III. BIOLOGIC EFFECTS OF EXPOSURE

Extent of Exposure

(a) Petroleum Ether

Petroleum ether is a mixture of volatile aliphatic hydrocarbons with a boiling range of about 30-60 C (86-140 F) [1-4]. Petroleum ether is sometimes referred to as benzin, benzine, petroleum benzin, canadol, light ligroin, and Skellysolve [2-5]. Reference is sometimes made to high-boiling petroleum ether. This terminology is essentially synonymous with ligroin or varnish makers' and painters' naphtha [3].

Physically, petroleum ether is a clear, colorless, nonfluorescent, volatile liquid [3]. It has a characteristic odor and is highly flammable [4]. Its flashpoint is about -46 to -57 C (-50 to -70 F) [6-8] and it has a specific gravity of about 0.64. Chemically, petroleum ether consists primarily of pentane and isohexane [3,4]. It typically contains no aromatics [6]. It is a low boiling fraction obtained from the fractional distillation of petroleum [1]. Additional physical and chemical properties are given in Table XIV-1.

Petroleum ether is used as a solvent for oils, fats, and waxes; a detergent; a fuel; in paints and varnishes; an insecticide; and in photography [2-4].

(b) Rubber Solvent

Rubber solvent is a mixture of hydrocarbons that boils in the range of 45-125 C (113-257 F) [1,2,9]. This solvent is sometimes referred to as benzine and lacquer diluent [4,10].

Physically, rubber solvent is usually a clear, colorless liquid with a specific gravity of about 0.74 [1,9]. It has a Kauri-Butanol value (the measurement of milliliters of solvent needed to cause cloudiness in a solution of Kauri gum and butyl alcohol; indicates aromatic content of the solvent) of 30-33 and therefore has a relatively low solvent power [2]. It is less volatile than petroleum ether [3]. Rubber solvent is primarily a mixture of paraffins (chiefly C5-C8) and aromatics [4,9]. The actual composition will vary depending on the boiling range, the refinery stocks from which the solvent is produced, and the method of preparation. In general, rubber solvent has 70-90% paraffins, 11-22% naphthenes, and 9-22% aromatics [11-14]. A sample of rubber solvent analyzed by Carpenter et al [9] showed 41.4% paraffins, 53.6% monocycloparaffins, 0.1% monoolefins, 1.5% benzene, and 3.4% alkyl benzenes. Additional physical and chemical properties are given in Table XIV-1.

Rubber solvent can be produced from a straight-run petroleum distillate of paraffin base crude [2]. It is used as a rubber cement diluent and as an agent in rubber dope mixing and rubber spreading [2,10].

The United States in 1965 produced 28,857,000 barrels (1 barrel = 159 liters or 42 gallons) of what was described as special naphthas (including rubber solvent and varnish makers' and painters' naphtha), which represented 0.7% of the total production of petroleum products [2]. In 1973, 33,083,000 barrels of special naphthas were produced, 0.7% of the total production of petroleum derivatives [15], in 1974, 33,537,000 barrels or 0.8% of the total production, and, in 1975, 27,325,000 barrels of naphthas [16].

NIOSH estimates that about 600,000 workers in the United States are potentially exposed to all "specialized" naphthas.

(c) Varnish Makers' and Painters' Naphtha

Varnish makers' and painters' (VM and P) naphtha is a mixture of hydrocarbons that has a boiling range of approximately 95-160 C (203-320 F) [1,10,17,18]. It is sometimes known as benzine, Naphtha 76, ligroin, or high boiling petroleum ether [10,18].

Physically, VM and P naphtha is a colorless to yellow liquid that has an aromatic odor [18]. It has a flashpoint (closed cup) of -7 to 13 C (20-55 F) and is classified as a type I B flammable liquid [18]. Its mean molecular weight ranges from 87 to 114 and it is composed of about 45-60% paraffins, 30-45% naphthenes, and 5-13% aromatics [11-14]. A sample of VM and P naphtha analyzed by Carpenter et al [17] showed 55% paraffins, 30% monocycloparaffins, 2% dicycloparaffins, and 12% alkylbenzenes. The hydrocarbon chain ranges chiefly from C7 to C11 [4]. Additional physical and chemical properties are given in Table XIV-1.

VM and P naphtha can be produced from a straight run distillate of paraffinic or mixed base crude [2]. It is used as a quick-evaporating paint thinner of moderate solvent power [2].

NIOSH estimates that about 600,000 workers in the United States are potentially exposed to all "specialized" naphthas.

(d) Mineral Spirits

Mineral spirits are a mixture of hydrocarbons that have a boiling range of 150-200 C (302-392 F) [1,19]. These compounds have also been termed white spirits, petroleum spirits, and light petrol [5,19,20].

Stoddard solvent is considered by some investigators to be synonymous with mineral spirits [19,21].

Mineral spirits are clear, colorless liquids with a "pleasant, sweetish odor," and are very slightly soluble in water [5]. They do not blacken or corrode a clean metallic copper strip in 30 minutes at the boiling point of the mineral spirits [22]. The solvent contains about 30-65% paraffins, 15-55% naphthenes, and 10-30% aromatic hydrocarbons [11-14]. Additional chemical and physical properties are given in Table XIV-1.

This solvent is produced from straight-run naphtha derived from a paraffin-base or mixed-base crude [2]. Mineral spirits are used as a general-purpose thinner, a solvent for paint and varnish industries, and a drycleaning agent [2,5,20].

NIOSH estimates that 61,000 workers in the United States are potentially exposed to mineral spirits.

(e) Stoddard Solvent

Stoddard solvent is a mixture of hydrocarbons, predominantly C9 to C11, that has a boiling range between 160 and 210 C (320-410 F) [1,21,23]. It is a clear, colorless liquid and has a minimum flashpoint of 38 C (100 F) [19,24]. The dry point ranges from 166 to 210 C (330-410 F). Its Kauri-Butanol value ranges from 27 to 45. It is insoluble in water but readily soluble in most organic solvents [19]. Stoddard solvent must be negative on a specific test for mercaptans, and the copper strip corrosion test (ability to blacken or corrode a strip of polished copper placed in the solution) for 3 hours at 100 C (212 F) must be negative [25]. Chemically, Stoddard solvent is a mixture of 30-50% straight and branched chain paraffins, 30-40% naphthenes, and 10-20% aromatic hydrocarbons

[11,14,19,23]. Additional chemical and physical properties are given in Table XIV-1.

While Stoddard solvent and mineral spirits are not always considered the same petroleum products and are used differently for different purposes in industry, their boiling ranges (Stoddard solvent, 160-210 C; mineral spirits, 150-200 C) [1] are almost identical and therefore their chemical compositions are similar. In fact, many investigators use the terms mineral spirits and Stoddard solvent interchangeably, and some consider Stoddard solvent to be a specific type of mineral spirits [3,4,18,19,21].

There are currently four classes of Stoddard solvent: regular Stoddard solvent, 140 flash solvent, odorless solvent, and low end point solvent [24]. The flashpoint, dry-point test (evaporation rate), and odor are used to classify the types of Stoddard solvent [24]. The flashpoint, Kauri-Butanol value, and dry point of four classes of Stoddard solvent are listed in Table III-1.

Stoddard solvent, used primarily as a drycleaning agent [25], can be produced from a straight-run distillate of paraffinic or mixed base crude [2]. It was reported in 1964 that industry uses 150 million gallons Stoddard solvent a year [25]. One gallon of Stoddard solvent will clean about 25-35 pounds of clothes [25]. It was estimated in 1964 that 55% of the volume of drycleaning in the United States is carried out in Stoddard solvent [25].

NIOSH estimates that 75,000 workers in the United States are potentially exposed to Stoddard solvent.

TABLE III-1

CHARACTERISTICS OF THE FOUR CLASSES OF STODDARD SOLVENT

Solvents	Properties					
	Flashpoint (C)		Dry Point (C)		Kauri-Butanol Value (KBV)	
	Average	Range	Average	Range	Average	Range
Regular Stoddard	43	39-51	195	187-209	36.8	30.7-44.5
140 flash	60	59-60	201	189-210	33.0	30.1-35.6
Odorless	52	49-54	198	191-207	27.6	27.2-28.7
Low end point	39	38-42	174	166-183	35.0	28.7-39.0

Adapted from reference 24

Flashpoint values have been used to classify all solvents used in the drycleaning industry and accordingly there are four classes of solvents used in the industry [26]. Class I solvents are flammable liquids having a flashpoint below 38 C (100 F). Class II solvents are flammable liquids with flashpoints at or above 38 C (100 F) but below 60 C (140 F). Class IIIA solvents are combustible liquids with flashpoints at or above 60 C (140 F) and below 93 C (200 F). Class IIIB solvents are combustible liquids with flashpoints at or above 93 C (200 F). Class IV solvents are classified as nonflammable.

Drycleaning plants or systems are classified into five categories according to the solvent used [26]. For example, a class I drycleaning plant would use a class I solvent such as 50 flashpoint naphtha, a class II drycleaning plant would use a class II solvent such as Stoddard solvent, a class IIIA drycleaning plant would use a class IIIA solvent such as 140 flash aliphatic solvent, and class IV and V drycleaning plants or systems would use a class IV solvent such a perchloroethylene. Class I drycleaning plants or systems are prohibited, and class IV and I drycleaning plants or systems do not use the solvents covered in this document.

(f) Kerosene

Kerosene is a mixture of petroleum hydrocarbons, with carbon chain lengths that range from C9 to C16 carbon atoms per molecule and distills between 175 and 325 C (347-617 F) [18,27]. Synonyms for kerosene include astral oil, coal oil, and No. 1 fuel oil [5].

Physically, kerosene is usually a pale yellow or water-white, mobile, low volatile, oily liquid that has a flashpoint (closed cup) of about 38-74 C (100-165 F) and is therefore considered a combustible compound [18]. The composition of kerosene varies depending on the source of crude oil and the method of refining. Kerosene is a complex mixture of aliphatic, naphthenic, and alkylated aromatic hydrocarbons. A typical analysis of kerosene indicates that there are about 25% normal paraffins, 12% branched paraffins, 30% monocycloparaffins, 12% dicycloparaffins, 1% tricycloparaffins, 16% mononuclear aromatics, and 5% dinuclear aromatics [28]. The aromatic content of kerosene ranges from 5 to 20% [27]. The predominant aromatic molecular types include indenes, diphenyls, methylnaphthalenes, and tetralins [27]. Additional chemical and physical

properties of kerosene are given in Table XIV-1.

