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.

Microscopic examinations of the distal lower extremity muscles of some of the animals were performed.

Mice exposed to 3,517 mg/cu m of n-hexane or greater showed abnormal electromyography, strength-duration curves indicative of denervation, prolongation of the electrical reaction time, depression of the flexor-extensor chronaxy reaction time, abnormal gait posture, decreased muscle mass, and degeneration of muscle fiber cells [79]. Mice exposed at 879 or 1,759 mg/cu m of n-hexane developed only abnormal electromyography patterns and altered strength-duration curves indicative of incomplete denervation. No neurotoxicity was observed in mice exposed at n-hexane concentrations of 100 ppm. The author concluded that peripheral nerve disorders were caused by a 1-year exposure to n-hexane at concentrations of 879 mg/cu m or greater.

Truhaut and associates [80], in 1973, exposed rats to airborne hexane at a concentration of 2,000 ppm (7,035 mg/cu m), 5 hours/day, 5 days/week, for 1-6 months. Technical grade hexane was used for the investigation. Analysis of the hexane gave the following results based on total volume: 0.3% n-pentane, 25.1% 2-methylpentane plus cyclopentane, 18.4% 3-methylpentane, 48.8% n-hexane, 8% methylcyclopentane, 1.2% methylhexane, and 1.2% benzene. The sciatic and saphenous nerves were removed from anesthetized rats at the end of the 5- to 6-month exposure period, mounted in a nerve chamber, and stimulated by square pulses of various voltages. The studies showed a decrease in the conduction rate of the nerves, an increase in the refractory periods, and a decrease in the excitability of the nerves. Microscopic examination of the nerves following 5-6 months of exposure to hexane showed retraction of the myelin sheaths and, in some

cases, a rupture of the Schwann cell membranes. The authors noted that impurities, such as 3-methylpentane, the cycloalkanes, and benzene in the technical grade hexane used for the studies, might have been responsible for some of the results observed.

In 1974, Swann et al [81] discussed the inhalation effects of various hydrocarbons, including n-pentane and n-hexane, on animal toxicity. Groups of four mice, weighing about 25 g each, were exposed to n-pentane and n-hexane at concentrations of 1,000, 2,000, 4,000, 8,000, 16,000, 32,000, 64,000, or 128,000 ppm (3,517, 7,035, 14,070, 28,139, 56,278, 112,556, 225,112, or 450,225 mg/cu m). Exposures were for 5-minute periods. The exposures were made in a chamber which allowed only the heads of the mice to be exposed to the solvent vapor while the rest of their bodies were enclosed in plethysmographs. Respiration patterns were recorded during the exposure period. Exposure to pentane up to 56,278 mg/cu m produced no anesthesia. Anesthesia was noted during the recovery period after exposures at 112,556 and 225,112 mg/cu m. At 450,225 mg/cu m, deep anesthesia was produced during the exposure period. Respiratory arrest occurred in one mouse about 4.8 minutes after exposure to pentane at 450,225 mg/cu m began. Respiratory irritation was noted at 225,112 and 450,225 mg/cu m. Concentrations of n-hexane up to 56,278 mg/cu m failed to produce anesthesia. At 112,556 mg/cu m of n-hexane, deep anesthesia was produced. At 225,112 mg/cu m, all mice experienced respiratory arrest, the first after 2.5 minutes and the last after 4.5 minutes of exposure.

(b) Rubber Solvent

In 1975, Carpenter and associates [9] examined, in a series of experiments, the toxic effects of rubber solvent vapor inhalation on male

rats, cats, and mice, and female dogs. Groups of 15 rats (100-200 g) were exposed to rubber solvent vapor at concentrations of 11,000, 21,000, 39,000, or 96,000 mg/cu m (about 2,800, 5,300, 9,800, or 24,200 ppm) based on a mean molecular weight of 97 calculated by mass spectrometry data and analyzed by gas chromatography for a single 4-hour period to determine an LC50 or to detect possible cellular damage. After the 4-hour exposure period, 5 rats were immediately killed and their organs examined microscopically, while the remaining 10 animals were observed for an additional 14 days.

Impairment of motor coordination and eye irritation were observed at vapor concentrations of 21,000 and 39,000 mg/cu m, respectively [9]. Convulsions followed by death were observed in all animals exposed to rubber solvent vapor at 96,000 mg/cu m. There were no toxic effects noted at the 11,000 mg/cu m concentration. Microscopic findings of liver sections were hyperplasia of Kupffer cells and increased hepatic mitotic figures which occurred at only the 96,000 mg/cu m concentration. No other microscopic changes were reported. The 4-hour LC50 was estimated to be 61,000 mg/cu m (15,000 ppm).

Female beagles were exposed to rubber solvent vapors, one each, at concentrations of either 5,900, 13,000, or 25,000 mg/cu m (1,500, 3,300, or 6,300 ppm) for a single 4-hour period to determine the earliest persistent signs of toxicity and to ascertain an appropriate level to be used in a subacute study [9]. Loss of coordination was observed at concentrations of 13,000 mg/cu m or greater, and eye irritation was noted at 25,000 mg/cu m. The eye irritation was more severe in the beagle exposed at 25,000 mg/cu m than the eye irritation seen in rats exposed at a similar concentration.

No observable effects occurred at 5,900 mg/cu m.

The acute CNS effects of a 4-hour exposure to rubber solvent vapor at a concentration of 49,000 mg/cu m (12,000 ppm) were examined in four male cats [9]. A time-related depression followed a sequential pattern that included ataxia, loss of proprioception, salivation, relaxation of the nictitating membrane, unconsciousness, tremors, and convulsions. One animal died 3 days after exposure to the solvent vapor. No other deaths or gross or microscopic tissue damage were reported to have occurred from this exposure.

Fifteen male rats (100-200 g) were used to determine the LT50 (time required to cause the death of 50% of the animals) of saturated rubber solvent vapor at a concentration of 180,000 mg/cu m (45,000 ppm) [9]. The animals were exposed to the solvent for 2, 4, or 8 minutes. The LT50 was calculated to be 4.3 minutes. Microscopic examination of the lungs of the animals exposed for 8 minutes showed areas of hemorrhage and perivascular edema.

Male rats (about 6 weeks old) and male beagles (under 2 years old) were divided into four groups of 25 and 4 each, respectively, and placed in inhalation chambers containing rubber solvent vapors at a concentration of 0, 1,900, 3,700, or 7,900 mg/cu m (0, 480, 930, or 2,000 ppm) based on a mean molecular weight of 97 calculated from mass spectrometry data [9]. The animals were exposed for 6 hours/day, 5 days/week. Three rats from each exposure concentration were killed for microscopic examination after 15 and 40 exposure days. All but 10 of the remaining rats (used for another experiment) and all of the beagles were killed after 62 and 63 days of vapor exposure, respectively. There were no animal deaths attributed to

rubber solvent vapor. Body weight gain was no different than that of the controls. No significant changes in blood urea nitrogen, serum glutamic-oxaloacetic transaminase, and serum glutamic-pyruvic transaminase tests and erythrocyte, and total and differential leukocyte counts resulted from solvent vapor inhalation at any exposure duration or concentration in the rats or dogs. Serum alkaline phosphatase was significantly higher after 62 days in all rats exposed to the rubber solvent vapor, but the authors concluded that this finding was an artifact which resulted from very low control alkaline phosphatase values. Microscopic examination of the various organ sections showed no tissue damage that could be attributed to the solvent vapors. Urinalysis showed an increase in specific gravity in the dogs exposed to rubber solvent vapors at 7,900 mg/cu m (2,000 ppm) for 63 days. The significance of this finding was unknown.

At the termination of the 62-day solvent inhalation period, 10 rats from each exposure concentration were exposed to rubber solvent vapor at 80,000 mg/cu m (20,000 ppm) for 5 hours to determine the animals' resistance to the toxic effects of the vapor [9]. No difference in mortality and in the median time of death were noted.

The authors [9] concluded that, since exposure of rats and dogs to 1,900 mg/cu m did not produce significant signs of toxicity and acute exposure of humans to 1,700 mg/cu m produced only slight eye and throat irritation, a hygienic standard for rubber solvent should be set at 1,700 mg/cu m (430 ppm).

(c) Varnish Makers' and Painters' Naphtha

In 1975, Carpenter et al [17] reported the effects of exposure to the vapors of varnish makers' and painters' (VM and P) naphtha in rats, dogs,

and cats. In a single exposure inhalation study, male rats were exposed to VM and P naphtha vapors at concentrations of 4,400, 9,800. or 26,000 mg/cu m (940, 2,100, or 5,600 ppm) based on a mean molecular weight of 114 calculated from mass spectrometry data and analyzed by gas chromatography for 4 hours. Rats at the higher concentration showed responses that were consistently dose related, which included eye irritation and CNS depression characterized by poor coordination and convulsions preceding death. Rats at the 26,000 mg/cu m concentration that died during or shortly after exposure had congested lungs and livers. Bile duct proliferation was noted in three of six livers examined microscopically, and sinusoids of the spleen contained increased numbers of leukocytes in three rats. Examined rats at the 9,800 and 4,400 mg/cu m VM and P naphtha concentrations had no appreciable abnormalities. Animals inhaling VM and P naphtha at 4,400 mg/cu m were reported not to have signs of intoxication during and after exposure and to have gained weight normally during the subsequent 14-day observation period. The authors estimated a single exposure 4-hour inhalation LC50 to be about 16,000 mg/cu m (34,000 ppm) for rats exposed to VM and P naphtha vapor.

Two dogs (one male, one female) were exposed to VM and P naphtha at a nominal concentration of 16,000 mg/cu m for 2 hours [17]. Eye irritation occurred in 30 minutes, tremors and mild ataxia in 1 hour, and dilation of the pupils in 1.5 hours. The male dog was prostrate in 1.5 hours. Apparent recovery occurred within 2 hours after cessation of the exposure. A third dog (male), exposed to VM and P naphtha vapor at 8,000 mg/cu m (1,700 ppm) for 4 hours, appeared normal during the exposure and thereafter.

Four male cats inhaling VM and P naphtha at 19,000 mg/cu m (4,100 ppm) for 4 hours exhibited progressive symptoms usually indicative of CNS depressive effects: salivation, dilation of the pupils, body tremors, prolapse of the nictitating membrane, poor coordination, vomiting, convulsions, and prostration [17]. All animals survived the exposure period, but one became moribund on the 5th day and was killed. Autopsy findings showed suppurative pneumonia.

To evaluate the effects of brief exposures to high concentrations, Carpenter et al exposed male rats to saturated VM and P naphtha vapor at 71,000 mg/cu m (15,000 ppm) [17]. The rats were exposed to the solvent vapor for 57, 30, 15, or 7.5 minutes and had mortality ratios of 5/5, 1/5, 0/5, and 0/5, respectively. The LT50 was estimated to be 37 minutes. Loss of coordination and convulsions were observed in rats which inhaled the vapor for 15 minutes or longer, but no signs of distress were observed during or after 7.5 minutes of exposure.

There was no increase in erythrocyte osmotic fragility in four rats that inhaled 22,000 mg/cu m (4,700 ppm) of VM and P naphtha for 35 minutes [17]. The mean initial hemolysis was in 0.46% and the final in 0.29% saline solution compared to mean control values of 0.50 and 0.31%.

In short-term inhalation experiments, Carpenter and associates [17] subjected 25 male rats and 4 male dogs to repeated daily inhalations of VM and P naphtha for 6 hours/day, 5 days/week, for 65 days. Naphtha at 0, 1,300, 2,800, or 5,800 mg/cu m (0, 280, 600, or 1,200 ppm) was inhaled by randomly assigned groups of animals. No outward signs of distress were observed in either species during the 65-day study. After 40 days, the rats at the 5,800 mg/cu m concentration had a significantly higher

percentage of neutrophils (24%), but a 9% lower lymphocyte count than controls. The total leukocyte count was not affected. These effects were not seen when the rats were killed after 65 days of exposure and therefore were not considered to be related to treatment. After 65 days of exposure, the rats had a significant (9%) lowering in erythrocyte count as compared to controls. There were no statistically significant differences between treated and control groups of rats in weight or in most measured blood chemistry values. Statistically significant differences were noted in the dogs exposed for 60 days to varnish makers' and painters' naphtha, viz: an increase in serum alkaline phosphatase activity (80%) and in reticulocyte count (47%) at the 5,800 mg/cu m concentration, a decrease in the serum glutamic-oxaloacetic transaminase activity (26%) at the 5,800 mg/cu m concentration, an increase in the liver weight to body weight ratio (21%) and a decrease in the reticulocyte count (25%) at the 2,800 mg/cu m concentration, and an increase in the reticulocyte count (4%) at the 1,300 mg/cu m concentration. The authors indicated that, because the values were in the normal ranges of their experimental animals and there were no specific anatomical lesions, the changes might be experimental artifacts rather than deleterious effects. There were no solvent-related microscopic changes seen in either the rats or dogs. Nephrosis was prevalent in the rats and may have masked solvent-related renal damage.

