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ENVIRONMENTAL HEALTH CONTROL FOR THE RUBBER INDUSTRY*

W. E. McCormick

Department of Environmental Control, The B. F. Goodrich Co., Akron, Ohio 44318

CONTENTS

Page

I. Introduction 513
II. Hazard control methods 514
III. Types of industrial health hazards 514
IV. Polymer manufacturing 515
A. Styrene butadiene rubber 515
B. Stereoregular rubbers 515
C. Nitrile rubbers 515
D. Neoprene rubbers 516
E. Butyl rubbers 516
F. Ethylene propylene rubbers 516
G. Polyurethane rubbers 516
V. Processing Chemicals and Accelerators 517
A. Carbon black 517
B. Siliceous dusts 518
1. Talc and soapstone 518
2. Kaolin 519
3. Mica 519
4. Submicron silicas 519
C. Organic solvents 520
1. Paraffin hydrocarbons 520
2. Aromatic hydrocarbons 520
3. Chlorinated hydrocarbons 521
a. Carbon tetrachloride 521
b. Ethylene dichloride 521
c. Trichloroethylene 521
d. Perchloroethylene 522
e. 1, 1, -Trichloroethane (methyl chloroform) 522
4. Acetates 523
5. Ketones 523
6. Alcohols 524
D. Primary accelerators 525
1. bis(Benzothiazolyl)disulfide 526
2. 2-Benzothiazolyl diethylthiocarbamyl sulfide 526
3. N, N'-bis(2-benzothiazolylthiomethylene)urea 526
4. Bismuth dimethyldithiocarbamate 526
5. Cadmium diethyldithiocarbamate 526

* This article is the first of two papers devoted to health control in the rubber industry. The second paper, to be printed later in Rubber Reviews, will deal with the toxicological effects of antioxidants and antiozonants.

6. Lead dimethyldithiocarbamate and lead dithiocarbamate 526
7. 2-Mercaptobenzothiazole 526
8. 2-Mercaptoimidazoline 526
9. *p*-Nitrosodimethylaniline 526
10. N-oxydiethylene-2-benzothiazole sulfenamide 527
11. Piperidinium pentamethylenedithiocarbamate 527
12. Poly-*p*-dinitrosobenzene 527
13. Selenium diethyl (or Dimethyl) dithiocarbamate 527
14. Tellurium diethyldithiocarbamate 527
15. Tetraethylthiuram disulfide 527
16. Tetramethylthiuram disulfide 528
17. Tetramethylthiuram monosulfide 528
18. Zinc diethyldithiocarbamate 528
19. Zinc dimethyldithiocarbamate 529
E. Secondary accelerators (activators) 529
1. *n*-Dibutylamine 529
2. Di-*o*-tolylguanidine 529
3. Diphenylguanidine 529
4. Hexamethylenetetramine 530
VI. References 530

I. INTRODUCTION

To present a review of the health problems and their control for the Rubber Industry requires the making of certain choices relative to the breadth of the discussion. It is well known that the Rubber Industry has many facets. These involve not only the conversion of the natural and synthetic polymers into usable articles, but the manufacture of chemicals, plastics, and numerous other materials. For this reason, this review is restricted to the manufacture of the commonly used synthetic polymers and to the operations incident to the conversion of these polymers and the natural polymer into marketable products.

Why should there be a concern with respect to the health problems of the Rubber Industry? (1) It is well known that many different chemicals are used, not only in the manufacture of polymers but in the conversion process[1]. The industry is a huge consumer of chemicals, and these run the gamut of highly hazardous to inocuous. Proper environmental controls must be applied in order to handle them safely. (2) An increased emphasis by governmental agencies for a safe working environment has also been an important factor. (3) And, finally, our society as a whole shows an increasing concern with respect to all environmental factors affecting life and property.

Industrial hygienists use a basic guiding principle for all environmental health hazard control: all materials are toxic to some degree, including such common essentials as water and oxygen. The problem is to determine the *level* or *quantity* at which a specific material is harmful or produces an adverse effect. The question is always, therefore, not whether a material is toxic; rather, is it *hazardous* (too much). It would be impossible for most industrial operations to occur if we had to have zero exposure of personnel to materials. The definition of the hazardous amount is frequently very difficult and time consuming, and involves skills of several disciplines, including those of toxicology and medicine. It requires the study of animals under controlled insult conditions and the ongoing observations of humans during their working lifetime.

II. HAZARD CONTROL METHODS

The methods used for the control of environmental health hazards in the Rubber Industry are those that are generally used elsewhere. These are:

Modification of the Process
Enclosure
Isolation
Substitution of a Material Which is Less Hazardous
Personal Protective Equipment
Ventilation
The Use of Shields or Barriers

It is well recognized that the science of industrial hygiene is a highly specialized one and those personnel engaged in it in the rubber industry must be well equipped by training and experience to evaluate properly manufacturing processes with respect to environmental hazards and to devise proper means of control. They must constantly be knowledgable in the ever changing spectrum of manufacturing operations and materials used. They must be well versed in proper techniques of air sampling that are applicable to the specific materials that present potential health hazards. Sufficient atmospheric evaluations must be made so that proper conclusions can be drawn as to whether or not a health hazard exists. If it does, then means of controlling it to safe levels must be devised.

The most effective control of environmental health hazards is accomplished by a combined use of appropriate environmental controls and proper examinations of personnel. The latter serve to pinpoint those individuals who are hypersensitive, as well as to provide proper documentary records for any future need by either the employee or the company. However, in order to be effective the examinations must be of a type whereby some biochemical change can be readily observed prior to the onset of symptoms or organic damage. The procedure must also be simple so that it can be readily done with little or no discomfort to the employee. It should be an index of over-exposure, not a diagnostic sign of existing disease. There are many acceptable procedures now being used for this purpose. Among them are: complete blood counts, chest x-rays, quantitative examinations of blood and/or urine for specific materials, such as lead and mercury; and liver function tests. However, there are still many materials that are used for which it is desirable to have some better index of overexposure.

III. TYPES OF INDUSTRIAL HEALTH HAZARDS

The actual and potential health hazards of the Rubber Industry fall into three general categories: (1) inhalation of airborne dusts, vapors, mists, *etc.*, (2) skin contact whereby either dermatitis is produced, or systemic absorption may occur (3) physical agents, such as ionizing radiation, noise, heat, and nonionizing radiation. Hazards from oral ingestion of toxic materials may be present, but in general, they are not the dominant factor. Oral ingestion can, however, be quite significant in the overall hazard of materials, such as lead, mercury, selenium, and others, because this factor may increase the *total* body burden.

A discussion of the specific hazards in the first two of these general categories will now be undertaken for polymer manufacture and processing operations.

