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Veterans Administration

Review of Literature on Herbicides, Including Phenoxy Herbicides and Associated Dioxins

Volume I
Analysis of Literature

Department of
Medicine and Surgery

VA Contract Number: V101(93)P-823
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Review of Literature on Herbicides, Including Phenoxy Herbicides and Associated Dioxins

Volume I

This report was prepared under a cost reimbursement-type contract awarded on a competitive bid basis on December 15, 1980. The contract will run for nine and one-half months and is funded at $111,743.

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CHAPTER 5

HUMAN EXPOSURE TO TCDD FROM INDUSTRIAL AND MILITARY USES

TCDD (2,3,7,8-tetrachlorodibenzo-para-dioxin) is formed as an unintentional byproduct during the manufacture of 2,4,5-trichlorophenol (TCP), when certain reaction conditions are met. TCP is a precursor in the manufacture of 2,4,5-T, and TCDD is introduced into preparations of 2,4,5-T during this precursor step.

TCDD is formed when two molecules of 2,4,5-trichlorophenol undergo a condensation reaction. Several conditions favor the formation of dioxins, including heat, pressure, photostimulation, and catalytic action. No definitive study has determined the temperature required to form TCDD from TCP (Esposito et al., 1980). Excessive temperature during the manufacture of 2,4,5-T is generally considered to be a major factor responsible for the presence of TCDD in 2,4,5-T.

At reaction temperatures above 225°C, the reaction of 1,2,4,5-tetrachloro benzene and ethylene glycol to form trichlorophenol becomes exothermic (May, 1973) and unless the temperature is reduced an explosion can ensue. Seven explosions in factories that were manufacturing trichlorophenol have been reported and are listed in table 5-1. An eighth incident, which occurred in France in 1956 and involved acute exposure during an operation to steam-clean trichlorophenol processing equipment, is also listed and described with the seven explosions. Large quantities of TCDD have been released in these accidents.

Occupational exposure to TCDD has occurred in factories when TCDD was formed in excessive amounts because the reaction temperatures were high enough to favor dioxin formation, but not high enough to become exothermic and produce an explosion. These incidents are listed in table 5-2. Two additional incidents of human exposure to TCDD are considered in this section and listed in table 5-3. In one incident, TCDD-contaminated salvage oil was sprayed on horse arenas in Missouri in 1971, resulting in human and animal exposures. In the second incident, three laboratory workers in England were exposed while they were heating trichlorophenol or potassium trichlorophenate, or handling the products.

Military exposure to TCDD resulted from the use of herbicides that contained contaminated 2,4,5-T. In this chapter, information on the exposure levels of TCDD from explosions and industrial exposures are summarized. The human effects of TCDD exposure reported after industrial accidents, occupational exposures, and military exposure are then compared.

5.1 INDUSTRIAL EXPLOSIONS

Exposure conditions and symptoms reported for the 8 accidents listed in table 5-1 are described in this section.

TABLE 5-1. INDUSTRIAL EXPLOSIONS

Table 5-1a. References on Industrial Explosions That Involved TCDD

YEAR	LOCATION	REFERENCES
1949	Monsanto Nitro, WV	Suskind (1978); VA (1980) Zack and Suskind (1980)
1953	BASF Ludwigshafen, W. Germany	Goldmann (1972); Goldmann (1973) Thiess and Frentzel-Beyme (1977)
1956	Rhone Poulenc Grenoble, France	Dugois et al. (1958)
1962	Italy	Joint NIESH/IARC Working Group (1978) Young et al. (1978)
1963	Philips-Duphar Amsterdam, Netherlands	Dalderup (1974); Berlin et al. (1976) Rawls and Sullivan (1976); Hay (1977)
1966	Rhone Poulenc Grenoble, France	Dugois et al. (1968) Rawls and Sullivan (1976)
1968	Coalite & Chemicals Products Bolsover, Derbyshire, U.K.	Jensen and Walker (1972) Jensen et al. (1972; May (1973)
1976	ICMESA Seveso, Italy	Commoner and Scott (1976; Hay (1976) Rawls and Sullivan (1976); Fara (1977) Gianotti (1977); Walsh (1977) Bonaccorsi, et al. (1978); Greim (1978) Laporte (1978); Reggiani (1978) Homberger, et al. (1979) Malizia, et al. (1979) Pocchiari, et al. (1979) Reggiani (1979); Strik (1979) Reggiani (1980); VA (1980); VA (1981)

Table 5-1b. References Which Review Industrial Exposures to TCDD

Forth (1977)
IARC (1977)
IARC (Joint NIESH/IARC-1978)
Hay (1979)
Moses and Moore (1979)
Esposito et al. (1980)
Hay (1977)
Firestone (1978)
Young et al. (1978)
Malizia et al. (1979)
Crow (1980)
Suskind (1980)

TABLE 5-2. INDUSTRIAL EXPOSURES

Table 5-2a. References on Industrial Exposures to TCDD

YEAR	LOCATION	REFERENCES
1949	Nordheim, Westfallen, West Germany	Baader & Bauer (1951)
1951-52	2 factories in Middle Rhein, W. Germany	Bauer et al. (1961)
1954	Boehringer, Ingelheim Hamburg, West Germany	Kimmig & Schulz (1957) Kimmig & Schulz (1957) Schulz (1957); Bauer et al. (1961)
1956	Diamond Alkali Newark, N.J.	Bleiberg et al. (1964) Poland et al. (1971)
1964	U.S.S.R.	IARC (1977)
1964	Dow Chemical (2,4,5-trichlorophenol production) Midland, Michigan	Firestone (1978) Cook et al. (1980) Rowe (1980)
1965-9	Spolana Czechoslovakia	Jirasek et al. (1973) Jirasek et al. (1974) Pazderova et al. (1974) Jirasek et al. (1976) Pazderova-Vejlupkova et al. (1980)
1970	Japan	Miura et al. (1974)
1972	U.S.S.R.	Zelikov and Danilov (1974)
1950-1975	Dow Chemical (2,4,5-T production) Midland, Michigan	Kramer (1974)* Ott et al. (1980) Townsend et al. (1980)*
1955 - 1977	Monsanto Nitro, West Virginia	VA (1980)

*unpublished reports

Table 5-2b Other Industrial Exposures[1]

YEAR	LOCATION	CHEMICAL MANUFACTURED	NUMBER OF WORKERS EXPOSED
1952-3	Boehringer West Germany	Trichlorophenol	37
1953-1971	Rhone Poulenc Grenoble, France	Trichlorophenol	59
1956	Hooker U.S.A.	Trichlorophenol	---
1960	Diamond Shamrock U.S.A.	Trichlorophenol	---
1970 (?)	Bayer West Germany	Trichlorophenol	5
1973	Linz Nitrogen Works Austria	Trichlorophenol	50
1974	Bayer Verdingen, West Germany	Trichlorophenol	5
1975[2]	Thompson-Hayward Kansas City, Kansas	Trichlorophenol	--
1979	Vertek Chemical Plant Jacksonville, Arkansas	2,4,5-T	190

[1]These incidents were listed first in Hay (1977) and later in subsequent lists; no reports that provide exposure levels or symptoms have been identified; the 1979 incident was mentioned in Suskind, 1980.

[2]This incident was listed as an explosion by Hay (1977) and as an occupational overexposure in subsequent lists by Young et al. (1978) and Esposito et al. (1980).