In an additional experiment, Carpenter et al [17] subjected rats surviving the 65-day exposure to VM and P naphtha to a "challenge" concentration of 27,000 mg/cu m for 4 hours (1.7 times the approximate 4-hour LC50 of 16,000 mg/cu m). The surviving rats from the two higher concentrations were found to be more resistant to the increased

concentration than air controls and naive controls (animals never used in the experiment). Animals dying during or shortly after exposure showed marked congested or hemorrhagic lungs, whereas survivors after 24 hours showed no remaining irritation.

The authors [17] concluded that, since exposure of rats and dogs at 2,800 mg/cu m did not produce treatment-related signs of toxicity, and acute exposure of humans at 4,100 mg/cu m, but not at 660 mg/cu m, produced eye, nose, and throat irritation, a hygienic standard for VM and P naphtha should be set at 2,000 mg/cu m (430 ppm).

(d) Mineral Spirits

In 1966, Rector and coworkers [82] reported the effects of a paint thinner on five species of animals exposed continuously (23.5 hours/day, 7 days/week) for 60-90 days or intermittently for 8 hours/day, 5 days/week, for a total of 30 exposures. The mineral spirits used in this study were obtained from a Navy supply depot under the listing of "Paint Thinner, Mineral Spirits Grade I." This type of mineral spirits had a boiling point range of 140-190 C, a mean molecular weight of 144-169, and a specific gravity of 0.786-0.787. The compound was analyzed as a complex mixture of 80-86% saturated hydrocarbons, 1% olefins, and 13-19% aromatics.

Air concentrations of mineral spirits for this study [82] were calculated from nominal input since no satisfactory analytical procedure was available at the time the experiments were begun. Later in the study, the airborne concentration of mineral spirits was monitored and found to be 95% of the calculated nominal input with an average deviation of 4.8%. The concentration of airborne mineral spirits remained relatively constant in monitored experiments.

In continuous 90-day exposure experiments, rats, guinea pigs, rabbits of both sexes, and male dogs and monkeys were exposed to mineral spirits with concentrations ranging from 114 to 1,271 mg/cu m except for approximately 30 minutes/day, which were required for feeding and servicing of cages and chambers [82]. Exposure of the dogs, monkeys, and rabbits to the mineral spirits at any of these concentrations failed to produce death. An occasional death was noted in the rats exposed to the mineral spirits but the number of deaths (3/106) was similar to that of the controls (6/224). In contrast, guinea pigs were very susceptible to the mineral spirits with deaths occurring in all groups exposed at a concentration of 363 mg/cu m or more. The rate of body weight gain was generally similar in test animals and in controls, except in guinea pigs and monkeys. The decline in body weight became apparent in guinea pigs at 619 mg/cu m and in monkeys at 555 mg/cu m, in continuous exposure experiments. Continuous exposure of the guinea pigs and monkeys to mineral spirits at a concentration of 1,271 mg/cu m for 90 days resulted in body weight losses of 4 and 9%, respectively.

In dogs exposed to mineral spirits at 238 and 619 mg/cu m, a marked alteration between the preexposure and postexposure leukocyte counts was found [82]. The differential leukocyte counts and hematocrit and hemoglobin values were within normal limits. No consistent pattern of dose-response blood relationships was found except for a minor, but consistent, increase in the postexposure leukocyte counts in both rabbits and guinea pigs. This change was seen in both exposed animals and chamber controls. Hematologic data from the animals exposed at 1,271 mg/cu m were not reported.

Gross examinations of all animals were conducted at the end of each study [82]. While no remarkable changes were noted, irritation and congestion of the lungs were commonly found in all species. The severity of the irritation and the number of animals involved appeared to be dose-related. The livers of several guinea pigs appeared "discolored and wrinkled." No gross abnormalities were seen in the spleen, kidneys, or heart of any other species that could be attributed to solvent exposure.

Microscopic examination of the heart, lungs, liver, spleen, and kidneys was carried out on all surviving dogs, rabbits, and monkeys, and on 50% of the surviving guinea pigs and rats [82]. In general, congested lungs were found only in animals exposed to mineral spirits at a concentration of 1,271 mg/cu m. At this level, the lung tissue of all species showed evidence of bronchitis and mixed inflammatory cell infiltration. While occasional signs of lung irritation were seen at lower concentrations, the number of animals involved was such that the lung irritation could not be definitely related to the exposure. Microscopic examination of the heart, spleen, and kidney sections showed no findings that could be related to the exposure, but examinations of the liver yielded a mixed pattern. Focal necrosis, sometimes associated with worms, was seen in the livers of rats, rabbits, dogs, and monkeys. Mild-to-moderate vacuolar changes in the plate cells were noted in some guinea pigs and monkeys exposed at 363 mg/cu m and higher. This finding, however, was variable, and the incidence of liver damage did not correlate well with the exposure concentration. The vacuolar changes seen in the livers of guinea pigs were distributed in the peripheral area of lobules, although central and diffuse changes were also commonly seen. While no peripheral vacuolar

changes in the hepatic plate cells were seen in the control guinea pigs, some patchy vacuolar changes were observed. The authors concluded that only the hepatic changes noted in the animals exposed at 513 and 1,271 mg/cu m of mineral spirits were likely to have been caused by solvent exposure.

To find the explanation for the high mortality seen in guinea pigs exposed to mineral spirits at concentrations of 550 mg/cu m, Rector et al [82] investigated the serum alkaline phosphatase activity, serum isocitric dehydrogenase activity, liver lactate production, and serum or plasma urea levels in 10 treated and 10 control guinea pigs. However, the results of this experiment did not explain the high mortality in the guinea pigs.

The authors [82] also conducted three intermittent exposure studies in which the same five species, viz, rats, guinea pigs, rabbits, dogs, and monkeys, were exposed 8 hours/day, 5 days/week, for 30-60 exposures to mineral spirits at concentrations of 593, 596, or 1,353 mg/cu m. In the first study, animals exposed at 1,353 mg/cu m for 6 weeks showed no toxic signs. Body weight gains and blood values were similar in both exposed and control animals. No consistent microscopic changes were found except for possible lung irritation in guinea pigs. Seven of eight guinea pigs exposed at 1,353 mg/cu m showed some lung congestion and emphysema, which were not seen in the controls, and one of seven showed vacuolar changes in hepatic plate cells. In the second study, animals exposed at 596 mg/cu m for 6 weeks showed no signs of toxicity, and body weights and the hematocrit, hemoglobin, and total leukocyte count were all within normal limits. One-half of the rats and guinea pigs were killed and their tissues were examined microscopically. No noteworthy changes were found. After a

2-week nonexposure interval, the remaining half of the rats and guinea pigs were reexposed for a second series of 30 exposures at 593 mg/cu m. No noticeable signs of toxicity occurred during this second reexposure period, and the hematocrit, hemoglobin content, and total leukocyte count were within normal limits. Following a 17-day observation period, the animals were killed for necropsy. Microscopic findings indicated greater focal lymphocytic involvement in the lungs of several exposed guinea pigs than in the controls. No noteworthy microscopic changes were reported in any other tested species. There were no deaths in the animals exposed at 593 mg/cu m of mineral spirits.

Of the five species examined in this study, the guinea pigs were found to be particularly susceptible to mineral spirits [82]. As the air concentration of mineral spirits increased above 363 mg/cu m, guinea pigs began to die. No deaths occurred in guinea pigs during continuous exposures at 114 and 238 mg/cu m; no adverse changes were noted at these levels in any other species exposed. From these short- and long-term inhalation studies, the authors recommended that a guideline for a 90-day exposure period in submarines to mineral spirits containing 15-20% aromatic hydrocarbons be set at 40 mg/cu m.

In 1974, Gillespie et al [83] reported the effects of various paint components, including mineral spirits, on inflammatory response and tissue resistance to infection. Albino rabbits (2-3 kg) were used to assess the inflammatory response to the various paint components. A subcutaneous injection of mineral spirits at a dose of 0.1 ml was made into a shaved portion of the rabbit's back, and 4 days later the diameter of the indurated margins of the skin was measured. The indurated margin was about

2.4 cm in diameter and was greater than the indurated margins caused by most of the other paint components. The assessment of the resistance of tissue to infection was accomplished by subcutaneous injection of 0.1 ml of bacterial inoculum (10,000 or 100,000 Staphylococcus aureus) and a mineral solvents sample (injected at an unknown volume) and by measuring the inflammatory responses in terms of amount of induration and pus formation 4 days later. Mineral spirits caused increased induration, inflammation, and tissue necrosis but did not impair the ability of the wound to resist infection. Similar results were seen with other paint solvents and pigments.

(e) Stoddard Solvent

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

In 1975, Carpenter et al [21] reported the effects on rats of the inhalation of Stoddard solvent at 2,400, 4,600, or 8,200 mg/cu m (420, 800, or 1,400 ppm), based on a mean molecular weight of 144 calculated from mass spectrometry data and analyzed by gas chromatography, for a single 8-hour period. Groups of 15 rats were used at each exposure level. Exposure to 8,200 mg/cu m of Stoddard solvent resulted in the death of one of the rats at the termination of the inhalation period. Eye irritation, slight loss of coordination, and a bloody exudate around the nostrils were noted. A concentration of 4,600 mg/cu m produced similar signs but no loss of coordination. Inhalation of Stoddard solvent at 2,400 mg/cu m for 8 hours failed to cause any visible response during or after exposure; body weight gains were normal during the subsequent 14 days.

When a female beagle was exposed to vapors of Stoddard solvent at a nominal concentration of 4,000 mg/cu m for 8 hours, it developed no signs of toxicity during or after the exposure [21]. Another female beagle inhaling Stoddard solvent at 8,000 mg/cu m (nominal concentration) for 8 hours developed eye irritation after 1 hour, increased salivation at 3 hours, tremors at 4 hours, and clonic spasms after 5 hours but survived the exposure.

Four male cats were exposed to vapors of Stoddard solvent at a nominal concentration of 10,000 mg/cu m until they died within 2.5-7.5 hours after the exposure began [21]. They had signs of CNS disorders which followed a time-related pattern. There was first a slowing of pupillary reaction to light, then tremors, clonic convulsions, and finally death.

In a short-term inhalation experiment, Carpenter et al [21] subjected groups of 25 male rats and 4 male dogs to repeated daily inhalations of Stoddard solvent for 6 hours/day, 5 days/week, for 13 weeks. The measured concentrations of solvent used in this study were 0, 480, 1,100, or 1,900 mg/cu m (0, 84, 190, or 330 ppm). Three rats from each exposure concentration were killed for tissue microscopic examination (adrenals, brain, pituitary, trachea, thyroid, parathyroid, lungs, heart, liver, kidneys, spleen, duodenum, pancreas, ileum, jejunum, colon, skeletal muscle, sciatic nerve, and bone marrow sections) after 14 and 37 exposure days and four from each exposure concentration at 65 exposure days. Ten rats from each level were used for a challenge exposure to determine whether the 65-day survivors were more or less sensitive to Stoddard solvent as a result of repeated vapor inhalation. All dogs and surviving rats were killed after 66 days and tissues were taken for microscopic

examination. Those tissues that were examined in the rats were also examined for the dog, as well as the tracheal bifurcation, pharnyx, tonsil, nasal mucosa, and stomach. Blood analysis (hematocrit, total erythrocyte count, reticulocyte, total and differential leukocyte counts, serum alkaline phosphatase, serum glumatic-pyruvic transaminase, serum glutamic-oxalacetic transaminase and blood urea nitrogen) was performed on rats killed after 3, 8, or 13 weeks and on dogs killed after 13 weeks.