IV. POLYMER MANUFACTURING

A. STYRENE BUTADIENE RUBBER

The manufacture of SBR polymers is done in modern plants with processes that are generally closed. It is well known that both styrene and butadiene are highly flammable and rigid controls must be in effect in the plants to prevent fires. The physiological effects of styrene and butadiene, in general, are mild[2]. With the advent of wide usage of these monomers during World War II, extensive studies on their effects were undertaken. Based upon the animal experimentation that was carried out, it was felt that no severe health hazards would accrue to personnel working with these materials in the (then) government owned plants[3,4]. Subsequent observation of personnel over many years has proven this conclusion to be correct. Styrene is quite irritating in vapor form with a TLV (Threshold limit value. As used here it refers to the levels recommended by the American Conference of Governmental Industrial Hygienists, 1969 list. The levels are intended to serve as guides for safe eight-hour continuous inhalation exposure.) of 100 ppm generally accepted. The liquid is also quite irritating to the skin and may cause severe dermatitis. A recent study by Stewart[5] indicates some signs of impairment of neurological function may occur in humans with a one-hour exposure to a vapor concentration of 375 ppm. In spite of its similar chemical structure to benzene it does not produce the serious blood dyscrasias that results from benzene exposure. Chronic effects have not been observed. Butadiene is a less irritating compound to the respiratory passages than styrene, and as in the case of styrene, chronic effects have never been observed. A TLV of 1000 ppm has been generally accepted. Acute exposures, of course, to either of these compounds may occur through accidents and improper handling in the plants. Both are capable of producing fatalities at high atmospheric levels.

B. STEREOREGULAR RUBBERS

Polybutadiene and polyisoprene are the principal products in this class. The polymerization of butadiene and isoprene is generally accomplished in hydrocarbon solvents through the use of alkyl aluminum compounds, using selected titanium compounds as catalysts. The manufacturing processes are essentially closed and provide little opportunity for excessive exposures to the monomers. Isoprene produces its physiological effect primarily as an anesthetic[6]. Chronic intoxication has not been observed; acute exposures may be serious depending upon their degree. The physiological effects of butadiene have been discussed in the previous section.

The aluminum alkyls are particularly hazardous from the standpoint of fire. Because they ignite spontaneously in the air, their handling in the manufacturing plant must be such that this will not occur. Accidental spillage on the body will produce serious, or even fatal burns.

C. NITRILE RUBBERS

These polymers are based upon the copolymerization of acrylonitrile and butadiene. One of their principal characteristics is their unusual oil resistance. The principal health hazard involved in their manufacture arises from acrylonitrile—a highly toxic substance. It is a liquid at ordinary temperatures and possesses moderate voltatility. Its principal physiological effect is that of a

hematoxin; similar to, but less severe than hydrogen cyanide[7,8]. It can be absorbed through the skin in amounts which may be harmful or even fatal, but its principal hazard arises through inhalation of its vapors—it has a TLV of 20 ppm. A specific treatment for acrylonitrile intoxication is available and has been described[9].

D. NEOPRENE RUBBERS

The polymerization of 2-chloro-1, 3-butadiene (chloroprene) results in a polymer, polychloroprene, with the trade name Neoprene. The monomer is hazardous and requires careful handling. It is a central nervous system depressant and is also toxic to the liver. It may be absorbed through the skin in harmful quantities. Loss of hair has been observed in personnel working around the polymerization processes. A TLV of 25 ppm of chloroprene is generally accepted. The polymer itself is free of any health hazard and has been used widely over a great many years.

E. BUTYL RUBBERS

The copolymerization at low temperature of isobutylene and isoprene in the presence of boron trifluoride and methyl chloride results in butyl rubber. Closed processes are used in the polymerization and there is little opportunity for exposure of personnel to hazardous materials. The physiological effects of isobutylene and isoprene are primarily anesthetic, with no evidence of chronic injury[6,11]. Accidental acute exposures, if they occur from either compound, can be harmful. Both compounds are flammable and rigid precautions must be observed in the manufacturing operations to prevent fires.

Boron trifluoride is a highly toxic, colorless gas. Its physiological effects have not been thoroughly investigated, but Torkelson and co-workers[12] have performed inhalation animal studies. Based upon their work, the principal effect appears to be marked irritation of the respiratory tract. A TLV of 1 ppm (as a ceiling level) has been established.

Methyl chloride is a moderately toxic compound possessing anesthetic properties. It may also produce kidney and liver damage, as well as central nervous system effects. The mortality may be as high as 35% of excessively exposed personnel[13,14]. A TLV of 100 ppm has been established.

F. ETHYLENE PROPYLENE RUBBERS

This class of rubbers result from the copolymerization of ethylene and propylene, in a hydrocarbon solvent system, using aluminum alkyl compounds, with various titanium or vanadium compounds as catalysts. Neither ethylene nor propylene possesses any severe health hazards[11]. Each has anesthetic properties, but chronic effects do not occur. Each is highly flammable and precautions must be taken in handling to prevent fire. High acute exposures to either of the vapors may result in anesthesia or fatality. The hazards of the aluminum alkyls have been discussed under "Stereoregular Rubbers". No TLV has been established for either ethylene or propylene, but it is generally recommended that atmospheric concentrations should not exceed 1000 ppm of either one.

G. POLYURETHANES RUBBERS

Polyurethanes are produced by reacting an isocyanate, usually either toluene diisocyanate (TDI), or methylene bis(phenyl isocyanate) (MDI), with either a polyester or a polyglycol. The isocyanates are highly toxic compounds[15–18]. Their principal physiological effect is on the respiratory tract, resulting in the production of asthmatic-like symptoms. Extremely low vapor concentrations may, in some individuals, initiate these symptoms. The response appears to be strongly related to certain allergies. A TLV of 0.02 ppm has been established for both TDI and MDI. This is an extremely low level and is frequently difficult to attain around manufacturing processes. Very rigid control is needed to be sure that these vapor levels will not be exceeded, requiring careful enclosure of the processes and the use of well designed process ventilation. Individuals with known allergies or with any evidence of pulmonary disease should not be assigned to any isocyanate vapor exposure.

In some types of polyurethane manufacture, amines are used as catalysts. In general, this class of compounds needs to be handled carefully from the standpoint of skin contact. The degree of hazard varies somewhat widely depending upon the type of amine, but many of those used in polyurethane manufacturing will produce skin irritation and, in some cases, serious skin damage. Precautions need to be taken so that such contact will not occur, and if it is accidental, the affected area should be washed immediately with soap and water. Spillage of most amines into the eye can produce serious damage. Appropriate eye protective devices must therefore be used when these compounds are handled; and first-aid eye washing facilities, using only water with prolonged irrigation (at least 15 minutes), must be immediately present. Exposure to the vapors of some amines will produce "halo vision." This can be a delayed effect, not occurring until some time following exposure. It is particularly insidious so far as safety is concerned because it may seriously interfere with vision after the employee leaves the manufacturing premises.

V. PROCESSING CHEMICALS AND ACCELERATORS

Because of the wide variety of materials used in rubber processing operations it is impossible to give a detailed review of each material. An attempt will be made, however, to discuss the actual or potential health hazards of those items which offer the most likely possibilities for occupational health problems.

A. CARBON BLACK

Other than the polymer itself, perhaps the most widely used material is carbon black, with many opportunities presented for dust exposure. There are now throughout the rubber industry, in both the United States and abroad, innumerable men and women who have had many years of dust exposure to carbon black. Allegations have frequently been made as to the harmfulness of such exposures. There is no actual evidence, however, to support such claims.

In 1952, Von Hamm and Mallette[19] demonstrated the extractability of a substance or substances from carbon black which would produce tumors in mice. A number of investigators have assumed, therefore, that carbon black is a potential carcinogen. However, Ingalls, in his extensive studies of workers in the carbon black manufacturing industry, and Nau[21–24], in his animal experiments, have both demonstrated the non-existence of any tumorigenic potential. Nau's work indicates that, although compounds, such as benzpyrene, can be identified as a sorbant on carbon black particles, it is bound so effectively to the carbon black that its carcinogenic potential is lost. This theory might well explain the incongruity which would appear to exist, whereby a known carcino-

gen is present on carbon black, and yet, the epidemiological experience over many years, of workers in the carbon black manufacturing industry and in the rubber industry, is entirely favorable.

