3. Human Effects

3.1 Clinical and Case Reports

Aldrin and dieldrin, particularly in oil solution, are readily absorbed through the skin, the respiratory mucosa, and the gastrointestinal tract (Hayes 1963). Untoward symptoms in humans are known to result from oral doses as small as 10 mg/kg (Committee on Toxicology 1960, Hayes 1963, Jager 1970). The acute median lethal dose by the oral route lies between 20 and 95 mg/kg in various mammals (Table 2.1.1) and presumably lies in the same range in humans (Committee on Toxicology 1960, Hodge et al 1967). Several human deaths have been ascribed to ingestion of dieldrin, but no reliable information about doses is available (Committee on Toxicology 1960, Hayes 1963, Pribilla 1963, Weinig et al 1966, Preda et al 1963, Jager 1970, Symanski 1970, Gupta 1975). When a toxic dose of aldrin or dieldrin has been ingested or has contaminated the skin, a more or less typical syndrome appeared from 20 minutes to 24 hours afterwards. In all cases the principal site of action was the central nervous system, and the principal sign was a series of convulsions. The convulsions were self-remitting but recurred with increasing severity, characteristically alternating with periods of severe depression (Princi 1957; Hayes 1957, 1963; Bell 1960; Hoogendam et al 1962, 1965; Kazantzis et al 1964; Jager 1970).

Convulsions induced by the cyclodiene insecticides may be preceded by subjective complaints, but frequently they occurred with no forewarning or prodromal signs or symptoms (Hoogendam et al 1962). Abnormalities of the EEG, such as bilateral synchronous theta wave activity and occasional

bilateral synchronous spike and wave complexes, have been seen in patients without clinical illness both before and after convulsion (Kazantzis et at 1964). Myoclonia indicates that a convulsive episode is imminent. Prodromal signs that have been reported include headache, visual disturbances, dizziness, sweating, insomnia, nausea, and malaise. Convulsions are accompanied by loss of consciousness and "frothing at the mouth" but not incontinence (Hayes 1957, Patel and Rao 1958). Death may result from anoxemia (Princi 1957; Hayes 1963; Hoogendam et al 1962, 1965). The interval between oral intake or skin contact and the onset of symptoms, as well as the clinical picture, depend on the dose absorbed.

Many cases of aldrin and dieldrin poisoning have been described in the medical literature. In 1951, Spiotta described a case of acute convulsive aldrin poisoning in a 23-year-old man who ingested an aldrin emulsifiable concentrate in an attempted suicide. The man had convulsions accompanied by typical EEG changes but completely recovered.

Other investigators also reported epileptiform convulsions and EEG abnormalities. Drowsiness, lack of appetite, headache, and "prickly sensation of the skin" were reported in a man who had been previously exposed to dieldrin and became ill when his reducing diet resulted in mobilization of fat and release of the pesticide into the blood (Paul 1959). Disturbed sleep rhythm and manic and irrational behavior have been reported as sequelae (Fry 1964). Other autonomic manifestations have also been described (Gowdey and Stavraky 1955).

Garrettson and Curley (1969) reported that in a 4-year-old child accidentally poisoned via oral ingestion EEG abnormalities declined gradually over a 6-month period, paralleling the decline of dieldrin concentrations in serum. However, dieldrin residues in fat remained high for at least 8 months despite treatment with anticonvulsants.

In contrast to the phenomena observed after acute poisonings, after repeated exposures several spraymen developed a syndrome indistinguishable from idiopathic epilepsy, except that it ceased when the exposure was terminated (Hayes 1957). Myoclonic jerks and major motor seizures were reported in humans and animals exposed for 6-12 months to aldrin and BHC in contaminated flour; two persons died (Gupta 1975). A motor polyneuropathy resembling the Guillain-Barré syndrome is a rare complication of exposure (Jenkins and Toole 1964). In the usual acute intoxication, recovery is complete or well advanced within 24 hours, but animal experiments and clinical experience (Hayes 1957, Patel and Rao 1958) indicate the possibility of seizures for many days after a single dose or repeated doses. EEG anomalies may persist for days after apparent clinical recovery (Hoogendam et al 1962).

Transient kidney damage has been reported in some acute poisoning cases (Spiotta 1951, Jacobs and Lurie 1967, Nelson 1953, Committee on Toxicology 1960). Liver damage has also been reported, in one case persisting for more than 1 year (Committee on Toxicology 1960, Garrettson and Curley 1969).