The hematologic findings on rats killed after 40 days of solvent exposure showed a 10, 14, and 11% lower erythrocyte count and a 4, 6, and 6% lower hematocrit at the 1,900, 1,100, and 480 mg/cu m concentrations as compared to controls, respectively [21]. Hemoglobin values were not statistically different at the 1,900 mg/cu m (330 ppm) concentration but were 7 and 9% lower than control values at the 1,100 and 480 mg/cu m concentrations, respectively. The authors did not consider these differences to be important since they were not dose related; the values were all within the range of normal values, and similar results were not seen at the termination of the experiment. Blood urea nitrogen was 31% higher in the rats exposed at 1,900 mg/cu m for 13 weeks. No other alterations in blood chemistry were noted.

Marked tubular regeneration in the kidneys and dilation of the loops of Henle which contained homogeneous eosinophilic and amorphous debris were evident in the rats exposed to vapors of Stoddard solvent at 1,900 mg/cu m (330 ppm) for either 8 or 13 weeks [21]. What was described by the authors as marked tubular regenerative changes of the kidneys may in fact indicate kidney damage. Dilation of the loop of Henle was also noted in three of nine rats exposed to 1,100 mg/cu m (190 ppm) for 13 weeks. In addition,

two out of nine rats exposed to 1,100 mg/cu m for 13 weeks showed evidence of marked tubular regeneration. The authors reported that the number of animals that showed dilation of the loops of Henle at the 1,100 mg/cu m concentration were not significantly different from control values. No microscopic abnormalities were noted at 480 mg/cu m (84 ppm). There were no toxic effects observed, at any concentration of Stoddard solvent used in this study, on canine chemical or cellular constituents or tissue sections.

At the termination of the 13-week inhalation experiment, 10 rats from each exposure concentration, including air controls and 20 naive controls were exposed to a challenge concentration of Stoddard solvent at 6,200 mg/cu m (1,100 ppm) for 6 hours [21]. No deaths occurred during this period and the authors concluded that repeated inhalation of solvent vapors did not change subsequent susceptibility to Stoddard solvent.

Since only slight eye irritation was reported by volunteers exposed at 850 mg/cu m but not at 140 mg/cu m and animal studies showed, in the authors' opinion, no signs of solvent-related toxicity, Carpenter et al [21] concluded that there was no reason to reduce the TLV of Stoddard solvent which at the time was 1,150 mg/cu m (200 ppm) [84].

In 1975, Carpenter and associates [56] reported the effects of inhalation of 140 flash aliphatic solvent (a type of Stoddard solvent) on mice, rats, cats, and dogs. Five groups of 16 male rats, weighing 100-150 g, inhaled the solvent at either 270, 450, 790, 1,900, or 2,900 mg/cu m (43, 71, 125, 302, or 461 ppm, respectively, based on a mean molecular weight of 154, calculated by mass spectrometry data and analyzed by gas chromatography) for 8 hours to determine a concentration that caused cellular injury. At concentrations greater than 270 mg/cu m, the solvent

was present in the form of a vapor-aerosol mixture. Two of 16 rats died at the 2,900 mg/cu m solvent concentration. There were no other animal deaths. Gross and microscopic examination showed no abnormalities. The only signs of toxicity were irritation of the skin of the extremities at 1,900 and 2,900 mg/cu m and a slight loss of coordination at 2,900 mg/cu m after 6.5 hours of exposure. Since only 2 of 80 animals died, an LC50 could not be determined.

One female beagle (10.4 kg) was exposed to 140 flash aliphatic solvent at a concentration of 1,700 mg/cu m (270 ppm) of solvent for 8 hours [56]. Transitory lacrimation, starting after 30 minutes of exposure and lasting 1 hour, was apparent. A 0.5-kg loss in body weight occurred during the exposure period and overnight, but body weight increased to 10 kg by the succeeding day. A second beagle (10 kg) was exposed to solvent vapor at a concentration of 210 mg/cu m (33 ppm) for 8 hours with no signs of distress except lacrimation that occurred between 5.5 and 7.5 hours of the exposure. Weight loss occurred during the period following exposure. No microscopic or blood chemistry changes were reported.

Four male cats were exposed to 140 flash aliphatic solvent at 440 mg/cu m (70 ppm) for 6 hours [56]. No effects on the CNS were evident as assessed by righting reflexes, placing reactions, aversion to foot pain, extensory thrust reflex, and pupillary contraction. Microscopically, there were no tissue lesions that were attributed to solvent inhalation. An additional four male cats were subjected to the solvent aerosol at a nominal concentration of 10,000 mg/cu m for 6 hours. No body weight changes or evidence of toxicity were noted.

Ten male rats (107.5 g, mean body weight) were exposed to an aerosol of 140 flash aliphatic solvent (0.5 μm) at a nominal concentration of 10,200 mg/cu m for 340 minutes [56]. Signs of toxicity appeared in the following sequence: wet mouth, sluggish movements by 2 hours, extremities irritated by 4.5 hours, tremors and one death by 5.5 hours, three dead by 5.7 hours, and no deaths thereafter during a recovery period of 7-14 days. Fourteen days after exposure, mean body weight gain was slightly less than the controls (88 versus 105 g, respectively). The daily weight gain changes were not reported by the authors. Two solvent-exposed animals were killed after 7 days and were found to have had pneumonia, but the three rats that died during the exposure period had no evidence of this change. There was no increase in erythrocyte fragility in six male rats that were exposed to "saturated" vapor for 7 hours.

Groups of 25 male rats and 4 male dogs were exposed to 140 flash aliphatic solvent at a concentration of 0, 49, 100, or 230 mg/cu m (0, 7.8, 16, or 37 ppm) for 6 hours/day, 5 days/week, for 72-73 days [56]. Three rats from each exposure concentration were killed for microscopic examination after 14- and 39-day intervals. Body weight was measured, and blood and urine were analyzed. Abdominal and thoracic organs, endocrine glands, bone marrow, and nerve tissue were sectioned and examined microscopically.

No exposure-related effects were found at any of the concentrations tested in rats [56]. Changes in serum alkaline phosphatase, body weight gain, and differential leukocyte counts occurred in some of the exposed groups but, in the authors' opinion, were not related to solvent exposure

because the changes were within normal limits of their animals or were not dose-related.

No toxic effects in dogs were reported to have resulted from solvent exposure [56]. Serum glutamic-pyruvic transaminase values for the dogs exposed to 140 flash aliphatic solvent at a concentration of 49 mg/cu m (7.8 ppm) after 14 weeks of treatment were higher than controls, but, since there was no dose-dependent relationship, the authors felt that this effect was not solvent-related. They [56] concluded that, based on the lack or toxicity results found in the inhalation studies with rats and dogs and on sensory responses of human subjects, a hygienic standard should be 230 mg/cu m (37 ppm).

(f) Kerosene

Deichmann et al [85], in 1944, investigated the effects of kerosene on the skin of rabbits. Kerosene was applied at a dose of 3 ml/kg to the skin of rabbits for 6 consecutive days. Gross examination findings showed hair loss and scaling and cracking of the epidermis but no evidence indicating systemic toxicity.

In 1963, Rebello and Suskind [86] described the effects of kerosene on the dermal reactivity of guinea pigs sensitized to 2,4-dinitrochlorobenzene (DNCB). Seventeen albino guinea pigs, weighing 300-400 g, were sensitized with a single intradermal injection of 0.1 ml of a 0.05% solution of DNCB in 50% alcohol-saline. The backs of the guinea pigs were shaved and 0.5 ml kerosene was applied to one side of the back every 3rd day for 2 weeks; the other side of the back was left untreated. The last kerosene application occurred 24 hours before the challenging procedure, which consisted of the application of 0.1 ml of 0.1, 0.05, and

0.01% DNCB to both the kerosene-treated and untreated skin. Biopsy specimens were taken from the animals at both treated and control sites immediately before testing and from corresponding challenge sites after 24 and 48 hours. The criteria for estimating the degree of reactivity were as follows: 0, no evidence of erythema; 1+, slight erythema; 2+, moderate erythema, 3+, intense erythema or erythema and swelling.

The control sites challenged with 0.01% DNCB were all scored as 0 while the kerosene-treated sites had 15 scores of 0 and 2 of 1+ [86]. Five control sites challenged with 0.05% DNCB were reported as negative, while 11 and 1 were scored as 1+ and 2+, respectively. The kerosene-treated sites challenged with 0.05% DNCB had the following scores: eight skin specimens, 0; three skin specimens, 1+; five specimens, 2+; and one skin specimen, 3+. Four control sites challenged with 0.1% DNCB were reported as negative while nine and four were scored as 1+ and 2+, respectively. The kerosene-treated sites challenged with 0.1% DNCB were scored as follows: four skin sites, 0; three skin sites, 1+; nine skin sites, 2+; and one skin site, 3+. Microscopic examination of the kerosene-treated skin showed an eczematous type of reaction with dermal edema, spongiosis, and vesiculation, as well as dermal infiltrate. Only mild swelling of the epidermis and a lymphocytic dermal infiltrate extending into the epidermis were seen in the untreated skin. The authors concluded that kerosene may increase the reactivity of guinea pig skin to certain sensitizing agents.

In 1946, Carpenter and Smyth [87] examined the effects of deodorized kerosene on the rabbit cornea. The eyes of untreated albino rabbits were checked for preexisting abnormal lesions by instillation of a 5% solution of fluorescein and, 20 seconds later, by distilled water; only rabbits with

healthy eyes were selected for experimentation. Two hours later, 0.5 ml of undiluted deodorized kerosene was applied to the center of the cornea while the eyelids were retracted. The eyelids were then held closed for 1 minute and then released. After 18-24 hours, the eyes were examined in strong diffuse daylight, stained with fluorescein, and the injury graded from 1 to 10. The deodorized kerosene had a 1 rating and was thus rated innocuous to the rabbit eye.

Grant [54], in 1974, reported that kerosene was essentially innocuous to the rabbit eye. No details were given.

In 1967, Narasimhan and Ganla [88] discussed the effects of kerosene given orally to Swiss albino mice and Belgian rabbits and ip to dogs. The composition of the kerosene used in this study was 80% paraffins and naphthenes (no unsaturates), 20% aromatics, 0.25% sulfur (maximum by weight), and 0.005% mercaptans (maximum by weight) and was representative of three different commercial samples of kerosene from Middle-Eastern crude oil. Mice weighing 30 g were given filtered kerosene orally at a dose of 1 ml. Controls for this experiment received 1 ml of distilled water orally. Twenty-four hours after kerosene was initially administered, a second 1-ml dose of kerosene was given to the mice. The mice became drowsy 12-15 minutes later. Difficulty in breathing and rapid respiration also were evident. The drowsiness became very pronounced by the 2nd hour. Neuromuscular strength, as determined by the "inclined plane method," was weaker in the mice treated with kerosene than in the controls. The mice recovered 4 hours after kerosene administration. However, their coats were shaggy and smelled of kerosene and their anogenital regions were stained. The mice gradually became normal in appearance and in feeding habits.

After the second oral 1-ml dose of kerosene, 24 hours after the initial one, animal response was qualitatively the same as after the first dose. Drowsiness was more pronounced, and, at the end of 5 hours, the mice became comatose. All died 8-10 hours after receiving the second dose. On gross examination, the kidneys, including cut surfaces, appeared to be undamaged. Kidney tissue examined microscopically, however, showed cloudy degeneration of the renal tubules and the glomeruli and pelves were congested. The spleen was normal by both gross and microscopic examination. Gross examination findings showed no changes in the lungs, pleurae, trachea, and hilar glands. Cut surfaces of the lungs were hyperemic. The main blood vessels were found to be dilated when examined microscopically and the alveolar walls were hyperemic. A few erythrocytes were found in some alveoli located in the basal lobes. The authors stated that no cellular exudate or inflammatory cell infiltration was found in the lungs or pleurae. The bronchi and bronchioles were normal with an intact mucosa. The livers were enlarged and pale, had yellow patches scattered on their surfaces, and smelled of kerosene. A film of kerosene appeared on the surface of the formalin fixative in which liver tissue was placed before microscopic examination. Microscopic examination showed normal central veins and centrilobular zones, but the intermediate zones showed vacuolation and cloudy degeneration. Vacuolation also occurred in the periportal zone, but to a lesser extent.

