Monsanto

ATTORNEY WORK PRODUCT
ATTORNEY-CLIENT PRIVILEGE

FROM (NAME—LOCATION—PHONE): Kathleen A. Johnson - G3WD (4-8054) Corporate EPS

DATE : October 1, 1984

cc File

SUBJECT :

REFERENCE :

TO : A. M. Ford - G3WD
J. T. Garrett - G2WB
D. L. King - Bowles, McDavid, Graff & Love
C. M. Love, III - Bowles, McDavid, Graff & Love
W. J. McCarville - G3WD
G. Rousch - G2WG
H. S. Scott -E2ND
D. F. Snively - E2ND
R. W. Thompkins, II - Bowles, McDavid, Graff & Love
M. S. Weinberg - Weinberg Consulting Group, Inc.
J. D. Wilson - G3WD

Attached is the final copy of the report entitled "Industrial Accidents Resulting in Potential Human Exposure to 2,3,7,8-Tetrachloribenzo-p-dioxin (TCDD)."

Kathleen A Johnson /dkr

Kathleen A. Johnson

KAJ:m
Attachment

CONFIDENTIAL
SUBJECT TO PROTECTIVE ORDER.

C23497

# INDUSTRIAL ACCIDENTS RESULTING IN POTENTIAL HUMAN EXPOSURE TO 2,3,7,8-TETRACHLOROBENZO-P-DIOXIN (TCDD)

(AUGUST 31, 1984)

PREPARED BY:
K. A. JOHNSON

TABLE OF CONTENTS

# I. BACKGROUND

## I. BACKGROUND

### A. Relation to the Nitro Litigation Case

2,4,5-trichlorophenoxy acetic acid (2,4,5-T) was manufactured at Monsanto's Nitro, West Virginia plant between 1948 and 1969. The intermediate 2,4,5-trichlorophenol (TCP), the primary starting material for 2,4,5-T, was also manufactured at Nitro. During the synthesis of TCP certain contaminants are also formed, in particular, the highly toxic substance, 2,3,7,8-tetrachlorodibenzo-p-dioxin (2,3,7,8-TCDD) is formed via the thermal condensation of two molecules of sodium 2,4,5-trichlorophenate (NaTCP). The amount of 2,3,7,8-TCDD formed is dependant on the reaction temperature: i.e., very little is formed below 150°C; at 180°C less than 1 mg/kg TCP is formed; and between 230°-260°C if heating continues for 2 hours about 1.6 g/kg TCP can be formed. [66]

On March 8, 1949 an industrial accident occurred at the Nitro plant. It involved the overheating of the TCP reactor which in turn resulted in the rupture disc being blown and the release of the reactor contents into the production building and surrounding areas. 117 workers eventually contracted chloracne (considered to be the hallmark of 2,3,7,8-TCDD exposure) as a result of exposure to the reaction residues. Over the course of normal TCP production operations (1948-1969) at the plant, an additional 111 employees also contracted chloracne.[126]

About 170 Nitro employees, current and retired, and some of the heirs of deceased employees have filed a multi-million dollar lawsuit against Monsanto Company for health damages incurred as a result of occupational exposure to ten specific chemicals. The plaintiffs contend that Monsanto did not provide a safe workplace or adequate safety equipment, and that Monsanto was deliberate in withholding from their workers hazard information on the long term health effects of the named chemicals. 2,4,5-T, chlorophenols (including TCP) and 2,3,7,8-TCDD are among the listed chemicals.

It should be kept in mind that little information was known about 2,3,7,8-TCDD during the 1950's and early 1960's. It was not identified as the chloracnegenic contaminant in TCP and its residues until 1957, by Kimmig and Schulz. Likewise, process modifications to limit the formation of 2,3,7,8-TCDD; lower tempertures around 150°C, were not identified until approximately 1957, by Sorge. This information although available in 1957, was not well publicized throughout the chemical community. Analytical methods with low enough sensitivities for detecting 2,3,7,8-TCDD in samples, process or otherwise, were not developed and published until 1966, by Dow. Although the adverse effects of 2,3,7,8-TCDD have been extensively studied for the past 20-25 years, much of the detailed toxicity information currently available was not developed until the last 15 years.