Kerosene can be produced in a refinery using a straight-run treated distillate from paraffinic or mixed crude, a solvent-treated distillate from paraffinic or mixed crude, or a solvent-treated distillate from aromatic crude [2]. Deodorized kerosene (washed with fuming sulfuric acid, followed by a sodium plumbite solution and sulfur) is a highly refined product of low aromatic content [4], often used in insect sprays [27].

Kerosene is used as a fuel, as a carrier for pesticides, as a weed killer, as a mold release agent in the ceramic and pottery industry, as a cleaning solvent, and in asphalt coatings, enamels, paints, thinners and varnishes [18,27].

The United States in 1965 produced 94,455,000 barrels of kerosene (including range oil) which represented 2.5% of the total production of petroleum derivatives [2]. In 1973, production was 80,126,000 barrels of kerosene, 1.7% of the total production of petroleum derivatives [15]. In 1974, kerosene production declined to 56,891,000 barrels, 1.3% of the total petroleum derivatives [15], and in 1975, 55,673,000 barrels of kerosene were produced [16].

NIOSH estimates that 310,000 workers in the United States are potentially exposed to kerosene.

A number of occupations where a potential for solvent exposure exists are listed in Table XIV-2 [1,2,5,10,19,29-31].

Historical Reports

There have been several instances in which workers cleaning equipment in rubber factories were overcome by solvent vapors [32-34]. Lawrence [33]

suggested that workers might have been intoxicated by solvent fumes if they worked over large tanks of rubber dissolved in naphtha and when room temperature was kept above 32 C (90 F) to aid the evaporation. Kulkow [34], in 1926, described numerous cases of poisoning after a 45-minute breakdown of the ventilation system in a factory which manufactured rubber galoshes, thus causing increased, but unmeasured, concentrations of petroleum naphtha and benzene. Ninety workers were affected and 30 required medical treatment. The type or extent of medical treatment was not reported.

In 1936, Hayhurst [35] reported several incidents of poisoning by petroleum distillates. Four men, 27-49 years old, brushed or submerged wood shingles by hand into a tank containing a solvent composed of one part petroleum naphtha and two parts kerosene (plus 4% creosote) and were exposed to the solvent vapors at an unknown concentration. The only ventilation in the room was from open windows and a door on one side of the room. One worker lost weight, became weak, and developed diarrhea, numbness, vertigo, and gastric disturbances after 11 months of exposure. Two months later, a physical examination showed undescribed cardiac disturbances, neurasthenia, paresthesia, increased respiration rate, and syncopal attacks following all work efforts. The second worker was exposed for 8 months and developed rashes and nervousness. Subsequently, he developed pruritus and low macular-type dermatitis on his arms. The third worker had been exposed to the solvent for 18 months when he showed signs of insomnia, nervousness, itching, and paresthesia. After a 1-year job transfer, the worker returned to the shingle-staining plant. He eventually developed sleeplessness, chronic headache, pain in the eyes, anorexia,

constipation, and nervousness. The fourth worker, who primarily inhaled solvent fumes, had been exposed to the solvent for 2 years before he developed weakness, gastric cramps, constant headache, anorexia, and nervousness. Subsequently, his reflexes became moderately exaggerated, and he developed diarrhea and lost weight. All of these workers were removed from exposure for periods in excess of 1 year. No followup studies of the solvent exposure were reported.

One man, 48 years old, was employed as a painter in an automobile assembly plant where he used mineral spirits as a degreaser and paint thinner [35]. The worker placed his hands in the solvent several times a minute during the working day. The normal workday was 8 hours, but he often worked up to 12 hours/day, 6 days/week. A mechanical ventilation system was in operation, but the solvent odor was still apparent. After about 3 years of steady employment, he quit his job because of ill health. He developed, during the course of his employment, a burning sensation in his nose and throat, "smarting" and watery eyes, headache, dizziness, anorexia, nausea, occasional vomiting, nervousness, prostration, muscle twitchings, loss of strength, and weight loss. Six years later, the man still was weak and thin, and was reported to be mentally incompetent and unstable. However, a report 11 years after solvent exposure indicated that the man was mentally alert and agile but still thin.

Hayhurst [35] also described seven other workers exposed to petroleum naphtha. The workers cleaned metal trays with the solvent in preparation for an enameling process. The work area did not have adequate ventilation. In general, the symptoms included a burning throat, drowsiness, "smarting" eyes, nausea, loss of appetite, headache, and nervousness.

A female worker who washed household appliance parts with naphtha developed dizziness, fainting, anorexia, and nausea after 1 month of solvent exposure [35]. The author reported that "a number of other girls were carried out unconscious from the plant."

Three workers, 27-41 years old, who were employed in a rubber factory and exposed to petroleum benzine for 2-5 years developed signs of solvent intoxication [35], ie, dizziness, headache, numbness of hands and feet, weight loss, anorexia, nausea, anemia, and bleeding from the nose and gums.

In 1938, Schwartz [36] reported the incidence of dermatoses in "basic" industries in the United States. Petroleum naphtha, benzine, and kerosene were reported to have been the cause of 3, 10, and 8 of 3,136 cases of occupational dermatoses. The author stated that exposure to materials of the broad classification of "solvents" caused 11% of the abnormalities that occurred in the United States and that about 1% of the industrial workers were involved.

Effects on Humans

(a) Petroleum Ether

Petroleum ether is primarily composed of pentanes and hexanes [3,4] and several studies have described the toxicity of these alkanes.

In 1953, Kjaer [37] described an incident in which petroleum ether was mistakenly used as an inhalation anesthetic before a craniotomy. A 56-year-old man developed severe clonic convulsions and considerable brain edema during the operation. According to Kjaer, these effects indicated central nervous system (CNS) irritation. The amount of petroleum ether inhaled was undetermined. Six days later, the patient was well enough to

be discharged from the hospital.

In 1970, Spruit et al [38] applied unspecified amounts of petroleum ether to the forearms of volunteers to observe dermal effects. Contact with the skin for 30 minutes caused disruption of the horny layer as indicated by subsequent skin peeling and increased water vapor loss from the injured skin. The average time of exposure before irritation appeared was about 20 minutes.

In 1936, Oettel [39] reported the effect of alkanes (pentane, hexane, heptane, and octane) on the intact skin of five volunteers. Circular glass dishes, 1 cm in diameter, were filled with the solvent and loosely attached to the forearm of each subject for 1 hour. Dermal exposure to these substances produced irritation characterized by erythema, hyperemia, swelling, and pigmentation. When solvent exposure was discontinued, marked increases in erythema and pigmentation accompanied with pain for up to 24 hours and followed by minor increases up to 96 hours were noted. The blistering properties of these solvents were also investigated by attaching dishes containing the alkanes to the thighs of the volunteers for 5 hours. Blisters formed on the alkane exposed areas. In addition, pentane exposure caused a constant burning sensation accompanied by itching. The intensity of these symptoms increased when the subject was exposed to hexane and heptane. No alkanes caused local anesthetic action. As carbon chain length increased, so did the time for pain to abate after the solvent was removed from the skin. Removal of pentane and hexane from the skin reduced pain in 15 and 90 minutes, respectively. After exposure to the alkanes was discontinued, the injured skin recovered with no scarring, and the author [39] concluded that the acute skin irritation was probably caused by

affected nerve endings and by histamine release and that the delayed effects were probably from cell damage and the accumulation of metabolic products.

Several investigators [40-43] have shown that hexane exposure causes polyneuropathy. Yamamura [42], in 1969, reported the effects on sandal makers of exposure to hexane in glue. The concentration of hexane in the air ranged from 500 to 2,500 ppm (1,759 to 8,793 mg/cu m). The initial symptoms included sensory impairment in the distal portion of the extremities in 88% of the subjects; almost 60% had reddish, rough, and cold skin of the distal portion of the arms. Muscle weakness was observed in 14%. Some of the workers with polyneuropathy also experienced loss of appetite, blurred vision, cold sensations of the extremities, general fatigability, headache, and weight loss. Muscle and nerve biopsies were taken from several workers. Light microscopic examination of the muscle tissues showed minimal fatty degeneration of the muscle fibers, diminution of fiber size, and slight proliferation of the sarcolemmal nuclei which indicated neurogenic atrophy and regeneration. Similar examination of the peripheral nerves generally showed demyelination and a milder axonal degeneration.

Inoue et al [44], in 1970, described the results of an analysis of the hexane solvent in the glue used by the sandal makers studied by Yamamura [42]. Gas chromatographic analysis indicated that the solvent contained 2-methylpentane, 3-methylpentane, methylcyclopentane, and n-hexane. The concentrations of the individual constituents were not given. After visiting the worksites of polyneuropathic sandle makers and measuring airborne hexane, the authors [44] concluded that the polyneuropathy was

probably caused by hexane at concentrations below 500 ppm (1,759 mg/cu m).

In 1971, Herskowitz and associates [40] examined three female employees working in a furniture factory who were exposed to n-hexane. These women worked in an enclosed, poorly ventilated room containing an open 189-liter drum of n-hexane solvent. Their job included dipping rags into the open drum and wiping excess glue from finished cabinets. Air samples of hexane were found to average 650 ppm (2,286 mg/cu m) and peaked at 1,300 ppm (4,573 mg/cu m). The subjects first noticed symptoms 2-4 months after beginning work and were admitted to a hospital 6-10 months later, where they complained of one or more of the following symptoms: abdominal cramps, burning sensations, numbness and weakness of the distal extremities, and paresthesia. Physical examination showed bilateral foot-drop gait, bilateral wrist drop, and absence of Achilles tendon reflexes. Biopsies of the sural nerves and the anterior tibial muscles of two of the patients were made. The muscles contained small angulated fibers and other fibers with clear central zones (denervation-type injury). Electron microscopic examination of small bundles of axons from the muscle sections showed that they contained increased numbers of neurofilaments and abnormal membraneous structures with clumping and degeneration of mitochondria, dense bodies, and bulbous formations. Motor-end plates had swollen terminal axoplasmic expansions, increased glycogen granules, dense bodies, large osmophilic membranes, synaptic folds, and vesicles. The sural nerve sections were normal under light microscopy, but electron microscopic examination revealed an occasional injury to myelinated axons. The authors concluded that all three workers showed signs and symptoms of sensorimotor polyneuropathy.

