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
1936	Lumber Company (user, not a manufacturer)	Mississippi/ United States	Use of Dowicide H	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	C	228	21,28,29,31,34,38 67,86
1949	N.A.	Nordrhein, Westfallen/ West Germany	PCP; TCP	N.A.	A	17	21,28,31,86
1952	N.A.	Nordrhein, Westfallen/ West Germany	TCP	N.A.	A	60	21,28,31,34,86
1952-53	Boehringer	Hamburg/ West Germany	TCP	A[e]	A	37	21,28,29,31,41,67, 83,86
1953	Badische Anilin and Soda Fabrik AG (BASF)	Ludwigshaven/ West Germany	TCP; 2,4,5-T	A	C	31-75[d]	21,28,29,31,34,38, 67,86
1953-71 *1956 *1966	Rhone-Poulene	Grenoble/ France	TCP	N.A.	A+C C C	97 Total 17 21	21,28,29,31,34,67 86
1954	Boehringer, Ingelheim	Hamburg/ West Germany	TCP; 2,4,5-T	A[e]	A	31	21,28,31,34,67,83 86
1956	Diamond Alkali	Newark, New Jersey/ United States	2,4-D; 2,4,5-T	N.A.	A	29	17,20,21,34,67,86

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 under pressure.
B. Same as A except ethylene glycol and monochlorobenzene used as solvents; 180°C; pressure not indicated.
C. Same as A except at atmospheric pressure.
D. Same as B except use xylene in place of monochlorobenzene; 160°C; pressure not indicated.

b. Cause of exposure: A. Occupational
B. Overheating of reactor
C. Overheating resulting in explosion

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.

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	Dow Chemical Co.	Midland, Michigan/ United States	TCP; 2,4,5-T	A	A	30-61[d]	21,28,29,31, 67,86
1964-69	Spolana	Czechoslovakia	TCP	C	A	72-80[d]-2-fatal[f]	21,28,29,31,34, 59,67,86
1968	Coalite and Chemical Products	Bolsover, Derbeyshire/ United Kingdom	TCP	B	C	79-90[d]	21,28,29,31,34, 38,67,86
1970	Coalite and Chemical Products	Hertfordshire/ United Kingdom	TCP	B	A	3	28
1970	N.A.	Japan	2,4,5-T; PCP	N.A.	A	25	21,28,31,67,86

a. Process Used:
A. TCP formed by alkaline hydrolysis of a 1,2,3,4-tetrachlorobenzene with sodium hydroxide in a solvent of methanol at 180°C under pressure.
B. Same as A except ethylene glycol and monochlorobenzene used as solvents; 180°C; pressure not indicated.
C. Same as A except at atmospheric pressure.
D. Same as B except use xylene in place of monochlorobenzene, and 160°C; pressure not indicated.

b. Cause of exposure:
A. Occupational
B. Overheating of reactor
C. Overheating resulting in explosion

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. Fatalaties explained in text.

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
1956	Hooker Chemical Co.	Niagra Falls, New York/ United States	TCP	N.A.	A+B	Many staff employees, number unknown	21,28,29,31,86
1959	Industrie Chimiche Melegnanesi Saronio	Milan/ Italy	TCP	N.A.	A	5	28,31,86
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]	21,28,29,31,86
1962	ICM	Saronno/ Italy	TCP	N.A.	C	5-13[d]	21,67,86
1963	Philips-Duphar	Amsterdam/ Netherlands	TCP	A	C	30-106[d]	21,28,29,31,34 38,67,86
1964	N.A.	Ufa/ U.S.S.R.	2,4,5-T	N.A.	A	128	21,28,29,31,34, 86

a. Process Used:
A. TCP formed by alkaline hydrolysis of a 1,2,3,4-tetrachlorobenzene with sodium hydroxide in a solvent of methanol at 180°C under pressure.
B. Same as A except ethylene glycol and monochlorobenzene used as solvents; 180°C; pressure not indicated.
C. Same as A except at atmospheric pressure.
D. Same as B except use xylene in place of monochlorobenzene, and 160°C; pressure not indicated.

b. Cause of exposure:
A. Occupational
B. Overheating of reactor
C. Overheating resulting in explosion

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. Fatalaties explained in text.

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
1972-73	Linz Nitrogen Works	Linz/ Austria	2,4,5-T	A	A	50	21,28,29,31,67 83,86
1974	Bayer	Uerdingen/ West Germany	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+C	5[d]	21,29,31,86
1976	Monsanto Company	South Wales/ United Kingdom	PCP	N.A.	A	N.A.	28
1976	ICMESA (Givaudan)	Meda and Seveso/ Italy	TCP	D	C	134 (124 children, 10 adults)	21,28,29,31,34, 38,67,70,86
1979	Vertac Inc.	Jacksonville, Arkansas/ United States	TCP; 2,4,5-T	N.A.	A	13 (possibly 74 or more exposed)	21

a. Process Used:
A. TCP formed by alkaline hydrolysis of a 1,2,3,4-tetrachlorobenzene with sodium hydroxide in a solvent of methanol at 180°C under pressure.
B. Same as A except ethylene glycol and monochlorobenzene used as solvents; 180°C; pressure not indicated.
C. Same as A except at atmospheric pressure.
D. Same as B except use xylene in place of monochlorobenzene; 160°C; pressure not indicated.

b. Cause of exposure:
A. Occupational
B. Overheating of reactor
C. Overheating resulting in explosion

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.

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 Merz and Werth'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	5,31
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

From the employee medical records it was determined that 49 out of the 61 workers had developed chloracne to various degrees of severity. The incidence of chloracne, however, was found to correlate more closely with the dates of exposure (higher number of cases prior to July, 1964) rather than by job classification, which would indicate that the contamination/exposure problem was wide spread through the department and not isolated.

Within the limitations of this study, i.e., small cohort size which imparts low statistical power, and the length of follow-up (14 years) which may be too short a latency period to assess the cancer outcome, 2,3,7,8-TCDD even at levels sufficient to produce chloracne did not appear to have adversely affected the mortality experience of this cohort. Four deaths were observed overall versus 7.8 expected. Of these, 1 was due to cardiovascular disease versus 3.8 expected; and 3 were due to cancer versus 1.6 expected. None of these findings were statistically significant at $\alpha=0.05$. Although the number of cancer related deaths were slightly above expected, no organ or tissue specificity was observed. It must be noted, that one of these cancers was due to a rare soft tissue sarcoma.

It was the conclusion of the authors of this study that 2,3,7,8-TCDD could not be considered a potent human carcinogen with organ or tissue specificity. A potent carcinogen, they contended, should have presented a higher frequency of cancer, even with a 14 year latency period. It was indicated that additional follow-up of this group's mortality experience would be required to determine if 2,3,7,8-TCDD is a weak human carcinogen.

Case studies of the 4 deaths from this cohort are presented below.

Case 1. - The subject worked 35 years with the company, beginning in 1928. During his first 17 years of employment he was a loader and truck driver. After a five-year absence, 14 of his remaining 18 years with the company were spent in the trichlorophenol area. During 1964, he worked on a job involving potentially high exposure to TCDD. Although a few comedones were observed on his face and back, his recurrent acne was described in 1964 as not typical of chloracne. He had a positive smoking history: a pack per day for an unknown number of years. In 1972, three years after his retirement at age 60, he died of adenocarcinoma, primary site unknown. No autopsy was performed.

Case 2. - The subject worked in construction and maintenance for 24 years. In 1964 he was assigned to trichlorphenol production, working in an area of low potential TCDD exposure. During this period, he was seen for a rash of the right ear and face. No definitive diagnosis of chloracne was made. Records indicate he was a cigarette smoker, averaging a pack per day for 35 years. He died of a fibrosarcoma in 1975 at age 53. Autopsy was performed.

Case 3. - The subject worked 31 years with the company, beginning in 1942. During 24 of these years, he worked in the trichlorophenol process area. Although in 1964 he was in the low-exposure category, he developed chloracne. He smoked a pack of cigarettes per day for 20 years. His death, in 1976 at age 56, was attributed to a glioma with metastases. No autopsy was performed.