A TLV of carbon black of 3.5 mg/m³ has been established. This indicates no severe health hazard. Carbon black is handled in rubber manufacturing plants, in partially closed processes, and with some process ventilation. It is not considered to be a material requiring any special handling so far as health hazards are concerned.

B. SILICEOUS DUSTS

A number of siliceous dusts are used in the rubber industry, and some in sizeable quantities. A brief review of each of the more common ones follows:

1. Talc and soapstone. Various materials used in the trade are commonly called "tales" or "soapstones". These are used principally for the dusting of rubber to prevent it sticking to itself. The two terms are used rather synonymously in the rubber industry without any attempt to identify the mineral composition. Talc is a silicate with a specific composition of $H_2Mg_3(SiO_3)_4$ and is referred to, mineralogically, as steatite. Other silicates which have been used frequently and referred to as either talc or soapstone are the following: Antophyllite $H_2Fe_7Mg_7Si_8O_{24}$, Chlorite $H_8Mg_5Al_2Si_3O_{18}$, Pyrophyllite $H_2Al_2Si_4O_{12}$, Serpentine $H_4Mg_3Si_2O_9$, and Tremolite $CaMg_3Si_2O_9$.

The literature contains many publications, some of which are contradictory, with respect to the physiological effects of talc. This can be explained by (1) inadequate knowledge as to the specific identity of the materials, (2) the author's failure to identify it properly, or (3) the investigator's failure to note the ingredients. It is well known that certain siliceous materials, most notably quartz (and other crystalline forms of free silica, such as crystobalite and tridymite) and asbestos, will produce, through long dust exposure, serious lung disease. Many of the mineral deposits of steatite, and the other five silicates listed above, contain appreciable quantities of associated free silica, usually in the form of quartz. One of them in particular, pyrophyllite, may contain as much as 40% quartz.

Numerous studies over the years have attempted to demonstrate the harmfulness (or the safety) of talcs, from the standpoint of dust inhalation. This began in 1933 with the report of Dreessen[25] and involved exposure to tremolite. It is generally recognized now that tremolite will produce definite pulmonary fibrosis through long exposure to its dust. Furthermore, the recent work of Kleinfeld[26] and his associates indicates an increased incidence of pulmonary cancer among older personnel who have been exposed over a period of years.

Hogue and Mallette[27] in 1949 reported on an epidemiological study involving 20 men engaged in rubber inner tube production, who had been exposed to talc dusts for periods ranging from 10 to 36 years. They concluded that there was no significant health hazard from talc *per se*, provided it did not contain free silica. Weiss and Boettner[28] have recently reviewed the problem of talcosis in relationship to the use of commerical talcs and conclude that the principal health problem arises from tremolite and free silica which might be associated with other dusting materials.

A TLV for talc and soapstone of 20 million particles per cubic foot of air has been established, in contrast to 5 million particles per cubic foot of air for tremolite. Steps should be taken around all processing operations to maintain dust levels below these values. In view of the acknowledged increased risk of tremolite dust and quartz dust, it seems prudent to use as dusting materials only those that are free of either of these ingredients.

2. Kaolin.—Kaolin, or more commonly called clay, is almost pure aluminum silicate having a chemical formula, $Al_2O_32SiO_2:2H_2O$. It is used as both a dusting material for rubber and as an ingredient. Kaolin has not been regarded as harmful by inhalation. In 1960 Edenfield[29], presented the results of a 5 year study involving 1130 empolyees in the Georgia kaolin manufacturing industry. This study strongly indicates there is no significant health hazard associated with the inhalation of kaolin dust. It does, however, show a probability of aggravating existing tuberculosis.

3. Mica.—The recent literature shows a paucity of information on the health effects of mica dust. It is generally felt that some adverse pulmonary effects will result from such inhalation over many years exposure. This is based largely upon the studies which were done in the early 40's by personnel of the United States Public Health Service and the State of North Carolina[30,31]. More recently, Heimann, and associates, have provided a brief report on a group of 61 workers in mica factories in Bihar, India[32]. This report indicates a very mild pneumoconiosis resulting from relatively high dust exposure.

4. Submicron silicas.—During the past two decades the use of certain very finely-divided silicas has become wide-spread in the rubber industry. These products are essentially 100% silica, but are amorphous rather than crystalline. A number of studies to evaluate the physiological effects of these products have been made. Some of the more common trade names are: HiSil, Silene, Cab-o-Sil, Aerosil.

In 1952, Jötten and Klosterkotter[33], reported that rats died following the intratracheal injection of 10 mg of Aerosil. In 1956, Swensson[34], and associates, found a significant toxic effect to rats and mice by both intraperitoneal, intravenous, and intratracheal injections. They used both amorphous and crystalline silicas; the amorphous being Aerosil manufactured in Germany. The amorphous variety was less lethal than the crystalline form with the same dosage. In a series of inhalation experiments in which several species of animals were used, Schepers and his associates[35–38], at the Saranac Laboratory, reported that the Degussa submicron amorphous silica did not produce fibrosis in rats, rabbits, or guinea pigs. However, pulmonary changes were observed, principally of an emphysematous type, and the tuberculous infective processes in guinea pigs appeared to be stimulated (not aggravated).

Volk[39] has reported on a 14-year observation of 215 employees working in a plant manufacturing Aerosil. The only significant finding in this group of employees was a slight interlobar pleuritis. There was no evidence of silicosis or pulmonary fibrosis.

Schepers[40] has reported on the effects of monkeys inhaling amorphous silica dust. In his experiment he used 5 animals for a 12 month's exposure to an atmospheric concentration of 0.43 mg/cubic ft. The trade name of the submicron silica is not identified but it was manufactured by dehydrating sodium silicate with alcohol. In all of the monkeys some pulmonary disease was found—principally emphysema, vascular damage, and cor pulmonale.

Plunkett and DeWitt[41] have reported on an 18-year study of the health records of 78 employees engaged in the manufacturing and processing of two commercial sub-micron silicas: Hi-Sil and Silene. Dust exposures ranged from

0.01 mg/cubic ft. of air to 5.77 mg/cubic ft. of air. No adverse effects, whatsoever, were observed.

The information, to date, on the sub-micron silicas seems to show definitely that they do not produce classical silicosis. Some of these products are made by precipitation from silicates, while others are made from the combustion of silica compounds. The data seem to indicate, based principally upon animal experimentation, that adverse tissue reactions may occur from some of these products. It seems prudent, therefore, to keep dust exposure of personnel handling these silicas to a minimum to be sure that no individual with existing pulmonary disease will be exposed to these dusts, and to perform periodic physical examinations on personnel who may be exposed.

C. ORGANIC SOLVENTS

A variety of organic solvents are used in rubber processing operations. Basically, these fall into six general classes: paraffin hydrocarbons, aromatic hydrocarbons, chlorinated hydrocarbons, acetates, ketones, and alcohols. These solvents are used, either as ingredients of adhesives or as tackifiers for adhering rubber to itself.

