

2. HEALTH EFFECTS

2.1 INTRODUCTION

The primary purpose of this chapter is to provide public health officials, physicians, toxicologists, and other interested individuals and groups with an overall perspective of the toxicology of 2-hexanone and a depiction of significant exposure levels associated with various adverse health effects. It contains descriptions and evaluations of studies and presents levels of significant exposure for 2-hexanone based on toxicological studies and epidemiological investigations.

In the evaluation of studies described in this chapter, the purity of the test compound was considered. As shown in the text, tables, and figures, three general categories of 2-hexanone purity were indicated in the studies:

- Purity of 96% or more
- 70% purity (technical grade)
- Purity was not stated in the cited publication

In technical grade 2-hexanone, the 30% impurity was identified as methyl isobutyl ketone, and the possible implications of its presence in the test substance were discussed.

2.2 DISCUSSION OF HEALTH EFFECTS BY ROUTE OF EXPOSURE

To help public health professionals address the needs of persons living or working near hazardous waste sites, the information in this section is organized first by route of exposure--inhalation, oral, and dermal--and then by health effect--death, systemic, immunological, neurological, developmental, reproductive, genotoxic, and carcinogenic effects. These data are discussed in terms of three exposure periods --acute (less than 15 days), intermediate (15-364 days), and chronic (365 days or more).

Levels of significant exposure for each route and duration are presented in tables and illustrated in figures. The points in the figures showing noobserved- adverse-effect levels (NOAELS) or lowest-observed-adverse-effect levels (LOAELS) reflect the actual doses (levels of exposure) used in the studies. LOAELS have been classified into "less serious" or "serious" effects. These distinctions are intended to help the users of the document identify the levels of exposure at which adverse health effects start to appear. They should also help to determine whether or not the effects vary with dose and/or duration, and place into perspective the possible significance of these effects to human health.

The significance of the exposure levels shown in the tables and figures may differ depending on the user's perspective. For example, physicians concerned with the interpretation of clinical findings in exposed persons may be interested in levels of exposure associated with "serious" effects. Public health officials and project managers concerned with appropriate actions to

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take at hazardous waste sites may want information on levels of exposure associated with more subtle effects in humans or animals (LOAEL) or exposure levels below which no adverse effects (NOAEL) have been observed. Estimates of levels posing minimal risk to humans (Minimal Risk Levels, MRLs) may be of interest to health professionals and citizens alike.

Estimates of exposure levels posing minimal risk to humans (MRLs) have been made, where data were believed reliable, for the most sensitive noncancer effect for each exposure duration. MRLs include adjustments to reflect human variability from laboratory animal data to humans.

Although methods have been established to derive these levels (Barnes et al. 1988; EPA 1989), uncertainties are associated with these techniques. Furthermore, ATSDR acknowledges additional uncertainties inherent in the application of the procedures to derive less than lifetime MRLs. As an example, acute inhalation MRLs may not be protective for health effects that are delayed in development or are acquired following repeated acute insults, such as hypersensitivity reactions, asthma, or chronic bronchitis. As these kinds of health effects data become available and methods to assess levels of significant human exposure improve, these MRLs will be revised.

2.2.1 Inhalation Exposure

Numerous studies have been conducted in which animals were exposed to 2-hexanone via inhalation. However, the purpose of many of these studies was to assess the potential effects of combined exposure to 2-hexanone and another substance (usually chloroform or methyl ethyl ketone [MEK]). Study design has consequently involved exposure to only one concentration of 2-hexanone as a control exposure. A single high dose of 2-hexanone was used in several other studies in order to elicit and study histopathological changes in the affected nervous tissue. In addition, the grade or purity of the 2-hexanone administered was not stated in many studies, or in some cases, hexanone with purity as low as 70% was used. As a result of these various complications, the usefulness of the available data is limited.

2.2.1.1 Death

The only lethality data available for inhalation exposure to 2-hexanone are from a study by Abdo et al. (1982) in which 1 of 5 hens exposed continuously to 200 ppm 2-hexanone (70% purity) died on day 72 of a 90-day study. At 400 ppm, 2 of 5 hens died by day 27. The cause of death was not stated. No deaths were observed in the groups exposed to 100 ppm and below.

The highest NOAEL value and a reliable LOAEL value for death in this species and duration category are recorded in Table 2-1 and plotted in Figure 2-1.

TABLE 2-1. Levels of Significant Exposure to 2-Hexanone - Inhalation

Key to figure ^a	Species	Exposure frequency/ duration	System	NOAEL (ppm)	LOAEL (effect)		Reference	Purity
					Less serious (ppm)	Serious (ppm)		
INTERMEDIATE EXPOSURE								
Death								
1	Hen	90 d 24 hr/d		100		200 (death)	Abdo et al. 1982	T
Systemic								
2	Human	+10 mo (occup)	Other		9 (up to 60 lb weight loss)		Allen et al. 1975	U
3	Rat	6 mo 7d/wk 22hr/d	Other	100			Egan et al. 1980	P
4	Rat	6 mo 5d/wk 8hr/d	Hepatic Renal	50 50			Duckett et al. 1979	U
5	Rat	11 wk 72 hr/wk 18 hr/d	Hemato Other		700 (decreased weight gain)	700 (40% decrease in WBCs)	Katz et al. 1980	P
6	Rat	25-29 wk 5d/wk 6hr/d	Other	100	1000 (decreased body weight)		Johnson et al. 1977	U
7	Hen	90 d 24 hr/d	Other	50	200 (42% weight loss)		Abdo et al. 1982	T
Neurological								
8	Human	+10 mo (occup)			9 (neuropathy)		Allen et al. 1975	U
9	Rat	6 mo 5d/wk 8hr/d				50 (histopathology)	Duckett et al. 1979	U

TABLE 2-1 (Continued)

Key to figure ^a	Species	Exposure frequency/duration	System	NOAEL (ppm)	LOAEL (effect)		Reference	Purity
					Less serious (ppm)	Serious (ppm)		
10	Rat	4 mo 5 d/wk 6 hr/d				1300 (nerve degeneration)	Spencer et al. 1975	U
11	Rat	6 mo 7d/wk 22hr/d				100 (histopathology)	Egan et al. 1980	P
12	Rat	6-9.5 wk 24hr/d				225 (paralysis, histopathology)	Saida et al. 1976	U
13	Rat	11 wk 72 hr/wk 18 hr/d				700 (neuropathy, histopathology)	Katz et al. 1980	P
14	Rat	29 wk 5d/wk 6hr/d			100 (neuropathy)		Johnson et al. 1977	U
15	Monkey	41 wk 5d/wk 6hr/d			100 (mild neuropathy)		Johnson et al. 1977	U
16	Hen	90 d 5 d/wk NDhr/d			100 (ataxia)		Abou-Donia et al. 1985a	T
17	Hen	90 d 24 hr/d		10	50 (ataxia)	200 (paralysis, histopathology)	Abdo et al. 1982	T
Developmental								
18	Rat	21 Gd 6hr/d				2000 (decreased pup survival and weight)	Peters et al. 1981	U
19	Rat	21 Gd 6hr/d			1000 (behavioral effects in offspring)		Peters et al. 1981	U

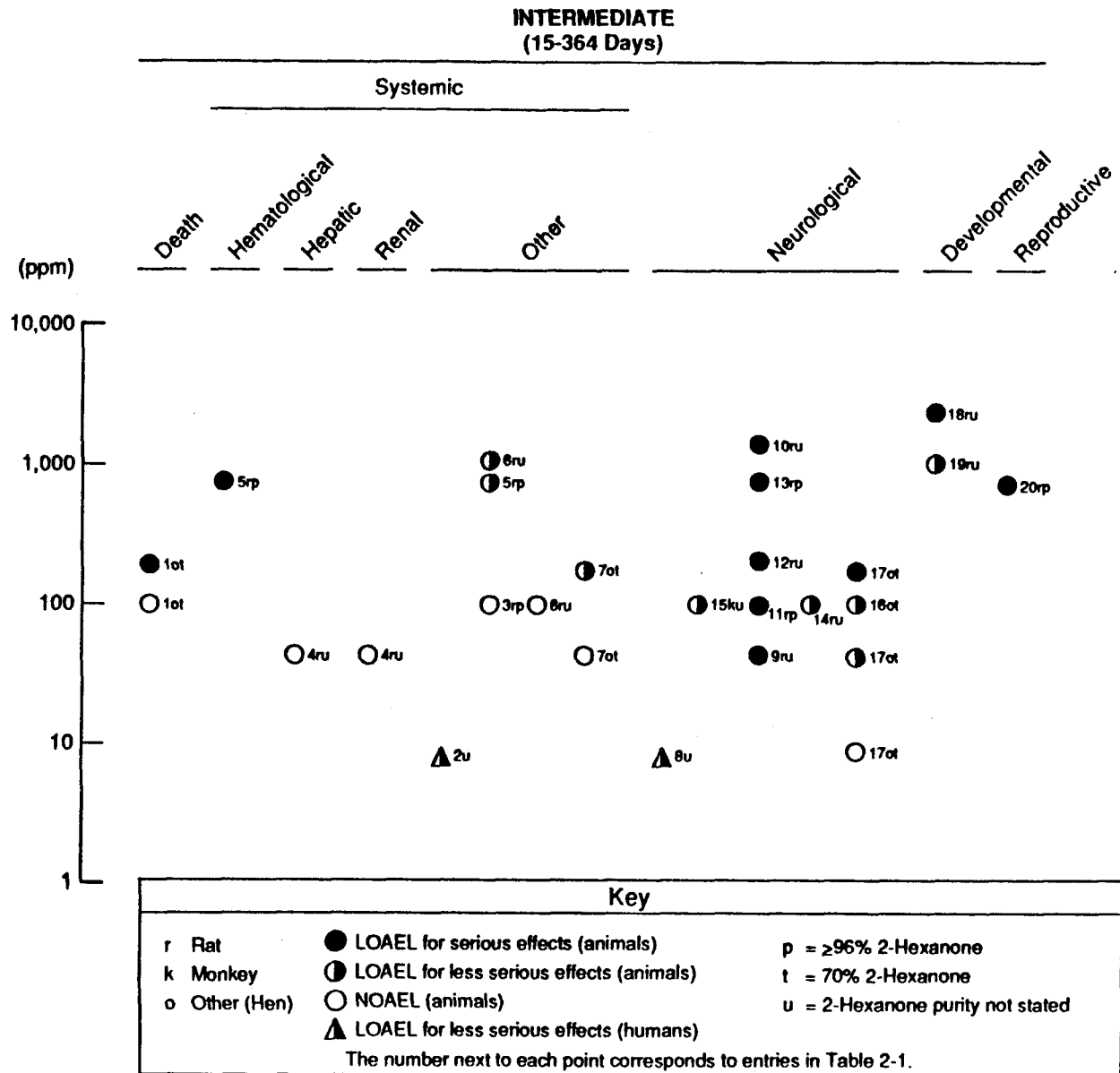
TABLE 2-1 (Continued)

Key to figure ^a	Species	Exposure frequency/ duration	System	NOAEL (ppm)	LOAEL (effect)		Reference	Purity
					Less serious (ppm)	Serious (ppm)		
Reproductive								
20	Rat	11 wk 72 hr/wk 18 hr/d				700 (decreased testes weight, histopathology)	Katz et al. 1980	P

^aThe number corresponds to entries in Figure 2-1.

d = day(s); Gd = gestation days; Hemato = hematological; hr = hour(s); lb = pounds; LOAEL = lowest-observed-adverse-effect level; mo = month(s); ND = no data; NOAEL = no-observed-adverse-effect level; occup = occupational; P = ≥96% 2-hexanone; T = 70% 2-hexanone; U = 2-hexanone purity not stated; WBC = white blood cells; wk = week(s)

FIGURE 2-1. Levels of Significant Exposure to 2-Hexanone – Inhalation



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2.2.1.2 Systemic Effects

The systemic effects observed after inhalation exposure to 2-hexanone are discussed below. The NOAEL values and all reliable LOAEL values for systemic effects in each species and duration category are recorded in Table 2-1 and plotted in Figure 2-1.

No studies were located regarding respiratory, cardiovascular, gastrointestinal, or dermal/ocular effects in humans or animals after inhalation exposure to 2-hexanone.

Hematological Effects. No studies were located regarding hematological effects in humans after inhalation exposure to 2-hexanone.

