## III. BIOLOGIC EFFECTS OF EXPOSURE

### Extent of Exposure

Ketones are compounds with a carbonyl group, C=O, which is attached to two carbon atoms. They are represented by the general formula RCOR' [1]. The 12 ketones discussed in this document are acetone, methyl ethyl ketone, methyl n-propyl ketone, methyl n-butyl ketone, methyl n-amyl ketone, methyl isobutyl ketone, methyl isoamyl ketone, diisobutyl ketone, cyclohexanone, mesityl oxide, diacetone alcohol, and isophorone. These ketones are known by a number of synonyms, some of which are listed, along with chemical and structural formulas of the compounds, in Table XI-1. Important physical and chemical properties are presented in Table XI-2.

Some of the applications of these ketones in industry are determined by the solvent properties, rate of evaporation, boiling point, viscosity, and availability [2]. Ketones are used as chemical intermediates in chemical manufacturing industries; as solvents for natural and synthetic resins in coating industries; as components in formulations such as inks, adhesives, and dyes; as extraction agents for lubricating oil; in wax refining; and for rare metal flotation in refining processes [1,3]. A list of occupations in which there is potential exposure to these ketones is presented in Table XI-3.

(a) Acetone

Acetone, $CH_3COCH_3$, is a colorless, highly volatile, flammable liquid with a burning taste and aromatic odor [4]. It is the simplest but most commercially important ketone [5]. Acetone occurs normally in small amounts in human blood and urine [6].

Commercially, acetone is produced by catalytic dehydrogenation of isopropyl alcohol or by oxidation of cumene [5]. Before World War I, small amounts of acetone were produced from the dry distillation of wood. In the mid-1920's, most acetone was manufactured by the dehydrogenation of isopropyl alcohol.

In 1976, about 1,922 million pounds of acetone were produced in the United States [7]. About 58% of the acetone produced in the United States and Puerto Rico was manufactured by oxidizing cumene, and the remaining 42% was made by dehydrogenating isopropyl alcohol [8]. About 25% of the acetone produced was used to make methyl methacrylate, 13% to make methyl isobutyl ketone, 10% as a solvent for protective coatings, and the rest was used in manufacturing diacetone alcohol, methyl isobutyl carbinol, isophorone, mesityl oxide, higher methacrylates, bisphenol A, and other chemicals [8].

In addition to being used as a chemical intermediate, acetone is an excellent solvent for many natural gums and resins, for cellulose derivatives such as nitrocellulose, cellulose esters, and ethyl cellulose, and for synthetic resins such as vinyl and modified phenolic types, alkyds, and methacrylates [5]. Acetone is also used as a solvent in manufacturing smokeless powder, cements, and artificial leather.

NIOSH estimates that 2,816,000 workers are potentially exposed to acetone in the United States.

(b) Methyl Ethyl Ketone

Methyl ethyl ketone, CH3COCH2CH3, is a colorless liquid with an acetone-like odor and is produced commercially either by dehydrogenation or selective oxidation of sec-butyl alcohol [1]. In 1976, about 524 million

pounds of methyl ethyl ketone were produced in the United States [7].

Methyl ethyl ketone is mainly used as a solvent for formulations of nitrocellulose [1]. It is also used in the manufacture of synthetic surface coatings made from acrylic resins, vinyl acetates, cellulose acetate-butyrate, ethyl cellulose, and vinyl chloride-vinyl acetate copolymers. Methyl ethyl ketone is used as a dewaxing solvent in the refining of lubricating oils. It is used to manufacture methyl isopropenyl ketone, sec-butyl amine, and 1,3-diketones.

NIOSH estimates that 3,031,000 workers are potentially exposed to methyl ethyl ketone in the United States.

(c) Methyl n-Propyl Ketone

Methyl n-propyl ketone, CH3(CH2)2COCH3, is a clear liquid with a strong odor resembling that of acetone but having a more ethereal character [9]. It is made primarily by the oxidation of 2-pentanol. Methyl n-propyl ketone is used as a solvent, either alone or in combination with other solvents.

NIOSH estimates that fewer than 500 workers are potentially exposed to methyl n-propyl ketone in the United States.

(d) Methyl n-Butyl Ketone

Methyl n-butyl ketone, CH3CO(CH2)3CH3, is a colorless liquid with a strong odor resembling that of acetone but more pungent [9]. Commercially, it is produced by the catalyzed reaction of acetic acid and ethylene under pressure.

Methyl n-butyl ketone is used in the lacquer industry as a solvent for lacquers and in lacquer and varnish removers [9]. It is a useful solvent for nitrocellulose, resins, oils, fats, and waxes.

NIOSH estimates that 222,000 workers are potentially exposed to methyl n-butyl ketone in the United States.

(e) Methyl n-Amyl Ketone

Methyl n-amyl ketone, CH3CO(CH2)4CH3, is a liquid with marked fruity odor [9]. It occurs naturally in oil of cloves and in Ceylon cinnamon oil [1]. Commercially, it is produced primarily by the catalytic dehydrogenation of 2-heptanol [9]. It is a useful solvent in synthetic resin finishes, particularly for metal roll coating [1].

NIOSH estimates that 67,000 workers are potentially exposed to methyl n-amyl ketone in the United States.

(f) Methyl Isobutyl Ketone

Methyl isobutyl ketone, CH3COCH2CH(CH3)2, is a colorless liquid with a pleasant odor [9]. It is manufactured commercially by the selective catalytic hydrogenation of the double bond in mesityl oxide.

Methyl isobutyl ketone is used as a solvent in synthetic resinous paints, lacquers, and varnishes [10]. It is also used as a solvent for adhesives, rubber cements, aircraft dopes with cellulose acetate-butyrate bases, 2,4-D, and DDT [1]. As an extractant, methyl isobutyl ketone is used in dewaxing mineral oils, refining tall oil, and cleaning metals [1]. In the recovery of uranium from fission products, methyl isobutyl ketone is used in the solvent extraction process [3].

NIOSH estimates that 1,853,000 workers are potentially exposed to methyl isobutyl ketone.

(g) Methyl Isoamyl Ketone

Methyl isoamyl ketone, CH3CO(CH2)2CH(CH3)2, is a colorless, stable liquid with a pleasant odor. It is used as a solvent for nitrocellulose, cellulose acetate, and acrylic and vinyl copolymers [11]. NIOSH estimates that 19,000 workers in the United States are potentially exposed to methyl isoamyl ketone.

(h) Diisobutyl Ketone

Diisobutyl ketone, (CH3)2CHCH2COCH2CH(CH3)2, is an oily liquid of low volatility with a peppermint odor [1]. Commercially, diisobutyl ketone is produced by the reduction of phorone or as a byproduct in the manufacture of methyl isobutyl ketone from acetone [1].

It is used as a solvent for nitrocellulose, milled crepe rubber, vinylite, and synthetic coatings [9] and as a dispersant for organosol-type resins. It is also used in the synthesis of inhibitors, dyes, pharmaceuticals, and insecticides [9]. It is useful as a dewaxing agent for lubricating oils [1].

An estimate of the number of workers who are potentially exposed to diisobutyl ketone in the United States is not available.

(i) Cyclohexanone

Cyclohexanone, C6H10O, is a colorless liquid with an odor suggestive of peppermint [12]. Cyclohexanone can be produced by the catalytic air oxidation of cyclohexane, by the catalytic dehydrogenation of cyclohexanol, or by the oxidation of cyclohexanol. The most common method probably is catalytic air oxidation of cyclohexane, which produces a mixture of cyclohexanol and cyclohexanone.

In 1975, about 554 million pounds of cyclohexanone were produced in the United States [13]. Its most commercially important use is as a chemical intermediate in the manufacture of adipic acid [3]. In lacquer industries, cyclohexanone is used as a solvent and thinner for lacquers that contain nitrocellulose or vinyl chloride polymers and copolymers [12]. It is used as a solvent for many resins, including vinyls, cellulose esters, ethyl cellulose, polystyrene, acrylics, and crude rubber [3]. It is also used in stain, spot, and paint removers, metal degreasers, adhesives, polishes, and lube oil [3].

NIOSH estimates that in the United States there are 1,190,000 workers potentially exposed to cyclohexanone.

(j) Mesityl Oxide

Mesityl oxide, $CH_3COCH{=}C(CH_3)_2$, is a colorless liquid with a strong odor of peppermint [9]. It is produced commercially by dehydration of diacetone alcohol or by autoxidation of acetone [1].

In 1975, approximately 46 million pounds of mesityl oxide were produced in the United States [14]. Mesityl oxide is used as a solvent for nitrocellulose, vinyl chloride-vinyl acetate copolymers, synthetic rubbers, gums, resins, and ink pastes [1]. It is found in paint and varnish removers, carburetor cleaners, stain removers, and flotation agents. It is also used to produce lubricating oil additives, plasticizers, and methyl isobutyl ketone [1].

NIOSH estimates that in the United States fewer than 500 workers are potentially exposed to mesityl oxide.

(k) Diacetone Alcohol

Diacetone alcohol, CH3COCH2C(CH3)2OH, is a colorless liquid with a pleasant, minty odor [1,2]. It is usually prepared by the aldol condensation of acetone with an alkaline catalyst [1].

Diacetone alcohol is an excellent solvent for cellulose acetate, nitrocellulose, vinyl chloride-vinyl acetate resins, and epoxy resins [1]. The pure (acetone-free) form is a component of castor oil-based hydraulic brake fluids. It also has numerous applications in the tanning industry [2].

NIOSH estimates that 1,350,000 workers are potentially exposed to diacetone alcohol in the United States.

(l) Isophorone

Isophorone, C9H14O, is a high-boiling (215.2 C), colorless liquid of low volatility with an odor resembling peppermint [9]. It is produced commercially by either of two methods, both of which require acetone as an intermediate. Acetone is passed over calcium oxide, hydroxide, carbide, or a mixture of these at 350 C, or it is heated at 200-250 C under pressure. Isophorone is used as a solvent for oils, fats, gums, and natural and synthetic resins and as a chemical intermediate.

NIOSH estimates that 1,507,000 workers are potentially exposed to isophorone in the United States.

## Effects on Humans

(a) Sensory Effects

A number of investigators have studied the irritating effects of ketones in humans. In 1943, Nelson et al [15] reported on the sensory

thresholds of ACETONE, METHYL ETHYL KETONE, and CYCLOHEXANONE in a study designed to determine comfortable working concentrations for these ketones. Concentrations were nominal, ie, they were calculated from weight loss in a bubbler or from dropping the ketone at a known rate onto a hot plate. An average of 10 men and women were exposed to each ketone at various concentrations for 3-5 minutes. In some studies, the experimenters themselves served as subjects. Each individual classified the effects on the eyes, nose, and throat as very irritating, slightly irritating, or causing no reaction. The odor was classified as absent, definite, moderate, strong, or overpowering. Finally, the subjects were asked to estimate if they could work for 8 hours in an atmosphere of the ketone at each given concentration. The concentration of the ketone that most subjects rejected as a working atmosphere was termed objectionable, and the next lower concentration tested was proposed as a tentative practical limit. In a similar study from the same laboratory published in 1946, Silverman et al [16] reported on the sensory thresholds for METHYL ISOBUTYL KETONE, DIISOBUTYL KETONE, MESITYL OXIDE, DIACETONE ALCOHOL, and ISOPHORONE. The experimental design was the same as that used by Nelson et al [15], except that an average of 12 men and women were exposed to the ketones for 15 minutes [16]. The results of these two studies are summarized in Table III-1.

For acetone, some irritation was reported at 300 ppm (711 mg/cu m), and methyl ethyl ketone produced mild eye irritation in some subjects at 200 ppm (588 mg/cu m) and slight nose and throat irritation at 100 ppm (294 mg/cu m) [15]. Nelson et al noted that methyl ethyl ketone at 300 ppm (882 mg/cu m) was objectionable, although this was below the concentration at

TABLE III-1

SENSORY THRESHOLDS IN HUMANS FOR KETONES

| Ketone | Highest Satisfactory Concentration* (ppm) | Irritating Concentration** (ppm) | | | Reference |
|---|---|---|---|---|---|
| | | Eyes | Nose | Throat | |
| Acetone | 200 | 500 | 500 | 500 | 15 |
| Methyl ethyl ketone | 200 | 350 | 350 | 350 | 15 |
| Methyl isobutyl ketone | 100 | 200 | >200 | >200 | 16 |
| Diisobutyl ketone | 25 | 50 | >50 | >50 | 16 |
| Cyclohexanone | 25 | 75 | 75 | 75 | 15 |
| Mesityl oxide | 25 | 25 | 50 | >50 | 16 |
| Diacetone alcohol | 50 | 100 | >100 | 100 | 16 |
| Isophorone | 10 | 25 | 25 | 25 | 16 |

*Concentration judged by majority of exposed volunteers to be satisfactory for an 8-hr exposure
**Concentration that caused irritation in the majority of subjects

which a majority of subjects experienced irritation. Most subjects considered methyl isobutyl ketone to have an objectionable odor at 200 ppm (820 mg/cu m), diisobutyl ketone above 25 ppm (145 mg/cu m), mesityl oxide above 50 ppm (201 mg/cu m), diacetone alcohol at 100 ppm (474 mg/cu m), and isophorone at 25 ppm (141 mg/cu m) [16]. After exposure to mesityl oxide, many subjects reported an unpleasant taste lasting 3-6 hours; subjects also noted an unpleasant taste from diacetone alcohol.

These sensory threshold studies [15,16] have certain shortcomings. The concentrations of ketones in the exposure chamber were calculated (nominal) rather than measured analytically, so the true concentration may have been lower than those reported. In the study by Nelson et al [15], the use of the experimenters as subjects was a possible source of bias, and the exposure periods of 3-5 minutes were not long enough to show if adaptation would occur. The 15-minute exposures used by Silverman et al [16] should have permitted a more accurate observation of olfactory fatigue and a better appraisal of increasing or decreasing irritation with continued exposure, but the authors did not discuss possible acclimatization. The fact that exposure duration did not approach that of a normal workshift is the major limitation of these studies. However, the data are useful as a guide to the relative irritating properties of ketones and the concentrations at which these appear.

Raleigh and McGee [17] investigated the effects on workers of exposure to acetone at high concentrations. Air samples from the workroom and the workers' breathing zones were collected in plastic bags at random times during the workshift. Breath samples from the workers were collected at end-expiration before, during, and after each workshift. All air samples were analyzed by gas-liquid chromatographic methods.

In July 1968 [17], nine workers were examined daily for 7 consecutive 8-hour workdays. Air samples were collected, and symptoms, such as headache, drowsiness, dizziness, nausea, or irritation of the eyes, nose, or throat, were looked for. A brief physical examination paid particular attention to the eyes, nose, and throat and to central nervous system (CNS) effects (gait, finger to nose test, and Romberg's sign). Average 8-hour

daily exposure concentrations for the workers were 1,006 ppm (2,386 mg/cu m, range 950-1,060 ppm; 2,252-2,386 mg/cu m). Breath samples showed a range of 1-420 ppm (2-995 mg/cu m) during the day, with a morning average of 56 ppm (133 mg/cu m) and an afternoon average of 221 ppm (524 mg/cu m). Eye irritation was reported by seven of the nine employees, with three of them reporting eye irritation more than once. Four complained of throat irritation, three of headache, three of lightheadedness, and two of nasal irritation, with one reporting nasal irritation twice. The authors said that these symptoms were intermittent and transient and that they occurred when the concentrations of airborne acetone were considerably higher than 1,000 ppm (2,370 mg/cu m). However, four workers had slight to mild irritation at 800-1,000 ppm (1,896-2,370 mg/cu m). On physical examination, one worker had a slight redness of the nasal mucous membranes, and one had slight congestion of the mucosa of the nose and throat. The authors concluded that there was no indication of CNS disorders.

In 1972, Raleigh and McGee [17] conducted an additional study of two men for three 8-hour shifts and two men for two 8-hour shifts. Physical examinations similar to those in the 1968 study were performed and the workers were also given a psychomotor test, but this test was subsequently shown to be unreliable in measuring psychomotor impairment from alcohol intoxication. Environmental samples contained essentially the same concentration of acetone as those in the first part of this study. Breath samples also showed a similar range of acetone concentrations; however, the concentration was considerably lower (20 ppm; 474 mg/cu m) in the morning than those taken from workers examined previously. Two of the four workers complained of eye irritation, with one reporting the irritation on two

occasions. One of the workers complained of throat irritation, and three noted nasal irritation. On physical examination, one employee had a slight throat congestion.

A correlation of odor threshold and eye irritation with exposure concentration was reported [17]. Most reports of odor detection occurred when the concentration of acetone was near or above 1,000 ppm (2,370 mg/cu m). Of 31 air samples in the 1968 study that were correlated with complaints of eye irritation, 10 were reported to contain acetone at 1,000-1,500 ppm, while the other incidents of eye irritation occurred above 1,500 ppm (3,555 mg/cu m). One individual showed a variable response, noting discomfort several times at concentrations between 1,042 and 6,053 ppm (2,470 and 14,346 mg/cu m) but, on another occasion, he reported no eye irritation at a concentration of 6,596 ppm (15,632 mg/cu m), although he did experience some burning of the throat.

Raleigh and McGee [17] concluded from these experiments that 1,000 ppm was a safe concentration for acetone since they did not consider the slight irritation at 800-1,000 ppm to be cause for concern. They also indicated that the irritation seen at much higher concentrations was mild and transient and that no objective evidence was available from the physical examinations to support the symptoms of eye irritation reported by the workers.

Matsushita et al [18] conducted a study to determine the maximum permissible concentration of acetone. Twenty-five healthy male students, about 22 years old, were divided into five groups. Four groups were exposed to acetone at concentrations of 100, 250, 500, or 1,000 ppm (237,

592, 1,180, or 2,370 mg/cu m) for 6 hours, and the remaining group served as a control. Methods of generating vapor-air mixtures or of measuring concentrations of airborne acetone were not presented.

The authors [18] reported that the subjects recognized the smell of acetone at all exposure concentrations, but that they seemed to get used to the smell. Most of the subjects exposed at 500 or 1,000 ppm had irritation of the nose, eyes, throat, and trachea. Only a few in the other groups had irritation.

In the groups exposed at 500 and 1,000 ppm, there were complaints of tension, general weakness, heavy eyes, or lack of energy the following morning. In the group exposed at 250 ppm, there were fewer complaints of the same nature. None of the volunteers exposed at 100 ppm had any complaints.

Although no sampling and analytical procedures were described, this study suggests that exposure to acetone at concentrations below 1,000 ppm can cause irritation of the eyes, nose, and throat.

In a 1935 report of an animal study, Patty et al [19] mentioned that men momentarily exposed to METHYL ETHYL KETONE at approximately 3.3 and 10% had intolerable irritation of the eyes and nose. Methyl ethyl ketone at 1% had a strong odor and was almost intolerable, while at 0.33% it had a moderate to strong odor and was moderately irritating to the eyes and nose.

In 1953, Carpenter et al [20] described the irritating effects of DIISOBUTYL KETONE in volunteers. Two men (25 and 32 years old) were exposed to diisobutyl ketone at 50 ppm (290 mg/cu m) for 3 hours in a 6.5-foot cube. Concentrations of airborne diisobutyl ketone were monitored by interferometry. The subjects recorded pulse rates and subjective symptoms

during the exposure. Both men had a transitory, slight irritation of the eyes and nose at the beginning of exposure [20]. They could smell and taste diisobutyl ketone throughout the exposure, but they reported no change in the taste of cigarettes smoked at the end of exposure. (Carpenter et al apparently thought smoking was a sensitive indicator of a nonspecific effect.) There was no significant change in pulse rate or blood pressure, and urine sugar and albumin tests 1 hour and 24 hours after exposure were negative. The two subjects estimated that a workplace atmosphere of diisobutyl ketone at 50 ppm would be satisfactory for an 8-hour exposure.

Ten days later, the same two men and another man, 43 years old, were similarly exposed to diisobutyl ketone at a concentration of 100 ppm (581 mg/cu m) for 3 hours [20]. Each subject drew six circles and six squares at the beginning, middle, and end of exposure. Initially, all three men experienced slight irritation of the eyes and nose. Diisobutyl ketone could be tasted by two subjects after 1 hour, and slight throat irritation was noted by one subject after 1.5 hours. Slight tearing occurred in one man, and the other two had slight headaches after 2 hours. After the exposure, two subjects felt slightly dizzy upon entering a fresh air atmosphere. The two men who smoked after the exposure complained of an unpleasant taste. Pulse rates, blood pressures, and the results of urinalyses were normal. Performance on the coordination tests was not affected by the vapor exposure. The subjects estimated that a workplace atmosphere of diisobutyl ketone at 100 ppm would be unsatisfactory. On the basis of comfort, the authors [20] recommended that workplace air should not contain diisobutyl ketone at concentrations higher than 50 ppm.

Smyth et al [21], in a report of animal toxicity, commented that MESITYL OXIDE had an objectionable odor to the investigators; however, they also pointed out that their dislike of the odor diminished rapidly with familiarity. This finding might indicate olfactory fatigue or adaptation to the odor.

(b) Systemic Effects

General systemic effects resulting from exposure to ACETONE and to METHYL ISOBUTYL KETONE have been described by several investigators. A 1903 report [22] described the death of a 12-year-old boy who lapsed into a state resembling a diabetic coma after a large celluloid dressing dampened with acetone had been applied.

In 1952, Harris and Jackson [23] described a case of acute ACETONE poisoning in a 10-year-old boy. He was exposed to acetone vapor at an unknown concentration in a warm room (about 82 F) while a lightweight hip cast was applied, reaching from nipple level to the right ankle, and including the left thigh. The cast consisted of glass and textile bandages set with a mixture of 90% acetone, 9% pentane, and 1% methyl salicylate.

About 8 hours after the cast was applied, the boy became restless, complained of a headache, and felt that the cast, although it fit loosely, was tight across his abdomen [23]. Approximately 4 hours later, he vomited, and persistent vomiting began 1.5 hours later. The patient became more restless, and, within 15 minutes, he collapsed. The cast was slit down the side but not removed. Eight hours after the original symptoms appeared, the boy was pale and almost stuporous. He continued to vomit, and his blood pressure was 80/60. His spontaneous speech was incoherent, although he could answer questions correctly. About 12 hours after the

original symptoms were noted, the cast was removed. The inside of the cast was wet and sticky and smelled of acetone. The skin that had been touching the cast was apparently unchanged.