1. Paraffin hydrocarbons.—*n*-Hexane and *n*-heptane, or commerical-name solvents based on one or both, are the principal paraffin hydrocarbons used in rubber processing. Both have been used for many years and the health experience has been entirely favorable. Von Oettingen[42] has extensively reviewed the toxicity of these as well as other aliphatic and aromatic hydrocarbons in his publication of 1940. Henderson and Haggard[43] state that the acute inhalation toxicity of heptane is somewhat higher than hexane—the former producing dizziness at a level of 5000 ppm within 4 minutes, while the latter produces the same effect in 10 minutes. Specter's information on the effects on mice are somewhat at variance with this. He reports[44] a lethal concentration for hexane between 34,000 and 42,600 ppm with a two hour exposure, but in the case of heptane, a level of 18, 337 ppm for the same length of time is required.

The commercial grades of both of these solvents may contain some aromatic hydrocarbons, including benzene. Concentrations ranging up to 5–6% by weight of benzene are not unusual. As will be discussed later, benzene is a highly toxic compound and careful handling is essential. Therefore, in the use of either hexane or heptane care should be taken to assure the absence of benzene, or if it is present, to establish appropriate controls for safe use.

Both of these solvents are highly flammable and fires from static electrical discharge around operations where they are used are not uncommon. Both will produce skin irritation, largely because of their defatting qualities.

2. Aromatic hydrocarbons.—In this class, the three solvents most commonly used in the rubber industry are benzene, toluene, and xylene—with corresponding commercial names of benzol, toluol, and xylol. At one time, benzene was quite widely used in rubber processing operations. This is no longer true, largely because of its insidious health hazards. It has been supplanted, for the most part, by either toluene or xylene so that its present uses are of a quite specialized nature. Physiological effects of each of these compounds has been extensively reviewed by Von Oettingen[42]. Acutely, xylene and toluene appear to be somewhat more toxic than benzene. The acute effects of all three are narcosis.

More importantly, however, from an industrial standpoint, are the long-term chronic effects. In this respect, benzene must be regarded as highly

hazardous and much more severe than either of the other two. This is based upon many years of experience[2]. The principal effect of chronic exposure to benzene is damage to the blood forming processes. Blood dyscrasias may result, with the most serious being aplastic anemia—this may be fatal. There appears to be a wide variation in susceptibility of individuals and this is unpredictable. Symptoms may occur after exposure has ceased. Some medical opinion holds that benzene may play some part in the production of leukemia, although this has not been definitely established. Although both toluene and xylene are closely related chemically to benzene, neither produce the serious blood effects of benzene as indicated by Gerarde[45–47]. The commercial grades of either, however, may contain appreciable quantities of benzene. Careful scrutiny must therefore be paid to their uses. Both are skin irritants and skin contact should be avoided.

Not only is it necessary to establish proper environmental controls to handle aromatic hydrocarbons safely, but physical examinations should also be performed on exposed personnel. This is particularly true in the case of benzene. These examinations should include a periodic complete blood count and the serial results carefully reviewed. Marked changes in the blood picture, particularly in a reduction of the total white count, become quite significant. If this trend is observed early, prior to the onset of symptoms, corrective measures can be taken to avoid injury to the individual.

3. Chlorinated hydrocarbons.—The most commonly used members of this class, in the rubber industry, are: carbon tetrachloride, ethylene dichloride (1, 2 dichloroethane), trichloroethylene, perchloroethylene, and methyl chloroform (1, 1, 1 trichloroethane). The health hazards of these vary, with carbon tetrachloride the most severe, and methyl chloroform the least. All will produce anesthesia and all are capable of producing liver and/or kidney damage. Von Oettingen[48] has extensively reviewed the physiological effects in both animals and humans of these as well as many other halogenated hydrocarbons.

a. Carbon tetrachloride. Carbon tetrachloride is a severely hazardous chemical[49,50]. It is particularly insidious in that low levels of exposure may produce very serious kidney injury. The currently recommended maximum level of 10 ppm *cannot be readily detected by most humans by odor.* Individual susceptibility varies quite widely. It is readily absorbed through the intact skin of experimental animals in toxic amounts, and Stewart and Dodd[51] have shown that it can be absorbed through human skin. Such contact should also be avoided because of the strong defatting action and subsequent skin irritation.

b. Ethylene dichloride (1, 2 dichloroethane). This is a significantly toxic compound. The data of Spencer and his associates[52], as well as that of Browning[53], indicate that it is strongly anesthetic and that fatalities can occur very quickly with exposures ranging up to 100,000 ppm (10% by volume). The same data of Spencer, with repeated inhalation by animals, as well as that of Heppel[54], indicates adverse effects at 200 ppm, but essentially no effects at 100 ppm with exposures 7 hours per day, 5 days per week, over many months, to rats, guinea pigs, rabbits, and monkeys. However, at a level of 1000 ppm there was a high degree of mortality to these animals and microscopic changes in the liver.

Ethylene dichloride can be absorbed through the skin, but it requires a large amount to produce significant systemic effects. Repeated or prolonged skin contact should be avoided because of the irritation resulting from its defatting action.

c. Trichloroethylene. This compound is strongly anesthetic as indicated by the work of Adams and associates[55]. In fact, pharmaceutical grades of it are

widely used as general anesthetic agents in concentrations varying from 5000 to 25,000 ppm by volume in air or oxygen. In 1960, Boulton and Sweet[55], on the basis of some 73,000 cases of surgical anesthesia, concluded that trichloroethylene was as safe as any other anesthetic agent in use at that time. Grandjean and coworkers[57] assert that neurologic changes may result from prolonged overexposure, while Williams[58] finds that such exposures may also cause minor injury to the liver.

For many years, it has been assumed that the use of alcohol was contraindicated with trichloroethylene. Cornish and Adefuin[59] have demonstrated that this does occur in rats.

Stopps and McLaughlin[60] have showed that no significant psychophysiological functional effect occurs in humans with prolonged exposure to 100 ppm, but that such effects do exist at higher levels and their severity increases as the atmospheric concentration increases. Stewart and coworkers[61] found that humans exposed to 200 ppm for 4–5 consecutive eight-hour periods, showed mild subjective symptoms, principally fatigue.

Stewart and Dodd[51] have demonstrated that trichloroethylene is absorbed through human skin, but that it is unlikely that the amount so absorbed will be harmful.

It is not uncommon to find that some employees using trichloroethylene in industry develop an habituation for it. Its mild, intoxicating effect, and subsequent euphoria, are found to be very pleasant and employees will frequently purposely inhale its vapors. This practice, of course, should be prohibited.

d. Perchloroethylene (tetrachloroethylene). Perchloroethylene is used in essentially the same types of operations as trichloroethylene. It is a somewhat higher boiling solvent and has certain advantages, therefore, for degreasing operations. It possesses strong anesthetic properties, and with sufficient exposure, may produce liver or kidney damage. Rowe[62] and associates found that single exposures to rats of 6000 ppm caused unconsciousness within a few minutes, but that 2000 ppm, inhaled for 14 hours, produced no similar effects. They also found that a concentration of 20,000 ppm caused the death of rats in approximately 4½ minutes. These same investigators found that human subjects exposed to an atmospheric concentration of 280 ppm for 2 hours, felt that motor coordination was impaired. Unconsciousness has been reported to have occurred in one individual exposed to an average atmospheric concentration of 275 ppm for 3 hours, followed by 1100 ppm for 30 minutes. Clinical recovery occurred rapidly; but, there was a prolonged effect upon the liver suggestive of mild hepatitis.