A reduction in total leukocyte counts to about 60% of control values ($p < 0.05$) was observed in rats intermittently exposed to 700 ppm 2-hexanone (96.1% purity) after 8 weeks of an 11-week study (Katz et al. 1980). Hemoglobin concentration, hematocrit, and differential white cell counts were similar to control values. Although the decrease in total white blood cell counts suggested an effect on bone marrow, the authors found no microscopic evidence of such damage. Therefore, the clinical significance of their findings was uncertain. In addition, only a single dosage level was used in the study.

Musculoskeletal Effects. No studies were located regarding musculoskeletal effects in humans or animals after inhalation exposure to 2-hexanone. Weakness and lack of coordination have been observed in several studies; however, these effects have been attributed to nerve damage (see Section 2.2.1.4).

Hepatic Effects. No studies were located regarding hepatic effects in humans after inhalation exposure to 2-hexanone.

There was no effect on hexobarbital-induced sleep times in rats exposed continuously to 225 ppm 2-hexanone (purity not stated) for 7 days (Couri et al. 1977). Thus, 2-hexanone exposure under these conditions does not seem to affect the hepatic microsomal enzyme activities associated with this response. No histopathological effects were seen in the livers of rats exposed to 50 ppm 2-hexanone (purity not stated) for 6 months (Duckett et al. 1979). However, no additional data on potential hepatic effects were found.

Renal Effects. No studies were located regarding renal effects in humans after inhalation exposure to 2-hexanone. No histopathological effects were seen in the kidneys of rats exposed to 50 ppm 2-hexanone (purity not stated) for 6 months (Duckett et al. 1979).

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Other Systemic Effects. The most common systemic effect observed following inhalation exposure to 2-hexanone is weight loss or a decreased rate of weight gain in developing animals.

A 1973 outbreak of distal polyneuropathy involving 86 of 1,157 employees was reported in a plant that had been using 2-hexanone for about 10 months in the production of plastic-coated and color-printed fabrics (Allen et al. 1975; Billmaier et al. 1974). (Neurological effects associated with this exposure are discussed in Section 2.2.1.4.) Clinical evaluations indicated that of 10 workers whose body weight was recorded, weight loss ranging from 3 to 60 pounds was observed in the eight workers found to have moderate to severe neurological impairment (Allen et al. 1975). Of the milder cases, no significant weight change could be correlated with the presence of the disorder. Atmospheric sampling conducted after this incident indicated that 2-hexanone levels averaged 9.2 ppm in front of the printing machines and 36 ppm behind the machines. After the use of 2-hexanone was discontinued, weight gain was uniformly noted in those who had lost weight.

In animal studies involving 3-6 months of inhalation exposure to 2-hexanone, both weight loss and decreased rates of weight gain in developing animals were noted.

A progressive but not statistically significant loss of body weight was reported in monkeys, beginning 4 months after exposure to 1,000 ppm 2-hexanone (purity not stated) (Johnson et al. 1977). These effects were not seen at 100 ppm. Exposure of rats to 1,000 ppm 2-hexanone (purity not stated) resulted in statistically significant weight loss at weeks 2-10 and 20-24 (Johnson et al. 1977). No effects were seen at 100 ppm in that study or in a similar 6-month study in rats (Egan et al. 1980). Other available single-dose level studies in rats generally support these observations. A marked reduction in weight gain was observed in rats exposed to 700 ppm 2-hexanone (96.1% purity) within 3 days of exposure during an 11-week study (Katz et al. 1980). Slow progressive weight loss (no details provided) in rats after 10 weeks of exposure to 1,300 ppm 2-hexanone (purity not stated) has also been reported (Spencer et al. 1975).

In hens, a clear dose-response relationship for effects on body weight resulting from inhalation of 2-hexanone was observed during a 13-week study by Abdo et al. (1982). No effects were seen at 10 or 50 ppm. Hens exposed to 100 ppm weighed about 92% of their initial weight at the end of 13 weeks of exposure. Hens exposed to 200 ppm weighed 58% of their initial weight after 10 weeks of exposure, and hens exposed to 400 ppm weighed 48% of their initial weight after 4 weeks of exposure. Hens exposed to 100 ppm 2-hexanone (70% purity) for 13 weeks had a nonsignificant increase in body weight (Abou-Donia et al. 1985a).

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It is noteworthy that in three species (monkeys, rats, and hens), 3-6 months of exposure to 2-hexanone at 100 ppm resulted in little or no effect on body weight parameters. Levels measured in the epidemiological study of exposed workers, however, were only 9.2-36 ppm (Allen et al. 1975). However, these levels were measured after the incident. If these low levels of 2-hexanone are a reasonably accurate indication of the conditions of human exposure that resulted in the observed weight loss, humans may be a very sensitive species with regard to this parameter. It is not clear whether the affected individuals had decreased appetites and/or food consumption levels in conjunction with their weight loss.

2.2.1.3 Immunological Effects

No studies were located regarding immunological effects in humans after inhalation exposure to 2-hexanone.

A reduction in total white blood cell counts to 60% of control values ($p < 0.05$), but no changes in differential white cell counts or evidence of bone marrow damage, was found in rats intermittently exposed to 700 ppm 2-hexanone after 8 weeks during an 11-week study (Katz et al. 1980). These findings, although inconclusive, suggest that immunological effects may warrant some consideration in future assessments of the potential toxicity of inhalation exposure to 2-hexanone.

2.2.1.4 Neurological Effects

In humans, the most important effect associated with inhalation exposure to 2-hexanone is neurological dysfunction, most commonly observed as peripheral neuropathy. Widespread attention was brought to this phenomenon after a 1973 outbreak of distal neuropathy in an Ohio fabric finishing plant that had introduced the use of 2-hexanone into its processing operations approximately 10 months before the first cases of neuropathy were reported. The screening of 1,157 employees resulted in the detection of 86 verified cases of neuropathy (Allen et al. 1975). Eleven of these cases were moderate to severe with both motor and sensory involvement; 38 were mild with sensory signs prevailing; and 37 were considered minimal, without clinical manifestations but with characteristic electrodiagnostic abnormalities. General characteristics of the neuropathy included muscle weakness, sensory loss (inability to discriminate pain, touch, temperature, or vibration) in the hands and feet, and diminution or loss of reflexes. Electromyographic (EMG) testing generally indicated that nerve conduction velocities (NCVs) were slower, especially in the ulnar, peroneal, tibial, and sural nerves, and the distal latencies (times to response) were prolonged in parallel to the reduction of the NCV. Other abnormalities included waves and fibrillations, especially in the more severe cases, and a decrease in the number and an increase in the size of motor unit potentials. No histological evidence of nerve damage was obtained in any of these patients. Atmospheric sampling conducted after this incident indicated that 2-hexanone levels in the

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processing plant averaged 9.2 ppm in front of the printing machines and 36 ppm behind them. After the use of 2-hexanone was discontinued, marked improvement was seen in the affected employees during the next few months, including all of the moderate-to-severe cases and most of the mild and minimal cases. However, the authors stated that it was not possible to rule out a possible synergistic effect with methyl ethyl ketone or with other chemicals used at the plant.

This industrial incident apparently prompted most of the ensuing animal research on the effects of inhalation exposure to 2-hexanone. Several studies were conducted in rats in an attempt to describe the histopathological basis of the observed neuropathy, and several other studies were concerned with the ability of 2-hexanone exposure to potentiate the adverse effects of exposure to other agents. As described above, most of the animal neurotoxicity studies involved the use of only a single dose of 2-hexanone, usually as a control group for comparison with the effects of combined exposure to 2-hexanone and another compound, and several other studies used a single high dose of 2-hexanone in order to elicit neurotoxicity and assess the accompanying histopathological changes.

In all animals studied, including monkeys, cats, rats, and chickens, the clinical observations generally indicated a progression from weakness and ataxia to complete paralysis of the limbs. These clinical observations were accompanied or preceded by morphological changes in the peripheral nerves, including an increase in the number of neurofilaments in the nerve fibers, axonal swelling, and inpouchings and thinning of the myelin sheath. It is also important to note that 2,5-hexanedione, a metabolite of 2-hexanone in rats, guinea pigs, and humans (DiVincenzo et al. 1976, 1978; Eben et al. 1979) has been observed to elicit severe neuropathy following oral administration to rats (Krasavage et al. 1980) and following oral, dermal, or intraperitoneal administration to hens (Abou-Donia et al. 1982, 1985b). Comparative studies of the relative neurotoxicities of 2-hexanone, 2,5-hexanedione, and other compounds have concluded that 2,5-hexanedione is a more potent neurotoxicant than 2-hexanone (Abou-Donia et al. 1982; Krasavage et al. 1980).

Severe neurotoxicity was reported in rats as a result of 7 days of continuous inhalation exposure to 225 ppm 2-hexanone (Couri et al. 1977). However, no data for this toxic effect were given in the study. Paralysis was observed in rats exposed to 225 ppm 2-hexanone (purity not stated) for 9.5 weeks or to 400 ppm for 6 weeks (Saida et al. 1976). Inpouchings of the myelin sheath of the peripheral nerves occurred as early as 16 days at both dose levels. Other histopathological findings included denuded fibers and swollen axons. Continuous inhalation exposure of rats to 2-hexanone (purity not stated), initially at 600 ppm but lowered to 400 ppm to prevent weakness and weight loss, resulted in hind limb dragging at 11-12 weeks (Mendell et al. 1974b). Histopathological observations were axonal swelling and demyelination of nerve fibers. In rats exposed to 100 ppm 2-hexanone for 25-29 weeks, there was a progressive, statistically significant decrease in the maximum motor

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conduction velocity (MCV) of the sciatic-tibial nerve at 29 weeks and of the ulnar nerve at 17 weeks. An effect on operant behavior, manifest as a reduced response rate in bar-pressing studies, was also reported. At 1,000 ppm exposure, these effects were seen earlier (Johnson et al. 1977). Rats exposed to 700 ppm 2-hexanone (96.1% purity) during an 11-week study developed clinical signs of neurotoxicity as early as the second week of exposure (Katz et al. 1980). Observations included reduced body muscle tone and weakened hind- and forelimb grasping of a wire mesh.

In a 6-month study, rats exposed to 100 ppm 2-hexanone (96.7% purity) did not demonstrate clinical signs of neuropathy. However, after 4 months of exposure, giant axonal swellings and demyelination were seen in fibers of the tibial nerves; by 6 months degeneration had ascended to the sciatic notch. In the central nervous system, 4-month observations included giant axonal swellings in the medulla oblongata and cerebellum. By 6 months the spinal cord had scattered fiber degeneration in the gracile tract and the lumbar region (Egan et al. 1980). In a 6-month study in rats, inhalation exposure to 50 ppm 2-hexanone (purity not stated) resulted in histopathological effects including demyelination of the sciatic nerve, and axonal hypertrophy and beading (Duckett et al. 1979). Rats exposed to 1,300 ppm during a 40-week study developed a pronounced symmetrical hindlimb footdrop, hindlimb and forelimb weakness, and nerve fiber swelling and degeneration (Spencer et al. 1975).

In a 10-month study, monkeys exposed to 1,000 ppm 2-hexanone had abnormal results in electrodiagnostic tests (Johnson et al. 1977). There was a progressive and statistically significant decrease in the maximum motor conduction velocity of the sciatic-tibial nerves starting at 4 months of exposure and a decrease in the maximum conduction velocity of the ulnar nerves starting at 1 month. Decreased amplitude of evoked muscle action potential was also seen at 1,000 ppm. Results of 100 ppm exposure were similar to those of controls except for a statistically significant decreased response in the ulnar nerve at the 1 and 3 month measurements and in the sciatic-tibial nerve only at 9 and 10 months. Recovery to pre-exposure values for motor conduction velocities took 2 months for the 100 ppm group and 6 months for the 1,000 ppm group.

Clinical signs of neuropathy were evident in cats after continuous inhalation exposure to 400-600 ppm 2-hexanone (purity not stated) for 5 weeks or more (Mendell et al. 1974b). (Initial exposure to 600 ppm was lowered to 400 ppm in order to prevent weakness and weight loss.) Hindlimb dragging was followed by forelimb weakness and eventual paralysis. The EMG studies showed a dramatic decrease (56%) in the ulnar nerve conduction velocity. Axonal swelling and demyelination of the nerve fibers were also observed. One of these cats was observed by Saida et al. (1976) for 4.5 months after exposure in order to assess recovery. The animal eventually regained the ability to walk, swollen axons were greatly reduced in number, and nerve fibers showed signs of remyelination.

