III. BIOLOGIC EFFECTS OF EXPOSURE

Extent of Exposure

Pentane, hexane, heptane, and octane are members of a homologous series of aliphatic hydrocarbons with the empirical formula C(n)H(2n+2). The molecular formula for each alkane in this series can be determined by setting n = 5, 6, 7, or 8. A complete listing of the alkane isomers included in this series is presented in Table XII-1. At room temperature, these four classes of alkanes are colorless, neutral liquids with a light petroleum odor. Additional physical properties of n-pentane, n-hexane, n-heptane, and n-octane are presented in Table XII-2 [1]. Physical properties of alkane isomers are presented in Table XII-3 [2-4].

Pentane, hexane, heptane, and octane are produced almost exclusively from crude petroleum by catalytic cracking [5], thermal cracking [5], hydrocracking [6], and catalytic reforming [5-8]. In the processes of catalytic and thermal cracking, high molecular weight hydrocarbons are broken down at high temperatures either with or without a catalyst into lower molecular weight mixtures. During the process of hydrocracking, high molecular weight hydrocarbons are broken down with hydrogen at high pressures and temperatures without a catalyst. In catalytic reforming, high molecular weight hydrocarbons are passed over a platinum catalyst at elevated temperatures in the presence of high pressure hydrogen to produce lower molecular weight mixtures which are then separated by distillation into high-purity fractions that include pentane, hexane, heptane, and octane. One-third of the pentane produced in the United States comes from another source, fractional condensation of natural gas [9]. Natural gas in

the United States contains an average of 0.4% pentane by volume [10].

The estimated US production of n-pentane and methylbutane (isopentane) in 1967 was 310,000 and 449,000 barrels/day, respectively [11]. This is equivalent to approximately 13 million gallons/day of n-pentane and 19 million gallons/day of methylbutane [11]. In 1974, the US Tariff Commission reported an annual production of 358,341,000 pounds (approximately 66 million US gallons) of hexane [9]. No production estimates were found for heptane or octane.

Alkanes are used in a variety of industrial applications and processes. A major use of pentane is in the formulation of gasoline [12]. Hexane is used commercially as a solvent in glues, varnishes, cements, and other products such as inks [13-15]. It is also used in the seed oil industry to extract the natural oils from various seeds, including soybeans and cottonseed [16]. Heptane and octane are used principally as solvents and to some extent in the formulation of gasoline [14,15].

A number of occupations with potential exposure to pentane, hexane, heptane, and octane are listed in Table XII-5 [11-15,17-24,26-31,118]. NIOSH estimates that 10,000 workers in the United States are potentially exposed to pentane and heptane and 300,000 workers are potentially exposed to octane. It is not clear if these estimates take into account fuel handling operations. NIOSH estimates that 2.5 million workers are potentially exposed to hexane.

Historical Reports

Early reports of exposures to pentane, hexane, heptane, and octane dealt, in most instances, with mixtures of alkanes rather than with pure

substances. For example, in 1942, Drinker et al [32] exposed volunteers to petroleum distillate. Ninety percent of the distillate boiled between 42 and 127 C, a range that included hexane in addition to several other components. A group of eight women ranging in age from 17 to 32 years was exposed to distillate vapor at a concentration of 140 ppm. Another group of 10 women ranging in age from 17 to 22 years was exposed to distillate vapor at a concentration of 150 ppm. The exposures were for 8 hours in a static chamber. The volunteers exposed at both concentrations complained of nausea, headache, and throat and eye irritation.

In 1942, Nelson et al [33] exposed volunteer groups which contained an average of 10 men and women to hexane at various vapor concentrations for 3-5 minutes. The purity of the hexane used for the study was not described. The authors [33] stated that hexane at a concentration of 500 ppm was quite "innocuous" to the volunteers (on short exposures). This was the lowest concentration investigated.

Pentane, hexane, and heptane were at one time investigated for use as anesthetics [12], but they produced undesirable side effects such as respiratory irritation and central nervous system inhibition leading to respiratory arrest [12,32,34,35]. In 1936, Henderson and Smith [35] compared the lethal and anesthetic concentrations of hexane in rats. They [35] found that exposure to hexane at a concentration of approximately 7% (70,000 ppm) was necessary to produce anesthesia, but at this concentration some rats also experienced respiratory arrest.

Effects on Humans

(a) Nervous System

Yamada [17], in 1972, investigated the cases of 17 workers who had reported symptoms of polyneuropathy while exposed to hexane vapor from 1960 to 1962 in Japan. Six of the workers were employed in small polyethylene-laminating plants where hexane was vaporized into the workroom air; the concentration of hexane vapor released during the process was 1,000-2,500 ppm. Symptoms of intoxication began in one worker after 1.5 months of exposure. The methods used to determine these vapor concentrations were not described. The hexane solvent used in these plants contained 16% methyl pentane, 20% methyl cyclopentane, and 64% n-hexane.

Eleven of the 17 employees worked in a pharmaceutical plant where a mixture containing 95% n-hexane was used to remove oil from the surfaces of tablets. The tablets were placed on wire netting, immersed in the n-hexane, removed, and then air-dried. The concentrations of n-hexane around the immersion box and in the center of the workroom were 1,000 ppm and 500 ppm, respectively. The first complaints, noticed within 1 month of exposure, were fatigue and loss of appetite, followed within 1-9 months by paresthesia in distal parts of the extremities, exhaustion, and difficulty in walking so severe that the employees' work and manner of living were affected. Within 6-18 months, muscular atrophy was so severe that the employees were hospitalized. As the cause of the malady was not recognized, exposures had continued. Yamada [17] therefore concluded that all of the workers had developed polyneuropathy because of exposure to hexane. He reported that the progress of the disease was arrested about 3 months after the termination of exposure to hexane and that gradual

recovery took place over periods extending from 6 to 30 months, according to the reports of department physicians.

In 1971, Herskowitz et al [13] described the effects of hexane vapor on three female employees who worked in a furniture factory in New York. The three employees worked in a poorly ventilated room, 3.6 x 3.6 meters, that contained an open 189-liter drum of n-hexane solvent. Their jobs included dipping rags into the open drum and wiping excess glue from finished cabinets. Air sampling indicated that they were exposed to n-hexane at concentrations in the air which averaged 650 ppm and peaked at 1,300 ppm. They first noticed symptoms 2-4 months after beginning work and were hospitalized 6-10 months later, when they complained of one or more of the following symptoms: headache; burning sensation of the face; abdominal cramps; numbness, paresthesia, and weakness of the distal extremities. Physical examination revealed bilateral foot-drop gait, bilateral wrist drop, and absence of Achilles tendon reflexes. Electromyographic examination revealed fibrillation potentials in the small muscles of the hands and feet, and nerve conduction studies showed decreased conduction time in the motor and sensory nerves of the arms and legs, indicating peripheral nerve damage. Biopsies were made of the anterior tibial muscle and sural nerves of two of the patients. The muscles contained small angulated fibers and other fibers with clear central zones (denervation-type injury). Small bundles of axons from the muscle sections were studied by electron microscopy and found to contain dense bodies and fibrous formations, increased numbers of neurofilaments, and abnormal membranous structures with clumped and degenerated mitochondria. Motor-end plates were also damaged, having swollen terminal axoplasmic expansions, an

increased number of degenerated mitochondria, and an increased number of glycogen granules, dense bodies, large osmiophilic membranes, synaptic folds and vesicles. The sural nerve sections were normal under light microscopy, but electron microscopy revealed dense bodies and many mitochondria in some myelinated axons. No information was provided concerning the recoveries of the patients from the effects of hexane.