An hour after the cast was removed, the patient fell into a deep sleep [23]. Three hours later, he was extremely ill and apathetic, and his respiration was rapid, deep, and irregular. His pulse rate was 132 and his blood pressure was 120/70. After taking a drink, he vomited a brownish material that gave a positive benzidine reaction, indicating that there was blood in the stomach. The urine contained acetone, diacetic acid, and sugar. The concentration of acetone in the blood about 6 hours after the cast had been removed was 15 mg/100 ml. (Normal values for acetone range from 0.3 to 2.0 mg/100 ml blood according to a table in Stedman's Medical Dictionary which probably lists values for adults [6]).

Supportive therapy consisting of intravenous (iv) administration of dextrose in saline was given following a presumptive diagnosis of acetone poisoning [23]. The patient's condition returned to almost normal after about 16 hours of therapy, although the smell of acetone on his breath was still noticeable. By the 4th day, his condition was normal, and no acetone was detected on his breath or in his urine.

Harris and Jackson [23] pointed out that they could not distinguish the relative amount of acetone absorbed through the lungs from that absorbed percutaneously. They stated that this patient had a habit of sleeping with his head under the covers, which would have increased the respiratory exposure. The authors thought skin absorption might have occurred, and they stated that previous work to determine skin absorption of acetone had not provided contact as extensive or as intimate as that

seen in this case. It is not clear whether the patient's illness was caused by skin absorption or inhalation of acetone or by both. One other study [24], however, described in detail a case where apparently less skin contact did not result in acetone absorption; this is discussed in more detail in Subsection (e) of this chapter. In addition, the possible contribution of pentane or methyl salicylate to this poisoning was not considered by the authors.

Ross [25] described adverse health effects in eight male workers, aged 30-57 years, who were exposed to acetone vapor. Four of them had been cleaning out a pit, 12 feet deep, in an enclosed building. Two 10-gallon tanks of acetone and two 10-gallon tanks of 1,1,1-trichloroethane were stored nearby. Draeger tube measurements in the pit, made 3 hours, 18 hours, and 1 week after the exposure, revealed acetone concentrations in excess of 12,000 ppm (28,440 mg/cu m) and 1,1,1-trichloroethane levels up to 50 ppm.

The workers in the pit noticed a "sweet sickly smell" and complained of throat and eye irritation, weakness of the legs, and headache during the morning shift [25]. After returning to work from lunch, one worker fainted, and several of the workers felt dizzy and lightheaded and reported weakness in the legs. One of the workers noted the dizziness and weakness after an exposure of 2 minutes. Urine samples from five of the eight workers taken 90 minutes after the original exposures showed acetone levels of 4.6-7.15 mg/100 ml of urine. Urine specimens taken from two other workers 45 hours after the episode showed a trace of acetone in one and 2.4 mg/100 ml in the other. Urine specimens collected from the eight workers 7 days after the exposure showed acetone concentrations ranging from 0.39 to

1.29 mg/100 ml. The diagnosis of "acute acetone intoxication" was made for these workers on the basis of their symptoms, urinary acetone concentrations, and environmental concentrations of airborne acetone. The authors did not consider the measured concentration of 1,1,1-trichloroethane (50 ppm) sufficient to cause adverse effects. Data presented by NIOSH in Criteria for a Recommended Standard....Occupational Exposure to 1,1,1-Trichloroethane (Methyl Chloroform) [26] are consistent with this conclusion. In that document NIOSH recommended an environmental limit of 350 ppm (1,910 mg/cu m) as a 15-minute ceiling. The effects observed in these workers indicate that acetone concentrations in excess of 12,000 ppm (28,440 mg/cu m) are an acute health hazard. The narcosis induced by acetone is cause for special concern, since it implies that exposure to acetone at lower concentrations may cause impaired judgment or other behavioral effects that could affect the health and safety of workers. These data, however, do not permit determination of a threshold value for judgmental impairment.

Parmeggiani and Sassi [27] investigated the effects of acetone in a collodion preparation department of a plant engaged in the production of cellulose acetate fibers. Eight workers had to dismantle a filter and replace the filter element, the two operations lasting about 3 hours. For the remainder of the day, these workers were not exposed to acetone. During removal, mounting, and changing of the filter, acetone concentrations ranged from 307 to 918 ppm (730 to 2,180 mg/cu m). The acetone concentration was determined following preliminary absorption in distilled water, apparently with an impinger. The specific method of analysis was not described. The temperature in the filter rooms was

maintained at 38-40 C (100-104 F). The authors examined the effects of acetone on seven of these workers, aged 19-53 years, who had been employed from 6 months to 13 years.

The first worker loaded the mixers, where acetone at a concentration of 25 ppm (60 mg/cu m) was found [27]. Examinations showed hyperemia of the conjunctiva and pharynx, rough breathing with some basal rhonchi, and slight choleduchol duodenal pain on palpation. He complained of asthenia, somnolence, occasional dizziness, and insomnia.

Of the other six workers who were exposed at 309-918 ppm, all complained of somnolence, four had eye and throat burning, two felt dizzy, and two felt inebriated, one had epigastric pain, one had a heavy head, and one complained of headaches [27]. The results of examination of one man were normal, but five had evidence of pharyngeal irritation, three had conjunctival irritation, and four had signs of lung irritation.

Although the authors [27] did not describe the method of analysis, and the temperature of the room may have contributed to the effects, this study does show that exposure to acetone at concentrations less than 1,000 ppm can cause harmful effects.

Parmeggiani and Sassi [27] also studied the elimination of acetone in workers. Based on a study in which acetone was administered orally to volunteers and then determined in the blood and breath, they were able to calculate a theoretical distribution ratio. Thus, in workers exposed to acetone for 3 hours at 833 ppm (2,000 mg/cu m), twice each shift with a 1-hour rest between exposures, the authors found an average concentration of 190 mg/liter at the end of work. They calculated that this corresponded to a blood acetone level of 85.5 mg/liter. Sixteen hours after the end of the

workshift, the concentration of acetone in the expired air declined to 32 μg/liter, which was equivalent to 14.5 mg/liter in the blood, according to the authors. In the opinion of the investigators, this was evidence that exposure to acetone at concentrations slightly less than the present Federal standard could lead to accumulation in the body. They added that, by the end of the weekend, ie, 48 hours after exposure, the acetone had disappeared.

Vigliani and Zurlo [28] discussed the health of factory workers who had been exposed to acetone at a concentration of 1,000 ppm (2,370 mg/cu m), 3 hours/day, for 7-15 years. These workers appeared to have been the same as those studied by Parmeggiani and Sassi [27], although the two reports differ in some details. All of the workers examined had inflammation of the respiratory tract, stomach, and duodenum and occasional dizziness and loss of strength. Similar effects were also reported in workers exposed at 700 ppm, (1,660 mg/cu m), but the authors did not specify whether this was a short- or long-term exposure. Exhaled air of workers exposed at 1,000 ppm for 3 hours/day at the end of the workshift contained 0.2 mg of acetone/liter and their urine contained 160 mg/liter. The next morning, acetone was detected at concentrations of 0.03 mg/liter in exhaled air and at 10 mg/liter in the urine. On Monday morning, no acetone was detected in exhaled air. The concentration of acetone in the urine at this time was not reported.

Gitelson et al [29] examined the development of clinical signs in a 42-year-old man who had ingested about 200 ml of acetone. An hour later, he was stuporous, with flushed cheeks, shallow respiration, and a regular pulse rate of 108. His temperature and blood pressure were normal, and,

although his abdominal reflexes were absent, he had normal tendon reflexes. His throat was red and swollen, and erosions were observed on the soft palate and around the entrance to the esophagus. His breath smelled strongly of acetone. His urine showed traces of albumin and a few hyaline casts and leukocytes but no sugar. It was strongly positive for acetone and acetoacetate.

The patient lapsed into a coma shortly after he was admitted to a hospital [29]. He was given supportive therapy and regained consciousness about 12 hours later. Six days later, he had pain when he moved his legs or hips, and he had hyperesthesia of the legs that gradually disappeared over 2 months.

Four weeks after ingesting the acetone, the man noticed an increased fluid intake and urine output [29]. An oral glucose tolerance test 2.5 months after the ingestion gave values in the diabetic range, although no family history of diabetes was reported. Another glucose tolerance test 2.5 months later gave values in the high normal range. During this test, the patient's urine contained a considerable amount of sugar.

Gitelson et al [29] stated that the cause of the persistent hyperglycemia in this patient was unknown, but, in referring to published case reports, they mentioned that this effect had also been seen in other patients with acetone poisoning. They speculated that the hyperglycemia might have resulted from an increase in acetoacetate caused by a metabolite of acetone.

In 1964, Linari et al [30] reported on a study of 19 employees who worked with METHYL ISOBUTYL KETONE for 20-30 minutes daily during an 8-hour shift. The ketone was mixed with other substances, including acetone [31],

and the workers centrifuged the resulting suspension. Analysis of the workplace air showed methyl isobutyl ketone at 500 ppm (2,050 mg/cu m) near the centrifuge while it was operating and at 80 ppm (328 mg/cu m) at the far sides of the room [30]. The authors noted that the concentration of methyl isobutyl ketone was either minimal or undetectable at the end of the centrifuging operation and that the workplace was naturally aerated and had forced ventilation. The workers were required to wear appropriate masks during the operation.

Weakness, loss of appetite, headache, burning in the eyes, stomach ache, nausea, vomiting, and sore throat were reported by more than half of the workers [30]. Insomnia, somnolence, heartburn, and intestinal pain were less frequent. Four workers had slightly enlarged livers, and six workers had a nonspecific form of colitis. Skin lesions, found in three workers, varied from erythema to small areas of peeling after an initial dry dermatitis. The results of the clinical chemistry tests were essentially normal, with only slight variation. Skin lesions disappeared after workers used protective gloves and creams, suggesting that contact with liquid ketone was largely responsible for the dermal effects.

Linari et al [30] concluded that methyl isobutyl ketone irritated the conjunctiva and respiratory tract and produced disturbances of the gastrointestinal tract and CNS. While this conclusion is probably correct (ie, it seems likely that methyl isobutyl ketone could produce the effects noted), the possible role of other contaminants, such as acetone, seems not to have been evaluated.

In a followup study, Armeli et al [31] reexamined 14 of the original 19 workers studied by Linari et al [30]. As in the first study, clinical

chemistry tests were performed and work histories were taken. The authors [31] noted that, in the 5 years since the first study, work practices had been greatly improved. In addition, all workers were required to wear air masks and gloves and to use barrier creams in operations where methyl isobutyl ketone was used. Analysis of the workplace air showed methyl isobutyl ketone at 100-105 ppm (410-431 mg/cu m) near the centrifuge and 50 ppm (205 mg/cu m) at the sides of the room. The authors noted that exposures lasted for 15-30 minutes daily.

Armeli and coworkers [31] reported that the results of clinical chemistry tests (red blood cell count, urine sedimentation, liver function, serum protein electrophoresis, glycemia, cholesterolemia, and lipid fractions) were essentially normal. The symptoms reported in the earlier study had nearly disappeared. Dermal lesions were also markedly reduced, but slight liver enlargement persisted in two workers. A few workers still reported CNS and gastrointestinal disturbances. The authors concluded that the improvements in work practices and engineering controls had reduced the symptoms of adverse effects. However, this study suggests that exposure to methyl isobutyl ketone at 50-105 ppm may produce harmful effects on workers.

In a written communication to the ACGIH TLV committee (GD Ware, June 1973), a copy of which was given to NIOSH during preparation of this document, it was reported that workers exposed to ISOPHORONE at 5-8 ppm complained of fatigue and malaise. After improvements in ventilation, isophorone concentrations were lowered to 1-4 ppm, and there were no further complaints.

(c) Effects on Skin

Dermal effects resulting from topical application of ACETONE were investigated by Lupulescu and Birmingham [32]. Small glass tubes containing about 1 ml of acetone were inverted on the right forearms of seven volunteers and held in place with tape for 90 minutes. Acetone was similarly applied to a second site that had been covered with a protective gel containing 50% water, 25% glycerin, 10-15% cellulose-methasol gum, and 2-3% unspecified preservative. Only the protective gel was applied to a third site on the same forearm. After 90 minutes, skin appearance was checked, and 4-mm skin samples were taken by punch biopsy from the treated areas of the forearm. The tissue samples were immediately fixed and prepared for light and electron microscopy. For scanning electron microscopy, similar biopsy experiments were performed using larger samples. Control specimens taken before exposure were similarly examined.

Gross examination of the skin showed only mild edema and hyperemia after contact with acetone [32]. No abnormal features were observed on skin protected with the gel. A reduction and desquamation of horny layers with intercellular edema were observed by light microscopy in the specimens exposed to acetone alone. Vacuoles surrounding the nuclei of the cells of the epidermis, particularly the stratum spinosum, were seen with the electron microscope. The scanning electron microscope showed that, after exposure to acetone, the cells of the stratum corneum were edematous, intercellular spaces were enlarged, and the desmosomes, which connect the cells, were broken apart. The usually organized pattern of the surface cells of the skin was not seen. Skin that had been protected with gel showed less severe effects under the scanning electron microscope.

The data from this study [32] show that dermal exposure to liquid acetone for 90 minutes can produce gross changes of the skin and ultrastructural damage to the upper layers of the contacted skin.

(d) Effects on the Nervous System

Smith and Mayers [33], in 1944, described working conditions and health effects in two factories where ACETONE and METHYL ETHYL KETONE were used as solvents in the waterproofing of raincoats. In one factory, workers applied vinylite resins dissolved in methyl ethyl ketone or acetone to the raincoats with brushes. They were probably exposed through skin contact and inhalation of vapor. Room air samples in this factory showed methyl ethyl ketone at 398-561 ppm (1,170-1,650 mg/cu m) and acetone at 330-495 ppm (782-1,170 mg/cu m). The sampling and analytical methods were not mentioned.

The authors [33] described two cases of possible ketone intoxication in this factory. One woman, 18 years old, developed gastric problems and watery eyes while at work. A few hours later, she was found unconscious and was taken to a hospital. Acetone was detected on her breath, her reflexes were hyperactive, and her face and limbs had occasional twitches. She had an elevated pulse (112 beats/minute), but her blood pressure was normal (128/70). Less than an hour after she was hospitalized, the woman had responded to nikethamide treatment, and a severe headache was the only effect still apparent. She was released from the hospital 2 days later.

The second worker was a 19-year-old woman who fainted at work [33]. She had a convulsion while unconscious but regained consciousness before she was taken to a hospital. She was confused at the time of admission and

suffered from a headache, but she had recovered enough to be released within an hour.

Because the women were exposed to acetone, methyl ethyl ketone, and vinylite resins, it is unclear whether the signs and symptoms were produced by exposure to only one of the compounds or were additive or synergistic effects from a combination of compounds. The effects, primarily in the CNS, may have been produced by both ketones since both cause CNS depression in animals according to a Public Health Service investigation [34].

In the second factory studied by Smith and Mayers [33], methyl ethyl ketone was used as a solvent for the resin with which the raincoats were made. Workers immersed their unprotected hands in the solvent, and they were also exposed by inhalation. Concentrations of methyl ethyl ketone in the workroom air ranged from 300 to 600 ppm (882-1,760 mg/cu m). Several workers had adverse health effects as a result of exposure. Some had dermatitis so severely that they could not work. Two men had dermatitis on the face that was attributed to exposure to methyl ethyl ketone in the air. Several workers experienced numbness in the fingers and arms, and one had a similar effect in the legs, which weakened when he tried to walk. Another worker stated that his shoulder felt as though it was made of dough and did not belong to him.

In 1971, Berg [35] reported a case of retrobulbar neuritis in an 18-year-old seaman who had been exposed to METHYL ETHYL KETONE while removing paint from an airplane hangar. Two other men who also were exposed had only mild respiratory symptoms and conjunctival irritation. The seaman noted a dull headache, mild vertigo, and diminished vision in both eyes. Two hours after exposure, he was alert, but his vision in both eyes was

"reduced to counting fingers." His vision, which had been 20/20 when he began military duty, was now 20/200. At this time, he had blurred vision, lightheadedness, and nausea. Although the conjunctivae were slightly congested, the results of an ophthalmoscopic examination were normal. Testing showed marked enlargement of the blind spots and superior arcuate-type defects in both eyes. The author noted that the man's clothing had an odor like that of acetone.

About 10 hours after exposure, the man's blood was analyzed for the first time, and unspecified amounts of methanol and formaldehyde were found [35]. Thirty-six hours after exposure, his vision had returned to 20/20 and his visual fields were normal. Daily analysis of blood serum showed no formaldehyde and steadily decreasing levels of methanol. Throughout his 6-day hospital stay, he noted a daily lessening of his dizziness and nausea.

Berg [35] postulated that the subject had optic nerve toxicity induced by methanol formed from the metabolism of methyl ethyl ketone. Berg did not rule out the possibility that methanol itself was the cause of the illness, although he pointed out that methanol toxicity produced a different clinical picture.

In 1975, Viader et al [36] investigated a case of peripheral neuropathy in a 55-year-old worker exposed to methyl ethyl ketone and other compounds. The worker was hospitalized in January 1974 for a loss of muscular strength in his hands, bilateral paresthesia of the fingers, and fatigue when he walked. He had a moderate weakness in all muscles of both hands, predominantly in the extensors of the fingers and the dorsal interosseal muscles, as well as weakness of the anterior tibial compartments of the legs. Tendon reflexes were present and normal, and

there was no amyotrophy or fasciculation. All signs of objective sensitivity were normal.

Viader et al [36] reported that an electromyogram showed peripheral neurogenic signs in all four limbs. Motor conduction velocities were slowed slightly in the external popliteal branch of the sciatic nerve. The man had no history of alcoholism, and his serum lead concentration (0.20 mg/liter) was normal. The authors noted that, 2.5 months after the worker was hospitalized, he had only a moderate weakness of the extensors of the fingers and the interossei of both hands and that his condition was judged to be further improved 10 months after the initial examination.

For 2 years before he was hospitalized, the worker had used a special adhesive and solvent to set plastic pipes into trenches about 2 meters deep [36]. Analysis of these products showed that the adhesive was 60% tetrahydrofuran and 40% polyester-type polymer. The solvent used to dissolve the adhesive was said to be 100% methyl ethyl ketone, but it is not clear if an analysis was performed. The author reported that the worker had manipulated the adhesive without gloves, cleaned his hands with the solvent, and inhaled the vapor at the bottom of the trench without a mask. Viader et al noted that the symptoms were similar to those of methyl n-butyl ketone poisoning (described in the study by Allen et al [37] discussed below). The authors concluded that the illness was caused by tetrahydrofuran, methyl ethyl ketone, or a combination of these agents. Although there is little doubt that this worker had signs of neurotoxicity, it is not clear what the causative agent was.

In August 1973, a case of severe peripheral neuropathy was diagnosed in a 22-year-old man who had worked for 2.5 years in the printing

department of a coated-fabric plant in Ohio, where some 275 chemicals, including METHYL ETHYL KETONE and METHYL n-BUTYL KETONE were used [37,38]. Since he was otherwise healthy, the symptoms were thought to be associated with exposure to a toxic chemical. The worker indicated that several others in the printing department had similar symptoms. An investigation was begun to identify neuropathy in other workers at the coated-fabric plant and to determine the causative agent. The investigation was conducted and supervised by a team of consultants from the company, the union, a hospital, the state health department, NIOSH, and the Center for Disease Control. The results of the investigation, discussed in detail in Epidemiologic Studies, implicated methyl n-butyl ketone as the probable cause of the neuropathy.

Allen et al [37] described the symptoms of the 22-year-old worker, which they considered to represent a typical case of motor and sensory neuropathy. He first noticed intermittent tingling sensations in his arms and legs, as if his limbs were "asleep"; those sensations progressed to weakness of the left leg about 3 months later. The leg weakness became worse, footdrop developed, and he had impairment of grip. The man lost 15 pounds over 8 months and was hospitalized after his condition was diagnosed as peripheral neuropathy. Physical examination showed prominent atrophy and occasional fasciculations of the intrinsic muscles of both hands. The man had severe weakness of the finger extensors and the dorsal and ventral interossei muscles and moderate weakness of the finger flexors and wrist pronators, supinators, extensors, and flexors. He also had moderate weakness of the iliopsoas, slight involvement of the quadriceps and hip adductors, bilateral footdrop, and severe weakness of the gastrocnemii, toe

extensors, and toe flexors. Except for absent finger jerks, reduced knee and hamstring reflexes on the right, and absent ankle jerks, the tendon reflexes were normal. Sensory testing showed a dense, bilateral loss of fast pricking pain over the toes, soles, and heels with a milder loss in the knees and similar defects in the hands up to the wrists. Temperature discrimination was impaired up to the knees, and light touch sensation was lost over the toes and fingers. Right peroneal nerve conduction velocity was slowed. Deep sensation was normal. Electromyography showed positive waves and fibrillations in many muscles. Other laboratory findings were essentially normal. Eight months after the man was hospitalized, his condition had markedly improved.

The authors [37] also described a case of motor neuropathy in a 43-year-old man who had been a pan washer at the coated-fabric plant for 18 years. He first noted a tendency of his knees to give way; this was followed by difficulty in picking up his feet, lifting heavy objects, and gripping small objects with his fingers. He reported a recent 25-pound weight loss. He was hospitalized and was found to have moderate, distal weakness of the arms and legs and mild, proximal weakness of the legs. Tendon reflexes and the results of sensory examinations were normal. An electromyogram showed positive waves and fibrillations in the distal muscles of the hands and a slowing of peroneal conduction velocities. Other laboratory findings were essentially normal. The man's condition was diagnosed as peripheral neuropathy of an undetermined origin. The condition of the man steadily improved, but he had slight weakness in the left ventral interossei. Otherwise, his strength was normal, and there was no atrophy.

Allen et al [37] next described a case of sensory neuropathy. A 55-year-old man, who had been a print operator for 27 years in the coated-fabric plant, first had a continuous sensation of his toes being "asleep," aching pain in the calf, and occasional momentary loss of balance or a feeling of lightheadedness. He also noted general fatigue, especially when carrying heavy loads. The man estimated that he had lost 50 pounds over the last 10 months. The results of a motor examination were entirely normal, showing completely normal strength and no atrophy or fasciculations in any muscle groups. All tendon reflexes were present and normal. Sensory examinations showed a decrease in temperature discrimination, in fast pricking pain, and in light touch over the entire right foot to the ankle and on the toes of the left foot. There was a similar sensory loss in all of the fingers of the right hand and in the fingertips of the left. Deep pain and position senses were normal. An electromyographic examination showed positive waves and fibrillations in extensor and flexor hallucis longus muscles. A followup examination, 7 months after the initial symptoms began, showed substantial improvements, but the man still had numbness of the toes and a loss of discrimination of superficial pain, temperature, and touch in both large toes. Electromyography showed only occasional positive waves without fibrillations in the left extensor hallucis longus.