Case 4. - The subject began working with the company in 1946 at the age of 41. He spent 20 years in the trichlorophenol area. In 1964 he was in the high-exposure group and, during this period, he developed mild chloracne on the face. He smoked for 30 years but quantity is not recorded. He died in 1976, seven years after his retirement, of hypertensive heart disease at the age of 71. No autopsy was performed.

b. Mortality Experience of Workers Exposed to 2,4,5-T

The cohort for this mortality study was selected by first determining who had worked in the department between 1951 and 1971, and second, who had worked in any of the following four jobs of interest; reactor operator, salt wheel operator, acid wheel operator and dryer operator. This selection method resulted in 204 men who had worked in the 2,4,5-T operation for one or more months in at least one of the four jobs listed above. The mortality experience of this group was compared by the indirect method with that of the United States white male population. The vital and employment status of the selected cohort as taken form Ott's report is presented in Table P-3.

TABLE P-3 - VITAL AND EMPLOYMENT STATUS OF 204 WORKERS EXPOSED TO 2,4,5-T AS OF DECEMBER 31, 1976

Vital and Employment Status	No. of Workers
Total group	204
Still employed	121
Retired	18
Deceased (company records)	9
Left employment other than through retirement	56
Deceased	2
Known alive	51
Follow-up through 1976 incomplete	3

TABLE P-4. - DURATION OF EXPOSURE BY DATE FIRST EXPOSED AMONG 204 EMPLOYEES EXPOSED TO 2,4,5-T.

Date Exposure Began	Total	Duration of Exposure* <1 year	1-2 years	3-4 years	5+ years
Total	204	157	30	9	8
1950-54	58	30	17	5	6
1955-59	45	36	6	2	1
1960-64	51	44	4	2	1
1965-69	35	32	3	0	0
1970+	15	15	0	0	0

* Fifty-nine of the 204 employees worked as ester operators for from <1 up to 77 months (11 of these employees had worked for at least one year as ester operators). The exposure durations as ester operators, or while employed in other capacities within the production department, were not included in the table since exposure intensities had not been estimated.

As noted by Ott, worker exposure for the purpose of this study was only expressed in terms of the worker's length of employment on the four jobs of concern. It did not take into account unmeasured exposures to 2,4,5-T, its esters, or other chemicals which the worker may have come into contact with during the course of employment in other cases. Table P-4, also taken form Ott's report, illustrates the duration of exposure of the cohort.

The mortality experience of this group by cause is presented in Tables 5 and 6. 11 total deaths were observed after a 20 year period versus 20.3 expected. Of these deaths, 4 were due to cardiovascular disease versus 9.1 expected, 1 was due to cancer versus 3.6 expected; and 6 were due to accidents and suicides versus 3.7 expected. An increase in observed deaths versus expected was only observed for the external causes category. However, these deaths which included 3 due to separate auto accidents (none of which occurred while the workers were employed in the 2,4,5-T plant), 1 due to a non-industrial fire, and 3 suicides by former workers who had been out of the department for more than 10 years, cannot be related to the handling of the TCP and 2,4,5-T. The cancer death was due to a respiratory malignancy in a worker who had been in the 2,4,5-T department for 8 years but who had a past history of smoking up to 2 packs of cigarettes per day. It was also noted that none of these workers, according to past medical records, had ever experienced chloracne or porphyria cutanea tarda.

TABLE P-5. - OBSERVED AND EXPECTED* DEATHS AMONG 204 EMPLOYEES EXPOSED TO 2,4,5-T, BY CAUSE AND DURATION OF EXPOSURE, 1950-1976.

Cause of Death Category	Total Exposed Group		Duration of Exposure: <1 year Total Exposure		1+ Years Total Exposure	
	Observed	Expected	Observed	Expected	Observed	Expected
All causes	11	20.3	6	13.3	5	7.0
Total Malignant Neoplasms	1	3.6	0	2.3	1	1.3
Diseases of Cardiovascular System	4	9.1	1	5.6	3	3.5
External causes (accidents and suicides)	6	3.7	5	2.8	1	0.9
All other causes	0	3.9	0	2.6	0	1.3

* Expected numbers of death based on U.S. white male mortality rates.

TABLE P-6. - OBSERVED AND EXPECTED* DEATHS AMONG 204 EMPLOYEES EXPOSED TO 2,4,5-T, BY CAUSE AND INTERVAL SINCE FIRST EXPOSURE, 1950-1976.

Cause of Death Category	Interval Since First Exposure: <10 yrs		10-14 Yrs		15-19 Yrs		20+ Yrs	
	O	E	O	E	O	E	O	E
All causes	3	6.6	0	4.7	4	4.6	4	4.4
Total Malignant Neoplasms	0	1.0	0	0.9	0	0.8	1	0.9
Diseases of Cardiovascular System	0	2.3	0	2.2	3	2.3	1	2.3
External causes (accidents and suicides)	3	1.3	0	0.8	1	0.5	2	0.4
All other causes	0	1.3	0	0.8	0	1.0	0	0.8

* Expected numbers of death based on U.S. white male mortality rates.
O= Observed
E= Expected

Ott, et. al., concluded that at the exposure concentrations of TCP and 2,4,5-T experienced by these workers (See Industrial Hygiene, Section 3a.) and within the limited scope of this study, no adverse mortality effects were observed in relation to the work environment. In addition, the mortality experience of the cohort compared favorably to that of the U. S. white male population and to the general mortality rate experienced at the Dow Midland plant.

c. Morbidity Study

Medical and morbidity information from 1976 to 1978 for two employee cohorts potentially exposed to 2,3,7,8-TCDD was compared with that of matched unexposed employees from the same plant. The first study group consisted of 204 employees who had worked in the manufacture of 2,4,5-T for at least one month between 1950 and 1971. The second group consisted of 61 employees who were involved in a 1964 chloracne incident which occurred during TCP manufacture. (Mortality studies have been conducted on both of these groups. Summaries of these studies were previously reported under subsections 4.a. and 4.b. of this section.) The control groups were selected from among other white males employed at the same location who had no potential exposure to 2,3,7,8-TCDD and who had participated in the same medical examinations between 1976 and 1978 as given the exposed cohorts.

Four controls were matched to each exposed person on the basis of year of birth ± 5 years, whether hourly or salaried, smoking habits, and, when possible, month and year of the most recent medical surveillance examination taken. Data of interest were derived from two separate sources: health examination findings from the routinely administered medical surveillance program offered by the company (Participation in the medical exams were only considered for this study between 1976 and 1978.), and morbidity surveillance as reflected in diagnosis from external medical service providers reported for payment of fee to the group insurance department.

The vital and employment status of the exposed cohorts as of December, 1978 is presented below in Table P-7. Demographic information on the exposed cohorts and their matched controls is shown in Table P-8.

Within the limitations of this type of cross sectional examination of medical and morbidity surveillance findings, the results showed few differences between the exposed cohorts and the unexposed matched controls. A significantly greater frequency of x-ray proved ulcer was reported in the cohort potentially exposed to 2,3,7,8-TCDD during the manufacture of 2,4,5-T and significantly more members of this group had been diagnosed as having diseases of the digestive system. Similar findings were absent in the more highly TCDD-exposed cohort who worked in the production of TCP, thus making it unlikely that 2,3,7,8-TCDD was the cause. A summary of the prevalence of disease for the study groups is presented in Table P-9.

TABLE P-7 - VITAL AND EMPLOYMENT STATUS OF EXPOSED COHORTS AS OF DECEMBER 31, 1978. (PERCENTAGE OF ORIGINAL COHORTS IN PARENTHESES)

Status	TCP cohort	2,4,5-T cohort
Original	61	204
Employed	40	116
Retired	11	21
Deceased	4	11
Left other than through retirement:	6	56
Deceased	0	2
Known alive	6	2
Unknown	0	52
Participated in medical surveillance exam	27(44)	87(43)
Eligible for medical care programme and morbidity surveillance	48(79)	135(66)

TABLE P-8 - COMPARISON OF EXPOSED COHORTS AND THEIR MATCHED CONTROLS ON SELECTED DEMOGRAPHIC VARIABLES.