Gaultier et al [36], in 1973, reported polyneuropathy in five individuals employed in a belt-manufacturing shop in Paris. The solvent used in this shop contained only 5% hexane; however, it also contained 14% heptane and 80% pentane. The symptoms in the three patients treated by the authors were anorexia, asthenia, paresthesia, fatigue, and bilateral, symmetrical muscle failure found mostly in the legs. Electromyographic and nerve conduction studies revealed the presence of diffuse, symmetrical peripheral nerve changes, such as slowed motor nerve conduction rates and signs of denervation in the legs. The authors [36] reported that recuperation was slow and, in one case, was still incomplete after 20 months. No information was given about the two individuals not treated by the authors.

In 1974, Yoshida et al [24] reported the electrophysiologic evaluations of four patients with peripheral polyneuropathy resulting from exposure to hexane. Electromyography indicated that fibrillation, fasciculation, and positive sharp waves were seen in the muscle tests on all patients. Motor nerve conduction velocity in the median, ulnar, and tibial nerves was reduced. Conduction velocity in sensory fibers of the finger-to-wrist segment of the median nerve was slowed in all patients and was diminished in the wrist-to-elbow segment as well. The somatosensory

evoked potentials were prolonged in three of the four patients who were examined. The electroencephalogram was normal in all four patients. The knee-jerk and Achilles tendon reflexes were absent and muscular atrophy was present, especially in the finger, pelvic girdle, lower leg, and foot muscles. The sensations of touch and heat were diminished. Microscopic examination of nerve and muscle biopsy specimens revealed abnormalities in both. The authors [24] diagnosed acute polyneuropathy from these observations.

In 1969, Yamamura [37] reported an outbreak of polyneuropathy resulting from exposure to hexane that was used as a glue solvent in sandal production in Japan. In 1967, it had been discovered that two workers had quadriplegia. Following this discovery, a 6-month epidemiologic investigation was initiated. Of 1,662 workers checked by questionnaire, 296 whose answers indicated the possible existence of neuropathy received medical examinations. Of these 296 workers, 93 (31%) were found to have polyneuropathy. All the patients with polyneuropathy had been engaged in the gluing process of sandal production. Manufacturing the sandals was a household industry where all production took place in the workers' homes. The dwellings were poorly ventilated, and many workers labored for more than 8 hours/day. The organic solvent used in the rubber glue was analyzed by gas chromatography and found to contain at least 70% n-hexane with a small amount of toluene. The concentrations of hexane in the air of the pasting rooms of the dwellings ranged from 500 to 2,500 ppm. The age of those with polyneuropathy ranged from 10 to 75 years and averaged 40 years. Of the 93 persons affected, 21 were males and 72 were females. The initial symptoms of the disease included sensory impairment in the distal portion

of the extremities in 82 workers (88%) and muscular weakness in 13 (14%). Some of those with polyneuropathy also experienced cold sensations of the extremities, blurred vision, headache, easy fatigability, anorexia, and weight loss at the time of onset of the disease. The symptoms and signs at the time of medical examination are summarized in Table III-1 [37].

The 93 patients were divided into three groups on the basis of the severity of neuropathic involvement [37]. Group I contained those with sensory polyneuropathy (53 patients); clinical examinations were performed on 11 patients. Group II contained those with sensorimotor polyneuropathy (32 patients); clinical examinations were performed on 25 patients. Group III contained those with sensorimotor polyneuropathy with amyotrophy (8 patients); clinical examinations were performed on all 8 patients. The results of the clinical examinations are summarized in Table III-2 [37]. The author did not mention a control population.

Muscle biopsies were made on the anterior tibial muscles of three of the patients in group III [37]. Light-microscopic examination showed fatty degeneration of the muscle fibers, diminution of fiber size, and slight proliferation of the sarcolemmal nuclei. In a transverse section, all muscle fibers appeared atrophic, while diminution of size varied randomly. Biopsies were made of peripheral nerves of six other patients in groups II and III. The peripheral nerves of one patient showed demyelination with the appearance of fat granules. The axons were destroyed in part of the demyelinated areas but, in five of the six patients, the axonal degeneration was mild compared with the demyelination. Yamamura [37] suggested that the exposure to hexane had resulted in demyelination and axonal degeneration, with demyelination being generally more pronounced.

TABLE III-1

SIGNS AND SYMPTOMS IN 93 SANDAL-PRODUCTION WORKERS EXPOSED TO HEXANE

Signs and Symptoms	No. of Cases	% of Total
Numbness	93	100.0
Coldness, redness, roughness of skin	55	59.2
Muscular weakness	40	43.0
Hypoactive reflexes	36	38.7
Dysesthesia	21	22.6
Emaciation	14	15.1
Blurred vision	13	14.0
Hyperactive reflexes	10	10.8
Muscular atrophy	8	8.6
Visual field constriction	7	7.5
Loss of sense of smell	5	5.4
Face numbness	5	5.4
Pain or tenderness	5	5.4
Anemia	3	3.3
Optic nerve atrophy	2	2.2
Facial muscle weakness	2	2.2
Optic nerve inflammation	1	1.1
Urination disturbance	1	1.1

Adapted from reference 37

TABLE III-2

CLINICAL FINDINGS IN SANDAL-
PRODUCTION WORKERS EXPOSED TO HEXANE

Laboratory Findings	Group*			Subtotal*
	I	II	III	
Urine:				
sugar content elevated	0/11	2/25	0/7	2/43
protein content elevated	1/11	0/25	0/7	1/43
urobilinogen content elevated	3/11	8/25	5/7	16/43
coproporphyrin content elevated	1/11	3/24	0/6	4/41
Blood:				
erythrocyte count <3,500,000/cu mm**	0/11	0/25	1/7	1/43
hemoglobin content <11 g/100 ml**	4/11	0/25	1/7	5/43
leukocyte count <4,000/cu mm**	0/11	0/25	1/7	1/43
>10,000/cu mm**	2/11	2/25	2/7	6/43
total protein content <6.5 g/100 ml**	0/11	0/25	1/8	1/44
albumin content <4.0 g/100 ml**	2/11	1/25	2/8	5/44
cholesterol content <150 mg/100 ml**	0/11	8/25	2/7	10/43
>250 mg/100 ml	1/11	0/25	0/7	1/43
thymol turbidity >4**	2/11	0/25	0/7	2/43
cephalin-cholesterol flocculation elevated	5/11	4/25	0/6	9/42
SGOT activity elevated	0/11	0/25	0/8	0/44
SGPT activity elevated	0/11	0/25	0/7	0/43
LDH activity elevated	3/11	10/25	4/6	17/42

TABLE III-2 (CONTINUED)