Table 5-3. REFERENCES ON OTHER HUMAN EXPOSURES TO TCDD

YEAR	LOCATION	POPULATION DESCRIBED	REFERENCES
1971	Missouri	Farm residents	Carter et al. (1975) Case (1976) Beale et al. (1977) Kimbrough et al. (1977) Crow (1980)
1970	England	3 laboratory workers	Oliver (1975)
1967-1970	Vietnam	Vietnamese residents	NRC (1974)
		Vietnamese refugees	Tung et al. (1971) Rose and Rose (1972) Tung et al. (1980)
		Vietnam veterans	Bogen (1979) Halprin (1980) Stellman & Stellman (1980) VA (1980)
		Vietnam military	Harmon (1971) Allen (1980)

5.1.1 Exposure Conditions

Several variables in the eight accidents that are relevant for a comparison of the data on health effects from these incidents are considered below. These variables include:

- Dosage
- Duration and routes of exposure
- Concomitant exposure
- Latency period
- Unexposed controls.

5.1.1.1 Dosage

The types and severity of health effects observed after TCDD exposure are presumably related to the doses of TCDD received. Unfortunately, almost no information on exposure levels following explosions or during occupational exposure has been published and only a very limited comparison of dosage levels and resultant health effects can be made.

In two early accidents, TCDD was not known to be a contaminant released during the accidents or a potential health hazard. In 1949, when the Nitro, West Virginia accident occurred, TCDD had not been identified as a potential contaminant of the manufacture of trichlorophenol. Only after TCDD was identified following similar explosions elsewhere was the etiologic role of TCDD in the Nitro incident assumed. An incident in 1956 in a French factory manufacturing 2,4,5-T resulted in numerous cases of chloracne. The report that described these cases (Dugois et al., 1958) also mentioned that the causative agent could not be identified at the time, although any measures taken to identify the cause were not mentioned. A new manufacturing procedure, begun 2 years before the incident, introduced steam into a process that had been performed at colder temperatures. This steam process was stopped following the accident and other precautions were instituted to prevent worker exposure to released vapors. Subsequently, no new cases were reported.

After the 1953 accident at the BASF factory, an extensive search for the agent responsible for the workers' health effects was made (Goldmann, 1972; 1973). Symptoms of chloracne that resembled the condition observed in the workers were reproduced in rabbits treated with crude extracts of the TCP distillate. None of the chemicals known to be present in the distillate were acnegenic when tested individually. A series of chemicals that were considered potential contaminants were synthesized, and several of these compounds, including TCDD and several chlorinated dibenzofurans, produced potent acnegenic responses. Analysis of the distillate for its dioxin content led to confirmation of the presence of TCDD. The concentration of TCDD the workers encountered remained unknown.

TCDD levels were measured after three explosions. After the 1963 explosion in Amsterdam, a soot-like substance was released into the factory.

Analysis of this substance revealed that it contained 1,000 ppm TCDD. Estimates of the total amount of TCDD released into the factory hall ranged from 30 to 200 g (Crow, 1980). After the 1968 explosion in England, levels of up to 40 mg of TCDD per m^2 were detected on wall surfaces (Crow, 1980). These levels are considered to correspond roughly to the amounts released in the Amsterdam factory. Three years after the explosion in England, two workers who worked with one of the few salvaged pieces of equipment came down with severe cases of chloracne within 3-4 weeks after they were exposed. TCDD could not be detected on the apparatus by either chemical or biological assays (May, 1973). Assays of the sebum discharged from the skin of one of the affected men 1 year after exposure did not contain measurable amounts of TCDD by the gas-liquid chromatographic method used, which had a lower detection limit of 0.1 ppm; the sebum flow rate was normal (Jensen et al., 1972).

After the explosion in Italy in 1976, a cloud that contained TCDD was released over the surrounding countryside. Extensive measurements of TCDD were made of the affected areas, which resulted in establishing three zones of contamination: zones A, B, and R had areas with up to 270, 44, and 15 ug of TCDD per m^2, respectively. Mean values for various parts of zone A were 15-29 ug/m^2 and for zone B were 4 ug/m^2. Soil samples from zones A, B, and R contained greater than 10, 0.1-10, and less than 10 ug TCDD per kg, respectively (Reggiani, 1978). In the previous accidents, vapors released during the explosions were contained in limited areas of the factories. In Seveso, vapors were released into the environment, diluting the TCDD concentration substantially.

Only one estimate of human TCDD body burdens based on measured tissue levels of TCDD was found in the published literature. A woman who lived in Seveso's zone A for 2 weeks (between the accident and the time when the evacuation was ordered) died in October 1976 of pancreatic cancer. This death was not attributed to TCDD exposure. Tissues removed at autopsy were analyzed for TCDD; the levels found led to an estimate of 0.5 mg of TCDD per kg body weight absorbed at the time of the incident, assuming a half-life of 30 days for TCDD (Reggiani, in VA, 1981). Information to compare relative exposures is inadequate. Even when the information on TCDD levels in the vicinity several months or years after the accident is available, only two attempts to measure it in people have been recorded. One attempt was successful, but was dependent on several pharmacokinetic assumptions and was based on measurements from one person at only one point in time. The actual levels workers were exposed to, the length of the exposure period, or the amounts absorbed remain unknown.

5.1.1.2 Duration and Routes of Exposure

The eight industrial accidents listed in table 5-1a are being considered together because they resulted in acute exposure of workers (or residents, in the Seveso incident) to TCDD during a short period of time. However, inadequate decontamination measures or lack of knowledge regarding the presence of TCDD and its high order of toxicity led, in most cases, to continued exposures after the explosions occurred. No specific decontamination procedures were described after the Nitro accident. Extensive efforts were made to decontaminate the BASF factory after the explosion, and manufacturing of other products

was eventually resumed. Two years after the decontaminated facility was reopened, the first new case of illness occurred. The facility was closed again and in 1969 the autoclave and contaminated equipment were demolished (Goldmann, 1972). Decontamination measures in the English facility were also inadequate, and 79 cases of chloracne were reported in workers who were not present during the explosion but were exposed only to the "decontaminated" facility. Consequently, the contaminated equipment was dismantled and buried (May, 1973). Despite extensive measures taken to decontaminate the Amsterdam facility, residual TCDD remained and the factory was dismantled and parts were encased in concrete and sunk in the Atlantic Ocean (Berlin, 1976; Dalderup, 1974). Decontamination efforts in zone A in Seveso have not been completed and the factory that released TCDD is not being used, even though TCDD was not released inside the facility.

Cases of chloracne occurred in people who were never in the factories where the explosions took place. People whose only exposure to TCDD was from contact with affected Nitro workers developed chloracne; in one case a man who drove a truck that had been parked near the factory developed chloracne (Suskind, 1978). The health effects of Nitro workers who were not present when the explosion occurred was the subject of a separate investigation, which is described in the next section. After the BASF and British explosions, family members of workers who never entered the facility developed chloracne (Goldmann, 1972; Jensen et al., 1972). Workers involved only in the cleanup operation in Amsterdam contracted chloracne (Rawls and Sullivan, 1976). The Seveso incident resulted in high exposures of zone A residents over a 2-week period (before evacuation was ordered), and low, continuous exposures of residents of zones B and R, based on TCDD analyses of soil samples. Residents of one zone ate food from other zones and worked and traveled between the zones, complicating exposure estimates for these people (Bonaccorsi et al., 1978). After the explosion in France in 1956, chloracne was reported only in workers (Dugois et al., 1958); however, not knowing that TCDD was the causative agent may have prevented investigators from relating other cases among family members to the factory incident. In conclusion, exposure to TCDD probably was not limited to acute exposure during the explosions, but in many cases involved long-term exposures to low levels of TCDD that were not removed during the decontamination process, and in some cases involved indirect exposure of people who were never in contact with the contaminated factories.