Demographic variable	TCP cohort	Controls	2,4,5-T cohort	Controls
Medical surveillance:				
No eligible for study	27	108	87	348
Mean age ± SD	45.4±7.6	45.4±7.8	42.8±8.2	42.8±8.3
Year of hire	1953.6±7.9	1953.3±9.2	1957.1±8.5	1956.6±8.3
Salaried	5	20	14	56
Paid by the hour	22	88	73	292
Current smoker	6	24	25	100
Ex-smoker	10	40	37	148
Non-smoker	11	44	25	100
Morbidity surveillance:				
No eligible for study	48	192	135	340
Mean age ± SD	49.2±9.5	49.2±9.6	45.3±10.2	45.3±10.2
Year of hire	1951.4±8.0	1951.7±10.5	1956.7±7.9	1955.0±10.6
Salaried	5	20	17	68
Paid by the hour	43	172	118	472

TABLE P-9 - COMPARISON OF NUMBER OF PREVALENT CASES OF SELECTED DISEASE CONDITIONS BY EXPOSURE GROUP: DIAGNOSES FROM MEDICAL CARE PROGRAMME, 1976-8.

Disease category	No. of prevalent cases			
	TCP cohort		2,4,5-T cohort	
	N_E(n=48)	N_C(n=192)	N_E(n=135)	N_C(n=540)
Malignant neoplasms (140-209)	1	4	4	9
Mn of liver (155)	0	0	0	1
Mn of trachea, bronchus, and lung (162)	1*	0	1	1
Mn of connective and other soft tissue (171)	0	1	0	0
Mn of skin (172-173)	0	1	0	2
Malignant lymphoma (200-202)	1*	0	0	0
Diseases of porphyrin metabolism (277·1)	0	0	0	0
Disease of the digestive system excluding liver disease (530-535, 555-558, 564·1)	3	10	17†	27
Disorders of the liver (570-573)	0	5	2	5
Glomerulonephritis (580-583)	0	0	0	0
Renal failure (584-586)	0	0	0	1
Infections of kidney (590)	0	0	0	0
Diseases of skin and subcutaneous tissues (680-686, 692, 695)	0	2	2	11

* Refers to a single individual.

† $R_{ML} = 2.51$ $X_{MH} = 2.957$, 90% Cl = 1.50-4.18.

N_E = Number of Prevalent cases among exposed cohort.

N_C = Number of prevalent cases among controls.

d. Other studies

Dr. Ralph Cook of Dow Chemical Company reported the incidence of 2 cases of rare soft tissue sarcoma in workers who had been potentially exposed to 2,3,7,8-TCDD while working at Dow's Midland, Michigan plant. Both workers were cigarette smokers.

Case 1 - Case 1 was born in 1921 and died in 1975 of a fibrosarcoma. He had hired into Dow in 1950, and in 1964 had been potentially exposed to 2,3,7,8-TCDD while working in the TCP plant. He had developed a facial dermatitis but had never been diagnosed as having had chloracne.

Case 2 - Case 2 was born in 1921, and died of a malignant fibrous histiocytoma (date not available). He hired into Dow in 1951 and was potentially exposed to 2,3,7,8-TCDD that same year. He had developed a definite case of chloracne.

Dr. Cook, also noted in his report that 2 Monsanto workers who had been potentially exposed to 2,3,7,8-TCDD also developed soft tissue sarcomas (See Section C for more information on these 2 cases). Both workers were also cigarette smokers. Dr. Cook indicated that although no cause-effect relationship could be established at this point in time, these 4 cases suggest that smokers who exhibit chloracne as a result of exposure to 2,3,7,8-TCDD, may be at an increased risk of developing soft tissue sarcomas.

Q. Company: Spolana
Location: Czechoslovakia
Date: 1964-1969
References: 21, 28, 29, 31, 34, 38, 59, 67, 86, 99, 100

1. Process Information

Both pentachlorophenol and 2,4,5-T and its esters were manufactured at the Spolana plant in Czechoslovakia. Detailed process information was presented by Jirasek and is quoted verbatim below.

"The final products of this process were sodium pentachlorophenolate, 2,4,5-trichlorophenoxyacetic acid and the latter's sodium salt and butyl ester. The primary raw material was technical grade trichlorobenzene which was produced in a neighboring building for the production of hexachlorocyclohexane (HCH) and lindane. The table shows the entire production scheme. The chlorination of trichlorobenzene produced tetrachlorobenzene and hexachlorobenzene. Sodium trichlorophenolate was produced by the alkaline hydrolysis of tetrachlorobenzene. The hydrolysis of tetrachlorobenzene with sodium hydroxide in the presence of methanol took place in an autoclave at 190°C and at 45 atm of pressure for one hour. After cooling, the methanol was distilled from the hydrolysate, the hydrolysate was diluted with water to a 25% concentration and it was then siphoned into a storage tank. The condensation of sodium trichlorophenolate with monochloroacetic acid produced sodium trichlorophenoxyacetate. Following cooling, centrifugation, and flushing with water, the dried sodium trichlorphenoxyacetate was picked out by hand and placed in small barrels. Some of this product was used to produce the butyl ester of trichlorophenoxyacetic acid. This production took place in another building.

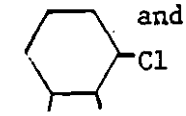
Other detailed process information, eg., process capacity, process design and equipment, reaction parameters, etc., were not reported in the published literature. In 1968, after the massive outbreak of chloracne the process was terminated.

TABLE Q-1: PRODUCTION SCHEME

Plant for production of HCH (hexachlorocyclohexane)

Plant for production of pentachlorophenol and sodium salts of trichlorophenoxyacetic acid

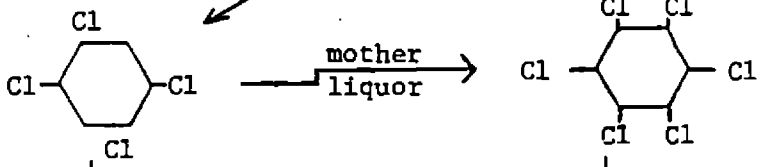
1,2,3-trichlorobenzene and its isomers(1,3,5 and 1,2,4)



Cl_2 Cl_2

1,2,4,5-tetrachlorobenzene

hexachlorobenzene



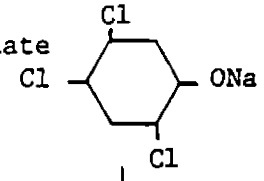
mother liquor

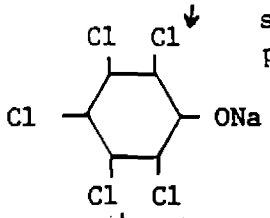
45atm, NaOH
190°C MeOH

NaOH
MeOH

sodium 2,4,5-trichlorophenate

sodium pentachlorophen



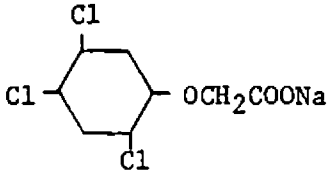


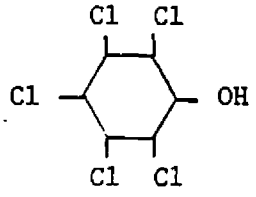
NaOH
MeOH

H_2SO_4

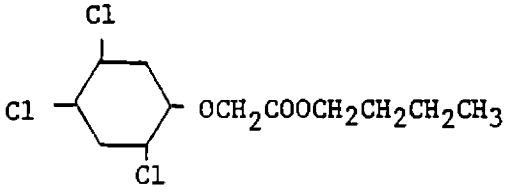
Sodium salt of 2,4,5-trichlorophenoxyacetic acid

pentachlorophenol





Plant for production of butyl ester



butyl ester of trichlorophenoxyacetic acid

023614

2. Incident Description

Between 1965-1969, 78-80 workers at the Spolana plant contracted chloracne. The first 2 cases, reported in 1965, were assumed to have been due to careless work habits since no other cases were reported. After about 1 year a massive outbreak occurred, and by 1969, 78-80 cases from all stages of production (including maintenance) in both the PCP and 2,4,5-T plants were reported. All cases were attributed to occupational exposure to 2,3,7,8-TCDD.