CLINICAL FINDINGS IN SANDAL-
PRODUCTION WORKERS EXPOSED TO HEXANE

Laboratory Findings	Group*			Subtotal*
	I	II	III	
creatine phosphokinase activity elevated	0/0	0/0	1/3	1/3
cholinesterase activity inhibited	6/11	18/25	2/6	26/42
serum test for syphilis (VDRL)	0/11	0/25	0/8	0/44
Cerebrospinal fluid:				
abnormal pressure	0/0	0/3	0/4	0/7
cell number >5/cu mm**	0/0	0/3	0/4	0/7
protein content >40 mg/100 ml**	0/0	0/3	1/4	1/7
globulin content elevated	0/0	0/3	0/4	0/7

*Number of people with abnormal findings/number of people examined
**Limits of normal values used by the authors for comparison

Adapted from reference 37

Although a positive urobilinogen reaction and positive cephalin-cholesterol flocculation tests were obtained in some cases, the normal values for serum transaminase activity were interpreted by the author as an indication that there was little likelihood of liver damage. He considered the depressed cholinesterase activity found in some of the patients as being possibly the result of factors extraneous to exposure to hexane, but it also could have been indicative of liver damage. No other data have been found which correlate hexane exposure with depressed cholinesterase activity or liver damage.

In 1973, Iida et al [38] published a followup investigation of the 93 Japanese sandal workers with polyneuropathic disturbances previously studied by Yamamura [37]. Iida et al [38] divided the patients into the same three groups defined in the earlier study. Yamamura [37] had reported that there were 8 patients in group III (sensorimotor polyneuropathy with amyotrophy), 32 in group II (sensorimotor polyneuropathy), and 53 in group I (sensory polyneuropathy). Iida et al [38] found that 2 years after the original study, there had been sufficient improvement so that no patients remained in group III, 5 were classified in group II, and 34 were classified in group I. A total of 51 patients had recovered. By 1972, there were 7 patients in group I, and 82 (92%) of the original 93 had recovered completely. Four patients were lost to the study; however, only one death (from stomach cancer) was reported.

Inoue et al [18], in 1970, published the results of an analysis of the hexane solvent in the glue used by the sandal makers who were studied by Yamamura [37]. Because of chronic benzene intoxication in vinyl-sandal manufacturing workers, benzene had been replaced approximately 10 years earlier by hexane as a glue solvent [18]. Gas-chromatographic analysis [18] indicated that the solvent contained 2-methylpentane, 3-methylpentane, methylcyclopentane, and n-hexane. The concentrations of individual constituents were not given. The authors [18] stated that most commercial hexane solvents contain these four compounds, with n-hexane constituting about 60% of the total. They [18] also reported that each dwelling where sandal workers had developed polyneuropathy was inspected, and single measurements of airborne hexane were made. The type of equipment used for

these measurements was not described. The reported results, although of limited value statistically, suggested that some workers classified as having group I or group II polyneuropathy may have developed polyneuropathy as a result of being exposed to n-hexane at concentrations below 500 ppm.

In 1976, Abbritti et al [39] reported an investigation of 122 Italian workers who developed polyneuropathy while working in shoe factories during the period of 1971-1974. All workers were interviewed and given electromyographic examinations in addition to other unspecified laboratory examinations to determine if other types of exposure were present that could cause polyneuropathy. Clinical and electromyographic details were not provided. In none of the observed cases was there evidence of contact with any other chemicals which might have caused polyneuropathy. The ages of the workers ranged from 15 to 59 years and averaged 35 years. Most of the symptoms of polyneuropathy were found in those who worked directly with solvents in gluing and cleaning processes. A high proportion of these were women. Polyneuropathy occurred most commonly in workers in small factories with fewer than 20 employees. Work was often done in small rooms at ground level or in basements with poor ventilation. The glue containers were left open during working hours. Even those not working directly with glues or solvents were exposed to solvent vapor at high concentrations; however, no exposure concentration data were reported for any of the factories. Analysis of the solvents and glues used in shoe factories in which 20 workers developed polyneuropathy indicated that they contained 79-95% alkanes including isopentane, n-pentane, 2-methylpentane, 3-methylpentane, n-hexane, iso-heptane, and n-heptane, although not all of these were present in each. These products also contained up to 18% cyclopentane,

methyl cyclopentane, or cyclohexane, and, in some cases, up to 3% toluene. The polyneuropathy reported by the authors was first thought to be caused by triorthocresyl phosphate [40], but numerous chemical analyses of glues and leathers taken from factories where the disease occurred showed that, in most instances, little or no triorthocresyl phosphate was present. They also stated that it was not clear whether one particular alkane was responsible for the development of neurotoxicity, or whether it was caused by the combined action of several alkanes.

In 1929, Patty and Yant [41] investigated the odor intensities and the symptoms produced by commercial pentane, hexane, and heptane. Analysis of the commercial materials showed that the pentane contained 1.3% butane, 20.8% isopentane, 76.5% n-pentane, and 1.4% hexane by volume. The commercial hexane sample contained nearly 100% hexanes, roughly one-third of which was believed to be composed of n-hexane. Although no analysis was performed for benzene, the authors [41] felt that the sample probably contained a trace of benzene because small quantities of aromatics had been found to distill over into hexane fractions during purification. The heptane sample was composed largely of isomers of n-heptane (about 75%). No further clarification of the composition of this isomeric fraction was given. The sulfur content of the samples was measured, since it would influence the odor intensity of the fraction. No analysis for sulfur was performed on the pentane sample; however, a later sample, prepared in a similar manner, did not show the presence of sulfur. A laboratory determination using the Kennedy lamp method, which is a turbidimetric method [42] of analysis, showed no sulfur in the hexane sample. Analysis of the heptane sample indicated a sulfur content of 0.004% by weight. The

authors [41] considered this high, since analysis of other heptane samples indicated the absence of sulfur. Groups of three to six volunteers were exposed to the vapor of each of the three alkanes at various concentrations in a 1,000-cubic foot static chamber. They were instructed to make independent notes on odor intensity and on symptoms at 2-minute intervals throughout the period of vapor introduction and for about 10 minutes afterward. These experiments were designed to simulate cases of continuous exposure. Tests were also conducted in which subjects were exposed to various concentrations and asked to note immediate effects. These experiments were designed to simulate the effect of entering existing contaminated atmospheres.

In the chamber, pentane, hexane, or heptane was allowed to drip from a buret onto a piece of cotton gauze suspended in front of a fan. The concentration of the vapor in the chamber was computed from the quantity of material introduced; it was also checked periodically by sampling and analysis. The method used for determining the vapor concentration in the chamber was not described.

In another series of tests, groups of volunteers were exposed to samples of pentane, hexane, and heptane that were purified by successive treatment with alkaline permanganate, water, concentrated sulfuric acid, and, finally, sodium hydroxide. The purified products were then distilled and a middle distillate with a temperature range of 3-4 C was collected to produce what was termed "purified grade." Purification of the commercial solvents markedly reduced the odor intensity. The physiologic responses, except for odor, produced by the commercial products were not found to differ from those of the purified samples.