In 1972, Yamada [41] investigated 17 workers reporting symptoms of intoxication from exposure to hexane vapor. Six worked in small polyethylene laminating plants where hexane was vaporized into the workroom air. The airborne hexane concentration ranged from 1,000 to 2,500 ppm (3,417 to 8,793 mg/cu m). Analysis of the hexane solvent showed that it was composed of 16% methyl pentane, 20% methyl cyclopentane, and 64% n-hexane. Eleven of the 17 workers were employed by a pharmaceutical company and used a 95% hexane solution to remove oil from the surface of tablets. The airborne hexane concentration in the center of the workroom was 500 ppm (1,759 mg/cu m), but in the immediate work area the concentration was 1,000 ppm (3,517 mg/cu m). The initial complaints of the workers were reported within 1 month of exposure and included fatigue, followed by, in 1-3 and 6-9 months at the latest, paresthesia in distal parts of the extremities and difficulty in walking. The author reported that the workers displayed signs and symptoms of polyneuropathy, but that the progress of the disease was halted 3 months after the cessation of exposure and gradual recovery took place over 6-30 months.

In 1975, Takeuchi and coworkers [43] reported on four persons exposed to petroleum benzine. These people worked in a brocade sash cleaning shop that had a small, poorly ventilated workroom. The work process involved placement of a brocade sash on a desk and scrubbing with a brush dipped frequently in petroleum benzine. The sash was then hung in the room to dry. The operation was very busy during the winter months and the employees usually washed sashes 12 hours or more a day. Each worker used 9-12 liters of benzine a day. In other seasons, when the plant was not as busy, the employees worked 8-9 hours/day and only 4.5-6 liters/day/worker

were used. The petroleum benzine was reported to contain 13% n-pentane, 12.5% n-hexane, 10% n-heptane, 7.5% n-octane, 3% benzene, 3% toluene, and 57% unspecified components.

A 16-year-old boy who had worked in the plant for 5 months began losing his appetite and weight and suffered from constipation, cold sensations in the lower extremities, and muscle weakness [43]. After 7 months, he had to quit his job because of great difficulties in walking. After leaving, he became worse, developed upper extremity impairment, and could not walk unaided. Two months later, the sensory disturbances of the extremities began to show some improvement, but, since he still suffered from walking difficulties, he entered a hospital. Neurologic examination showed decreased sensation and moderate symmetrical weakness in the hands and feet, and muscle atrophy in the forearms and beneath the midthighs. The tendon reflexes were diminished in all extremities, and the patellar and Achilles tendon reflexes were absent. No Babinski's sign was present. The abdominal skin reflexes were normal. An electromyogram study showed fibrillation voltages in the distal portion of the extremities. The electroencephalogram was normal. Examination of the blood showed no abnormalities. Urinalysis results indicated only increased urobilinogen.

The second investigation involved a 34-year-old man who started working in a brocade sash shop in 1957 [43]. After 7 years, he bought his own shop where he worked 12 hours/day or more. Seven months later, he began losing weight and appetite and suffered from irritability and insomnia. In the autumn of 1965, when business slackened, his health improved, but, during the winter, he developed paresthesia and decreased sensation in the hands and feet. He eventually could not walk or use his

hands. He left work and 5 months later his condition had improved so that he could do manual work, but he still could not walk. Subsequently, it was noted that his condition worsened from winter to spring and improved from summer to autumn. In 1971, neurologic examination showed weakness and atrophy of the small muscles of his hands and feet. Tendon reflexes of the upper extremities and the Achilles tendon reflexes were diminished, but the patellar tendon reflexes were exaggerated. Ankle clonus was found. There was no Babinski's sign. Abdominal skin reflexes were impaired. The cranial nerves and blood showed no abnormalities.

The third instance involved a 17-year-old boy who, after being employed in the brocade sash cleaning workshop for 7 months, began suffering from insomnia, irritability and walking difficulties [43]. He visited a physician who diagnosed his illness as polyneuropathy, but the treatment (unspecified) was not helpful. He became unable to walk and was admitted to a hospital as a suspected case of poliomyelitis. After 3 months, he left the hospital without any improvement in his condition. In the next 13 months, without any treatment, he gradually recovered.

The final investigation involved a 19-year-old woman who worked in the factory for 6 months before she developed irritability, insomnia, and weight loss [43]. Eight months later, she quit her job after walking became difficult. Three months later, her condition improved, and she went to work in another occupation.

Although determination of the air concentrations of petroleum benzine were not made at the time these workers experienced their illness, analysis of the concentrations of petroleum benzine and its major constituents in the workroom air was subsequently made. The resultant values are given in

Table III-2 [43]. The components were analyzed by gas chromatography, but the assumptions made in determining the total petroleum benzine content (last column in table) were not stated. The concentration of petroleum benzine and n-hexane did not exceed 4,400 and 844 mg/cu m, respectively.

TABLE III-2

CONCENTRATION OF VAPOR IN THE BROCADE SASH WORKROOM

Location in Workroom	Solvent Concentration (ppm)				
	n-Pentane	n-Hexane	n-Heptane	n-Octane	Total Petroleum Benzine*
Under worker's nose	210	240	41	15	1,250 (4,400 mg/cu m)
1.5 meters in front of worker	150	150	38	40	895 (2,800 mg/cu m)
2.0 meters to left of worker	90	100	42	33	545 (1,920 mg/cu m)
Near doorway	20	50	26	13	273 (960 mg/cu m)
Under worker's nose with fan operating	50	60	20	20	445 (1,160 mg/cu m)

*Conversions from ppm to mg/cu m are inconsistent and do not reflect a uniform molecular weight assumption. These values reflect the actual data reported by the authors.

Adapted from Takeuchi et al [43]

The authors indicated that, if the concentration of petroleum benzine rose higher than 4,400 mg/cu m, irritation of the mucous membrane would have become unbearable and a narcotic effect would have occurred. The potential effects of dermal exposure, although not measured, could not be disregarded as a potential route of intoxication. The authors felt that these four subjects represented cases of polyneuropathy that were probably caused by n-hexane exposure.

In 1973, Gaultier and associates [45] studied five workers employed in a belt-manufacturing shop and exposed to unknown concentrations of a solvent vapor. The solvent was composed of 80% pentane, 14% heptane and 5% hexane. Three of the workers were examined and reportedly had anorexia, asthenia, paresthesia, fatigue, and bilateral and symmetrical muscle failure. Recuperation was very slow [45]. The authors concluded that alkanes other than hexane may cause polyneuropathy.

For additional information on pentane and hexane toxicity, the reader is referred to the NIOSH document entitled Criteria and Recommendations.... Occupational Exposure to Alkanes.

(b) Rubber Solvent

In 1975, Carpenter et al [9] studied the odor and sensory thresholds of volunteers exposed to rubber solvent vapor. To determine the odor threshold, six volunteers between the ages of 25 and 49 years were exposed for about 10 seconds to a series of concentrations of rubber solvent vapor. The range of the odor threshold was reported to be between 6.4 and 64 mg/cu m (1.6 and 16 ppm) based on a mean molecular weight of 97 calculated from mass spectrometry data and analyzed by gas chromatography as detected 17 and 75% of the time, respectively. The authors suggested that the most

probable odor threshold concentration was about 40 mg/cu m (10 ppm).

Human sensory response in volunteers, 25-60 years old, was determined in daily 15-minute inhalation studies of measured vapor concentrations of rubber solvent ranging from 1,700 to 8,100 mg/cu m (430 to 2,000 ppm) [9]. Eye and throat irritation responses of volunteers exposed to rubber solvent vapor at 1,700 mg/cu m (430 ppm) were all slight and transitory. One out of seven volunteers noted eye irritation, and two out of seven had throat irritation at 3,100 mg/cu m (780 ppm). Eye irritation and headache in two cases each were reported at 6,700 mg/cu m (1,700 ppm) after the discontinuation of exposure. One of six volunteers had the same symptoms at 8,100 mg/cu m (2,000 ppm), and they subsided unaided within 10 minutes after the discontinuation of exposure. The authors concluded that a concentration of 1,700 mg/cu m (430 ppm) could be tolerated without complaint.

(c) Varnish Makers' and Painters' Naphtha

Carpenter et al [17] carried out inhalation studies on volunteers to determine the odor and sensory threshold for VM and P naphtha vapors. The odor threshold was determined in an exposure chamber using six subjects between 25 and 48 years of age. The subjects were exposed to the solvent vapor for 10 seconds at concentrations ranging from 0 to 70 mg/cu m (0 to 15 ppm based on a mean molecular weight of 114 calculated from mass spectrometry data; analyzed by gas chromatography). The odor threshold was estimated to be about 4 mg/cu m (0.86 ppm). The sensory threshold was determined with seven volunteers between 25 and 59 years of age. Exposures were limited to one 15-minute exposure/day at solvent concentrations ranging from 660 to 4,100 mg/cu m (140 to 880 ppm). Olfactory fatigue was

noted at all concentrations. At the highest concentration tested of 4,100 mg/cu m (880 ppm), definite throat and eye irritation was produced.

In 1976, Wilson [46] reported on the effect of petroleum naphtha vapor exposure on humans. A storage tank of petroleum naphtha at a refinery became overheated and the naphtha vaporized and escaped from the tank. What was described as a vapor cloud was reported to have remained close to the ground for a short, unspecified period of time during which individuals were briefly exposed to the vapor. Although the concentration of vapor was not measured, it was sufficiently high enough to stall the engines of two motor vehicles which were driven into the vapor cloud, suggesting to Wilson that a possible oxygen deficiency within the cloud might have occured. The petroleum naphtha had a boiling range of 84-164 C (183-327 F) and was composed of 84% paraffins, 3% olefins, 11% naphthenes, and 2% aromatics, and therefore may be considered similar to both VM and P naphtha and rubber solvent. There was probably little or no benzene in the petroleum naphtha since benzene boils at 80.1 C.

Eighteen of the 19 individuals were examined by Wilson [46] immediately after exposure. They all had labored breathing and two were cyanotic. Several were excited and hyperactive but none were drowsy. There were no signs of burns or irritation of the mucous membranes. The lungs of all the subjects were clear to auscultation. Treatment consisted of oxygen administration, and the labored breathing and cyanosis disappeared. Chest roentgenograms showed no abnormalities. One individual was reported to have premature ventricular contractions. No other individuals had any cardiac arrhythmia. All of the individuals had tremors and complained of mild nausea shortly after cessation of the oxygen

therapy. These symptoms were eliminated by the use of a sedative-antispasmodic drug. All the individuals returned to work 30 minutes after their arrival to the health center except for one older person who had remained in the vapors longer than the others. He was free of symptoms within 30 minutes but was observed a little longer as a safety precaution. Blood counts and urinalyses were made on all of the exposed individuals and the results were all normal. A followup examination after 5 years showed no medical problems that could be attributed to the petroleum naphtha vapor exposure.