3. Human Exposure and Illness

a. Industrial Hygiene

As reported by Jirasek the production of both the primary products took place in a four story building with graded floors. This was noted as one of the reasons why the entire building was contaminated with the high risk substance (2,3,7,8-TCDD), and why workers involved in several stages of production at various locations received sufficient exposure to contract chloracne.

The building was not sufficiently airtight, local exhausts were in most cases improperly installed and hermatization and mechanization were insufficient. Initially, sodium tetrachlorophenolate was escaping from the centrifuge into the work space in the form of a mist. A series of tasks such as the removal of solid substances and the pumping of liquids were performed by hand. Pack out of the dried sodium trichlorophenate into small barrels was also done by hand. The workers were dressed in linen work clothes. The thorough cleaning and frequent changing of the work clothing was impossible to guarantee protection over the entire interval of production. Rubber gloves and respirators were used at some work sites. The conditions surrounding the production of the butyl ester of trichlorophenoxyacetic acid were the same as those described above.

No measurements of the concentration of 2,3,7,8-TCDD in air were taken. However, 2,3,7,8-TCDD was found in the final product (levels not given), and was also found in the plaster and on the inside furnishings of the building up to a concentration of 2,400 ppm.

Other detailed industrial hygiene information, eg., employee work history, exposure levels, exposure duration, etc. by which an assessment of worker exposure and dose could be made was not reported in the literature. Therefore, it is not possible to establish any conclusions regarding dose-response for this exposed cohort.

b. Initial Medical Reports

80 out of 400 employees who worked in this production area became ill. With the exception of 2 female laboratory technicians, all the patients were males between the age of 18-57 (4 below 20; 46 between 21-30; 11 between 31-40; 10 between 41-50 and 7 between 51-57). In most cases, the symptoms of chloracne developed slowly with comedones, and follicular hyperkeratosis noted mainly on the face. In 17 patients the disease started in an unconventional manner, with the chloracne lesions forming on the extremities, primarily the legs. In only 6 patients did edema and erythema of the face precede the onset of chloracne. Only the severe cases (number not given) were reported to have developed infections of the lesions. (The contents of the cysts upon evacuation gave off a rancid odor, similar to that noted by Dugois in the Grenoble accident.) Atrophied scars eventually developed in place of cysts and abscesses, and hyperpigmentation of the face was observed. Although the face was the primary site, chloracne, in some cases, developed around the ears, back of the neck, back, chest and the genitals.

78 of the affected employees were examined shortly after the onset of illness. The findings of this exam included: 76 cases of chloracne, and 11 cases of hepatic lesions with a deficiency in porphyrin metabolism (Porphyria cutanea tarda was diagnosed. 2 of these cases did not have chloracne.). Of the 55 workers further examined for internal and neurologic affects, about half showed decreased lipid metabolism; one third showed minor biochemical deviations and mild hepatic lesions at the onset of illness; 17 cases were found with central nervous system disorders, the majority with lesions of the peripheral neurons of the lower extremities (verified by EMG); and most of the cases exhibited physical disorder diagnosed as acute neurasthenic syndrome. The internal and neurologic symptoms exhibited by these 55 cases are listed in Table Q-2, as taken from reference 59.

In addition to the above diagnosed symptoms, the workers also had a series of subjective difficulties. These included: tiredness, weakness in the lower extremities, muscle pains, slowness and insomnia, increased perspiration, lack of appetite, headaches and other disorders in the mental and sexual spheres. The complaints were more recurrent and more intense in patients with the more extensive skin symptoms. In more serious acne cases, a significant weight loss was also noted.

TABLE Q-2 - PHYSIOLOGIC, NEUROLOGIC, PSYCHIATRIC, AND DERMATOLOGIC OBSERVATIONS FOR FIFTY-FIVE MALES WITH TCDD INTOXICATION*

	Percent of patients (N = 55)
Medical lesions	
Porphyria cutanea tarda	20
Only uroporphyrinuria	21
Hypercholesterolemia	56
Hyperlipemia	67
Hyperphospholipemia	42
Diabetes mellitus	8
Low glucose tolerance test value	19
Hepatic lesions	20
Increased total blood proteins	13
Increased plasma	
γ globulins	36
a_1 globulins	44
Decreased plasma albumin	33
Neurological lesions	
Pathological changes without any connection with exposure to TCDD	8
Polyneuropathy	23
Encephalopathy	7
Psychiatric changes	
Severe neurotic symptoms and signs with disorder of vegetative nervous system	64
Neurasthenia syndromes with depressive component	11
Depressive syndromes with endogenous component	8
Pseudeoneurasthenia syndromes in patients with arteriosclerosis of central nervous system	14
Skin lesions	
Chloracne of different severity	95

* All results were obtained at the beginning of intoxication.

It should be noted that only the most severe cases exhibited all of the symptoms listed in Table Q-2, and that the extent of organ damage between individuals was not uniform. The severity of the illness was not found to be related to the duration of exposure, job status or age.

4. Medical Follow-up of Exposed Group

The results of a 10 year medical follow-up study of the 55 male workers who were admitted to the Department of Occupational Diseases University Hospital in Prague for the first time in 1968-1969 for suffering from illness due to 2,3,7,8-TCDD exposure was reported by Pazderova-Vejlupkova. (See Table Q-2 for initial symptoms for these 55 workers) (Note, this was not an epidemiology study.) The progression of illness was found not to be linear. In some patients, the symptoms initially present after exposure became more severe. In others however, organs and systems that were functionally normal at the start of their illness later became impaired. The severity of organ damage varied between patients, and the deterioration and subsequent improvement in the individual organs and systems was unpredictable. Five years after exposure and the onset of illness, the health status of most patients stabilized and some even improved. After 10 years, 6 patients had died, 5 refused further medical care, and of the remaining 44 their conditions were noted to have improved but were still not completely healthy. Most of these 44 workers eventually re-entered the workforce.

In Table Q-3 are presented the causes of death for the 6 deceased exposed workers. Two men were killed via traffic accidents, one died of liver cirrhosis, two died of a bronchogenic lung cancer, and one died of an atypical arteriosclerosis. Since the latency period between exposure and death of the two patients with bronchogenic cancer was so short, 2 and 3 years later, it is unlikely that exposure to 2,3,7,8-TCDD was the cause of the cancer. In regards to the man who died of atypical arteriosclerosis, Jirasek contends that this case was due to acute intoxication by 2,3,7,8-TCDD.

Ten years after the initial intoxication, most patients still had deviations in lipid metabolism, with mean serum cholesterol levels being significantly higher than controls, and high phospholipid levels continuing. The increase in alpha 1 and gamma globulins disappeared, but there was a steady increase in mean blood protein. One-fifth of the patients were reported to have a diabetic glycemic curve and one-fifth had a pathological flat glucose tolerance test. At the time of the report, pathological excretions of uroporphyrins and cutaneous manifestations of porphyria cutanea tarda (disturbance in porphyria metabolism characterized by chronic skin lesions) were "very rare". On the basis of liver tissue examinations, it was concluded that generally only slight morphologic changes were present, even in generally severe poisoning cases, manifested in moderate

steatosis (fatty degeneration), periportal fibrosis, or activation of Kupfer cells. Lesions of the peripheral neuron tended to deteriorate during the first 3-4 years of illness. After 10 years, polyneuropathy was still present in 17% of the patients. The percentage of patients with neurasthenia (neurosis characterized by chronic fatigue, depression, insomnia, etc.) syndromes, with depressive components was 83% at the beginning of the illness; after 10 years, 58% of the patients were observed to have neurotic symptoms without depressive or anxiety components.