No symptoms were noted after exposure to pentane at concentrations up to 5,000 ppm for 10 minutes. Exposure to hexane at 5,000 ppm caused marked vertigo after 10 minutes but heptane at a concentration of only 1,000 ppm caused slight vertigo after 6 minutes of exposure [41]. Exposure to heptane at 5,000 ppm resulted in marked vertigo, inability to walk straight, and hilarity after 4 minutes, and similar signs and symptoms, including incoordination, after 7 minutes. Although it was not clear from the study whether these effects resulted from exposure to the alkanes at concentrations which slowly increased to the reported levels, or from exposure at constant concentrations, these results indicated that the alkane concentration required to produce physiologic response decreased as the number of carbon atoms in the compound increased. The authors concluded that both odor intensity and physiologic response increased markedly in humans upon exposure to alkanes with increasing numbers of carbon atoms.

(b) Skin

In 1936, Oettel [43] studied the effects of liquid alkanes on the intact skin of five human volunteers. Circular glass dishes, 1 cm in diameter, were filled with undiluted hexane, heptane, or octane and were loosely attached to the anterior surface of each subject's forearm for 1 hour. Open glass rods were used to administer pentane; this allowed for the release of the vaporized sample. Blister-inducing properties were also investigated by attaching the dishes containing alkanes to the thighs of the volunteers for 5 hours. The alkanes used in all the experiments were purified by distillation; however, no analysis was reported. Dermal exposure to the liquid alkanes resulted in the immediate development of

irritation characterized by erythema, hyperemia, swelling, and pigmentation. After 5 hours, blisters formed on the alkane-exposed areas. When exposed to pentane, the subjects complained of constant painful burning sensations accompanied by itching. The intensity of these symptoms increased when the subjects were exposed to hexane and heptane. Exposure to octane resulted in diffuse and undefinable sensations. No anesthetic action was reported with any of the alkanes tested, even after 5 hours of skin contact.

The length of time necessary for the sensation of pain to disappear following the removal of these alkanes from the skin increased as the carbon number of the alkanes increased. When pentane was removed from the skin after 5 hours, the pain subsided in 15 minutes; it subsided in 90 minutes with hexane, in 120 minutes with heptane, and in 180 minutes with octane. After 1-hour exposures, Oettel [43] observed marked increases in erythema and skin pigmentation accompanied by pain for a period of up to 24 hours, followed by minor increases in erythema and pigmentation which culminated in a peak effect in 96 hours. According to the author, the exposed skin then gradually returned to normal; no scars were observed. He [43] concluded that the acute effects caused by dermal exposure to the alkanes were probably due to histamine release and the delayed effects were probably due to cellular damage and the accumulation of metabolic products.

In 1975, Nomiyama and Nomiyama [23] investigated the absorption rates of hexane and toluene through the skin of humans. An unspecified number of subjects immersed their hands up to the wrists in a dish containing analytically pure hexane (95% n-hexane) for 1 minute. At intervals following skin exposure, breath, blood, and urine samples were analyzed for

hexane by gas chromatography. The authors were unable to detect hexane in either the breath or the blood of any of the subjects following exposure to n-hexane. The detection limit for hexane was 1 ppm in the breath and 3.5 ppm in the blood. The authors did not describe any physiologic effects.

Animal Toxicity

In 1974, Swann et al [44] investigated the inhalation toxicity of various hydrocarbons including reagent grade n-pentane, n-hexane, n-heptane and iso-octane. Groups of four (sex unspecified) Swiss mice weighing approximately 25 g each were exposed for 5-minute periods to n-pentane and n-hexane at each of the following concentrations: 1,000, 2,000, 4,000, 8,000, 16,000, 32,000, 64,000, and 128,000 ppm. In addition, similar groups of mice were exposed for 5-minute periods to heptane and iso-octane at concentrations of 1,000, 2,000, 4,000, 8,000, 16,000, 32,000, and 48,000 ppm. Only the heads of the mice were exposed to the solvent vapor in a 1-liter chamber; the rest of their bodies were enclosed in plethysmographs as in the Alarie method [45]. Respiration patterns (rate, depth, configuration) were recorded before and during the exposure period and during a 5-minute postexposure recovery period. Alarie's system used an aerosol generator to produce particles with diameters smaller than 0.5 microns. The use of an aerosol generator could explain why some of concentrations reported by Swann et al [44] exceeded the air saturation concentrations reported in Table XII-2 [1].

Exposure [44] to pentane at 16,000 and 32,000 ppm produced no anesthesia; light anesthesia was noted during the recovery period after exposures at 32,000 ppm and 64,000 ppm. At 128,000 ppm, deep anesthesia

was produced during exposure to pentane. Respiratory arrest occurred in one mouse approximately 4.8 minutes after exposure to pentane at 128,000 ppm began. Respiratory irritation, indicated by sporadic body movements, was noted at 32,000, 64,000, and 128,000 ppm.

n-Hexane at a concentration of 8,000 ppm produced no anesthesia during exposure; this concentration produced respiratory patterns similar to those produced by pentane at 32,000 and 64,000 ppm. n-Hexane at 32,000 ppm produced deep anesthesia in the mice. At 64,000 ppm, all four mice had respiratory arrest within 4.5 minutes of exposure. The respiratory irregularities which the mice developed during exposure to n-heptane at 32,000 ppm and 48,000 ppm were similar to those resulting from exposure to n-hexane at 64,000 ppm. Exposure to n-heptane at 48,000 ppm produced respiratory arrest in three of the four mice in the group after 3.75 minutes of exposure. No anesthesia was noted in mice exposed to iso-octane at concentrations up to 8,000 ppm. At 16,000 ppm of iso-octane, there was no apparent anesthesia, but the respiratory pattern of the mice was similar to that resulting from exposure to heptane at 48,000 ppm. One mouse had "sudden" respiratory arrest during the recovery period after exposure to iso-octane at 16,000 ppm. All the mice in the iso-octane group stopped breathing within 4 minutes of exposure at 32,000 ppm, with no apparent anesthesia. The evidence indicates that the higher the carbon number of a hydrocarbon, the greater the anesthetic activity of its vapor, and the lower the concentration required to produce respiratory irritation and respiratory arrest in mice.

In 1967, Miyagaki [46] reported a study of the effects of hexane on the nerves and muscles in the hind legs of mice. The animals were exposed

to hexane at five different concentrations in static chambers for 24 hours/day, 6 days/week, for 1 year. Pure Swiss-strain male mice were separated into 6 groups of 10 mice each and exposed at the following concentrations: group 1, 100 ppm; group 2, 250 ppm; group 3, 500 ppm; group 4, 1,000 ppm; group 5, 2,000 ppm; and group 6, controls. The mice were approximately 8 weeks old at the beginning of the study, and the mean body weights in each of the six groups ranged from 32.3 to 34.6 g. The concentrations inside the static chambers were measured three times daily during the exposure with an n-hexane-calibrated interferometer.