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Continuous inhalation exposure of hens to 2-hexanone (purity not stated) initially at 200 ppm, then lowered to 100 ppm to prevent weakness and weight loss, resulted in overt clinical signs of neuropathy at 4-5 weeks when the animals could no longer stand (Mendell et al. 1974b). Histopathological observations included axonal swelling and demyelination of nerve fibers. In a go-day inhalation study in hens followed by a 30-day recovery period, neurological effects were not apparent in the group exposed to 10 ppm 2-hexanone (70% purity) (Abdo et al. 1982). Mild ataxia (diminished leg movements and reluctance to walk) was seen with 4 weeks of exposure to 50 ppm; this progressed to near paralysis by 13 weeks. At higher levels, these effects were seen earlier. Exposure to 200 ppm resulted in mild ataxia after 2 weeks and paralysis after 10 weeks. Demyelination and axonal swelling were seen in the spinal cord at 50 ppm and in both the spinal cord and peripheral nerves at 100 ppm and above. During the 30-day recovery period, slight clinical improvement was seen in the 50 ppm group. In another go-day study, hens exposed to 100 ppm 2-hexanone (70% purity) had mild ataxia after 39 days of exposure but no evidence of histopathological changes in nerve tissue (Abou-Donia et al. 1985a).

As noted above, the test compound used in two of the studies in hens, Abdo et al. (1982) and Abou-Donia et al. (1985a), was technical grade 2-hexanone with a purity level of 70%. The other 30% component of this formulation was methyl isobutyl ketone. In a 90-day study in which hens were exposed to pure methyl isobutyl ketone at 1,000 ppm via inhalation, this compound failed to induce neurotoxicity (Abou-Donia et al. 1985c). However, in hens simultaneously exposed to 1,000 ppm n-hexane (which by itself was mildly neurotoxic), with increasing concentrations of methyl isobutyl ketone (100-1,000 ppm) there was a dose-related response of increasingly severe ataxia progressing to paralysis. In addition, histopathological changes of the nervous system progressed to degeneration of the spinal cord and lesions in the peripheral nerves. These results are important to note because they serve to illustrate that a potential for synergistic interaction or potentiation exists with combined exposure to methyl isobutyl ketone and at least one other compound, n-hexane. It is, therefore, possible that combined exposure to 2-hexanone and methyl isobutyl ketone, as in the Abdo et al. (1982) and Abou-Donia et al. (1985a) studies can result in synergistic interaction or a potentiation effect (see Section 2.6).

In addition to the neurological effects in the studies described above, behavioral alterations were reported in the offspring of pregnant rats exposed to 1,000 ppm 2-hexanone (purity not stated) during and after gestation (Peters et al. 1981) (see Section 2.2.1.5).

The highest NOAEL value in hens and all reliable LOAEL values for neurological effects in each species in the intermediate-duration category are recorded in Table 2-1 and plotted in Figure 2-1.

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2.2.1.5 Developmental Effects

No studies were located regarding developmental effects in humans after inhalation exposure to 2-hexanone.

Behavioral alterations were reported in the offspring of pregnant rats exposed to 1,000 ppm or 2,000 ppm 2-hexanone (purity not stated) during 21 days of gestation (Peters et al. 1981). These effects consisted of reduced activity in the open field, increased activity in the running wheel, and deficits in avoidance conditioning. Offspring of treated dams (both dose levels) clung to an inclined screen longer than offspring of controls at all ages (newborn, weanling, puberty, and adult) except geriatric in which results were similar to those of controls. For offspring in the puberty and adult categories, pronounced sex differences were noted, with females in all exposure categories (including controls) clinging from 24% to 100% longer than males. However, the biological significance of this observation is unknown. There was a decreased rate of avoidance learning in puberty-aged females of treated dams and increased random movement in both puberty-aged and adult offspring of treated dams. Behavioral tests in most cases indicated that maternal exposure to 2-hexanone was associated with hyperactivity in the young and decreased activity in the geriatric stage, which the authors speculated to be due to premature aging resulting from the earlier hyperactivity. It is not clear whether these effects are the result of transplacental exposure to 2-hexanone or of postnatal exposure to 2-hexanone and/or its metabolites via the milk of the exposed dams.

In addition, decrements were observed in the weight gain of pregnant rats exposed to 1,000 ppm or 2,000 ppm 2-hexanone during 21 days of gestation (Peters et al. 1981). These decreases were 10% and 14%, respectively; statistical significance was not addressed. Rats in the 2,000 ppm exposure group were observed to eat less than did the controls. There was also a significant decrease in the number and weight of live offspring of dams in the 2,000 ppm exposure group.

The LOAEL values for developmental effects in rats in the intermediateduration category are recorded in Table 2-1 and plotted in Figure 2-1.

2.2.1.6 Reproductive Effects

No studies were located regarding reproductive effects in humans after inhalation exposure to 2-hexanone.

Marked and significant reductions in absolute and relative testes weight and atrophy of testicular germinal epithelium were observed in male rats exposed to 700 ppm 2-hexanone for 11 weeks (Katz et al. 1980).

The LOAEL value for reproductive effects in rats for the intermediate-duration category is recorded in Table 2-1 and plotted in Figure 2-1.

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2.2.1.7 Genotoxic Effects

No studies were located regarding genotoxic effects in humans or animals after inhalation exposure to 2-hexanone.

2.2.1.8 Cancer

No studies were located regarding cancer effects in humans or animals after inhalation exposure to 2-hexanone.

2.2.2 Oral Exposure

Several studies were conducted in which only a single high dose of 2-hexanone was orally administered to rats in an attempt to induce and consequently study the resulting neurotoxic effects. In addition, only a few of the studies were conducted using 2-hexanone of a stated purity of 96% or better. Other studies used a formulation containing 70% 2-hexanone or the purity of the test substance was not stated. As a result, the usefulness of the existing data base using the oral route is limited.

2.2.2.1 Death

An LD₅₀ of 2,590 mg/kg was calculated for a gavage administration of 2-hexanone (purity not stated) to rats (Smyth et al. 1954). One of 4 hens administered 2-hexanone (70% purity) at 2,000 mg/kg by gavage died (Abou-Donia et al. 1982). No lethality occurred in 24 hours in 6 male rats that received 2-hexanone (>99% purity) at 1,500 mg/kg by gavage (Hewitt et al. 1980a).

The highest NOAEL value, a reliable LOAEL value for death and an LD₅₀ value for these species in the acute-duration category are recorded in Table 2-2 and plotted in Figure 2-2.

2.2.2.2 Systemic Effects

The systemic effects observed after oral exposure to 2-hexanone are discussed below. The highest NOAEL values and all reliable LOAEL values for systemic effects in each species and duration category are recorded in Table 2-2 and plotted in Figure 2-2.

No studies were located regarding respiratory, cardiovascular, gastrointestinal, hematological, musculoskeletal, or dermal/ocular effects in humans or animals after oral exposure to 2-hexanone.

Hepatic Effects. No studies were located regarding hepatic effects in humans after oral exposure to 2-hexanone.

TABLE 2-2. Levels of Significant Exposure to 2-Hexanone - Oral

Key to figure ^a	Species	Route	Exposure frequency/ duration	System	NOAEL (mg/kg/day)	LOAEL (effect)		Reference	Purity
						Less serious (mg/kg/day)	Serious (mg/kg/day)		
ACUTE EXPOSURE									
Death									
1	Rat	(G)	1x				2590 (LD50)	Smyth et al. 1954	U
2	Rat	(GO)	1x		1500			Hewitt et al. 1980a	P
3	Hen	(G)	1x				2000 (death of 1/4)	Abou-Donia et al. 1982	T
Systemic									
4	Rat	(G)	1x	Hepatic	1500			Hewitt et al. 1986	U
5	Rat	(GO)	1x	Hepatic Renal	1500 1500			Hewitt et al. 1980a	P
INTERMEDIATE EXPOSURE									
Systemic									
6	Rat	(G)	90 d 5d/wk 1x/d	Other		660 (weight loss)		Krasavage et al. 1980	P
7	Rat	(GW)	40 wk 1x/d	Hepatic Renal	400 400			Eben et al. 1979	P
Neurological									
8	Rat	(G)	90 d 5d/wk 1x/d				660 (paralysis, histopathology)	Krasavage et al. 1980	P
9	Gn pig	(W)	24 wk			600 (abnormal pupil response)		Abdel-Rahman et al. 1978	U

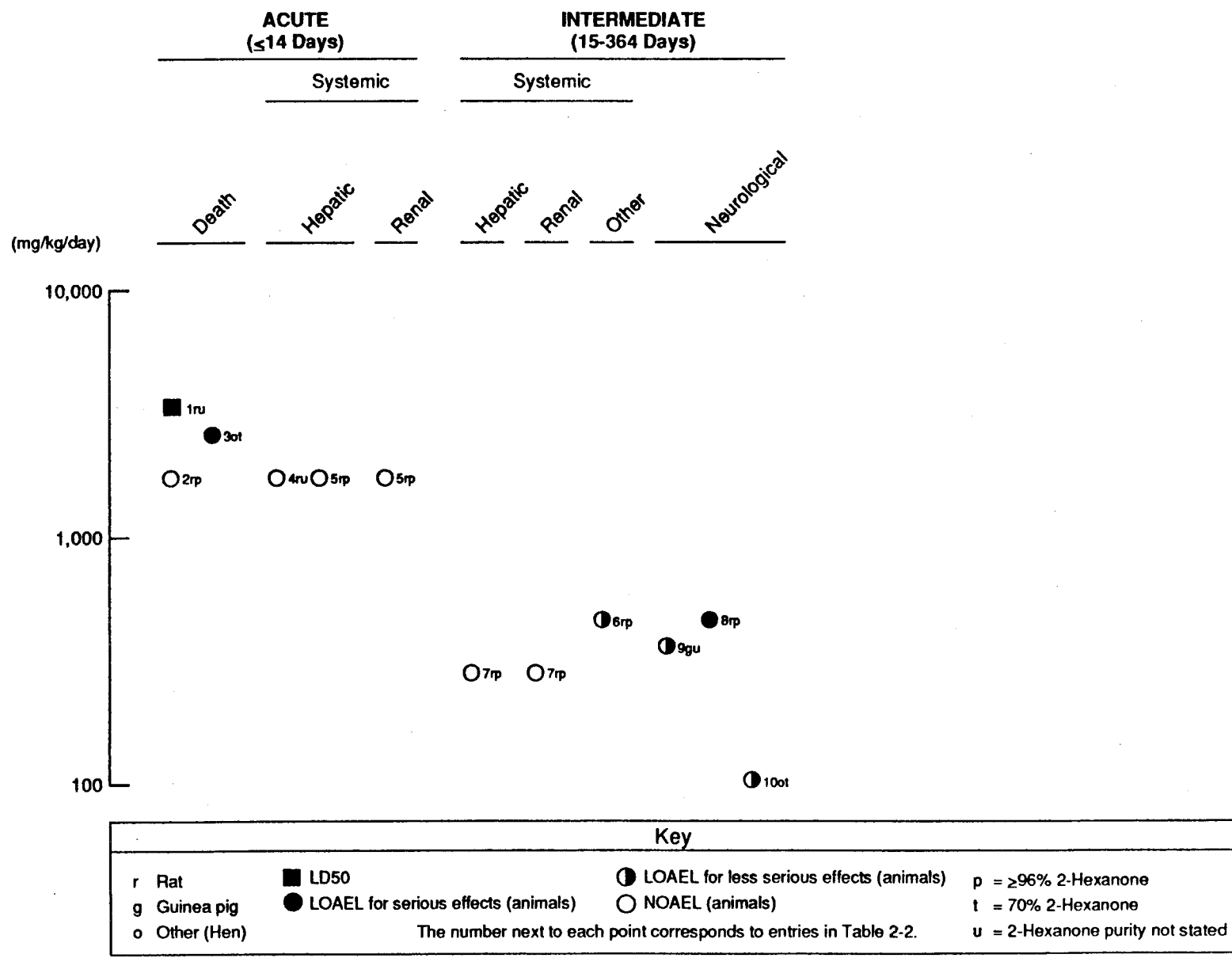
TABLE 2-2 (Continued)

Key to figure ^a	Species	Route	Exposure frequency/ duration	System	NOAEL (mg/kg/day)	LOAEL (effect)		Reference	Purity
						Less serious (mg/kg/day)	Serious (mg/kg/day)		
10	Hen	(G)	90 d 7d/wk 1x/d			100 (ataxia)		Abou-Donia et al. 1982	T

^aThe number corresponds to entries in Figure 2-2.

d = day(s); (G) = gavage; (GO) = gavage - oil; Gn pig = guinea pig; (GW) = gavage - water; Hemato = hematological; LD50 = lethal dose, 50% mortality; LOAEL = lowest-observed-adverse-effect level; NOAEL = no-observed-adverse-effect level; P = ≥96% 2-hexanone; T = 70% 2-hexanone; U = 2-hexanone purity not stated; (W) = water; wk = week(s); x = time(s)

FIGURE 2-2. Levels of Significant Exposure to 2-Hexanone – Oral



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Various studies were conducted in rats in which the potential hepatic effects of oral administration of 2-hexanone combined with exposure to another agent were assessed. In rats given single doses of 2-hexanone up to 1,500 mg/kg by gavage, no effects were observed on liver histology, plasma glutamic-pyruvic transaminase levels (as a measure of centrilobular necrosis), measurements of the permeability of the biliary tree, malondialdehyde production (as a measure of lipid peroxidation), or total bilirubin levels in plasma (Cowlen et al. 1984b [2-hexanone purity not stated]; Hewitt et al. 1980a [2-hexanone purity >99%]; Hewitt et al. 1986 [2-hexanone purity not stated]). Rapid depletion of hepatic glutathione (GSH) levels was observed in rats given a single gavage dose of 2-hexanone (purity not stated) at 1,000 mg/kg (Cowlen et al. 1984a) and at 1,500 mg/kg (purity not stated) (Branchflower and Pohl 1981). The effect at 1,000 mg/kg was reported to be transient. Branchflower and Pohl (1981) postulated that this depletion might be associated with the potentiation of toxic effects from chloroform (CHCl_2) when coadministered with 2-hexanone, since depletion of hepatic GSH could allow more phosgene (COCl_2) (the toxic oxidation product of chloroform) to react with sensitive tissue components.