Sixteen dogs, weighing 7-8 kg, each were given kerosene ip at a dose of 50 ml/kg [88]. After 1 hour, the adverse effects in dogs resembled those seen in mice in that they appeared sedated and drowsy. They also had rapid respiration, difficulty in breathing, and tachycardia. The dogs'

breath and urine smelled of kerosene. After 6 hours, the tachycardia persisted and the difficulty in breathing had increased. While cornea and conjunctival reflexes were present, the dogs gave no response to painful stimuli such as pinpricks. When forced to stand, the animals staggered. Liver function was affected and eventually severely impaired as shown by the sulfobromophthalein test increasing from an average of 4.6% retention at 0 hours to an average of 48.9% at 4 hours. In 7 or 8 hours, two of the dogs had tremors in their extremities, five had brief convulsions, and the remaining dogs, although not having convulsions, gradually became comatose. In a few hours, all animals were dead. At autopsy, the lungs appeared congested, but no fluid could be removed from the tracheobronchial tree. The bronchi and alveoli appeared to be normal when examined microscopically, although the blood vessels were dilated. No exudate or inflammatory cells were found. Gross examination of the kidneys showed no lesions; however, microscopically, severe cloudy degeneration was observed. The urinary bladder was severely congested and denuded in some areas. Livers appeared congested. Microscopic examination of the liver parenchyma showed cloudy degeneration with intense hyperemia.

Rabbits, weighing 1.5 kg, received kerosene orally at a dose of 70 ml/kg body weight [88]. Three hours later, the animals developed tachycardia and their body temperature was reported to increase to 38.6 C. This is a low temperature for normal rabbits and the authors did not indicate the initial body temperature. The coats were shaggy and stained with kerosene. Rapid respiration persisted throughout the day, and labored breathing occurred 19 hours after the administration of kerosene. Corneal responses were still present as was the response to painful stimuli. At 22

hours, breathing was even more difficult and the animals lost their righting reflexes. The extensor tone appeared to increase as the rabbits' necks became rigid and their extremities were completely extended. The animals went into convulsions and died without going into a coma. Blood glucose tests indicated progressivly decreasing blood glucose. Superficial yellow areas appeared on the liver, and cut sections showed areas of focal necrosis. Where complete tissue destruction had occurred, necrotic parenchyma and inflammatory cells were observed microscopically. At other sites, fatty degeneration was evident. Congestion was the only change seen in the lung parenchyma and bronchioles. The kidney tubules showed cloudy degneration with "frayed" cell margins. The glomeruli were severely congested.

The authors [88] concluded that ingested kerosene severely impaired liver function, which led to low blood glucose and eventual death. They further stated that the lowest value of blood glucose coincided with the onset of convulsions seen in rabbits and dogs and with the onset of coma as seen in dogs. Since only hyperemia of the lungs was observed, and, since there was no possibility of aspiration (because of the choice of animal and route of administration), the authors concluded that the cause of death from kerosene was not primarily the result of pneumonia but rather of acute liver damage.

In 1972, Wolfsdorf and Kundig [89] reported a study in which vervet monkeys were used to determine if the lung effects after kerosene ingestion were the result of absorption and excretion of the solvent by the lungs.

Monkeys, weighing 1.8-2.75 kg, were divided into three test groups of five monkeys each [89]. The test animals were anesthetized and then

weighed. Group I animals were sham tracheostomized, group II animals received a tracheostomy and had a plastic endotracheal tube inserted with the proximal end tied off. Both group I and II animals received kerosene at a dose of 45 ml/kg body weight via a nasogastric tube. Group III was tracheostomized and had cannulas inserted as had group II. Group III then received kerosene at a dose of either 1.0 ml iv or 0.2 ml in 5 ml of normal saline endotracheally. Six to 8 hours after treatment, all the test animals that survived were killed using an iv injection of barbiturate. The lungs were removed and examined macroscopically and microscopically, and the lung weight/body weight and the lung wet weight/dry weight ratios were determined. A control group consisted of 22 healthy monkeys ranging in weight from 1.8 to 5.4 kg. The animals were killed and their lungs were removed; lung weight/body weight and lung wet weight/dry weight ratios were determined.

Both mean ratio values for groups I and III were significantly greater than those of the control group but group II were not significantly different from the controls [89]. The mean lung weight/body weight and lung wet weight/dry weight ratios for Groups I and III were not significantly different. Lung lesions were present in four of five animals in group I. The number of animals with lesions in group III was not stated. Macroscopic and microscopic examination of the lungs from groups I and III showed heavy edematous lungs with patchy hemorrhagic areas. The lungs from group II animals were not distinguishable from the lungs of the control group.

The authors [89] concluded that the adverse pulmonary effects after kerosene ingestion were not the result of absorption and excretion of the

solvent through the lungs but rather the result of aspiration of the kerosene directly into the tracheobronchial tree. They based their conclusions on the fact that both group I and group II animals received kerosene nasogastrically, but, when aspiration was prevented in group II animals by a tracheostomy, no lung lesions were seen nor were the lung weight ratios significantly different from the controls. Group I and group III test animals both showed similar lung damage that had been produced in group III animals by the iv or endotracheal administration of kerosene. Furthermore, the mean lung weight ratios for both groups differed significantly from the controls.

In 1969, Volkova et al [90] described the effects of various types of kerosene on rats, mice, rabbits, and cats. The animals (unknown age and sex) were exposed to either lamp fuel kerosene, lamp fuel export type B, or lamp fuel export type A at aerosol concentrations of 500, 1,200, 2,500, or 12,000 mg/cu m for 2 hours/day for either 1 day or 2-4 weeks. During the experiment, the animals were observed for signs of gross toxicity and breathing rates. At the end of the experiment, the animals were killed and blood samples were taken for various unspecified analyses. Microscopic examination of the organs of the respiratory tract also was performed. The diameter of the aerosol particles was either 7 or 16 μm. The kerosene was combined with a mixture of equal weight of freon 11 and freon 12 so that the overall kerosene content was either 25 or 40% by weight. Lamp fuel kerosene was shown to have the highest aromatic content of the kerosenes and lamp fuel export type A the lowest, although chemical composition data were not reported.

Although very few quantitative data were reported, the authors [90] indicated that exposure to lamp fuel kerosene at 500 mg/cu m (droplet size, 7 μm) caused tracheitis, bronchitis, and an increase in the erythrocyte sedimentation rate. In addition to these effects, concentrations at 2,500 mg/cu m caused peribronchitis. A single exposure at 500 mg/cu m did not cause any signs of toxicity. Lamp fuel kerosene dispersed in particles of 16 μm at 1,200 mg/cu m for 2-4 weeks did not cause toxicity, but, at 12,000 mg/cu m, leukocytosis, a decreased erythrocyte sedimentation rate, and a 15-20% decrease in the respiratory rate were observed. Tracheitis, bronchitis, and pneumonia were also present. In all cases, lamp fuel kerosene caused conjunctivitis.

An aerosol of type B kerosene was found to be less toxic than lamp kerosene [90]. A single inhalation of this kerosene (droplet size, 7 μm) at 500 mg/cu m did not cause any signs of toxicity. Repeated exposure at this concentration and droplet size produced a 15-20% decrease in the respiratory rate and caused inflammation of the respiratory organs. With an aerosol concentration of 500 mg/cu m, no changes in the blood occurred, but, if the kerosene concentration was 2,500 mg/cu m, leukocytosis and monocytosis developed. In addition, pneumonia was seen in most animals. An increase in the diameter of the aerosol particles from 7 to 16 μm with single exposures to type B kerosene at 1,200 mg/cu m did not alter the toxicity. On repeated exposure to the same aerosol concentration, leukocytosis and bronchitis developed. If the aerosol concentration was 12,000 mg/cu m, the animals developed desquamative bronchitis and pneumonia in addition to leukocytosis. Type B kerosene caused conjunctitivits in exposed animals, regardless of dose or particle size.

A 7-μm aerosol of type A kerosene at 500 mg/cu m for either 1 day or 3-4 weeks of exposure had no toxic effects. Concentrations of type A kerosene at 2,500 mg/cu m only caused pulmonary polyemia in mice and rats. Larger particles (16 μm) of type A kerosene, at 1,200 mg/cu m, failed to cause signs of toxicity. If the concentration was increased to 12,000 mg/cu m, pulmonary polyemia and slight irritation of the mucous membranes occurred.

The authors [90] concluded that the toxicity of kerosene aerosols of various types differed, depending on the composition of the kerosene, its dispersion, and the frequency and duration of exposure. Purified kerosene was less toxic than the unpurified type. Although the purification procedure probably reduced the aromatic content, it is not possible to quantitatively correlate aromatic content with toxicity since no chemical composition data were given.

In 1976, Carpenter et al [67] described the effects of inhalation of deodorized kerosene vapors and aerosols on rats, mice, dogs, and cats. Six 90- to 120-g male albino rats were exposed for 8 hours to air "substantially" saturated with deodorized kerosene vapors. The approximate airborne concentration for this exposure was 100 mg/cu m (14 ppm) based on a mean molecular weight of 171 calculated from mass spectrometry data and analyzed by gas chromatography. The exposed rats showed no signs of discomfort or toxicity during the exposure, and the mean weight gain of 60 g during the 14-day observation period was not abnormal. After the 14-day observation period, the rats were killed and examined. No unusual pathologic findings were reported. A second group of six male rats were exposed to an aerosol of deodorized kerosene 6 hours/day for 4 days. The

mean airborne concentrations of the aerosol on the 4 days were 9,600, 6,900, 7,000, and 7,400 mg/cu m. The droplets in the aerosol averaged less than 1 μm in diameter.

After 1.25 hours of exposure on the 1st day, the rats showed a slight loss of coordination and were sluggish after 2.75 hours [67]. On the 2nd day of exposure, the rats were sluggish after 3 hours but showed good coordination. By the end of the second exposure, the extremities of the rats were red. On days 3 and 4, the condition of the rats did not appreciably change. After 1 day of no exposure, the extremities of the rats were dry with flakes forming. The dryness and flaking continued for 3 additional days, at which time one of the six rats showed a slight hair loss. The weights of the animals remained almost unchanged during the exposure and 1 day after exposure. The mean weight gain for the rats over a 14-day observation period was 63 g and was considered by the authors to be within acceptable limits. When six male albino rats inhaled deodorized kerosene at a concentration of 5,900 mg/cu m as an aerosol for 6 hours, no increase in osmotic-erythrocyte fragility was seen as compared with control rats immediately after exposure. Four male cats of mixed breed exposed at 6,400 mg/cu m for 6 hours showed no effect.

Separate groups containing 25 male rats and 4 male beagles each were exposed to deodorized kerosene at mean measured airborne concentrations of 20, 48, or 100, mg/cu m (approximately 2.9, 6.9, or 14 ppm, respectively) or to solvent free air 6 hours/day, 5 days/week, for 67 days [67]. The criteria of response for these exposures were body weight change and blood and urine analyses. Baseline blood values were measured in the dogs before the 1st day of inhalation. The values in rats were compared with a control

group that breathed solvent-free air.

Only two rats died during the 67-day study. One of eight died after 30 days of exposure at 100 mg/cu m. This animal had no weight loss before death [67]. Autopsy indicated pneumonia as the cause of death. The other death occurred after 16 days of exposure at 48 mg/cu m (6.9 ppm). This animal lost 40 g in weight during the 7 days preceding death. Abscess bronchopneumonia was believed to be the cause of death in this rat. The urine pH was increased, and specific gravity of the urine was decreased in the surviving rats after 8 weeks at 100 mg/cu m. There was a slight decrease in the rats' erythrocyte count in the 48 mg/cu m group at 8 weeks, which was not considered abnormal by the authors. Differential blood smears of rats exposed to kerosene at 20 mg/cu m showed a low value for immature neutrophils at 8 weeks and a slight increase in the ratio of neutrophils at 13 weeks. An elevated serum alkaline phosphatase value was reported after exposure at 100 mg/cu m for 8 weeks. This finding was the only abnormality in blood chemistry. The animal was sick when killed, and pleural adhesions and abscess bronchopneumonia were found at necropsy. Microscopic examination of tissues removed from the rats exposed at all three exposure concentrations showed no dose-related changes. The incidence of tubular regeneration was neither dose-related nor higher than that of controls with one exception. After 13 weeks, seven of nine rats exposed at 20 mg/cu m were reported to have had slight tubular regeneration as compared with two of eight rats in each of the higher exposure concentrations and with three of nine rats in the control group. In dogs exposed at 20 mg/cu m, there was a slight but significant increase in the body weight after 13 weeks. Occasional lesions were seen in the organs of

exposed and control dogs, but they were not considered to be related to the deodorized kerosene exposure.

