss of memory, drowsiness, dimness of vision, confusion and dullness of mentality, and tremors have all been described.

Degeneration of the pyramidal tracts have been described by Dorner.[10] The effect of chronic petroleum distillate poisoning on the blood is a matter of controversy. It is usually felt that the effect of gasoline fumes on the blood differs from that of benzene only in degree. It must also be mentioned that certain petroleum distillates are suspected of containing carcinogenic substances. At the present time considerable research is being performed along this line.

Treatment:

The treatment of acute petroleum distillate poisoning should be directed towards the prevention of respiratory and circulatory collapse. Following intense exposures pulmonary edema usually occurs. Oxygen therapy, preferably using a face mask and positive pressure, is indicated. Saturated clothing should be removed. Circulatory and respiratory stimulants may be necessary. Bronchopneumonia may develop. The antibiotics may then be necessary. Most of these patients are quite nervous and restless. Sedation may be indicated. Conjunctivitis may be treated by dropping 1:1,000 adrenalin solution into the eyes four times daily, followed by cold applications. Boric acid ophthalmic ointment may also be used. Iron medication should be given if an anemia develops.

The maximum allowable concentrations of gasoline have been stated to vary from 100 to 1,000 p.p.m. The values for these materials are indicated in Table I. These solvents are not considered to be severely toxic and in most cases the values are based more on personal comfort than on toxic requirements. Skin contact should be avoided.

Ketones

IN THE manufacture of American-made rubber, acetone (dimethyl ketone), methyl ethyl ketone (butanone), methyl isobutyl ketone, and methyl amyl ketone are used.

Chemical and Physical Properties:

The ketones are colorless, volatile, inflammable

liquids with a fruity-like odor. Their chemical formulas are: Acetone—$CH_3 \cdot CO \cdot CH_3$; methyl ethyl ketone—$CH_3 \cdot CO \cdot C_2H_5$; methyl isobutyl ketone—$CH_3 \cdot CO \cdot C_4H_9$; methyl amyl ketone—$CH_3 \cdot CO \cdot C_5H_{11}$. Their boiling points range from 56°C (acetone) to 152°C (methyl amyl ketone). Their specific gravities range from 0.79 to 0.82. They are useful because of their high volatility and solvent power.

Mode of Action and Symptomatology:

In our experience no cases of occupational disease have been attributed to the ketones. A narcotic action has been attributed to acetone when given to animals. It is known that when individuals are exposed to moderate concentrations of acetone, it may be found in the urine without clinical symptoms being noted. It is wise to suspect that the ketones have a narcotic action and may cause a depression of the body temperature, respiration and heart rate. Exposure to excessive atmospheric concentrations of most of the ketones results in severe optic and respiratory irritation.

Treatment:

Treatment is entirely symptomatic.

Prophylaxis:

Atmospheric concentrations should be maintained below the values given in Table I. Personal comfort is the determining factor as to the tolerable atmospheric concentration. Skin contact should be avoided.

Acetates

THE following acetates are used in the manufacture of American-made rubber: Methyl, ethyl, propyl, isopropyl, butyl, and isoamyl.

Chemical and Physical Properties:

The chemical formulas of the acetates are: Methyl—$CH_3 \cdot CO_2CH_3$; ethyl—$CH_3 \cdot CO_2 \cdot C_2H_5$; propyl—$CH_3 \cdot CO_2 \cdot CH_2 \cdot C_2H_5$; isopropyl—$CH_3 \cdot CO_2 \cdot CH(CH_3)_2$; butyl—$CH_3 \cdot CO_2 \cdot CH_2 \cdot CH_2 \cdot C_2H_5$; and isoamyl—$CH_3 \cdot CO_2 \cdot CH_2CH_2CH \cdot (CH_3)_2$. They are colorless, volatile, inflammable liquids. Their specific gravities vary from 0.87 to 0.92. Their boiling points vary from 57°C to 142°C. They have a mildly pleasant odor. They are used as solvents.

Mode of Action and Symptomatology:

This group of substances has an irritating action on the respiratory passages. They are also irritating to the eyes and may cause a slight narcosis. In general, the acetates are considered to be among the safest of the solvents. No cases have ever been reported of genuine acetate poisoning.

Treatment:

Treatment is entirely symptomatic.

Prophylaxsis:

The suggested maximum allowable concentrations for these materials are shown in Table I (page 203).

These solvents are not considered severely toxic, and in most cases the values are based more on comfort than on toxic requirements. Frequently in rubber processing, the atmospheric concentrations can be adequately controlled by means of enclosure and natural ventilation. Skin contact may result in dermatitis and should therefore be avoided.

Alcohols

METHYL, ethyl, isopropyl, amyl, and butyl alcohol are all used in the manufacture of American-made rubber.