In screening 1,157 employees by electrodiagnostic examinations, interviews, and a questionnaire, Allen et al [37] identified 194 suspected of having peripheral neuropathy or other neurologic disorders. These employees were examined by electromyography and laboratory studies and were later given followup examinations. Eighty-one were either normal or showed

results that were of doubtful importance to the study. Twenty-seven had neurologic disorders other than toxic polyneuropathy, such as diabetic neuropathy. Toxic polyneuropathy was diagnosed in 86 workers. Eleven of these had characteristic, disabling, peripheral neuropathy that was rated moderate to severe, and 38 had signs of neuropathy and characteristic electrodiagnostic abnormalities that were rated mild. Of the 86, 37 had no objective clinical findings, but they did have characteristic electrodiagnostic abnormalities and were classified as having minimal motor involvement.

The authors [37] described the neurologic pattern as a distal, motor, and sensory disorder that had an insidious onset with minimal loss of reflexes. Initial symptoms in those workers with prominent motor involvement included slowly developing weakness of the hands or feet accompanied by slapping gait or by difficulty moving their fingers or grasping heavy objects. Others had intermittent tingling paresthesia of the hands or feet. Pain was minimal or absent. Of the 10 patients in the group moderately to severely affected, in which body weight was monitored, 8 experienced weight losses ranging from 3-60 pounds. In the milder cases, no substantial weight changes were observed.

In the 11 moderate to severe cases, a combination of motor and sensory loss or of motor and reflex loss was observed [37]. In the 38 mild cases, sensory loss predominated. Muscle weakness commonly involved the intrinsic muscles of the hands and feet and the long extensors and flexors of the digits. Sensory loss was roughly symmetrical and was usually confined to the feet or fingers. Loss of reflexes was minimal, and no evidence of autonomic dysfunction was seen. Cranial nerve abnormalities

were noted in only one patient, who had unilateral sensory loss on the face. The authors noted that about one-sixth of the affected subjects continued to show progressive dysfunction for 3-5 months after all possibility of exposure had been eliminated.

Summarizing their electrodiagnostic findings in these workers, the authors [37] stated that electromyographic abnormalities were approximately symmetrical and were either restricted to a distal distribution or greater in degree in distal muscles than in proximal ones. In the moderately to severely affected group, positive waves and fibrillations were found in all 11 employees. Eight of these workers also had abnormal motor unit potentials. In the 38 mild cases, 31 had positive waves, 22 had fibrillations, and 23 had motor unit potential abnormalities. In the 37 cases of minimal involvement, 29 had positive waves, 16 had fibrillations, and 16 had abnormalities in motor unit potential. After serial examination, positive waves and fibrillations subsided, but polyphasic and abnormally large motor unit potentials became more abundant. The authors noted that, in general, electromyograms and nerve conduction velocities correlated with the clinical severity of neuropathy. The results of clinical chemistry tests were within normal ranges; however, significantly lower erythrocyte cholinesterase activities ($P<0.001$) and significantly higher plasma cholinesterase activities ($P<0.001$) as compared to volunteers and neurologically normal patients were found. Cholinesterase activities did not correlate with severity of the neuropathy. The significance of the lower erythrocyte cholinesterase activities and elevated plasma cholinesterase activities is not clear, though liver cell damage might explain the changes in plasma esterases.

To determine the causative agent, Allen et al [37] and Billmaier et al [38] investigated the processes and chemicals used in the plant and correlated this information with the incidence of polyneuropathy in various departments. These findings are reported in Epidemiologic Studies.

In 1976, Mallov [39] reported on spray painters who had worked with two formulations of paint on the Cannelton Dam and the Newburgh Dam. The older formulation contained 22% methyl isobutyl ketone and 22% methyl isoamyl ketone. In the new formulation, these two solvents were replaced by 44% methyl n-butyl ketone. Both formulations contained 3.1% of a tricresyl phosphate plasticizer. Gas-liquid chromatographic analysis by NIOSH did not detect triorthocresyl phosphate in the paint. The limit of sensitivity of this method was 0.1% by weight. The new formulation, containing methyl n-butyl ketone, was first used sometime after September 15, 1972, at Cannelton, where over 22,900 liters were used; at Newburgh, it was first used sometime after July 1972. Because there were no handwashing facilities, some workers washed their hands with paint thinners, including one containing methyl n-butyl ketone. Twenty-six men who worked at the two sites were examined, and medical and occupational histories were taken during the spring of 1974. Three men had clinical evidence of peripheral neuropathy.

One of the men with peripheral neuropathy was a 42-year-old painter who had worked on the Cannelton Dam from September 1972 until August 1973 [39]. In July 1973, he complained of weight loss, numbness and tingling in his feet, and a progressive weakness in both legs which progressed to his arms. His condition deteriorated so that he could not stand up without help or even turn a key in a lock. Examination showed bilateral footdrop

and an absence of ankle jerks, knee jerks, and brachioradialis reflexes. Sensation was mildly diminished or normal in the fingers and feet bilaterally. An electromyogram showed an increase in insertional activity, fibrillation potentials, positive sharp waves, and many polyphasic muscle potentials. The left median nerve latency was increased, while the conduction velocity was decreased. Alcoholism, diabetes, cancer, uremia, collagen diseases, and porphyria were ruled out as causative agents. Blood lead levels were mildy elevated (55 $\mu$g/100 ml), but a 24-hour urine sample contained normal lead levels (67 $\mu$g/liter). Normal and elevated levels were judged from statements taken from a chapter on metal poisoning in a medical text book [40]. An EDTA provocative test indicated a previous absorption of lead that was described as excessive. The worker had used lead paint extensively until 1.5 years before the onset of his illness. These blood and urine lead levels were probably not sufficiently high to have been associated with neuropathy, but a high body burden sufficient to have caused neuropathy may have existed.

The second case was that of a 35-year-old man who had been a painter at Cannelton from April to October 1973 [39]. His initial symptoms were tingling in his extremities, burning and freezing sensations in the soles of his feet, cramps in his calves, and weakness in his legs and hands. The worker eventually was unable to rise from a sitting position without help, and he could not push down the top of his shaving-cream can. Examination showed a bilateral footdrop and a left wristdrop. Muscle weakness was apparent in the distal muscles of the arms and legs and in the proximal muscles of the legs. Reflexes in both legs were said to be markedly diminished. His condition subsequently improved, but the absence of ankle

jerks and weakness in the foot persisted. Sensation was mildly impaired distal to the midcalf and midforearm. Two 24-hour urine specimens contained normal levels of lead (5.1 and 8 μg/liter). Nothing was found in the man's medical history to explain his condition.

The third case was that of a 43-year-old painter who had worked at the Cannelton Dam from September 1970 to April 1972 and from October 1972 to April 1973 [39]. He had also worked at the Newburgh Dam from April 1972 to October 1972 and from April 1973 to November 1, 1973. In October 1973, he noticed weakness in his feet, legs, and hands and numbness and tingling in his hands and feet. He noted in November that his feet were slapping down consistently when he walked, and he fell 25-30 times during the last few weeks of November and the 1st week of December. During this time, he had constant numbness in both feet and legs below the midcalf, and he experienced numbness in his hands and wrists for several hours two or three times each day from November 1 until the middle of December. He also had transient tingling on the backs of his hands, which was provoked by rubbing, and steady aches in his calves. When he was examined 3.5 months after the onset of his illness, he no longer had sensory symptoms but his lower extremities still felt weak. He also had an absent right ankle jerk, weakness in his right foot, and diminished pinprick, light touch, and vibratory sensation in his right foot. Blood lead levels were normal (25 μg/100 ml). Mallov [39] stated that all three workers, according to their work histories, had ample opportunity for respiratory and skin absorption of methyl n-butyl ketone and that all had developed neuropathy within 4 months of each other. The first patient had the greatest opportunity for skin absorption, since he did not wear gloves and changed his work clothes

only once a week. Mallov stated that, although the first patient had a previous exposure to lead, lead probably did not play a role in his neuropathy, because sensory loss is not characteristic of lead neuropathy. Mallov also believed that the tricresyl phosphate present in the paint had no relationship to the onset of neuropathy, since none of the ortho-isomer was present and since tricresyl phosphate had been used by the Army Corps of Engineers for 24 years without incident.

Davenport et al [41] have also described a case of progressive polyneuropathy in a 35-year-old furniture finisher. Unlike his coworkers, the man sometimes did not use his face mask and he often used a thinner to clean his hands. Six months before the man became ill, the manufacturer of the lacquers and solvents used in this process had substituted methyl n-butyl ketone for methyl isobutyl ketone on a volume for volume basis. Methyl n-butyl ketone was present in a concentration of 20% in the finish, 12% in the thinner, and 7% in the sealer. Toluene, xylene, n-butyl alcohol, and acetone were also present in various proportions, and the thinner contained 5% methanol.

The man first noticed tingling in his feet and mild clumsiness while walking. Two weeks later, he was unable to walk. He also developed paresthesia in his fingers. Three months later he was much stronger and was able to walk unassisted. A sural nerve biopsy taken at this time showed enlarged axons and axons packed with fine filaments measuring 10-15 nm in thickness, which were very similar to those described by Allen et al [37].

RL Barnes (written communication, January 1978) informed NIOSH of the occurrence of peripheral neuropathy in workers employed in a dewaxing unit

of a Texas refinery. The dewaxing unit uses a conventional solvent extraction method for removing high melting point hydrocarbons from petroleum to produce oils with adequate lubricating properties over a broad temperature range. This process involves mixing methyl ethyl ketone and toluene with various petroleum fractions. Airborne methyl ethyl ketone and toluene were found in the workroom.

NIOSH initiated a health hazard survey of this operation, but, until the investigation and data evaluation have been completed, no conclusions can be drawn at this time.

(e) Absorption and Excretion Studies

Cesaro and Pinerolo [24] studied the percutaneous absorption of ACETONE in volunteers. Eight healthy men with no evident physiologic disturbances were enclosed nude in a sealed box for 20-30 minutes with their heads protruding through a hole in the box. Cotton compresses were used in an attempt to saturate the chamber with acetone. Each subject breathed through a rubber mask with tubes leading to another room. Acetone was sprinkled on each subject's skin with a cotton compress during the exposure. Total ketone bodies in the blood, which included preformed acetone and acetone derived from diacetic acid or beta-oxybutyric acid, was determined before and immediately after exposure. The average value before exposure was 0.89 mg%, while after exposure it was 0.90 mg%. They concluded that acetone was not absorbed through healthy human skin.

Using the apparatus of Cesaro and Pinerolo [24], Parmeggiani and Sassi [27] studied the percutaneous absorption of acetone. The method was the same except the subject lightly applied acetone to his skin with a saturated cotton pad for 30 minutes. A total of 15 g of acetone was used.

The subject was then kept in the chamber for 1.5 hours. After the exposure, blood acetone levels were 40 mg/liter as compared with only a trace before exposure. Acetone concentrations in the urine were 10 mg/liter before exposure and 70 mg/liter at the end of exposure. These data indicate that acetone was absorbed through the skin. The apparent contradiction between these results and those obtained by Cesaro and Pinerolo are most likely attributed to the longer period of exposure. Also, there was a greater chance in this study for liquid acetone to contact the skin. From these studies, it appears that percutaneous absorption of acetone is dependent on the extent of exposure.

DiVincenzo et al [42], in 1973, reported acetone excretion and blood chemistry changes in humans exposed to acetone vapor. Nine male employees, aged 22-62 years, volunteered to participate in the experiment, but participation was contingent on medical approval. It is unclear whether all nine participated in the experiments. Those that did participate fasted for 8 hours before they were exposed to acetone at 100 or 500 ppm (237 or 1,185 mg/cu m), followed by 2 hours at rest, 2 hours with exercise, or 4 hours at rest. They avoided using toothpaste and mouthwash because they might contain contaminants that could interfere with the analysis. Those who exercised either remained seated or jogged for 5 minutes and rested for 10 minutes. Before exposure and 24 hours later, blood samples were collected for hematologic and clinical chemistry testing. Exhaled breath, venous blood, and urine samples were also collected at regular intervals during and after exposure. These samples were analyzed for acetone by gas-liquid chromatography. The authors [42] concluded that there was no appreciable change in the blood chemistry of any of the

subjects exposed to acetone at 100 or 500 ppm for 2 or 4 hours. However, for those exposed for 4 hours, no clinical data (blood chemistry) were reported. It is unclear, in addition, whether or not the clinical data presented were those for men who exercised; since the authors reported a twofold increase in acetone absorption during exercise, which was not reflected in an increase in the urine acetone concentration, the clinical data for men who exercised might have differed from those who did not exercise.

Analysis of the subjects' expired air during the 2-hour exposures and up to 7 hours afterwards showed that, after the first 15 minutes, approximately 75-80% of the inspired vapor was absorbed by the blood and 20-25% remained in the dead space volume [42]. The ratio of acetone absorbed to that eliminated remained constant during exposure, indicating that body compartment saturation did not occur. The exposure concentration of acetone and the concentration in the expired air were directly proportional both during and after exposures. The wash-out curves of the vapor showed that, up to 7 hours after exposure ended, acetone was not entirely eliminated from the body. However, data on the normal concentration of acetone in expired air were not given. The character of these curves suggested to the authors that repeated daily exposures at higher concentrations would allow acetone to accumulate in the body.

The concentrations of acetone vapor in the breath also depended on length of exposure and intensity of exercise during exposure at 100 ppm for 2 hours [42]. Increasing the exposure from 2 to 4 hours caused an increase in postexposure respiratory excretion of acetone, but the excretion was less than twice that measured for the 2-hour exposure. The significance of

these findings is uncertain because of the small number of subjects used in the study and the wide variation in concentrations. Assuming the uptake to be directly dependent on time and concentration, this decrement indicated that excretion was carried out through other routes, such as urinary or percutaneous, or that metabolic breakdown of the acetone was occurring. The increased excretion in the exercising subjects indicated that the increase in minute volume resulting from the exposure was responsible for an increased uptake of the acetone vapor.

Analysis of whole blood samples for acetone showed that a 2-hour exposure was not sufficient to produce steady-state conditions [42]. This exposure duration was too short to allow saturation of the body water compartment. The half-life of the acetone in the blood was calculated to be about 3 hours for subjects at rest who were exposed at 100 ppm for 2 hours, and the authors concluded that their postexposure results indicated that acetone disappeared from the blood at a constant rate that was independent of the initial concentration (zero-order kinetics).

Analysis of urine for acetone did not show a relationship that was directly proportional to the exposure concentration [42]. However, no attempt was made to regulate urinary volume during the collection period, so this relationship might be directly proportional under rigorously controlled conditions.

DiVincenzo et al [42] concluded that the absorption of acetone by humans was directly proportional to the magnitude of exposure. They also pointed out that physical activity increased absorption and that absorption was related to the minute volume of air breathed. They suggested that, since the concentrations of acetone in expired air and blood were directly

proportional to the extent of exposure, these indices might be used for biologic monitoring. The authors' finding that acetone can accumulate in the body is significant because it suggests that longer periods of exposure may produce toxicity.

Munies and Wurster [43] investigated the percutaneous absorption of METHYL ETHYL KETONE in volunteers. Absorption was studied using hydrous, anhydrous, and normal skin. An absorption cell that was previously described by Wurster and Kramer [44] was used to keep the ketone in contact with the forearm of the subject. For hydrous conditions, water was mixed with methyl ethyl ketone in the cell. For anhydrous conditions, the cell was first filled with magnesium perchlorate. Expired air was analyzed by gas chromatography. Exposures lasted 8 hours.

The authors [43] reported that methyl ethyl ketone was found in the expired air 2.5-3 minutes after contacting normal skin. A plot of the concentration of the ketone in expired air showed that a plateau value for elimination was reached in 2-3 hours. In anhydrous skin, the plateau value was reached in 4-5 hours. Under hydrated skin conditions, methyl ethyl ketone was found in the expired air within 30 seconds; the concentration rose to a maximum in a few minutes and then declined to a plateau in about 2 hours.

The authors [43] supplied data on the analysis of one sample of expired air which showed chromatographic peaks corresponding to those for methyl ethyl ketone, acetone, acetaldehyde, methanol, and ethanol. Munies and Wurster did not discuss these results, but the data may indicate that these compounds represent biotransformation products of the methyl ethyl ketone used in this study. However, the data might also represent

contamination of the methyl ethyl ketone used in this study inasmuch as the authors did not present any information on the source or purity of their sample. This investigation demonstrated that methyl ethyl ketone is rapidly absorbed through the skin and is rapidly excreted in the expired air.

In 1978, DiVincenzo et al [45] reported on the respiratory uptake, excretion, and skin absorption of METHYL n-BUTYL KETONE in humans. Three men, aged 22-53 years, were exposed to air containing methyl n-butyl ketone at 100 ppm (410 mg/cu m) for 4 hours and at 10 or 50 ppm (41 or 205 mg/cu m) for 7.5 hours with a half-hour lunch break after 4 hours of exposure. For skin exposures, the absorption cell method of Munies and Wurster [43] was used to determine the absorption of liquid 14C-methyl n-butyl ketone and the influence of methyl ethyl ketone on the absorption of methyl n-butyl ketone in a 9:1 mixture (by volume). Fifteen milliliters of methyl n-butyl ketone or the ketone mixture, each containing 20 microcuries of 1-14C-methyl n-butyl ketone, was placed in contact with a shaved area on the inner forearm for 60 minutes. Precautions were taken to ensure that the ketones were not inhaled. Skin absorption was calculated from the 12-hour cumulative excretion of radiolabeled methyl n-butyl ketone in breath and urine. Two volunteers also ingested 2 microcuries of 1-14C-methyl n-butyl ketone in a dose of 0.1 mg/kg. The 12-hour cumulative excretion of radioactivity in breath and urine was compared with the 12-hour excretion from volunteers exposed by skin contact.

In humans exposed to methyl n-butyl ketone at 10 and 50 ppm for 7.5 hours, the mean breath concentration was 1.4 and 9.3 ppm (5.7 and 38.1 mg/cu m), respectively [45]. Fifteen minutes after exposure at 10 and 50

ppm, the expired air contained 0.1 and 0.5 ppm (0.4 and 2.0 mg/cu m), respectively, and, 3 hours after exposure at 50 and 100 ppm, no methyl n-butyl ketone was found in the expired air. Exposure to methyl n-butyl ketone at 100 ppm for 4 hours produced an average breath concentration of 22 ppm after 2 hours of exposure. The authors noted that between 75 and 92% of the vapor inhaled was absorbed, with greater retention at lower concentrations.

During and after exposure at 10 or 50 ppm, no methyl n-butyl ketone was found in the serum; however, it was detectable during exposure at 100 ppm [45]. Neither methyl n-butyl ketone nor its metabolites were detected in the urine during or after exposure. However, 2,5-hexanedione was found in the urine for 1-3 hours after exposure.

Two volunteers, given methyl n-butyl ketone orally, excreted a maximum amount of 14C-labeled carbon dioxide at 4 hours after exposure. Eight days after the subjects received methyl n-butyl ketone, 39.5% of the dose had been excreted in the breath, while 26.3% of the dose had been recovered in the urine.

Methyl n-butyl ketone was readily absorbed through the skin, both alone and in combination with methyl ethyl ketone. When only methyl n-butyl ketone was applied, two volunteers absorbed 16.0 and 26.8 mg, respectively, about 0.1% or more of the amount applied; when the mixture was applied, the amount of total solvent absorbed was reported as 14.0 and 18.7 mg. The authors reported that the absorption rates ranged from 4.2 to 8.0 μg/minute/sq cm for pure methyl n-butyl ketone and the mixture with methyl ethyl ketone. However, it is not certain that the total solvent absorbed from the mixture contained methyl ethyl ketone and methyl n-butyl

ketone in a 9:1 ratio, since radiolabeled methyl ethyl ketone was not used.

The authors [45] concluded that methyl n-butyl ketone was readily absorbed through the lungs, gastrointestinal tract, and the skin and that it was metabolized by at least two pathways, one forming respired carbon dioxide and the other forming 2,5-hexanedione. The major metabolite was respiratory carbon dioxide.

DiVincenzo and colleagues [45] pointed out that the absorption of methyl n-butyl ketone through human skin can be substantial. Assuming that the surface area of the hands is about 0.074 sq m and that the rate of absorption of methyl n-butyl ketone was 5 μg/minute/sq cm, they calculated that 222 mg would be absorbed through the skin in 1 hour. By comparison, exposure to methyl n-butyl ketone at 25 ppm for 1 hour by inhalation would result in absorption of 92 mg, assuming a minute volume of 20 liters/minute and 75% absorption by the lungs. This study, then, demonstrates that percutaneous absorption can be an important route of exposure to methyl n-butyl ketone.

## Epidemiologic Studies

In 1973, NIOSH was involved in an intensive and concerted occupational health investigation involving several state, Federal, and private organizations [46]. The purpose of this investigation was to determine the causative agent in an outbreak of peripheral neuropathy in workers employed in a coated-fabric plant. Allen et al [37] and Billmaier et al [38] reported their findings on this outbreak. Clinical findings from these workers and three typical cases of peripheral neuropathy, as reported by Allen et al [37], have been described in Effects on Humans.

Billmaier et al [38] also presented data on the same population, although they reported slightly different figures.

Additional cases of suspected neuropathy were initially identified in print department workers through clinical examination and a short neurologic history [38]. Workers suspected of having neuropathy received electrodiagnostic tests, including electromyogram and nerve conduction studies. Because these tests are objective and sensitive, the investigators then decided to use electromyograms and nerve conduction tests to screen all workers at the plant for evidence of subclinical peripheral neuropathy after slight abnormalities were found in the tests of selected workers not employed in the print department.

The electromyograms and nerve conduction tests of 192 of the 1,157 workers examined (17%) had abnormalities that could be associated with peripheral neuropathy [38]. After the employees received clinical evaluations, the investigators classified findings on these 192 workers by using a rating scale based on signs, symptoms, and electrodiagnostic tests. They reported that findings from 72 workers were within normal limits, 24 were not indicative of any definite abnormality, 28 were indicative of suspected abnormality, and 68 were indicative of peripheral neuropathy.

Using data from questionnaires or from company records, Billmaier et al [38] determined that, of those workers with definite evidence of peripheral neuropathy, 21.9% were from the print shop (38 of 173) and only 3.0% were from other departments (30 of 984). The difference between the percentages is statistically significant ($P<0.001$, using a chi-square test). Twenty of the 68 workers had diabetes or other conditions that can cause or contribute to neuropathy; 2 worked in the printing department and

18 worked in nonprinting departments. None of the workers in the nonprinting departments had severe peripheral neuropathy. Of the 38 workers from the print department with peripheral neuropathy, 27 operated the printing machines, 10 were helpers, and 1 washed ink pans by hand with recovered solvent. Nine of these workers had severe peripheral neuropathy. Operators spent virtually all of their time, and the helpers spent about half their time, near the printing machines when they were running. The number of print-department workers developing neuropathy, by job category, is compared with data from other departments in Table III-2.