From the results of these animal studies which showed a lack of toxicity at 100 mg/cu m and human sensory irritation studies which indicated that 140 mg/cu m was tolerable, Carpenter et al [67] suggested a hygienic standard of 100 mg/cu m (14 ppm) for deodorized kerosene.

Light petroleum hydrocarbons, such as kerosene, have a low toxicity when ingested and retained in the stomach, but, if the solvent reaches the lungs, extensive lung damage and death can occur [91]. In 1963, in an article in the Industrial Hygiene News Report [91], Gerarde and Eckardt were reported to have studied the aspiration hazard of kerosene. These investigators administered kerosene at 40 doses of 5 ml each by stomach tube to two rats. The animals appeared healthy and had normal lungs. Only minor losses of skin around the anus were noticed. After an administration of kerosene at 0.1 ml directly into the trachea of both rats, the animals developed hepatization of the lungs and acute cardiopulmonary congestion and subsequently died. Similar experiments were performed with chickens and rabbits with comparable results.

Gerarde [92], in 1963, reported the effect of increasing doses of kerosene given by tracheal insufflation, on the mortality of male rats (200-275 g). The animals that received 0.05, 0.10, 0.15, 0.20, or 0.25 ml had mortality ratios, 72 hours after administration, of 0/10, 4/10, 9/10, 9/10, and 10/10, respectively. The authors also reported that hydrocarbons having low viscosity, not exceeding 45 Saybolt Seconds Universal (SSU) at 100 F, would be readily aspirated. Kerosene has a viscosity of 32 SSU at 100 F.

Gross et al [93], in 1963, reported that an intratracheal injection of kerosene at sublethal doses of 0.05 ml and 0.02 ml produced either an acute exudative reaction or a chronic proliferative inflammation. The acute reaction was mainly of a leukocytic character and involved scattered, small clusters of alveoli. Other alveoli contained exudates consisting mainly of serous fluid or fibrin. In general, the acute inflammatory response was of mesodermal origin. The chronic inflammation was characterized by the enlargement of visible alveolar cells and an increase in their number. Many of the cells had large, excessively dark, round nuclei and basophilic, lacy cytoplasm. The vascular periadventitial tissue was usually edematous and infiltrated by sparsely distributed monocytes. In general, the chronic inflammation was of endodermal origin. The acute response reached its apex after 3 days while the chronic inflammation reached its peak in 10 days, gradually declining with remnants of the inflammation still demonstrable more than 1 month after the kerosene administration.

In 1965, Schwartz and coworkers [94] found that intratracheal administration of kerosene to rats at a dose of 0.2 ml was followed within minutes by development of noisy, labored ventilation. There was frequently a frothy nasal discharge which had a serosanguinous appearance. The gross adverse effect was that of a hyperemic and hemorrhagic pulmonary parenchyma. Microscopic examination of the tissue showed marked diffuse capillary engorgement, venous congestion, intraalveolar edema and a frequent occurrence of subepithelial vacuolation with separation of the bronchial lining.

In 1972, Steele et al [95] reported the effects of kerosene insufflation by studies in rats and dogs. Eighty white rats were used to determine the LD50 of intratracheally administered kerosene. This dose was subsequently used in a study to assess the value of corticosteroid and antibiotic treatment in hydrocarbon-induced pneumonitis in dogs. The intratracheal LD50 was determined to be 0.6 ml/kg, and this dose was administered with a catheter into the upper portion of the trachea of 20 dogs (3.8-32.3 kg), half of which received dexamethasone im at a dose of 2 mg immediately after kerosene instillation and 1 mg every 6 hours for 48 hours and ampicillin im at a dose of 25 mg/kg every 6 hours for 10 days. There were no significant differences between treated and control animals with respect to mortality, blood pH, pO2, pCO2, leukocyte count, and clinical appearance. Roentgenographic examination showed the presence of pneumonia within 24 hours after kerosene aspiration. The animals that died within a short time had lungs that were heavy and had massive confluent hemorrhages. No areas of crepitation were found, and all lobes were equally affected in both lungs. The cut surfaces showed extensive hemorrhage throughout the parenchyma and copious amounts of bloody fluid exudate. Microscopic examination revealed hemorrhage and epithelial destruction in the medium and small bronchi. The lung parenchyma showed extensive destruction with alveoli filled with bloody exudate, cell debris, and large numbers of inflammatory cells. Upon gross examination of the lungs of the animals that survived a 21-day observation period, the authors found patchy areas of normal-appearing parenchyma with normal crepitation. There were large areas of hyperemic edematous parenchyma with

focal areas of necrosis and abscess formation. Microscopic examination showed extensive areas of inflammation with microabscess formation.

Correlation of Exposure and Effect

(a) Petroleum Ether

Spruit et al [38], in 1970, reported that dermal exposure to petroleum ether caused disruption of the horny layer of the skin in humans. The average time of exposure before the appearance of irritation was about 20 minutes. No other reports have been found concerning the dermal toxicity of petroleum ether, but Oettel [39] conducted a study using pentane and hexane, the major constituents of petroleum ether, to evaluate the toxicity of these compounds and reported in 1936 that dermal exposure to pentane or hexane for up to 1 hour resulted in the development of irritation in humans characterized by erythema, hyperemia, swelling, and pigmentation. After 5 hours of exposure, these alkanes produced skin blisters.

Several studies have related industrial exposure to hexane with the development of polyneuropathy [40-43]. Yamamura [42], in 1969, reported the effects on workers after exposure to hexane, a constituent of the glue used in the production of sandals. The concentration of hexane in the air ranged from 1,759 to 8,793 mg/cu m. The initial symptoms included sensory impairment in the distal portion of the extremities. Inoue et al [44], in a followup study on the sandal workers, indicated that polyneuropathy could have developed as a result of exposure at concentrations of n-hexane below 1,759 mg/cu m. In 1971, Herskowitz et al [40] examined employees working in a furniture factory who were exposed to n-hexane. Air samples of hexane

were found to average 2,286 mg/cu m and peaked at 4,573 mg/cu m. The patients complained of one or more of the following symptoms: abdominal cramps, burning sensations, numbness and weakness of the distal extremities, and paresthesia. In 1972, Yamada [41] investigated 17 workers reporting symptoms of intoxication from exposure to hexane vapor. Six worked in polyethylene laminating plants where airborne hexane concentrations ranged from 3,517 to 8,793 mg/cu m. The 11 other 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 1,759 mg/cu m, but, in the immediate work area, the concentration was 3,517 mg/cu m. The initial worker complaints were fatigue and loss of appetite, followed by paresthesia in distal parts of the extremities and difficulty in walking. In 1975, Takeuchi et al [43] reported on four persons exposed to petroleum benzine who worked in a brocade sash cleaning shop in a poorly ventilated workroom. In general, within 1-9 months the workers experienced fatigue, loss of appetite, difficulties in walking, muscle weakness, paresthesia, irritability, insomnia, and weight loss. Although determination of the air concentrations of petroleum benzine were not made at the time the workers developed their illness, analysis of the concentrations of petroleum benzine and its major constituents in the workroom air was subsequently made. The concentration of petroleum benzine and n-hexane did not exceed 4,400 and 844 mg/cu m, respectively. The authors [43] indicated that, if the concentration of petroleum benzine rose higher than 4,400 mg/cu m, irritation of the mucous membranes would have become unbearable and a narcotic effect would have occurred. The effects of dermal exposure,

although not measured, could not be disregarded as a potential route of intoxication. In all the above cases, the authors [40-44] concluded that the workers had signs and symptoms of polyneuropathy. Gaultier et al [45] stated that other alkanes other than n-hexane may also cause polyneuropathy.

In 1967, Miyagaki [79] reported the neurotoxic effects of n-hexane exposure in mice. The animals exposed at n-hexane concentrations greater than 879 mg/cu m for 24 hours/day, 6 days/week, for 1 year developed signs of neurotoxicity while mice similarly exposed at 352 mg/cu m of hexane showed no abnormalities.

Truhaut et al [80] exposed rats to a technical grade hexane at a concentration of 2,000 ppm, 5 hours/day, 5 days/week, for 1-6 months. The hexane contained 0.3% n-pentane, 25.1% 2-methylpentane plus cyclopentane, 18.4% 3-methylpentane, 48.8% n-hexane, 8% methylcyclopentane, 1.2% methylhexane, and 1.2% benzene. Studies on the sciatic and saphenous nerves indicated that this solvent caused a decrease in the conduction rate, an increase in the refractory period, and a decrease in the excitability of the nerves.

(b) Rubber Solvent

Carpenter et al [9] exposed volunteers for about 10 seconds to rubber solvent vapor to determine its odor threshold. The authors concluded that the most probable threshold concentration was about 40 mg/cu m (10 ppm) given the determined range of 6.4-64 mg/cu m (1.6-16 ppm). Volunteers were also exposed to rubber solvent vapor at one of a series of concentrations from 1,700 to 8,100 mg/cu m (430-2,000 ppm) for one 15-minute period/day. Slight transitory eye, nose, and throat irritation responses were noted at

concentrations of 3,100 mg/cu m (780 ppm) and above, as well as four cases of lightheadedness and one of headache at the 8,100 mg/cu m concentration, both of which were reported to have subsided within 10 minutes after exposure. At the 3,100 mg/cu m concentration, one volunteer reported eye irritation and two others throat irritation. One of six exposed to rubber solvent at 8,100 mg/cu m reported eye and throat irritation.

The authors [9] also reported the toxic effects of rubber solvent inhalation in animal toxicity studies. Groups of rats were each exposed at 11,000, 21,000, 39,000, or 96,000 mg/cu m (2,800, 5,300, 9,800, or 24,200 ppm) for a single 4-hour period. Impairment of coordination and eye irritation were observed at concentrations greater than 11,000 mg/cu m. Convulsions and death occurred at 96,000 mg/cu m. The calculated 4-hour LC50 was reported to be 61,000 mg/cu m (15,000 ppm). Female beagles were exposed to rubber solvent vapors at concentrations of 5,900, 13,000, or 25,000 mg/cu m (1,500, 3,300, or 6,300 ppm) for a single 4-hour period. Loss of coordination was observed at concentrations of 13,000 and 25,000 mg/cu m. No observable effects occurred at 5,900 mg/cu m.

The acute CNS effects of a 4-hour exposure to rubber solvent vapors at 49,000 mg/cu m (12,400 ppm) were examined in male cats [9]. A time-related and sequential pattern of events occurred which included ataxia, loss of proprioception, salivation, relaxation of the nictitating membrane, unconsciousness, tremors, and convulsions. Gross and microscopic examination of tissues showed no lesions related to solvent exposure.

Male rats and beagles were exposed to either 0, 1,900, 3,700, or 7,900 mg/cu m (0, 480, 930, or 2,000 ppm) of rubber solvent, 6 hours/day, 5 days/week, for up to 62-63 days [9]. There were no animal deaths

attributed to rubber solvent. There were no changes in body weight gain, blood chemistry, or hematology that resulted from solvent exposure. Serum alkaline phosphatase was higher after 62 days in all rats exposed to rubber solvent, but the authors suggested that this finding was an artifact which resulted from very low control alkaline phosphatase levels. Microscopic examination of various organ sections showed no tissue damage that could be attributed to the solvent vapors. There was a significant increase in the specific gravity of the urine of dogs exposed at 7,900 mg/cu m for 62 days. The significance was not reported by the investigators.