In a 40-week study in which rats were administered 2-hexanone at 400 mg/kg/day, the levels of liver enzymes (alanine aminotransaminase and aspartate transaminase activities) measured at 4-week intervals were normal (Eben et al. 1979).

Renal Effects. No studies were located regarding renal effects in humans after oral exposure to 2-hexanone.

In studies in which rats were given a single gavage dose of 2-hexanone up to 1,500 mg/kg, no alterations were observed in renal morphology, renal cortical p-aminohippurate accumulation, plasma creatinine concentration (Brown and Hewitt 1984), blood urea nitrogen (BUN), renal GSH levels (Branchflower and Pohl 1981), ornithine carbamyl transferase (OCT) activities, or accumulation of p-aminohippurate (PAH) or tetraethylammonium (TEA) (Hewitt et al. 1980a). In male rats given 2-hexanone at 1,500 mg/kg, however, 9.6% of the renal tubules examined were degenerated (as compared with 1% of controls) (Hewitt et al. 1980a). The statistical significance of this finding was not addressed. Plasma urea concentrations were normal in rats that received daily gavage administrations of 2-hexanone at 400 mg/kg/day for 40 weeks (Eben et al. 1979). Other Systemic Effects. No studies were located regarding effects on body weight in humans after oral exposure to 2-hexanone.

Decreased weight gain was (specific data and statistical significance not provided) reported in rats given daily doses of 400 mg/kg/day for 40 weeks (Eben et al. 1979). Rats given 2-hexanone (undiluted) by gavage at

2. HEALTH EFFECTS

660 mg/kg/day in a 90-day study, weighed about 65% of control weights by 10 weeks of exposure (Krasavage et al. 1980). However, it is not clear from the data provided whether these rats were too weak or ataxic to eat.

2.2.2.3 Immunological Effects

No studies were located regarding immunological effects in humans or animals after oral exposure to 2-hexanone.

2.2.2.4 Neurological Effects

No studies were located regarding neurological effects in humans after oral exposure to 2-hexanone.

Neurological effects resulting from oral administration of 2-hexanone have been reported in three species of animals. In hens that received a single gavage dose of 2-hexanone at 2,000 mg/kg, mild weakness was observed on the day of administration, followed by apparent recovery in 4-5 days. Hens that received 100 mg/kg showed no signs of neurotoxicity (Abou-Donia et al. 1982). In a subchronic (90-day) phase of the same study, hens administered 2-hexanone at 100 mg/kg/day or higher developed severe ataxia or near paralysis. There was also evidence of histopathological changes including swelling or degeneration of thoracic and lumbar regions of the spinal cord. Some of the observations were described by the authors as equivocal.

Severe hindlimb dragging or paralysis was observed in all rats that received 2-hexanone (undiluted) by gavage at 660 mg/kg/day at about day 56 (8 weeks) of a 90-day study (Krasavage et al. 1980). Morphologic changes indicative of "giant axonal" neuropathy included multifocal axonal swellings and myelin infolding and paranodal retraction. In rats that received 400 mg/kg/day in a 40 week study, there was a temporary weakness of the hindlimbs from 17 to 28 weeks of exposure (Eben et al. 1979). Improvement was observed after that period.

Abnormal pupillary responses to light (measured by changes in pupillary diameter) were observed in guinea pigs given 2-hexanone in drinking water at dosage levels of approximately 600 mg/kg/day during a 24-week study (Abdel-Rahman et al. 1978). Effects were seen from the first week of treatment.

It is important to note that 2,5-hexanedione, a metabolite in the blood and urine of rats and in the urine of guinea pigs orally administered 2-hexanone (DiVincenzo et al. 1976; Eben et al. 1979), has been demonstrated to elicit severe neurotoxicity following oral, dermal, or intraperitoneal administration to hens (Abou-Donia et al. 1982; 1985b) and following oral administration to rats (Krasavage et al. 1980).

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Reliable LOAEL values for neurological effects in each species in the intermediate-duration category are recorded in Table 2-2 and plotted in Figure 2-2.

2.2.2.5 Developmental Effects

No studies were located regarding developmental effects in humans or animals after oral exposure to 2-hexanone.

2.2.2.6 Reproductive Effects

No studies were located regarding reproductive effects in humans after oral exposure to 2-hexanone.

Male rats that were given 2-hexanone at 660 mg/kg/day (undiluted) by gavage in a 90-day study were observed to develop atrophy of the germinal epithelium of the testes (Krasavage et al. 1980). However, the statistical significance of this observation was not addressed.

2.2.2.7 Genotoxic Effects

No studies were located regarding genotoxic effects in humans or animals after oral exposure to 2-hexanone.

2.2.2.8 Cancer

No studies were located regarding cancer effects in humans or animals after oral exposure to 2-hexanone.

2.2.3 Dermal Exposure

Very little information was located regarding health effects in humans or animals after dermal exposure to 2-hexanone.

2.2.3.1 Death

No studies were located regarding death in humans or animals after dermal exposure to 2-hexanone.

2.2.3.2 Systemic Effects

No studies were located regarding respiratory, cardiovascular, gastrointestinal, hematological, musculoskeletal, hepatic, or renal effects in humans or animals after dermal exposure to 2-hexanone.

Dermal/Ocular Effects. No studies were located regarding dermal/ocular effects in humans after dermal exposure to 2-hexanone.

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Application of undiluted 2-hexanone to the skin of rabbits for 24 hours resulted in Grade 1 (least severe) irritation (Smyth et al. 1954). Ocular instillation resulted in Grade 3 (moderate) corneal necrosis.

2.2.3.3 Immunological Effects

No studies were located regarding immunological effects in humans or animals after dermal exposure to 2-hexanone.

2.2.3.4 Neurological Effects

No studies were located regarding neurological effects in humans after dermal exposure to 2-hexanone.

2-Hexanone (99% purity) applied to the backs of hens' necks at 100 mg/kg/day for 90 days resulted in gross ataxia (Abou-Donia et al. 1985b). Histological changes observed were swollen axons without obvious fragmentation of the axon or myelin sheath. No precautions against licking were mentioned in the study.

The LOAEL for neurological effects in hens in the intermediate-duration category is recorded in Table 2-3.

No studies were located regarding the following health effects in humans or animals after inhalation exposure to 2-hexanone:

2.2.3.5 Developmental Effects

2.2.3.6 Reproductive Effects

2.2.3.7 Genotoxic Effects

2.2.3.8 Cancer

2.3 TOXICOKINETICS

Data on the toxicokinetics of 2-hexanone, as described in this section, were derived from studies using 2-hexanone with purity of 97% or more. As discussed below, absorption of this compound has been demonstrated in humans, dogs, and rats after administration via inhalation, oral, or dermal exposure. Very little information is available on distribution. A metabolic pathway has been proposed based on the metabolites of 2-hexanone identified in the blood of guinea pigs and rats after intraperitoneal and oral administration, respectively. Expired breath and urine appear to be the main routes of excretion for 2-hexanone and its metabolites.

TABLE 2-3. Levels of Significant Exposure to 2-Hexanone - Dermal

Species	Route	Exposure frequency/ duration	System	NOAEL (mg/kg/day)	LOAEL (effect)		Reference	Purity
					Less serious (mg/kg/day)	Serious (mg/kg/day)		
INTERMEDIATE EXPOSURE								
Neurological								
Hen		90 d 7d/wk 1x/d			100 (ataxia)		Abou-Donia et al. 1985b	P

d = day(s); LOAEL = lowest-observed-adverse-effect level; NOAEL = no-observed-adverse-effect level; P = >96% 2-hexanone;
wk = week(s); x = time(s)

2. HEALTH EFFECTS

2.3.1 Absorption

2.3.1.1 Inhalation Exposure

The available data indicate that 2-hexanone is well absorbed after administration via the inhalation route. An analysis of the expired breath of humans who inhaled 2-hexanone at 10 or 50 ppm for 7.5 hours or 100 ppm for 4 hours indicated that 75%-92% of the inhaled 2-hexanone vapor was absorbed by the lungs and respiratory tract (DiVincenzo et al. 1978).

Similarly, beagles that inhaled 2-hexanone at 50 or 100 ppm for 6 hours absorbed 65%-68% of the inhaled vapor (DiVincenzo et al. 1978).

2.3.1.2 Oral Exposure

2-Hexanone also appears to be well absorbed after oral administration. Humans who ingested a single capsule containing ^{14}C -2-hexanone at 0.1 mg/kg excreted about 40% of the ^{14}C in breath and 26% in urine during the next 8 days (DiVincenzo et al. 1978). This indicates that the absorbed amount averaged at least 66% of the administered dose.

Administration of $1\text{-}^{14}\text{C}$ -2-hexanone at 20 or 200 mg/kg by gavage to rats resulted in excretion of about 1.2% of the administered radioactivity in the feces, about 44% in the breath, 38% in urine, and 16% remaining in the carcass (DiVincenzo et al. 1977). The results were similar at either dosage level. These findings suggest that about 98% of the administered dose was absorbed.

2.3.1.3 Dermal Exposure

2-Hexanone is also absorbed after dermal application. The excretion of ^{14}C in the breath and urine of two human volunteers was measured after a 60-minute occlusive application of ^{14}C -2-hexanone to their shaved forearms (DiVincenzo et al. 1978). Calculated skin absorption rates were 4.8 and 8.0 pg/min/cm²; however, the fraction of 2-hexanone that was absorbed was not calculated. ^{14}C -Hexanone was also applied to the clipped thorax of beagle dogs, and absorption was observed to be slow at first but increased dramatically after 20 minutes. At 60 minutes, 77 mg of 2-hexanone had penetrated the skin (DiVincenzo et al. 1978). The fraction of applied 2 hexanone that was absorbed was not calculated.

2.3.2 Distribution

2.3.2.1 Inhalation Exposure

No studies were located regarding distribution in humans or animals after inhalation exposure to 2-hexanone.

2. HEALTH EFFECTS

2.3.2.2 Oral Exposure

No studies were located regarding distribution in humans after oral exposure to 2-hexanone.

In rats administered a single dose of ^{14}C -2-hexanone at 200 mg/kg by gavage, tissue distribution was reported to be widespread with highest counts in the liver and blood. No quantitative data were given on tissue distribution (DiVincenzo et al. 1977). An analysis of subcellular distribution of the ^{14}C label in liver, brain, and kidney tissue indicated highest counts were associated with the crude lipid fraction and protein, with some recovery in DNA, and little or none in RNA.