The routes of exposure of TCDD are speculative. TCDD exposure by the workers was probably by pulmonary and dermal routes. The Seveso residents were probably exposed by the oral route, in addition, since food supplies were contaminated. Children who played outdoors had potential for much higher inhalation and dermal exposures than adults who remained inside.

5.1.1.3 Concomitant Exposures

Chemicals other than TCDD were present in the factories or were released during the explosions. The types and amounts of chemicals released are subject to speculation, as no results of quantitative or qualitative analyses of vapors during explosions were made. However, trichlorophenol was likely to be present in most cases and the early skin burns observed within the first two days of the Seveso accident have been attributed to trichlorophenol

(Walsh, 1977). Sodium hydroxide, sodium chlorophenate, other phenates, and ethylene glycol were probably present in Stack emissions of the ICMESA plant (Melvin, personal communication).

The phase of the trichlorophenol reaction that was taking place when the accidents occurred probably affected the types and amounts of polychlorinated chemicals that were released. In the 1963 accident in Amsterdam, the accident occurred during the beginning of the reaction when mainly tetrachlorobenzene was likely to be present and polychlorinated dibenzofurans were likely to be produced. The accidents in 1968 in the United Kingdom and in 1976 in Seveso occurred near the end of the reaction when mainly trichlorophenol was likely to be present, which produces TCDD (Joint NIEHS/IARC Working Group, 1978).

Some of the symptoms that were not observed in all accidents may have been the result of concomitant exposure to chemicals found only in specific incidents. However, different levels and durations of TCDD exposure may also be responsible for effects seen only after certain accidents. Some symptoms were not mentioned in descriptions of patients from some of the accidents because they were associated with conditions that probably were not suspected and could not be diagnosed without performing specific tests. For example, diagnosis of porphyria cutanea tarda requires that urine samples be analyzed for porphyrin content. This analysis is not routine and other symptoms of porphyria cutanea tarda, such as hirsutism and hyperpigmentation, may have gone unnoticed if porphyria was not suspected.

5.1.1.4 Latency Period

In comparing the consequences of these industrial accidents on human health, the duration of time that has elapsed between the accident and examination of patients is significant. Hepatotoxicity, measured by liver enzyme tests, was observed in the United Kingdom and Seveso workers, in tests performed several days or weeks after the accidents, but in both groups of patients these effects were transient and were not observed in subsequent tests (May, 1973; Reggiani, 1978).

The onset of early symptoms of chloracne, including redness and itching, was evident several days after exposure. Comedones that are characteristic of chloracne, on the other hand, may take 2 months to develop, but in severe cases such as occurred at the Nitro plant, lesions were still evident 28 years later (Crow, 1980). The results are complicated even when the time interval between the accident and examination are known, because exposure may have continued during an unknown part of this interval and the duration of sympto in some cases correlates to the severity of exposure, an unknown variable. The time between exposure and the onset of symptoms other than chloracne usually was not mentioned in reports of the accidents and was understandably more difficult to identify, as in the case of asthenia.

5.1.1.5 Unexposed Controls

Most reports and studies of workers exposed to TCDD are descriptive. They usually have not included data from control groups, as a basis for

comparison of experimental data. Two exceptions are the control group of Italian children who were compared to the TCDD-exposed children in Seveso for immunologic characteristics (Pocchiari et al., 1979), and several control groups in Germany used to evaluate the incidence of mortality in the BASF workers (Thiess and Frentzel-Beyme, 1977).

5.1.2 Symptoms Experienced After Exposure

Table 5-4 lists some of the symptoms reported after the industrial explosions. Except for Seveso data, all symptoms were observed in workers.

5.1.2.1 Chloracne

Chloracne occurred in exposed people after all eight accidents and is considered characteristic of TCDD exposure. The clinical symptoms that developed in all of these workers appear to have been similar in nature, varying primarily in severity and duration. These symptoms have been described clearly in most reports and have been the subject of several reviews (Birmingham, 1964; Schulz, 1968; Crow, 1970; Braun, 1970; Taylor, 1974; Crow, 1978a; Crow, 1978b; Taylor, 1979).

After some accidents, chloracne was severe, resulting in lesions still apparent many years after exposure ended. After the Nitro accident, 14 of the 122 people originally affected still had skin lesions 28 years later (Crow, 1980). The most severe cases involved workers considered most likely to have received high exposure to TCDD. After the explosion in Amsterdam, about 50 cases of chloracne developed. Thirteen years later, 10 cases remained (Hay, 1977).

Seventy-nine workers in the factory in England developed chloracne; however, only seven cases remained 4 years later. Chloracne did not develop in any of the 13 men who survived the original explosion (May, 1973). The lower doses of TCDD likely to have been encountered in the decontaminated British factory probably explains the lower severity, compared to workers in the Nitro and Amsterdam accidents.

Most of the 134 cases of chloracne from the Seveso accident occurred in children; however, only school-aged children, and not adults, were systematically screened for chloracne (Bonaccorsi et al., 1978). Children were not directly exposed in any of the other incidents but sometimes developed chloracne after contact with an exposed parent (Goldmann, 1972; Jensen et al., 1972). The Seveso data suggest that children may have a greater sensitivity to the acnegenic effects of TCDD than adults. The potential differences in exposure, between children (who were likely to have played outside) and adults, may have contributed to the differences in symptoms between children and adults.

Chloracne has appeared in many cases without any other apparent health effects. Half of the 42 chloracne cases from the BASF accidents had no other symptoms (Goldmann, 1972), and only two or three of the 44 workers in the

TABLE 5-4: HEALTH EFFECTS FROM INDUSTRIAL ACCIDENTS INVOLVING TCDD

Year	Location	No. Affected	Organ Systems Affected:										
			Dermal	Renal	Hepatic	Neuro.	Asthenia	Blood	GI	Lipid Metab.	Immuno.	CV	Pulm.
1949	Nitro, W.Va.	228	+		+	+	+	+		+			+
1953	BASF, W. Ger.	55	+	+	+	+	+					+	+
1956	Grenoble, Fr.	17	+		+		+						
1963	Amsterdam, Neth.	44	+		-		+		+				
1968	Bolsover, Derbyshire U.K.	79	+		-		+	+	-				
1976	Seveso, Italy	134	+		+	+	+	+	+		+	-	

Code: (+) An effect was observed;

(-) An effect was not observed in patients examined (or questioned) about the effect;

( ) Patients were not examined or questioned, regarding any effects in the indicated organ system.

Amsterdam accident (Crow, 1980) and the 79 workers in England (May, 1973; Hay, 1977) who developed chloracne had any other adverse effects; these effects were limited to asthenia. These trends have led to the conclusion that chloracne is the hallmark of TCDD poisoning (Crow, 1980). After most accidents, only patients that developed chloracne were examined further for other symptoms.

5.1.2.2 Porphyria Cutanea Tarda

This condition results from a disturbance in the capacity to break down hemoglobin, which leads to high levels of porphyrins in the liver and urine. Like chloracne, it is a relatively unusual condition which is not frequently encountered in other occupational situations; some cases have been shown to be inherited, rather than acquired.