Neuropathy was more prevalent in those who ate on the job and in those who worked overtime [38]. Printing department workers who developed peripheral neuropathy ranged from 20 to 57 years of age and had worked in the area for 5 weeks to 27 years. However, printing department workers who developed peripheral neuropathies did not differ significantly in either age or length of employment from those who did not develop the condition ($P>0.05$). Workers with peripheral neuropathy from other departments tended to be older than affected workers from the printing department ($P<0.05$) and older than workers in the other departments who did not develop neuropathy ($P<0.05$).

Symptoms were first noticed by 89% of the workers (34 of 38) between December 1972 and September 1973 [38]. These symptoms started most frequently in the summer months. In contrast, only 53% of the workers (16 of 30) in the other departments first noticed symptoms of neuropathy between December 1972 and September 1973, and the onset of symptoms was distributed more evenly throughout the 10 months. The condition of all

TABLE III-2

OCCURRENCE OF NEUROPATHY IN EMPLOYEES EXPOSED TO METHYL n-BUTYL KETONE IN PRINT AND NONPRINT DEPARTMENTS

| Group | Ill | Not Ill | Total |
|---|---|---|---|
| Nonprint departments | 30* | 954 | 984 |
| Print department (total) | 38** | 135 | 173 |
| Operators*** | 27 | 42 | 69 |
| Helpers*** | 10 | 49 | 59 |
| Foremen | - | 21 | 21 |
| Service helpers | 1 | 15 | 16 |
| Not known | - | 8 | 8 |
| Total, all departments | 68 | 1,089 | 1,157 |

*Includes 18 persons with diabetes or other conditions that can cause or contribute to neuropathy
**Includes 1 person with diabetes and another on isoniazid therapy
***Operators required to be close to the printing modules virtually 100% of their time had a significantly higher incidence of peripheral neuropathy ($P<0.001$) than helpers who spent about 50% of their time at the printing machines.

Adapted from reference 38

employees with peripheral neuropathy who worked in the print department improved after they were removed from exposure.

The investigators [38] tentatively concluded that the incidence of peripheral neuropathy in workers from other departments represented a

background level in a working population. They cautioned, however, that these workers were not a true control group, since the condition of workers in other departments with peripheral neuropathies improved when they were away from work.

To identify the agents most likely associated with the development of neuropathy, the investigators [38] obtained information on work practices and production, including any changes that might have occurred. The inks used in the printing department contained resins, stabilizers, plasticizers, pigments, and solvents, but the investigators noted that mists were not formed from the inks. This statement was apparently based on visual observation. They concluded that the workers were exposed primarily to solvents by skin contact and to solvent vapors by inhalation. The investigation revealed that apparently there had been no recent increase in the concentration of any of the airborne compounds used in the printing process. The substitution of methyl n-butyl ketone for methyl isobutyl ketone was the only major process change that had occurred in the past 7 years. To comply with community air pollution requirements, plants in other states owned by the same company had begun to substitute methyl n-butyl ketone for methyl isobutyl ketone. (According to the authors, methyl isobutyl ketone is photochemically reactive and thus can be a factor in the formation of smog.) At this plant, substitution of methyl n-butyl ketone for methyl isobutyl ketone began in August 1972 and was completed in January 1973.

Five or 10-minute area samples were taken near 9 of the 17 printing machines and analyzed by gas chromatography for 9 solvents (methyl ethyl ketone, methyl n-butyl ketone, methyl isobutyl ketone, hexane, toluene,

xylene, methyl alcohol, acetone, and mineral spirits) and for methyl methacrylate [38]. Average concentrations of airborne methyl ethyl ketone were 331 ppm (976 mg/cu m) in front of the printers (range 104-670 ppm; 307-1,976 mg/cu m), 516 ppm (1,522 mg/cu m) in back of the printers (range 85-763 ppm; 251-2,250 mg/cu m), and 147 ppm (434 mg/cu m) in the nearby "wind-up" area (range, 39-338 ppm; 115-997 mg/cu m). The average air concentrations of methyl n-butyl ketone were 9.2 ppm (37.7 mg/cu m) in front of the printers (range 2.3-21.7 ppm; 9.4-89.0 mg/cu m), 36.0 (147.6 mg/cu m) ppm in back of the printers (range 2.5-156.0 ppm; 10.2-639.6 mg/cu m), and 6.1 ppm (25.2 mg/cu m) in the wind-up area (range 1.0-17.5 ppm;4.1-71.8 mg/cu m). The concentrations of the other eight airborne compounds were stated by the authors to be very low [38]. The investigators also found that the workers had not worn respirators or gloves, had eaten in the work areas, had washed their hands with solvent, and had used rags soaked with solvent to clean equipment and machinery.

Another report [47] indicated that no cases of neuropathy were found at a similar plant that used methyl ethyl ketone but not methyl n-butyl ketone. The results of electrodiagnostic studies of 21 workers in that plant were essentially normal. However, tetrahydrofuran was also used on occasion at the plant where cases of neuropathy developed. It was not used at the other plant.

Billmaier et al [38] and Allen et al [37] concluded that the outbreak of peripheral neuropathy in printing department workers was probably associated with exposure to methyl n-butyl ketone. Most of the printing department workers with peripheral neuropathy first noticed symptoms during the summer of 1973, about 6 months after the substitution of methyl n-butyl

ketone for methyl isobutyl ketone was completed. Production had been very limited, but no new cases of peripheral neuropathy were identified after methyl n-butyl ketone had been removed from the printing process. The authors stressed that exposures to airborne methyl n-butyl ketone near the printer were substantially below those recommended in the Threshold Limit Value (TLV) list.

## Animal Toxicity

### (a) General Effects

#### (1) Acetone

Studies conducted in the 1920's [48,49] indicated that single injections of acetone in a variety of experimental animals produced depression of the respiratory and vasomotor centers. In 1920, Sollmann [50] demonstrated that, when rats consumed 1.8 ml/kg of acetone/day, growth and food consumption were reduced. No rats died after 4 months of exposure. In 1927, Walton et al [51] compared the toxicities of diacetone alcohol and acetone. Diacetone alcohol was considered to be a polymer of acetone by the authors. Rats were injected iv with various amounts of the ketones. The authors concluded that diacetone alcohol was somewhat more toxic than acetone because narcosis developed more rapidly and there was a more constant depression of respiration. Both substances also decreased blood pressure.

DiVincenzo et al [42] exposed three male beagle dogs to acetone vapor at concentrations of 100, 500, and 1,000 ppm (237, 1,185, and 2,370 mg/cu m) for 2 hours [42]. A comparison of data from breath and blood samples from the dogs with the human data presented earlier showed that the dogs

absorbed about five times more acetone than did humans on a weight-corrected basis, but the breath concentrations were significantly higher in humans at similar intervals in the study. The postexposure blood acetone concentrations of the dogs were similar to those of humans, and the calculated half-life was also about 3 hours.

(2) Methyl Ethyl Ketone

In 1935, Patty and associates [19] described the effects of exposure to methyl ethyl ketone on guinea pigs. According to the manufacturer, the methyl ethyl ketone was 92.3% ketone as determined by acetylation. Information on impurities was not given.

Guinea pigs in groups of six were exposed to airborne methyl ethyl ketone at concentrations of approximately 10.0, 3.3, 1.0, and 0.33% by volume, as determined by an iodometric method, for various durations up to 810 minutes [19]. Twenty-four guinea pigs served as controls. The organs of animals that died during exposure and of some animals killed on the 4th and 8th days after exposure were examined macroscopically.

The authors [19] reported that the signs of toxicity exhibited by the animals were, in the order of occurrence, irritation of the nose and eyes, tearing, incoordination, narcosis, gasping, and death. The guinea pigs exposed to methyl ethyl ketone at 0.33% showed no abnormal signs during or after 810 minutes of exposure. Those exposed at approximately 1.0% showed irritation of the nose in 2 minutes and eyes in 4 minutes, tearing in 40 minutes, incoordination in 90 minutes, and unconsciousness in 240-280 minutes, but no gasping respiration or deaths occurred during or after 810 minutes of exposure. At the two higher concentrations of methyl ethyl ketone, the exposure time before these signs of toxicity appeared was much

shorter, and deaths occurred in 200-260 minutes at 3.3% and in 45-55 minutes at 10%. The authors did not specify the number of animals that died after each exposure.

The guinea pigs that died during exposure had emphysema, slight congestion in the brain, and marked congestion of the systemic organs, especially in the lungs [19]. All guinea pigs exposed at 10.0% for more than 30 minutes developed corneal opacities. These diminished, and they had nearly disappeared in most animals 8 days after exposure. The guinea pigs killed immediately after exposure of up to 180 minutes to methyl ethyl ketone at 3.3 and 10% had slight congestion in the brain and moderate congestion of the lungs, liver, and kidneys. These findings were absent in nearly all animals killed for necropsy 4-8 days after exposure. Whether this suggests reversibility of the morbid changes or differential susceptibility of test animals, eg, early deaths among animals with preexisting changes, is not clear.

These results show that methyl ethyl ketone at a concentration of 5-10% was dangerous to the life of guinea pigs in 30-60 minutes and that 0.3% was the maximum concentration that could be tolerated for several hours without serious disturbance [19]. It was not clear whether death was caused by irritation of the lungs or by narcosis. Methyl ethyl ketone has warning properties (eye and nose irritation) in concentrations that were apparently otherwise harmless to guinea pigs exposed for several hours.

(3) Methyl n-Propyl Ketone

In 1936, Yant et al [52] reported the effects of methyl n-propyl ketone on guinea pigs. Groups of six guinea pigs of unspecified sex and weight were exposed to methyl n-propyl ketone at concentrations of

1,500, 5,000, 13,000, and 50,000 ppm (5,250, 17,600, 45,760 and 176,000 mg/cu m) as determined by an iodometric method for up to 810 minutes. Twenty-four guinea pigs served as controls. The organs of some guinea pigs were examined macroscopically. Since the saturation concentration of the compound at 25 C is 21,000 ppm (73,920 mg/cu m), some of the compounds may have been present in particulate form at the higher exposures, even though they were apparently produced at 30 C.

The guinea pigs exposed at 1,500 ppm had no abnormal signs during the 810-minute exposure [52]. At 5,000 ppm, nose and eye irritation occurred in 3 minutes, tearing in 5 minutes, incoordination in 270 minutes, unconsciousness in 460-710 minutes, and labored breathing in 570-710 minutes, but no guinea pigs died during or after the exposure. The authors noted that the time of onset for these signs decreased rapidly with increases in concentration and that death occurred after 50 minutes of exposure at 50,000 ppm. The authors did not mention the number of animals in each group with these signs, but they did report that animals that did not die during exposure survived the 4- or 8-day observation period after exposure.

Animals that died during the exposure had slight congestion of the brain and marked congestion of the systemic organs, including lungs that were emphysematous, edematous, and markedly congested [52]. Animals with marked incoordination, narcosis, and a gasping-type respiration that were killed immediately after exposure had little or no congestion of the brain and slight to moderate congestion of the lungs, liver, and kidneys. These findings were absent in nearly all animals killed for necropsy 4-8 days after exposure. No gross abnormalities were found in animals exposed to

methyl n-propyl ketone for 270 minutes at 5,000 ppm and for up to 810 minutes at 1,500 ppm.

These results [52] show that exposure to methyl n-propyl ketone at a concentration of 50,000 ppm for 30-60 minutes was lethal to guinea pigs. The authors' findings show that methyl n-propyl ketone caused death by narcosis and that the principal gross abnormalities were congestion, edema, and hemorrhage of the lungs, liver, and kidneys of the guinea pigs. The authors noted that a concentration of 1,500 ppm of methyl n-propyl ketone could be tolerated by guinea pigs for several hours with only slight signs or no signs at all.

(4) Methyl Isobutyl Ketone

MacEwen et al [53] exposed rats, mice, dogs, and monkeys for 24 hours/day to methyl isobutyl ketone at concentrations of 100 or 200 ppm (410 or 820 mg/cu m) for 2 weeks and, in an experiment designed to evaluate toxicity under spacecraft cabin conditions, exposed dogs, rats, and monkeys to methyl isobutyl ketone at approximately 100 ppm for 90 days. The 2-week preliminary range-finding experiments were conducted in an altitude chamber at normal atmospheric pressure with an airflow of 40 cu ft/minute and a temperature of 22 C. Gas-liquid chromatography was used to determine the concentrations every 5 minutes from samples collected near the breathing zone of dogs. Four monkeys, 8 dogs, 40 mice, and 50 rats were exposed to methyl isobutyl ketone at each concentration and 3 monkeys, 4 dogs, 20 mice, and 25 rats, used as controls in identical inhalation chambers, received no ketone exposure. One monkey in each group was implanted with cortical electrodes for evaluation of CNS effects. Body weights and the results of clinical chemistry, hematologic, and electroencephalographic

(EEG) tests were determined before and after exposure. Organ-to-body weight ratios, macroscopic and microscopic tissue examinations, and blood pH and gas tests were performed. Spontaneous activity measurements were taken, and adverse signs were noted during the exposure.

The only findings in which exposed animals differed significantly from controls were heavier kidneys and higher kidney-to-body weight ratios in the rats exposed at 100 ppm and the higher liver and kidney weights and correspondingly increased organ-to-body weight ratios in rats exposed at 200 ppm [53]. Microscopic examination of the kidneys of exposed rats showed toxic nephrosis of the proximal tubules at both 100 and 200 ppm. The authors concluded that the kidney was the primary organ affected by methyl isobutyl ketone.

MacEwen et al [53] then conducted a 90-day exposure experiment. Two male Rhesus monkeys, 8 male beagle dogs, and 100 male Wistar rats were exposed for 24 hours/day at 5 psia (about one-third of an atmosphere) to methyl isobutyl ketone at about 100 ppm (410 mg/cu m). Controls consisted of an identical number of unexposed male animals. Every other week, starting 1 month before the exposure began, the dogs and monkeys were weighed and blood samples were taken for various hematologic and clinical chemistry determinations. Liver function tests were performed before and immediately after exposure, and serum acid phosphatase and serum glucuronidase determinations were made before exposure began and on the 30th and 60th days of exposure. After the 90-day exposure, two dogs were observed for 60 days to determine if the effects were reversible. The other dogs were killed and examined grossly, and organ samples were examined microscopically. Rats were weighed before exposure and every

other week during the exposure. Two exposed rats and two control rats were killed at weekly intervals for 3 weeks and then every other week thereafter, and their organs were grossly examined. After the rats had been exposed for 2 weeks, 10 were removed from exposure, and 2 of them were killed every 2 weeks and examined to determine if the kidney lesions seen in the short-term studies were reversible. At the end of the 90-day study, 10 rats were saved and were later killed serially for reversibility studies, 10 were killed for microscopic examination of tissues, and the remaining rats were killed and organ weights were determined.

The results of clinical chemistry and hematologic measurements in dogs and monkeys showed no significant differences between experimental and control animals [53]. Serum glucuronidase activity was much higher in exposed monkeys than in controls, but this condition also existed in baseline measurements. The authors did not relate this condition to methyl isobutyl ketone exposure. No differences between exposed and control dogs were found in sections of heart, lungs, brain, liver, spleen, kidneys, adrenal gland, or pituitary gland tissues. The only microscopic change found in monkeys was focal chronic inflammation of the kidneys in one exposed animal.

There was no statistically significant difference in the weight gained by exposed and control rats [53]. As in the 2-week exposure, the exposed rats had significantly heavier livers and kidneys ($P<0.01$) and corresponding increases in organ-to-body weight ratios for these two organs. All exposed rats showed hyaline droplet degeneration of the proximal tubules of the kidneys with occasional foci of tubular necrosis after the 90-day exposure. Rats removed from exposure after as few as 15

days also showed some kidney changes, although hyaline droplets grew larger with time. No adverse changes were observed in rat livers. Kidney tubular damage was reversible in those rats observed for 60 days after being exposed to methyl isobutyl ketone for 15 days. The rats exposed for 90 days recovered but did so more slowly than those exposed for less time.

(5) Diisobutyl Ketone

In 1953, Carpenter et al [20] studied the effects of single and repeated exposures to diisobutyl ketone on rats and guinea pigs. For single exposures, groups of six Sherman rats were exposed to diisobutyl ketone at a concentration of 2,000 ppm (11,640 mg/cu m). Seven of 12 female rats died after a single 8-hour exposure to diisobutyl ketone at 2,000 ppm, but all 6 exposed males survived [20]. The experiment was repeated with Carworth Farms Wistar rats using an undescribed number of males and females. All survived a single 8-hour exposure to diisobutyl ketone at 2,000 ppm. The authors concluded that the effects noted were due to differences in susceptibility between strains of rats.

In repeated exposure studies, groups of 15 male Sherman rats weighing 145-197 g and 15 females weighing 128-162 g were exposed for 7 hours/day, 5 days/week, for 6 weeks to diisobutyl ketone at concentrations of 125, 250, 530, 920, and 1,650 ppm (728, 1,455, 3,085, 5,354, and 9,603 mg/cu m), measured 4 times/day with an interferometer. In addition, groups of 10 male guinea pigs weighing 288-360 g were exposed at 125 or 250 ppm. Exposed animals and unexposed controls were weighed weekly, and the liver and kidneys were weighed at the termination of the study. The lungs, liver, kidneys, spleen, and adrenals of animals exposed to diisobutyl ketone at 250, 530, 920, and 1,650 ppm were examined microscopically,

except that only lungs, liver, and kidneys in animals exposed at 125 ppm were examined.

Exposure to diisobutyl ketone at 1,650 ppm killed all 15 female rats during the 1st day of exposure [20]. Only 2 of 15 male rats died, but all the males were prostrate at the end of the 1st day, and about half had poor coordination at the end of the 2nd day. These signs were not observed during the other 28 days of exposure. The 13 males that survived the 30-day exposure had reportedly significantly lower body weights and higher kidney and liver weights than did the controls (no P value given). No major microscopic changes were noted in the adrenals, kidneys, liver, lungs, and spleen of survivors, but five male rats had cloudy swelling of the liver, and eight had moderate lung congestion. The authors noted that 5 of 15 control males had similar lung involvement. Major lung, kidney, and liver abnormalities were found in the male and female rats that died during the 1st day of exposure.

No rats died when they were exposed for 30 days to diisobutyl ketone at 125, 250, 530, or 920 ppm [20]. Liver and kidney weights were significantly increased in male and female rats exposed to diisobutyl ketone at 920 and 530 ppm (no P value given). Similar organ weight increases occurred in females exposed at 250 ppm. There were no abnormalities noted in rats exposed at 125 ppm. Male guinea pigs had significantly lower liver weights after exposure to diisobutyl ketone at 250 ppm, but no P value was given [20]. No toxic effect in rats or guinea pigs was noted at 125 ppm.

(6) Cyclohexanone

In 1943, Treon et al [54] reported on the effects of cyclohexanone exposure on rabbits and monkeys. Groups of four rabbits of unspecified sex, age, and weight were exposed to cyclohexanone at average concentrations of 190-1,414 ppm (762-5,670 mg/cu m) for 6 hours/day, 5 days/week, for 10 weeks, and at 3,082 ppm (12,359 mg/cu m) for 6 hours/day, 5 days/week, for 3 weeks. In addition, one rhesus monkey was exposed at an average concentration of 608 ppm for 6 hours/day, 5 days/week, for 10 weeks. Cyclohexanone concentrations were determined colorimetrically throughout the exposures. Animal weights were determined daily, and microscopic examinations were performed 2 months after the termination of exposure.

Only the rabbits exposed at 3,082 ppm lost weight [54]. The body temperatures in exposed animals were similar to those of control animals, except in animals exposed at 3,082 ppm. In this case, the mean daily decrease was more than five times that observed in controls. Two of the four rabbits died at 3,082 ppm. They had no convulsions or tremors, but narcosis and incoordination were observed. Rabbits exposed at 3,082 ppm and at 1,414 ppm had distended ear veins, excess salivation, and conjunctival irritation throughout the daily exposures. Although narcosis and incoordination were not seen at 1,414 ppm, there was some lethargy. Exposures at 309 and 773 ppm (1,239 and 3,100 mg/cu m) produced less ocular irritation than did the exposures at higher concentrations. Exposure at 190 ppm produced no noticeable behavioral abnormalities. Cyclohexanone at 190 ppm induced barely demonstrable degenerative changes in the liver and kidneys of rabbits exposed for 300 hours. The authors reported that the

monkey exposed at 608 ppm for 300 hours had extensive injury to the heart muscle, lungs, liver, and kidneys.

The work of Treon et al [54], although it lacks experimental detail, does provide evidence that repeated exposure of rabbits to cyclohexanone at 190 ppm produces slight liver and kidney damage. The effects in the one monkey may not be appropriately attributed to the exposure, because it was suffering from a chronic bronchopulmonary infection.

(7) Mesityl Oxide

Hart et al [55] exposed mice and rabbits to saturated atmospheres of mesityl oxide. Concentrations were varied by changing the atmospheric temperature. Mice were exposed at concentrations ranging from 0.6 to 2.4%. Toxic signs included eye and nose irritation, gasping respiration, rocking convulsions, narcosis, vasodilatation, cyanosis, and death. Deaths occurred in 23 minutes after exposures at 2.4%, in 84 minutes after exposure at 1.3%, and in 135 minutes after exposure at 0.6%. Rabbits showed only eye and nose irritation when they were exposed at 1.3% for 30 or 90 minutes.

Mice and rabbits were also repeatedly exposed to mesityl oxide at 1.3% [55]. Ten mice were exposed for 15 minutes daily. After 5 exposures, none had died, and, after 11 exposures, 3 had died. When the exposures were increased to 30 minutes/day, all of 10 mice died within 6 days. Six rabbits showed only slight eye and nose irritation when they were exposed for 30 minutes/day for 15 days; however, when the exposures were increased to 60 minutes/day, the six rabbits developed spastic paralysis within 10 days and died 7-11 days after the paralysis was first observed.

The authors [55] also investigated the effects of mesityl oxide applied to the skin. Only 1 of 10 mice died when 0.1 ml of mesityl oxide was applied to the intact skin in the lumbar region; however, when 0.5 ml was applied, narcosis developed within 15 minutes, and death occurred in 3-9 hours.