In animals the percutaneous toxicity of dieldrin is almost as high as its oral toxicity (see Section 2.1.2). Dermal exposure usually results in systemic poisoning, without skin irritation or local sensitization except secondary to the solvent or vehicle, which is usually kerosene or xylene (Bundren et al 1952). However, Ross (1964) reported an incident of nonspecific dermatitis occurring on the legs of 288 police officers who wore wool socks impregnated with dieldrin as a mothproofing agent. Nelson (1953) and D'Eramo and Croce (1960) also reported contact dermatitis caused by aldrin. In addition, skin diseases such as scleroderma may facilitate cutaneous absorption of dieldrin, resulting in systemic poisoning (Starr and Clifford 1971).

One case of suicide by intravenous injection has been reported (Schwar 1965).

3.2 Studies in Volunteers

A 2-year study of volunteers with measured exposure to dieldrin was conducted with the primary purpose of studying the pharmacokinetics of dieldrin in men (Hunter et al 1967, 1969). The subjects were 13 healthy men, aged 21-52 years, with no history of recent occupational exposure to pesticides. Four groups of three or four men were given recrystallized dieldrin (99% HEOD) in gelatin capsules daily for 2 years at doses of 0, 10, 50 and 211 μg dieldrin/day. Added to the normal dietary intake from background contamination, this increased the daily intakes to approximately 14, 24, 64, and 225 μg/day, respectively. In addition to measurements of dieldrin concentrations in blood and fat, which were summarized in Section 1.5.4, urinalysis,

EEG studies, polygraphic recording of cardiorespiratory function, electromyographic studies, and blood chemistry, including estimation of blood plasma protein and urea, activity of plasma alkaline phosphatase, SGPT, and SGOT, and cholinesterase activities in erythrocytes and plasma, were performed. Full clinical examinations were made after 3, 9, 15, 18, and 24 months of exposure. The subjects were observed for 8 months after exposure was discontinued.

No changes were observed in any of the measured parameters, and no clinical or subjective symptoms attributable to exposure were recorded (Hunter et al 1967, 1969). A preliminary examination of the concentrations of p,p'-DDE in the blood of the volunteers (resulting from general environmental exposure) did not show any significant decrease relative to that of the control group (Jager 1970); such a decrease might have occurred if the exposure to dieldrin had significantly increased microsomal enzyme activity.

3.3 Studies of Occupationally Exposed Workers

The most extensive studies of occupationally exposed workers are those conducted at a manufacturing plant in the Netherlands and summarized by Jager (1970). Some followup studies of more highly exposed workers were reported by Versteeg and Jager (1973). A total of 826 men worked full-time in the plant for various periods between 1955 and 1968. Maintenance workers, plant cleaners, and formulators were included in this count, as well as operators. The workers were divided as follows:

Group A: 277 workers with exposure shorter than 1 year;

Group B: 316 workers with exposures of 1-4 years;

Group C: 223 workers with exposures of 4-13.25 years.

Group C was subdivided as follows:

Group C-1: 52 workers who left the company and could not be contacted for followup;

Group C-2: 75 workers transferred to other plants but still under medical surveillance;

Group C-3: 106 workers still working in the insecticide plant and having periodic medical examinations.

Within groups C-2 and C-3 three "extreme exposure" groups were identified:

Group C-2a: 17 workers transferred because insecticide levels in their blood exceeded intoxication thresholds;

Group C-2b: 9 workers who had had an episode of insecticide intoxication;

Group C-3a: 35 operators with an insecticide exposure of more than 10 years (through January 1, 1968). Their average length of exposure at that time was 11.1 years.

A number of workers with pre-existing medical disorders, primarily EEG changes, skin diseases, mental disturbances, or neurologic diseases, were rejected or preventively transferred from insecticide work (Jager 1970).

Although most or all of the workers in the extreme exposure group were exposed to aldrin and dieldrin, most were also exposed at times to endrin, Telodrin, or to organophosphate insecticides. The

mean dieldrin level in the blood of the "extreme exposure" group was 0.039 µg/ml. Those in aldrin/dieldrin workers at the time of exposure were in the range 0.022-0.078 µg/ml (Jager 1970).

Of 54 episodes of intoxication in the plant, 23 were attributed to aldrin or dieldrin, 15 of which involved convulsive seizures. Only a few of these episodes involved Group C workers (Jager 1970). With one exception, aldrin/dieldrin intoxications were not peracute but were preceded by prodromi or, in some cases, by a gradual increase of dieldrin levels in the blood. The threshold level of dieldrin in the blood for overt intoxication was determined to be 0.15-0.20 µg/ml, and that for induction of convulsions was about 0.30 µg/ml (Jager 1970).