Porphyria cutanea tarda was observed after the Nitro incident, and symptoms of this condition, including hirsutism and hyperpigmentation, were observed along with urine and liver changes (Suskind, 1978). After the Seveso accident, several cases of increased porphyria excretion and hyperpigmentation were observed; chromatographic examination of urine samples for levels of porphyrins excreted revealed patterns resembling mild chronic hepatic porphyria (Strik, 1979). These effects were observed only in a small portion of the exposed people in Seveso and were transient.

Porphyria cutanea tarda was not mentioned in the accounts from the other accidents. High doses of TCDD or repeated exposures may be required before this condition is observed. The possibility that concomitant exposures may have produced this condition in the Nitro and Seveso patients cannot be ruled out.

5.1.2.3 Hepatotoxicity

Aside from the liver function tests mentioned above, which showed transient effects immediately after exposure in workers exposed in England (May, 1973) and Seveso (Reggiani, 1978), hepatotoxicity was reported after other accidents. Hepatomegaly was observed in Nitro workers (Suskind, 1978) and Seveso residents (Bonaccorsi et al., 1978); hepatitis occurred in four of the 42 affected workers in the BASF factory (Goldmann, 1973) and hepatic disorders were mentioned (but not described) as a consequence of the accident in France in 1956 (Dugois, 1958).

Unlike chloracne, hepatotoxicity has not been reported consistently after TCDD accidents. When it is reported, it is absent in a large proportion of the people that develop chloracne. Furthermore, the different manifestations of hepatotoxicity, including hepatitis, hepatomegaly, and transient abnormal liver function tests may have resulted from different causes or as secondary or compensatory effects of TCDD exposure. It is not clear whether parameters of hepatic structure or function were even examined in the incidents that do not mention them.

5.1.2.4 Neurological Effects

Neurological effects were reported after every accident. These effects always included asthenia and in particular, fatigue. The incidence of fatigue varied. The frequency of this complaint was low among the affected workers in the Amsterdam and United Kingdom accidents (Crow, 1980; May, 1973; Hay, 1977), but was one of the few symptoms other than chloracne that was mentioned.

Other neurologic symptoms that were described after the Nitro, BASF, French, and Seveso accidents included headaches, sleep disturbances, irritability, and confusion (Suskind, 1978; Goldmann, 1972; Dugois et al., 1958; Walsh, 1977). The subjective nature of these symptoms decreases the reliability of identifying their frequency or severity. Peripheral neural damage involving the sensory organs and polyneuritis were mentioned in the Nitro and BASF workers. Pain in the extremities was mentioned by Nitro workers (Suskind, 1978) and encephalomyelitis occurred in some BASF workers.

Seven of the 42 BASF workers with chloracne developed problems related to the central nervous system (Goldmann, 1972; 1973). Delayed peripheral nerve conduction was observed by one examiner, but not by another examiner who studied the same population from Seveso (see VA; 1981). Seveso workers were examined for neurological function; 4 percent (8 subjects) were diagnosed as having polyneuropathy of peripheral nerve fibers. Three of these people were hospitalized and diagnosed as having polyneuropathy of the lower extremities. Other common causes of polyneuropathy were ruled out in these patients (Pocchiari et al., 1979).

5.1.2.5 Other Effects

Gastrointestinal effects were observed after the Seveso accident (Bonaccorsi et al., 1978) and the accident in France in 1956, although no other details were provided from the latter incident (Dugois et al., 1958). The delay in evacuation following the Seveso accident may have led to ingestion of TCDD-contaminated food. Oral exposure was unlikely after the other incidents and may explain why gastrointestinal effects occurred only after the Seveso incident.

Effects on the kidneys, heart, lung, and spleen each were reported in only the BASF workers (Goldmann, 1972; 1973) and, therefore, do not appear to be consistent effects of acute TCDD exposure. Different types of blood effects were reported for three of the accidents and were transient in one case (Suskind, 1978; May, 1973).

Reproductive effects were examined after the incidents in Amsterdam (Rawls and Sullivan, 1976) and Seveso (Homberger et al., 1979; Rehder et al., 1978; Reggiani, 1978), but no effects were demonstrated. Data on reproductive effects from the Seveso incident are considered in another section of this report.

Immune function was evaluated after only the Seveso incident (Reggiani, in VA, 1981; Homberger et al., 1979). In vitro tests produced evidence of decreased immune competence, although the affected children at Seveso did not

experience a higher incidence or severity of childhood diseases than children from other parts of Italy.

5.1.2.6 Mortality

No deaths were attributed directly to TCDD exposure immediately after the accidents.

Long-term mortality studies are being carried out on people exposed to or affected by the accidents at Nitro, BASF, Amsterdam, the United Kingdom, and Seveso. The incidence of death from cancers and from cardiovascular causes was not elevated in a study of the Nitro workers (Zack and Suskind, 1980). Of the 17 deaths among the BASF workers that occurred in the 24-year period after the accident, six were attributed to cancers, including four gastrointestinal cancers. The first death was caused by pancreatic necrosis and involved the first worker who entered the "decontaminated" facility; he was not present when the accident occurred (Thiess and Frentzel-Beyme, 1977).

A higher-than-expected incidence of death from myocardial infarction has been observed in the Amsterdam workers (Zack and Suskind, 1980; Joint NIEHS/IARC Working Group, 1978). Only one death has occurred in the workers from England, and was caused by coronary thrombosis (Joint NIEHS/IARC Working Group, 1978). The Seveso data on mortality rates indicate that the accident did not produce an observable increase in the death rate (Homberger et al., 1979).

The long latency period expected for cancers to develop requires that mortality studies should be conducted on a long-term basis; IARC is coordinating efforts in this area. In general, the number of deaths among the approximately 500 people affected in these incidents is very small. Trends have emerged in the data that exist today to indicate that TCDD exposure may increase the likelihood of death from cancer or cardiovascular reasons, but these trends were found in only one of the groups of workers and were not duplicated in any other.

5.1.3 Conclusions

In conclusion, chloracne and asthenia are consistently reported in the accidents described above. The incidence of asthenia is low compared to the incidence of chloracne. The subjective nature of asthenia complicates evaluating its significance as a primary effect of TCDD or a secondary effect of patients suffering from the discomfort and disfigurement of chloracne and the fears associated with exposure to toxic agents.

Other neurological disorders and hepatic disorders were commonly observed after these accidents. They were usually studied in chloracne patients and were more likely to occur in groups of workers with incidences of asthenia, although the specific symptoms involving these organ systems varied after the accidents. Peripheral neuritis and hepatomegaly were the most commonly encountered of these conditions.

Porphyria cutanea tarda occurred in the Nitro workers, who in general suffered more types of effects and more severe effects than workers from most of the other accidents, except for the BASF workers. These workers may have been exposed to the highest level of TCDD, as was suggested above.

5.2 OCCUPATIONAL EXPOSURE THAT DID NOT INVOLVE EXPLOSIONS

Twenty incidents other than explosions have been reported that resulted in exposure of workers to TCDD. These incidents are listed in table 5-2.