The hexane used for the study was a commercial grade solvent. Gas-chromatographic analysis of the hexane showed that it contained 65-70% n-hexane. Although the author [46] stated that the remaining hydrocarbons were principally other hexane isomers, their individual concentrations and identities were not reported. The mean hexane concentrations in the chambers throughout the year were 99 ppm (100 ppm intended), 272 ppm (250 ppm intended), 552 ppm (500 ppm intended), 1,030 ppm (1,000 ppm intended), and 1,900 ppm (2,000 ppm intended).

The hind legs of the mice were examined after the 1-year exposure. Electromyographic responses, strength-duration curves, electrical reaction times, and flexor-extensor chronaxie ratios were recorded; examinations for gait posture, muscle atrophy, and distal muscle integrity were performed. Miyagaki [46] did not explain why only six mice/group in groups 1-3 were examined, although he indicated that only three mice in group 4 and four mice in group 5 were examined because they were the only survivors in those groups. Abnormal posture and muscle atrophy were slight in the animals exposed at 250 ppm, but were more pronounced in those exposed at 500 ppm

and at all higher concentrations. Light fibrillation was detected in the electromyograms of mice exposed at 250 ppm. No fibrillation was recorded for those exposed at 500 ppm, but definite fibrillation waves were recorded for mice exposed at 1,000 and 2,000 ppm. High spiking voltages were also observed in the electromyograms of those exposed at 1,000 and 2,000 ppm. Above 500 ppm, complex NMU (neuromotor unit) voltages appeared, along with weakening of the interference waves and a decrease in voltages. At concentrations of 250 ppm and greater, the height of the strength-duration curve increased with an increase in concentration.

This increase showed, according to the author [46], slight-to-serious damage to the peripheral nerve-motor branches at the neuromuscular junctions. The flexor-extensor mean chronaxie ratio was approximately 1.6 for the exposure at 100 ppm and for the control mice. It then decreased to 1.2 at 250 ppm and to 1.0 at 500 ppm. However, at 1,000 and 2,000 ppm, a reversal of the flexor and extensor means took place to produce chronaxie ratios of 0.5 and 0.6, respectively. Also, the electrical reaction time, ie, the time that elapsed between electrical stimulation of muscle tissue and the resulting electrical discharge, was longer in the muscles of mice exposed to hexane at 1,000 and 2,000 ppm than in normal muscle. Marked muscular atrophy also was observed in those exposed to hexane at 1,000 and 2,000 ppm.

Miyagaki [46] interpreted the fibrillation, the weakening of interference waves, and the tendency toward higher potential discharges and prolongation of discharge time observed in electromyograms as evidence of peripheral neurogenic damage and nerve degeneration. He also pointed out that the high spiking NMU voltages observed in the electromyograms and the

reversal of the flexor-extensor chronaxie ratios observed at 1,000 and 2,000 ppm might indicate central nervous system damage; however, he stated that further studies were needed to determine the effects of hexane on the central nervous system.

The histologic examinations of the hind leg muscles after exposure to hexane at 1,000 and 2,000 ppm showed atrophy and degeneration of the muscle fiber. The study indicated that a neurotoxicity threshold between 100 and 250 ppm existed in mice. Miyagaki [46] found neurotoxic effects in the animals exposed to hexane at 250 ppm and at all higher concentrations, whereas no definite abnormalities were observed in those exposed to hexane at 100 ppm or in the control mice. Furthermore, no abnormal changes were found in the electromyograms and in the intensity-duration curves in the control mice or in those exposed at 100 ppm, but were noted in 67% of the mice exposed at 250 ppm and in all of those exposed at 500 ppm and higher concentrations. However, the author [46] pointed out that, although hexane at 100 ppm seemed to be harmless to mice, it would be imprudent to consider 100 ppm harmless to humans. He reported no data on human susceptibility.

Truhaut et al [20], in 1973, exposed Wistar rats to airborne hexane at a concentration of 2,000 ppm and to heptane at a concentration of 1,500 ppm, 5 hours/day, 5 days/week, for 1-6 months. Technical grade hexane and heptane were 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, 45.8% n-hexane, 8% methylcyclopentane, 1.2% methylhexane, and 1.2% benzene. The analysis of the heptane gave the following results based on total volume: 9.8% 2-methylhexane, 2,3-dimethylpentane, and cyclohexane; 16.2%

3-methylhexane; 52.4% n-heptane; 18.2% 2,4-dimethylhexane, methylcyclohexane, and toluene; 3.3% methylheptane; 0.1% benzene; and 2.8% toluene (assayed separately). The authors [20] did not state how the analyses were performed. The sciatic and saphenous nerves were removed from anesthetized rats at the end of the 1- to 6-month exposure period, mounted in a nerve chamber, and stimulated by square pulses of various voltages. The stimulations and responses were displayed on an oscilloscope. The studies showed a decrease in the threshold conduction rate (undefined), an increase in the refractory periods, and a decrease in the excitability of the nerves. Microscopic examination of the nerves after 5-6 months of exposure to hexane or heptane showed retraction of the myelin sheaths and, in some cases, a rupture of the Schwann cell membranes. The authors [20] noted that impurities, such as 3-methylpentane in the technical grade hexane and 3-methylhexane in the heptane used for the studies, might have been responsible for some of the results observed. The cycloalkanes, benzene, and toluene present in the technical hexane and heptane may also have contributed to the results observed.

In 1971, Kimura et al [47] studied the single-dose oral toxicity of 16 common solvents, including hexane, in different age groups of rats: newborn (1- to 2-days-old, 5-8 g), 14-day-old (16-50 g), young adult (80-160 g), and older adult (300-470 g). Groups of six male Sprague-Dawley rats were used for the young and older adult studies, and groups of 6-12 Sprague-Dawley rats of both sexes were used for the newborn and the 14-day-old studies. The hexane used was of analytical grade, meeting American Chemical Society specifications. The undiluted solvents were administered orally to nonfasted rats. A precise LD50 value for hexane could not be

determined for the newborn rats because of measurement limitations, but amounts equivalent to less than 1 ml/kg body weight were fatal. The acute oral LD50 was 24.0 ml/kg for 14-day-old rats, 49.0 ml/kg for young adults, and 43.5 ml/kg for older adult rats.

Fuhner [12], in 1921, reported the results of a study of the narcotic effects of gasoline and its components on white mice. Hydrocarbons of "highest purity" were obtained for the experiments; however, no analysis of chemical purity was reported, although the boiling range for each substance was given. The pentane had a boiling range of 30-35 C; hexane, 66-71 C; heptane, 96-100 C; and octane, 122-125 C. Mice were individually exposed to each of the alkanes in 11.2- to 11.3-liter glass-stoppered widemouthed flasks. Each hydrocarbon substance being investigated was introduced onto filter paper for evaporation inside a flask. Air samples were taken periodically from the flask for analytical determinations by unspecified methods. One mouse was exposed in each flask at each concentration. Mice lay on their sides when exposed to pentane at concentrations ranging from 0.27 to 0.38 g/liter for 28-116 minutes. Exposures to pentane at concentrations of 0.32, 0.37, and 0.38 g/liter resulted in loss of reflexes after 97, 50, and 21 minutes, respectively. Full recovery followed the termination of exposure. One mouse, exposed to pentane at 0.38 g/liter, suffered a complete loss of reflexes after 26 minutes and died after 37 minutes.