The purposes of this report are twofold. First, it provides a compilation, in summary form, of most of the information currently available in the published literture on each industrial accident involving human exposure to 2,3,7,8-TCDD as a result of TCP/2,4,5-T production. Second, it presents a comparison between Monsanto's 1949 TCP accident and similar TCP accidents worldwide.

B. Toxicity Overview of 2,3,7,8-TCDD

Of the total 75 possible chlorinated dibenzodioxins, the toxicity of 2,3,7,8-TCDD has been the most extenisvely studied since it is considered to be the most potent man-made toxin presently known. A brief summary of the toxicity of 2,3,7,8-TCDD is presented below.

1. Effects in Animals [34,128]

Acute Toxicity - The susceptibility of animals exposed to 2,3,7,8-TCDD varies significantly among different species. The acute oral LD50 for TCDD in various species include:

| Animal | LD50 (ug/kg bodyweight) |
|---|---|
| Guinea pig | 0.5 |
| Rat (male) | 22 |
| Rat (female) | 45 |
| Muskrat | 114 |
| Rabbit | 115 |
| Hamster | 5,051 |

Animals receiving lethal or toxic doses have a chronic and progressive weight loss followed by death after a somewhat delayed period. The amount of hepatic necrosis varies with the isomer and the species. Hepatic necrosis produced by TCDD probably contributes to the death of rats and rabbits. These effects are much less in mice and minimal in guinea pigs and monkeys.

Embryotoxicity and Teratogenicity - 2,3,7,8-TCDD is embryotoxic and teratogenic in mice in repeated or single doses of as little as 1-10 ug/kg body weight, causing increased frequencies of cleft palate and kidney abnormalities. In rats embryolethal effects occurred at doses around 0.5 ug/kg body weight, and produced kidney anomalies, intestinal hemorrhages and general edema in the fetuses.

Mutagenicity - Short-term mutagenicity testing (Ames and similar tests) with 2,3,7,8-TCDD gave mixed results, a few tests were positive but most were negative. 2,3,7,8-TCDD was negative in a dominant lethal mutagenicity study in rats. And was without effect on bone marrow cells of male rats after single doses by different routes. Repeated doses of 2,3,7,8-TCDD produced a significant, but weak, increase in the number of chromosome aberrations in bone marrow cells.

Carcinogenicity - 2,3,7,8-TCDD has shown to be carcinogenic in both mice and rats. These studies are of interest in that they show an increased incidence of tumors. They do not provide a basis for deciding whether TCDD acts as an initiator or a promoter. This is "Particularly important because equivocal evidence is lacking that TCDD is a mutagen or is metabolized, and no evidence is available that TCDD and/or metabolite(s) bind covalently to macromolecules."

Other Effects - 2,3,7,8-TCDD has been shown to affect the lymphoid system in mice, rats, guinea pigs and monkeys. This results in suppression of cell-mediated immunity, particularly in young animals, and increases in susceptibility to infection. 2,3,7,8-TCDD has caused chloracne in rabbits (rabbit ear test) and in monkeys.

Chick edema disease, resulting from toxic fats in the feed of broiler chickens, has been produced by various dibenzodioxins, including 2,3,7,8-TCDD.

A variety of other effects have been reported in one or more animal species; bone marrow hypoplasia, testicular degeneration, hyperplasia of renal pelvis and urinary bladder, hemorrhage in the intestines and adrenals, and the induction of various enzymes.

2. Effects on Humans [28,128]

To date, no studies of humans include a quantification of exposure to 2,3,7,8-TCDD. Klingman, in studies conducted on prison volunteers, did determine that between 16 and 7,500 ug of 2,3,7,8-TCDD is required to produce chloracne in man. [28]

Chloracne is the most consistent clinical feature of 2,3,7,8-TCDD exposure to man. Other findings identified from exposure as a result of industrial accidents and/or occupational exposure may include: neuromuscular symptoms (weakness and pain with nerve conduction abnormalities), porphyria cutanea tarda, hepatic dysfunctions, hyperlipidemia, cutaneous hyperpigmentation and hirsutism, chronic eye irritation, emotional disorders and neuropsychiatric syndromes.