Nine incidents, listed in part 5-2b of the table, were listed in a table by Hay (1977) and have appeared on several subsequent lists of accidental exposures, but no other information on the circumstances of exposure or clinical manifestations of TCDD exposure have been reported and the incidents are not described in this section. The incident in 1975 in Kansas was described by Hay as an explosion, but was listed as an industrial exposure in more recent lists by Young et al. (1978) and Esposito et al. (1980). Three incidences of industrial exposure occurred in West Germany: in Westfallen in 1949, in Middle Rhein in 1951-52, and in Hamburg in 1954 (table 5-2).

5.2.1 Exposure Conditions

TCDD was identified as the likely cause of chloracne in several incidents, although the work environment was not sampled in any of the factories to determine actual levels of contamination to which workers were exposed. Workers in Westfallen who developed symptoms in 1949 were working with pentachlorophenol. Trichlorophenol was used only briefly in this facility and at the time was not considered to be the source of the intoxications (Baader and Bauer, 1951).

The relationship of TCDD to adverse health effects was determined for several incidents. TCDD was identified in the byproduct material of the Hamburg factory and one of the investigators confirmed that it was acnegenic after he applied it on his own skin and developed lesions resembling those seen in the workers. Other materials, including the purified trichlorophenol preparation and its trichlorophenol precursor, were not acnegenic in animal studies (Bauer et al, 1961). TCDD was identified on walls and in some of the products manufactured at the Czechoslovakian factory. The air was not analyzed and no quantitative analysis of any samples was reported (Pazderova-Vejlupkova et al., 1980).

Levels of TCDD were determined in the workplace for products made at several factories. Diamond Alkali had produced 2,4,5-T with a TCDD contamination level of 10-25 mg/kg at the time chloracne was identified among workers at this plant. Manufacturing procedures were changed to decrease this contamination level, and 7 years later a reexamination of the workers revealed marked improvement in their clinical picture as well as a reduction in the TCDD level to 1 mg/kg (Poland et al., 1971). At the Dow Chemical facility, air sampling revealed 2,4,5-T concentrations up to 0.8 mg/m^3. The TCDD levels were not measured, but between 1966 and 1972 the TCDD levels were required to be no higher than 1 ppm (Ott et al., 1980).

5.2.1.1 Duration and Routes of Exposure

In general, the appearance of symptoms of chloracne in workers has been interpreted as an indication that toxic chemicals were being released, and usually has resulted in changes in manufacturing conditions, improvements in industrial hygiene, and the elimination of new cases of chloracne. However, the intervals between the start of exposure, the appearance of symptoms, and the decrease or elimination of exposure have not been identified in most of the accounts, precluding any estimates of latency periods between exposure and symptoms, or threshold doses, or time periods below which symptoms do not occur. The health of Dow workers 6 years after chloracne was first diagnosed was reported, but no data were presented on their health status when the problem was first diagnosed (Firestone, 1978; Rowe, 1980).

Unlike the incidents involving accidents, the occupational exposures offered a reasonable risk for oral exposure in cases where food was stored or consumed in the workplace. The relative importance of exposure by various routes of exposure was seldom mentioned in reports and is not known.

5.2.1.2 Concomitant Exposures

Other than trichlorophenol, 2,4,5-T, and TCDD, chemicals to which workers were exposed were rarely mentioned in the reports discussed in this section. In two cases, however, concomitant exposures were mentioned and in both of these cases certain adverse health effects observed in the workers could be attributed to these chemicals. Seven of 10 workers exposed to pentachlorophenol in the Westfallen factory in 1949 developed bronchitis. This symptom was not reported in the other incidents (except for one case in the Hamburg workers) and may have been caused by pentachlorophenol (Baader and Bauer, 1951).

A mortality study of the Monsanto workers revealed a ninefold higher incidence of bladder cancer than expected. However, exposure to paramenobithenol (PAB), a known bladder carcinogen, was confirmed in at least 80 percent of these cases (Gaffey in VA, 1980). The impact of concomitant exposure to other chemicals on the health of workers exposed to TCDD is impossible to evaluate, as many of these people worked in the chemical industry for several decades (see VA 1981) and were exposed to a wide variety of chemicals.

5.2.1.3 Unexposed Controls

Most reports provided descriptions of health of workers, without any comparison to control groups. Control groups were used in evaluating the results of the second study of Diamond Alkali workers (Poland et al., 1971) and in the Czechoslovakian study to establish an expected range of values for the metabolic tests performed on the workers (Pazderova-Vejlupkova et al., 1980).

5.2.2 Symptoms Experienced After Exposure

Table 5-5 lists organ systems that were affected in workers who were occupationally exposed to TCDD. Symptoms discussed in this section are related to:

- Chloracné
- Porphyria cutanea tarda
- Hepatotoxicity
- Neurological effects
- Other effects.

5.2.2.1 Chloracne

As observed after the industrial accidents, almost every industrial exposure in table 5-2 has included cases of chloracne and, in fact, the appearance of chloracne has usually initiated the suspicion of TCDD exposure. Frequently, other clinical symptoms are reported only for patients that developed chloracne. Severe cases of chloracne occurred from the early exposures, including ten cases in 1949, nine of which remained 1 1/2 years after exposure ended. Seventeen workers were involved in the pentachlorophenol operation, but the skin conditions of the seven men who were not examined were not stated (Baader and Bauer, 1951).

Twenty-nine workers in the Diamond Alkali plant were diagnosed with chloracne, although the total number of workers exposed to potential TCDD-contaminated operations was not reported (Bleiberg et al., 1964). Seven years later, 18 percent of 73 workers at this facility had chloracne (Poland et al., 1971). In 1964, chloracne was reported in 69 of 83 workers in the USSR (IARC, 1977) and in 49 of 60 workers at Dow in the U.S. (Cook et al., 1980).

Other incidents of chloracne involving 78 workers in Czechoslovakia (Jirasek et al., 1973), 14 in Japan (Miura et al., 1974), and one in 1972 in the USSR (Zelikov and Danilov, 1974) were reported without giving the total numbers exposed. In these last two incidents, chloracne was the only clinical symptom observed. However, a 20-year study of Dow workers involved in the manufacture of 2,4,5-T revealed no chloracne or any other health effects among these workers (Kramer, 1974; Ott et al., 1980; Townsend et al., 1980).

5.2.2.2 Porphyria Cutanea Tarda

Porphyria cutanea tarda was observed in workers from two factories. Among 78 Czechoslovakian workers examined, 76 had chloracne and 11 had hepatic lesions and disorders of porphyrin metabolism; one of the 11 did not have chloracne (Jirasek et al., 1973; 1974; 1976; Pazderova et al., 1974; 1980). Eleven of the 29 Diamond Alkali workers examined had porphyria cutanea tarda (Bleiberg et al., 1964). In the study 7 years later, none of the 73 workers had porphyria (13 had chloracne) and the authors of this report (Poland et al., 1971) concluded that chloracne and porphyria cutanea tarda were two independent disease entities in these workers.

TABLE 5-5: HEALTH EFFECTS OF OCCUPATIONAL EXPOSURE TO TCDD

			Organ Systems Affected:										
Year	Location	No. Affected	Dermal	Renal	Hepatic	Neuro.	Asthenia	Blood	GI	Lipid Metab.	Immuno	CV	Pulm.
1949	Nordheim,W.Ger.	17	+			+							+
1952	Middle Rhein, W. Ger.	60	+				+						
1954	Boehringer Hamburg, W. Ger.	31	+		+	+	+		+			+	+
1956	Diamond Alkali Newark, N.J.	29	+		+	+	+	+	+	+			
1964	USSR	128	+		+		+		+				
1964	Dow Chemical Midland, Mich.	60			-		+						
1965-69	Spolana Czeckoslovakia	78	+		+	+	+						
1970	Japan	14	+		-					+			
1972	USSR	1	+					-	-				

Code: (+) An effect was observed;

(-) An effect was not observed in patients examined (or questioned) about the effect;

( ) Patients were not examined or questioned, regarding any effects in the indicated organ system.