Chemical and Physical Properties:

Their chemical formulas are: Methyl—CH_3OH, ethyl—C_2H_5OH; isopropyl—$(CH_3)_2CH\ OH$; butyl—$C_2H_5CH_2CH_2OH$; and amyl—$C_5H_{11}OH$. They are colorless, inflammable, volatile liquids with characteristic odors. Their specific gravities vary from 0.79 to 0.81. Their boiling points vary from 65°C to 138°C. They are used as solvents.

Mode of Action and Symptomatology:

Methyl alcohol is a source of grave injury to many industrial workers. It has a specific action on the optic nerve, and with long enough exposure, blindness may result. The action is that of inflammation of the optic nerve followed by atrophy. A considerable amount of methyl alcohol poisoning was noted during prohibition days when wood alcohol was used in large amounts with subsequent optic nerve degeneration and blindness.

The other alcohols, because of their volatility are not considered to be especially dangerous. Cases of narcotic poisoning have been attributed to them but not proved. The higher alcohols, like butyl and amyl, have in addition an irritant action as well as some poisonous action on the protoplasm.

Treatment:

If methyl alcohol is taken internally, the use of an emetic is indicated. Four per cent sodium bicarbonate, as a gastric lavage, is excellent. When the toxic action results from absorption through the skin, a lavage is of no benefit Because an acidosis results, due to the formation in the system of formic acid from the methyl alcohol, sodium bicarbonate or sodium lactate intravenously is advisable. It can also be given by mouth. This treatment should be continued until the acidosis has been corrected. The patient should be kept warm and symptomatic treatment offered. With the exception of the eyes most abnormalities from chronic exposure clear up after removal of the exposure. The treatment of exposure to the other alcohols is entirely symptomatic.

Prophylaxis:

Atmospheric concentrations should be kept below the values shown in Table I. As with all solvents prolonged skin contact should be avoided. This is especially true of methyl alcohol, which can be absorbed through the skin in sufficient quantities to be harmful. Periodic physical examinations of personnel exposed to methyl alcohol should be made at two to three month in-

tervals. This should include an ophthalmologic examination.

Carbon Disulfide

CARBON disulfide has played an important part for many years in the rubber industry. Sulphur is incorporated into both crude and American-made rubber. It is also used in the manufacture of viscose rayon. It has long been recognized as an industrial poison.

Chemical and Physical Properties:

The chemical formula is CS_2. It is a colorless, highly inflammable liquid with a characteristic odor. The specific gravity is 1.26: The boiling point is 46°C. It is used as a solvent.

Mode of Action and Symptomatology:

The Pennsylvania Department of Labor and Industry[11] has done a complete series of clinical, anatomical, and experimental studies on carbon disulfide. Poisoning was found to be present even when exposure was not great. It was found that chronic carbon disulfide intoxication may involve all parts of the central and peripheral nervous systems beginning with psychic symptoms. Later peripheral neuropathy and damage to the cranial nerves, decrease of corneal and pupillary reflexes, as well as pyramidal and extrapyramidal signs occur. Varying degrees of Parkinsonism were also observed. The commonest form of carbon disulfide poisoning is neuritis which may affect any of the nerves but most commonly involves the nerves of the limbs and certain of the cranial nerves. Both the motor and sensory nerve fibers are affected causing abnormal sensations and loss of power. Pain is usually associated with these symptoms. The most striking and disastrous effects are upon the brain. The mental symptoms run the gamut from simple irritability and depression to manic depressive insanity. The most important point is the prevention of such poisoning.

Treatment:

There is no specific treatment for chronic carbon disulfide poisoning. A diet high in vitamin content with an adjunct of vitamin B complex may be of value. Liver extract may be given. For the acute case, five to 7% carbon dioxide in oxygen inhalations should be used along with respiratory and circulatory stimulants.

Prophylaxis:

This is one of the most toxic of industrial solvents. Atmospheric concentrations should not exceed 20 p.p.m. This necessitates the use of the compound in only those places where proper enclosure and ventilation can be provided. Its high volatility further adds to the control demands. Skin contact must be avoided. Periodic physical examinations, which include a careful evaluation of neurological symptoms should be made at monthly intervals on all exposed personnel. At the first intimation of any unusual symptoms indicative of carbon disulfide over-exposure, the employee should be removed from contact with the compound. The drinking of alcoholic beverages by exposed personnel should be discouraged.

Summary

THE principal ingredients of butadiene-type American-made rubber are enumerated and discussed. Toxicological properties, results of over-exposure, treatment of over-exposure and prophylaxis are described. An attempt has been made to review and coordinate the current literature with the author's personal experiences and observations.

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