## II. ROUTES OF HUMAN EXPOSURE TO 2,3,7,8-TCDD

## II. Routes of Human Exposure to 2,3,7,8-TCDD

### A. Industrial Accidents and Occupational Exposure

2,3,7;8-TCDD is formed as a stable, unwanted, contaminant during the manufacture of 2,4,5-trichlorophenol. It is formed by the thermal condensation of two molecules of sodium trichlorophenate. The amount produced is dependent upon the reaction temperature, with little formed below 150°C and as much as 1.6 g. 2,3,7,8-TCDD formed per kg TCP at temperatures between 230°C-260°C. [66]

Much of the 2,3,7,8-TCDD formed during the reaction is removed by the purification techniques used to refine the crude TCP, and hence the products of its end use; i.e., 2,4,5-T, esters of 2,4,5-T, and hexachlorophene. Prior to 1965 commercially available 2,4,5-T contained up to or exceeding 30 ng/kg 2,3,7,8-TCDD (roughly equivalent to 30 ppm by weight); 2,4,5-T containing less than 0.05 mg/kg 2,3,7,8-TCDD (roughly equivalent to 0.05 ppm by weight) is currently available. Commercially available hexachlorophene which was used as a bactericide in many toiletries, contained less than 15 ug/kg 2,3,7,8-TCDD (roughly equivalent to 0.015 ppm by weight).

Human exposure to 2,3,7,8-TCDD has occurred in industry by occupational exposure to 2,3,7,8-TCCD contaminated TCP, waste residues of TCP, and products which utilize TCP including 2,4,5-T, esters of 2,4,5-T and hexachlorophene. Exposure has also occurred as a direct result of industrial accidents and subsequent clean-up activities from the accident.

Ten industrial accidents in TCP plants have been reported in the literature whereby workers have been potentially exposed to 2,3,7,8-TCDD. Twenty-one instances of occupational exposure to 2,3,7,8-TCDD from either TCP or 2,4,5-T production, and three instances of potential occupational exposure to other dioxins (for example hexachlorodibenzodioxin contaminants in pentachlorophenol or PCP.) have also been cited in the literature. Five of the twenty-one instances of occupational exposure have occurred in plants where industrial accidents have also occurred. It is highly probable that each plant manufacturing TCP has experienced a certain amount of health problems arising from exposure, primarily mild sporadic cases of chloracne to 2,3,7,8-TCDD and other chloracnegenic dioxins. However, these episodes have not been published. A listing of industrial exposure incidents are presented in Table 1.

The exact number of persons exposed and affected as a result of these incidents is unknown but approximates 2,000.

### B. Research Laboratory Incidents [5,21,28,31,41,57,86]

Factory process workers involved with the manufacture of TCP and 2,4,5-T and its esters have not been the only ones to be potentially exposed to 2,3,7,8-TCDD. Five laboratory accidents have been recorded in the literature whereby the researchers who were conducting experiments with dioxins have become exposed to 2,3,7,8-TCDD. A tabular summary of these incidents is presented in Table 2. Of these incidents, the one which occurred in 1970 in the United Kingdom is of particular interest and will be further discussed below.

TABLE 1: Summary of Industrial Incidents Resulting in Possible Exposure to 2,3,7,8-TCDD

| Date of Incident | Manufacturer | Plant Locations | Product | Process Used[a] | Cause of Exposure[b] | Number of Persons Affected | References |
|---|---|---|---|---|---|---|---|
| 1936 | Lumber Company (user, not a manufacturer) | Mississippi/ United States | Use of Dowicide B | Treating lumber | A | 300-400 | 5 |
| 1937 | Dow Chemical Co. | Midland, Michigan/ United States | 2-(2-chlorophenyl) phenol; tetrachlorophenol | N.A.[c] | A | 21 | 5 |
| 1949 | Monsanto Company | Nitro, West Virginia/ United States | TCP; 2,4,5-T | A | B<br>A | 228 total<br>117<br>111 | 2,5,21,28,29,31,34,38 55,67,86,89,109,114, 118,125,126 |
| 1949 | N.A. | Nordrhein, Westfalen/ West Germany | PCP; TCP | N.A. | A | 17 | 4,21,28,31,34,86,112 |
| 1952 | N.A. | Nordrhein, Westfalen/ West Germany | TCP | N.A. | A | 60 | 21,28,31,34,86,112 |
| 1952-53 | Boehringer | Hamburg/ West Germany | TCP | A[e] | A | 17 | 21,28,29,31,41,67, 83,86,97,112,118 |
| 1953 | Badische Anilin und Soda Fabrik AG (BASF) | Ludwigshaven/ West Germany | TCP; 2,4,5-T | A | B | 11-75[d] | 2,5,21,24,28,29,31, 34,38,67,80,83,86, 97,112,118 |
| 1951-71<br>*1956<br>*1966 | Rhone-Poulenc | Grenoble/ France | TCP | N.A. | A+B<br>B<br>B | 97 total<br>17<br>21 | 5,21,28,29,31,34,67 86,114,117,120,123 |
| 1954 | Boehringer, Ingelheim | Hamburg/ West Germany | TCP; 2,4,5-T | A[e] | A | 31 | 21,28,31,34,67,83 86,104,112 |