The Japanese workers did not have porphyria cutanea tarda (Miura et al., 1974) and no other mention of porphyrin analyses or symptoms of this disease were mentioned in the accounts of the other industrial exposures. Hyperpigmentation occurred in all of the workers in Westfallen (Baader and Bauer, 1951), and was observed in the Hamburg workers (Kimmig and Schulz, 1957) and in both studies of the Diamond Alkali workers (Bleiberg et al., 1964; Poland et al., 1971), it was not observed in the 1972 Soviet exposure (Zelikov and Danilov, 1974). Descriptions of this symptom were inadequate to classify it as a manifestation of chloracne or porphyria.

5.2.2.3 Hepatotoxicity

Liver biopsies from Hamburg workers revealed hepatic disorders in a few cases, which involved fatty infiltration of iron deposits. Liver impairment was observed in some patients with severe chloracne who were exposed in 1964 in the Russian factory (IARC, 1977). Liver enlargement and abnormal liver function tests were observed in the Czechoslovakian workers (Jirasek, 1974; Pazderova-Vejlupkova et al., 1980), although the Dow workers had normal liver function tests (Firestone, 1978).

Hepatotoxicity observed after the industrial accidents is manifested in different ways. Reports rarely mention whether a patient was examined for a palpable liver and liver function tests appear not to have been done in other workers.

5.2.2.4 Neurological Effects

Neurological disorders were observed in workers from all of the early industrial exposures (the first seven are listed in table 5-5). Asthenia was observed in the Middle Rhein and Hamburg workers listed in table 5-2 (Bauer et al., 1961), in the Russian workers exposed in 1964 (IARC, 1977), in the Czechoslovakian workers (Pazderova-Vejlupkova et al., 1980) and in one Dow worker who experienced depression (Firestone, 1978). The Diamond Alkali workers were administered the Minnesota Multiphasic Personality Inventory (Poland et al., 1971). Scores for one part of the test were found to correlate with the severity of chloracne of the workers. Headaches, fatigue, sweating, dizziness, and sleep disturbances were the most common asthenic symptoms reported. Weakness of the lower extremities was reported in the same groups of workers that experienced asthenia. Joint pain, peripheral neuropathy or loss of sensory function was also reported for each of these groups of workers.

5.2.2.5 Other Effects

Gastrointestinal problems were common among the same groups of workers that experienced asthenic symptoms. Abdominal pains were reported in 30 percent of the Diamond Alkali workers (Poland et al., 1971) and in some of the Hamburg workers (Bauer et al., 1961; Kimmig and Schulz, 1957) and in the Russian workers exposed in 1964 (IARC, 1977). Nausea, vomiting, and diarrhea

in one group of workers (Poland, 1971), and decreased appetite and weight loss in another (Bauer et al., 1961), were reported. One of the Dow workers continued to experience difficulty in swallowing 6 years after TCDD exposure had ceased (Firestone, 1978). Increased serum cholesterol levels were observed in 10 percent of the Diamond Alkali workers (Poland et al., 1971) and in the Japanese workers (Miura et al., 1974); there is no evidence that serum cholesterol was analyzed in other workers. No abnormal hematology results were observed for the Russian workers exposed in 1972 (IARC, 1977), although 10 percent of the Diamond Alkali workers had decreased white blood cell counts (Poland et al., 1971).

The only cardiovascular problems reported were in the Hamburg workers and included orthostatic hypotension (Bauer et al., 1961).

Chronic bronchitis observed in West German workers might have been attributable to pentachlorophenol exposure, as mentioned above.

5.2.2.6 Mortality

A mortality study of workers suspected of industrial exposure was performed on workers at Monsanto who were employed between 1949 and 1969, the year Monsanto ceased production of trichlorophenol (Gaffey, in VA, 1980). The study included an identification of the causes of the 164 deaths that occurred among a total of 885 workers. Higher than normal incidences of deaths from bladder cancer, lung cancer, and arteriosclerotic heart disease were reported. The ninefold increase over the expected number of deaths from bladder cancer was attributed to exposure of these workers to paramenobitherol, a bladder carcinogen. The other two causes of death were increased both in TCDD-exposed workers and in all other workers as well, and was attributed to exposure to the industrial environment, with no increased risk attributed to TCDD exposure. Mortality studies were also performed on Dow workers involved in the 1964 outbreak of chloracne (Ott et al., 1980) and in 2,4,5-T production (Cook et al., 1980). Neither study identified an increased mortality with industrial exposure; however, only 4 and 11 deaths, respectively, have occurred in the two study populations.

5.2.3 Conclusions

In general, the signs of toxicity in workers exposed to TCDD were similar whether or not the exposure involved an explosion. Chloracne was by far the most common condition recognized in workers. Earlier incidents of occupational exposure, which occurred prior to 1970 or accidents before 1960, in general produced more symptoms, higher frequencies of affected workers among those exposed, and worse cases of chloracne than reported for later incidents. If workers experienced only one condition, it is was almost always chloracne (partly biased by the way the studies were conducted); if they had two, the second one was asthenia.

These trends are general impressions; as described in the foregoing discussion, inadequate descriptions of worker health, lack of analyses, and

lack of reporting results in quantitative terms precludes making strong statements regarding these trends. These trends also suggest that workers involved in the earlier incidents were exposed to higher TCDD levels than other workers. A logical hypothesis that emerges from this soft evidence is that hepatic and neurological effects require a higher threshold dose than chloracne.

Porphyria cutanea tarda requires specialized tests to detect; it may also require high or extended TCDD exposure, or may have a slightly different etiology than the other symptoms, or a different time course to explain its relative infrequency. Animal studies have produced evidence that porphyria cutanea tarda results from chronic exposure and not acute exposure to TCDD. Since no decontamination followed the Nitro accident, these workers probably were exposed over a long period of time; these were the only workers who had symptoms of porphyria after an industrial explosion. Human data are in agreement with animal studies in this instance.

Two human health effects which were common after industrial exposure but not after the explosions were gastrointestinal disorders and elevated serum cholesterol levels.

The actual extent of the consequences of TCDD accidents and occupational exposures on human health cannot yet be stated with confidence because: 1) most reports did not identify the number of workers who were exposed but not affected; 2) the descriptions of the health status of workers who did not develop chloracne were not provided; and 3) the incidence and severity of health effects were rarely compared to appropriate control groups.

5.3 HUMAN EXPOSURE TO TCDD FROM INDUSTRIAL WASTE DISPOSAL, AND LABORATORY EXPOSURE

Two incidents are considered in this section and are listed in tables 5-3 and 5-6. One incident considered in this section involved human exposure to TCDD in industrial waste that was combined with salvage oil and sprayed on three horse arenas in Missouri to control dust. The second incident involved three scientists in two government laboratories in England. Two men had heated trichlorophenol (or its potassium salt, in one case) to synthesize TCDD for use as an analysis standard, and the third handled one of the samples after it was diluted. Despite their awareness of potential hazards and precautions to avoid personal exposure, they developed chloracne and other health effects.