2.3.2.3 Dermal Exposure

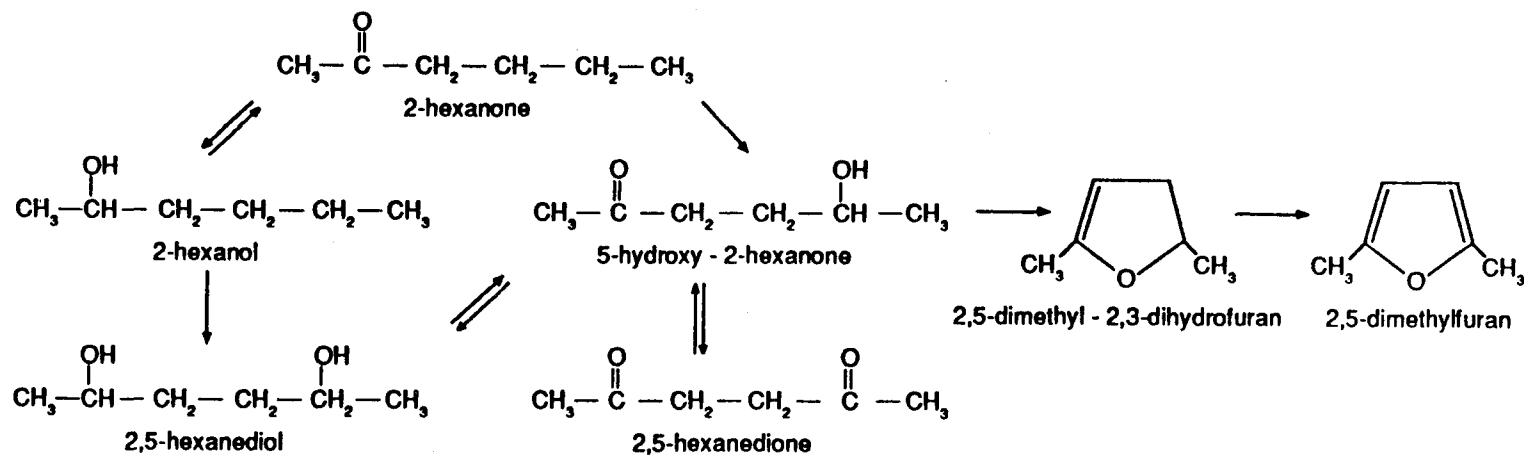
No studies were located regarding distribution in humans or animals after dermal exposure to 2-hexanone.

2.3.3 Metabolism

The proposed metabolic pathway for 2-hexanone, based on 2-hexanone metabolites identified in blood during intraperitoneal studies in guinea pigs (DiVincenzo et al. 1976) and oral studies in rats (DiVincenzo et al. 1977) is presented in Figure 2-3. Because inhalation exposure of humans to 2-hexanone has resulted in the appearance of carbon dioxide in expired air and 2,5-hexanedione in serum, DiVincenzo et al. (1978) have hypothesized that the metabolic pathway for 2-hexanone is similar in humans and experimental animals. The metabolism of aliphatic ketones has generally been found to proceed via reduction to the corresponding secondary alcohol, which accounts for the formation of 2-hexanol. An alternate pathway is oxidation of the 5-methylene group to the corresponding alcohol, 5-hydroxy-2-hexanone, which may be followed by further oxidation to the diketone 2,5-hexanedione. Another possibility in the metabolism of 2-hexanone is the cyclization of 5-hydroxy-2-hexanone to the corresponding dihydrofuran and oxidation to 2,5-dimethylfuran (DiVincenzo et al. 1977). However, the formation of these furan moieties may be the result of thermal dehydration and cyclization during gas chromatography (DiVincenzo et al. 1977). In addition, the gamma-valerolactone found in the urine (not shown in figure) is hypothesized to result from alphaoxidation of 5-hydroxy-2-hexanone to 2-keto-5-hydroxyhexanoic acid, decarboxylation and oxidation to 4-hydroxypentanoic acid, and lactonization to gamma-valerolactone (DiVincenzo et al. 1977).

A strong relationship has been noted between the concentration of 2,5-hexanedione in the urine and the onset of neuropathic symptoms (Eben et al. 1979). Similarly, 2,5-hexanedione was described as eliciting severe neurotoxic symptoms following oral, dermal, or intraperitoneal administration to hens (Abou-Donia et al. 1982, 1985b) and following oral administration to rats (Krasavage et al. 1980).

Figure 2-3. Proposed Metabolic Pathway for 2-Hexanone *



*Adapted from DiVincenzo et al. 1976, 1977

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There are two major hypotheses related to the mechanism of neurotoxicity of 2,5-hexanedione: covalent binding with axonal components of nerve tissue and inhibition of enzymes associated with the production of energy in this tissue. In vitro studies in which 2,5-hexanedione was incubated with proteins demonstrated that this compound binds to the lysine ϵ -amino group resulting in the formation of the substituted pyrrole adduct ϵ -N-(2,5-dimethylpyrrolyl)norleucine (DeCaprio et al. 1982). Covalent binding of 2,5-hexanedione with axonal components leading to pyrrole formation and protein cross-linking was hypothesized as a possible initiation step leading to axonal degeneration and thus may account for the neurotoxic effects observed with exposure to gammadiketones in general (DeCaprio et al. 1982, 1988). In vivo confirmation of pyrrole formation was reported based on the presence of ϵ -N-(2,5-dimethylpyrrolyl)norleucine in the hydrolyzed serum of a hen that had received 2,5-hexanedione at 200 mg/kg/day by gavage for two weeks (DeCaprio et al. 1982).

Other studies have demonstrated that both 2-hexanone and 2,5-hexanedione can inhibit sulfhydryl-dependent enzymes such as fructose-6-phosphate kinase (an enzyme in the pentose phosphate pathway) and glyceraldehyde-3-phosphate dehydrogenase (an enzyme in the glycolytic pathway) (Sabri et al. 1979b; Sabri 1984). Both of these neurotoxicants inhibited fructose-6-phosphate kinase crystallized from rabbit muscle or in rat brain homogenates; in each case, 2,5-hexanedione was the far more potent inhibitor (Sabri et al. 1979b). Preincubation with dithiothreitol protected this enzyme from inhibition, which suggests that these compounds interfere with the sulfhydryl groups required for fructose-6-phosphate kinase activity. However, dithiothreitol could not restore enzyme activity after these compounds had been added. In addition, fructose-6-phosphate kinase activity was also reduced in the brain homogenates of rats that had received 2,5-hexanedione at 0.5% of their drinking water for 10-12 weeks (Sabri et al. 1979b). Crystalline glyceraldehyde-3-phosphate dehydrogenase from rabbit muscle was also inhibited by both compounds; in this case, 2-hexanone was the more potent inhibitor (Sabri 1984). Levels of ATP were reduced in cat sciatic nerves treated with 2,5-hexanedione (Sabri 1984). 2-Hexanone was found to irreversibly inhibit rat brain and rabbit muscle creatine kinase and mouse brain adenylate kinase (Lapin et al. 1982).

In addition, oral administration of 1-¹⁴C-2-hexanone to humans or rats results in the appearance of ¹⁴CO₂ in the expired breath (DiVincenzo et al. 1977, 1978), indicating oxidation/cleavage of the alpha carbon. Administration of SKF525A (a mixed function oxidase inhibitor) to rats before oral administration of 2-hexanone resulted in a marked decrease in the excretion of respiratory ¹⁴CO₂ for the first 4 hours after administration, followed by a marked increase at 4-8 and 12-24 hours. This suggests that this oxidative step is mediated by a microsomal mixed function oxidase system (DiVincenzo et al. 1977).

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2.3.4 Excretion

2.3.4.1 Inhalation Exposure

In humans exposed to 2-hexanone via inhalation at 10 or 50 ppm for 7.5 hours or to 100 ppm for 4 hours, unchanged 2-hexanone (but none of its metabolites) was found in expired air, and neither 2-hexanone nor any of its metabolites was found in urine during or after exposure (DiVincenzo et al. 1978). 2-Hexanone was not detected in the expired air 3 hours after exposure to 50 or 100 ppm. These results suggest slow clearance and possible accumulation of 2-hexanone in humans exposed by this route.

In beagle dogs exposed to 2-hexanone via inhalation at 50 or 100 ppm for 6 hours, 32% and 35%, respectively, of the inhaled vapor was excreted in the expired breath (DiVincenzo et al. 1978). By 3-5 hours after exposure, 2-hexanone was no longer detected in expired air. Excretion via other routes was not addressed.

2.3.4.2 Oral Exposure

In two humans who received a single oral dose of 1-¹⁴C-2-hexanone, breath excretion of ¹⁴CO₂ CO, reached a peak within 4 hours, then decreased slowly over the next 3-5 days. Average overall recovery of the ¹⁴C-label in 8 days was 40% in breath and 26% in urine. Feces were not analyzed (DiVincenzo et al. 1978).

In rats administered a single oral dose of 1-¹⁴C-2-hexanone, DiVincenzo et al. (1977) observed similar results. Radioactivity in breath accounted for about 45% of the administered dose (5% was in unchanged 2-hexanone; 40% was in ¹⁴CO₂); 35% was found in the urine; 1.5% was recovered in the feces; and about 15% remained in the carcass. In male rats that received daily gavage doses of 2-hexanone at 400 mg/kg/day for 40 weeks, very low concentrations of free 2-hexanone were detected in the urine from the third week. A maximum concentration of approximately 20 ug was reached in the 17th week (Eben et al. 1979). Similarly, free 2,5-hexanedione was found in the urine after 3 weeks and peaked in the 17th week. Free and conjugated 2,5-hexanedione were present in the urine from the 1st week of the study. The conjugated form peaked in the 7th week; whereas excretion levels of the free form were fairly consistent throughout the study. A strong correlation was observed in this study between the onset of neuropathy and the urinary concentration of 2,5-hexanedione when 2-hexanone, 2,5-hexanedione or 2,5-hexanedione was administered orally to rats at 400 mg/kg/day.

2.3.4.3 Dermal Exposure

¹⁴C from 1-¹⁴C-2-hexanone applied to the forearms of two human volunteers was found in the breath and urine (DiVincenzo et al. 1978). In one subject,

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excretion was similar by both routes; in the other subject, the levels were much higher (about 3:1) in the breath. Levels of radioactivity in feces were not measured.

2.4 RELEVANCE TO PUBLIC HEALTH

As discussed in Section 2.2, estimates of levels of exposure to 2-hexanone posing minimal risk to humans (MRLs) were to have been made, where data were believed reliable, for the most sensitive noncancer effect for each route and exposure duration. However, no MRLs could be derived for 2-hexanone. No data were located on effects of acute-duration or chronic-duration inhalation exposure to 2-hexanone in humans or animals. Available information concerning effects of intermediate-duration inhalation exposure in humans and animals identifies neurological effects as the most sensitive indicator of toxicity, but this information does not reliably identify the threshold for this effect. Therefore, no inhalation MRLs were derived. Available information on acute-duration oral exposure in animals does not identify the most sensitive effect, and while available information on intermediate-duration oral exposure to 2-hexanone in animals suggests that neurotoxicity may be the most sensitive effect, data do not reliably identify the threshold for neurotoxicity. No information was located on effects of chronic-duration exposure to 2-hexanone in humans or animals. Therefore, no oral MRLs were derived. Acute-duration, intermediate-duration, and chronic-duration dermal MRLs were not derived for 2-hexanone due to the lack of an appropriate methodology for the development of dermal MRLs.

As demonstrated in humans as well as in laboratory animals, the most important concern associated with exposure to 2-hexanone is neuropathy. In all species observed, this neurological effect is generally accompanied by effects on body weight. Based on the results of animal studies, other potential concerns are adverse hematological effects and effects on reproduction and fetal development.

Death. There are no data to suggest that lethality is a concern for humans exposed to 2-hexanone via any route. Lethality data in animals include an inhalation study by Abdo et al. (1982) in which 1 of 5 hens died after 72 days of continuous exposure to 200 ppm and 2 of 5 hens died by day 27 of exposure to 400 ppm. No deaths were recorded in hens exposed to 100 ppm for 90 days. An oral LD_{50} of 2,590 mg/kg has been reported for rats (Smyth et al. 1954). No lethality studies using the dermal route have been located. These findings suggest that lethality is possible with very high concentrations of 2-hexanone. However, it is unlikely that humans in any setting would be exposed to levels high enough to result in death.

Systemic Effects.

Hematological Effects. There is no evidence that adverse hematological effects occurred in workers exposed to 2-hexanone (Allen et al. 1975). The

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potential hematological effects of exposure to 2-hexanone were investigated in an inhalation study by Katz et al. (1980) in which rats were exposed to 700 ppm 2-hexanone intermittently for 11 weeks. No effects were observed on hemoglobin concentration, hematocrit, or differential white blood cell counts. However, at about 8 weeks, total white cell counts were reduced to about 60% of control values. Since there was no evidence of a corresponding effect on bone marrow, the authors stated that the clinical significance of this finding was uncertain. However, it is possible that hematological effects may occur in humans exposed to 2-hexanone by inhalation.