Hart et al [55] found no significant abnormal changes by gross examination of the organs of mice that died after single exposures to mesityl oxide; however, mice that died after repeated exposures had necrotic spots in the liver, lung hemorrhages, and alimentary tract distention. Microscopic examination revealed necrosis, parenchymatous atrophy, and immature polynuclear cells in the liver. Some tubular degeneration in the kidneys and edema and hemorrhage in the lungs were also noted. Similar microscopic changes were found in rabbits after repeated exposures to mesityl oxide. The authors concluded that a concentration of about 0.7% of mesityl oxide was the maximum that could be inhaled by mice for an hour without fatal results. In rabbits, however, no deaths were observed at a concentration of 1.3%.

In 1942, Smyth et al [21] reported the effect on rats and guinea pigs after 6 weeks of 8-hour daily exposures (5 days/week) to mesityl oxide at 50, 100, 250, or 500 ppm (201, 402, 1,005, or 2,010 mg/cu m). Ten male Wistar rats and 10 guinea pigs of both sexes were used at each exposure concentration. No distinction was made between species in reporting the results because, according to the authors, the results differed only slightly. Nose and eye irritation was noted at the two higher exposure concentrations but not at 50 or 100 ppm. Exposure at 500 ppm was stopped after 10 days because of high mortality (13/20, 65%). No deaths occurred

in the groups exposed at 50, 100, or 250 ppm. Poor growth was noted in the survivors of the 250-ppm exposure but not in those exposed at 50 or 100 ppm. Blood changes were not apparent at any exposure concentration. Albumin was noted in the urine at the two higher concentrations but not at the lower two. Adverse liver and kidney changes were noted in all but the lowest exposure group. These changes increased proportionally with the dose. Liver damage was confined to congestion, but kidneys had dilated Bowman's capsules and swollen convoluted tubular epithelium. The lungs were often congested. The authors also determined that, in animals that died from the 500-ppm mesityl oxide exposures, the cause of death was the anesthetic effect on the circulatory and respiratory systems.

Smyth et al [21] supplemented their repeated-exposure studies by exposing rats and guinea pigs to mesityl oxide at high concentrations for short periods. At 13,000 ppm (52,130 mg/cu m), all 20 animals died after an exposure of 1 hour; at 2,500 ppm (10,050 mg/cu m), all the animals died after an 8-hour exposure; at 1,000 ppm (4,020 mg/cu m), 68% of the exposed animals died after 8 hours; and at 500 ppm, 30% died after 8 hours. Deaths resulted from narcosis; dead animals had some evidence of lung irritation.

The authors [21] concluded that mesityl oxide acted primarily as a narcotic. They also observed that, in rats and guinea pigs, "no effect whatever" was seen after 30 exposures to mesityl oxide for 8 hours at a concentration of 50 ppm.

In 1949, Carpenter et al [56] reported the results of an experiment to determine the extent of the acute toxicity of industrial compounds, including mesityl oxide. Groups of six male or female albino Sherman rats were exposed for 4 hours to compounds at successively higher concentrations

until two, three, or four of the animals died during a 14-day observation period. The investigators found that exposures to mesityl oxide at about 1,000 ppm (4,020 mg/cu m) killed two to four of the six rats in 14 days. They concluded that mesityl oxide should be considered a moderate hazard.

(8) Diacetone Alcohol

Lehmann and Flury [57] cited the results, but not the experimental details, of an unpublished study by E. Gross on the toxicity of diacetone alcohol. Repeated sc injections of 0.08 ml in rats caused exhaustion, but the animals recovered. Three rabbits given 2 ml of diacetone alcohol orally 12 times/day had kidney injury, slight narcosis, and albumin and sugar in the urine. One of the three rabbits died. Inhalation of diacetone alcohol at 2,100 ppm (9,975 mg/cu m) for 1-3 hours by mice, rats, rabbits, and cats caused restlessness, signs of irritation, head colds, and excitation followed by sleepiness. Rabbits also had kidney injury.

As was mentioned in the discussion of animal toxicity of acetone, there is evidence that diacetone alcohol caused earlier narcosis and a more constant depression of respiration in rats injected by vein than did acetone.

(9) Isophorone

Smyth et al [21], in 1942, described the toxicity of isophorone in rats and guinea pigs. Ten male Wistar albino rats (weighing 90-120 g) and 10 guinea pigs (weighing 250-300 g) were exposed to isophorone at concentrations, as determined by an interferometer, ranging from 25 to 500 ppm for 8 hours/day, 5 days/week, for 6 weeks. Weights were recorded weekly, blood cell changes were analyzed, and nose and eye

irritation was noted during exposures. Pooled urine samples were examined at least once, and microscopic examination was performed on selected animals.

The effects in the two species differed only slightly, with the rats being slightly more sensitive [21]. One animal exposed at an unknown but high concentration developed corneal necrosis. Chronic conjunctivitis and nasal irritation, sometimes followed by the appearance of a bloody exudate, were caused by repeated exposure to isophorone at a concentration of 500 ppm (2,825 mg/cu m) but not at 200 ppm (1,130 mg/cu m). Lungs were irritated by isophorone at unspecified concentrations. These concentrations produced congestion, capillary leakage, and desquamation of the epithelium that was not further described by the authors.

Growth was inhibited in all animals exposed to isophorone at concentrations of 100, 200, and 500 ppm (565, 1,130, and 2,825 mg/cu m) [21]. No blood cell changes were observed in animals exposed to isophorone at a concentration of 25, 50, 100, or 200 ppm (141, 282, 565, or 1,130 mg/cu m), although unspecified blood cell changes were noted in some animals exposed to isophorone at 500 ppm. Only animals exposed to isophorone at a concentration of 500 ppm excreted albumin in the urine. In addition, the urine of animals exposed to isophorone at a concentration of 500 or 200 ppm contained a substance that reduced Benedict's solution. The authors suggested that a detoxification product was responsible because isophorone alone did not reduce Benedict's solution.

Many animals exposed to isophorone had pale or brown kidneys, pale livers, congested spleens and lungs, and discolored bile [21]. However, exposure at 25 ppm produced neither microscopic abnormalities nor deaths.

Liver changes were reported in one of six animals exposed to isophorone at 50 ppm, in none of seven at 100 ppm, in none of six at 200 ppm, and in one of eight at 500 ppm. Kidney changes were found in four of six animals exposed at 50 ppm, in six of eight at 100 ppm, in four of seven at 200 ppm, and in six of nine at 500 ppm. No further information was provided on the liver and kidney changes.

All 20 animals survived exposure to isophorone at a concentration of 50 ppm, 2 of 16 died at 100 ppm, 3 of 18 died at 200 ppm, and 9 of 20 died at 500 ppm [21]. Animals that were killed by repeated exposure to isophorone had severely injured kidneys, lungs, or both. The kidneys of survivors were congested, and had dilation of Bowman's capsule and cloudy swelling in the convoluted tubules. Lungs were congested and had desquamation of bronchial epithelium sometimes followed by pneumonia. The liver was less affected than the lungs or kidneys, but it was congested with prominent Kupffer cells and cloudy swelling. The authors concluded that repeated exposure to isophorone had caused toxic effects, primarily on the kidneys and lungs, and that isophorone at 25 ppm caused no apparent adverse effects after exposures for up to 6 weeks. In an earlier study, Smyth and Seaton [58] found that single exposures to isophorone killed rats by narcosis, probably by paralysis of the respiratory center.

(b) Comparative Effects

In 1940, Specht et al [34] reported on an extensive study on the acute toxicity of a number of ketones in guinea pigs. In one series of experiments, five members of a homologous series--acetone, methyl ethyl ketone, methyl n-propyl ketone, methyl n-butyl ketone, and methyl n-amyl ketone--were compared. In another series of experiments, four six-carbon

ketones--methyl isobutyl ketone, methyl n-butyl ketone, cyclohexanone, and mesityl oxide--were compared. Measurements included rectal temperature, respiratory rate, and heart rate during each experiment. The authors attempted to correlate clinical signs and narcotic effectiveness with such physical properties as the number of carbon atoms, oil-to-water partition coefficients, and surface tension. The concentration of each ketone was determined by iodine titration, except for cyclohexanone, which was determined by titration of hydrochloric acid liberated after oxime formation.

Ten female guinea pigs of mixed stock weighing 400-600 g were exposed to the ketones at various concentrations and duration as shown in Table III-3 [34]. Ten unexposed guinea pigs served as controls. The clinical signs were reported during the experiments at only one representative concentration. Squinting, tearing, and rubbing of the eyes were considered to represent irritation of the cornea and conjunctiva, whereas sneezing, coughing, salivation, retching, and rubbing of the nose and mouth represented irritation of the buccal, nasal, and pharyngeal passages. These results, given in Table III-3, together with some apparently similar data developed by Specht and coworkers [59,60], suggest that irritative potency increases as the carbon number increases.

Specht et al [34] also reported that acetone produced immediate irritation at 50,000 ppm (118,500 mg/cu m) but no irritation at 10,000 ppm (23,700 mg/cu m). Methyl n-propyl ketone produced immediately an irritating effect at 2,500 ppm (5,925 mg/cu m) as well as at 10,000 ppm. Methyl ethyl ketone, however, produced immediate effects only at much higher concentrations. Methyl n-butyl ketone was even more irritating

TABLE III-3

IRRITATION IN GUINEA PIGS PRODUCED BY EXPOSURE TO KETONES

| Ketone | Concentration (ppm) | Duration* (min) | Eyes | | Upper Respiratory Tract | | | |
|---|---|---|---|---|---|---|---|---|
| | | | Tearing | Squinting | Salivation | Coughing | Rubbing of Nose | Nasal Discharge |
| Acetone** | 20,000 | 25 | 1 | 1 | 0 | - | 0 | - |
| Methyl ethyl ketone | 25,000 | 10 | 2 | 3 | 3 | - | 2 | - |
| Methyl n-propyl ketone | 10,000 | 10 | 4 | 3 | 4 | 3 | 0 | 3 |
| Methyl n-butyl ketone | 6,000 | 15 | 4 | 4 | 4 | 2 | 4 | 1 |
| Methyl n-amyl ketone | 2,000 | 10 | 4 | 4 | 2 | 1 | 2 | - |
| Methyl isobutyl ketone*** | 16,800 | 1 | 4 | 4 | - | 2 | 4 | - |
| Cyclohexanone | 4,000 | 10 | 4 | 4 | 4 | - | 0 | 2 |
| Mesityl oxide | 5,000 | 5 | 4 | 4 | 4 | 4 | 4 | - |

Key: 0=negative, 1=slight, 2=moderate, 3=marked, 4=extreme
*Observed effects may have occurred at any time during exposure up to time indicated.

**Adapted from reference 60
***Adapted from reference 59
Data on other ketones adapted from reference 34

than methyl n-propyl ketone, producing immediate irritation at concentrations as low as 1,200 ppm. Immediate, strong effects were also noted with methyl n-amyl ketone and mesityl oxide at all concentrations tested. Immediate irritation was not found below concentrations of 10,000 ppm for methyl isobutyl ketone, but it occurred at all concentrations tested above 10,000 ppm. The authors also noted that methyl n-butyl ketone and cyclohexanone produced a clouding of the cornea that persisted beyond the exposure period, but they did not mention whether or not it abated.

In addition to the irritant effects noted above, Specht et al [34] reported that the ketones used in this study produced narcosis, CNS depression, and respiratory dysfunction. These data are summarized in Table III-4. The values depicted represent the product of the exposure concentration and the duration of exposure (Ct product) calculated from the data presented by Specht et al. The criterion for a particular effect's being significant was arbitrary. In this case, a decrease of 30 breaths/minute, 50 heartbeats/minute, or body temperatures 4 C below controls was considered significant. The first reported time at which this decrease occurred was then multiplied by the concentration of the ketone.

The data in Table III-4 suggest that, as the number of carbon atoms in these ketones increases, there is generally a decrease in the Ct product to produce a particular toxic effect. Although there are Ct products that do not fit into this model, the general trends suggest that CNS depression increases with increasing carbon numbers. Methyl n-amyl ketone was aberrant in this respect, probably because it was not lethal at this concentration. The Ct of methyl n-amyl ketone for the first death at 5,000

TABLE III-4

Ct* PRODUCTS FOR KETONES
(X 1,000)

| Ketone Name | Concentration (ppm) | No. of Carbon Atoms | First Death** | Respiration | Pulse Rate | Rectal Temperature | Reference |
|---|---|---|---|---|---|---|---|
| Acetone | 20,000 | 3 | 26,800 (1) | 4,800 | 4,800 | 10,800 | 60 |
| Methyl ethyl ketone | 25,000 | 4 | 4,500 (1) | 750 | 2,250 | 3,750 | 34 |
| Methyl n-propyl ketone | 10,000 | 5 | 5,100 (3) | 350 | 1,400 | 1,400 | 34 |
| Methyl n-butyl ketone | 6,000 | 6 | 2,400 (2) | 780 | 360 | 780 | 34 |
| Methyl n-amyl ketone | 18,100 | 7 | No deaths in 890 min*** | 90 | 1,720 | 1,720 | 34 |
| Cyclohexanone | 4,000 | 6 | No deaths in 355 min | 120 | 1,320 | 1,320 | 34 |
| Methyl isobutyl ketone | 18,000 | 6 | 1,428 (1) | 420 | 622 | 1,008 | 59 |
| Mesityl oxide | 5,000 | 6 | 1,950 (2) | 300 | 1,200 | 1,200 | 34 |

*Ct product units in ppm-minutes
**Product unit at which first death occurred; number of deaths in parentheses
***Product was 1,400 at 5,000 ppm

ppm (a concentration not described in detail by Specht et al [34]) was calculated as 1,400 x $10^3$ ppm-minutes, a value that agrees with the above observation that carbon number and mortality are directly related.

In Table III-4, there is evidence that the relationship of mortality, CNS effects, and respiratory dysfunctions with carbon number may also apply to those six-carbon ketones (mesityl oxide, cyclohexanone, methyl isobutyl ketone) that are not straight chain ketones. Although there appears to be little correlation between the type of rearrangement (cyclization, unsaturation, or branching) and the Ct product, the Ct products are generally less than those of the five-carbon ketone, methyl n-propyl ketone. However, when these Ct products are compared with those of methyl n-butyl ketone, there are many discrepancies.

Selected animals from each exposure group were killed and examined to determine macroscopic and microscopic adverse effects on organs and tissues [34]. Occasional scattered liver cells containing fat droplets were found in a few animals. Congested liver capillaries were found in animals exposed to each of the ketones except acetone. The authors concluded that, in general, few or no significant changes were found in the liver. Each of the ketones produced slight to marked congestion of the interalveolar capillaries in the lungs. Various degrees of congestion of the interstitial capillaries of the kidneys were found in all guinea pigs. Hemorrhaging was found in the pulp of the spleen of all animals, and it was usually perifollicular in those exposed to acetone. Hemosiderosis was frequently found. Congestion of the capsular capillaries of the adrenal glands occurred in all animals except those exposed to acetone. Extravasation of red blood cells into the adrenal gland occurred in animals

exposed to methyl n-butyl ketone and methyl n-propyl ketone at 40,000 ppm. Fat droplets were present in adrenocortical cells of all animals. Congestion of the pia-arachnoid vessels and capillaries of the cerebral cortex occurred in guinea pigs exposed to methyl n-butyl ketone. The brains of other animals were not examined. No microscopic changes were observed in the heart, stomach, or pancreas.

Specht et al [34] concluded that there was no marked variation among the animals exposed to various ketones. The most consistent observation was congestion, and the organs most affected, in decreasing order, were lungs, kidneys, spleen, adrenals, and brain. Distention of renal tubules was also common, but liver congestion was considered negligible. Specht et al concluded that all of the ketones studied produced a general, progressive narcosis that best correlated with the partition coefficient between olive oil and water. Mesityl oxide was somewhat aberrant in this respect. All of the ketones produced irritation of mucous membranes and a transient reflex depression of the respiratory and heart rate that furnished a limiting index for adequate warning properties during inhalation.

Specht et al [34] presented olive oil-to-water partition coefficients for eight of the ketones. A comparison of these partition coefficients with LD50's for the ketones is given in Table III-5. Since factors such as the sex and strain of the rats used sometimes differed for the compounds tested, a detailed comparison of the LD50's is not valid.

TABLE III-5

COMPARISON OF PARTITION COEFFICIENTS
OF KETONES WITH LD50's

| Ketone | Partition Coefficient* (oil to water) | Oral LD50 in Rats (g/kg) | Sex | Reference |
|---|---|---|---|---|
| Acetone | 0.1 | 8.5 | F | 61 |
| Methyl ethyl ketone | 1.9 | 5.5 | F | 61 |
| Methyl n-propyl ketone | 16.6 | 3.7 | M | 61 |
| Methyl n-butyl ketone | 26.5 | 2.6 | M | 62 |
| Methyl n-amyl ketone | 42.2 | 1.7 | F | 61 |
| Methyl isobutyl ketone | 20.6 | 2.1 | M | 63 |
| Cyclohexanone | 24.1 | 1.5 | M | 64 |
| Mesityl oxide | 4.6 | 1.1 | - | 65 |

*Adapted from reference 34

It appears that lipophilicity and oral toxicity are directly related for the five homologous ketones. As the affinity of the ketone for the oil increases, the oral toxicity correspondingly increases. The correlation is not applicable to the nonlinear six-carbon ketones.

(c) Effects on the Skin and Eyes

Smyth et al [61,62] studied primary skin irritation produced by a number of ketones on rabbits. The authors scored the reactions produced on the clipped skin of five albino rabbits within 24 hours of application of 0.01 ml of undiluted ketone or of dilutions in water, n-propylene glycol, or kerosene. Each ketone was graded according to its irritant effect. Grade 1 produced the least visible capillary congestion in undiluted form, grade 6 produced necrosis when undiluted, and grade 10 produced necrosis from a 0.01% solution.

The grades found for the ketones were acetone, 1; methyl ethyl ketone, 2; methyl n-propyl ketone, 1; methyl n-amyl ketone, 4; methyl isoamyl ketone, 1 [61]; and methyl n-butyl ketone, 1 [62]. Further experimental details or results were not presented.

The effects of acetone and of cyclohexanone on the eyes have been studied by Rengstorff et al [66]. In one experiment, 0.5 ml of either ketone was applied to the clipped skin on the back of albino guinea pigs. Four additional guinea pigs were given sc injections of 0.05 ml of a 1:1 mixture of either ketone in saline, and 12 more were injected sc with 0.05 ml of 5% of either ketone in saline. Guinea pigs were injected with acetone or cyclohexanone three times/week for 3 weeks. Eyes were examined 60 or 90 days after the initial application of the ketone and then every 30 days for up to 6 months after the experiment began. As a control, the eyes of over 500 other guinea pigs from the same colony were examined.

Cataracts developed in guinea pigs given acetone or cyclohexanone either by injection or dermal application [66]. Of the 12 guinea pigs given acetone cutaneously for 3 weeks, two developed cataracts by the 3rd

month. Cutaneous administration of cyclohexanone produced cataracts, which were first seen in the 5th or 6th month in 3 of 12 guinea pigs. Subcutaneous administration of acetone and cyclohexanone caused cataracts to form in 7 of 16 and 2 of 16 exposed guinea pigs, respectively. Generally, the cataracts in these guinea pigs were first seen by the 3rd month and were still apparent in later examinations. However, lens damage was occasionally reversed within 3 months after being observed. No cataracts formed in the control guinea pigs. Microscopic examination of a guinea pig that developed cataracts after cutaneous exposure to acetone showed extensive lens damage. Eosinophilic deposits were found in the subcapsular areas of the lens, and the lens epithelium could not be distinguished from the capsule. The eyes of a control guinea pig showed no abnormal features.

In a second experiment, two guinea pigs of each sex and one rabbit were given 1 ml of acetone cutaneously two times/day, 5 days/week for 4 weeks, and an equal number of animals were given acetone for 8 weeks [66]. Four guinea pigs and two rabbits were given saline cutaneously and four unexposed guinea pigs served as controls. The animals' eyes were examined once a week for 8 weeks and then every other week until 6 months after the initial exposure. Cutaneously applied acetone produced cataracts in guinea pigs but not in rabbits. Two of the eight exposed guinea pigs had bilateral cataracts, while none of the controls had lens defects. It cannot be determined whether the negative findings were caused by the small number of animals used or by the rabbit being less sensitive to the ocular effects of acetone. However, these studies demonstrated the ability of acetone and cyclohexanone to produce cataracts in albino guinea pigs.

Carpenter and Smyth [67] studied the effects on the rabbit cornea of a large number of chemical agents, including acetone, diisobutyl ketone, cyclohexanone, mesityl oxide, diacetone alcohol, and isophorone. A ranking system from 1 to 10 was used by the authors to numerically score the extent of ocular damage. In a typical experiment, a variable amount of the substance was applied to the center of the corneas of normal albino rabbits. Eighteen to 24 hours later, the eye was examined in strong diffuse daylight, and damage to the corneas and irises was scored. The eye was then stained with fluorescein to determine the extent of necrosis. A score of 5 represented severe injury. This score corresponded to necrosis covering 75% of the cornea after staining or more severe necrosis covering a smaller area. The volume of the test substance also affected the score.

The authors [67] assigned an injury grade of 1 to diisobutyl ketone, a grade of 4 to isophorone, and a grade of 5 to acetone, cyclohexanone, mesityl oxide, and diacetone alcohol. Substances such as acetic anhydride and sulfuric acid (5% solution) had grades of 9, and sodium hydroxide (1% solution) had a grade of 10.

Truhaut et al [68] studied the effects of isophorone on the eyes of rabbits. The official procedure of the US Food and Drug Administration was used for this investigation (Federal Register 29:13009, September 16, 1964), except that Bourgogne rabbits were used instead of albino rabbits. This procedure, described earlier by Draize and coworkers [69], consists of instilling 0.1 ml of the test compound into the eyes of six rabbits. The eyes are then examined and the degree of injury is noted after 24, 48, and 72 hours. Either ulceration, or opacity of the cornea, inflammation of the iris, and conjunctival swelling are considered positive reactions. A test

is considered positive if four or more animals have a positive reaction. An acute ocular index rating with a maximum value of 110 is then derived [69].

Truhaut and coworkers [68] reported that four rabbits had pronounced opacity of the cornea which extended over the entire surface. All rabbits had inflammation of the eyelids and conjunctiva accompanied by a pronounced purulent discharge. Microscopic examination showed that the corneal epithelium was frequently reduced or nonexistent and sometimes had signs of ulceration. Inflamed cells in the cornea were also observed. Accordingly, the authors judged isophorone to be a moderate eye irritant. They assigned an acute ocular irritation rating of 20/110 to isophorone.