a. Process Used: A. TCP formed by alkaline hydrolysis of 1,2,4,5-tetrachlorobenzene with sodium hydroxide in a solvent of methanol at ~180°C, and ~20 atm. pressure. Temperature and pressure may vary slightly between companies....see text
B. Same as A except temperature = 190°C; pressure = 45 atmospheres.
C. TCP formed by alkaline hydrolysis of 1,2,4,5-tetrachlorobenzene with sodium hydroxide in solvent mixture of ethylene glycol and orthodichlorobenzene, at ~180°C and atmospheric pressure.
D. Same as C except xylene used in place of orthodichlorobenzene; reaction temperature 150°C-170°C; conducted at atmospheric pressure.

b. Cause of exposure: A. Occupational
B. Overheating resulting in the blow out of the vessel's rupture disk. (Often misquoted as explosions.)

c. N.A. - not available
d. Number of persons reported to be affected varied by author.
e. Boehringer modified procedure to low temperature method in 1957-1958.
f. Fatalities explained in text.
g. Exposure due to hexachlorodibenzodioxin contaminants in PCP.
h. Hooker used the ethylene glycol process. Specifics not cited in literature.

TABLE 1: Summary of Industrial Incidents Resulting in Possible Exposure to 2,3,7,8-TCDD

| Date of Incident | Manufacturer | Plant Locations | Product | Process Used[a] | Cause of Exposure[b] | Number of Persons Affected | References |
|---|---|---|---|---|---|---|---|
| 1956 | Diamond Alkali | Newark, New Jersey/ United States | 2,4-D; 2,4,5-T | N.A. | A | 29 | 17,21,28,29,31,34 67,86,116,118,119 |
| 1956 | Hooker Chemical Co. | Niagra Falls, New York/ United States | TCP | C[h] | A?B | Many staff employees, number unknown | 21,28,29,31,66, 86 |
| 1959 | Industrie Chimiche Melegnanesi Saronio | Milan/ Italy | TCP | N.A. | A | 5 | 21,28,31,67,86, 122 |
| 1959 | Thompson-Hayward | Kansas City, Kansas/ United States | TCP | N.A. | A | N.A. | 28 |
| 1960 | Diamond Shamrock | United States | TCP | N.A. | A?B | Many+1 fatal[f] | 17,21,28,29,31, 34,67, 86, 116, 118,119,127 |
| 1963 | Philips-Duphar | Amsterdam/ Netherlands | TCP; 2,4,5-T | A | B | 30-145[d] | 21,28,29,31,34 38,67,86,113 |

a. Process Used: A. TCP formed by alkaline hydrolysis of 1,2,4,5-tetrachlorobenzene with sodium hydroxide in a solvent of methanol at ~180°C, and ~20 atm. pressure. Temperature and pressure may vary slightly between companies....see text.
B. Same as A except temperature = 190°C; pressure = 45 atmospheres.
C. TCP formed by alkaline hydrolysis of 1,2,4,5-tetrachlorobenzene with sodium hydroxide in solvent mixture of ethylene glycol and orthodichlorobenzne, at ~180°C and atmospheric pressure.
D. Same as C except xylene used in place of orthodichlorobenzene; reaction temperature = 150°C-170°C; conducted at atmospheric pressure.

b. Cause of exposure: A. Occupational
B. Overheating resulting in the blow out of the vessel's rupture disk. (Often misquoted as explosions.)

c. N.A. - not available
d. Number of persons reported to be affected varied by author.
e. Boehringer modified procedure to low temperature method in 1957-1958.
f. Fatalities explained in text.
g. Exposure due to hexachlorodibenzodioxin contaminants in PCP.
h. Hooker used the ethylene glycol process. Specifics not cited in literature.