(d) Mineral Spirits

In 1958, Kegels [47] reported the effects of white spirits on a 36-year-old man who cleaned floors with copious amounts of the solvent. He had no previous history of serious illness. The man and several women had been exposed to white spirits for at least 4 months. He was constantly surrounded by "clouds" of solvent, but neither airborne measurements of white spirits nor daily exposure times were quantitated. When some women complained of nausea and vomiting, the use of white spirits was stopped. The author indicated that the white spirits boiled between 153 and 185 C and contained 83% paraffins and 17% aromatics.

The man showed no blood abnormalities when medically examined, but 3 months later, he complained of fatigue and pallor [47]. A physician's diagnosis was that he was suffering from overwork. Several months later, the patient still had abnormal symptoms. A second physician performed a blood analysis and sternal puncture and indicated that the subject had either aplastic anemia or aleukemic leukemia. Subsequently, he was

diagnosed as having aplastic anemia with thrombocytopenia and leukopenia (80% lymphocytes and 20% neutrophils).

Treatment consisted of three blood transfusions, but his condition did not improve and he was admitted to a hospital [47]. Signs of purpura on the skin and mucous membranes now appeared. The initial blood analysis showed decreased erythrocytes (2,480,000/cu mm), leukocytes (2,300/cu mm), platelets (34,000/cu mm), and hemoglobin (45%). After several blood transfusions and iron and liver extract injections, the employee's condition improved and he returned to work. However, shortly thereafter, he developed articular rheumatism which was treated with cortisone. He was treated continuously for aplastic anemia and rheumatism by blood transfusions and iron, liver extract, and adrenocorticotropic hormone injections.

About 2 years later, after several intermittent periods of infection, the patient again felt fatigued and weak [47]. Hematologic examination showed severe decreases in erythrocytes (1,710,000/cu mm) and leukocytes (2,800/cu mm). A sternal puncture biopsy examination showed marked hypocellularity. Urobilinogen was present in the urine, indicating signs of liver dysfunction probably caused by hemosiderosis. The subject died a few months later from septicemia. Kegels indicated that this subject probably had a sensitivity to white spirits, since other workers exposed to white spirits did not develop aplastic anemia. The possible role of benzene in the etiology of the disease should be considered, even though the boiling range of white spirits should preclude any benzene being present, since trace amounts of benzene could have been present in the solvent as contaminants.

In 1975, Astrand and associates [48] examined the effects of white spirits on human alveolar air and blood solvent concentrations during rest and exercise. The white spirits used in the study consisted of 83% aliphatic and 17% aromatic components.

Fifteen men, 20-34 years of age, were used in the study [48]. In initial trials, subjects were exposed to 2,500 or 5,000 mg/cu m of white spirits. The concentrations of mineral spirits were determined by gas chromatography. The duration of exposure was not reported. Nausea and vertigo were apparent at both concentrations.

The authors [48] decided that subsequent experiments should be conducted with white spirits at concentrations that ranged from 1,000 to 2,500 mg/cu m to reduce the discomfort of the men and to accurately analyze the solvent content in alveolar air and blood. Five subjects each inhaled both 1,250 and 2,500 mg/cu m of white spirits for 30 minutes at rest and then during exercise at an intensity of 50 watts. Four subjects were exposed at 1,250 mg/cu m for 30 minutes during rest and in three 20-minute exercise periods at intensities of 50, 100, and 150 watts which are equivalent to the amount of energy used in light industrial work, manual labor, and heavy manual work, respectively [49]. Two subjects were first exposed for 30 minutes to 2,500 mg/cu m of white spirits in atmospheric air (20.90% oxygen, 0.04% carbon dioxide, and 79% nitrogen) and then to the solvent in a mixture of 21% oxygen, 4% carbon dioxide, and 75% nitrogen during a 30-minute rest period and a 30-minute exercise period (intensity of 50 watts). Two subjects were exposed to white spirits at 1,250 mg/cu m in the air for 30 minutes during rest followed by three 30-minute exposures during exercise at an intensity of 100 watts. The two remaining subjects

were each exposed at rest to 1,000, 2,500, 1,500, and 2,000 mg/cu m for one 30-minute period. The white spirits concentration or work rate changes were made after each 30-minute period without interrupting exposure. Alveolar air samples were collected during exposure, and arterial and venous blood samples were taken from preplaced catheters in the brachial artery and medial cubital vein, respectively. Heart rate and blood lactic acid content were determined in some subjects at the end of each exposure period. Cardiac output, oxygen uptake, and volume of expiratory and alveolar air were determined in all subjects after 20 minutes of each exposure period.

During exercise, three subjects had occasional premature atrial beats as shown by electrocardiograms; however, they were of the same type as those observed during rest [48]. One man developed premature atrial beats exclusively in conjunction with solvent exposure (concentration not reported). Another displayed gradual flattening, and, ultimately, inversion of the T wave during exposure to white spirits. This subject had no symptoms, and the electrocardiogram became normal a few days after solvent exposure (concentration not reported). No differences were noted in heart rate, alveolar ventilation, or oxygen uptake either at rest or during exercise at an intensity of 50 watts during exposure at 1,250 and 2,500 mg/cu m of white spirits. Cardiac output was normal at rest and increased in an normal manner as work increased during exposure at 1,250 and 2,500 mg/cu m of white spirits. Blood lactate content was unaffected by white spirits exposure.

The authors [48] found that the concentrations of aliphatic and aromatic white spirits components in the air and blood differed

considerably. After a 30-minute exposure at rest to white spirits at 1,250 mg/cu m (1,038 mg/cu m of the aliphatic component), the concentration of the aliphatic component in the alveolar air was 255 mg/cu m (25% of the concentration in the inhaled air). The corresponding arterial and venous blood concentrations were 1.7 and 1.3 mg/kg, respectively. During the 50-watt exercise, the alveolar aliphatic component concentration increased to about 515 mg/cu m or about 50% of the concentration in the inhaled air. The arterial and venous blood concentrations were 3.5 and 2.4 mg/kg, respectively. During exposure at rest to about 210 mg/cu m of the aromatic components of white spirits (at a white spirits concentration of 1,250 mg/cu m), the aromatic concentration in the alveolar air after 30 minutes was about 30 mg/cu m, about 15% of the concentration in the inhaled air. The corresponding arterial and venous blood concentrations were both 0.2 mg/kg. During exercise at 50 watts, the alveolar concentration of the aromatic components increased to about 20% of the concentration in the inhaled air. The aromatic component concentrations in the arterial and venous blood were 0.9 and 0.6 mg/kg, respectively.

Exposure to white spirits at a concentration of 2,500 mg/cu m (2,075 and 425 mg/cu m of the aliphatic and aromatic components, respectively) at rest produced alveolar concentrations of the aliphatic and aromatic components of 563 and 56.4 mg/cu m, respectively [48]. The arterial and venous aliphatic component concentrations were 3.4 and 2.2 mg/kg, respectively, while the arterial and venous aromatic components concentrations were 0.6 and 0.4 mg/kg. Alveolar air and arterial blood concentrations of the aliphatic components after white spirits exposure at 2,500 mg/cu m during exercise were approximately double those at the

resting level. The aromatic components in the alveolar air during exercise, however, were only 50% of those at the resting level. The increases in the aromatic components of the arterial and venous blood during exercise were similar to those seen for the aliphatic components.

When exercise intensity was increased successively to 150 watts during exposure to white spirits at a concentration of 1,250 mg/cu m, the alveolar aliphatic component concentration rose in steps from 256 to 622 mg/cu m, while the aromatic components rose from 28 to 59 mg/cu m [48]. In general, the alveolar concentrations of the aliphatic and aromatic components of white spirits in these studies leveled off after 10 minutes exposure and remained relatively unchanged during the rest of the exposure period. In contrast, the arterial and venous blood concentrations rose continuously throughout each exposure. The blood concentrations did show a plateau only after exposure at 1,250 mg/cu m of white spirits for 90 minutes.

In these studies, the authors [48] found a linear relationship between the arterial and alveolar concentrations of the aliphatic and aromatic components; the venous concentrations paralleled arterial concentrations. The total uptake of the aliphatic and aromatic components by the subjects was determined at rest during four consecutive 30-minute exposure periods. The uptake values were 59, 53, 47, and 46% of the total amount of the aliphatic components and 70, 64, 59, and 58% of the total amount of the aromatic components. During 50-watt exercise, the uptake was about 39% for the aliphatic components and 69% for the aromatic components. Thus, the proportion of aliphatic to aromatic components taken up decreased during exercise. However, the total uptake, measured in milligrams/period

of exposure, was slightly greater during exercise than at rest for both the aliphatic and aromatic components.

Astrand et al [48] concluded that measuring the solvent content of the inhaled or alveolar air was less reliable than measuring the blood concentration of aliphatic and aromatic components when assessing uptake, since the aliphatic components reacted as if they were not very soluble in blood while the aromatic components were relatively soluble. The authors noted that more solvent reached the blood during exercise than during rest. Thus, as would be expected, the degree of physical activity associated with a worker's job may influence solvent vapor toxicity.

In 1975, Gamberale and coworkers [50] studied the effects of exposure to white spirits (mineral spirits) on humans. Performance tests were conducted in perceptual speed, reaction time, short-term memory, numerical ability, and manual dexterity. Two sets of experiments were performed. In the first experimental series, 14 men, 18-34 years of age, were separated into 2 equal groups. One group was first studied under experimental conditions with exposure to white spirits and then, 7 days later, with exposure to air. The subjects in the second group were studied in a similar manner but in the reverse order. Under the experimental conditions, the first group was exposed to white spirits at 625, 1,250, 1,875, and 2,500 mg/cu m for four consecutive 30-minute periods. The concentration was increased after each 30-minute period without interrupting exposure. Gas chromatography was used to determine the white spirits concentration. The white spirits were supplied through a low air resistance breathing valve and mouthpiece. The presence or absence of white spirits was disguised by the introduction of menthol crystals into

the mouthpiece, since previous studies indicated that the subjects might taste and smell the solvent [48] which might, therefore, influence the experimental results. The five performance tests were always carried out in the same sequence during the final 20 minutes of each exposure period. Alveolar air samples were taken every 5 minutes and heart rate was monitored. At the termination of the experiment, the subjects were asked several questions to ascertain their perception of the experimental conditions.