(d) Effects on the Nervous System

Mendell et al [70] exposed rats, cats, and chickens to methyl n-butyl ketone to observe its effects on the peripheral nervous system. Four Sprague-Dawley rats and four domestic cats were initially exposed to methyl n-butyl ketone at 600 ppm (2,460 mg/cu m), 24 hours/day, 7 days/week, for up to 12 weeks. Chickens were initially exposed at 200 ppm (820 mg/cu m). Exposures were later adjusted to 100 ppm (410 mg/cu m) for chickens and to 400 ppm (1,640 mg/cu m) for rats and cats to minimize complications from starvation and weight loss. Environmental conditions in the exposure chamber were maintained at a normal atmosphere. Methyl n-butyl ketone concentrations were monitored by gas chromatography. Pair-fed animals were used as the controls. Electromyographic studies were performed weekly on all cats exposed to methyl n-butyl ketone. The electromyograms were recorded from several muscles, eg, the supraspinatus, triceps, and extensor carpi, with monopolar electrodes. At the end of the experiment, exposed

animals and an equal number of control animals were killed, and selected muscles were examined by light microscopy. Thin sections of the sciatic nerve were examined by electron microscopy.

All the exposed animals developed peripheral neuropathy during the exposure [70]. The earliest sign of peripheral neuropathy in chickens was the inability to stand at 4-5 weeks. Cats dragged their limbs at 5-8 weeks and later had forelimb weakness. Rats dragged their hindlegs at 11-12 weeks. Exposed rats greatly increased their water intake.

Between 4 and 6 weeks, electromyographic examination of all exposed cats showed abnormal insertional activities accompanied by positive waves [70]. Fibrillation potentials appeared in their muscles while they were at rest and accompanied insertional activity during the 9th and 10th weeks. In all exposed cats, the ulnar nerve conduction velocity was decreased between 7 and 9 weeks to an average of 50 meters/second. (Normal velocity in that laboratory was 115.) The electromyographic changes occurred in all the muscles tested. Although a few polyphasic potentials were seen at 8-9 weeks, the amplitude of motor unit action potentials did not differ significantly from that of controls.

The authors [70] concluded that peripheral neuropathy had been induced in all three species exposed to methyl n-butyl ketone at 100-600 ppm (410-2,460 mg/cu m) for 1,440 hours (24 hours/day for 2 months). This conclusion correlated well with their earlier finding that peripheral neuropathy developed in workers exposed to methyl n-butyl ketone for 1,584 hours (22 days/month, 8 hours/day, for 9 months). They also concluded that the neuropathy observed in the animals was similar, according to clinical criteria, to that seen in affected workers who used methyl n-butyl ketone.

In both cases, the neuropathy involved predominantly motor or muscular weakness, and the nerve conduction velocity decreases noted in humans were also seen in the exposed animals.

Spencer et al [71] studied the effects of methyl n-butyl ketone and methyl isobutyl ketone on adult rats. Six rats were exposed to each ketone for 6 hours/day, 5 days/week, for 4 months. Three rats served as controls. The concentration of methyl n-butyl ketone in the exposure chamber was calculated as 2,000 ppm (8,200 mg/cu m) and determined to be 1,300 ppm (5,330 mg/cu m) when analyzed by gas-liquid chromatography. The concentration of methyl isobutyl ketone in the exposure chamber was measured at 1,500 ppm (6,150 mg/cu m) by gas-liquid chromatography; the authors noted that approximately 3% methyl n-butyl ketone was present as a contaminant. The rats were examined periodically for signs of neurologic effects. After the 4-month exposure, the rats were killed, and various nerve tissues were examined microscopically.

Slight narcosis was observed after 4 hours of exposure to methyl n-butyl ketone, and some loss of coordination was noted after 5.5 hours of exposure [71]. Slow progressive weight loss was evident from the 73rd day of exposure to the end of the exposure period. Animals developed symmetrical hindleg footdrop between the 3rd and 4th months of exposure. Severely affected rats also exhibited proximal hindleg and foreleg weakness.

Microscopic examination showed a consistent distribution of peripheral and CNS damage [71]. Degeneration of the peripheral nerve fibers was most evident in the intramuscular and distal portions, although scattered changes were evident in the sciatic nerve up to the level of the

dorsal root ganglia. The authors noted that the most prominent early nerve fiber abnormality was an axonal dilatation associated with localized fiber swelling. Longitudinal sections of nerve fibers and teased fibers showed focal, internodal, paranodal, or nodal axonal swellings. Neither internodal demyelination nor remyelination was observed.

Animals exposed to methyl isobutyl ketone for 4 months showed a normal rate of weight gain, a slight narcosis during exposure, and no signs of neurologic dysfunction [71]. Microscopic examination of CNS tissues and proximal parts of the peripheral nervous system was insignificant. Frank distal nerve fiber degeneration was not observed. However, the most distal sections of the ulnar and tibial nerves had many axons with dilated mitochondrial remnants, adaxonal Schwann cell invaginations, and case focal swellings. The authors concluded that methyl isobutyl ketone was relatively ineffective in producing neurologic dysfunction. They noted that the minimal neuropathic changes induced by methyl isobutyl ketone may be related to the presence of the 3% methyl n-butyl ketone as a contaminant of the methyl isobutyl ketone used in this study.

This study [71] showed that, at a methyl n-butyl ketone concentration of 2,000 ppm, there was a progressive, symmetrical, distal neuropathy that spread proximally with time. The minimal neuropathic changes induced by methyl isobutyl ketone were most probably related to methyl n-butyl ketone, which was a contaminant.

In 1975, Raleigh and coworkers [72] reported on the toxicity of methyl n-butyl ketone in cats. Cats were exposed to methyl n-butyl ketone at 100 or 330 ppm (410 or 1,353 mg/cu m) for 6 hours/day, 5 days/week for approximately 5 months. No evidence of clinical neuropathy was observed.

However, minimal microscopic changes were observed in nerve fibers supplying the interosseous muscle of cats that were exposed at 330 ppm for about 4.5 months. No microscopic changes were found in cats exposed at 100 ppm.

In other studies, the authors [72] reported that neuropathy was produced in cats that were injected twice daily sc with 150 mg/kg of methyl n-butyl ketone, 5 days/week, for 2 months and in dogs that were injected twice daily sc with 150 mg/kg of methyl n-butyl ketone, 5 days/week, for 2-4 months. No clinical neuropathy was seen in guinea pigs that had unreported amounts of methyl n-butyl ketone applied to the skin repeatedly for about 8 months.

In 1976, Saida et al [73] studied the effects of methyl n-butyl ketone on the nervous system of rats and the effects of methyl ethyl ketone on methyl n-butyl ketone toxicity. The authors [73] studied two groups of Sprague-Dawley rats. In the first group, 12 rats weighing 190-210 g were exposed to methyl n-butyl ketone vapor at a concentration of 400 ppm continuously (24 hours/day, 7 days/week), the concentrations being monitored by the gas chromatographic method of Mendell and colleagues [70]. They were serially killed and examined microscopically for neurologic changes. In the second group, 12 rats each weighing 160-180 g were continuously exposed to methyl n-butyl ketone at a concentration of 225 ppm (922 mg/cu m), to methyl ethyl ketone at 1,125 ppm (3,319 mg/cu m), or to a combination of methyl n-butyl ketone at 225 ppm and methyl ethyl ketone at 1,125 ppm. These rats were also serially killed and examined microscopically for neurologic changes. Control animals held under similar conditions were not exposed. A number of rats exposed to methyl n-butyl

ketone at 400 ppm (1,640 mg/cu m) were killed on the 16th, 28th, and 42nd days, and rats exposed at 225 ppm were killed on the 16th, 25th, 35th, 55th, and 66th days.

Paralysis occurred 42 days after exposure to methyl n-butyl ketone at 400 ppm and 66 days after exposure to methyl n-butyl ketone at 225 ppm [73]. The authors reported that an increase in the number of neurofilaments and inpouching of the myelin sheath were apparent many weeks before the onset of paralysis. In animals exposed to methyl n-butyl ketone at 400 ppm for 16 days, the number of neurofilaments significantly increased and had increased further when measured after 42 days of exposure. In addition, after 42 days of exposure to methyl n-butyl ketone at 400 ppm, rats had significantly fewer neurotubules ($P<0.01$) than did controls.

The authors [73] reported that the number of inpouchings of myelin sheaths in individual teased nerve fibers was strongly correlated with the duration of exposure. In the late stages of neuropathy when the animals were paralyzed, the authors occasionally observed Wallerian degeneration of nerve fibers.

To determine the earliest site of damage, Saida et al [73] studied the anterior horn cells, nerve roots, nerve trunks, intramuscular nerves, and motor endplates. No abnormalities were found in the motor endplates or intramuscular nerves of the intrinsic foot muscles in rats exposed to methyl n-butyl ketone at 225 ppm for 16 days or to a combination of methyl n-butyl ketone and methyl ethyl ketone at 225:1,125 ppm for 16 days. However, rats exposed to the combination did have more neurofilaments and inpouchings of the myelin sheath of the sciatic nerve. After 25 days of

exposure to the combination, similar changes in the nerve roots and intramuscular nerves were noted when clinical paralysis was present, but no abnormalities were observed in the axon terminals or postsynaptic membrane at the neuromuscular junction. After 66 days of exposure to methyl n-butyl ketone at 225 ppm, rats had denervation of motor endplates. No abnormalities were observed in anterior horn cells and dorsal root ganglion cells.

When the authors [73] compared the effects of methyl n-butyl ketone at 225 ppm, of methyl ethyl ketone at 1,125 ppm, and of the two substances combined at a ratio of 225:1,125 ppm, they noted striking differences in toxicity. With methyl ethyl ketone alone at 1,125 ppm, no peripheral neurotoxicity occurred in rats for up to 55 days; additional exposure for up to 5 months did not produce abnormalities. Rats exposed to methyl n-butyl ketone at 225 ppm did not develop paralysis until they had been exposed for 66 days. However, rats exposed to the combination developed paralysis after 25 days of exposure. The authors noted that the time of onset of inpouchings of myelin sheaths, axonal swelling, and denudation of axons was greatly shortened in rats exposed to the combination. The authors concluded that the earliest microscopic change produced by methyl n-butyl ketone was an increase in the number of neurofilaments in large myelinated nerve fibers. Axonal swelling and myelin thinning occurred with longer exposures. Inpouchings of the myelin sheath also occurred early in neuropathy and increased in number as exposure continued.

These studies show that methyl ethyl ketone alone at 1,125 ppm did not produce peripheral neuropathy in rats after repeated exposure.

However, methyl ethyl ketone shortened the latency period of the onset of methyl n-butyl ketone-induced peripheral neuropathy.

Spencer and Schaumburg [74] studied the effects of repeated sc injections of three ketones individually and in combination. Each cat was injected twice daily with 150 mg/kg of the test substances. Eight cats were injected with undiluted methyl n-butyl ketone, six with methyl ethyl ketone, four with methyl isobutyl ketone, four with a 9:1 mixture of methyl ethyl ketone and methyl n-butyl ketone, and six with a 9:1 mixture of methyl ethyl ketone and methyl isobutyl ketone for 5 days/week for up to 8.5 months. Four cats received twice-daily injections of an equivalent volume of saline, and three other cats given no injections were used to study normal tissue.

Two series of 20 biopsies were performed on some cats [74]. Tissue samples were taken from the right hindfeet after 45 days and from the left hindfeet after 135 days. Tissues sampled at biopsy included pacinian corpuscles, branches of the lateral plantar nerves, and portions of a superficial interosseous muscle.

Morphologic studies were conducted on three cats that received methyl n-butyl ketone for 2, 4, and 6 months [74]. The tissues sampled were the pacinian corpuscles in hindfeet, the sciatic, tibial, peroneal sural, and plantar nerves in the hindlegs, the proximal and distal hindleg muscles, the lumbosacral dorsal root ganglia and corresponding dorsal and ventral roots, and multiple levels of the spinal cord and medulla oblongata.

The authors [74] reported that the cats often salivated excessively and showed signs of narcosis shortly after injections. Abscesses and skin ulcers appeared at the injection site in several animals. All 10 cats

receiving injections of methyl ethyl ketone or a 9:1 mixture of methyl ethyl ketone and methyl n-butyl ketone died after 31-93 days. Two cats receiving injections of methyl n-butyl ketone alone died after 7 and 93 days. The cats given methyl isobutyl ketone did not die.

Spencer and Schaumburg [74] detected neurologic dysfunction only in cats that were given methyl n-butyl ketone alone. The first sign of peripheral neuropathy was a weakness of the hindquarters after 8-10 weeks of methyl n-butyl ketone injections. After 10-12 weeks, the cats had severe hindleg footdrop and, by 16 weeks, they could not walk. Cats injected with methyl ethyl ketone, methyl isobutyl ketone, or 9:1 mixtures of methyl ethyl ketone with methyl n-butyl ketone or methyl isobutyl ketone had no neurologic dysfunction.

Cats given methyl n-butyl ketone and a 9:1 mixture of methyl ethyl ketone and methyl n-butyl ketone had nerve fiber damage [74]. Tissues from the cats given the other ketones appeared normal. Cats given methyl n-butyl ketone for 45 days had a proliferation of neurofilaments in pacinian corpuscles with subsequent degeneration of axoplasm. After 135 days, pacinian corpuscles were either denervated or had extensive axonal damage. Focal giant axonal swelling was seen in plantar nerves and interosseous muscles. No changes were apparent in hindleg tissues from cats that received a 9:1 mixture of methyl ethyl ketone and methyl n-butyl ketone for 45 and 135 days; however, after 8.5 months, tibial nerve branches contained abnormal numbers of fibers that had segmental remyelination. Pacinian corpuscles appeared normal.

The peripheral and central nervous systems were studied in three cats that received methyl n-butyl ketone for 2, 4, and 6 months [74]. One cat

given injections for an unspecified period had no signs of neurologic dysfunction, but parts of its peripheral nervous system showed changes characteristic of neuropathy induced by methyl n-butyl ketone. The other two cats had overt signs of neuropathy. There was microscopic evidence in the cat that was treated for 4 months, but the authors discussed both cats in general. The cats had nerve fiber degeneration, proximal muscle fiber atrophy, and axonal swellings in the sciatic nerve. Giant axonal swellings of myelinated fibers, enlargement of nerve terminals, and total fiber breakdown were found in the CNS.

Spencer and Schaumburg [74] concluded that methyl n-butyl ketone produced a primary axonal degeneration that affected the distal regions of nerves first and then progressed proximally. To describe this pattern, they referred to an earlier study [75] in which they proposed the term "central-peripheral distal axonopathy."

They [74] found microscopic evidence of neuropathy in cats that received a 9:1 mixture of methyl ethyl ketone and methyl n-butyl ketone. They noted that this subclinical damage appeared to be caused by methyl n-butyl ketone in the amount given (15 mg/kg), but they also pointed out that, as reported by Saida et al [73], methyl ethyl ketone may have potentiated the toxicity of methyl n-butyl ketone.

This study [74] further confirmed that methyl n-butyl ketone is a neurotoxic agent. It also showed that repeated administration of only methyl ethyl ketone produced no clinical or microscopic evidence of neuropathy. Repeated injections of methyl isobutyl ketone of 98.8% purity and of a 9:1 mixture of methyl ethyl ketone and methyl isobutyl ketone also produced no clinical or microscopic evidence of neuropathy. These findings

confirm the suggestions of Spencer et al [71] that the subclinical plantar nerve damage in rats exposed to commercial grade methyl isobutyl ketone for up to 5 months was probably caused by 3% methyl n-butyl ketone in the methyl isobutyl ketone used for this study.

Krasavage et al [76] also found neurotoxic effects of methyl n-butyl ketone. Two groups of 18 male Sprague-Dawley rats were exposed at vapor concentrations of 100 and 330 ppm for 6 hours/day, 5 days/week, for 72 weeks. Beginning at 4 weeks and continuing at about 6-week intervals for the first 52 weeks, rats were killed and examined by light and electron microscopy.

Neuropathy (hindlimb weakness and microscopic evidence of nerve damage) was seen only in rats that were exposed at 330 ppm (1,353 mg/cu m) [76]. This first appeared in 1 rat after 149 exposures. Although weight gain was depressed in both groups, no evidence of neurotoxicity, either clinical or microscopic, was observed at 100 ppm.

DeJesus et al [77] studied the effects of methyl n-butyl ketone and methyl ethyl ketone on peripheral nerves of Wistar rats. Animals were exposed for 6 hours/day, 5 days/week to methyl n-butyl ketone vapor at 60 ppm (246 mg/cu m) for 6 weeks, and at 100 ppm (410 mg/cu m) for 4 weeks, and at 1,050 and 1,450 ppm (4,305 and 5,945 mg/cu m) for 5 weeks. Rats were also exposed to methyl ethyl ketone vapor at 2,150 ppm for 6 weeks and at 4,740 ppm (13,983 mg/cu m) for 4 weeks.

Rats exposed to methyl n-butyl ketone at 1,050 and 1,450 ppm developed typical signs of peripheral neuropathy. These signs were hindleg dragging, decreased motor conduction velocities in sciatic nerves, decreased evoked muscle action potentials, and weight loss. Rats exposed

to methyl ethyl ketone at 2,150 and 4,740 ppm and rats exposed to methyl n-butyl ketone at 60 and 100 ppm had no signs of peripheral neuropathy.

Schaumburg and Spencer [78] studied the effects on the hypothalamus and optic nerve tract of cats given 2,5-hexanedione, a compound suggested to be a neurotoxic metabolite of methyl n-butyl ketone. Four young adult cats were given 0.5% 2,5-hexanedione in their drinking water for up to 136 days and then were perfused with a fixative. Two untreated cats served as controls. After 60-75 days, cats had an unsteady gait and distal weakness in the lower extremities. Further treatment produced a progressive symmetrical weakness with footdrop. At the time of perfusion, cats were quadriparetic and unable to walk. Visual loss, abnormal pupillary reflexes, nystagmus, staggering, and hoarseness were not observed.

The authors [78] found evidence of giant axonal degeneration that was similar to the findings of other investigations [71,74]. They also found advanced distal fiber degeneration in the rostral gracile, dorsal spinocerebellar, and caudal corticospinal tracts. In contrast, early axonal swellings were found throughout the mammillary bodies, the lateral geniculate body and distal optic tract, and the superior colliculus that were not associated with necrosis, macrophage accumulation, or hemorrhage. The optic nerves, vestibular nuclei, dorsal medial thalamic nuclei, and inferior colliculi were normal. The authors suggested that these changes might be responsible for the alterations of memory and vision that have occasionally been reported in n-hexane neuropathy. They thought that CNS degeneration might be irreversible.

Goldberg et al [79] studied modifications to behavior in rats induced by inhalation of vapors from several industrial solvents, including

acetone. Conditioned avoidance and escape in a modified pole-climbing test were the two behavioral patterns observed. Rats were trained to climb the pole within 2 seconds after receiving a stimulus. Any delay of response greater than 6 seconds was considered a significant change in behavior.

Female CFE rats, weighing 140-180 g, were selected for exposure according to their training performance in the behavioral testing apparatus before exposure [79]. The rats, in groups of 8-10, were exposed at nominal concentrations of 3,000, 6,000, 12,000, and 16,000 ppm (7,110, 14,220, 28,440, and 37,920 mg/cu m). The actual concentrations, as determined by an interferometer, were found to be within 10% of these concentrations. Rats were exposed for 4 hours/day, 5 days/week, for 2 weeks, and tested for performance before and after each exposure. Rats exposed to acetone at concentrations above 3,000 ppm showed some behavioral changes, but no alteration of avoidance or escape behavior was observed in rats exposed at 3,000 ppm [79]. At 6,000 ppm 38% of the rats showed an inhibition of avoidance behavior after the 1st day of exposure and 25% after the 2nd day, but no decrement was reported after the remaining exposures. None of the animals exposed at this concentration showed decreased escape behavior. After the first exposure at 12,000 ppm, 50% of the rats showed inhibited avoidance response and 12% showed inhibited escape response. After the second exposure, avoidance response was inhibited in 37%, but the escape response was no longer inhibited. After three exposures, the avoidance response was inhibited in 25% of the rats, and no further inhibition occurred after additional exposures. Several rats exposed at 12,000 or 16,000 ppm developed muscular incoordination after one exposure; however, no signs of muscular incoordination were noted after subsequent exposures.

Of the rats exposed at 16,000 ppm, 62% had an inhibition of the avoidance response after one exposure. The escape response was inhibited in 25% of these animals after one exposure; however, as in the previous group, no inhibition was observed on subsequent days. The avoidance response was inhibited in 37% of the rats after 2 exposures, in 37% after 3 exposures, and in 25% after 4, 5, and 10 exposures. The inhalation of acetone did not significantly affect the growth rate of exposed animals compared to control rates.

Goldberg and coworkers [79] showed that acetone at concentrations of 6,000 ppm or more modified avoidance and escape in rats. Many of the rats exposed at 12,000 and 16,000 ppm developed tolerance, and escape responses were less inhibited than avoidance responses by exposure to acetone. Inhalation of acetone at increasing concentrations produced modification of behavior in an increasing proportion of the experimental population.

Johnson et al [80] studied the effects of methyl n-butyl ketone on behavior and the nervous system. Groups of 10 albino male rats and 8 male monkeys were exposed to methyl n-butyl ketone at 97 or 976 ppm (398 or 400 mg/cu m) for 6 hours/day, 5 days/week. Similiar but unexposed groups of rats and monkeys served as controls. For neurologic tests in rats and monkeys, maximum motor conduction velocities, absolute refractory period, and muscle action potentials were recorded. In addition, electroencephalograms and visually evoked potentials were recorded from monkeys.

For behavioral studies, 12 Sprague-Dawley albino rats were trained on a multiple fixed ratio 5, fixed interval 3-minute schedule (mult FR5FI3) [80]. Six standard operant test enclosures with a press bar, food cup, and

feeder were used. A red light was associated with the fixed ratio and a yellow light with the fixed interval of the operant schedule. Inter-response times were recorded separately from each component of the multiple schedule of reinforcement. Stability in responding was reached after 20-40 days of training. For recovery studies, three monkeys from each exposed group were neurologically tested monthly until recovery was evident. Motor conduction velocity in the sciatic tibial nerve was the measurement used to evaluate neurologic recovery because, as the authors stated, it had given the earliest indication of methyl n-butyl ketone-induced neurotoxicity at both exposure levels.

After 25 weeks of exposure to methyl n-butyl ketone at 976 ppm the experiment was terminated because hindlimb drag was evident in both rats and monkeys [80]. The authors reported that exposure at 976 ppm reduced motor conduction velocities in ulnar and sciatic-tibial nerves, decreased the evoked muscle action potentials, lengthened implicit time of visually evoked potentials, impaired operant behavioral performance, and reduced body weight.

In monkeys, the first significant decrease in motor conduction velocity occurred after 4 months of exposure at 976 ppm [80]. At 97 ppm, the first significant decrease in motor conduction velocity occurred after 9 months. In rats exposed at the higher concentration, a significant decrease in motor conduction velocity occurred after 13 weeks.