TABLE 1: Summary of Industrial Incidents Resulting in Possible Exposure to 2,3,7,8-TCDD

| Date of Incident | Manufacturer | Plant Locations | Product | Process Used[a] | Cause of[b] Exposure | Number of Persons Affected | References |
|---|---|---|---|---|---|---|---|
| 1964 | N.A. | Ufa/ U.S.S.R. | 2,4,5-T | N.A. | A | 128 | 21,28,29,31,34, 86,115 |
| 1964 | Dow Chemical Co. | Midland, Michigan/ United States | TCP; 2,4,5-T | A | A | 30-61[d] | 17,21,28,29,31, 67,86,92,93 |
| 1964-69 | Spolana | Czechoslovakia | PCP; TCP; 2,4,5-T | B | A | 72-80[d] 2-fatal[f] | 21,28,29,31,34 38,59,67,86 |
| 1968 | Coalite and Chemical Products | Bolsover, Derbeyshire/ United Kingdom | TCP; 2,4,5-T | C | B | 79-90[d] | 21,28,29,31,34, 38,47,48,49,67, 86,118, |
| 1970 | Coalite and Chemical Products | Hertfordshire/ United Kingdom | TCP; 2,4,5-T | C | A | 4 | 28,124 |
| 1970 | N.A. | Japan | 2,4,5-T; PCP | N.A. | A | 25 | 21,28,31,67,86, 121 |

a. Process Used: A. TCP formed by alkaline hydrolysis of 1,2,4,5-tetrachlorobenzene with sodium hydroxide in a solvent of methanol at ~180°C, and ~20 atm. pressure. Temperature and pressure may vary slightly between companies....see text.
B. Same as A except temperature = 190°C; pressure = 45 atmospheres.
C. TCP formed by alkaline hydrolysis of 1,2,4,5-tetrachlorobenzne with sodium hydroxide in solvent mixture of ethylene glycol and orthodichlorobenzno, at ~180°C and atmospheric pressure.
D. Same as C except xylene used in place of orthodichlorobenzene; reaction temperature = 150°C-170°C; conducted at atmospheric pressure.

b. Cause of exposure: A. Occupational
B. Overheating resulting in the blow out of the vessel's rupture disk. (Often misquoted as explosions.)

c. N.A. - not available
d. Number of persons reported to be affected varied by author.
e. Boehringer modified procedure to low temperature method in 1957-1958.
f. Fatalities explained in text.
g. Exposure due to hexachlorodibenzodioxin contaminants in PCP.
h. Hooker used the ethylene glycol process. Specifics not cited in literature.

TABLE 1: Summary of Industrial Incidents Resulting in Possible Exposure to 2,3,7,8-TCDD

| Date of Incident | Manufacturer | Plant Locations | Product | Process Used[a] | Cause of[b] Exposure | Number of Persons Affected | References |
|---|---|---|---|---|---|---|---|
| 1972 | N.A. | U.S.S.R. | TCP | N.A. | A | 1 | 21,28,31,86,91 |
| 1972-73 | Linz Nitrogen Works | Linz/ Austria | TCP; 2,4,5-T | A | A | 50 | 21,28,29,31,67 83,86 |
| 1974 | Bayer | Uerdingen/ West Germany | TCP; 2,4,5-T | A | A | 5 | 21,28,29,31,67 83,86 |
| 1975 | Thompson-Hayward | Kansas City, Kansas/ United States | TCP | N.A. | A+B | 5[d] | 21,29,31,86 |
| 1976 | Monsanto Company | South Wales/ United Kingdom | PCP | N.A. | A[g] | N.A. | 28 |
| 1976 | ICMESA (Givaudan) | Meda and Seveso/ Italy | TCP | D | B | 12 workers[d] 187 (159 children, 28 adults from Seveso population) | 11,13,21,28,31, 34,38,67,70,81, 82,86,90,101 |
| 1979 | Vertac Inc. | Jacksonville, Arkansas/ United States | TCP; 2,4,5-T; 2,4-D | N.A. | A | 13 (possibly 74 or more exposed) | 21,68,79 |

a. Process Used: A. TCP formed by alkaline hydrolysis of 1,2,4,5-tetrachlorobenzene with sodium hydroxide in a solvent of methanol at ~180°C, and ~20 atm. pressure. Temp. and pressure may vary slightly between companies....see text.
B. Same as A except tempeature = 190°C; pressure = 45 atmospheres.
C. TCP formed by alkaline hydrolysis of 1,2,4,5-tetrachlorobenzene with sodium hydroxide in solvent mixture of ethylene glycol and orthodichlorobenzene, at ~180°C and at atmospheric pressure.
D. Same as C except xylene used in place orthodichlorobenzene; reaction temperature = 150°C-170°C; conducted at atmospheric pressure.