These same investigators found that repeated seven hour inhalation exposures of rats at an atmospheric concentration of 2500 ppm, caused rapid death. Rats, monkeys, and rabbits tolerated repeated exposures of 400 ppm without ill effects, but guinea pigs did not. Stewart[63] and his coworkers believed that human vapor inhalations above 200 ppm may be a real hazard, principally because of the production of disorientation and noticeable light-headedness.

Stewart and Dodd[51] have shown that perchloroethylene can be readily absorbed through the skin; however, the amount so absorbed is unlikely to be harmful. Skin contact should be avoided because of the solvent's irritant effect, principally because of its defatting action.

In experiments with rats, Cornish and Adefuin[59] failed to find any evidence of a potentiating effect of perchloroethylene and ethyl alcohol.

c. Methyl chloroform (1, 1, 1 trichloroethane). The least hazardous of the commonly used chlorinated hydrocarbons is methyl chloroform. While it is not completely inocuous, its serious physiological effects, such as liver and kidney damage, are much less severe than those of other chlorinated hydrocarbon solvents. This is in marked contrast to 1, 1, 2 trichloroethane which is a highly toxic and hazardous compound.

Acutely, the most important physiological effect of methyl chloroform is a depression of the central nervous system. Experiments with dogs have indicated that ventricular arrhythmia can be produced similarly to that from other chlorinated hydrocarbon solvents[64]. Torkelson and his coworkers[65] used rats, guinea pigs, rabbits, and monkeys with repeated atmospheric exposures over a six month period; of 500, 1000, 2000, and 10,000 ppm concentrations. They found no effects upon any of the animals at the 500 ppm level. Above this, some effects were observed—primarily anesthesia. These same authors provide an excellent review of the literature on the physiology of methyl chloroform.

Stewart and his coworkers[66] carried out inhalation experiments with six human volunteers at atmospheric levels ranging from approximately 500 ppm to 2650 ppm for periods of time of 15 minutes to 186 minutes. The conclusions were that methyl chloroform acts principally as an anesthetic agent and has only slight capacity to cause irreversible injury to liver or kidneys. Stewart and Dodd[51] have shown that methyl chloroform can be absorbed through human skin, but the degree of absorption is insufficient to cause any systemic poisoning. Skin irritation will result from repeated or prolonged skin contact, principally because of the defatting effect. Cornish and Adefuin[59] in work with rats, found no potentiation of the toxicity of methyl chloroform by ethyl alcohol.

4. Acetates.—In this class of solvents, two—ethyl acetate and isopropyl acetate—are commonly used in the rubber industry. The latter is the one in greater use. Amyl acetate is used, but in a very limited way. Von Oettingen[67] has extensively reviewed the physiological effects of ethyl and isopropyl acetate, as well as others of the same series. Some of the information contained in his review, as well as that by Browning[53], would indicate some evidence of cumulative effects. Such effects, however, have not been seen in recent usage and it could well be that some of the earlier reports were solely the result of impurities. The principal effect of these esters is anesthesia and this effect increases in potency as one ascends the homologous series, *i.e.*, amyl acetate is a more severe anesthetic than ethyl acetate.

All three of these esters are irritating to mucous membranes to some degree. This is the predominant effect found on a day-to-day basis. The work of Nelson and associates indicates that atmospheric levels of 400 ppm of ethyl acetate and 200–300 ppm of amyl acetate are irritating to humans.[68] However, exposures of ethyl acetate, ranging up to 1500 ppm for several months, have produced no unusual signs or symptoms to personnel[69]. Silverman and his coworkers[70] have observed irritant effects on the eyes of humans at a level of 200 ppm for isopropyl acetate.

The present TLV's for the acetates are based primarily upon irritant effects, rather than upon any known chronic systemic insult. The only needed control in actual usage is the maintenance of atmospheric concentrations below such irritant levels by means of suitable process enclosure and/or ventilation.

The acetates may produce skin irritation through repeated or prolonged skin contact, primarily because of their defatting action.

5. Ketones.—The three ketones in common use in the rubber industry are: acetone, methyl ethyl ketone, and methyl isobutyl ketone. Physiologically, these compounds are classed as narcotics. This effect, however, is rarely seen

in industry and usually occurs only under accidental, acute-type exposures. All are irritating to the eyes and mucous membranes at certain atmospheric levels, and this effect is observed long before any signs of narcosis appear. In general, the irritant and narcotic potencies increase with increasing molecular weight.

Human experience with acetone exposures has been very favorable. One study involving daily exposures up to 2000 ppm over a 15 year period showed no evidence of adverse effects. Considerable attention has been paid to acute exposures to animals and is summarized by Patty[71]. These data indicate that varying narcotic responses will occur, depending upon the atmospheric concentration and time of exposure. Nelson and associates report that eye irritation will result to humans beginning at about 200 ppm in the air[68].

Browning has reported that there are no recorded instances of human illness resulting from the use of methyl ethyl ketone (2-butanone)[53]. Elkins[72] indicates that no permanent ill effects have been observed in humans with exposures of 700 ppm; although transitory effects, such as headaches, throat irritation, *etc.*, do occur. He felt that atmospheric concentrations above 330 ppm become objectionable. Patty and coworkers[73] have reported that a single atmospheric exposure of 100,000 ppm, in air, cause no deaths in guinea pigs after several minutes, and that a one-hour exposure of 10,000 ppm was without serious consequences. Further experiments with guinea pigs by Specht and colleagues[74], using vapor exposure levels of 1.0, 2.5, and 5.0% by volume, confirmed Patty's findings and the basic physiological effect of narcosis. Nelson and his associates report that atmospheric levels of 350 ppm, in air, caused significant irritation in human volunteers[68]. Methyl isobutyl ketone (2-hexanone) is a somewhat more potent narcotic than the two preceding ketones. The Shell Chemical Corporation has reported[75] that mice exposed for 30 minutes to 19,500 ppm became anesthetized, and that concentrations above 20,000 ppm produced deep anesthesia with subsequent death. Smyth[76] found that rats survived a 2000 ppm exposure for four hours, but that death occurred at an atmospheric level of 4000 ppm for the same period of time. Elkins[72] has reported that humans exposed to approximately 100 ppm complained of headache and nausea, but that these complaints were essentially eliminated when the atmospheric exposure was reduced to 20 ppm. One chronic study with animals has been reported by Shell Chemical Company[75]. In this, mice were given 20 minute daily exposures to atmospheric levels of 20,000 ppm over a 15 day period. Some deaths occurred.

There is little, if any, data on the skin absorption of these ketones. There is ample experience, however, based upon many years use in American industry, that if such absorption occurs it produces no ill effects. Skin irritation may occur from repeated or continued contact, principally as a result of the defatting action of these ketones.

In general, one can say that the aliphatic ketones, as a class, and specifically these three, are compounds with a low degree of toxicity and a very low risk of health hazard in their regular use.

6. Alcohols.—Three alcohols are used in the rubber industry: methyl, ethyl (in the denatured form), and isopropyl. As a class, the principal physiological effect of these compounds is narcosis, and the potency of this effect increases with increasing molecular weight.