After 10 years, the investigators considered 24% of the patients to be free of psychiatric symptoms (vs. only 3% origianally). Chloracne had completely cleared up in 1/5 of the cases, more than half had only small cysts and comedones remaining, and 15% still had florid manifestations of this condition.

TABLE Q-3 - CAUSE OF DEATH FOR SIX PATIENTS WITH TCDD INTOXICATION*

	Age(yr)	Exposure	Duration of Intoxication	Severity of TCDD Intoxication Cause of Death and Post-Mortem Findings
1.	57	9 mo	2 yr	Severe type of TCDD intoxication. Unusual type of very severe arteriosclerosis of cerebri, liver, pancreas, and kidneys. Dementia cerebri. Immediate cause of death: bronchopneumonia.
2.	59	3 yr	2 yr	Severe type of TCDD intoxication. Bronchogenic carcinoma.
3.	47	2,5 yr	3 yr	Severe type of TCDD intoxication. Bronchogenic carcinoma.
4.	31	15 shifts	4 yr	Slight signs of TCDD intoxication. Traffic accident-comminuited fractures of lower extremities. Immediate cause of death: fat embolisation to lungs.
5.	63	7 mo	5 yr	Severe chloracne and slight signs of lipid metabolism disorder. Traffic accident-fractura coli femoris. Cause of death: bronchopneumonia hypostatica.
6.	40	32 shifts	9 yr	Severe type of TCDD intoxication: about 3 yr before death; complicated with hepatitis epidemica, type B. Macronodular cirrhosis with signs of portal hypertension, ascites. Cause of death: hepatic coma.

* Taken from reference 59.

R. Company: Coalite and Chemical Products
Location: Derbeyshire/U.K.
Date: 1968
References: 21, 28, 29, 31, 34, 38, 47, 48, 49, 67, 86, 118

1. Process Information

The following detailed account of the process used at the Coalite plant in Derbyshire, U.K. has been taken verbatim from May's 1973 report on the 1968 trichlorophenol incident at the Coalite plant. Capacity information was not given.

"Production of 2,4,5-trichlorophenol (2,4,5-TCP) began in August, 1965, at Bolsover, Derbyshire at the Fine Chemicals Unit of Coalite and Chemical Products Limited.

TCP production was maintained in the fine chemicals unit, an open-plan building consisting of 4 steel product row decks.

1,2,4,5-tetrachlorobenzene and ethylene glycol were charged to the reactor together with ortho dichlorobenzene and 100°Tw caustic soda solution (Fig. 1).

The vessel was heated by oil and reaction took place at about 180°C with an arbitrary upper limit of 200°C. The progress of the reaction was monitored by sampling, and on completion the vessel contents were cooled to 140°C. Steam was then injected into the reaction vessel in order to recover the ortho dichlorobenzene which was used purely as a solvent to prevent blocking of the condenser by solid tetrachlorobenzene. After the ortho dichlorobenzene ceased to be evolved, the reaction mixture was run into water in the separator. The contents of the separator were acidified with concentrated sulfuric acid at a temperature of about 70° to 80°C. After the separation of the organic layer containing 2,4,5-TCP from the aqueous phase, agitation was continued for a further 15 minutes and the contents of the vessel were allowed to stand for two hours. The aqueous phase was then siphoned off and transferred to a storage vessel, and a second waterwash was added to the organic layer. A third wash was also required, and finally a wash of town water was run to the effluent treatment drain. Since about 1966-67 caustic soda flake has been added at this stage.

The aqueous phase consisting of the washings which contained sodium chloride, ethylene glycol and digol was distilled under vacuum to remove water. When the base temperature of the still reached 120°C distillation was discontinued and the still contents were transferred to a centrifuge where the precipitated salts were removed by filtration. The liquor remaining after filtration, which consists essentially of ethylene glycol, was fractionated and the glycol, thus recovered, was recycled to the first stage of the process.

Distillation

The organic material which was separated off was distilled at a vacuum of 20 mm of mercury. The residues from the still were run to waste, the fronts were recycled to the organic layer from the washing process, and the main fraction produced was agricultural grade 2,4,5-TCP. In the Coalite process a proportion of the pure or pharmaceutical grade of 2,4,5-TCP was produced by a further fractionation of the agricultural grade. The residues from this second distillation were fed back into the primary distillation and the fronts were added to the agricultural grade material for sale. The main distillation was the pharmaceutical grade material.

The agricultural grade was reacted with monochloracetic acid to give 2,4,5-trichlorophenoxyacetic acid (2,4,5-T) and the pharmaceutical grade was condensed with formaldehyde to form hexachlorophene.

Production had been maintained for three years on the above basis. If the arbitrary temperature deadline was reached the process was cooled by lowering the temperature of the heating oil. This regulation was manually controlled."

It is interesting to note that the Coalite process did not use either pressure or agitation in the autoclave step. It was believed by Coalite, that their process unlike those which had produced accidents before, could not cause an explosion. In addition, in the event of an unforeseen rise in temperature, they thought there would be fewer and less dangerous toxic by-products formed.

FIGURE R-1:

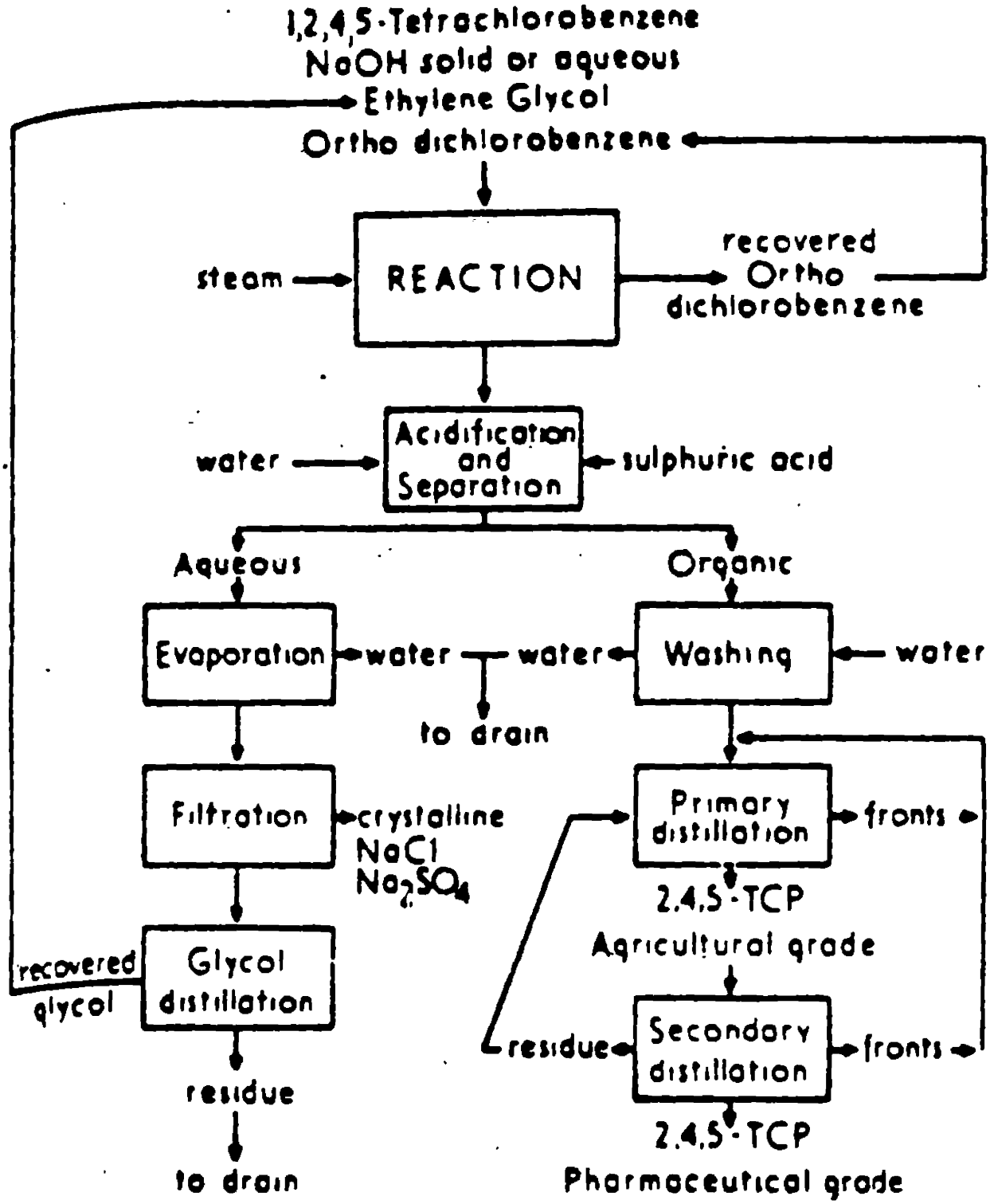


FIG. 1. Schematic representation of the reaction in 1,2,4,5-trichlorophenol production.