b. Cause of exposure: A. Occupational
B. Overheating resulting in the blow out of the vessel's rupture disk. (Often misquoted as exposions.)

c. N.A. - not available
d. Number of persons reported to be affected varied by author.
e. Boehringer modified procedure to low temperature method in 1957-1958.
f. Fatalities explained in text.
g. Exposure due to hexachlorodibenzodioxins contaminants in PCP.
h. Hooker used the ethylene glycol process. Specifics not cited in literature.

TABLE 2: Summary of Laboratory Incidents Resulting in Exposure to 2,3,7,8,-TCDD

| DATE OF INCIDENT | LOCATION/LAB/PERSON | EXPERIMENT | CAUSE OF EXPOSURE | NUMBER OF PERSONS AFFECTED | REFERENCES |
|---|---|---|---|---|---|
| 1957 | West Germany/ Labworker working with "Sandermann" | Attempting to confirm the structure of Herz and Wirth's original "perchlorophenyleneoxide" by chlorinating dibenzo-p-dioxin to OCDD. Because of decrease solubility and decreased reactivity the reaction stopped at 2,3,7,8,-TCDD | Not specified in literature. | 1 | 5,21,31,41 |
| 1957 | West Germany/ "Schulz" | Self administered skin test with 2,3,7,8-TCDD | Dermal, patch test | 1 | 5 |
| 1957 | United States/ "Dietrich" | Investigation of substitution reactions of dibenzo-p-dioxin | Not specified in literature. | 1 | 5,11 |
| 1970 | Harpenden, United Kingdom/U.K. Ministry of Agriculture Labs-Plant Pathology Lab | A. Synthesis of dioxins by heating TCP in an alkaline solution with a catalyst. | Apparent inadequate protection although used lab hoods, protective clothing and kept reaction systems closed up. | 1 | 21,28,57,86 |
| | "Lee" | B. Synthesis of dioxins by heating potassium trichlorophenate in a closed system. | Same as above. | 1 | 21,28,57,86 |
| | | C. Worker in same lab as B except working with dilute dioxin standards. | Same as above. | 1 | 21,28,57,86 |
| 1978 | United States/ Dow Company-lab worker. | Working with 2,3,7,8-TCDD. | Improper disposal of lab wastes. | 1 | 21 |

In and around 1969-1970 reports of additional health effects and possible teratogenicity from exposure to 2,4,5-T contaminated with 2,3,7,8-TCDD were published in the United States. After hearing of this information, a general concern arose in the United Kingdom over the use of 2,4,5-T for agricultural and forestry use. It was considered that if the 2,3,7,8-TCDD content of the 2,4,5-T could be limited to 1 ppm or less, and if it were applied in use as recommended, no significant health hazard existed. A need subsequently became evident, to monitor the 2,3,7,8-TCDD levels in the 2,4,5-T products. The United Kingdom Ministry of Agriculture Labs - Plant Pathology Lab in Harpenden, United Kingdom was charged with this analytical task. Since pure standards of 2,3,7,8,-TCDD were not available, the scientists set out to synthesize the standards, but only after what were believed to be adequate safety precautions were taken.

Oliver in a report on this laboratory exposure incident provided very detailed descriptions of each of the 3 cases of exposure. These case descriptions are presented below and are verbatim from Oliver's report.