Aside from the narcotic effect, however, methyl alcohol (wood alcohol) has a peculiar and serious effect upon the optic nerve. Frequent instances

of partial or total blindness from drinking it are regularly observed in the popular press. Sayers and his coworkers[77] found that dogs exposed to atmospheric levels of 10,000 ppm repeatedly for brief periods, developed no abnormalities. Leaf and Zatman[78] have calculated that repeated eight-hour exposures to 3000 ppm will lead to increased methanol concentrations in the body. Sterner and Fassett[79] have found that repeated short exposures to 400–500 ppm, and approximate one-half hour exposures of 1000–2000 ppm produced no demonstrable effects. Elkins[72] has reported that delayed death may occur in humans following a working day at an atmospheric concentration of 40,000 ppm. It is well known that methyl alcohol is readily absorbed through the skin. Therefore, in any industrial uses of this compound, this route of absorption must be seriously considered. Not only must atmospheric concentrations be maintained below the TLV (200 ppm) but skin contact must be prohibited; otherwise, the total body burden of methyl alcohol may be sufficient to produce injury even though the atmospheric TLV is satisfactory.

The use of ethyl alcohol as a beverage has been a part of human civilization for thousands of years. Its inebriating effects, whether by oral ingestion or by inhalation, if in sufficient amounts, are well known. Secondary effects, of course, can be more serious and subtle ones, principally liver damage. However, in the industrial use of this compound chronic effects are unknown. It is one of the safest industrial solvents. Generally, one of the several standard denatured formulations are used rather than the 95 or 100% pharmaceutical grades. Some of the denatured formulae contain compounds, such as methyl alcohol and benzene. The quantities present are normally insufficient to be of any concern, unless the use is under very adverse conditions of either direct skin contact or inhalation. Extensive animal experimentation with ethyl alcohol has occurred and this is well summarized by Patty[80].

Physiologically, *n*-propyl alcohol (propanol) and its isomer (isopropyl alcohol) are similar. The latter is perhaps more commonly used than the former. Browning[53] indicates there is very little risk for humans from the inhalation of either of these isomers. Lehman and Flury[81] state that mice can tolerate one hour of exposure to 4000 ppm without any signs of intoxication. Von Oettingen[82] has also shown that mice exposed to concentrations of 24,000 ppm for 100 minutes showed no after effects. Nelson and associates[68] found that 3 to 5 minutes exposure to 400 ppm of isopropyl alcohol produced mild irritation to the eyes, nose, and throat in human volunteers. These same investigators found that an atmospheric level of 200 ppm was the highest concentration acceptable to humans for an 8 hour period. On the other hand, Sherberger and coworkers[83] have found that this level is the minimum odor that most humans can identify.

Skin absorption of either ethyl or isopropyl alcohol is not a problem. While skin irritation may result from either compound with repeated or prolonged skin contact, it is unusual to find this occurring. Both are used therapeutically for skin cleansing, and as "rubbing" alcohol.

D. PRIMARY ACCELERATORS

Organic accelerators have been used in the manufacture of rubber products for many years. The chief purpose of these compounds is vulcanization of the polymer, whether it be natural or man-made. Those in current use vary quite widely in chemical composition. Many were "tailor made" for specific applications. The physiological effects of only those for which toxicological data

available are in this section. In general, the quantities of these compounds used are small at any one time, and exposure opportunities are limited.

1. bis Benzothiazolyl disulfide.—This compound has a very low oral toxicity as indicated by an approximate LD_{50} of 7 gm/kg for rats in a single oral administration. When added to the daily diet of rats at levels of 5000, 10,000 and 20,000 ppm and fed over a 31 day period, retardation of growth occurred, but there was no gross or microscopic pathology observed. A dosage of 10 gm/kg when applied for a 24 hour period to the skin of rabbits, produced no irritation[84].

The long experience in using benzothiazyl disulfide as an accelerator in the rubber industry has been quite favorable. No special handling precautions are needed.

2. 2-Benzothiazolyl-N, N, -diethylthiocarbamyl sulfide.—Little information exists on the physiological effects of this accelerator.

A single oral LD_{50} for the rabbit of 2.7 gm/kg has been reported[85]. It is moderately irritating to the skin of most individuals. No special handling precautions in its use are necessary, other than the prevention of skin contact.

3. N, N'-bis (2-benzothiazolyl thiomethylene) urea.—Mallette and von Hamm[86] determined an oral LD_{50} for rats of 6.0 gm/kg, indicative of a very low acute toxicity. The also found very mild skin irritative effects, using both rabbits and humans. There are no reports of any adverse experience in using this accelerator.

4. Bismuth dimethyldithiocarbamate.—Based upon the presence of the bismuth ion, one would expect a moderate toxicity. The only available data is that provided by the R. T. Vanderbilt Company, indicating an oral LD_{50} for rats of greater than 3 gm/kg and for mice, greater than 20 gm/kg[87]. This same company recommends avoiding breathing of dust and skin contact.

5. Cadmium diethyldithiocarbamate.—No toxicological information appears to be available on this specific compound. However, it should be regarded as a toxic material, similar to other cadmium salts. Inhalation of it and skin contact with it should be prevented.

6. Lead dimethyldithiocarbamate and lead dithiocarbamate.—These compounds should be regarded as significantly toxic, although no specific information appears to be available.

7. 2-Mercaptobenzothiazole.—The approximate lethal dose of this accelerator has been found to be greater than 100 mg/kg for wild rats and greater than 500 mg/kg for domestic rats by single oral administration[88]. There are no known cases of ill effects resulting from the use of 2-mercaptobenzothiazole in industry. It is not regarded as a material requiring any special handling, although Schwartz believes it has been the cause of dermatitis from rubber articles[89].

8. 2-Mercaptoimidazoline.—This is the technical grade of ethylene thiourea. Seifter[90] lists this compound among those causing hyperplasia of the thyroid glands of rats (goiterogenic). The acute lethal oral dose for rats was found to be greater than 100 mg/kg[88]. There are no reports of ill effects from the industrial use of this compound.

9. p-Nitrosodimethylaniline.—This compound is highly irritating to the skin, as a primary irritant and as a sensitizer[91].

10. N-oxydiethylene-2-benzothiazole sulphenamide.—A single oral LD_{50} for rats greater than 7.5 to 10 gm/kg when administered as a 10% suspension in Wesson Oil has been reported[84]. Sucessive doses of 1 gm/kg per day administered to rats for 12 days showed some effect of weight gain, but no mortality. Also, the dermal application of 1 gm/kg to rabbits using the standard cuff test showed only slight skin irritation, and a dosage of 0.5 gm kept in contact with the skin of rabbits for 24 hours as an aqueous paste was not irritating[84].

The experience in using this accelerator in the rubber industry has been entirely favorable. No special handling precautions are indicated.

11. Piperidinium pentamethylenedithiocarbamate.—On the basis of oral studies with rats, Mallette and von Hamm[86] determined an LD_{50} of 0.25 gm/kg, and classed the compound as "highly toxic." They also observed a slight degree of primary irritation and a moderate degree of sensitization when applied to the skin of humans.

It seems prudent, therefore, to avoid inhalation and skin exposure of this accelerator.

12. Poly p-dinitrosobenzene.—Experimental animal studies[92] show the approximate lethal dose when administered to rats by a stomach tube as a single dose (20% aqueous suspension) to be 1500 mg/kg. These studies also showed that a dosage of 300 mg/kg administered as a 15% aqueous suspension, on ten successive occasions over a period of two weeks to six rats, produced only a temporary slight weight loss and mild discoloration of skin. No gross or microscopic pathology was detected when the animals were sacrificed. Prolonged exposure will cause a contact dermatitis in some persons.