Except for signs and symptoms of intercurrent diseases not related to insecticides and the clear specific signs and symptoms, in some cases, of overt poisoning, no abnormalities were observed in the long-term exposure groups (Jager 1970). Specifically, no increases in liver size or enzyme activity (alkaline phosphatase, SGOT, SGPT, LDH) were recorded in the extreme exposure groups. EEG patterns generally returned to normal after intoxication episodes. Absenteeism due to sickness or accident was higher in insecticide workers than in other workers in the same plant, but no single type of disease or accident was associated with exposure. Through 1973, when a few workers had worked in the plant for up to 18 years, two cases of cancer and one death had been reported in groups C-2 and C-3 (Jager 1970, Versteeg and Jager 1973); this compares with an expected number of three or

four in a group from the general population with the same age distribution (Seidman 1974).

In a statistical study, serum alkaline phosphatase and SGOT levels were found to increase with insecticide levels in the blood. This was attributed to "adaptation" of the liver to the chemicals. However, it was not established whether the correlation was with levels of dieldrin, Telodrin, or both (Jager 1970).

Workers exposed to endrin exhibited a marked increase in excretion of 6-beta-hydroxycortisol and a marked decrease in tissue storage levels of p,p'-DDE resulting from general environmental exposure. Both of these changes are indicative of stimulation of liver microsomal enzymes. However, workers exposed to aldrin/dieldrin showed no significant changes (Jager 1970). In a subsequent study, 14 aldrin/dieldrin workers showed a statistically significant increase over controls in urinary excretion of D-glutaric acid (another indirect measure of microsomal enzyme activity); endrin workers showed a larger increase (Hunter et al 1972). Dieldrin levels in the blood of the workers involved averaged 0.026 µg/ml but were not significantly correlated with D-glutaric acid excretion.

Other studies of workers occupationally exposed to aldrin/dieldrin have been considerably less detailed. Fletcher et al (1959) observed no clinical poisoning symptoms in spraymen in East Africa dermally exposed to dieldrin at 1.8 mg/kg/day. A 2-year study of 256 spraymen in Arakan, Burma, (dosage not reported) also failed to reveal any symptoms of toxicity in workers or household animals exposed

to the spray (U Than Pe and Venkat Rao 1960). Six workers at a pesticide formulating and packaging plant had aldrin and dieldrin in their blood at levels of 10-125 ppb and 100-312 ppb, respectively (Mick et at 1971). Although these levels exceed the threshold for intoxication identified by Jager (1970), the workers reported no complaints or health problems to the company physician. Hayes and Curley (1968) studied workers in a manufacturing plant whose exposure (estimated from levels in plasma and fat) was estimated to be in the range 0.72 mg/man/day. They were unable to find a relationship between dieldrin exposure and use of sick leave.

According to the AMA's Committee on Toxicology (1960), the proportion of workers poisoned in public health spraying programs involving the use of dieldrin around the world varied from 2 to 40 percent, with the proportion of cases involving convulsions ranging from 47 to 100 percent. Patel and Rao (1958) reported 20 cases of intoxication in 297 workers spraying dieldrin in India. Blázquez and Bianchini (1956) reported 22 cases in workers spraying dieldrin in Venezuela. Subsequently 51 cases of poisoning were reported in 285 workers spraying dieldrin in Venezuela (Committee on Toxicology 1960, Hayes 1957; Table 3.3.1). Hayes (1957) listed 13 cases of intoxication, including 1 fatality, in 92 spraymen in Ecuador, and 8 cases in 40 spraymen in Nigeria. Zavon and Hamman (1961) stated that nine countries had reported cases of dieldrin intoxication in spraymen, due predominantly to gross and continued exposure over a prolonged time period. Incidents usually occurred 3-8 months after a sprayman had

TABLE 3.3.1

POISONING IN SPRAYMEN EXPOSED TO DIELDRIN*

Duration of Exposure (months)	Spraymen Exposed for the Specified Duration		Total No. of Spraymen Exposed for the Specified Duration or Longer	Percentage of Poisoning in Total No. Exposed
	No.	Cases of Poisoning		
0- 3.9	69	0	285	0
4- 7.9	38	5	216	2
8-11.9	26	9	178	5
12-15.9	54	14	152	9
16-19.9	41	13	98	13
20-23.9	45	4	57	7
21-27.9	7	6	12	50
28-31.9	1	0	5	0
32-35.9	0	0	4	0
36-39.9	4	0	4	0
0-39.9	285	51	285	18