> Case A. - White male scientist, born in 1942. In July 1970 he was attempting to synthesize dioxin by heating trichlorophenol in an alkaline solution in the presence of a catalyst. This was carried out in a chemical fume cupboard with an aircooled condenser tube passing from the top of the heated vessel through the extract vent of the cupboard. He wore an overall and disposable plastic gloves, taking the utmost care to avoid skin contamination. The dioxin evolved sublimed on the upper part of the condenser tube although undoubtedly much must have also passed into the extract ducting of the fume cupboard.
>
> About eight weeks after this he began to develop chloracne with a typical distribution on the pinnae, behind the ears, and on the forehead and malar regions of the neck. A less extensive eruption appeared on the arms and truck. The genital area was unaffected. There had been no preceding excessive oiliness of the skin. He had suffered severe acne as an adolescent and there remained a tendency to seborrhea of the scalp. He had noted no other symptoms related to this attack. The urine had always been normal in colour. There was no hair fall nor hirsutism. He had noticed increasing fatigue and a tendency to headache but these did not seem to be related to his exposure to dioxin. There were emotional disturbances.
>
> His previous medical history revealed nothing of significance except an attack of jaundice at the age of 13.
>
> He was first seen in November 1970 when apart from chloracne physical examination was unremarkable. Liver function tests were normal and there was no porphyrinuria. The rash was persistent in spite of treatment and gradually subsided over the next 12 to 18 months when the incident was regarded as closed.
>
> In view of the possibility of the development of later symptoms suggested by the history of patient C he was recalled for examination in October 1973. He then showed almost complete clearance of the chloracne with only a few isolated

blackheads. There was some scattered pigmentation of the areas affected by the chloracne but this was probably part of a generalized tendency to freckles. There were some slightly depressed pigmented scars along the hairline of the forehead. The texture of the skin was normal. Nothing else of significance was found on physical examination. He had noticed no abnormalities in his general health or wellbeing since his earlier examination.

A full blood biochemical analysis was undertaken and this revealed a surprisingly high blood cholesterol (7-8 mmol/L.; 302 mg/100 ml) for a man of his age. No other significant biochemical changes were detected, the liver function tests were again normal, and no porphyrinuria was present.

Case B. - White male scientist, born in 1932. In May 1970 on two separate occasions about one week apart he was engaged in the preparation of a dioxin standard by heating prepared potassium trichlorophenate in a closed system. An overall and plastic gloves were worn and the apparatus was set up in a fume cupboard with rigorous precaution to avoid inhalation or skin contact.

About five to six weeks after the experiments he noticed an excessive oiliness of the skin, first affecting the nose and then spreading to the lower part of the cheeks and downwards onto the neck. He likened the appearance to the skin being smeared with melted butter. Two to three weeks later (about eight weeks after the experiments) typical chloracne started to develop, affecting in sequence the sides of the nose, the lower parts of the cheeks, the ears, the front of the neck, the chin and finally behind the ears and the back of the neck. There was none on the chest or back. In addition, a follicular rash appeared on the hairy parts of the backs of the fingers and hands and to a lesser extent on the forearms. In contrast to the chloracne this follicular rash cleared rapidly. It was also noticeable that the development of the chloracne appeared to come in two waves about one week apart, corresponding to the interval between the two earlier chemical experiments.

He was first seen in November 1970 when the chloracne was well established. At that time he had no other significant symptoms and his previous history was unremarkable apart from a history of skin sensitivity to hydroxylamine some years previously. The skin did not reveal any evidence of increased fragility and the urine was normal in colour although it was not tested for porphyrins. Blood examination at this time showed no evidence of liver damage. The serum cholesterol was not estimated on this occasion.

The skin was treated by gentle expression of the comedones and it was noted that the sebaceous material had a strong rancid odour. The chloracne gradually subsided over the ensuing year and the episode was considered closed.

For the same reasons as patient A he was also recalled for examination in October 1973. It became evident that during the summer of 1972 and the following winter months (two to two and a half years after the original episode) he had in fact been

unwell with a number of unusual symptoms. Most noticeable was a marked tendency to colicky abdominal pains with excessive flatulence. This was aggravated by eating breakfast foods containing oats, and this symptom has persisted. He had no loss of appetite but there was an unexplained loss of about 1 stone (6-5 kg) in weight from which he has gradually recovered. He complained of oppressive headaches and a remarkable and unusual loss of vigor and drive with excessive fatigue. He became easily irritable and was prone to episodes of uncharacteristic anger. His concentration was diminished. There was no loss of libido. Concurrently with these symptoms he started to develop longer and darker hair growth on the shoulders, upper part of the back, the infraclavicular region, and around the nipples. Larger dark hairs developed on the eyebrows, which tended to extend laterally towards the temporal hairline. These hair changes subsequently regressed so that by the time of his examination in October 1973 the hair distribution was nearly back to normal.