It would appear, therefore, that this accelerator is not particularly toxic. There are no known cases of poisonings in its use. No special handling precautions are required. While it may cause dermatitis in an occasional person, this is not regarded as a serious problem.

13. Selenium diethyl (or dimethyl) dithiocarbamate.—These compounds, because of the selenium atom, should be regarded as significantly toxic, although no specific information appears to be available.

14. Tellurium diethyldithiocarbamate.—This compound, because of the tellurium atom, should be regarded as significantly toxic, although no specific information appears to be available.

15. Tetraethylthiuram disulfide.—This compound has had extensive animal and clinical studies, primarily because of its use in the treatment of alcoholism. In 1948 Hald and others[93,94] discovered that tetraethylthiuram disulfide produced marked discomfort in humans, when ingested following alcohol consumption. Since that time considerable animal and human studies have been made so that there is perhaps more real physiological data on this compound than on any other accelerator. The compound is marketed as a drug under the trade name *Antabuse*. The World Health Organization has adopted the generic name of *Disulfiram*. It is believed that its striking effects following alcohol consumption are the result of an increased production of acetaldehyde in the body because of the presence of tetraethylthiuram disulfide in the blood. Marked disconfort occurs, exhibited by flushing, sweating, cardiac palpitation, dyspnea, tachycardia, fall in systolic and diastolic blood pressure, nausea, and vomiting. Prolonged use of tetraethylthiuram disulfide does not produce a

tolerance to it; in fact, subsequent uses usually produce more acute effects. Antabuse must be used with discretion and only under proper medical supervision.

Oral feeding of rats and rabbits with daily dosages of 1 mg and 60 mg, respectively, for 10 months' duration produced no influences on growth, body weight, appearance, or blood picture[94]. In humans no effect has been observed following repeated daily oral administration of 0.25 to 1 gm for months[95]. Brieger and Hodes[96] obtained single oral LD_{50}'s on the rabbit of 2.05 gm/kg. These same authors report no significant effects following exposure of rabbits to an atmospheric concentration of 0.0019 mg/liter for five weeks, five days per week, seven hours per day. Rats have been fed daily dietary levels of 100 ppm, 300 ppm, 1000 ppm, and 2500 ppm for periods ranging up to two years[97]. Gross and microscopic effects were observed at 2500 ppm level, including marked effects on growth and mortality rates. Lower dosages showed a slight to moderate effect on growth.

The use of tetraethylthiuram disulfide in industry has been entirely favorable and no special handling precautions are needed. Similar effects on workers under the influence of alcohol, as those observed with ingestion of the drug have been observed by the author, following inhalation of the vapors or dust of this compound.

16. Tetramethylthiuram disulfide.—Considerable toxicological study has been given to this important accelerator. Brieger and Hodes[96] have obtained a single oral LD_{50} for the rabbit of 210 mg/kg. These same investigators have found liver and kidney damage when fed to rabbits in four to six successive doses of 0.1 to 0.13 gm/kg each. Inhalation experiments on rabbits at an atmospheric concentration of 0.0019 mg/liter over a five week period showed similar damage. Brieger and Hodes[95] also applied the dry powder to the skin of humans and approximately 9% showed slight erythema. Hanzlik and Irvine[98] estimated the fatal dose, when administered to rats orally, to be 0.35 gm/kg. A single oral LD_{50} for the rat has been given as approximately 865 mg/kg[99]. The U. S. Food and Drug Administration has established a tolerance of 7 ppm on various fruits and vegetables when this compound is used as a pesticide[100].

The industrial experience with the use of tetramethylthiuram disulfide has been excellent. There are no reported cases of ill effects other than an occasional case of dermatitis. Inhalation of the dust should be kept to a minimum.

17. Tetramethylthiuram monosulfide.—Toxicological studies with animals[92] have showed the minimum lethal dose for mice by intraperitoneal injection to be 1 mg; for rats, 5 mg; and for guinea pigs, 10 mg. These studies have also showed minimum lethal values by stomach tube of 10 mg/kg for guinea pigs, 100 mg/kg for rabbits, and 100 mg/kg for cats and dogs. When rats were fed a daily dosage of 1000 ppm in the diet, death occurred in one to three days.

This compound is regarded as moderately hazardous in industrial use. Dust exposure to operating personnel should be prevented through the use of adequate ventilation and/or personal protective equipment. Skin contact should be kept to a minimum.

18. Zinc diethyldithiocarbamate.—The only reported toxicology of this compound is that of Brieger and Hodes[96] in which a single oral LD_{50} value for the rabbit for 0.60 gm/kg has been obtained.

This accelerator has had a long, favorable experience in the rubber industry. No special handling precautions are necessary.

19. Zinc dimethyldithiocarbamate.—Brieger and Hodes[96] have determined a single oral LD_{50} for rabbits of 0.4 gm/kg. Hodge[101] has determined LD_{50} values, with single oral administrations, of 1400 ± 99 mg/kg for the rat, and 100 to 150 mg/kg for the guinea pig.

Two years feeding studies of rats at dietary levels of 25, 250, and 2500 ppm and a one year feeding of dogs at daily levels of 0.5, 5, and 25 mg/kg by Hodge and coworkers[102], showed a "no-effect" level of 250 ppm for rats and 5 mg/kg/day for dogs. The U. S. Food and Drug Administration has established a tolerance of 7 ppm for the use of this compound on various fruits and vegetables when used as a pesticide[103].

Kiligman and Rosenweig[104] found that a 5% concentration in a propylene glycol—Carbowax 4000 base was nonirritating to human skin.

This aecelerator has had a long, quite favorable experience in the rubber industry. No special handling precautions are necessary.

E. SECONDARY ACCELERATORS (ACTIVATORS)

The available toxicology on the secondary accelerators (often called activators) in most common use follows.

1. n-Dibutylamine.—Smyth and associates[105] have reported an oral LD_{50} for rats of 0.55 gm/kg and a dermal LD_{50} for rabbits of 1 gm/kg. When rats were exposed to an atmospheric concentration of 250 ppm for four hours, no deaths occurred, but at 500 ppm all died. These same investigators found the compound would severely damage rabbit eyes and was strongly irritating to rabbit skin.

This compound should be regarded as a severe skin and eye hazard. Its vapors are markedly irritating.

2. Di-o-tolylguanidine. —This compound has been described as having a relatively low order of toxicology. A lethal dose of 120 mg/kg (guinea pigs and rabbits) has been reported[106]. A minimum lethal dose for guinea pigs of 120 mg/kg when fed as the hydrochloride as a single oral dose, and 80 gm/kg for rabbits has been obtained[92]. These studies indicated liver and kidney damage; animals which were fed repeated small doses showed little evidence of cumulative effects.

There are no known cases of poisonings as a result of using di-*o*-tolyl guanidine in industry. Schwartz and associates[89] list it as a primary skin irritant and sensitizer. Skin contact should be avoided in its handling.

3. Diphenylguanidine.—This accelerator is considered to be a moderately toxic compound in view of its reported LD_{50} to mice of 0.52 gm/kg when administered as a single oral dose[84]. Ten repeated applications to the skin of rabbits at a dosage of 1 gm/kg in both dry and paste forms did not produce signs of systemic toxicity. When rats were fed a daily dietary level of 1000 ppm over a 28 day period, marked retardation of growth occurred, caused by refusal to take adequate food. A dietary level of 100 ppm for the same length of time showed no effect.