(c) Varnish Makers' and Painters' Naphtha

Carpenter et al [17] reported the effects of exposure to VM and P naphtha on human odor and sensory responses. The authors concluded that the odor threshold was about 4 mg/cu m (0.86 ppm). In assessing the sensory responses to VM and P naphtha, Carpenter et al subjected volunteers to 15-minute exposures to the naphtha at concentrations ranging from 660 to 4,100 mg/cu m (140 to 880 ppm). Olfactory fatigue was noted at all concentrations. Solvent concentrations up to 2,100 mg/cu m (450 ppm) caused only slight or transitory eye and throat irritation in two of seven subjects which the authors considered "sporadic sensory responses." At the highest concentration tested, 4,100 mg/cu m (880 ppm), definite throat and eye irritation was produced.

In an acute inhalation study, rats were exposed to VM and P naphtha at 4,400, 9,800, or 26,000 mg/cu m (940, 2,100, or 5,600 ppm) for 4 hours [17]. Animals exposed to 4,400 mg/cu m of VM and P naphtha were reported to be free from distress during and after exposure. All animals exposed at 26,000 mg/cu m died. Responses of the rats at the highest concentration

were eye irritation and CNS depression characterized by poor coordination followed by convulsions and death. The authors estimated an approximate 4-hour LC50 of 16,000 mg/cu m (3,400 ppm) for VM and P naphtha.

Two dogs were exposed to VM and P naphtha at a nominal concentration of 16,000 mg/cu m (3,400 ppm) for 2 hours [17]. Eye irritation, tremors, mild ataxia, and mydriasis were evident. One animal became prostrate after 1.5 hours but recovered after cessation of solvent exposure. A third dog was exposed to VM and P naphtha at 8,000 mg/cu m (1,700 ppm) for 4 hours and appeared normal during and after solvent exposure.

Cats inhaling VM and P naphtha at 19,000 mg/cu m for 4 hours exhibited progressive symptoms usually indicative of CNS depression: salivation, mydriasis, body tremors, prolapse of the nictitating membrane, poor coordination, vomiting, convulsions, and prostration [17]. All of the animals survived the exposure, but one became moribund shortly thereafter and was killed. Autopsy showed suppurative pneumonia.

In short-term inhalation studies, Carpenter et al [17] subjected rats and dogs to repeated daily inhalation of VM and P naphtha for 6 hours/day, 5 days/week, for 65 days. The concentrations of solvent used were 0, 1,300, 2,800, or 5,800 mg/cu m. No outward signs of distress were observed in either species during the study. Rats exposed to VM and P naphtha at 5,800 mg/cu m showed a significant decrease in erythrocyte count after 65 days of exposure. The following statistically significant differences were noted in the dogs exposed for 65 days to VM and P naphtha: an increase in serum alkaline phosphatase at the 5,800 mg/cu m concentration, an increase in the ratio of liver weight to body weight and a decrease in the reticulocyte count at the 2,800 mg/cu m concentration, and increases in

reticulocyte counts at the 5,800 and 1,300 mg/cu m concentrations. The authors felt that the above changes were unimportant and could possibly be experimental artifacts rather than serious deleterious effects.

(d) Mineral Spirits

In 1975, Astrand et al [48] reported on the effects of white spirits (mineral 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. In the initial trials, men were exposed at 2,500 or 5,000 mg/cu m for an unspecified period of time. Nausea and vertigo were apparent at both concentrations. 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. In addition, their studies [48] indicated that more solvent reaches the blood during exercise than during rest. This finding, in the absence of changes in alveolar ventilation, suggests changes in the respiratory transport.

In 1975, Gamberale et al [50] reported 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. Men exposed to white spirits at 625, 1,250, 1,875, and 2,500 mg/cu m for four continuous 30-minute periods showed no impairment of the five performance tests. Exposure to 4,000 mg/cu m of white spirits for 50 minutes had no effect on perceptual speed, numerical ability, and manual dexterity. 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 authors concluded that there was a risk

of subjective distress and adverse effects on psychomotor and intellectual functions in a worker exposed to 2,500 mg/cu m who is doing light industrial work, since the alveolar air concentrations of white spirits in workers at rest exposed at 4,000 mg/cu m was similar to the white spirits alveolar air concentration of workers exposed at 2,500 mg/cu m doing light physical activity [48,50].

Rector et al [82], in 1966, described the effects of mineral spirits on five species of animals exposed continuously for 60-90 days or exposed intermittently, 8 hours/day, 5 days/week, for a total of 30-60 exposure periods. In continuous 90-day exposure experiments, rats, guinea pigs, rabbits, dogs, and monkeys were exposed to mineral spirits of concentrations ranging from 114 to 1,271 mg/cu m (18-200 ppm, assuming a molecular weight of 156). Exposure of the dogs, monkeys, and rabbits to the mineral spirits at all concentrations tested failed to induce mortality. An occasional death was noted in the rats at all concentrations, but the number of deaths was similar to that of the controls. In contrast, the guinea pigs were very susceptible to the mineral spirits with deaths occurring in all groups subjected at a concentration of 363 mg/cu m (60 ppm) or greater. No deaths occurred in the guinea pigs exposed at 114 or 238 mg/cu m (18 or 37 ppm). The rate of body weight gain generally was similar in test animals and in controls except in guinea pigs and monkeys exposed at the highest concentration of 1,271 mg/cu m. In the overall study, no consistent pattern of dose-response hematologic realtionships was found, and, therefore, some of the alterations seen in preexposure and terminal leukocyte counts could not be attributed to solvent exposure. Although no remarkable changes were noted

on gross examination of all animals, lung irritation and congestion were observed in all species. In general, the observations of congested lungs were substantiated microscopically in only those animals exposed to mineral spirits at 1,271 mg/cu m, where lung tissue showed evidence of bronchitis and mixed inflammatory cell infiltration. Microscopic examination of the heart, spleen, and kidneys did not show adverse findings that could be attributed to solvent exposure.

Rector et al [82] also conducted three intermittent exposure studies in which the same five species were exposed 8 hours/day, 5 days/week, for 30-60 exposures to mineral spirits at concentrations of 593-596 or 1,353 mg/cu m (93-94 or 212 ppm). The animals exposed at 1,353 mg/cu m for 6 weeks showed no toxic signs and body weight patterns and hematologic values were similar to those of the controls. No consistent microscopic changes were found except for possible lung irritation and liver damage in guinea pigs exposed at 1,353 mg/cu m. Animals exposed at 596 mg/cu m for 6 weeks showed no signs of toxicity and body weight gains and hematologic parameters were all within normal limits. No noteworthy microscopic tissue changes were reported. After a 2-week recovery interval, several rats and guinea pigs who were exposed previously to 596 mg/cu m were reexposed for a second series of 30 exposures at 593 mg/cu m. There were no noticeable signs of toxicity during this second reexposure and hematologic parameters were within normal limits. After a 17-day observation period, the animals were killed and autopsied. The only noteworthy microscopic finding was focal lymphocytic involvement in the lungs of some exposed guinea pigs.

(e) Stoddard Solvent

Braunstein [51] reported follicular dermatitis on the hands and arms of a worker after 2 weeks of dermal exposure to liquid Stoddard solvent. He also complained of nausea when initially inhaling the solvent. Eventually, this worker developed obstructive jaundice and subacute yellow liver atrophy.

Scott et al [52] observed four cases and Prager and Peters [53] one case of aplastic anemia after dermal exposure to liquid Stoddard solvent.

Markel and Shmunes [74], in 1974, cited the results of a Stoddard solvent hazard evaluation of a greeting-card company. Workers were exposed to Stoddard solvent at 99-1,906 mg/cu m (average 438 mg/cu m) in their working environment and the authors [74] concluded that, under the conditions found at the time of the survey, Stoddard solvent was not toxic and did not constitute a hazard to health.

In 1974, Larsen and Shmunes [75] found that Stoddard solvent used to clean polishing machines was probably the cause of dermatitis in several industrial workers. These workers also complained of headache and eye and nose irritation. Although Stoddard solvent concentrations of less than 20 ppm (115 mg/cu m) were detected, the authors felt that higher concentrations could have occurred immediately after the polishing machines were cleaned with Stoddard solvent and could have been the cause of the headache and eye and throat irritation.

Carpenter et al [21] determined both the odor and the sensory thresholds for Stoddard solvent. The odor threshold was found to be between 0.5 and 5 mg/cu m (0.09 and 0.9 ppm). The sensory threshold was found to be between 850 and 2,700 mg/cu m (150 and 470 ppm) for a 15-minute

exposure. No irritation was noted at 140 mg/cu m (24 ppm), while slight, transient eye irritation occurred in one volunteer at 850 mg/cu m and in all at 2,700 mg/cu m, some with tearing. Slight dizziness also was reported at 2,700 mg/cu m by some of the subjects. The volunteers experienced olfactory fatigue at all of the concentrations tested, but recovered fully within 10 minutes after exposure ended.

Nelson et al [55] similarly observed that volunteers exposed to Stoddard solvent for 3-5 minutes at air concentrations in excess of 400 ppm (2,290 mg/cu m) suffered irritation of the eyes, nose, and throat.

Carpenter et al [56] described odor threshold sensory irritation in humans exposed to 140 flash aliphatic solvent. The odor threshold was about 4 mg/cu m (0.6 ppm). Minor eye irritation was the only discomfort noted by subjects exposed to 140 flash aliphatic solvent at either 110 or 310 mg/cu m (17 or 49 ppm) for 15 minutes. This response was expressed by the same subject during each inhalation period and did not persist after exposure. All subjects reported olfactory fatigue at both concentrations. The subjects felt that 310 mg/cu m (49 ppm) could be an acceptable concentration for an 8-hour day.

In 1975, Carpenter et al [21] examined the effects of Stoddard solvent inhalation in rats, mice, cats, and dogs. Rats inhaled Stoddard solvent at 0, 2,400, 4,800, or 8,200 mg/cu m (0, 420, 800, or 1,400 ppm) for 8 hours. The highest concentration, 8,200 mg/cu m, was not lethal to the rats during the exposure period, but one rat died while being removed from the exposure chamber. No other animal deaths occurred. Loss of coordination, eye irritation, and bloody nasal exudate were reported to have occurred in the animals exposed at 8,200 mg/cu m. When rats inhaled

4,600 mg/cu m, they showed similar symptoms but no loss of coordination. Inhalation at 2,400 mg/cu m failed to cause any response during or after solvent exposure. A beagle exposed at 8,000 mg/cu m (1,400 ppm) for 8 hours developed eye irritation, salivation, tremors, and clonic spasms but did not die. There were no toxic effects seen in a dog exposed at 4,000 mg/cu m (700 ppm) of Stoddard solvent for 8 hours. Cats were exposed to Stoddard solvent at a nominal concentration of 10,000 mg/cu m (1,700 ppm) until death ensued between 2.5 and 7.5 hours of exposure after showing signs of CNS depression. In short-term inhalation experiments, Carpenter et al subjected rats and dogs to repeated daily inhalations of Stoddard solvent for 6 hours/day, 5 days/week, for 13 weeks. The concentrations of solvent used in the study were 0, 480, 1,100, or 1,900 mg/cu m (0, 84, 190, or 330 ppm). No animals died as a result of solvent exposure. The authors did not consider that the solvent exposure caused changes in blood chemistry or hematology except for blood urea nitrogen levels in rats after 13 weeks of exposure at 1,900 mg/cu m since the changes were not dose related. Marked tubular regeneration in the kidneys and dilation of the loops of Henle were evident in rats exposed to Stoddard solvent vapor at 1,900 mg/cu m for either 8 or 13 weeks. Similar renal changes were seen following 8 and 13 weeks' exposure to Stoddard solvent at 1,100 mg/cu m. The authors [21] reported that the loop of Henle dilation seen after 13 weeks was not statistically significant.

Carpenter et al [56] exposed rats, cats, mice, and dogs in a series of experiments to 140 flash aliphatic solvent. Rats were exposed to the solvent at concentrations of either 0, 270, 450, 790, 1,900, or 2,900 mg/cu m (0, 43, 71, 125, 302, or 461 ppm) for 8 hours. Two of 16 rats died at

the 2,900 mg/cu m concentration. There were no other animal deaths. The only signs of toxicity were skin irritation at 1,900 and 2,900 mg/cu m and minor loss of coordination at 2,900 mg/cu m of 140 flash aliphatic solvent. A beagle was exposed at either 210 or 1,700 mg/cu m (33 or 270 ppm) of solvent for 8 hours. Both concentrations caused transitory tearing and weight loss. Cats exposed at 440 mg/cu m or 10,000 mg/cu m of solvent for 6 hours showed no signs of CNS disturbance. Rats exposed at 10,200 mg/cu m of solvent aerosol for 340 minutes showed signs of toxicity: wet mouth, sluggish movement, irritated extremities, tremors, and death. Groups of rats and dogs were exposed to either 0, 49, 100, or 230 mg/cu m (0, 7.8, 16, or 37 ppm) of 140 flash aliphatic solvent for 6 hours/day, 5 days/week, for 72-73 days. In the authors' opinion, there were no treatment-related effects of solvent inhalation at any of the concentrations tested in rats or dogs.