Hepatic Effects. There are no data on hepatic effects occurring in humans exposed to 2-hexanone; however, these effects have been investigated in several studies in animals using inhalation or oral administration. No effect was found on hexobarbital-induced sleep times in rats continuously exposed to 2-hexanone via inhalation at 225 ppm for 7 days (Couri et al. 1977); no histopathological effects were found in the livers of rats exposed to 50 ppm for 6 months (Duckett et al. 1979). In studies conducted via the oral route, single-dose administration of 2-hexanone at levels up to 1,500 mg/kg did not result in effects on liver histology, plasma glutamic-pyruvic transaminase levels (as a measure of centrilobular necrosis), permeability of the biliary tree, malondialdehyde production (as a measure of lipoperoxidation), or total bilirubin levels in plasma (Cowlen et al. 1984b; Hewitt et al. 1980a, 1983, 1986). The results of liver enzyme measurements (alanine aminotransferase, aspartate aminotransferase) given at 4-week intervals were normal in rats receiving 2-hexanone at 400 mg/kg/day for 40 weeks (Eben et al. 1979). Hepatic effects were reported in two studies. The rapid depletion of glutathione (GSH) levels was observed in the livers of rats given a single dose of 2-hexanone at 1,500 mg/kg (Branchflower and Pohl 1981), and in another study, an increased liver to body weight ratio was found in rats given 2-hexanone at the same dose (Hewitt et al. 1983).

Based on the available data in animals, 2-hexanone does not appear to be hepatotoxic. However, there is evidence to indicate that it can greatly enhance the hepatotoxicity of other chemicals such as chloroform (see Section 2.6).

Renal Effects. There are no available data to suggest that renal effects are a potential risk associated with human exposure to 2-hexanone. No histopathological effects were seen in the kidneys of rats exposed to 50 ppm 2-hexanone via inhalation for 6 months (Duckett et al. 1979). Renal effects were also investigated in a study in which rats were administered a single gavage dose of 2-hexanone at 1,500 mg/kg. Degenerative changes were reported in 9.6% of the renal tubules in treated animals, as compared with a 1% incidence in controls (Hewitt et al. 1980a). The statistical significance of this finding was not addressed. However, these data do not support a concern for potential renal effects in humans exposed to 2-hexanone.

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Dermal/Ocular Effects. 2-Hexanone applied to the skin of rabbits was minimally irritating; ocular instillation resulted in moderate corneal necrosis (Smyth et al. 1954). Human ocular contact with this chemical would, therefore, be of concern.

Other Effects. In both animals and humans, the most common systemic effect observed following inhalation or ingestion of 2-hexanone was weight loss or decreased weight gain in developing animals. Weight loss and decreased weight gain may be secondary to loss of appetite or inability to feed. Weight loss, ranging from 3 to 60 pounds was reported by Allen et al. (1975) in workers exposed to 2-hexanone for several months in a fabric-finishing plant. These losses were generally seen in the workers with more severe neurological impairment (peripheral neuropathy). Weight loss and decreased rates of weight gain in developing animals were reported in several species exposed via inhalation including rats (Johnson et al. 1977; Katz et al. 1980; Spencer et al. 1975), and hens (Abdo et al. 1982). In most of these studies, little or no effect on body weight was observed with exposure to 100 ppm or less. In oral studies, effects on body weight were also reported in rats (Krasavage et al. 1980). These observations indicate that weight loss in adults and decreased weight gains in children would be an area of concern associated with exposure to 2-hexanone.

Immunological Effects. There is no information on the immunological effects of human exposure to 2-hexanone. Reductions in total white blood cell count to 60% of control values were reported in rats intermittently exposed to 700 ppm 2-hexanone via inhalation for about 8 weeks (Katz et al. 1980). Because there were no effects on differential counts or evidence of bone marrow damage, the full implications of their findings to potential immunological effects in humans are not clear. It is interesting to note that in male mice given either single or 7 daily oral doses of 2,5-hexanedione, a metabolite of 2-hexanone, at a dose that was too low to elicit neurotoxicity (20% of the LD₅₀), there were reductions in the cellularity of the spleen, thymus, and mesenteric lymph nodes. Abnormal results in immune function tests such as delayed hypersensitivity reaction tests, plaque-forming cell assay, phagocytosis by adherent peritoneal exudate cells, and resistance to endotoxin shock were also reported (Upreti and Shanker 1987). In female rats given single or 7 daily oral doses of 2,5-hexanedione at 10%-50% of the LD₅₀ decreased cellularity of various lymphoid organs was also observed (Upreti et al. 1986). These studies suggest that immunological effects may be an area of potential concern for humans exposed to 2-hexanone.

Neurological Effects. Neurological effects are the most likely public health concern associated with exposure to 2-hexanone. Peripheral neuropathy was reported in workers using 2-hexanone in fabric finishing operations (Allen et al. 1975). In animal studies, neuropathy progressing from mild ataxia to paralysis was reported in inhalation studies using cats (Mendell et al. 1974b; Saida et al. 1976), monkeys (Johnson et al. 1977), rats (Johnson et al. 1977; Saida et al. 1976), and hens (Abdo et al. 1982), and in oral studies using

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rats (Eben et al. 1979; Krasavage et al. 1980), guinea pigs (Abdel-Rahman et al. 1978), and hens (Abou-Donia et al. 1982). Pathological alterations in hens, cats, and rats have been reported to be similar and the clinical manifestations in the experimental animals and the exposed workers were comparable (Mendell et al. 1974b).

Examination of the affected nerves in these test species indicated that demyelination and axonal swelling were generally associated with the observed clinical effects. A significant finding was that in rats that became paralyzed as a result of 2-hexanone exposure at 225 ppm for 9.5 weeks or to 400 ppm for 6 weeks, histopathological changes of the peripheral nerves occurred as early as 16 days at both exposure levels (Saida et al. 1976). In another study, no clinical signs of neuropathy were observed in rats exposed to 100 ppm 2-hexanone for 6 months, whereas histopathological changes of both peripheral nerves and tracts of the spinal cord were seen after 4 months of exposure (Egan et al. 1980). These findings suggest that nerve degeneration may also occur in exposed humans well before the characteristic symptoms of peripheral neuropathy (muscle weakness and sensory loss in the hands and feet) become apparent. Electromyographic testing, as used in some of the studies discussed in Sections 2.2.1.4 and 2.2.2.4, appears to be sensitive enough to detect abnormalities in the conduction characteristics of nerves before clinical manifestations occur.

Ultrastructural studies of nerve fibers in the peripheral and central nervous systems of exposed animals from several of their studies have led Spencer and Schaumberg (1977b) to the use of the term "dying-back" to describe the nature of the pathology. The most distal extremities of the longest and largest axons appear to be affected first; axonal degeneration seems to, Progress proximally to fibers in the central nervous system.

Developmental Effects. There are no available data on the developmental effects of human exposure to 2-hexanone. Concern that the offspring of women exposed to 2-hexanone during pregnancy may be at risk for developmental effects comes from an inhalation study in which behavioral alterations were seen in the offspring of pregnant rats exposed to 1,000 ppm 2-hexanone during gestation (Peters et al. 1981). These effects consisted of reduced activity in the open field, increased activity in the running wheel, and deficits in avoidance conditioning. There was also a decrease in the number and birth weight of live offspring of these rats. These findings suggest that neonate survival may be a concern for human exposure.

Reproductive Effects. There are no available data on the reproductive effects of human exposure to 2-hexanone. Reproductive effects may be a concern for women exposed to 2-hexanone based on the findings of an inhalation study in which there were decrements in the weight gain of pregnant rats exposed to 2,000 ppm 2-hexanone during gestation (Peters et al. 1981).

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In addition, marked and significant reductions in absolute and relative testes weight and atrophy of testicular germinal epithelium were reported in male rats exposed to 700 ppm 2-hexanone via inhalation for 11 weeks (Katz et al. 1980), and atrophy of the testicular germinal epithelium was also observed in male rats that received 2-hexanone at 660 mg/kg/day by gavage during a 90-day study (Krasavage et al. 1980). Histological changes and reduced testicular weight have also been observed in rats that received 2,5-hexanedione for 4 weeks at 1% of their drinking water (about 1,400 mg/kg/day) (Boekelheide 1987). These observations suggest that effects on semen production and male fertility may be a concern for men exposed to 2-hexanone.

Genotoxic Effects. No studies were located regarding the potential genotoxic effects in humans or animals following any route of exposure to 2-hexanone. No in vitro studies have been located for 2-hexanone.

Cancer. No studies were located regarding the potential carcinogenic effects in humans or animals following any route of exposure to 2-hexanone.

2.5 BIOMARKERS OF EXPOSURE AND EFFECT

Biomarkers are broadly defined as indicators signaling events in biologic systems or samples. They have been classified as markers of exposure, markers of effect, and markers of susceptibility (NAS/NRC 1989).

A biomarker of exposure is a xenobiotic substance or its metabolite(s) or the product of an interaction between a xenobiotic agent and some target molecule(s) or cell(s) that is measured within a compartment of an organism (NAS/NRC 1989). The preferred biomarkers of exposure are generally the substance itself or substance-specific metabolites in readily obtainable body fluid or excreta. However, several factors can confound the use and interpretation of biomarkers of exposure. The body burden of a substance may be the result of exposures from more than one source. The substance being measured may be a metabolite of another xenobiotic substance (e.g., high urinary levels of phenol can result from exposure to several different aromatic compounds). Depending on the properties of the substance (e.g., biologic half-life) and environmental conditions (e.g., duration and route of exposure), the substance and all of its metabolites may have left the body by the time biologic samples can be taken. It may be difficult to identify individuals exposed to hazardous substances that are commonly found in body tissues and fluids (e.g., essential mineral nutrients such as copper, zinc, and selenium). Biomarkers of exposure to 2-hexanone are discussed in Section 2.5.1.

Biomarkers of effect are defined as any measurable biochemical, physiologic, or other alteration within an organism that, depending on magnitude, can be recognized as an established or potential health impairment or disease (NAS/NRC 1989). This definition encompasses biochemical or

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cellular signals of tissue dysfunction (e.g., increased liver enzyme activity or pathologic changes in female genital epithelial cells), as well physiologic signs of dysfunction such as increased blood pressure or decreased lung capacity. Note that these markers are often not substance specific. They also may not be directly adverse, but can indicate potential health impairment (e.g., DNA adducts). Biomarkers of effects caused by 2-hexanone are discussed in Section 2.5.2.

A biomarker of susceptibility is an indicator of an inherent or acquired limitation of an organism's ability to respond to the challenge of exposure to a specific xenobiotic substance. It can be an intrinsic genetic or other characteristic or a preexisting disease that results in an increase in absorbed dose, biologically effective dose, or target tissue response. If biomarkers of susceptibility exist, they are discussed in Section 2.7, "POPULATIONS THAT ARE UNUSUALLY SUSCEPTIBLE."

2.5.1 Biomarkers Used to Identify and/or Quantify Exposure to 2-Hexanone

2-Hexanone and its various metabolic products (2-hexanol, 2,5-hexanedione, 5-hydroxy-2-hexanone, 2,5-dimethylfuran) can be measured in biological tissue, fluid, and excreta (Fedtke and Bolt 1986; Nomeir and Abou-Donia 1985; White et al. 1979). The currently available information, however, does not indicate whether the levels of these substances can be used to calculate or estimate corresponding levels of exposure to 2-hexanone. An additional complication is that because the same metabolites have been identified in the urine of rats orally exposed to n-hexane (Fedtke and Bolt 1986), the selection of a specific biomarker for exposure to 2-hexanone is thus unlikely.

2.5.2 Biomarkers Used to Characterize Effects Caused by 2-Hexanone

There are currently no subtle or sensitive biomarkers of effects associated with exposure to 2-hexanone. Electromyographic testing, however, may prove to be useful in the detection of nerve conduction abnormalities in their early stages, even before they are accompanied by clinical manifestations. Specific electrodiagnostic patterns associated with exposure to 2-hexanone have not been clearly delineated.