2. Incident Description

The 1968 incident at the Coalite plant has been thoroughly documented in the published literature by May. On April 23, 1968 at midnight the reaction temperature of the trichlorphenol batch reached 175°C and subsequently rose steadily for 50 minutes. When it reached a temperature in excess of 250°C an "explosion" of considerable violence occurred. The supervising chemist was killed by falling masonry. Investigation of the incident indicated that the accident had a dual nature. At 225°C the reaction became exothermic which led to a buildup in pressure and the eventual rupture of the vessel. (It was unclear from the published literature whether "rupture of the vessel" was meant literally, or that the vessel's rupture disc had been blown.) Ethylene glycol and orthodichlorobenzene vapours were released from the vessel in sufficient quantitiy that upon mixing with atmospheric oxygen became an explosive mixture. A nearby overhead electric lamp, was thought to have been the source which detonated the explosive mixture. Extensive damage was done to the plant and the building in the area of the explosion with much of one wall being demolished. However, most of the four floors of the building went unaffected by either the blast or contamination with residue.

The entire manufacturing unit was immediately shut down in order to investigate the accident and to assess the health status of the 14 workers who were in the building at the time of the accident. Although initial clinical findings did show some abnormalities in liver function tests and blood tests, within ten days the values returned to normal. These findings were thought reassuring, so the building was reopened. The trichlorophenol area, and other damaged and obviously dirty areas were sealed off to be decontaminated at a later date. The rest of the plant was cleaned, and production was resumed.

For a time work continued normally. The process operators were monitored closely, but all remained well. The first to show symptoms of exposure were the maintenance workers, maintenance engineers, fitters, plumbers and electricians, who only entered the unit on occasion to do specific jobs. These men, unlike the chemical workers, did their work with their bare hands, which suggested that the plant surfaces were contaminated and their exposure was due to skin contact. From May to December of that year 79 cases of chloracne developed.

The building was again closed, and restricted for entry unless the person was outfitted with special protective clothing including a full face mask, gloves and boots. A special decontamination facility for persons exiting the building was also set up.

After conducting biological tests on rabbits, it was obvious the entire building had to be cleaned and resurfaced. Heavily contaminated equipment was demolished and buried 150 feet down into a coal mine shaft. After decontamination efforts were complete, biological tests were repeated. When all tests showed negative results, the building was reopened for new construction. The plant reopened for production in 1969. The new operation included many modifications and multiple safety features to prevent similar recurrences of this incident. This new process, however, was later shut down in October of 1976, due to public concern which heightened after the Seveso accident.

3. Human Exposure and Illness

a. Industrial Hygiene

May, in his 1982, 10 year medical follow-up of the exposed workers from this incident, described the work force which manned this production unit and their exposure experience. His description was as follows:

> "The unit was manned by 24 shift process operators, three shift chemists, and about 20 general maintenance workers, a total of 47 to 50 men. Eight of the shift process operators worked exclusively on TCP production, the shift chemists did so occasionally as also did the maintenance men, a total of 31 to 34 . A maximum of 34 men therefore came into immediate contact with the process by nature of their duties and a further 16 by their presence in the unit building. None had chloracne before the 1968 incident.
>
> Three members of the research and development staff had previously contracted a very mild form of chloracne that had gone unrecognized.
>
> After the incident workers, largely maintenance men (fitters, plumbers, electricians and laborers) were drawn from over the whole plant site for cleaning-up and restorative purposes. In the immediate aftermath the risk to this type of operative was not recognised, and development of chloracne among some of these increased the total number of cases to 79 in the course of six months denotes the period over which diagnosis was made and reaction time would be governed by factors such as individual dosage and sensitivity."

Worker exposure occurred as a result of the explosion, and through skin contact with the contaminated residues on the surface of process equipment. The 14 workers who were in the building at the time of the explosion were probably exposed by both inhalation of vapors, dust and mists, and by skin contact with the reactor contents. Workers entering the building later on to resume the process were probably exposed to skin contact only. The regular production workers were noted to have worn chemical resistant gloves while in the area. However, the maintenance workers used no protective equipment.

Other detailed industrial hygiene information, eg. employee work history, exposure levels, exposure duration, other protective equipment used, etc., by which an assessment of the worker's exposure and dose can be made was not reported in the published literature.

b. Initial Medical Reports

Initial clinical and laboratory findings on the 14 men who were in the building at the time of the accident showed the following: 2 complained of fatigue, and 3 complained of tightness in the chest, however, examination revealed nothing of concern; 13 showed at least one liver function test to be abnormal; 5 showed abnormal white blood cell counts; and 3 had glycosuria. After 10 days, however, practically all the tests returned to normal.

As indicated above 79 cases of chloracne developed between May to December, 1968 after the building was reopened for production. Some of the cases developed malar erythema prior to the onset of the chloracne. Those who did generally became severe and persistent cases. Some cases occurred within a few days after exposure while others took 3 to 4 months to develope after the last known exposure. The areas affected included the face, neck, ears, extensor aspect of the arms, lateral aspects of the thighs and calves, the back and the chest. Treatment with oxytetracyclin, zinc sulfide solutions and UV radiation considerably improved the affected worker's skin conditions within 4-6 months. However, some patients showed little improvement even after 4 years of treatments. Other than the occurrence of hyperpigmentation in some cases, no other symptoms were reported for this exposed cohort.

In 1973, 13 cases of chloracne developed in the workers within this building. 7 of the cases were of fresh contraction or recrudescence, while 7 involved new cases in men not associated with the 1968 episode. These cases, together with 4 other cases which developed in 2 contract workers and their family in 1971 (See Section S for discussion on these cases.) brought the total number of cases up to over 90.

4. Medical Follow-up of Exposed Group

Ten years after the occurrence of the 1968 incident at Coalite in which 79 workers contracted chloracne due to exposure to 2,3,7,8-TCDD, (later a total of 90 cases developed) a medical study was conducted to determine the effects on the exposed cohort.

Although the whereabouts of all the living cases was known, 89 out of 90, only those employees who were still employed at the time of the study were studied. Of the 46 remaining, 41 agreed to participate. Two control groups totaling 85 workers were selected from within the plant and were matched to the study cohort by sex and age. However, according to May, it was not possible to match the groups for occupational and social status. The make-up of these 3 study groups is listed below.

Group A - No dioxin exposure; mainly management and laboratory staff but with some plant workers: 31 employees, average age 42-47.

Group B - Possible dioxin exposure; mainly plant workers but with some laboratory and management staff: 54 employees, average age 41-49.

Group C - Dioxin exposure with chloracne; mainly plant workers with some laboratory staff: 41 employees, average age 38.5.