(f) Kerosene

Several investigators have shown that kerosene can cause dermatitis [61,85,94]. In addition, several studies have examined the mechanism of action of the kerosene-induced skin irritation [62-64].

In 1963, Rebello and Suskind [86] found that kerosene increased the reactivity of guinea pig skin to 2,4-dinitrochlorobenzene (DNCB), a sensitizing agent. Dermal administration of kerosene increased the dermal irritation caused by DNCB. Based on the results of this study, it is possible to speculate that other sensitizing agents, such as pollen or certain drugs, may heighten the response to dermal kerosene exposure and result in augmented toxicity. Several theories have been postulated to explain the increased dermal reactivity to sensitizers after pretreatment

with chemical agents. The chemically treated skin may provide a larger quantity of appropriate protein for conjugation and consequent conversion of a particular chemical into an antigen. The chemicals may enhance the rate of formation of a complete antigen by increasing the permeability of the skin to substances such as DNCB. Finally, the mononuclear cells and macrophages may be increased as a result of chemical treatment and therefore increase the degree of sensitization. The results from the studies by Lupulescu et al [62,63] tend to support the latter two theories with respect to dermal kerosene treatment.

In 1939, Cavanagh and Wilner [57] described a fatal case of aplastic anemia that resulted from dermal exposure to kerosene where the patient had rubbed kerosene on her legs daily for several months. The authors concluded that the aplastic anemia seen in the patient may have been the result of the aromatic hydrocarbon content of the kerosene.

In 1955, Johnson [58] investigated a presumable sensitivity of a person to kerosene. The patient developed hypoplastic anemia with a deficiency of all cell elements and hypoplastic marrow after recurrent exposure to kerosene for a 3-year period. The author [58] suggested, however, that aromatic hydrocarbons of the benzol series present in kerosene may have been responsible for the myelotoxicity in this individual.

Hiebel et al [59] observed bone marrow depression after dermal exposure to kerosene in one patient and by a combination of dermal and oral routes in two patients.

In 1946, Carpenter and Smyth [87] related that the application of 0.5 ml of deodorized kerosene into the eye of rabbits produced no adverse

effects. However, Volkova et al [90] found that animals exposed to unpurified kerosene in an aerosol developed conjunctivitis.

In 1969, Volkova et al [90] noted that aerosols of purified kerosene were less toxic than aerosols of unpurified kerosene. Exposure to unpurified kerosene at 500 mg/cu m caused respiratory irritation and leukocytosis.

In 1976, Carpenter et al [67] determined the odor and sensory thresholds for deodorized kerosene determined in a group of volunteers. The odor threshold was approximately 0.6 mg/cu m (0.09 ppm). Fifteen-minute exposures to kerosene at a mean measured vapor concentration of 140 mg/cu m (20 ppm) were easily tolerated without sensory irritation. A slight decrease in olfactory acuity, but not total fatigue, was noted in two subjects. The 140 mg/cu m concentration of deodorized kerosene was deemed by the subjects to be acceptable for an 8-hour workday, based on the 15-minute exposure.

In 1976, Carpenter et al [67] examined the effects of inhalation of deodorized kerosene vapors and aerosols on rats, mice, dogs, and cats. Male rats were exposed for 8 hours to air "substantially" saturated with deodorized kerosene vapors. The approximate air concentration for this exposure was 100 mg/cu m (14 ppm). The exposed rats showed no signs of discomfort or toxicity during the exposure. After the 14-day observation period, the rats were killed, examined, and found to have no unusual or exposure-related findings. A second group of male rats were exposed to an aerosol of deodorized kerosene for 6 hours/day for 4 days. The mean air concentrations of the aerosol on the 4 days were 9,600, 6,900 7,000, and 7,400 mg/cu m. After 1.25 hours of exposure on the 1st day, the rats

showed a slight loss of coordination and were sluggish after 2.75 hours. On the 2nd day of exposure, the rats were sluggish but showed good coordination. By the end of the second exposure, the extremities of the rats were red. On days 3 and 4, the condition did not appreciably change. After 1 day of no exposure, the extremities of the rats were dry with flakes forming. The dryness and flaking continued for 3 additional days at which time one rat showed a slight hair loss. The weights of the animals remained almost unchanged during the exposure and at 1 day postexposure. Four male cats of mixed breed exposed to deodorized kerosene at 6,400 mg/cu m as an aerosol for 6 hours showed no toxic effects. Separate groups of 25 male rats and 4 male beagle dogs were exposed to deodorized kerosene at mean measured air concentrations 20, 48, or 100 mg/cu m (approximately 2.9, 6.9, or 14 ppm, respectively) or to solvent-free air for 6 hours/day, 5 days/week, for 67 days. The criteria of response for these exposures were body weight change and blood and urine analyses. Only two rats died during the 67-day study. One died after 30 days of exposure at 100 mg/cu m. This animal had no weight loss prior to death. Autopsy showed that death might have been from pneumonia. The other death occurred after 16 days in rats exposed at 48 mg/cu m. This animal lost 40 g of weight during the 7 days before death. Abscess bronchopneumonia was believed to be the cause of death in this rat. The urine pH was increased and specific gravity of the urine was decreased after 8 weeks, which were not considered abnormal by the authors. Differential blood smears of rats exposed at 20 mg/cu m showed a low value for immature neutrophils at 13 weeks. An elevated serum alkaline phosphatase value was reported after exposure at 100 mg/cu m for 8 weeks in a single rat. This finding was the only

abnormality in blood chemistry. The animal was sick when killed and pleural adhesions and abscess bronchopneumonia were found at autopsy. Microscopic examination of tissues removed from the rats exposed at all three concentrations showed no dose-related changes. The incidence of tubular regeneration was neither dose related nor higher than controls with one exception. After 13 weeks, seven of nine rats exposed at 20 mg/cu m had slight tubular regeneration as compared with two of eight rats at each of the higher exposure concentrations and three of nine rats in the control group. In dogs exposed at 20 mg/cu m, a slight increase in the body weight of dogs was reported after 13 weeks. Occasional lesions were seen in the organs of the dogs in the exposed and control groups. The lesions were not considered by the authors to be related to the deodorized kerosene.

Light petroleum hydrocarbons, such as kerosene, have a low toxicity when ingested and retained in the stomach, but, if the solvent is aspirated directly into the lungs, extensive lung damage and death can occur [91]. Several investigators [91,92,94,95] have reported that 0.1-0.2 ml of kerosene administered into the trachea can cause death. In addition, there are numerous cases of kerosene poisoning in humans by aspiration or ingestion of the liquid [68-70].

Carcinogenicity, Mutagenicity, Teratogenicity, and Effects on Reproduction

There is no present reason for suggesting that these solvents, if they are free of carcinogenic aromatics such as benzene, would cause cancer, birth defects, or germinal mutations. McMichael et al [76], in 1975, demonstrated an association between leukemia and jobs entailing exposure to solvents but did not identify the exact etiologic agent.

Benzene, a known myelotoxic agent, was used by these workers and it may have been the causative agent. Downing [65], in 1952, related that a man exposed to various solvents and greases including kerosene developed a epidermoid carcinoma. The etiologic agent responsible for the carcinoma was unknown since the worker was exposed to a wide variety of substances.

TABLE III-3

EFFECTS OF PETROLEUM ETHER EXPOSURE ON HUMANS

Number of Subjects	Route of Exposure	Duration of Exposure	Observed Effects	Reference
1	Respiratory	-	Severe clonic convulsions	37
-	Dermal*	10-30 min	Skin irritation, peeling of skin, water vapor loss from injured skin	38

*1 ml

TABLE III-4

EFFECTS OF RESPIRATORY EXPOSURE TO RUBBER SOLVENT ON HUMANS

Number of Subjects	Exposure Concentration	Duration of Exposure	Observed Effects
7	8,100 mg/cu m (2,000 ppm)	15 min	Olfactory fatigue in 6/7, light-headedness in 4/7, reddening of sclera in 2/7, eye, nose, and throat irritation in 1/7
7	6,700 mg/cu m (1,700 ppm)	"	Olfactory fatigue in 7/7, eye and throat irritation and reddening of sclera in 2/7, light-headedness and nose irritation in 1/7
7	3,100 mg/cu m (780 ppm)	"	Olfactory fatigue in 5/7, throat irritation in 2/7, eye and nose irritation in 1/7
7	1,700 mg/cu m (430 ppm)	"	Olfactory fatigue in 7/7, eye and nose irritation in 1/7
6 (two trials)	640 mg/cu m (160 ppm)	10 sec	All detected odor
6 (two trials)	64 mg/cu m (16 ppm)	"	Odor detected by 9/12
6 (two trials)	6.4 mg/cu m (1.6 ppm)	"	Odor detected by 2/12

Adapted from reference 9

TABLE III-5

EFFECTS OF RESPIRATORY EXPOSURE TO
VARNISH MAKERS' AND PAINTERS' NAPHTHA

Number of Subjects	Exposure Concentration	Duration of Exposure	Observed Effects
7	4,100 mg/cu m (880 ppm)	15 min	Olfactory fatigue in 6/7, eye irritation in 3/7, throat irritation in 4/7
7	2,100 mg/cu m (450 ppm)	"	Olfactory fatigue in 5/7, eye and throat irritation in 2/7
7	1,400 mg/cu m (300 ppm)	"	Olfactory fatigue in 3/7, throat irritation in 2/7, eye irritation in 1/7
7	660 mg/cu m (140 ppm)	"	Olfactory fatigue in 6/7, eye irritation in 2/7, throat irritation in 1/7
6 (two trials)	70 mg/cu m (15 ppm)	10 sec	All detected odor
6 (two trials)	7 mg/cu m (1.5 ppm)	"	Odor detected by 11/12
6 (two trials)	0.7 mg/cu m 0.15 mg/cu m		Odor detected by 2/12

Adapted from reference 17

TABLE III-6

EFFECTS OF RESPIRATORY EXPOSURE TO MINERAL SPIRITS ON HUMANS

Number of Subjects	Exposure Concentration	Duration of Exposure	Observed Effects	Reference
-	500 mg/cu m	-	Severe nausea, vertigo	48
-	2,500 mg/cu m	-	"	48
14	625-2,500 mg/cu m	Up to 2 hr	No effects on perceptual speed, reaction time, short-term memory, numerical ability, and manual dexterity	50
8	4,000 mg/cu m	50 min	Prolonged reaction time, probable impaired short-term memory	50

TABLE III-7

EFFECTS OF RESPIRATORY EXPOSURE TO STODDARD SOLVENTS ON HUMANS

Number of Subjects	Exposure Concentration	Duration of Exposure	Observed Effects
6	2,700 mg/cu m (470 ppm)	15 min	Eye irritation in 6/6, olfactory fatigue in 5/6, dizziness in 2/6, throat irritation in 1/6
6	850 mg/cu m (150 ppm)	"	Olfactory fatigue in 6/6, eye irritation in 1/6
6	140 mg/cu m (24 ppm)	"	Olfactory fatigue in all
6 (two trials)	5-50 mg/cu m (1 - 9 ppm)	10 sec	Odor detected by 11/12
"	0.5 mg/cu m (0.1 ppm)	"	None detected odor

Adapted from reference 21

TABLE III-8

EFFECTS OF STODDARD SOLVENTS ON HUMANS AT UNKNOWN CONCENTRATIONS

Number of Subjects	Route of Exposure	Duration of Exposure	Observed Effects	Reference
1	Dermal and possibly respiratory	10 wk	Follicular dermatitis, jaundice	51
1*	"	2/mon 2 yr	Excessive uterine bleeding, purplish discolorations of skin, moderate marrow hypoplasia, death	52
1**		4-5/wk 6 mon	Fatigue, moderate marrow hypoplasia, death	52
1	"	2 yr	Purplish discolorations of skin, fatigue, pallor, marked marrow hypoplasia, death	52
1	"	20 yr	Slight reduction of all formed elements in blood	52
10	Respiratory	3-5 min***	Eye, nose, and throat irritation	55