He described worrying difficulties with muscular and mental coordination as though he were not fully in control of his limbs. Writing was difficult and labored, and such tasks as sorting objects into groups resulted in frequent errors. He had some blurring of vision. There was at the time no obvious explanation for these symptoms and no domestic or working stress. The symptoms were nevertheless bad enough for him to consult his general practitioner who treated him symptomatically. All the symptoms, with the exception of the indigestion and flatulence after eating oats, fully subsided over a period of about six months.

Examination in October 1973 revealed a few acneiform spots on the neck and some irregularity of the skin of the face at the site of the earlier chloracne. Physical examination was otherwise unremarkable.

Blood examination showed no evidence of liver damage and no significant biochemical changes with the exception of a raised serum cholesterol (7-9 mmol/L.; 305 mg/100 ml). Electrophoretic strip indicated a type of 2A hyperlipoproteinaemia. Serum triglycerides were 1.3 mmol/L. (114 mg/100 ml). The urine showed no porphyrinuria. Thus as in patient A there was evidence of a mild hypercholesterolaemia.

Case C. - White male scientist, born in 1940. He was a colleague of patient B, working in the same laboratory in 1970 but not actually engaged in the experiments to prepare dioxin. He had, however, been working in the following few months with the diluted dioxin standard prepared by patient B. All his work had been done with the utmost caution and with special care to avoid personal contamination.

He first reported with abnormal symptoms in June 1973. These symptoms had been present over the preceding 12 months and he had become increasingly concerned that they might be related to his work with dioxin. With the exception of skin abnormalities his symptoms had a remarkable similarity to those of patient B., in both character and timing.

He had never had any chloracne or evidence of skin fragility. The urine was always normal in colour. He had however noticed an uncharacteristic and inexplicable loss of energy and drive since about April 1973. He experienced marked loss of concentration to the extent that he felt he was not doing justice to his job. There were no headaches and no loss of libido. He complained of vague indigestion with very marked flatulence, worse after farinaceous foods, and intermittent diarrhea. He had some loss of appetite, probably related to a marked diminution in his sense of taste, but his weight remained steady. There were occasional palpitations. He had a peculiar sensation of flickering of vision in the peripheral visual fields and a transient period of difficulty in sleeping. There were occasional superficial neuralgic pains with a patchy distribution over the left thigh.

Early in 1973 he had a spell of markedly increased oiliness of the skin, especially on the forehead. About this time he noticed the development of longer, coarse hair growth on the shoulder, intraclavicular region, upper back, and below the scapulae. Longer darker hairs grew in the eyebrows, which tended to extend laterally toward the temporal hairline. A few isolated long dark hairs grew on the backs of the hands. By November 1973, although there had been slight improvement, this hirsutism had not fully regressed. In contrast to the body hirsutism, he had noticed a clearly recognizable thinning of the scalp hair, which has persisted but not progressed.

Examination in June 1973 was unremarkable apart from the hirsutism. A full blood analysis showed normal liver function and the only significant abnormality was, as in the other patients, a hypercholesterolemia (310 mg/100 ml).

Blood examination was repeated in July 1973 when the liver function tests were normal and hypercholesterolemia (8.0 mmol/L.; 310 mg/100 ml) was confirmed. The electrophoretic strip showed a type 2A hyperlipoproteinemia. Serum triglycerides were 0.9 mmol/L. (80 mg/100 ml). No porphyrinuria was detected.

C. Environmental Contamination

The third major route by which humans have been exposed to 2,3,7,8-TCDD and other dioxins is through environmental contamination. These sources include: consumption of food-stuffs which have been inadvertently contaminated with dioxins; application of phenoxy herbicides for agricultural and forestry management purposes; aerial application of phenoxy herbicides, primarily 2,4,5-T and 2,4,-D, as defoliants for wartime purposes; and contamination of waterways and soils by improper disposal of waste residues containing dioxins. Recent reports have also indicated that dioxins are formed and emitted into the environment in trace quantities by the incineration of municipal wastes.

Numerous citations are found in the literature on the contamination of the environment by dioxin and the resultant health effects exhibited by the public. A brief summary of some of these incidents are presented in Table 3.