The animals also lay on their sides when exposed to hexane at concentrations ranging from 0.12 to 0.15 g/liter for durations of 29-123 minutes with no loss of reflexes. Death occurred in five of nine mice at concentrations ranging from 0.14 to 0.18 g/liter.

Exposure to heptane at concentrations ranging from 0.06 to 0.08 g/liter resulted in narcosis followed by respiratory arrest in four of eight mice. Exposure to octane at 0.025 g/liter produced no noticeable signs of narcosis after 180 minutes, but at 0.031 g/liter, the mice lay on their sides after 1 hour of exposure. Exposure to octane at 0.04 g/liter caused narcosis in the mice.

In addition to administration by inhalation, the gasoline components were injected into mice subcutaneously [12]. Because pentane has a boiling point below the body temperature of mice, pneumoderma occurred when 0.1 cc of pentane was injected. Hexane and heptane were lethal when administered in large subcutaneous injections; however, Fuhner [12] did not specify the size of the injections which caused death. When 1 cc of octane was injected, it was not distributed because of poor absorption and remained under the skin for an unspecified number of weeks until the skin became necrotic and sloughed off. Skin damage appeared to be the only effect resulting from subcutaneous exposure to octane. Pentane, hexane, and heptane also caused skin damage; however, the nature of the damage was not described.

In 1929, Lazarew [34] investigated the toxicity of various components of gasoline. An unspecified number of white mice were exposed to pentane, hexane, heptane, octane, and to two isomers of heptane and octane, 2-methylhexane and 2,5-dimethylhexane, respectively. The mice were exposed in 10-liter flasks for 2 hours to determine the minimal airborne concentrations at which (1) they lay on their sides, (2) loss of reflexes occurred, and (3) death resulted. The chemical purity of the alkanes was not reported. The methods used for exposure were the same as those

reported earlier in a study by Fuhner [12].

The airborne concentrations at which the mice lay on their sides were 200-300 mg/liter for pentane, 100 mg/liter for hexane, 40 mg/liter for heptane, 50 mg/liter for 2-methylhexane, 35 mg/liter for octane, and 70-80 mg/liter for 2,5-dimethylhexane. The minimum vapor concentration necessary to produce loss of reflexes was not determined for either pentane or 2,5-dimethylhexane, and it could not be determined for hexane, heptane, or 2-methylhexane since reflexes remained until death in some mice. A loss of reflexes was observed in mice exposed to octane at 50 mg/liter. The concentration of pentane producing death could not be determined, but mice exposed to hexane at 120-150 mg/liter, to heptane at 75 mg/liter, or to 2-methylhexane at 70-80 mg/liter died. A lethal concentration could not be obtained for either octane or 2,5-dimethylhexane because of their low vapor pressures. The lengths of exposure resulting in prostration, loss of reflexes, and death were not given. Lazarew [34] concluded that the acute toxic action of hydrocarbons in a homologous series increases with an increase in carbon number and that the branched isomers were less toxic than straight-chain alkanes. Ratios of alkane concentrations necessary to produce the first toxicity signs (mice lying on their sides) were calculated on the basis of the molar concentrations necessary to produce this effect. The ratio of heptane to octane was 1.3, pentane to hexane was 3.0, and hexane to heptane was 2.9. The author [34] concluded that octane was about nine times more toxic than pentane based on these molar ratios (1:3:3).

Tsobkallo [48], in 1947, reported the effects of heptane on respiration and blood pressure in decerebrated cats. The method used for

monitoring respiration and blood pressure was not described in this report. Cats weighing 2.1-3.3 kg were exposed for 5 minutes to heptane vapor at concentrations of 25, 50, and 100 mg/liter through a tracheal cannula connected through a spirometer. After the exposure to heptane, the cats were exposed to fresh air for 20 minutes. The authors stated that exposure to heptane at all of the concentrations investigated caused an initial increase in respiration rate and then a decrease to below normal. The blood pressure decreased during heptane exposure, then rapidly returned to normal during the recovery period. These effects rapidly dissipated after exposure ended.

Bohlen et al [49], in 1973, investigated the absorption and distribution of hexane in rat tissues. An unspecified number of female albino rats weighing 200-230 g were exposed to airborne hexane in a desiccator at a concentration of 170 g/cu m (5% by volume). The concentration was maintained by blowing compressed air over a reservoir of liquid hexane. Inhalation periods ranged from 2 to 10 hours. Gas-chromatographic analysis was used to determine the concentrations of hexane in the blood, brain, liver, adrenals, kidneys, and spleen after the animals were anesthetized and the organs removed. The hexane concentration in all tissues, with the exception of the liver, increased to a tissue saturation concentration within 4-5 hours. The concentration of hexane continued to increase in the liver throughout the longest exposure. The saturation concentrations for hexane were 0.14 mg/g in the spleen, 0.15 mg/g in the blood, 0.49 mg/g in the adrenals, 0.39 mg/g in the brain, and 0.20 mg/g in the kidneys. Exposure to hexane did not change the amounts of tissue lipids found in the rats, with the exception of that found in the liver.

The lipid content of the liver increased linearly with the duration of exposure. The continuous accumulation of lipids, exclusively triglycerides, increased the affinity of the liver for hexane and indicated to the authors why saturation in the liver was not reached during exposure. Exposure to organic solvents, anesthetics, and other substances, such as ethanol, can result in fatty liver from triglyceride accumulation [50].

Nomiyama and Nomiyama [23], in 1975, studied the absorption rates of hexane and toluene through the skin of the shaved backs of an unspecified number of rabbits. Gauze containing a measured quantity of hexane was applied to the shaved backs of the animals [23]. The gauze was then covered, taped, and allowed to remain in contact with the skin for 24 hours. The unabsorbed n-hexane was measured to determine the quantity that had been absorbed through the skin. After exposing the rabbits to toluene in a similar manner, the authors reported that after 3 hours, 10 times more n-hexane than toluene had been absorbed. Since the authors neither performed tissue analysis nor recorded observations concerning the effects of hexane on the rats, the results of this study are of limited application.

A proposed metabolic pathway for n-hexane and methyl n-butylketone is shown in Figure III-1.