From the answers to these questions, the authors [50] concluded that exposure to white spirits probably did not affect the subjective reactions in the psychologic experimental series. No difference in the heart rate of the subjects was noted between treatment and control situations. There was no impairment of the five performance tests as a result of solvent exposure. The resulting air concentrations of aliphatic components of the white spirits were about 175, 300, 450, and 600 mg/cu m at the 625, 1,250, 1,975, and 2,500 mg/cu m exposures, respectively; aromatic component concentrations at these exposures were about 25, 40, 50, and 75 mg/cu m. The solvent vapor concentrations were determined by gas chromatography.

In the second experiment [50], eight of the subjects who participated in the first experiment were exposed to 4,000 mg/cu m of white spirits for 50 minutes. During the final 20 minutes of exposure, the same performance tests used in the first experiment were performed. The subjects were also studied under control conditions without exposure to white spirits, as in the previous experiment. Half of the subjects were studied during control conditions 2 days before and the other half 2 days after the experimental trial. White spirits had no effect on perceptual speed, numerical ability,

and manual dexterity [50]. There was, however, a definite prolongation of reaction time and a possible impairment of short-term memory as a result of exposure at 4,000 mg/cu m. The alveolar concentrations of the aliphatic and aromatic components of the white spirits were about 850 and 100 mg/cu m, respectively.

(e) Stoddard Solvent

In 1940, Braunstein [51] reported that a 26-year-old man who worked in a drycleaning factory and had his forearms and hands wetted with or immersed in Stoddard solvent during most of the workday developed follicular dermatitis of the exposed skin after 2 weeks of employment. In the following 1 or 2 weeks, he felt nauseated after inhaling the fumes in the workroom. He continued to work in the factory for about 8 weeks longer before seeking medical aid after yellowing of the skin and four or five vomiting episodes had occurred. He was admitted to a hospital about 3 months after his first exposure to solvent.

The patient felt weak and had lost 6 pounds during the previous 2 months; however, he regained this loss by the time of discharge from the hospital 1 month later [51]. Abnormalities shown by physical examination were jaundiced skin and eyes and a moderately enlarged liver. Temperature, pulse, and respiration values were normal. A roentgenogram of the abdomen was normal. He had an increased serum icteric index, decreased glucose tolerance, and increased erythrocyte resistance to hemolysis. The urine had traces of albumin, sugar, and urobilin; the feces contained bile. The blood urea nitrogen (BUN) content was increased; total erythrocyte count and hemoglobin value were decreased; total leukocyte count was normal; and some abnormal-sized erythrocytes were noted. A skin sensitization test

with Stoddard solvent was "highly" positive. The diagnosis was obstructive jaundice originating in the liver parenchyma and subacute yellow atrophy of the liver. In the next 3 weeks, the values for bile retention gradually returned toward normal and the dermatitis disappeared. One year later, the blood icteric index was again elevated, which, in the opinion of the author, meant that the man had latent jaundice and possibly permanent liver damage.

The clinical histories of four people reported to have aplastic anemia as a result of exposure to Stoddard or Stoddard-like commercial solvents were discussed by Scott et al [52] in 1959. Three of the subjects died. In the first fatality, a housewife used a Stoddard-type solvent as well as carbon tetrachloride for spot-cleaning household rugs two or three times a month for 2 years before excessive uterine bleeding and purpura appeared. No history of exposures other than to the two mentioned solvents could be obtained. A bone marrow smear was classified as hypocellular, ie, there were 4% normoblasts, 26.5% lymphocytes, 4% plasma cells, no megakaryocytes, and a myeloid/erythroid ratio of 5:1. A sternal bone marrow biopsy showed moderate hypoplasia, since there was a slight decrease in the overall number of cells and an increased number of lymphoid elements. At autopsy, focal hyperplasia was found.

The second fatal case was a high school student who had cleaned his hands in Stoddard solvent, four or five times/week, during a 6-month course in automotive mechanics [52]. He had been taking tripelennamine hydrochloride and diphenhydramine hydrochloride, both reported by the authors to be potential myelodepressants, for several years for his seasonal allergy. Two months after the automotive mechanics course ended,

the student became bruised easily and had symptoms of anemia. The patient's bone marrow aspirate smear was hypocellular: 34.0% normoblasts, 34.5% lymphocytes, 0.3% plasma cells, decreased megakaryocytes, and a myeloid/erythroid ratio of 1:1. A sternal bone marrow biopsy showed marked hypoplasia since there was severe hypocellularity with a predominance of lymphoid elements. The autopsy report indicated moderate hypoplasia with all normal elements present.

The third fatal case was a man who periodically over 2 years used Stoddard solvent to remove paint from his hands [52]. The patient denied using other potentially toxic agents. An episode of purpura, pallor, and fatigue occurred 1 year before his illness was first recognized, and it apparently subsided spontaneously. There was no clear chronologic relationship between the intermittent symptoms and the periods of exposures to the solvent. The bone marrow aspirate smear was classified as slightly hypocellular: 14.5% normoblasts, 35.7% lymphocytes, 1.0% plasma cells, decreased megakaryocytes, and a myeloid/erythroid ratio of 3.2:1. Autopsy findings showed marked hypoplasia of the bone marrow with alternating areas of aplasia and hypercellularity resulting from an increase in lymphoreticular elements.

The fourth patient was a housewife who had used a Stoddard-type solvent as a drycleaning agent for 20 years [52]. Once every year, she immersed the family clothing in a large open tub containing the solvent, usually working indoors. Nothing else in the woman's medical history indicated other types of exposure that could have resulted in her illness. The patient's bone marrow smear was classified as normal in cell number: 63.9% normoblasts, 13% lymphocytes, 2.3% plasma cells, decreased

megakaryocytes, and a myeloid/erythroid ratio of 0.3:1. The sternal bone marrow biopsy showed normal bone development with an increase in the lymphoid elements. After splenectomy, which was also performed on the first and third patients, this patient's condition improved and she was listed as surviving.

The authors [52] concluded that these four cases implicated Stoddard-type solvents as possible myelotoxic agents capable of producing aplastic anemia. However, they gave no information on the composition of the solvent and were thus not in a position to rule out a possible role of myelotoxic compounds such as benzene.

In 1970, Prager and Peters [53] described a 41-year-old man who had been frequently exposed to "Solvasol #5," a Stoddard-type solvent, for 16 years in the course of his employment as a heavy-equipment mechanic. The patient had been well until 3 months before his admittance to the hospital, during which period he felt progressively more tired and lightheaded and bruised easily. Physical examination showed diffuse petechiae and some ecchymotic areas of the skin. No enlargement of the liver or spleen was found by palpation. Blood tests showed an initital hemoglobin level of 7.9 g%, a hematocrit reading of 22%, and a leukocyte count of 2,000 cells/cu mm with 18% segmented cells, 77% mature lymphocytes, 3% atypical lymphocytes, and 2% monocytes. The platelet count was 9,000 cells/cu mm. A sample of sternal bone marrow showed no marrow particles. Bone marrow taken from the ilium showed a marked decrease in the number of cells and in all cellular elements. The results from the following laboratory tests were either negative or normal: buffy coat smear, leukocyte alkaline phosphatase, haptoglobin, fluorescent antinuclear antibodies, and thrombin. The patient

was diagnosed as having aplastic anemia. He died 11 months later. Post-mortem examination showed a diffuse intracerebral hemorrhage of the right occipital lobe. The bone marrow smear showed a marked decrease from normal in the number of cells and in all cellular elements. The authors suggested that Stoddard solvents, although presumably free of benzene because of the solvent's boiling range, might contain a myelotoxic agent which remains to be identified.

Grant [54], in 1974, reported that Stoddard solvent was essentially innocuous to the human cornea. No details were given.

However, in 1943, Nelson et al [55] had described the subjective sensory responses (eye, nose, and throat irritation) of 10 men and women to Stoddard solvent at a given concentration for 3-5 minutes. The authors had observed that solvent concentrations greater than 400 ppm were irritating to the eyes, nose, and throat of most subjects. The concentration that volunteers thought would be satisfactory (presumably in terms of comfort) for an 8-hour exposure was less than 400 ppm. No analytical method or assumption on molecular weight was reported; however, if the average molecular weight were 140, the equivalent concentration would be 2,290 mg/cu m.

In 1975, Carpenter and associates [21] used six volunteers, ages 25 to 48, to determine the odor threshold for Stoddard solvent. The volunteers were exposed to Stoddard solvent at graded concentrations ranging from 0 to 50 mg/cu m (0 to 9 ppm) based on a mean molecular weight of 144; this weight was calculated from mass spectrometry data and analyzed by gas chromatography for 10 seconds. The odor threshold was between 0.5 mg/cu m (0.09 ppm) and 5 mg/cu m (0.9 ppm). The sensory threshold to

vapors of Stoddard solvent was determined for six volunteers, ages 25-59. The volunteers were subjected to the solvent at concentrations of 140, 850, and 2,700 mg/cu m (24, 150, and 470 ppm) for a 15-minute exposure. No eye irritation was noted at 140 mg/cu m, but slight and transitory eye irritation occurred in one of six volunteers at 850 mg/cu m (150 ppm). At 2,700 mg/cu m (470 ppm), all six experienced eye irritation, three with tearing. Slight dizziness also was reported by two subjects at the 2,700 mg/cu m concentration (470 ppm). Olfactory fatigue occurred at all concentrations tested. Volunteers who experienced olfactory fatigue recovered full acuity within 10 minutes after they were removed from exposure.

In 1975, Carpenter et al [56] examined the odor and sensory thresholds to 140 flash aliphatic solvent, a type of Stoddard solvent, in humans. To determine the odor threshold, a group of six volunteers, 22-49 years old, inhaled the solvent at a series of vapor concentrations for about 10 seconds each in the following sequence: 4, 0.4, 0, 40, 4, 0, 40 and 0.4 mg/cu m. Sixty percent of the volunteers perceived the 4 mg/cu m concentration (0.6 ppm), but none could detect the 0.4 mg/cu m level (0.06 ppm based on a mean molecular weight of 154, calculated from mass spectrometry data and analyzed by gas chromatography).

The sensory threshold was determined in six subjects, 22-61 years old. They inhaled the 140 flash aliphatic solvent at concentrations of 110 mg/cu m (17 ppm) and 310 mg/cu m (49 ppm) for 15-minute periods. The solvent was inhaled at each concentration once daily for 2 days. Slight dryness of the eyes was reported by one of the subjects during the inhalation of 110 and 310 mg/liter (17 and 49 ppm, respectively) of the

solvent. This response did not persist after exposure ended. No other volunteers reported discomfort at either solvent concentration. Olfactory fatigue occurred within the first 6 minutes of inhalation of the solvent at either concentration. The volunteers stated that exposures at concentrations of 110 or 310 mg/cu m would be acceptable for an 8-hour workday.