It should be noted that the makeup of the control group, Group A, has been criticized as being ill matched and also as having devalued the study. The group has been reported to be not an age and occupation matched population, but rather an inhomogeneous group, which included office management rather than other chemical workers. The Executive Employment Medical Advisory Service (EMAS), (Great Britain's equivalent of O.S.H.A.) criticized the composition of the 3 study groups and considered them ill matched. In addition, they noted that although there were no signs of illness in the workers which could be related to dioxin exposure, it would be improper to extrapolate the findings of the survey in any general way. EMAS recommended further routine medical follow-up of the exposed cohort.

The study conducted by Coalite was comprised of the collection of detailed employment and medical histories, and a comprehensive clinical examination including biochemical and hematological studies for determining chromosome damage, effects on the immune system, and effects on blood lipid levels and liver functions. A summary of the findings of this study are listed below. Comments from other sources which dispute May's findings are included in parenthesis.

- Reproduction, Teratogenic and Embryotoxic Effects

  Dr. Eric Blank of Sheffield University conducted tests for chromosome damage on the 3 Coalite study groups. No chromosome damage was observed.

  The surviving children of parents in all three groups were normal and healthy. No evidence was given in their histories to suggest that any of them had suffered from cleft palate or hydronephrosis, the teratogenic

effects found in animals upon exposure to 2,3,7,8-TCDD, or for that matter, any other congenital deformity.

Apart from the occurrence of a miscarriage, in the wife of a dioxin exposed worker, which showed an "incomplete fetus" there was no history or evidence of congentital abnormality or teratogenicity.

(Grace Ziem of John Hopkins University points out the numbers are probably inadequate to evaluate fetal outcomes.)

- Carcinogenicity

There were no observed deaths from neoplasms nor any evidence of carcinoma of any kind in the relevant population.

(Grace Ziem of John Hopkins University noted that May's study was not designed to evaluate carcinogenicity and that the 10 year latency period is too short for most tumors to be clinically apparent.)

- Chloracne

In the dioxin exposed cohort, Group C, 22 cases of chloracne were still present after ten years. These were reported to be mild to minimal cases. According to May, "This ultrasensitive 'chloracne response mechanism' had not only, in our subjects, failed to be accompanied by other clinical signs, but there had been a consistent and complete absence of acceptable biochemical indicators of toxicity both before, during and after the chloracne response.

The implication is that there must be a comparatively wide gap in dosage, albeit still in tiny quantities, before the onset of secondary indicators of toxicity."

(Note: There is a discrepancy here between what May reports and what Hay reports in his review. Hay indicated that there were abnormalities found in some of the biochemical tests, liver function and immunity, however, May discounted their existence in his report. See biochemical results, below.)

- Biochemical Results

Cholesterol, triglycerides, gamma glutamyl transferase, D glucaric acid, alkaline phosphatase and bilirubin levels were measured for all 3 study groups. The mean results of these tests are reported in Table R-1.

TABLE R-1 - BIOCHEMISTRY: MEAN FIGURES

Laboratory Range	Group	A	B	C
3.5-7.8	Cholesterol	6.6	6.03	5.97 mmols
Up to 2.0	Triglycerides	1.83	1.93	2.03 mmoles
Up to 35	Gamma glutamyl transferase	27.7	37	39 IUI
Up to 3.5	D glucaric acid	1.52	2.14	2.07
Up to 14.5	Alkaline phosphatase	7.7	7.8	8.8 KA units 100 ml
Up to 18	Bulirubin	10.6	9.9	9.6 mmmoles

These data show that with the exception of triglycerides in Group C and gamma glutamyl transferase in Groups B and C, the mean results for all parameters in all groups falls within the accepted normal limits. May concludes that "while there are differences between groups in this series of tests, these differences while interesting, are not clinically significant to any individual and are not considered to be related to employment." May indicated the differences to be due to social factors such as alcohol consumption, and use of medications.

(Hay included in his review on this incident, the results of tests conducted on the Coalite study groups by outside contractors. Dr. Anthony Ward of Sheffield University conducted tests on the immune system, and Dr. Jenny Martin of the Chesterfield Royal Hospital evaluated blood lipids and liver function. Dr. Ward's results suggested that the dioxin-exposed group of workers had suffered from reduced immune capability and that their "short-term immunological memory" had been impaired. Workers in the category of "possible dioxin exposure" showed changes which were intermediate between the control and the main study group.

Dr. Martin's results showed that the dioxin-exposed group had a greater incidence of impaired liver function as measured by the enzyme gamma-glutamyl transpeptidase. Furthermore, when the results for serum cholesterol, triglyceride, and high-density lipoprotein were subjected to multivariant analysis, they showed a significant difference between the dioxin-exposed group and the control. In the dioxin-exposed group, levels of serum cholesterol and triglyceride were higher and high-density lipoprotein lower than in the controls. These are factors commonly held to employ an increased risk of developing cardiovascular disease. These results, however, were not statistically significant.

Dr. Martin was requested by Coalite to not publish her results. Later, after realizing that the study had been devalued by Coalite's selection of a control group, Martin conducted a second smaller scale study of her own. This included 8 of the Coalite workers who had suffered chloracne, compared with a matched control group.

As in the first study, the results showed increased serum cholesterol and reduced serum high-density lipoprotein in the dioxin-exposed group. The differences were considerably more marked than in the original, larger study. However, they are not statisically significant, a point which Martin notes, but says is simply due to the small number of subjects involved.)

Dr. May concluded from this study that, "Apart from persisting minor chlorance in half the subjects, it has not been possible to show any essential difference in any of the parameters studied between those individuals who evinced clinical evidence of dioxin exposure and their colleagues. Owing to the apparent extreme sensitivity of chloracne response it is suggested that in the absence of this condition the more unusual evidences of dioxin intoxication are unlikely to be found.

S. Company: Coalite and Chemical Products
Location: Hertfordshire/U.K.
Date: 1971
References: 28, 124

1. Process Information

2,4,5-trichlorophenol was manufactured at the Coalite plant by the alkaline hydrolysis of 1,2,4,5-tetrachlorobenzene with sodium hydroxide in a solvent mixture of ethylene glycol and ortho dichlorobenzene. The reaction temperature was at 180°C. The pressure was not specified in the literature. (There was a discrepancy in the published literature as to whether orthodichlorobenzne or orthochlorobenzne was used.)

For additional information on this process see Section R, which describes the 1968 Coalite incident.

2. Incident Description

Since this incident occurred secondary to the 1968 run-away reaction at the Coalite plant (See Section R) only the specifics of this incident will be presented here.

All parts of the damaged/contaminated plant from the 1968 incident were eventually demolished and buried. The exception, was a few large reaction vessels which had been repeatedly steam cleaned. These vessels were thought to have been decontaminated since rabbits housed within the vessels after cleaning showed no ill effect. However, 3 years later with the appearance of chloracne in two outside contractors this was shown not to be the case. The two contractors in question were hired to install/replumb the reactors into a new reaction facility separate from the location of the old contaminated area. Approximately four weeks later both contracted chloracne. In addition, family members of the workers, the son of one and the wife of the other, came down with chloracne as a result of contact with the contractors clothing.

Note: Dr. G. May of Coalite disagrees that the contractors came in contact with 2,3,7,8-TCDD from this replumbing job. His basis for this stand includes the fact that samples taken from the vessels after cleaning were negative for 2,3,7,8-TCDD down to a detection limit of 1 part in 10^{10} parts, and the fact that further biological assays were also negative.

3. Human Exposure and Illness

a. Industrial Hygiene

No detailed hygiene information, eg., exposure levels, exposure duration, protective clothing used, etc., was reported in the literature whereby an assessment of the individual's exposure and dose could be determined.

The ill effects exhibited were attributed to contact with 2,3,7,8-TCDD. It is apparent from reviewing the literature that poor personal hygiene practices were responsible for the contact/exposure of family members since the contaminated work clothes were brought home. Poor personal hygiene and lack of personal protection probably contributed to the exposure of the contractors.

b. Initial Medical Reports

Both contract workers, the son of one worker and the wife of the other, eventually came down with chloracne to various degrees. No other clinical symptoms of significance were reported. Liver function tests were normal as were the serum lipid tests. Case study reports on these individuals are presented below in Subsection 4.