2.6 INTERACTIONS WITH OTHER CHEMICALS

Based on the results of several animal studies, exposure to 2-hexanone can result in the potentiation and exacerbation of adverse effects associated with the administration of other toxic compounds. Oral administration of 2-hexanone followed by intraperitoneal administration of chloroform to rats has resulted in a variety of hepatic and renal effects including decreased hepatic glutathione levels, increased plasma levels of glutamic pyruvic transaminase and blood urea nitrogen, and degeneration and necrosis of hepatic and renal tissue (Branchflower and Pohl 1981; Brown and Hewitt 1984; Cowlen et al. 1984a, 1984b; Hewitt et al. 1980a,b, 1983). Similarly, oral

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administration of both 2-hexanone and chloroform to rats resulted in altered permeability of the biliary tree (Hewitt et al. 1986). In these studies, some or no effect on the end points of interest was observed after administration of 2-hexanone or chloroform alone; administration of both substances resulted in statistically significant and dramatic changes in these effects.

These authors have speculated that 2-hexanone potentiates the hepatic toxicity of chloroform by decreasing glutathione levels (Branchflower and Pohl 1981; Hewitt et al. 1980a) and by increasing the metabolism of chloroform to the potent hepatotoxicant, phosgene (Branchflower and Pohl 1981; Cowlen et al. 1984a, 1984b). Branchflower and Pohl (1981) have speculated that the metabolism of chloroform to phosgene may also be involved in the renal toxicity seen in these studies.

2-Hexanone has also been shown to potentiate the neurotoxic effects of some compounds. In hens, dermal or inhalation exposure to 2-hexanone in combination with dermal application of the pesticide 0-ethyl-0-4-nitrophenyl phenylphosphonothioate (EPN) has resulted in earlier onset and far more severe clinical and histological manifestations of neurotoxic effects than with either chemical exposure alone (Abou-Donia et al. 1985a, 1985b). The authors speculated that this potentiation effect may have been due to induction of hepatic microsomal cytochrome P-450 by EPN, leading to increased metabolism of 2-hexanone to its neurotoxic metabolite, 2,5-hexanedione. An alternate explanation is that local trauma to the nervous tissue produced by 2-hexanone and EPN might increase vascular permeability and thus increase the entry of these compounds and their metabolites from circulation.

A study in which rats were exposed via inhalation to a combination of 2-hexanone and methyl ethyl ketone resulted in the potentiation of severe neurotoxic effects including paralysis and histopathological changes. These effects were either not observed or they occurred at much lower frequencies when either of the two compounds was administered separately (Saida et al. 1976).

These results suggest that persons living or working in the vicinity of hazardous waste sites or workers who are exposed to 2-hexanone in combination with any of the potentially toxic substances discussed above may be at special risk for the effects of exposure to the combination of chemicals.

2.7 POPULATIONS THAT ARE UNUSUALLY SUSCEPTIBLE

No population has been identified which is unusually susceptible to toxic effects resulting from 2-hexanone exposure.

2.8 MITIGATION OF EFFECTS

This section will describe clinical practice and research concerning methods for reducing toxic effects of exposure to 2-hexanone. However, because some

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of the treatments discussed may be experimental and unproven, this section should not be used as a guide for treatment of exposures to 2-hexanone. When specific exposures have occurred, poison control centers and medical toxicologists should be consulted for medical advice.

Human exposure to 2-hexanone may occur by inhalation, ingestion, or dermal absorption (see Chapter 5). Dermal exposure to 2-hexanone may cause ocular and skin irritation. Exposure by any route may cause peripheral neuropathy, with nerve degeneration and paralysis (see Section 2.2).

Procedures for reducing toxic effects following acute, high level exposure to 2-hexanone include measures to reduce or eliminate further absorption. Following dermal or ocular exposure, these procedures include removing contaminated clothing and thoroughly washing the skin and eyes (Bronstein and Currance 1988; Stutz and Janusz 1988). Following acute, high level oral exposure, these procedures include emptying the stomach, using care to avoid aspiration of the gastric contents, followed by administration of activated charcoal and a cathartic to stimulate fecal excretion (Stutz and Janusz 1988).

The half-life of 2-hexanone and its metabolites in blood plasma has not been established; however, elimination from the body does appear to occur in less than 24 hours following both inhalation and ingestion exposures (DiVincenzo et al. 1977, 1978). 2-Hexanone is not known to accumulate over time in any tissues in the body (see section 2.3.4). While elimination enhancement through stimulation of metabolism of 2-hexanone may reduce some forms of toxicity, if used within the short time that 2-hexanone is retained in the body, there is the risk that these same metabolic reactions may form reactive metabolites such as 2,5-hexanedione. Furthermore, concurrent exposures to other substances may also occur for which stimulation of these same metabolic pathways is contraindicated. Therefore, the benefit of stimulating specific metabolic pathways to enhance 2-hexanone elimination is unclear and should be studied further.

The major toxic effect of exposure to 2-hexanone is neuropathy. Neuropathy can be caused by both 2-hexanone and its metabolite 2,5-hexanedione. A reduction of the neuropathy caused by exposure to 2-hexanone could theoretically be achieved through shunting of metabolism to less toxic metabolites. However, as discussed above, the toxicity of those other metabolites, and the effect of the treatment on metabolism of other potential toxicants, would have to be clearly assessed.

Two major hypotheses concerning the mechanism of action of either 2-hexanone or 2,5-hexanedione have been suggested (see section 2.3.3 Metabolism). These mechanisms are 1) inhibition of sulfhydryl dependent enzymes (Lapin et al. 1982; Sabri et al. 1979b; Sabri 1984), and 2) covalent binding to axonal components leading to pyrrole formation, protein crosslinking, and axonal degeneration (DeCaprio et al. 1982, 1988). Dithiothreitol has been shown to reduce the inhibition in one of the inhibited enzymes in vitro, suggesting

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that blocking accessibility of the sulfhydryl groups may be an effective method of blocking toxic effects (Sabri et al. 1979b).

Interaction of 2-hexanone with EPN (Abou-Donia 1985a) and methyl ethyl ketone (Saida et al. 1976) may occur through the potentiation of the production of 2,5-hexanedione. An effective method of reducing the neurotoxic effects of combined exposures to these compounds would be to pharmacologically block the metabolic pathways that lead to the production of 2,5-hexanedione, given the same caveats presented for interference with metabolic pathways presented above. Increasing the breakdown or clearance of 2,5-hexanedione might also be effective.

2-Hexanone has been found to enhance the hepatotoxicity of chloroform in animals (Branchflower and Pohl 1981). This may occur in part through depletion of glutathione levels by 2-hexanone, and in part by a 2 hexanone-mediated increase in the production of phosgene from chloroform (Branchflower and Pohl 1981; Cowlen et al. 1984a). It is possible that ensuring sufficient glutathione stores in the body may reduce the chances of toxic effects following combined acute exposure to 2-hexanone and chloroform. Specific blockage of the production of phosgene, through the inhibition of liver cytochrome P450, might be an effective method of reducing liver damage. However, an analysis of the net effect of this inhibition on the toxicity of the combined exposure would need to be made prior to recommending this method as a mitigation treatment.

2.9 ADEQUACY OF THE DATABASE

Section 104(i)(5) of CERCLA, as amended, directs the Administrator of ATSDR (in consultation with the Administrator of EPA and agencies and programs of the Public Health Service) to assess whether adequate information on the health effects of 2-hexanone is available. Where adequate information is not available, ATSDR, in conjunction with the National Toxicology Program (NTP), is required to assure the initiation of a program of research designed to determine the health effects (and techniques for developing methods to determine such health effects) of 2-hexanone.

The following categories of possible data needs have been identified by a joint team of scientists from ATSDR, NTP, and EPA. They are defined as substance-specific informational needs that, if met, would reduce or eliminate the uncertainties of human health assessment. In the future, the identified data needs will be evaluated and prioritized, and a substance-specific research agenda will be proposed.

2.9.1 Existing Information on Health Effects of 2-Hexanone

The existing data on health effects of inhalation, oral, and dermal exposure of humans and animals to 2-hexanone are summarized in Figure 2-4.

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FIGURE 2-4. Existing Information on Health Effects of 2-Hexanone

		SYSTEMIC									
		Death	Acute	Intermed.	Chronic	Immunologic	Neurologic	Developmental	Reproductive	Genotoxic	Cancer
Inhalation			●			●					
Oral											
Dermal											

HUMAN

		SYSTEMIC									
		Death	Acute	Intermed.	Chronic	Immunologic	Neurologic	Developmental	Reproductive	Genotoxic	Cancer
Inhalation	●		●			●	●	●			
Oral	●	●	●			●		●			
Dermal		●				●					

ANIMAL

● Existing Studies

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The purpose of this figure is to illustrate the existing information concerning the health effects of 2-hexanone. Each dot in the figure indicates that one or more studies provide information associated with that particular effect. The dot does not imply anything about the quality of the study or studies. Gaps in this figure should not be interpreted as "data needs" information (i.e., data gaps that must necessarily be filled).

Figure 2-4 graphically depicts the information that currently exists on the health effects that have been observed or studied in humans or animals following exposure to 2-hexanone. Data on intermediate-duration systemic and neurologic effects in humans were derived from a single study of workers exposed to 2-hexanone for about 10 months. Although there is more information on animals, as discussed below, certain factors, such as the use of 2-hexanone of low or unknown purity or the use of a single dosage level in the test protocol, complicate the interpretation of these studies and limit their usefulness.

Some information is available from animal studies conducted via the inhalation route in several categories of toxicity including lethality, systemic effects resulting from intermediate-duration exposure, neurologic, reproductive, and developmental effects. In studies conducted via the oral route, some information is available on lethality, systemic effects resulting from acute- or intermediate-duration exposure, reproductive effects, and neurologic effects. Only two studies using the dermal route were available. These provided information on acute and neurologic effects.

2.9.2 Data Needs

As discussed in previous sections, many of the currently available studies on 2-hexanone used a single dose level of the test compound, the purity of the test compound was not stated in some studies or in some cases, the purity was stated to be as low as 70%. Therefore little or no dose-response information is available in the existing database. In addition, studies using 2-hexanone of low purity introduce the complications associated with exposures to multiple substances and the potential for chemical interactions. As a result, the available data are limited in their usefulness and must be interpreted with caution.

Acute-Duration Exposure. Currently, no data are available on humans for this exposure duration for any route of exposure. In addition, there is no information on acute toxicity in animals following inhalation exposure. Lethality data are available for the rat and hen via the oral route (Abou-Donia et al. 1982; Hewitt et al. 1980a; Smyth et al. 1954). Existing data are insufficient to derive an MRL for any route of exposure. Acute-duration studies for all routes of exposure using a range of exposure concentrations would be useful in determining potential target organs, especially the nervous system, to identify any dosage thresholds, and to establish dose-response relationships for these effects. Brief human exposure to 2-hexanone may occur

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at hazardous waste sites, at the site of accidental spills, or in the workplace.

Intermediate-Duration Exposure. The currently available data on humans exposed to 2-hexanone for this duration period is based on a study of workers exposed to 2-hexanone for about 10 months (Allen et al. 1975). Peripheral neuropathy and weight loss were the major observations. Repeated-dose studies in rats, cats, monkeys, hens, and guinea pigs indicate that the nervous system is the primary target of 2-hexanone exposure via inhalation (Abdo et al. 1982; Abou-Donia et al. 1985a; Duckett et al. 1979; Egan et al. 1980; Johnson et al. 1977; Katz et al. 1980; Saida et al. 1976; Spencer et al. 1975), oral (Abdel-Rahman et al. 1978; Krasavage et al. 1980), or dermal (Abou-Donia et al. 1985b) exposure for this duration. In addition, decreased weight gain has been reported in rats and hens exposed via inhalation, decreased white blood cell counts in rats exposed via inhalation (Abdo et al. 1982; Johnson et al. 1977; Katz et al. 1980), and decreased weight gain in rats exposed via gavage (Krasavage et al. 1980). However, the data were not sufficient to derive an MRL for any route. Intermediate-duration (90-day) studies in animals via the inhalation and dermal routes would be useful in developing dose-response relationships, especially in relation to neurological effects. Such information would be valuable for predicting human health effects, because the potential exists for such exposure among populations in the vicinity of hazardous waste sites and in the workplace. In addition, because 2-hexanone has been found in surface water, groundwater, and drinking water in the vicinity of hazardous waste sites, a 90-day study using the oral route would also be useful. These studies should also include investigation of a number of endpoints including the potential hematological, immunological, developmental, and reproductive effects of exposure to 2-hexanone, because the available data indicate that these are areas of potential concern in humans.