DiVincenzo et al [51], in 1976, reported on the metabolism of n-hexane, methyl n-butyl ketone, and other aliphatic ketones in guinea pigs. All chemicals were dissolved in corn oil (25% solution) and injected intraperitoneally in a single dose of 450 mg/kg body weight in male guinea pigs weighing from 250-450 g. Blood samples were collected 1, 2, 4, 6, 8, 12, and 16 hours after the doses were administered. The serum was

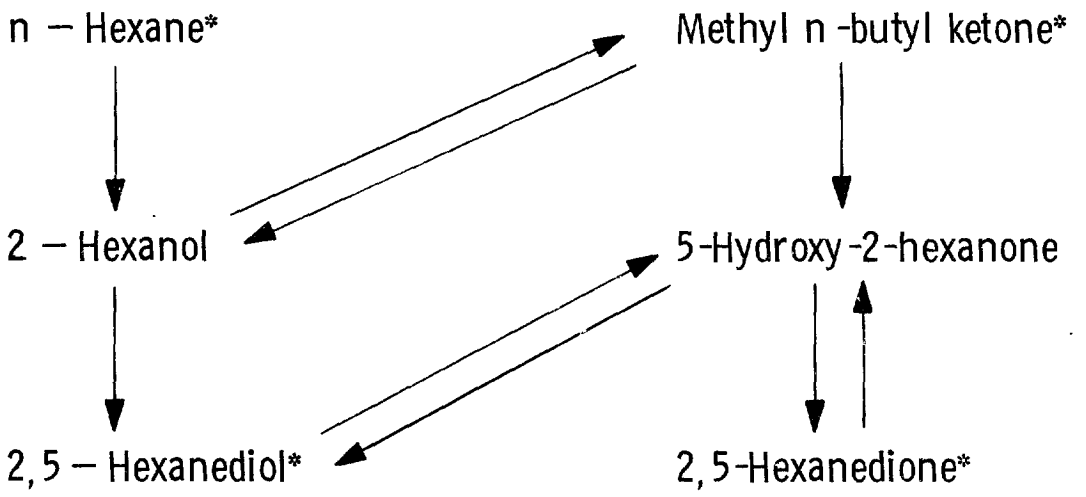

FIGURE III-1

PROPOSED METABOLIC PATHWAY FOR METHYL n-BUTYLKETONE AND n-HEXANE

*These compounds have been shown to be neurotoxic [51-54].

Adapted from Spencer (written communication, 1976)

separated and then analyzed within 48 hours by gas chromatography for n-hexane, aliphatic ketones, and their metabolites. Identification of metabolites was performed by gas chromatography coupled with mass spectrometry. The compounds used in the study were reagent grade. The authors [51] were most interested in the metabolism of aliphatic ketones, but they did report on the identification of two metabolites of n-hexane. The metabolites identified were 5-hydroxy-2-hexanone and 2,5-hexanedione; several other metabolites were detected but not identified. Because no quantitative determinations were made for n-hexane or its metabolites, recoveries could not be calculated. The authors [51] concluded from their

investigation that n-hexane and methyl n-butyl ketone are metabolized to the same compounds and thus have the same neurotoxicity.

Correlation of Exposure and Effect

For many years, alkanes were thought to be relatively nontoxic [29,41] although they were recognized as being fire hazards [55-59]. Patty and Yant [41] determined that exposures to airborne pentane at a concentration of 5,000 ppm for 10 minutes and to hexane at 2,000 ppm for 10 minutes caused no symptoms of intoxication, although exposure to hexane at 5,000 ppm for 10 minutes caused marked vertigo. Heptane caused slight vertigo after 6 minutes at 1,000 ppm, moderate vertigo after 4 minutes at 3,500 ppm, marked vertigo after 4 minutes at 5,000 ppm, and incoordination after 7 minutes of exposure at 5,000 ppm. These results indicated that the alkane concentrations required to produce a physiologic response decreased as the number of carbon atoms in the compound increased.

No data have been reported on health effects resulting from dermal exposure within the workplace. Oettel [43], however, studied the effects of certain alkanes on the skin of humans under controlled laboratory conditions. He found that dermal exposure to alkanes for up to 1 hour produced irritation characterized by erythema, hyperemia, swelling, and pigmentation. After 5 hours of exposure, the alkanes produced blisters on the skin.

No studies that correlate environmental concentrations of pentane, hexane, heptane, and octane with observed toxic effects have been found, except for those relating industrial exposures to hexane with the development of polyneuropathy [13,17,18,24,36-38]. Neither were any long-

term epidemiologic studies of low-level occupational exposures to alkanes found.

In 1960, the first cases of polyneuropathy resulting from hexane exposure were observed in Japan [17]. There has been no clear documentation demonstrating the neurotoxicity of pentane, heptane, or octane, although, in many cases, the solvent thought to cause polyneuropathy contained one or all of these alkanes as constituents in a hydrocarbon mixture [17,18,36]. For example, in a Paris belt-manufacturing shop [36] where five employees were found to have polyneuropathy, the solvent responsible for the neurotoxicity contained 5% hexane, 14% heptane, and 80% pentane.

Studies conducted on mice and rats [12,20,44] support the hypothesis that as the carbon number of the alkanes increases, the adverse effects produced by equivalent doses of the alkanes tend to increase. Lazarew [34] concluded from his study of the comparative inhalation toxicities of 2-methylhexane and 2,5-dimethylhexane versus n-heptane and n-octane in mice that straight-chain alkanes are more toxic than their branched isomers.

The uptake and distribution of hexane in rats were investigated by Bohlen et al [49]. The hexane was administered to the rats by inhalation. Analysis of blood, brain, liver, adrenals, kidneys, and spleen for hexane showed that all the tissues except the liver reached saturation concentrations within 4-5 hours. The concentration of hexane in the liver continued to increase throughout the exposure, probably because of continued triglyceride accumulation in the organ.

Carcinogenicity, Mutagenicity, Teratogenicity and Other Effects on Reproduction

No studies have been found that are related to the carcinogenic, mutagenic, or teratogenic potential of pentane, hexane, heptane, or octane. Since these compounds are not related chemically to compounds known to have carcinogenic, mutagenic, or teratogenic activity, there is no present reason to suspect that they will be found to have such activity.

Summary Tables of Exposure and Effects

The effects of exposure to pentane, hexane, heptane, and octane on humans, which were presented in detail in Chapter III, are summarized in Tables III-3, III-4, III-5, and III-6, respectively; those of exposures to pentane, hexane, heptane, and octane on animals are shown in Tables III-7, III-8, III-9, and III-10, respectively.

TABLE III-3

EFFECTS OF PENTANE EXPOSURE ON HUMANS

Routes of Exposure	Subjects	Exposure Concentration and Duration	Effects	Reference
Respiratory	3 - 6 men and women	Up to 5,000 ppm 10 min	No symptoms	41
Dermal	5 men and women	Undiluted 5 hr	Blister formation, no anesthesia	43
"	"	Undiluted 1 hr	Irritation, itching, erythema, pigmentation, swelling, painful burning sensation, reduced pain 15 min after removal	43

TABLE III-4

EFFECTS OF HEXANE EXPOSURE ON HUMANS

Routes of Exposure	Subjects	Exposure Concentration and Duration	Effects	Reference
Respiratory	3 - 6 men and women	5,000 ppm 10 min	Marked vertigo	41
"	6 men and women	2,500 - 1,000 ppm 10 - 12 hr/d -	Drowsiness in 0.5 hr, fatigue, loss of appetite in some, paresthesia in distal extremities	17
"	93 men and women	2,500 - 500 ppm -	Sensory impairment in distal portion of extremities, muscle weakness in 13, cold sensation of extremities in some, blurred vision, headache, easy fatigability, anorexia, weight loss by onset of polyneuropathy	37
"	3 - 6 men and women	2,000 ppm 10 min	No symptoms	41
"	11 men and women	1,000 - 500 ppm 3 - 6 mon	Fatigue, loss of appetite in some, paresthesia in distal extremities	17
Dermal	5 men and women	Undiluted 5 hr	Blister formation, no anesthesia	43
"	"	Undiluted 1 hr	Irritation, itching, erythema, pigmentation, swelling, painful burning sensation, reduced pain 90 min after removal	43