*Under practical working conditions in Venezuela

Adapted from Hayes 1957

started regular use of the pesticide. The spray programs involved applications of solutions of 0.68-2.5 percent dieldrin to surfaces at rates of 0.27-1.0 g/m^2 (Hayes 1957). Symptoms reported in studies of workmen exposed to dieldrin and aldrin for prolonged periods include dizziness, insomnia, muscle twitching, increased blood pressure, and electroencephalography (EEG) abnormalities consisting of bilateral synchronous theta-wave activity and occasional bilateral synchronous spike and wave complexes (Hayes 1957, Zavon and Hamman 1961, Committee on Toxicology 1960, Blázquez and Bianchini 1956). Removal from exposure was followed by reduction or complete loss of EEG abnormalities and convulsions, generally within a few months (Hoogendam et al 1962, 1965; Kazantzis et al 1964; Avar and Czégledi-Jankó 1970). Hayes (1957) also listed the following signs and symptoms in spraymen exposed for 30 or more weeks: blurred vision, diplopia, tinnitis, sweating, difficulty in sleeping and bad dreams, nausea, alteration of reflexes, incoordination, nystagmus, and change in personality. Blázquez and Bianchini (1956) reported hepatomegaly in 10 of 22 dieldrin-exposed sparymen, in addition to the symptoms listed by Hayes (1957). In one survey, EEG abnormalities were found in about one-third of spraymen not clinically ill (Hayes 1957). Avar and Czégledi-Jankó (1970) reported preconvulsive changes and EEG abnormalities in one worker with a concentration of HEOD in the blood as low as 0.05 ppm. Prior and Deacon (1969) noted spontaneous sleep in otherwise healthy subjects. Nelson (1953) reported contact dematitis

in workers exposed to 25% aldrin dust, together with "transient bronchial complications due to inhalation of concentrated fumes."

Takahashi et al (1976) reported significantly higher C-reactive protein levels in the sera of workers chronically exposed to dieldrin and pentachlorophenol than in controls. Serum levels of gamma$_2$-globulin were significantly associated with concentrations of dieldrin in serum. Elevated C-reactive protein levels were considered to indicate the presence of tissue inflammation.

In a study of five male farmworkers exposed to a mixture of herbicides and pesticides, including dieldrin, four were found to have suffered impotence after chronic exposure; sexual function was recovered after exposure was terminated (Espir et al 1970). Peck (1970) suggested that their exposure to dieldrin might have induced an increased metabolism of testosterone that led to a deficiency of this hormone.

Dean et al (1975) found no significant increase in the frequency of chromosome abnormalities in lymphocytes from 22 workers occupationally exposed to aldrin and dieldrin.

3.4 Epidemiologic Studies in the General Population

A number of epidemiologic searches for health effects associated with general uses of aldrin/dieldrin have been conducted in various parts of the United States, with generally negative results (USDHEW 1969). However, such studies are difficult to conduct in the general population, ie, in nonoccupationally exposed persons, because residues of dieldrin are widespread in the environment. Virtually everyone is exposed to traces of dieldrin in food, and residues of

dieldrin have been found in the tissues of almost every person examined (Train 1974). Accordingly it is impossible to identify unexposed groups for rigorous comparison with exposed groups.

However, since residues of dieldrin are retained in tissues for months or years after exposure, it is possible to use these residues as indirect measures of the intensity of past exposure. A number of epidemiologic studies have been published in which correlations have been sought between various pathologic conditions and tissue levels of dieldrin.

In a study of 38 autopsy cases, there was an association between high residues of organochlorine compounds and malignant tumors. The highest residues of organochlorine compounds were associated with carcinomas, cachexia, and a variety of focal or generalized abnormalities of the liver. However, these reported associations were with total organochlorine residues, not specifically with dieldrin (Casarett et al 1968).

In another investigation of various pesticides in fat samples taken at autopsy, the average concentration (in ppm) of dieldrin was 0.55 ± 0.34 in 40 cases of carcinoma, 0.47 ± 0.22 in 5 cases of leukemia, 0.51 ± 0.18 in 5 cases of Hodgkin's disease and 0.21 ± 0.15 in 42 "control" cases. Each of the differences from the control level was statistically significant (Radomski et al 1968). The data from this study suggested a relationship between dieldrin levels in adipose tissues and cases of portal cirrhosis and hypertension.

Davies et al (1975) compared levels of dieldrin in the adipose

tissues of 122 cancer victims with those in 122 matched controls. The average dieldrin level was 0.3 ppm in each group. There were no significant differences between dieldrin residue levels in cancer patients and controls, either when the patients were grouped together or divided according to the primary site of cancer. Robinson et al (1965) found no significant differences between dieldrin levels in the fat of 7 cancer victims, 29 victims of cardiovascular diseases, and 7 accident victims sampled at autopsy.

Dacre and Jennings (1970) reported that dieldrin levels were significantly higher in the lung tissues of 26 persons who died of lung canger than in persons who died of other causes. Dieldrin concentrations were significantly higher in cirrhotic than in noncirrhotic livers in an autopsy study of Oloffs et al (1974). However, when expressed on a lipid basis, the dieldrin levels were similar in the two groups.

D'Ercole et al (1976) detected no correlation between dieldrin residues in the blood of newborn infants and maternal age, sex of newborn, birth weight, or incidence of congenital anomalies. Residues were found in premature infants but were not significantly different from those in full-term infants.