Operant behavior in rats exposed at 976 ppm first appeared to be significantly impaired after 2 weeks [80]. No effects on operant behavior were found after exposure at 97 ppm.

The study of Johnson et al [80] is in agreement with the findings of other investigators [70-72,74] on the neurotoxicity of methyl n-butyl ketone. An interesting finding was the impaired operant behavior after 2 weeks of exposure at 976 ppm because other measurements indicated that 21 weeks of exposure was necessary to produce detectable nerve damage. These findings are consistent with a suggestion that modification of behavior might occur in humans exposed to methyl n-butyl ketone before the onset of peripheral neuropathy.

Anger and coworkers [81] described, in a report available only as an abstract, the effects of methyl n-amyl ketone by inhalation exposures and ip injections on multiple fixed ratio, fixed interval (MULT FRFI) response rates in rats. Twelve rats were injected intraperitoneally (ip) with methyl n-amyl ketone at 18, 37, 74, and 175 mg/kg and were tested 15 minutes after treatment.

At 18 mg/kg, there was little effect on the fixed interval response rate, a moderate decrease in FI rate at 37 and 74 mg/kg, and a near cessation of responding at 175 mg/kg. Changes were statistically significant at 37, 74, and 174 mg/kg. Inhalation exposures to methyl n-amyl ketone at concentrations in excess of 1,600 ppm (7,472 mg/cu m) had effects similar to those in animals that were injected with 175 mg/kg.

Johnson et al [82] described an electrodiagnostic study of the neurotoxicity of methyl n-amyl ketone. Rats and monkeys were exposed to methyl n-amyl ketone at 0, 131, and 1,025 ppm (612 and 4,787 mg/cu m) for 6 hours/day, 5 days/week for 9 months. Conventional procedures were used throughout the study. None of the animals showed any clinical signs of illness during the course of the study. No impairment in locomotion,

grip, or gait was observed. Electrodiagnostic studies in the form of maximum motor conduction velocities in sciatic-tibial and ulnar nerves in all exposed animals did not differ significantly from those of controls. Microscopic examination revealed no tissue damage.

This study [82] provides evidence that methyl n-amyl ketone is not neurotoxic. Because methyl n-amyl ketone is one of the two closest homologs of methyl n-butyl ketone, methyl n-propyl ketone being the other, this evidence suggests that the straight-chain 6-carbon structure is essential for producing neurotoxic effects.

(e) Metabolism

The metabolic pathways for the degradation and biotransformation of the ketones are not completely understood. Several intermediates and endproducts have been identified for methyl n-butyl ketone, methyl ethyl ketone, methyl isobutyl ketone, and cyclohexanone, and, correspondingly, several steps in the pathway have been postulated for these ketones. In general, the proposed pathways include an oxidative hydroxylation to the corresponding hydroxy ketone, followed by a reduction to the secondary alcohol or further oxidation to the dione. Although data do not exist for the other ketones, it is reasonable to suggest that they also follow these metabolic steps.

DiVincenzo et al [83] reported that male guinea pigs metabolized methyl n-butyl ketone, methyl isobutyl ketone, or methyl ethyl ketone, after a single ip dose of 450 mg/kg, to their corresponding alcohols, with subsequent oxidation steps occurring as shown in Table III-6. In general, all three ketones were both oxidatively and reductively metabolized. Oxidation occurred by hydroxylation of the omega-1 carbon, ie, the next to

the last carbon, to form the corresponding hydroxy ketone, and reduction occurred at the carbonyl group to form the corresponding secondary alcohol. Although the proportion of metabolites may differ, omega-1 oxidation and carbonyl reduction appear to be the initial steps in the metabolic pathways in guinea pigs.

TABLE III-6

METABOLISM OF SOME KETONES BY GUINEA PIGS

| Ketone | Half-Life (min) | Clearance Time (hr) | Metabolites | Clearance Time (hr) |
|---|---|---|---|---|
| Methyl isobutyl ketone | 66 | 6 | 4-hydroxy-4-methyl-2-pentanone | 16 |
| | | | 4-methyl-2-pentanol | - |
| Methyl ethyl ketone | 270 | 12 | 2-butanol | 16 |
| | | | 5-hydroxy-2-butanone | 16 |
| | | | 2,3-butanediol | 16 |
| Methyl n-butyl ketone | - | - | 5-hydroxy-2-hexanone | - |
| | | | 2,5-hexanedione | - |
| | | | 2-hexanol | |

Adapted from reference 83

DiVincenzo et al [83] concluded that the predominant metabolite of methyl n-butyl ketone was 2,5-hexanedione, which could be reduced to 5-hydroxy-2-hexanone but was probably not significantly converted to 2,5-hexanediol. Comparison of the metabolism of the hydroxy ketone and the dione showed that the formation of the dione was favored. Another metabolite, 2-hexanol, could be further metabolized to 2,5-hexanediol, 5-hydroxy-2-hexanone, 2,5-hexanedione, and to methyl n-butyl ketone. When n-

hexane was injected ip into guinea pigs at 250 mg/kg, 5-hydroxy-2-hexanone and 2,5-hexanedione were detected [83]. The authors noted the importance of finding 5-hydroxy-2-hexanone and 2,5-hexanedione as common metabolites of n-hexane and methyl n-butyl ketone because n-hexane also has been reported to cause peripheral neuropathy [84].

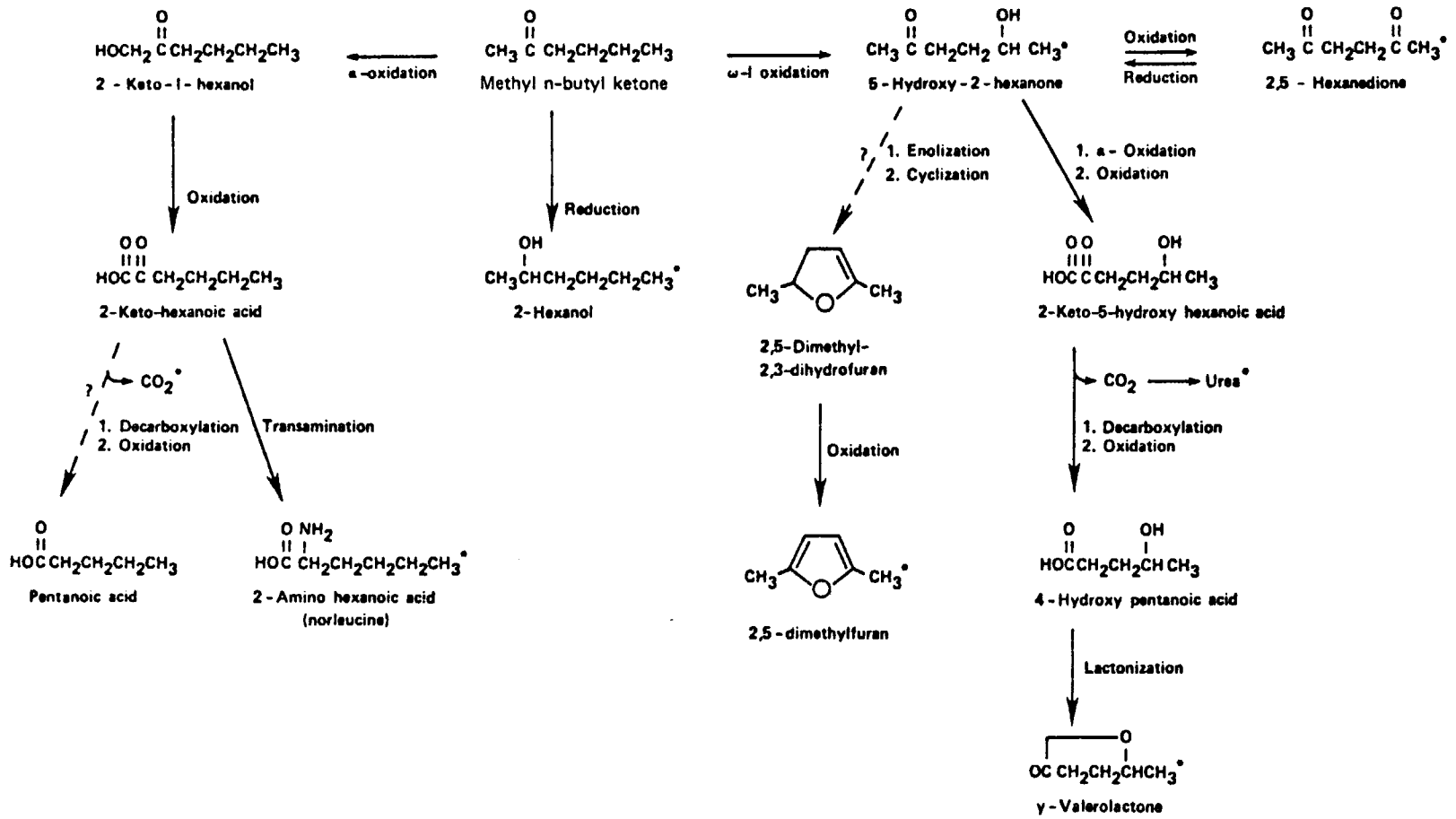
A later study by DiVincenzo and colleagues [85] in which 20 or 200 mg/kg of 14C-methyl n-butyl ketone was given by gavage to rats showed that about 6% of the administered dose was excreted in the breath as unchanged methyl n-butyl ketone and 38% as carbon dioxide. An additional 40% of the dose was excreted in the urine, and 8% remained in the carcass after 6 days. Serum metabolites were reported as 2-hexanol, 5-hydroxy-2-hexanone, and 2,5-hexanedione. Metabolites identified in urine were 2-hexanol, 5-hydroxy-2-hexanone, 2,5-hexanedione, 2,5-dimethylfuran, gamma-valerolactone, norleucine, and urea. Besides the reduction of the carbonyl group and oxidation of the omega-1 carbon atom, a major metabolic pathway was the oxidation of the alpha carbon to form an alpha-keto acid. Decarboxylation of this acid apparently accounted for most of the respiratory carbon dioxide produced. Transamination of the alpha-keto acid to form the amino acid, norleucine, was a minor metabolic pathway.

The authors [85] noted that pretreatment with SKF 525A produced an increase in respiratory carbon dioxide and a decrease in urinary radioactivity, suggesting that omega oxidation was mediated by a microsomal mixed-function oxidase system. Phenobarbital pretreatment increased the amount of labeled carbon dioxide in the first 4 hours but did not alter its subsequent output. A proposed metabolic pathway developed largely from information on guinea pigs is shown in Figure III-1.

Krasavage et al [86] studied the neurotoxic effects of several methyl n-butyl ketone metabolites and n-hexane in rats. Equimolar doses of 6.6 millimoles/kg were given by gavage to male Charles River rats 5 days/week for 90 days. Relative neurotoxicity was evaluated by comparing the time of onset of severe hindleg weakness. The compounds studied were methyl n-butyl ketone, n-hexane, 2,5-hexanedione, 2,5-hexanediol, 5 hydroxy-2-hexanone, and 2-hexanol.

Microscopic and clinical examination showed that each compound except n-hexane produced a typical giant axonal neuropathy and severe hindleg footdrop [86]. The relative order of the neurotoxicity of the hexacarbon compounds studied, in decreasing order, was 2,5-hexanedione, 5-hydroxy-2-hexanone, 2,5-hexanediol, methyl n-butyl ketone, and 2-hexanol. No evidence of neuropathy was found in n-hexane-treated animals or in controls.

Couri et al [87] reported that aniline hydroxylase activity was significantly increased in liver microsomal preparations from rats exposed continuously or intermittently (7 hours/day) for 7 days to a combination of methyl ethyl ketone and methyl n-butyl ketone ($P<0.05$). The continuous exposure significantly increased aminopyrine demethylase, para-nitrobenzoate reductase, and neoprontosil reductase activities in the microsomal preparations ($P<0.01$). Intermittent exposure caused a significant decrease in para-nitrobenzoate reductase activity ($P<0.05$), but it did not affect aminopyrine demethylase or neoprontosil reductase activities. The explanation for the discrepancy in the data on the effect of ketone exposure on the activity of para-nitrobenzoate reductase is not apparent. However, it seems evident that methyl ethyl ketone can stimulate




* Designates compounds actually identified as metabolites.
From DiVincenzo et al [83]

FIGURE III–1

PROPOSED PATHWAY FOR THE METABOLISM OF [1-14 C] METHYL n-BUTYL KETONE

methyl n-butyl ketone metabolism and thus increase the production of 2,5-hexanedione which is neurotoxic [72].

In 1943, Treon et al [88] found a decrease in the ratio of inorganic sulfates to total sulfates and an increase in the level of glucuronic acid in the urine of rabbits exposed to cyclohexanone. On the basis of a monomolecular conjugation, the investigators determined that approximately 45-50% of the administered oral dose was excreted in conjugation with glucuronic acid. Elliott et al [89] also reported that rabbits given 248 mg/kg of cyclohexanone by stomach tube eliminated 66% (51-86%) of the administered dose as cyclohexylglucuronide in the urine. Because cyclohexanol also was metabolized to cyclohexylglucuronide, it is possible that cyclohexanone is first reduced to cyclohexanol and then is conjugated with glucuronic acid. James and Waring [90] showed that rabbits and rats given oral doses of cyclohexanone excreted trace amounts of hydroxycyclohexylmercapturic acid and cis-2-hydroxycyclohexylmercapturic acid in the urine. From these data [88-90], it seems reasonable to conclude that the principal metabolic pathway of cyclohexanone in rats and rabbits is reduction to cyclohexanol and subsequent conjugation with glucuronic acid.

Abdel-Rahman et al [91] found a peak blood methyl n-butyl ketone concentration of 650 μg/ml in male rats given a 160-mg ip dose of methyl n-butyl ketone. The half-life for the rapid elimination from the blood was about 10 minutes, followed by a slower phase of elimination with a 7-hour half-life. When male rats were continuously exposed to methyl n-butyl ketone at 400 ppm for either 6 or 60 days, the parent compound could not be detected in the blood.

Guinea pigs receiving phenobarbital prior to methyl n-butyl ketone ip injections had increased 2-hexanol concentrations in the blood at 100 minutes after exposure and substantially increased 2,5-hexanedione concentrations at 50, 100, and 180 minutes after exposure [91]. In rats, phenobarbital conditioning increased 2-hexanol concentrations 200 minutes after exposure and increased 2,5-hexanedione concentrations at 50, 100, 160, and 200 minutes after exposure. Phenobarbital also enhanced the urinary excretion of 2,5-hexanedione in rats and of methyl n-butyl ketone, 2-hexanol, and 2,5-hexanedione in guinea pigs.

In another experiment, 61% of a total ip dose of tritiated methyl n-butyl ketone administered to rats was recovered in 72 hours [91]. In the first 24 hours, 12.7% was excreted in the expired air, 31.8% in the urine, and 2% in the feces; in the first 72 hours, these values were 12.8, 40.1, and 7.9%, respectively.

Raleigh and coworkers [72] also reported that 2,5-hexanedione was a major metabolite of methyl n-butyl ketone in several species of animals. Peripheral neuropathy was produced in rats by a daily sc injection of an average of 340 mg/kg of 2,5-hexanedione, 5 days/week, for 19 weeks or by an average dose in drinking water of 520 mg/kg/day for about 2 months. Although many experimental details were omitted, these findings are in agreement with the results of other investigators [71,78,92].

(f) Carcinogenesis, Mutagenesis, Teratogenesis, and Effects on Reproduction

No studies implicating the ketones as possible carcinogens or mutagens were found in the literature. However, some studies that produced

negative results were found. McCann et al [93] found that acetone was not mutagenic in the Ames test. Van Duuren et al [94] applied 0.1 ml of acetone 3 times/week to the skin of mice for 1 year and found no evidence of tumors 208 days later. McLaughlin et al [95] injected 39 and 78 mg of acetone into the yolks of fertile chick eggs prior to incubation and found no evidence of teratogenicity. DiPaolo et al [96] used an acetone concentration of 0.02% or less in the growth medium of cultures of embryonic cells of the Syrian hamster uterus and found no transformation to altered clones of diminished cloning efficiency. NIOSH found no evidence of mutagenic activity in cyclohexanone by the Ames test (G Taylor, written communication, March 1978).

Schwetz et al [97] exposed pregnant Sprague-Dawley rats to methyl ethyl ketone in a study of possible teratogenic effects. On days 6-15 of gestation, 23 rats were exposed to methyl ethyl ketone for 7 hours/day at an average concentration of 1,126 ppm, and 21 rats were exposed at an average concentration of 2,618 ppm. A control group of 43 pregnant rats was exposed to filtered room air. Observations and measurements included maternal and fetal mortality, gross appearance and body weight, maternal liver weight and behavior, number of resorptions, and serum glutamic-pyruvic transaminase (SGPT) activity on day 21 of gestation.

No gross anomalies were observed in the dams exposed at either concentration [97]. Exposure to methyl ethyl ketone did not appreciably affect the number of corpora lutea/dam, the number of implantation sites/litter, the number of live fetuses/litter, or the percentage of resorptions. Methyl ethyl ketone at 1,126 ppm significantly reduced the fetal body weights and fetal crown to rump length ($P<0.05$), but these

changes were not apparent in rats exposed at the higher concentration. No gross anomalies were observed in the fetuses of rats exposed at 1,126 ppm, but four fetuses were affected at the higher concentration. Two of these had short lower jaws, and two had no tails with an imperforate anus. The authors stated that these anomalies had never been seen in over 400 control litters that had been examined in their laboratory. The total incidence of skeletal anomalies was significantly greater than the control incidence for the group exposed at 1,126 ppm but not in the rats exposed at 2,618 ppm. The most prevalent skeletal effects involved the sternum, and rats exposed at 2,618 ppm had a significantly greater number of sternal anomalies than did the controls. Total soft tissue effects, including subcutaneous edema and dilated ureters, were more frequent in the offspring of exposed rats than in the controls, but the difference was significant only at the higher concentration.

Exposure to methyl ethyl ketone did not affect maternal body weight, maternal liver weight, liver appearance, SGPT activity, or the general behavior of the rats [97].

Rats exposed at the higher concentration occasionally ate less food than did controls; while this difference was statistically significant during two 2-day measuring periods, the difference was only about 10-15%. The authors concluded that methyl ethyl ketone, on the basis of these results in fetuses from dams exposed to the solvent, was embryotoxic, fetotoxic, and potentially teratogenic to rats. It is difficult to draw conclusions from this study with confidence because of the lack of a dose-response relationship from such effects as total skeletal anomalies and fetal size, ie, crown to rump length. On the other hand, the greater

incidence of sternebral and soft tissue anomalies at the higher concentration lends some credence to the results. It is noted that the data were analyzed by litters rather than in terms of individual animals. An analysis of data on individual animals might also have been useful.

Because of the possible implications of this study in terms of hazards to unborn children of working mothers, it is important that this work be verified or refuted by additional research, both in terms of this specific ketone and in terms of other ketones.

Griggs et al [98] studied the effects of cyclohexanone on chick embryos. Fertile eggs were placed in a 37 C incubator containing cyclohexanone at an undescribed concentration. Two groups of eggs were exposed for 3 or 6 hours prior to incubation. Three other groups were similarly exposed for 3, 6, or 12 hours after being incubated for 96 hours. After exposure, eggs were kept in hatching incubators for 13 days, and then most embryos were examined for viability, gross appearance, and microscopic changes in the heart, liver, and brain [98]. In addition, blood serum tests, including determinations of serum cholesterol, bilirubin, albumin, uric acid, urea nitrogen, lactate dehydrogenase, lipids, alkaline phosphatase, calcium, inorganic phosphate, serum glutamic-oxaloacetic transaminase (SGOT), mean packed erythrocyte volume, and hemoglobin concentration, were performed on selected embryos.

The body weight of all exposed embryos without incubation before exposure were significantly less than those of their respective controls ($P<0.01$) [98]. In contrast, the weights of the exposed embryos that had 96 hours of incubation before exposure varied with respect to controls. The only changes in serum indices after exposure to cyclohexanone were a

decreased calcium level and an increased inorganic phosphate concentration and SGOT activity. Gross inspection of the chicks showed no effects on the head, beak, toes, eyes, and feathers. No changes were found in the hearts and brains that were examined, but livers of exposed chicks appeared darker than those of the controls.

Chicks that hatched from eggs exposed to cyclohexanone for 3 hours after a 96-hour incubation could not stand and exhibited spastic motions when they tried to move [98]. Their only anatomical abnormality was a curling inwards of their toes. No changes were noticed in the chicks that hatched from eggs exposed for 6 or 9 hours, but 20-50% of the exposed eggs did not hatch compared to 10-20% of the control eggs. The authors did not examine the nervous systems and therefore could not determine whether cyclohexanone acted centrally or caused lesions in the peripheral nervous system. Interpretation of the implications of these results should, if possible, await confirmation in placental mammals.

Correlation of Exposure and Effect

All of the ketones except methyl isoamyl ketone have been reported to cause some degree of systemic organ damage [20,21,34,54,57,99] which generally occurred only at very high concentrations. Some of the ketones, however, have produced significant organ damage at lower concentrations. Cyclohexanone at 608 ppm for 300 hours produced extensive injury to heart muscle, lungs, liver, and kidneys in monkeys [54]. Mesityl oxide at 250 ppm for 240 hours caused congestion in livers and lungs and dilated Bowman's capsules and swollen convoluted tubular epithelium in the kidneys

of guinea pigs [21]. Isophorone at 500 ppm for 240 hours produced severely injured kidneys or lungs or both in rats and guinea pigs.

All of the ketones except methyl isoamyl ketone have been reported to produce irritation of the eyes, nose, or throat. Specht et al [34] gave evidence suggesting that the irritation produced by the homologous ketones increased in proportion to the number of carbon atoms. Acetone, for example, was only slightly irritating at 20,000 ppm, but methyl n-butyl ketone was extremely irritating at 6,000 ppm. The nonhomologous six-carbon ketones (methyl isobutyl ketone, cyclohexanone, and mesityl oxide) were also extremely irritating. Specht et al [34] found that methyl n-butyl ketone and cyclohexanone at 6,000 and 4,000 ppm, respectively, produced clouding of the corneas of guinea pigs that persisted after the exposure period. Rengstorff et al [66] found that cutaneous application of 0.5 ml of acetone or cyclohexanone and sc administration of 0.05 ml of acetone or cyclohexanone, three times/week for 3 weeks, produced cataracts in guinea pigs. Generally, the cataracts were first seen 3 months after treatment with the ketones. In some cases, lens damage was reversed within the first 3 months.