(f) Kerosene

In 1939, Cavanagh and Wilner [57] described a case of aplastic anemia in a 59-year-old woman who, for several months before the onset of her illness, rubbed household kerosene on her legs every night as a remedy for "stiff joints." Her initial complaints were shortness of breath, weakness, easy fatigability, and several unaccountable nosebleeds. She also discovered black and blue marks scattered over her body. These symptoms gradually progressed until she required bedrest. Physical examination revealed that the patient was obese and had a waxy pallor. Her blood pressure was 120/80, pulse rate was 80 beats/minute, and respiration rate was 20 breaths/minute. There were no heart or lung abnormalities. The liver was palpable.

The patient was hospitalized for 4 months before succumbing to a gas gangrene infection [57]. During this period, frequent nosebleeds occurred and there were marked weakness and mental depression. The erythrocyte count ranged from 950,000 to 3,400,000; abnormal erythrocytes were observed several times. Hemoglobin content varied from 14 to 64%, the leukocyte count diminished progressively, reaching 900 with decreased neutrophils predominating, and the platelet count never exceeded 10,000. At autopsy, the sternal bone marrow showed a marked aplastic state that involved

primarily granulocytes and platelets. The authors suggested that the aplastic anemia seen in the patient may have been the result of the aromatic hydrocarbon content of the kerosene, but they gave no supporting detail.

In 1955, Johnson [58] related the case of a 58-year-old man exposed to a degreasing solvent containing kerosene. This man, who was hospitalized in April 1955 and expired in June 1955, was employed from 1928 to 1930 in a factory plating lead batteries. When "lead poisoning showed up in the blood," he was transferred from that job. From 1952 to 1955, he worked in a machine shop where his job involved delivering airplane parts, and he also spent 3 or 4 days every week degreasing airplane parts. Usually, he immersed his hands in a solvent composed of 29 parts kerosene and 1 part paraffin jelly, cosmoline, the latter being incorporated for the purpose of reducing skin irritation. In February 1955, the man began having fever, chills, coughing, and pleuritic chest pain and was hospitalized. Severe anemia was diagnosed. The patient was treated with 10 blood transfusions, penicillin, and tetracycline. He returned to work in spite of continued chest pain and intermittent fever and felt progressively weaker and fatigued. In April 1955, he was rehospitalized with persistent blood-stained sputum and fever and was transferred to another hospital where he died in June. The patient's illness was diagnosed as typical hypoplastic anemia with pancytopenia and hypoplastic marrow with no evidence of leukemia. Johnson considered it probable that this patient had a particular sensitivity to the solvent. Further, she suggested that benzene or other aromatic compounds were components of kerosene and might have been responsible for the blood effects, but she did

not have quantitive data on the benzene content.

Hiebel et al [59], in 1963, found three incidents of bone marrow suppression associated with dermal and oral exposure to kerosene. The first incident involved a 52-year-old woman who, for 34 years, had applied kerosene poultices to a painful lumbar area about two or three times a year. The poultices were prepared by soaking cotton balls with kerosene, applying them to the back with adhesive tape and leaving them in contact with the skin for 1-3 days until blistering occurred. The patient had on two occasions mixed kerosene with sugar, ignited the mixture, and, after the flame had extinguished itself, ingested the charred sugar. On physical examination, the patient was noted to be obese and to have hypertension. Hematologic examination showed an erythrocyte count of 1.99 million cells/cu mm, a leukocyte count of 5,850 cells/cu mm (42% neutrophils, 4% immature neutrophils, 4% eosinophils, 36% lymphocytes, 13% monocytes, and 1% basophils), and a normal platelet count. A sternal bone marrow smear was slightly hypocellular. Erythropoiesis was greatly depressed and both eosinophils and lymphocytes were increased. Study of the bone marrow suggested a lymphoma. The diagnosis was aplastic anemia from long-term exposure to kerosene.

The second incident involved a 71-year-old male who had generalized aches and pains in most of his joints for the preceding 3 years and had treated these with a kerosene massage two or three times a week [59]. The patient had a hemoglobin level of 11.2 g/100 ml, an erythrocyte count of 3.84 million cells/cu mm, a leukocyte count of 1,750 cells/cu mm (24% neutrophils, 5% immature neutrophils, 11% lymphocytes, and 10% monocytes), and a platelet count of 366,000 cells/cu mm. Bone marrow specimens were

hypocellular. The authors suggested that the decrease in neutrophils resulted from kerosene-induced bone marrow suppression.

The third incident involved a 52-year-old woman who took a teaspoon of kerosene and sugar to treat her colds [59]. She averaged three colds a year, and she had used this cold remedy for approximately 45 years. In addition, for about 40 years, she had used a dust cloth saturated with kerosene to clean her furniture. The patient's blood pressure was 180/100 mmHg. Analysis of the blood showed a hemoglobin level of 14.1 g/100 ml and a leukocyte count of 2,500 cells/cu mm (36% neutrophils, 49% lymphocytes, 13% monocytes, and 2% eosinophils). The bone marrow was hypocellular with normoblastic erythropoiesis, "toxic" granulopoiesis, and increased eosinophils. The diagnoses were leukopenia secondary to kerosene exposure, essential hypertension, and arteriosclerotic heart disease. The possibility of exposure to aromatic hydrocarbons as components of the kerosene was not commented upon by the author.

In 1947, Klauder and Brill [60] described the effects of kerosene on human skin. Kerosene of a paraffinic nature (composition not given) was applied in a patch test to an unspecified site on 20 white and 14 black subjects. In performing the patch test, six drops of kerosene were applied to a piece of gauze (1-inch square) and then placed on the skin. The gauze was covered with wax paper and kept in contact with the skin for 24 hours. The skin was then graded from 0 to 4+ (1+, mild erythema; 2+, well-defined erythema; 3+, erythema with edema, and with or without a few blisters; and 4+, erythema, edema, and many blisters, or serous exudation.)

All of the white subjects reacted to the paraffinic type kerosene: 4 had reactions of 2+ or less, 10 had 3+ reactions, and 6 had 4+ reactions

[59]. Of the 14 black subjects tested, six did not react, seven had reactions of 2+ or less, and one had a 4+ reaction. Patch tests were also performed with a naphthenic-type kerosene (composition was not specified) on white subjects. All reacted positively, and seven had 4+ reactions.

The authors [60] concluded that the skin of black subjects was more resistant to kerosene-induced irritation than the skin of white subjects and that naphthenic kerosene was a greater irritant than paraffinic kerosene. They found that, of the substances tested, solvents boiling below 232 C (450 F) were primary irritants and indicated that the correlation of boiling range with irritant action applied to the paraffin type of petroleum products and not to the naphthenic type or highly aromatic products, whether derived from petroleum or other sources.

In 1973, Tagami and Ogino [61] reported four cases of dermatitis caused by kerosene. The first case involved an 8-year-old boy who had handled kerosene the previous night. On physical examination, a strong smell of kerosene was noted. There was a well-defined reddened area on the arm topped with a large, sterile, 2 cm, soft, pus-containing blister and scattered smaller blisters. The second case was a 2-year-old boy who complained of soreness in the genital region about 10 hours after playing with a kerosene can. Physical examination was made the following day and showed diffuse well-defined redness and swelling in the genitocrural region. There were two denuded areas with tiny, soft elevations of the skin containing pus. The third case concerned a 2-year-old girl who had played with a kerosene pump. She complained of burning on the right arm the following day. Physical examination showed diffuse redness near the elbow with a scattering of small pus-containing blisters and a large area

of denudation. A definite odor of kerosene was perceived on the skin. In the fourth case, a 15-year-old boy noted a burning eruption on his neck with a well-defined reddened area with small pus-containing blisters, a day after he handled kerosene. The neck portion of his sweater smelled of kerosene. Oral and dermal corticosteroids brought about improvement of the skin irritation.

To experimentally reproduce the four previously described clinical cases, Tagami and Ogino [61] performed several studies on the effects of dermal kerosene administration. The forearm of one volunteer was exposed in a patch test to kerosene. One hour after kerosene application, a burning sensation developed and was followed at 2 hours by slight redness. By 7 hours, the skin was very tender and red, extending beyond the patch test site. A large firm blister with several small blisters was observed at 12 hours, but there was no longer any burning sensation. After 24 hours, the large blister became soft and filled with pus. The blister broke easily leaving a raw surface. The authors concluded that the experimental lesion corresponded with those seen in clinical cases of kerosene dermatitis.

Tagami and Ogino [61] also used patch tests to study the effects on skin of different concentrations of kerosene. Refined kerosene was used as the test material and diluted to 40, 55, 70 and 85% concentrations in mineral oil. The subjects were 22 white and 12 black adult male volunteers. About 0.1 ml of the material was placed on a 1.5-sq cm cloth and then sealed to the midback skin under impermeable plastic tape. After 24 hours, the patches were removed and the skin was graded on a scale of 0-5 for irritation.

All volunteers showed skin irritation to the 85% kerosene solution [61]. The 70 and 55% kerosene solutions caused skin irritation in 85 and 24% of the volunteers, respectively. No skin irritation was reported at the 40% kerosene concentration. The authors noted that 85% kerosene was more toxic to the skin of whites than to the skin of blacks, 2.95 versus 2.50. Microscopic examination of skin biopsy samples were made 7 and 24 hours after kerosene application. At 7 hours, there were intercellular and intracellular edema, pyknosis, and eosinophilic cytoplasm of the upper epidermal cells. Dense perivascular lymphocytic infiltration was observed in the upper dermis. After 24 hours, the epidermis showed prominent spongiosis, exocytosis, and blister formation. The blisters were intraepidermal, often subcorneal. The intravesicular cells were composed of lymphocytes with some eosinophils and neutrophils.

Tagami and Ogino [61] also investigated the effect of age and the influence of skin region on kerosene-induced skin irritation. To assess the effect of age on kerosene-induced skin irritation, young male whites, 21-31 years old (average 26.4), and 10 older male whites, 58-82 years old (average 68.3), were patch-tested with 85% kerosene on the midback. No significant differences in skin irritation were noted between the age groups. To assess the influence of skin region on kerosene-induced skin irritation, patches of 85% kerosene were applied for 24 hours on the midback, abdomen, forearm, forehead, and lower leg of nine male blacks. The results indicated that the forehead was the least susceptible region. The authors suggested that the decreased sensitivity of the forehead to kerosene was caused by the extensive blood supply of this region which rapidly removed kerosene from the skin before extensive damage could occur.