TABLE III-4 (CONTINUED)

EFFECTS OF HEXANE EXPOSURE ON HUMANS

Routes of Exposure	Subjects	Exposure Concentration and Duration	Effects	Reference
Respiratory, dermal, and oral	1 woman 27 yr	1,300 - 650 ppm 2 mon	Frequent headaches, abdominal cramps, burning sensation of face, numbness of distal extremities, decreased left ulnar nerve conduction rate	13
"	1 woman 47 yr	"	Abdominal cramps, numbness of distal extremities, paresthesia, bilateral foot and wrist drop, sensory impairment of extremities, decreased left ulnar nerve conduction rate	13
"	1 woman 46 yr	1,300 - 650 ppm 4 mon	Weakness in extremities, moderate weakness and sensory impairment of distal extremities, decreased left ulnar nerve conduction time	

TABLE III-5

EFFECTS OF HEPTANE EXPOSURE ON HUMANS

Routes of Exposure	Subjects	Exposure Concentration and Duration	Effects	Reference
Respiratory	3 - 6 men and women	5,000 ppm 15 min	Marked vertigo, incoordination, hilarity for 30 min	41
"	"	5,000 ppm 7 min	Marked vertigo, incoordination of space, hilarity in some	41
"	"	5,000 ppm 4 min	Marked vertigo, inability to walk straight, hilarity	41
"	"	3,500 ppm 4 min	Moderate vertigo	41
"	"	2,000 ppm 4 min	Slight vertigo	41
"	"	1,000 ppm 6 min	"	41
Dermal	5 men and women	Undiluted 5 hr	Blister formation, no anesthesia	43
"	"	Undiluted 1 hr	Irritation, itching, erythema, pigmentation, swelling, painful burning sensation in skin, reduced pain 120 min after removal	43

TABLE III-6

EFFECTS OF OCTANE EXPOSURE ON HUMANS

Routes of Exposure	Subjects	Exposure Concentration and Duration	Effects	Reference
Dermal	5 men and women	Undiluted 5 hr	Blister formation, no anesthesia	43
"	"	Undiluted 1 hr	Diffuse and undefinable burning sensations, reduced pain 180 min after removal	43

TABLE III-7

EFFECTS OF PENTANE EXPOSURE ON ANIMALS

Routes of Exposure	Species	No.	Exposure Concentration and Duration	Effects	Reference
Respiratory	Mice	1	129,200 ppm 37 min	Decreased respiration rate, loss of reflexes, death by 37 min of exposure	12
"	"	4	128,000 ppm 5 min	Irritation, deep anesthesia, respiratory arrest in 1 by 4.75 min of exposure	44
"	"	1	108,800 ppm 26 min	Lying down by weakened reflexes	12
"	"	-	102,000 - 68,000 ppm 2 hr	Lying down	34
"	"	1	91,800 ppm 66 min	Temporary lying down	12
"	"	4	64,000 ppm 5 min	Irritation, anesthesia during recovery period	44
"	"	4	32,000 ppm 5 min	Anesthesia during recovery period	44

TABLE III-8

EFFECTS OF HEXANE EXPOSURE ON ANIMALS

Routes of Exposure	Species	No.	Exposure Concentration and Duration	Effects	Reference
Respiratory	Mice	4	64,000 ppm 5 min	Irregular respiratory pattern, respiratory arrest by 2.5-4.5 min	44
"	"	1	51,120 ppm 9 min	Death after spasms, no narcosis	12
"	"	1	42,600 ppm 127 min	Loss of reflexes, death	12
"	"	-	42,600 - 34,080 ppm 2 hr	Death	34
"	"	-	36,920 ppm 127 min	"	12
"	"	1	34,080 ppm 123 min	Light narcosis	12
"	"	-	32,000 ppm 5 min	Deep anesthesia	44
"	"	-	28,400 ppm 2 hr	Lying down	34
"	"	4	16,000 ppm 5 min	No anesthesia	44
"	"	4	8,000 ppm 5 min	"	44

TABLE III-8 (CONTINUED)

EFFECTS OF HEXANE EXPOSURE ON ANIMALS

Routes of Exposure	Species	No.	Exposure Concentration and Duration	Effects	Reference
Respiratory	Mice	7	1,000-2,000 ppm 6 d/wk 1 yr	Marked abnormal posture and muscular atrophy; in electromyographic tests, fibrillation at rest, complex NMU voltage and high amplitude NMU voltage during movement, and weakened interference waves during strong contractions; increased electrical reaction time; reversal of flexor-extensor chronaxy ratio	46
"	"	6	500 ppm 6 d/wk 1 yr	Abnormal posture and muscular atrophy	46
"	"	19	250 - 2,000 ppm 6 d/wk 1 yr	Higher strength-duration curve with increased concentrations	46
"	"	6	250 ppm 6 d/wk 1 yr	Slightly abnormal posture and muscular atrophy; in electromyographic tests, some fibrillation at rest	46
Oral	Rats	-	49.0 ml/kg*	LD50 (young adults, 80-160 g)	47
"	"	-	43.5 ml/kg*	LD50 (older adults, 300-470 g)	47
"	"	-	24.0 ml/kg*	LD50 (14 d of age, 16-50 g)	47
"	"	-	Less than 1.0 ml/kg*	LD50 (24-48 hr of age, 5-8 g)	47

*Analytical grade, meeting American Chemical Society specifications

TABLE III-9

EFFECTS OF HEPTANE EXPOSURE ON ANIMALS

Route of Exposure	Species	No.	Exposure Concentration and Duration	Effects	Reference
Respiratory	Mice	4	64,000 ppm 5 min	Respiratory arrest in 3 by 3.75 min of exposure	44
"	"	4	32,000 ppm 5 min	Irregular respiratory pattern	44
"	"	-	18,300 ppm 2 hr	Death in 2 hr	34
"	"	4	16,000 ppm 5 min	No anesthesia	44
"	"	-	9,760 ppm 2 hr	Lying down	34
"	Cats (Decerebrated)	-	24,400 - 6,100 ppm 5 min	Decreased blood pressure during exposure, rapid return to normal during recovery period; initial increased respiration, then decreased	48

TABLE III-10

EFFECTS OF OCTANE EXPOSURE ON ANIMALS

Routes of Exposure	Species	No.	Exposure Concentration and Duration	Effects	Reference
Respiratory	Mice	4	32,000 ppm 5 min	Respiratory arrest in 4 by 4 min of exposure	44
"	"	4	16,000 ppm 5 min	Respiratory arrest in 1 during recovery period	44
"	"	1	12,840 ppm 185 min	Decreased respiration rate, death by following day	12
"	"	-	10,700 ppm 2 hr	Loss of reflexes	34
"	"	-	8,560 ppm 55 min	Narcosis	12
"	"	-	7,490 ppm 2 hr	Lying down	34
"	"	-	6,634 ppm 1 hr	"	12
"	"	-	5,350 ppm 48 min	No narcosis	12