5.3.1 Exposure Conditions

The dosage, route, and duration of exposure, and concomitant exposures and control groups for the incidents involving TCDD exposure at the Missouri horse arenas and the British laboratory, are described in this section.

TABLE 5-6: HEALTH EFFECTS OF HUMAN EXPOSURE TO TCDD

Location	Organ Systems Affected:										
	Dermal	Renal	Hepatic	Neuro.	Asthenia	Blood	GI	Lipid Metab.	Immuno	CV	Plum.
United Kingdom[a]	+		-	+	+	-	+	+			
Missouri[b]	+	+	-	+	+	-	+				
Vietnam Veterans[c]	+			+	+		+			+	+
Vietnam Veterans[d]	+		+	+	+		+		+		
Vietnam Veterans[e]	+			+	+		+				
Vietnam Refugees[f]	+			+	+		+				

Code: (+) An effect was observed;

(-) An effect was not observed in patients examined (or questioned) about the effect;

( ) Patients were not examined or questioned, regarding any effects in the indicated organ system.

Reference a - United Kingdom, Oliver, 1975
Reference b - Missouri, Beale et al., 1977
Reference c - Vietnam Veterans, VA, 1980
Reference d - Vietnam Veterans, Bogen, 1979
Reference e - Stellman and Stellman, 1980
Reference f - Rose and Rose, 1972

5.3.1.1 Dosage

Investigation into the cause of a high incidence of animal mortality and human illness at three horse arenas in Missouri led to the identification of levels of 31.8-33.0 ug of TCDD per gram soil at the farm where human illness occurred (Carter et al., 1975). The date of sample collection and analyses was not reported. The source of TCDD was traced to an industrial hexachlorophene producer in Missouri who disposed of distillate residues from its trichlorophenol production with the same company that sprayed the arenas. The waste residue that remained in the storage tank at the industrial site in 1974 was found to contain 306-456 ug of TCDD per gram residue.

Estimates of the potential amounts of TCDD synthesized by the British scientists, or of amounts of trichlorophenol or potassium trichlorophenate initially used to synthesize TCDD, were not reported. One of the workers handled only a diluted sample of TCDD. This worker developed symptoms of asthenia, but not chloracne. The other two men worked with the concentrated lots of TCDD they synthesized, and both developed chloracne (Oliver, 1975).

5.3.1.2 Route and Duration of Exposure

Human illness from the Missouri incident occurred in four children and in the mother of two of the children (Carter et al., 1975). These children played in the contaminated arena. The child most severely affected played in the arena daily between the time of spraying and recognition of symptoms. The major exposure was probably dermal. The arena was sprayed on May 26, 1971 and hemorrhagic cystitis was diagnosed in one child on August 21, 1971. The time of appearance of other symptoms in the patients, including skin lesions, was not stated.

Since the laboratory workers took precautions to avoid contact by skin or inhalation, their routes of absorption are unknown. Although symptoms did not develop in two of the three scientists until two years after the day they synthesized or handled TCDD, no intervening instances of potential exposure could be identified (Oliver, 1975).

5.3.1.3 Concomitant Exposures and Controls

The chemical compositions of the salvage oils sprayed on the arenas were not reported. Potentiating or synergistic effects of combinations of hydrocarbon compounds, including the effects of solvents on the rate of dermal absorption of TCDD, are presently only matters for speculation.

The laboratory workers were also exposed to many other chemicals. This factor was considered when a control group was established to compare the results of serum cholesterol values. This group was comprised of laboratory workers who were exposed to the same chemicals as the patients, except that they had no known exposure to TCDD (Oliver, 1975).

5.3.2 Symptoms Experienced After Exposure

Symptoms reported in the children that played in the sprayed horse arenas (and one parent) and in the British scientist are described here, under the categories:

- Chloracne
- Porphyria cutanea tarda
- Hepatotoxicity
- Neurological effects
- Other effects.

5.3.2.1 Chloracne

The original reports of the health effects of people exposed to the TCDD-contaminated horse arenas did not mention the presence of chloracne. Later communications by an interested dermatologist with the physicians who examined the patients revealed that the 6-year-old girl who was diagnosed as having hemorrhagic cystitis, as well as her mother and 10-year-old sister, had skin conditions which included blackheads and were consistent with chloracne. The inquiring dermatologist concluded that the conditions were probably mild and went unnoticed by clinicians who were inexperienced in diagnosing chloracne or did not expect to see this condition (Crow, 1980). Twin 2-year-old boys from the second arena that was sprayed also developed skin conditions consistent with chloracne (Crow, 1980). No accounts of this Missouri incident ever clarified the number of people who resided on the farms that were sprayed or the proportion of exposed people who were affected. As observed in the Seveso incident, children were more affected than adults, but their exposure, was likely to be higher from play than adult exposure.

One of the three British laboratory workers developed chloracne, with no other symptoms. The other two workers were from a second laboratory. Only one of these two workers developed chloracne. Other symptoms that developed in the workers from the second laboratory were very similar (Oliver, 1975).

5.3.2.2 Porphyria Cutanea Tarda

There is no indication that urinary porphyrins were measured after the Missouri incident. This analysis was performed after the laboratory workers contracted chloracne, but no evidence of porphyria was produced. Two of the workers developed hirsutism and the third developed an unusual pigmentation which was attributed to chloracne (Oliver, 1975).

5.3.2.3 Hepatotoxicity

Liver function tests performed on the 6-year-old girl from Missouri and on the three laboratory workers were all negative (Beale et al., 1977; Oliver,

1975). Hepatomegaly or other evidence of hepatotoxicity were not mentioned in accounts of either incident.

5.3.2.4 Neurological Effects

The mother and sister of the affected child complained of intermittent headaches at the time hemorrhagic cystitis was diagnosed in the younger child (Carter el al., 1975). No other evidence of neurological effects was produced at that time (within 4 months of the onset of exposure) or at a 5-year followup examination which included a detailed neurological examination of the younger child (Beale et al., 1977).

Two of the British laboratory workers experienced several symptoms of asthenia, including, in particular, fatigue and irritability. Both reported experiencing transient visual problems. One worker reported having headaches and difficulty in muscular and mental coordination and the other worker experienced neurologic pain in one thigh. These symptoms emerged 2 years after the workers were exposed to TCDD (Oliver, 1975).

5.3.2.5 Other Effects

Hemorrhagic cystitis in the 6-year-old girl from the sprayed Missouri farm was accompanied by hematuria and proteinuria (Beale et al., 1977). These symptoms were resolved 1 week after they were recognized, although hemorrhagic areas of the bladder were still demonstrable by cystoscopy 3 months later.

The mother and sister complained of abdominal pains and diarrhea. Two of the laboratory workers also experienced abdominal pains and flatulence (Oliver, 1975).

One worker reported having lost about 6.5 kg in weight but experienced no loss in appetite. The second experienced a loss in appetite (but no weight loss) as well as diarrhea and indigestion.

Three years after the exposure took place, all three workers had elevated serum cholesterol values (above 300 mg/100 ml).

5.3.2.6 Conclusions

These two incidents reaffirm that chloracne is a likely consequence of TCDD exposure. They also demonstrate that chloracne may not be an obvious effect and can be overlooked by the examining physician. Furthermore, neurological symptoms can occur in workers with or without chloracne. The latency period for symptoms to develop can be on the order of 2 years.