To test this possibility, four subjects were given patch-tests with 85% kerosene on a site previously injected intradermally with 0.1% naphazoline hydrochloride, a vasoconstrictor, at a dose of 0.1 ml in normal saline [61]. Seventy-five percent of the volunteers showed more pronounced skin irritation on the naphazoline-treated area. Thus, the extent of skin irritation was related to blood flow through the exposed area.

Using 17 subjects previously exposed topically on the midback to an 85% kerosene-15% mineral oil mixture, Tagami and Ogino [61] studied the permeability of the stratum corneum to a solution of 1.5% 3,3,4,5-tetrachlorosalicylanilide (TCSA) in ethylene glycol monomethyl ether. No correlation was found between skin irritation and the penetration time of TCSA, and the authors concluded that irritability was related to the inherent reactivity of the skin.

In 1973, Lupulescu et al [62] described the effects on the ultrastructure of the skin of six men from dermal applications of kerosene. Four small glass tubes, each containing about 1 ml of kerosene, were taped in a vertical position on the forearms. The kerosene was left in contact with the skin for 30 or 90 minutes. Skin sections, 4 mm in diameter, were removed from two of the sites on each man's arm immediately after exposure; similar sections were removed 72 hours later. Control specimens were taken from each subject before exposure. The test sites were not cleaned either before or after the procedure. The samples were fixed and examined with an electron microscope at magnifications of 5,600-18,000 X.

Specific changes were observed in the skin ultrastructure after the 90-minute skin exposure to kerosene [61]. The number of skin horny layers was reduced and the keratin pattern was disorganized in the samples taken

immediately after exposure. Large lacunar formations which contained fibrils in their lumina were present. The plasma membranes appeared thick and some horny cells were disrupted and disintegrated. Some keratinocytes were severely damaged, cell membranes were thick and disrupted, and tonofilaments were clumped. Advanced cell damage was seen in the stratum spinosum. Several spinous cells were undergoing destruction, and most of the cytoplasm appeared homogenous and structureless. The nuclei were reduced in size and indented with peripheral chromatin. A fine granular material had largely replaced the cytoplasm. The nucleus was elongated and poor in chromatin and contained a granular-globular structure. In the 72-hour samples, Langerhans cells retained their ultrastructural pattern. No mitotic figures were observed. Skin specimens examined 72 hours after the 90-minute exposure were similar to those of the controls. The skin that was exposed to kerosene for only 30 minutes showed appreciably fewer changes than the skin exposed for 90 minutes. Few cells underwent destruction or vacuolation. The intracellular spaces were enlarged and the desmosomes were disrupted. The changes seen in the stratum corneum were similar to those seen after the 90-minute kerosene exposure, but were less pronounced.

The authors [62] concluded that exposure of the skin to liquid kerosene caused large lacunae in the horny spinous cells and marked nuclear changes after the 90-minute exposure. Both the stratum corneum and stratum spinosum were affected by kerosene. While intercellular edema and disruption of the tonofilaments occurred in many types of epidermal damage, Lupulescu and associates considered the observed changes in the keratin pattern to be specific effects of liquid kerosene exposure.

In another 1973 report, Lupulescu et al [63] described the penetration and transport of kerosene. Human skin (healthy and psoriatic) was exposed to tritiated kerosene for 90 minutes. Electron microscopic autoradiography findings showed that most of the kerosene was present over the horny layers, in the intracellular spaces of the stratum spinosum, and between desmosomes. Kerosene was also found surrounding the nuclear chromatin of spinous cells. In the authors' opinion, the presence of labeled kerosene in the nucleus suggested that the solvent may have interfered with mitosis. Forty-eight hours after exposure to kerosene, only small traces of the solvent were found and these were located near the collagen fibers in the upper corneum. The only major difference between healthy and psoriatic skin was that, in the latter, more kerosene was seen between collagen fibers. From this observation, Lupulescu and coworkers suggested that a more rapid penetration of the solvent had occurred through psoriatic skin.

In 1975, Lupulescu and Birmingham [64] used electron autoradiographic techniques to study the effects of kerosene on DNA, collagen, and protein synthesis in humans. The effects of kerosene, which was administered dermally at a dose of 1 ml on the forearm, were measured in terms of DNA incorporation of tritiated methylthymidine, collagen incorporation of tritiated proline, or protein incorporation of tritiated leucine during the respective syntheses of these cellular components. Quantitative analysis after the concomitant administration of tritiated leucine intradermally at a dose of 20 microcuries, after 90 minutes of exposure, showed a marked decrease in silver grains in the photographic plate as compared with controls or untreated areas, indicating a decrease in protein synthesis in

the exposed areas. Intradermally injected tritiated methylthymidine at a dose of 20 microcuries or tritiated proline at a dose of 20 microcuries was used to examine the effects on DNA and on collagen synthesis, respectively. Analysis of electron microscopic autoradiograms after 90 minutes of exposure showed that kerosene had no effect on either DNA or collagen synthesis. Thus, the authors concluded that the dermal cellular damage resulting from kerosene exposure was probably caused by inhibition of protein synthesis.

In 1952, Downing [65] reported a clinical case in which an epidermoid carcinoma developed on the dorsum of the left hand of a 63-year-old man, who had been employed as a grease-pit worker at a service station for 20 years. (The article stated 20 years in the case report and 30 years in one of the figures.) His job entailed cleaning trucks with gasoline and performing general maintenance work with kerosene and various other unspecified solvents. Prior to May 1947, a large lump developed on the back of the worker's left hand. The lump was surgically removed and microscopic analysis of the excised tissue showed that the lump was a epidermoid carcinoma. Since the initial surgery, the man had returned to work and had persistent dermatitis on both hands; keratoses and benign epitheliomas, as well as small recurring epidermoid carcinomas, had developed. In addition, the man received x-ray therapy on his left hand. While not stated in the article, it is believed that the x-ray therapy was initiated when the smaller lesions occurred.

The data presented in this case report [65] are insufficient to implicate kerosene as the agent that caused the epidermoid carcinoma, as gasoline and many other undefined solvents were used by the worker. In

addition, there was no medical or occupational history prior to the man's employment at the service station.

Grant [54], in 1974, has commented that kerosene and deodorized kerosene were essentially innocuous to the human cornea. No details were given.

In 1964, Davies [66] cited an incident of a man becoming intoxicated from inhaling jet fuel vapor. The jet fuel was type JP-4 and was described as being more like the composition of kerosene than that of gasoline. No other composition data were given. The 32-year-old male pilot was in flight for 7 minutes when he began to feel groggy and weak. He immediately started breathing 100% oxygen and subsequently the oxygen was filtered through water and under pressure, but there was only a slight alleviation of the symptoms. The pilot also noted that the engine was making an unusually loud noise and he decreased power. A distinct but unidentifiable odor was perceived by the pilot. Being unable to alleviate his symptoms, the pilot landed the plane and was taken to an infirmary.

Physical examination showed a well-developed, well-nourished male who was dressed in clothing that smelled of fuel [66]. He appeared moderately intoxicated and was excessively jovial. There was a slight stagger in his gait, and he complained of a mild headache. No other abnormalities were noted. Neurologic examination showed the following positive findings: slight staggering on walking; slight but definite slurring of speech; a loss of position sense in which the patient failed to maintain equilibrium when standing with feet together and eyes closed; and possible decreased sensation to painful stimuli. The only laboratory study performed was for carboxyhemoglobin which was normal. After examination, the pilot was given

rest. After 26 hours, he reported that he still did not feel normal. One week after the incident, there were no adverse effects of intoxication, and he returned to work. He stated that hypoxia had not caused the condition. The airplane and breathing equipment were examined to determine if a leak caused the intoxication. The breathing mask was found to be in good condition, but the aircraft engine had developed a fuel leak. Fuel fumes were not noticed in the cockpit but, had the access doors of the plane been closed and had the engine heat vaporized the fuel, fumes would have entered the cockpit in high concentrations through the compressor system. The author suggested that, based on the assumption that JP-4 fuel is similar in CNS toxicity to gasoline, the concentration of fuel in the cockpit must have been 3,000-7,000 ppm to intoxicate the pilot within 7 minutes.

In 1976, Carpenter and colleagues [67] described the odor and sensory irritation thresholds of humans exposed to airborne concentrations of deodorized kerosene. The odor threshold was based on the responses of six volunteers ranging in age from 23 to 49 years to a series of airborne concentrations given for approximately 10 seconds each/day for 2 days. The odor threshold for this solvent was found to lie in the range from 0.2 to 2 mg/cu m (0.03 to 0.3 ppm) based on a mean molucular weight of 171 calculated from mass spectrometry data and analyzed by gas chromatography. The authors stated that the odor threshold was probably 0.6 mg/cu m (0.09 ppm).

To determine the sensory threshold, six volunteers, ranging from 20 to 63 years in age, inhaled a vapor concentration of 140 mg/cu m (20 ppm) for 15 minutes [67]. The authors stated that 140 mg/cu m (20 ppm), as measured by gas chromatography, probably represented the maximum airborne

concentration at which this deodorized kerosene vapor is representative of its liquid phase. This exposure concentration was easily tolerated by the volunteers, with none reporting any discomfort or irritation. Two did, however, report a slight decrease in olfactory acuity but not complete olfactory fatigue. The volunteers judged that 140 mg/cu m (20 ppm) of deodorized kerosene, based on a 15-minute exposure, would be acceptable for an 8-hour workday.

There are numerous cases of kerosene poisoning by aspiration or ingestion of the liquid [59,68-70]. In 1934, Nunn and Martin [68] reported 65 cases of kerosene poisoning in children with an overall mortality of 9.2%. In the fatal incidents, the patients lived 2-18 hours after ingestion and aspiration of the kerosene. These subjects were cyanotic and had moist rales in both lungs and rapid, shallow respirations. In the nonfatal episodes, 32% showed evidence of pneumonitis. Body temperature and pulse rates ranged from 97 to 106 F and 110 to 150 beats/minute, respectively. Respiration rates were very rapid, ranging from 50 to 80 breaths/minute in those patients who developed pneumonitis. Erythrocyte and hemoglobin counts were within normal limits, but leukocyte counts varied from normal to 21,000 cells/cu mm. Occasionally, urinalysis showed the presence of albumin.