Chronic-Duration Exposure and Cancer. There is currently no available information on humans or animals exposed to 2-hexanone for this duration period via any route of exposure. Chronic exposure studies using the inhalation, oral, and dermal routes would be useful, because chronic low level exposure via each of these routes is likely to occur in the vicinity of hazardous waste sites or in occupational settings. Data derived from 90-day studies would be useful in determining the dose levels to be used for the chronic-duration studies.

There is currently no information on the carcinogenic potential of 2-hexanone. Chronic-duration studies conducted via any route of exposure should assess this potential effect, since persons living in the vicinity of hazardous waste sites or in occupational settings may be chronically exposed to low levels of 2-hexanone via the oral, inhalation, and dermal routes.

Genotoxicity. There are currently no in vivo or in vitro studies that address the genotoxic potential of 2-hexanone. A battery of in vitro genotoxicity tests with 2-hexanone would be useful as a preliminary step in

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assessing its mutagenic potential and determining if further genotoxicity tests would appear to be warranted.

Reproductive Toxicity. There is no information on the effects of 2-hexanone on reproductive parameters in exposed humans via any route of exposure. Available data in animals indicate that inhalation exposure of pregnant rats to 2-hexanone resulted in reduced maternal weight gain (Peters et al. 1981). In male rats, reduced testicular weights and atrophy of the testicular germinal epithelium were reported to result from inhalation exposure (Katz et al. 1980) and atrophy of the testicular germinal epithelium from oral exposure (Krasavage et al. 1980). Because of the limited data base for all routes of exposure, it would be useful to have 90-day studies for all three routes in order to investigate the potential dose-response relationship of exposure to this compound on a number of end points including sperm count and reproductive organ pathology. Because effects on reproduction have been observed, a multi-generation study would be helpful in assessing the potential impact of 2-hexanone exposure on the reproductive capacity of persons living in the vicinity of hazardous waste sites and exposed workers.

Developmental Toxicity. There is no information on the effects of exposure to 2-hexanone via any route on human development. There are no animal studies using the oral or dermal routes. The currently available data for animals is based on a single inhalation study in pregnant rats indicating that 2-hexanone exposure resulted in decreased litter size and pup weight (Peters et al. 1981). Additional studies investigating a number of developmental end points, and a dose-response relationship via inhalation, oral and dermal exposure would be useful in assessing the potential risks to persons exposed to 2-hexanone in the vicinity of hazardous waste sites or in the workplace.

Immunotoxicity. There are currently no data on the effects of 2-hexanone on the human immune system via any route of exposure. Animal data included an inhalation study in which there was a 40% decrease in peripheral white blood cells in rats exposed to 2-hexanone (Katz et al. 1980). In addition, 2,5-hexanedione, a metabolite of 2-hexanone, was shown to adversely affect lymphoid organs of the immune system in rats and to cause impairment of immunity in mice (Upreti and Shanker 1987). Immunological assessments, including analysis of peripheral blood components and effects on lymphoid tissue, conducted as part of intermediate- or chronic-duration studies and skin sensitization tests would be useful in developing a dose-response relationship and assessing the potential risk to chronically exposed persons in the vicinity of hazardous waste sites or to exposed workers.

Neurotoxicity. The nervous system has been clearly established as the major target for 2-hexanone in humans exposed via inhalation (Allen et al. 1975) and in animals exposed via any route of exposure (Abdel-Rahman et al. 1978; Abdo et al. 1982; Abou-Donia et al. 1982, 1985a,b; Duckett et al. 1979; Egan et al. 1980; Johnson et al. 1977; Katz et al. 1980; Krasavage et al.

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1980; Saida et al. 1976; Spencer et al. 1975) and in the offspring of pregnant rats exposed via inhalation (Peters et al. 1981). However, most of the available information is derived from studies using 2-hexanone of low or unknown purity or using it at a single dosage level, its usefulness is limited. Animal data that would clearly establish dose-response relationships for neurological effects, including histopathological damage as well as clinical manifestations, as a result of exposure to pure 2-hexanone via all routes of exposure and using a range of exposure durations would be useful. This information would be valuable in assessing the potential risks of neurotoxicity in persons exposed to 2-hexanone in the vicinity of hazardous waste sites or at the workplace.

Epidemiological and Human Dosimetry Studies. The only epidemiological information that is currently available is the study of workers exposed to 2-hexanone for about a year (Allen et al. 1975). Humans may be exposed to 2-hexanone -through contaminated air in the workplace and in the vicinity of hazardous waste sites and consumption of and dermal contact with contaminated water, especially in the vicinity of hazardous waste sites. Epidemiological studies that followed populations exposed to 2-hexanone, either in the vicinity of hazardous waste sites or in the workplace, would be useful in assessing adverse health effects in humans. In any such studies, emphasis should be placed on neurological, hematological, immunological, reproductive, and developmental effects. Similarly, human dosimetry studies of these populations would be useful in associating 2-hexanone levels with the reported effects.

Biomarkers of Exposure and Effect. Measurement of 2-hexanone and its metabolites in blood or urine may not provide an adequate indication of exposure to this substance, since these metabolites may also result from exposure to *n*-hexane (Fedtke and Bolt 1986; Nomeir and Abou-Donia 1985; White et al. 1979). Further work in developing unequivocal evidence of exposure to 2-hexanone would be useful.

The major target organ of 2-hexanone in humans is the nervous system (Allen et al. 1975), and morphological effects may occur before clinical manifestations of toxicity (Egan et al. 1980). Therefore, the identification of sensitive nonmorphological effects of 2-hexanone exposure (such as a certain pattern of responses in electromyographics testing) would be useful.

Absorption, Distribution, Metabolism, and Excretion. Although some information is available on each of these topics from studies conducted in several species, more information in each of these areas would be useful. In addition, because most of these studies were conducted by the same group of researchers, further studies in other laboratories in each of these areas would be useful in confirming the available data.

Available data indicate that 2-hexanone is readily absorbed by humans and various animal species after inhalation, oral, or dermal administration

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(Di Vincenzo et al. 1977, 1978). However, information on the rates of absorption via the inhalation and oral routes, as well as estimates of the fraction of the applied dermal dose that is absorbed, would be useful in assessing potential absorption by exposed humans. In addition, information on potential determinants of absorption such as dose level and nutritional status would also be helpful.

Distribution data are limited to a single study in rats using the oral route (DiVincenzo et al. 1977); no quantitative information was provided. The use of multiple species and a comparison of tissue levels of 2-hexanone associated with multiple doses via each route of exposure would be useful in assessing the likelihood that 2-hexanone will reach various potential target organs in exposed humans.

The proposed metabolic pathway for 2-hexanone is based on blood metabolites identified during intraperitoneal studies in guinea pigs (DiVincenzo et al. 1976) and oral studies in rats (DiVincenzo et al. 1977). The metabolite 2,5-hexanedione has also been found in human serum after inhalation exposure (DiVincenzo et al. 1978). Because studies in rats exposed to 2-hexanone have indicated a strong relationship between the concentration of 2,5-hexanedione in the urine and the onset of neuropathic symptoms (Eben et al. 1979), it would be useful to also have this information for humans.

Limited excretion data are available in humans receiving 2-hexanone via inhalation, oral, and dermal exposure, in dogs via inhalation exposure, and in rats via oral exposure (DiVincenzo et al. 1977, 1978). However, human data on excretion of 2-hexanone via feces are not available, and the available information in dogs concerns excretion via exhaled breath only. In these and any other studies, information on all routes of excretion would help to evaluate the potential for 2-hexanone clearance in the exposed species. Excretion data in rats receiving 2-hexanone via inhalation and dermal application and in other species receiving 2-hexanone via all three routes would be useful for comparison with the human data and to assess the comparative risks of exposure by each route. In addition, information on excretion rates in each species via each route would be helpful in understanding how long 2-hexanone and its metabolites may persist in the body.

Comparative Toxicokinetics. The toxicokinetic studies available in both humans and animals (dogs, rats, and guinea pigs) suggest that there may not be any major differences in the kinetics of this compound across certain species. Metabolites of 2-hexanone in the expired breath (carbon dioxide) of humans and rats exposed via the oral route and the presence of 2,5-hexanedione in the serum of humans exposed via inhalation, as well as in the blood and urine of orally exposed rats and the intraperitoneally exposed guinea pigs, suggest that there is a similar metabolic pathway in humans and experimental animals (DiVincenzo et al. 1976, 1977, 1978). Confirmation of this assumption would be useful. Similar toxic effects, neuropathy and weight loss, have been noted in several species (humans, monkeys, rats, cats, hens, and guinea pigs)

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(Abdel-Rahman et al. 1978; Abdo et al. 1982; Abou-Donia et al 1982, 1985a,b; Allen et al. 1975; Duckett et al. 1979; Egan et al. 1980; Johnson et al. 1977; Katz et al. 1980; Krasavage et al. 1980; Saida et al. 1976; Spencer et al. 1975). Therefore, it would also be useful to investigate patterns of distribution, to identify target organs, and to measure rates of excretion in several species and to identify blood metabolites in humans in order to investigate interspecies similarities and differences. Studies in this area would be valuable for predicting toxic effects in humans and for studying the mechanisms of action of this chemical.

Mitigation of effects. Recommended methods for the mitigation of acute effects of 2-hexanone poisoning include prevention of absorption of 2-hexanone from the gastrointestinal tract by administration of emetics, binding agents and cathartics or administration of oxygen if exposure is by inhalation (Bronstein and Currance 1988; Stutz and Janusz 1988). No information was located concerning mitigation of effects of lower-level or longer-term exposure to 2-hexanone. Further information on techniques to mitigate such effects would be useful in determining the safety and effectiveness of possible methods for treating 2-hexanone-exposed populations surrounding hazardous waste sites.

2.9.3 On-going Studies

No research on the toxicity or toxicokinetics of 2-hexanone is known to be in progress.

There are, however, some studies currently in progress that are investigating the mechanism of neurotoxicity of the 2-hexanone metabolite, 2,5-hexanedione. A study is being conducted at the Oregon Health Sciences University, under the direction of Dr. Bruce Gordon Gold, to correlate the time course of any abnormal expression of phosphorylated neurofilament epitopes (a pathological alteration which occurs in several human neurofibrillary disorders including amyotrophic lateral sclerosis) and distal swellings and axonal degeneration in chronic 2,5-hexanedione neuropathy (in addition to other chemically-induced neuropathies). It is the intention of this study to establish a more universal marker for the presence of secondary changes in neuronal perikarya and to clarify the significance of these alterations in several human disorders such as amyotrophic lateral sclerosis.

In a study being conducted at Case Western Reserve University under the direction of Dr. Lawrence Sayre, trifluoromethyl-substituted analogs of 2,5-hexanedione will be synthesized, compared with the parent compound in chemical model studies, and evaluated for neurotoxicity in rats. This is part of an effort to address how gamma-diketone-induced pyrrole formation at neurofilament-based lysine epsilon-amino groups leads to neurofilament accumulations. Nuclear magnetic resonance (NMR) studies will provide direct visualization of the nature of chemical modification.

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Other research being conducted at Case Western Reserve University under the direction of Dr. Lawrence Sayre is a study in which analogs of 2,5-hexanedione will be synthesized, studied chemically, and biologically evaluated in an effort to clarify the structural basis of toxicity, particularly in respect to the direct chemical modification of neurofilament proteins by these analogs or any of their metabolites.

A study to investigate the possible selective vulnerability of specific neuron types or neuronal components to 2,5-hexanedione, as well as to acrylamide, is being conducted at the Medical College of Georgia under the direction of Dr. Barry Goldstein. The aim of this project is to study the functional changes caused by these compounds in sensory and motor systems which either have different diameter axons or differing levels of adaptation. Electrophysiological studies will determine the time course and severity of involvement of various nociceptors, muscle spindles, and motor unit types to these chemicals. Axoplasmic transport changes will be examined in axons of varied diameter and in different motor unit types (and adaptation levels). The goal is to determine whether there is selective vulnerability of neurons to these toxicants, and if so, whether it is based on axonal diameter or on the functional ability to maintain discharge.

A project at Duke University, under the direction of Dr. Doyle Graham, is investigating the molecular pathogenesis of the neuropathy associated with 2,5-hexanedione. The goal is to synthesize novel analogs of 2,5-hexanedione and the putative crosslinking metabolites of other toxicants in order to test specific steps in the pathogenetic schemes and to define the identities of the crosslinking adducts. This project includes the synthesis of a series of gamma-diketones which, through the presence of electron-withdrawing or electron-donating groups, will enhance or impair the rate of pyrrole formation and retard or facilitate oxidation of the resulting pyrrole ring.