Gastrointestinal problems and elevated serum cholesterol levels were common results of these incidents, as well as of other occupational exposures described in the previous section. Hypercholesterolemia remained 3 years after exposure in all three laboratory workers, while only residual signs of hirsutism in one worker and indigestion and flatulence in the second worker remained.

The level of TCDD in the soil in Missouri arenas also provides a comparison of exposure levels to levels from other incidents, although the source that reported this level (Carter et al., 1975) did not indicate whether this level was present shortly after the spraying when toxicity was recognized, or several years later, when the industrial storage tank was assayed for TCDD.

5.4 HUMAN EXPOSURE TO TCDD FROM MILITARY USE OF HERBICIDES

This section addresses five populations whose alleged exposure to TCDD are thought to be related to military use of herbicides in Vietnam.

5.4.1 Exposure Conditions

Health effects have been reported which the reporters suggested were associated with military use of chemicals in South Vietnam. Reports of health effects, listed in table 5-3, include conditions submitted as claims by Vietnam veterans (VA, 1980), symptoms observed by a physician who conducted a 10-month study of 78 Vietnam veterans (Bogen, 1970), the results of a nationwide study conducted by mail on 535 Vietnam veterans (Stellman and Stellman, 1980), a survey of 98 Vietnam refugees in Hanoi (Rose and Rose, 1972), and a survey of health effects of Vietnamese by the National Academy of Sciences (NRC, 1974).

5.4.1.1 Dosage

An estimate of 0.080 ug of TCDD per kg of topsoil in South Vietnam has been set forth based on the amount of TCDD in herbicides used in Vietnam, the size of the areas sprayed and the rates of spraying (Westing, 1978). Using the same methods of estimation, these authors estimated that contamination of the Missouri horse arenas was 110,000 ug TCDD/kg, compared to 32,000 ug TCDD/kg actually measured by Carter et al. (1975) and 5.9 ug TCDD/kg in Seveso soil.

Estimates from another source were based on surface area (Reggiani, 1978); for South Vietnam an estimated .083 g/ha of TCDD was applied, compared to 5,900 g/ha in Missouri and 5.6 and 0.013 g/ha in zones A and B, respectively, in Seveso.

A committee organized in 1971 to evaluate the effects of herbicide use in Vietnam set forth as one of its goals quantitative analyses of Vietnamese soil for herbicide residue levels, but security problems in postwar South Vietnam precluded obtaining any Vietnamese soil for analysis (NRC, 1974).

5.4.1.2 Route and Duration of Exposure

The major routes of herbicide exposure of U.S. servicemen in South Vietnam were dermal and inhalation, assuming they consumed U.S. military food rations. Vietnamese citizens were also exposed by ingestion when their food sources were sprayed.

The refugees whose symptoms were described by Rose and Rose (1972) all experienced alleged exposure to spray missions. They were requested to report the effects of the last spray mission they experienced; 95 percent had experienced at least two spray missions and 60 percent had experienced at least three missions. The survey was conducted between 1970 and 1971. All three of the reports of symptoms of Vietnam veterans in table 5-3 were published between 1979 and 1980, at least 10 years after herbicide use in Vietnam ceased.

5.4.1.3 Concomitant Exposures

The health effects of herbicides used in war are difficult to distinguish from those caused by other elements of war. The skin rashes and eye problems that were reported by Vietnamese refugees immediately after some spray missions have been attributed to CS spray missions, for example (Rose and Rose, 1972).

Pentachlorophenol, a wood preservative used in Vietnam, is produced by a process that is likely to introduce dioxins and chlorinated dibenzofuran contaminants, but not TCDD. Symptoms from these contaminants are likely to be indistinguishable from those of dioxin (Moses and Moore, 1979).

5.4.1.4 Controls

The complaints submitted by Vietnam veterans or by Vietnamese refugees have not been compared to symptoms reported by other veterans or refugees not known to be exposed to TCDD. Only one systematic examination of people known to have been in Vietnam between 1966 and 1969 (the period of heavy use of defoliants) has been conducted by physicians and reported (Bogen, 1979). No details of study design or methods were reported, however, and no clinical biochemical analyses or standardized procedures were described which would provide objective parameters for comparison. Furthermore, no control group was employed in the study and the study population was self-selected.

5.4.2 Symptoms Experienced After Exposure

Symptoms observed in Vietnamese or Vietnam veterans and suspected to be related to military use of herbicides are listed in table 5-6.

5.4.2.1 Chloracne

Skin rashes or conditions were reported in each study. However, no study included a description of skin conditions that would allow comparisons to be made with chloracne. Among the Vietnamese refugees, 16 percent reported prolonged skin conditions that involved pustules, scabs, or eczema.

In a book prepared by the U.S. Army (Harmon, 1971), skin diseases encountered in the military in Vietnam were described. Chloracne was not

mentioned. A 1-year field study conducted in South Vietnam in 1966-67 and reported by Harman showed cystic acne to be the major dermatologic disease which resulted in medical evacuation. This condition occurred primarily in soldiers who previously had acne and experienced a worsening of the condition about 6 weeks after they arrived in Vietnam. Allen (1977) reported about 7 percent of the U.S. military hospital admissions in Vietnam from 1965-1972 were for skin diseases. About 10 percent of cases examined in a U.S. Army dermatology clinic between 1970-1971 were cases of acne.

A recent report (Halprin, 1980) has suggested that chloracne has been uncommon among Vietnam veterans, even when examinations were conducted by dermatologists familiar with this condition and specifically seeking evidence for it.

5.4.2.2 Porphyria Cutanea Tarda and Hepatotoxicity

Little evidence for these conditions has been reported. Hepatitis and jaundice were reported by 10 percent and 5 percent, respectively, of Vietnam veterans that filed claims (VA, 1980).

5.4.2.3 Neurologic Effects

Veterans and refugees have reported fatigue, dizziness, and other symptoms of asthenia (VA, 1980; Bogen, 1979; Rose and Rose, 1972; Stellman and Stellman, 1980). Peripheral neuritis, joint pain, or numbness and sensory problems were also commonly reported (VA, 1980; Bogen, 1979; Stellman and Stellman, 1980).

5.4.2.4 Other Effects

Gastrointestinal problems were reported by most groups and usually involved diarrhea, vomiting, and abdominal pains. Increased susceptibility to infections (Bogen, 1979), and pulmonary and cardiovascular problems (VA, 1980) were each reported by one group.

Reproductive problems were reported in four of the reports and involved child deaths, miscarriages, or birth defects (Tung et al., 1971; Rose and Rose, 1972; Stellman and Stellman, 1980; NRC, 1974). However, the incidents were not documented, nor compared to expected rates for control groups. The types of birth defects and proportions of each were also not presented.

A high incidence of carcinogenicity was also claimed, but the type of cancers and expected rates were not presented.

5.4.3 Conclusions

The information on human health effects from exposure to TCDD in Vietnam suffers from lack of any systematic approach to collecting and documenting

data by health professionals. Furthermore, exposure levels in Vietnam are unknown and the groups described do not seem to constitute those likely to have had higher than usual exposure to herbicides in particular (as would be expected of military personnel involved in spray missions, for example).

The symptoms reported were non-specific and are logically associated with many components expected to be present in a war zone. A comparison of symptoms presented in the cited reports to those of control groups would be needed to establish higher than expected frequencies of adverse effects.

CHAPTER 5.

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