Diphenylguanidine is a powerful emetic in dogs in single oral doses of as little as 10 mg/kg. The dog appears to be unusually susceptible to this com-

pound. A dosage of 10 mg/kg per day administered to two dogs in divided doses for a total of 21 doses in 24 days was reasonably well tolerated[84]. However, dogs were killed by single exposures to concentrations of dust of the compound that produced no effect on rats or guinea pigs.

Inhalation studies[107] using a concentration of 500 mg/cu meter with a half hour exposure (animal species unidentified) have shown mild hypnotic effects.

There are no reported cases of systemic effects of diphenyl-guanidine in industry. However, it should be regarded as moderately toxic and unnecessary exposure to it prevented. It is regarded as a primary irritant and sensitizer by Schwartz[89]. An inhalation threshold of 0.5–1.0 mg/m^3 has been suggested in Russia, because of reported adverse human effects and animal experimentation[108].

4. Hexamethylenetetramine.—This compound has been used for many years in the rubber industry and has been recognized as a skin sensitizer[89]. During World War II it was extensively used for the manufacture of the explosive RDX, but with no problem of dermatitis.

Spector[109] reports the subcutaneous lethal dose for the mouse, rat, guinea pig, and cat as 450 mg/kg, 200 mg/kg, 300 mg/kg, and 200 mg/kg, respectively. According to Hutschenrenter[110], 8 out of 14 rats developed local sarcomas when injected repeatedly with a 35–40% solution subcutaneously.

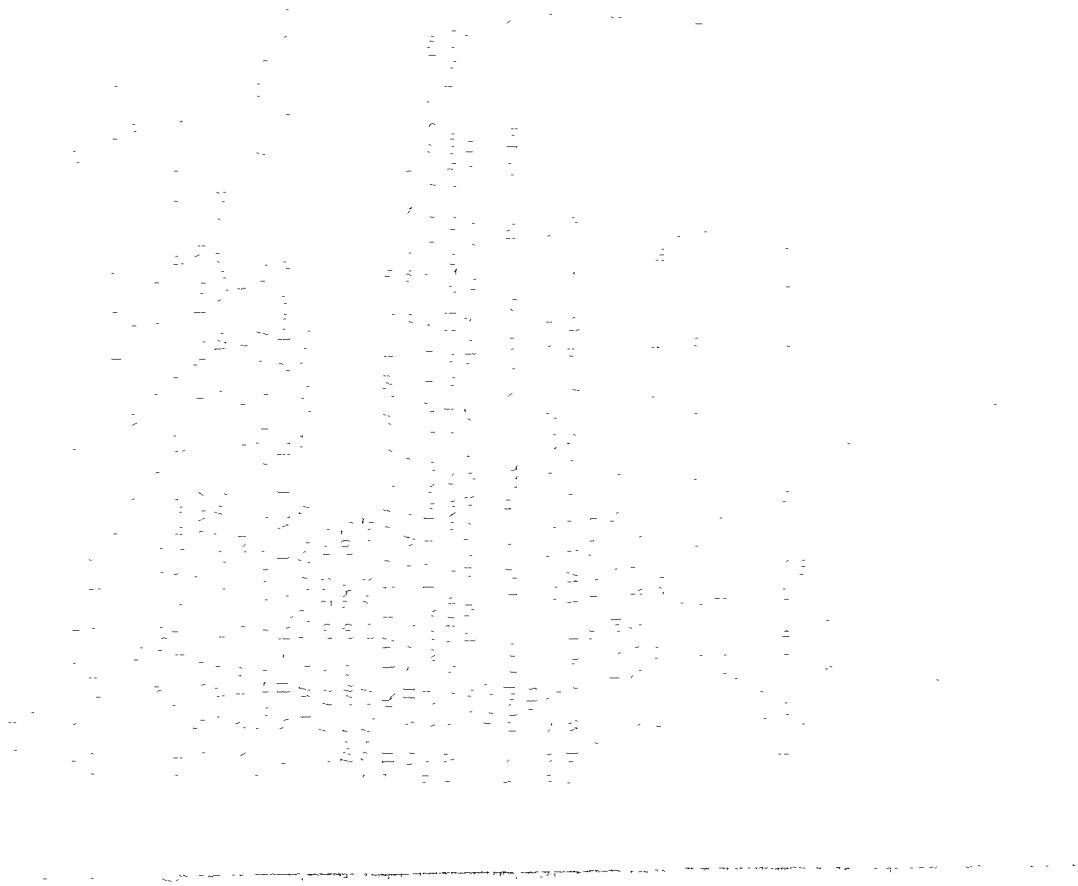
When used therapeutically, side reactions, such as urinary tract irritation, skin rashes, and digestive disturbances occurred[111].

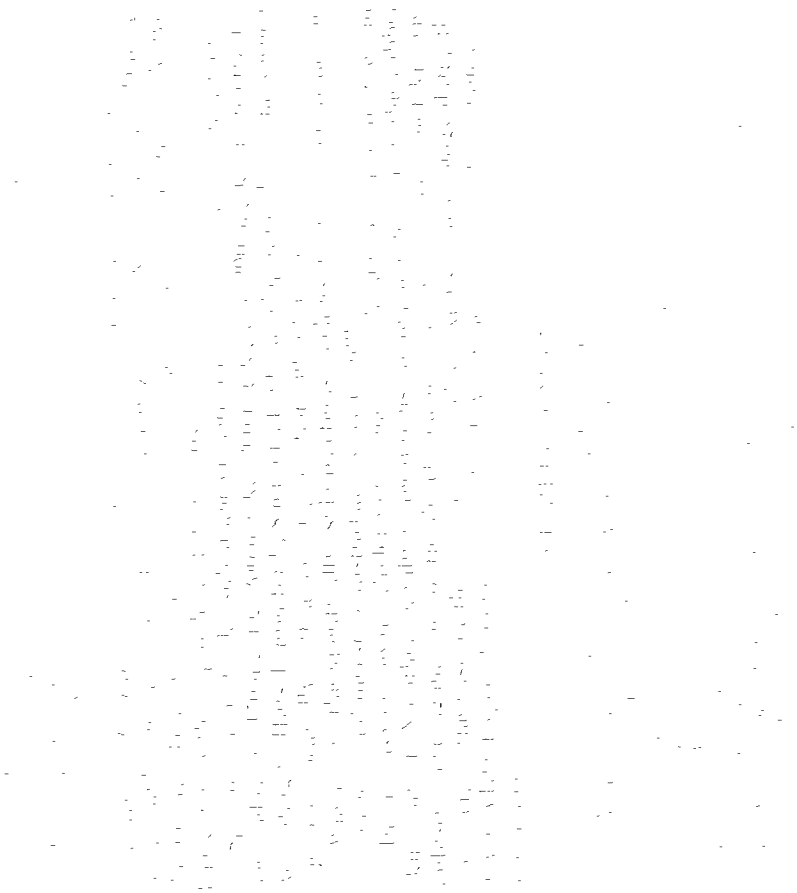
In the use of hexamethylenetetramine, care should be taken to prevent skin contact. No other handling precautions are required for use in the rubber industry. The significance of the development of mouse sarcomas is not known; however, as the basis of this, and on the lack of extensive toxicology data, the FAO-WHO Expert Committee on Food Additives recommended against its use in foods[112].

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