The results of sensory threshold studies in humans [15,16] also indicate that the high molecular-weight ketones are, in general, more irritating. Isophorone, a ketone that contains nine carbon atoms, was perceived as being irritating by the subjects at significantly lower concentrations than those of acetone and methyl ethyl ketone that caused irritation [15]. Yant et al [52] reported that methyl n-propyl ketone at 1,500 ppm produced moderate to marked irritation of the eyes and nose of humans after an unspecified exposure period. Raleigh and McGee [17] found

eye, nose, and throat irritation in a small group of workers exposed to acetone for 8 hours at an average concentration of 1,000 ppm. Matsushita et al [18] reported that most subjects exposed to acetone at 500 and 1,000 ppm had irritation of the eyes, nose, and throat.

Probably because of their excellent lipid solvent properties and, thus, their defatting action, the liquid ketones produce adverse effects on the skin. Lupulescu and Birmingham [32] found intercellular edema and disruption of the cells of the keratin layer in volunteers exposed to liquid acetone. Smith and Mayers [33] reported that methyl ethyl ketone at 300-600 ppm produced dermatitis in exposed workers after an unspecified period of exposure. Linari et al [30] found skin lesions in 3 of 19 workers exposed to methyl isobutyl ketone at 80-500 ppm for 20-30 minutes daily. These lesions were described as varying from erythema to small desquamative areas after an initial dry dermatitis. In a follow-up study, Armeli et al [31] reported that dermal lesions were markedly reduced. At that time, workers were required to wear gloves and barrier creams. The workplace environment contained methyl isobutyl ketone at 50-105 ppm, and exposures lasted for 15-30 minutes daily. These findings and the ability of ketones to dissolve lipids suggest that ketones in liquid form may cause dermatitis. The question of whether ketone vapor can cause dermatitis is not settled, but it seems unlikely; except for some exposures to methyl ethyl ketone vapor that appeared to be responsible for dermatitis of the face [33], liquid contact was the more likely cause.

Smyth et al [61,62] studied the primary skin irritation produced by ketones on rabbits. Methyl n-amyl ketone produced the most severe irritation of the ketones considered in this document and was assigned a

grade of 4. (Grade 6 compounds produced necrosis when applied undiluted.) Methyl ethyl ketone was grade 2, and acetone, methyl n-propyl ketone, and methyl n-butyl ketone were grade 1, indicating minimal visible capillary injection.

Little information was available on percutaneous absorption, although the more lipid-soluble ketones would be expected to penetrate the skin more readily than the less lipid-soluble ketones. In this respect, Cesaro and Pinerolo [24] demonstrated that acetone concentrations in the blood were not increased after nude volunteers were exposed to acetone vapor at unspecified concentrations for 20-30 minutes. However, Parmeggiani and Sassi [27] showed that acetone was absorbed percutaneously when applied to the skin of a subject for 30 minutes and the subject remained in a chamber for an additional 1.5 hours. This was demonstrated by the levels of acetone found in the blood and urine. Munies and Wurster [43] showed that methyl ethyl ketone was excreted in the expired air in a few minutes after the ketone was placed on the forearm of volunteers. Billmaier et al [38] suggested that skin absorption was probably a contributing factor in the development of peripheral neuropathy in the workers exposed to methyl n-butyl ketone in a coated-fabric plant. Studies by DiVincenzo and colleagues [45] support this theory. They demonstrated that methyl n-butyl ketone was absorbed through the skin of volunteers at the rate of 4.2-8.0 μg/minute/sq cm.

All of these ketones except methyl isoamyl ketone have been reported to cause narcosis or signs of CNS depression. However, had this compound been studied, it seems likely that it, like the related ketones, would also have been found to have caused CNS depression. Acute intoxication of a 10-

year-old boy with acetone resulted in collapse, stupor, and incoherence [23]. Eight workers exposed to acetone at a concentration greater than 12,000 ppm felt dizzy and lightheaded and reported weakness of the legs [25]. Raleigh and McGee [17] noted headache and lightheadedness in workers exposed to acetone for 8 hours at an average concentration of 1,000 ppm. Parmeggiani and Sassi [27] found irritation of the eyes, nose, throat, and lungs and CNS disturbances in workers exposed to acetone at 307-918 ppm. The authors attributed these effects to slight accumulations of acetone in the body resulting from repeated exposure to the compound. Vigliani and Zurlo [28] reported occasional dizziness and loss of strength in workers exposed to acetone at 1,000 ppm 3 hours/day for 7-15 years. DiVincenzo et al [42] exposed nine volunteers to acetone at 100 or 500 ppm for 8 hours with no symptoms reported except for an awareness of acetone at 500 ppm. He also presented evidence that acetone might accumulate in the body at these concentrations.

GD Ware (written communication, June 1973) reported to the ACGIH that isophorone at 5-8 ppm caused fatigue and malaise in workers. When concentrations were reduced to 1-4 ppm, no adverse effects were reported.

In animals, Specht et al [34] reported narcosis and decreased rectal temperature, respiratory rate, and pulse rate in guinea pigs exposed to acetone, methyl ethyl ketone, methyl n-propyl ketone, methyl n-butyl ketone, methyl n-amyl ketone, methyl isobutyl ketone, mesityl oxide, or cyclohexanone. Exposures lasted from 204 to 1,405 minutes. Their findings, as summarized in Table III-4, indicated that in general the high molecular weight ketones were stronger narcotic agents than the low molecular weight ketones. Carpenter et al [20] reported that male rats

exposed to diisobutyl ketone for 7 hours at 1,650 ppm were prostrate at the end of the 1st day and had poor coordination at the end of the 2nd day. Lehmann and Flury [57] found that diacetone alcohol caused exhaustion in rats, mild narcosis in rabbits, and sleepiness in mice, rabbits, and cats. Smyth and Seaton [58] noted that single exposures to isophorone produced narcosis in rats and guinea pigs.

It is well established that the ketones can produce narcosis at high concentrations, so it seems reasonable to infer that modification of behavior or impairment of judgment could also occur. Exposure to acetone at concentrations that were less than those causing unconsciousness in humans did produce stupor, dizziness, and lightheadness, as might be expected [17,23,25]. Such effects could lead to serious consequences in the workplace. Goldberg et al [79] found that, in rats, acetone at concentrations of 6,000 ppm produced modification of behavior involving avoidance and escape patterns. Johnson and colleagues [80] demonstrated that the response rate in operant behavioral performance was decreased in rats that were exposed to methyl n-butyl ketone at 976 ppm for 6 hours/day, 5 days/week, after 2 weeks of exposure. Anger and coworkers [81] studied rats trained on a multiple fixed-ratio, fixed-internal (FRFI) schedule of reinforcement. They found methyl n-amyl ketone at 175 mg/kg ip produced a near cessation in the fixed interval response rates. Similar effects that were not statistically significant were found in rats exposed at 1,600 ppm.

Peripheral neuropathy is the most serious occupational illness related to exposure to these ketones. Exposure to methyl n-butyl ketone has been associated with this neurologic disorder [37,38,47].

Allen et al [37] reported that 11 workers in a coated-fabric plant

had a characteristic disabling peripheral neuropathy that was described as a distal, motor, and sensory disorder with an insidious onset and minimal reflex loss. Electromyographic abnormalities were approximately symmetrical and were either restricted to a distal distribution or greater in degree in distal muscles than proximal ones. Some of the affected workers had washed their hands with a solvent that contained methyl n-butyl ketone, although employees who operated the printing machines had ample opportunity to inhale the solvent vapors. Analysis of the area around the print machines showed methyl ethyl ketone at 331-516 ppm and methyl n-butyl ketone at 9.2-36 ppm. Other investigators [39,41] have found similar signs of neurologic disorders in workers exposed to methyl n-butyl ketone. These studies also indicated that skin contact with methyl n-butyl ketone contributed to the development of the peripheral neuropathy.

The incidence of peripheral neuropathy in the print department of the coated-fabric plant was 21.5%, which was highly significant ($P<0.001$) when compared to other departments [37,47]. Area atmospheric samples showed that printers were exposed to methyl n-butyl ketone at calculated TWA concentrations ranging from 2 to 50 ppm. However, because of the poor work practices at the coated-fabric plant, it was not certain whether the outbreak of peripheral neuropathy was caused by inhalation or skin absorption of methyl n-butyl ketone or by a combination of both routes of exposure. Questionnaire results showed that workers washed their hands with the solvent containing methyl n-butyl ketone, cleaned machines with rags dipped by hand in open containers of the solvent, and washed their work clothes with the solvent at the plant. Since methyl n-butyl ketone penetrates human skin [45], it is highly probable that skin absorption, as

a result of the aforementioned poor work practices, played a significant part in the development of peripheral neuropathy in this case.

DiVincenzo et al [45] have shown that about 75-92% of inhaled methyl n-butyl ketone was absorbed by volunteers. When applied to the skin of volunteers, about 5 μg/minute/sq cm was absorbed. From these data, it can be calculated that immersion of both hands in liquid methyl n-butyl ketone for 15 minutes results in the absorption of approximately 13% of the amount of ketone absorbed by a worker who is exposed to airborne methyl n-butyl ketone at the average TWA concentration of 13.1 ppm. If the immersion time had been as much as 30 minutes/day, the contribution of percutaneous ketone would have been about one fourth. There is no good information on the role of ingestion in these intoxications, but it is thought to have been minor or perhaps even negligible.

Several studies on animals have confirmed that methyl n-butyl ketone causes peripheral neuropathy [70,71,74,76,77,80,91]. Mendell et al [70] reported peripheral neuropathy in chickens, rats, and cats exposed to methyl n-butyl ketone at 200-600 ppm for 24 hours/day, 7 days/week. Krasavage et al [76] found that methyl n-butyl ketone vapor at 330 ppm, but not at 100 ppm, caused clinical and microscopic evidence of neuropathy in rats. DeJesus and coworkers [77] found no evidence of neuropathy in rats exposed to methyl n-butyl ketone vapor at 60 and 90 ppm. In contrast, Johnson et al [80] reported that decreased motor conduction velocities occurred in monkeys exposed at 97 ppm for 9 months.

Although most of the available evidence indicates that, of these ketones, only methyl n-butyl ketone can cause peripheral neuropathy, studies implicating other ketones have been found [33,36,71]. Viader et al

[36] found evidence of peripheral neuropathy in a man who worked with an adhesive composed of 60% tetrahydrofuran and 40% of a polyester-type polymer. The man also worked with a solvent that was reported to be 100% methyl ethyl ketone. Viader postulated that the man's illness was caused by exposure to methyl ethyl ketone or by a combined exposure. Smith and Mayers [33] reported that workers exposed to methyl ethyl ketone at concentrations ranging from 300-600 ppm developed numbness of the fingers and arms. One worker complained of numbness in the legs. Spencer et al [71] found minimal neuropathic changes in rats exposed to methyl isobutyl ketone, but they attributed this to the presence of methyl n-butyl ketone as a contaminant, a reasonable conclusion in the light of their later study [74] showing that methyl isobutyl ketone of greater than 98.8% purity caused no neurotoxic effects.

In animals, several studies [73,74,77] have shown that methyl ethyl ketone alone did not produce neurotoxicity. However, methyl ethyl ketone did shorten the latency period for the onset of neurotoxic effects of methyl n-butyl ketone in cats. The reason for this effect is not understood. Couri et al [87] reported results that indicated that methyl ethyl ketone might have stimulated the metabolism of methyl n-butyl ketone, which might explain the enhancement of toxicity. Saida et al [73] found no evidence of neuropathy in rats exposed continuously to methyl ethyl ketone at 1,125 ppm for about 7 months. Spencer and Schaumburg [74] found no neuropathy in rats injected sc twice daily with 150 mg/kg for 5 days/week for 8.5 months. DeJesus et al [77] were unable to demonstrate any neuropathy in rats exposed to methyl ethyl ketone at 2,150 ppm for 6 weeks or at 4,740 ppm for 4 weeks.

Johnson et al [82] exposed rats and monkeys to methyl n-amyl ketone at 131 and 1,025 ppm for 6 hours/day, 5 days/week for 9 months and found no evidence of neuropathy. This finding is particularly significant because methyl n-amyl ketone is one of the two closest homologs of methyl n-butyl ketone.

DiVincenzo et al [83] demonstrated that in guinea pigs methyl ethyl ketone, methyl n-butyl ketone, and methyl isobutyl ketone were metabolized by omega-1 oxidation to form the corresponding hydroxy ketone, and by carbonyl reduction to form the corresponding secondary alcohol. The hydroxy ketone underwent further transformation to the diol by reduction or to the dione by oxidation. They noted that 2,5-hexanedione and 5-hydroxy-2-hexanone were also metabolites of n-hexane, which has been shown to cause peripheral neuropathy.

Krasavage et al [86] found in a study with rats that the relative order of neurotoxicity for methyl n-butyl ketone and its metabolites was 2,5-hexanedione, 5-hydroxy-2-hexanone, 2,5 hexanediol, methyl n-butyl ketone, and 2-hexanol. n-Hexane was not neurotoxic under the conditions of this experiment.

Saida et al [73] have shown that methyl ethyl ketone increased the toxicity of methyl n-butyl ketone, whereas methyl ethyl ketone alone at 1,125 ppm was not neurotoxic in cats [73,74]. Rats continuously exposed to methyl n-butyl ketone at 225 ppm developed paralysis in 66 days. Animals exposed to a combination of methyl n-butyl ketone at 225 ppm and methyl ethyl ketone at 1,125 ppm developed paralysis after 25 days of exposure.

Spencer and Schaumburg [92] have shown that 2,5-hexanedione (previously shown by other investigators [83,91] to be a metabolite of

methyl n-butyl ketone) produced a pattern and distribution of peripheral and CNS degeneration similar to that produced by methyl n-butyl ketone itself. They suggested that the CNS degeneration might not be reversible [78]. However, Abdel-Rahman et al [91] found that phenobarbital pretreatment protected against the neurotoxic effects of methyl n-butyl ketone. They suggested that protection might have resulted from an increased rate of excretion of 2,5-hexanedione.

In a later study, DiVincenzo and colleagues [85] demonstrated that respiratory carbon dioxide was the major excretory product of methyl n-butyl ketone.

The vapor pressure and thus the volatility of the homologous ketones is inversely proportional to the number of carbon atoms (see Tables XI-1 and XI-2). Therefore, although the higher ketones are more toxic, exposure by inhalation would tend to be less as the number of carbons increases, thus reducing the relative hazard of the ketones. Because lipid solubility is directly proportional to the number of carbon atoms, the hazard associated with skin absorption would be expected to be greater with the higher ketones because the affinity of the higher ketones for dermal lipids would increase. These factors are important considerations in developing a hygiene program for the ketones.

## Carcinogenicity, Mutagenicity, Teratogenicity, and Effects on Reproduction

No reports that implicated ketones as carcinogens or mutagens were found; some negative results were found for acetone [93-96] and for cyclohexanone (G Taylor, written communication, March 1978).

Schwetz et al [97] exposed pregnant rats to methyl ethyl ketone vapor and found some evidence of teratogenicity; however, because of the lack of a dose-response relationship in some of the effects, this evidence of teratogenicity should not be extrapolated to human effects until the effects on rats are confirmed or clarified. Griggs et al [98] demonstrated that embryos exposed to cyclohexanone produced chicks that could not stand and that exhibited spastic motions. In the absence of such information as data on placental transfer of ketones or their metabolites, whether these data from nonplacental embryos apply to human embryonic development is not evident.

Summary Tables of Exposure and Effect

Tables of selected effects of the ketones are presented below. Tables III-7 and III-8 show the irritative and systemic effects of the ketones, respectively, on humans. Table III-9 summarizes effects of the ketones on animals. Lastly, the effects on animals from inhaling methyl n-butyl ketone are given in Table III-10.

TABLE III-7

IRRITATION PRODUCED BY SOME KETONES IN HUMANS*

| Ketone | Concentration/Duration | Effects | Reference |
|---|---|---|---|
| Acetone | 800-1,000 ppm/8 hr | Slight-moderate eye irritation | 17 |
| " | 500 ppm/6 hr | Irritation to eyes, nose, throat, and trachea | 18 |
| " | 500 ppm/2-4 hr | No symptoms | 42 |
| Methyl ethyl ketone | 33,000 ppm/momentary | Intolerable eye and nose irritation | 19 |
| " | 3,300 ppm/momentary | Moderate eye and nose irritation | 19 |
| Diisobutyl ketone | 100 ppm/3 hr | Slight eye and throat irritation, slight headache | 20 |
| " | 50 ppm/3 hr | Slight transitory eye and nose irritation | 20 |

*See also Table III-1

TABLE III-8

SYSTEMIC EFFECTS OF KETONES ON HUMANS

| Ketone | Concentration/Duration | Effects | Reference |
|---|---|---|---|
| Acetone | Unknown | Vomiting, narcosis | 23 |
| " | Greater than 12,000 ppm/? | Throat and eye irritation, dizziness, weakness | 25 |
| " | Greater than 12,000 ppm/2 min | Dizziness and weakness | 25 |
| " | 1000 ppm/3 hr/d, 7-15 yr | Inflammation of respiratory tract, stomach, duodenum; occasional dizziness, loss of strength | 28 |
| Acetone and Methyl ethyl ketone | 330-495 ppm/? 398-561 ppm/? | Eye irritations, gastrointestinal disturbances, headache, and narcosis | 33 |
| Methyl ethyl ketone (possibly methanol) | Unknown | Retrobulbar neuritis | 35 |
| Methyl ethyl ketone | 300-600 ppm | Dermatitis of the face, numbness of fingers and legs | 33 |
| Methyl ethyl ketone and tetrahydrofuran | Unknown | Peripheral neuropathy | 36 |
| Methyl n-butyl ketone and methyl ethyl ketone | 6.1-36.0 ppm 147-516 ppm | " | 37,38 47 |
| Methyl n-butyl ketone | Unknown | " | 39,41 |
| Methyl isobutyl ketone | 80-500 ppm/20-30 min/d | Weakness, loss of appetite, headache, eye irritation, stomach ache, nausea, vomiting, and sore throat | 30 |
| " | 50-105 ppm/15-30 min/d | CNS and gastrointestinal disturbances in a few workers | 31 |

TABLE III-9

EFFECTS OF KETONES ON ANIMALS*

| Ketone | Concentration/Duration | Animal | Effects | Reference |
|---|---|---|---|---|
| Acetone | 0.5 ml on the skin, 0.05 ml sc/3 times/wk, 3 wk | Guinea pigs | Cataracts | 66 |
| Methyl ethyl ketone | 33,000-100,000 ppm/200 min | " | Gasping death, emphysema, slight congestion of brain, marked congestion of systemic organs especially the lungs, and corneal opacities | 19 |
| " | 3,300 ppm/810 min | " | No abnormal signs | 19 |
| " | 1,125 ppm/24 hr/3, 55 d | Rats | No evidence of peripheral neuropathy | 74 |
| " | 1,126 or 2,618 ppm/7 hr/d on d 6-15 of gestation | Pregnant rats | Embryotoxicity, fetotoxicity and possible teratogenicity | 98 |
| Methyl n-propyl ketone | 50,000 ppm/50 min | Guinea pigs | Death, slight congestion of brain and marked congestion of systemic organs | 52 |
| " | 1,500 ppm/810 min | " | No abnormal signs | 52 |
| Methyl n-amyl ketone | 1,025 ppm/6 hr/d for 2 wk | Rats and monkeys | No evidence of peripheral neuropathy | 82 |
| Methyl isobutyl ketone | 200 ppm/24 hr/d for 2 wk | Mice, rats, dogs, and monkeys | Heavier liver and kidneys in rats | 53 |
| " | 100 ppm/24 hr/d for 2 wk | " | Heavier kidneys in rats | 53 |
| " | 100 ppm at 258 mm Hg/24 hr/d 90 d | Monkeys, dogs, rats | Inflammation of kidneys in 1 monkey, hyaline droplet degeneration of proximal tubules in all rats, normal clinical and hematologic measurements | 53 |
| " | 150 mg/kg/twice/d, 5 d/wk 8.5 mo | Cats | No evidence of peripheral neuropathy | 74 |
| Diisobutyl ketone | 1,650 ppm/7/hr/d, 5 d/wk for 6 wk | Rats | Higher kidney and liver weights, death, no microscopic changes except cloudy swelling of the liver and moderate lung congestion | 20 |
| Cyclohexanone | 608 ppm/300 hr | Monkey | Extensive injury to heart muscle, lungs, liver, and kidneys | 54 |
| " | 190 ppm/300 hr | Rabbits | Slight degenerative changes in liver and kidneys | 54 |
| " | 0.5 ml on the skin, 0.05 ml sc/3 times/wk, 3 wk | Guinea pigs | Cataracts | 66 |
| " | Unknown/3-12 hr | Chick eggs | Embryotoxic | 98 |
| Mesityl oxide | 13,000 ppm/30 min/d 6 d | Mice | Necrotic spots in liver, lung hemorrhage, alimentary tract distension, and death | 55 |
| " | 250 ppm/8/hr/d, 5/d/wk 6 wk | Guinea pigs and rats | Congested livers and lungs, dilatated Bowman's capsules and swollen convoluted tubular epithelium | 21 |
| Isophorone | 500 ppm/8 hr/d, 5 d/wk 6 wk | " | Severely injured kidneys and/or lungs, and death | 21 |

*All of the ketones produced some irritation and narcosis.

TABLE III-10

EFFECTS ON ANIMALS EXPOSED
TO METHYL n-BUTYL KETONE BY INHALATION

| Species | Concentration (ppm) | Duration | Observed Effects | Reference |
|---|---|---|---|---|
| Rats | 1,300-2,000* | 3-4 wk | Hindlimb footdrop | 71 |
| " | 1,050* | 5 wk | Peripheral neuropathy | 77 |
| Rats and monkeys | 976* | 25 wk | Hindlimb dragging | 80 |
| Rats | 400 - 600** | 5-8 wk | " | 70 |
| " | 400** | 42 d | Paralysis | 73 |
| " | 330* | 30 wk | Peripheral neuropathy | 3 |
| " | 225** | 66 d | Paralysis | 73 |
| " | 100* | 72 wk | No evidence of neuropathy | 76 |
| " | 100* | 4 wk | " | 77 |
| " | 60* | 6 wk | " | 77 |
| Cats | 400 - 600** | 11-12 wk | Limb dragging | 70 |
| " | 330* | 4.5 wk | Minimal microscopic changes | 72 |
| " | 100* | 4.5 mo | No evidence of neuropathy | 72 |
| Chickens | 100 - 200** | 4-5 wk | Unable to stand | 70 |
| Monkeys | 97* | 9 mo | Decreased motor conduction velocity | 80 |

*6 hr/d, 5 d/wk
**Continuous