*Carbon tetrachloride exposure also occurred.
**Tripelennamine and diphenhydramine were taken by patient for seasonal allergy.
***Greater than 2,290 mg/cu m

TABLE III-9

EFFECTS OF RESPIRATORY EXPOSURE TO 140 FLASH ALIPHATIC SOLVENT ON HUMANS

Number of Subjects	Exposure Concentration	Duration of Exposure	Observed Effects
6	110-310 mg/cu m (17- 49 ppm)	15 min/d 2 d	Olfactory fatigue in 6/6, eye irritation in 1/6
6 (two trials)	40 mg/cu m (6 ppm)	10 sec/d 2 d	Odor detected by all 12
"	4 mg/cu m (0.6 ppm)	"	Odor detected by 7/12
"	0.4 mg/cu m (0.06 ppm)	"	None detected odor

Adapted from reference 56

TABLE III-10

EFFECTS OF RESPIRATORY EXPOSURE TO DEODORIZED KEROSENE ON HUMANS

Number of Subjects	Exposure Concentration	Duration of Exposure	Observed Effects
6	140 mg/cu m (20 ppm)	15 min	Slight olfactory fatigue in 3/6
6 (two trials)	100 mg/cu m (3 ppm)	10 sec/d 2 d	Odor detected by all 12

Adapted from reference 67

TABLE III-11

EFFECTS OF EXPOSURE TO KEROSENE ON HUMANS

Number of Subjects	Route of Exposure	Amount	Duration of Exposure	Observed Effects	Reference
6	Dermal	1 ml	30-90 min	Cellular damage of skin	62
6	"	"	90 min	"	64
1	"	-	3 yr	Fever, chills, cough, pleuritic pain, marrow hypoplasia, reduction of all formed elements of blood, death	58
4	"	-	-	Dermatitis, erythema, blisters, burning sensations	61
1	"	-	24 hr	Burning sensations at 1 hr, slight erythema at 2 hr, erythema and tenderness at 7 hr, blister formation at 12 hr, pus-filled blisters at 24 hr	61
34	"	85% kerosene	"	Dermatitis in all	61
34	"	70% kerosene	"	Dermatitis in 85%	61
34	"	55% kerosene	"	Dermatitis in 24%	61
34	"	40% kerosene	"	No dermatitis	61
1	Dermal and oral	2-3 doses/yr	25 yr	Reduction of erythrocytes, slight marrow hypoplasia	59
1	Dermal	"	3 yr	Marrow hypoplasia, reduction of neutrophils	59
1	-	3 doses/yr	45 yr	Marrow hypoplasia, changes in formed elements of blood	59

TABLE III-11 (CONTINUED)

EFFECTS OF EXPOSURE TO KEROSENE ON HUMANS

Number of Subjects	Route of Exposure	Amount	Duration of Exposure	Observed Effects	Reference
1	Oral	-	-	Headache, intense labored breathing, vomiting, epigastric pain, moderate fever, jaundice, pulmonary lesions	70
-*	Oral and aspiration	-	-	Upper respiratory tract infections, pneumonia and stupor in some	69
-**	"	-	-	Rapid and shallow respiration, sounds of rales, cyanosis, pneumonia	68
-	Respiratory	-	7 min	Grogginess, slurring of speech, slight staggering on walking, possitive Romberg's sign, mild muscular weakness	66

*204 incidents of kerosene ingestion in children
**65 incidents of kerosene ingestion in children

TABLE III-12

EFFECTS OF RESPIRATORY EXPOSURE TO RUBBER SOLVENTS ON ANIMALS

Species	Exposure Concentration	Duration	Observed Effects
Rats	180,000 mg/cu m (45,000 ppm)	2-8 min	Convulsions by 2 min of exposure, death of 50% of the rats by 4.3 min
"	96,000 mg/cu m (24,000 ppm)	4 hr	Loss of motor coordination, convulsions followed by death
"	61,000 mg/cu m (15,000 ppm)	"	LC50
"	39,000 mg/cu m (9,800 ppm)	"	Loss of motor coordination, eye irritation
"	11,000 mg/cu m (2,800 ppm)	"	No effects
"	1,900 - 7,900 mg/cu m (480 - 2,000 ppm)	6 hr/d 5 d/wk 13 wk	No significant effects
Mice	250,000 mg/cu m (63,000 ppm)	1 min	Respiratory tract irritation
"	130,000 mg/cu m (33,000 ppm)	"	No effects
Cats	49,000 mg/cu m (12,400 ppm)	4 hr	CNS depressant effects
Dogs	13,000 -25,000 mg/cu m (3,300 - 6,300 ppm)	"	Loss of motor coordination, eye irritation
"	5,900 mg/cu m (1,500 ppm)	"	No effects
"	1,900 - 7,900 mg/cu m (480 - 2,000 ppm)	6 hr/d 5 d/wk 13 wk	No significant effects

Adapted from reference 9

TABLE III-13

EFFECTS OF RESPIRATORY EXPOSURE TO
VARNISH MAKERS' AND PAINTERS' NAPHTHA ON ANIMALS

Species	Exposure Concentration	Duration	Observed Effects
Rats	71,000 mg/cu m (15,000 ppm)	-	Loss of motor coordination, convulsions followed by death of 50% of the rats by 37 min
"	25,000 mg/cu m (5,460 ppm)	4 hr	Death in 10/10
"	16,000 mg/cu m (3,400 ppm)	"	LC50
"	4,400-9,800 mg/cu m (920-2,060 ppm)	"	No significant effects
"	1,300-5,800 mg/cu m (273-1,200 ppm)	6 hr/d 5 d/wk 65 wk	"
Mice	36,000 mg/cu m (7,700 ppm)	1 min	Decreased respiration rate in 5/6
"	12,000 mg/cu m (2,600 ppm)	"	Slightly decreased respiration rate
Cats	19,000 mg/cu m (4,100 ppm)	4 hr	CNS depressant effects
Dogs	16,000 mg/cu m (3,400 ppm)	2 hr	Eye irritation, tremors, poor coordination, dilatation of pupils, prostration in a male dog with 1.5 hr of exposure
"	8,000 mg/cu m (1,700 ppm)	4 hr	No significant effects
"	1,300-5,800 mg/cu m (273-1,200 ppm)	6 hr/d 5 d/wk 65 wk	"

Adapted from reference 17

TABLE III-14

EFFECTS OF RESPIRATORY EXPOSURE TO MINERAL SPIRITS ON ANIMALS

Species	Exposure Concentration	Effects
Guinea pigs	1,353 mg/cu m*	Emphysema and lung congestion exhibited in some
"	596 mg/cu m*	No effects
"	1,271 mg/cu m**	Body weight loss of 4%
"	550 mg/cu m**	Death in 16/51
"	513 mg/cu m**	Death in 12/59
"	363 mg/cu m**	Death in 4/15
"	238 mg/cu m**	Death in 0/15
Monkeys	1,271 mg/cu m**	Body weight loss of 9%
"	619 mg/cu m**	Body weight loss of 6.4%
"	555 mg/cu m**	Body weight loss of 7.7%
"	504 mg/cu m**	Body weight gain of 1%
"	Controls	Body weight gain of 0.8%

*30 doses, 8 hr/d, 5 d/wk
**90-d continuous exposure

Adapted from reference 82

TABLE III-15

EFFECTS OF RESPIRATORY EXPOSURE TO STODDARD SOLVENTS ON ANIMALS

Species	Exposure Concentration	Duration	Observed Effects
Rats	8,200 mg/cu m (1,400 ppm)	8 hr	Eye irritation, blood exudate around nostrils, slight loss of coordination
"	4,600 mg/cu m (800 ppm)	"	Eye irritation, bloody exudate around nostrils
"	2,400 mg/cu m (420 ppm)	"	No effects
"	1,100-1,900 mg/cu m (190- 330 ppm)	6 hr/d 5 d/wk 13 wk	Marked tubular regeneration of kidneys
"	480 mg/cu m (84 ppm)	"	No effects
Mice	10,000 mg/cu m (1,700 ppm)	1 min	Decreased respiration rate
"	4,400 mg/cu m (770 ppm)	"	No effects
Cats	10,000 mg/cu m (1,700 ppm)	-	CNS depressant effects
Dogs	8,000 mg/cu m (1,400 ppm)	8 hr	"
"	4,000 mg/cu m (700 ppm)	"	No significant effects
"	480-1,900 mg/cu m (84- 330 ppm)	6 hr/d 5 d/wk 13 wk	"

Adapted from reference 21

TABLE III-16

EFFECTS OF RESPIRATORY EXPOSURE TO
140 FLASH ALIPHATIC SOLVENT ON ANIMALS

Species	Exposure Concentration	Duration	Observed Effects
Rats	10,200 mg/cu m* (1,620 ppm)	340 min	Wet mouth, sluggish movement, irritation of extremities, tremor, death in 3/10
"	2,900 mg/cu m* (461 ppm)	8 hr	Skin irritation of extremities, slight loss of coordination, death in 2/16
"	1,900 mg/cu m** (302 ppm)	"	Skin irritation of extremities
"	270 - 790 mg/cu m** (43 - 125 ppm)	"	No effects
"	49 - 230 mg/cu m (8 - 37 ppm)	6 hr/d 5 d/wk 72 wk	"
Mice	350 mg/cu m (56 ppm)	-	No respiratory tract irritation
"	12,000 mg/cu m* (1,906 ppm)	-	"
Cats	440 mg/cu m** (70 ppm)	6 hr	No significant effects
"	10,000 mg/cu m* (1,588 ppm)	-	No CNS depressant effects
Dogs	210 -1,700 mg/cu m* (33 - 280 ppm)	8 hr	Transitory lacrimation

TABLE III-16 (CONTINUED)

EFFECTS OF RESPIRATORY EXPOSURE TO
140 FLASH ALIPHATIC SOLVENT ON ANIMALS

Species	Exposure Concentration	Duration	Observed Effects
Dogs	49 - 230 mg/cu m (8 - 37 ppm)	6 hr/d 5 d/wk 73 wk	No significant effects

*Nominal concentration
**At concentrations exceeding 270 mg/cu m (43 ppm), the solvent was in the form of a vapor-aerosol mixture.

Adapted from reference 56

TABLE III-17

EFFECTS OF RESPIRATORY EXPOSURE TO
DEODORIZED KEROSENE ON ANIMALS

Species	Exposure Concentration	Duration	Observed Effects
Rats	6,000-9,600 mg/cu m* (840-1,344 ppm)	6 hr/d 4 d	Slight loss of coordination, sluggishness, irritation of extremities
"	5,900 mg/cu m* (826 ppm)	6 hr	No effects
"	100 mg/cu m (14 ppm)	8 hr	"
"	100 mg/cu m (14 ppm)	6 hr/d 5 d/wk 67 d	Death of 1 from pneumonia
"	48 mg/cu m (7 ppm)	"	Death of 1 from abscess bronchopneumonia
Mice	6,900 mg/cu m* (966 ppm)	-	No effects on upper respiratory tract
Cats	6,400 mg/cu m* (896 ppm)	6 hr	No effects
Dogs	20 - 100 mg/cu m (3 - 14 ppm)	6 hr/d 5 d/wk 67 d	"

*The droplets in the aerosol averaged less than 1 μm in diameter.

Adapted from reference 67

TABLE III-18

EFFECTS OF KEROSENE EXPOSURE ON ANIMALS

Route of Exposure	Species	Exposure Concentration	Effects	Reference
Oral	Rats	5 ml*	Appeared normal, excoriations around anus	91
"	Mice	1 ml/d**	Abnormal and rapid respiration, neuro-muscular strength weakening, death after 2nd dose	88
"	Rabbits	70 ml/kg	Tachycardia, high body temperature, rapid respiration, convulsions, death	88
ip	Dogs	50 ml/kg	Tachycardia, rapid respiration, drow-siness, convulsions, tremor, coma, death	88

*40 doses
**2 d