In 1956, McNally [69] reviewed the major findings on 204 children admitted from 1946 to 1954 to an Alabama hospital after ingesting kerosene. All of the patients showed upper respiratory tract infections and rales and rhonchi were heard in 10% of the subjects. Thirty percent of the patients were diagnosed as having pneumonia. The roentgenologic reports of the chest varied from patchy infiltration to diffuse interstitial pneumonia.

Forty percent of the patients were lethargic, 8% were semicomatose, and none had convulsions. Urinalysis findings showed the presence of albumin in 30% of the incidents, ranging from a trace to 3+. Leukocyte counts varied from 4,500-31,900 cells/cu mm and the lymphocytes varied from 10-79%. The hemoglobin content ranged from 7 to 11.5 g/100 ml.

Truffa and Montalenti [70], in 1969, described an incident of acute lung disease and jaundice from accidental ingestion of kerosene. A man had ingested and possibly aspirated an unknown quantity of kerosene while he attempted to syphon this substance. There were no immediate disturbances, but, a few hours later, he developed a headache and an intense difficulty in breathing followed subsequently by vomiting, epigastric pain, and malaise. On physical examination, the following abnormalities were found: moderate blueness of the lips, evidence of right lung congestion, small inhalation rales and harsh breathing, intensified abdominal pain upon pressure, moderate fever (38.3 C), and marked jaundice. A chest roentgenogram showed the presence of zonal parenchymal thickening. There was an elevation of the serum glutamic-oxaloacetic transaminase and serum glutamic-pyruvic transaminase. The patient fully recovered several weeks after the kerosene ingestion.

Epidemiologic Studies

Epidemiologic studies indicated that refined petroleum solvents can cause dermal, eye, nose, and throat irritation. Menstrual disturbances and leukemia may develop as a result of exposure to solvents containing benzene. Polyneuropathy was reported to develop in workers exposed to jet fuel that was composed of raw gasoline and kerosene. Thus, neurologic

dysfunction may result from exposure to solvents.

In 1944, Hamilton-Paterson and Browning [71] investigated the toxic effects on women exposed to industrial rubber solutions. The investigation was conducted in two parts. In the first, sample groups from 13 factories (a total of 200 women were studied) were clinically examined and had blood counts made. These blood counts were compared with the counts of 200 control women. In the second part of the study, all the women working in one factory were similarly compared with a group of women in the same factory who had never been in contact with rubber solutions. The effects of rest were also examined in this group of women. The rubber solution used in these factories contained varying amounts of benzine and aromatic hydrocarbons (5-20%). Although adequate ventilation was provided, it was not possible for the workers to avoid inhaling the fumes. Approximately 41% of the workers complained of symptoms probably related to their occupations. The major symptoms were: exhaustion, headache, dizziness, nausea, vomiting, and difficulty in breathing. The pertinent blood finding was a decreased leukocyte count which resulted primarily from a decrease in neutrophils. There was no significant variation from controls in the erythrocyte count, and it was not possible to evaluate the results of hemoglobin measurements because they varied unreasonably, having been done at different laboratories. After the workers had been free from exposure to the rubber solution for 3 months, their blood findings returned to control levels. The authors [71] suggested that the decreased leukocyte count resulted from benzene exposure, but neither the benzene content of the solution nor of the air was determined. Excessive uterine bleeding was observed in 7 of 45 women, 40-50 years old, and 4 of 131 women between 19

and 39 years old complained of increased frequency of menstrual periods. The authors felt that these menstrual disturbances may have been the result of benzene poisoning, but they also indicated that the uterine bleeding may have been a menopausal symptom or a response to uterine disease, and that the increase in menstrual frequency may have been associated with the change from domestic to factory work. No gynecologic examinations were performed on the women, and no definite conclusions were made concerning the etiology of the menstrual disturbances.

In 1962, Kaplan and Zeligman [72] found that the use of kerosene or mineral spirits mostly for cleaning caused dermatitis in 10 of 98 railroad maintenance workers. The extent or duration of vapor exposure or liquid contact was not reported.

In 1973, Ramos and Shama [73] reported that exposure to petroleum distillate (naphtha) caused dry throats, burning or tearing of eyes, mild headaches, dizziness, respiratory irritation, and, in some cases, dermatitis in workers of an electric company. They determined that the TWA exposures to the distillate vapors ranged from about 25 to 274 mg/cu m based on charcoal sampling and gas-chromatographic analysis. There was no apparent relationship between solvent concentration and symptom development. The dermatitis was believed to be caused by direct contact with the petroleum distillate, and it ranged from mild redness to fissuring and blister formation.

Markel and Shmunes [74], in 1974, described the evaluation of Stoddard solvent hazard at a greeting-card company. Twelve workers were exposed to a concentration of Stoddard solvent of 99-1,906 mg/cu m (average, 438 mg/cu m) in their working environment. Gas chromatographic

techniques were used to determine the solvent vapor concentration. The author concluded on the basis of pulmonary function tests (forced expiration volume, and forced vital capacity) and a serologic antigen test that, under the conditions found at the time of the survey, Stoddard solvent did not constitute a hazard to the health of the workers.

In 1974, Larsen and Shmunes [75] reported that Stoddard solvent used to clean polishing machines were probably the cause of dermatitis in several industrial workers. The workers also complained of headaches and eye and nose irritation. Although the detectable concentrations of Stoddard solvent were less than 20 ppm (115 mg/cu m), the authors felt that higher concentrations could have occurred immediately after the polishing machines were cleaned with Stoddard solvent, which could have caused the headache and eye and throat irritation. The analytical method and assumption used in converting the data to ppm were not stated in the paper.

McMichael and associates [76], in 1975, presented an epidemiologic study involving rubber workers that indicated an association between leukemia and jobs entailing exposure to solvents. The authors did not specify which types of solvents were used by the workers, although they mentioned that benzene was once the solvent of choice. After noting that leukemias in general demonstrated a threefold excess in mortality in the 40-64 age range, and with further subclassification of the International Classification of Diseases categories to identify specific leukemias, a sevenfold excess of deaths from lymphatic leukemia in the 40-64 age range was observed. Six of eight deaths were from chronic lymphatic leukemia. Myeloid leukemia was the next highest category in this age range, showing a twofold excess. The question of whether the observed mortality excesses

were associated with specific job categories within the rubber industry was then investigated. Nineteen of 70 occupational titles were associated with solvent exposure and were grouped as heavy, medium, and light solvent exposure. A discriminant function analysis based on time spent in various work groups and independent of the previously observed mortality excess revealed a statistically significant positive association between solvent exposure and lymphatic leukemia. The average solvent exposure time was approximately 11 years. The leukemia seen in these affected workers was lymphatic in character. In benzene poisoning, the leukemia tends to be either the hemocytoblastic (or stem cell) or the myeloblastic type. Thus, benzene may not have been the agent causing the leukemia in the present study. The authors suggested that an unidentified substance presently being used may have been the carcinogen, since four cases of leukemia developed in workers employed in recent decades.

In 1976, Knave and coworkers [77] reported the effects of long-term exposure to jet fuels in aircraft factory workers. The jet fuels were types MC 75 and MC 77 and had raw gasoline and kerosene as their principal components. The workers were exposed to the fuel during the production, installation, and testing of fuel systems for planes. The airborne concentrations of fuel were not routinely determined, but the authors indicated that, on one occasion, the airborne levels were measured in three workrooms. The concentrations were between 500 and 3,000 ppm (3,476 and 20,859 mg/cu m assuming a molecular weight of 170).

From employer's records and interviews with workers, 29 employees considerably exposed to fuel vapors from 1955 on were selected for the study [77]. The exposed workers were divided into two groups, depending on

the degree of exposure. The 13 workers belonging to group A were either continuously exposed for several hours daily to "high" concentrations of jet fuel or were exposed for no less than 20 minutes to "high" concentrations at least every 2nd or 3rd week. The 16 members of group B were exposed intermittently but exposure was less frequent than that found in group A. All 29 workers were exposed for at least 29 years. They were given a neurologic examination and were questioned about the occurrence of "restless legs," muscle cramps, pain in the extremities, distal paresthesia, numbness, and paresis.

All workers in group A stated that they repeatedly experienced one or more of the following symptoms when exposed to the fuel vapors: dizziness, headache, nausea, palpitations and pressure on the chest, a slight cough, and pain upon inhalation [77]. Seven of 16 workers in group B experienced similar acute symptoms. The authors reported that 92 and 56% of the workers in groups A and B had one or more of these symptoms and that the symptoms were chronic, neurasthenic, and psychasthenic. In groups A and B, 85 and 38%, respectively, of the workers had symptoms, and 77 and 44% had signs of polyneuropathy. Fuel vapor exposure did not affect the vibration sensation threshold and nerve conduction velocity, although conduction velocities tended to decrease.

The authors [77] concluded that many of the workers studied had definite signs and symptoms of neurasthenia, psychasthenia, and polyneuropathy. This study did not establish a definite relationship between exposure to pure kerosene and polyneuropathy since n-hexane, an agent known to cause polyneuropathy [78], may have been a part of the fuel mixture.

The authors [77] pointed out that obvious eye irritation was not present in exposed workers; they suggested that kerosene was not an eye irritant, in contrast to gasoline, apparently interpreting that most of the exposures were from kerosene. Since the exposures stemmed from installation and testing of fuel systems rather than from spills, the less volatile kerosene might have been volatilized to a greater extent than gasoline, if temperatures, air movements, and proportions of components of the fuels were appropirate.

Animal Toxicity

(a) Petroleum Ether

There are several animal toxicity studies on individual alkanes and alkane mixtures that demonstrate that one or more of these materials can cause peripheral nerve disorders, CNS depression, and skin and respiratory irritation, and they are reviewed in detail in the NIOSH criteria document on alkanes [78]. To evaluate the toxicity of petroleum ether, its two major components, pentanes and hexane, will be briefly discussed.

Miyagaki [79], in 1967, reported the neurotoxic effects of n-hexane exposure on 8-week old male mice. The mice were separated into 6 groups of 10 each and exposed to either 0, 100, 250, 500, 1,000, or 2,000 ppm (0, 352, 879, 1,759, 3,517, or 7,035 mg/cu m) of n-hexane for 24 hours/day, 6 days/week, for 1 year. Tests designed to evaluate neurotoxicity were made on the distal portion of the lower extremities and they included electromyography, strength duration curves, electrical reaction time, and determination of the flexor-extensor chronaxy ratio. Evaluations of the effect of n-hexane on gait, posture, and muscular atrophy were also made.