4. Medical Follow-up of Exposed Group

a. Case studies

The following case studies are presented from Jensen's report.

Cases 1 and 2 were temporarily employed as pipe-fitters for the same firm. Case 1 had never been in the works before; Case 2 had, but had not been involved in the explosion or its aftermath. They were to set up a new installation away from the site of the explosion, refitting one of the cleaned tanks. Within four weeks both had developed severe chloracne.

Case 1, Mr. M. H., aged 24 -
February 1971: Onset of acute erythema of the face, followed by creamy coloured cystic lesions and later comedones of chloracne; facial lesions were chiefly on malar regions but ears, nose and neck were also involved. Elsewhere, folliculitis and comedones on trunk and proximal limbs. The patient is otherwise well with no pruritus and no previous history of acne. Biopsy from the face showed marked keratotic follicular plugging and scanty sebaceous glands.

Case 2, Mr. R. S., aged 41 -
March 1971: Onset of symptoms similar to those of Case 1. This patient is also otherwise in good health with no pruritus; he has no previous history of acne. After 11 months he shows some improvement.

Case 3, S.S., son of R. S., aged 4 -
Case 3, the son of Case 2, was regularly in close contact with his father whilst still wearing his working clothes.
June 1971: Developed comedones on the cheeks and ears, similar in type and distribution to his father's. He has no previous history of acne, no pruritus, and is otherwise in good health.

Case 4 -
Case 4 was the wife of Case 1. 11 months after the time of her husband's exposure, she developed chloracne.

T. Company: Not Available
Location: Japan
Date: 1970
References: 21, 28, 31, 67, 86, 121

1. Process Description

Detailed process information on this plant was not available in the published literature. It was noted, however, that both pentachlorophenol (PCP) and 2,4,5-T were manufactured in this plant.

2. Incident Description

All cases were attributed to occupational exposure.

3. Human Exposure and Illness

a. Industrial Hygiene

No industrial hygiene information, eg., employee work history, chemicals exposed to, duration of exposure, exposure levels, protective clothing used, etc., was published in the literature. Therefore, no assessment of worker exposure and dose can be made.

b. Initial Medical Report

25 workers from this plant, 11 from the PCP department; and 14 from the 2,4,5-T department, came down with chloracne around 1970. No other symptoms were reported at that time.

4. Medical Follow-up of Exposed Group

Three years after these 25 workers had developed chloracne, they were examined to determine if there were any instances of porphyria cutanea tarda. At the time of this evaluation, it was noted that the worker's chloracne conditions had not been completely cured despite improvements in industrial hygiene measures at the plant.

The results of this study as reported by Miura are cited below:

- The ALA in urine for the PCP exposed group (1.47±0.53 mg/l) and the 2,4,5-T exposed group (1.6-±0.65 mg/l) was found to be within the normal range, and showed no significant difference from the levels found for the control group (15 persons: 1.27±0.40 mg/l).

- The coroporphyrin levels in urine for the PCP exposed group (46.6±36.2 ug/day) and the 2,4,5-T exposed group (44.8±20.6 ug/day) also showed no significant difference from the levels found in the control group (32.9±14.8 ug/day).

- No urinary uroporphyrin was detected.

- One worker from the PCP department did show high urinary coproporyrin levels (140 ug/day) and elevated serum GOT and GPT values (both >50).

Miura concluded that although the possibility for chlorophenols by themselves to induce PCT was remote, it could not be ruled out completely.

U. Company: Not Available
Location: USSR
Date: 1972
References: 21, 28, 31, 86, 91

1. Process Information

The process involved was the manufacture of 2,4,5-trichlorophenol. Specific information on the process, eg. process design, process equipment, capacity ,chemicals used, reaction parameters, etc., was not given in the references used.

2. Incident Description

The one case reported was attributed to occupational exposure. Zelikov did allude to other cases having had occurred but did not report of any of them.

3. Human Exposure and Illness

One worker, a 32 year old male who had worked for 9 years as a metal worker, and then 3 months as an equipment operator in the 2,4,5-trichlorophenol plant, came down with a classic case of chloracne shortly after starting to work in the 2,4,5-trichlorophenol plant. He had had no incidence of skin disease prior to working in this department. Dermatological symptoms included: itching; chloracne on the face, neck, back and forearms characterized by many reddish brown pimples, keratinized cysts and folliculitis; and hyperpigmentation. Examination of the internal organs indicated that they were not diseased. In addition, both blood and urine exams were normal.

As a preventative measure this worker was transferred from the 2,4,5-trichlorophenol department, and immediately placed under medical treatment. Within 1½ months significant improvements were made, however, some hyperpigmentation persisted.

There is no industrial hygiene information in the literature whereby an assessment of this worker's exposure to the various chemicals in the 2,4,5-trichlorophenol department, can be made.

The occurrence of this case, and possibly others, did reportedly result in improvements in the work environment of this department, and were effective in the control of chloracne. The following measures were taken: improved exhaust ventilation on the process; apparatus was hermetically sealed; all workers were provided with special clothing, rubber gloves and aprons; and medical exams of the workers are conducted regularly.

4. Medical Follow-up of Exposed Group

No follow-up studies on this singular case have been found in the literature.

V. Company: Linz Nitrogen Works
Location: Linz/Austria
Date: 1972-1973
References: 21, 28, 29, 31, 67, 83, 86

1. Process Information

Prior to 1975, trichlorophenol was manufactured by the old high temperature method. (Assumed to be alkaline hydrolysis of 1,2,4,5-tetrachlorbenzene to 2,4,5-trichlorphenol by using sodium hydroxide, in a solvent of methanol at 180°C, and increased pressure.) In 1975, the process technology was purchased from Boehinger to modify the process to the low temperature method, i.e., alkaline hydrolysis of 1,2,4,5-tetrachlorbenzene to 2,4,5-trichlorophenol using sodium hydroxide in a solvent of methanol at 157°C, and a pressure of 19.5 atmospheres.

2. Incident Description

All cases reported to be due to occupational exposure.

3. Human Exposure and Illness

50 chloracne cases were reported in 1973 as a result of occupational exposures. The exact nature of the exposures, i.e., duration of exposure, exposure concentrations, job descriptions, etc., were not specified in the available literature sources. Symptoms, other than chloracne, were also not specified.

According to Reggiani, waste oils and residues from the contaminated walls and ceiling from some of the industrial episodes were analyzed for TCDD content. The sample from Linz Nitrogen works, location not specified, resulted in 140 ppm TCDD.

4. Medical Follow-up of Exposed Group

There have been no further studies published on this group concerning their mortality and/or morbidity experience.

W. Company: Bayer
Location: Uerdingen/West Germany
Date: 1974
References: 21, 28, 29, 31, 67, 83, 86

1. Process Information

Although not specifically stated, it was inferred in the literature that trichlorophenol was manufactured at the Bayer plant by the alkaline hydrolysis of 1,2,4,5-trichlorobenzene with sodium hydroxide in a solvent of methanol. Other details of the manufacturing process, eg., equipment, reaction parameters, etc., were not cited.

Production of 2,4,5-trichlorophenol stopped at the Bayer plant in Dormagen, West Germany in February, 1976 and in the Uerdingen, West Germany plant on August 4, 1976. Reportedly both units closed due to a decreased demand for 2,4,5-trichlorophenol.

2. Incident Description

All cases were attributed to occupational exposure from the tearing down and rebuilding of the methanol distillation-rectification column.

3. Human Exposure and Illness

a. Industrial Hygiene

Although a brief job description for the workers has been reported (see above), the levels at which they were exposed to the various chemicals, and their duration of exposure has not been reported (probably not determined). Therefore, an assessment of worker exposure and the dose received cannot be made. It was noted by Varhenholt that protective clothing, including total body covering with an oxygen supply for the more hazardous operations, was used by the workers to avoid any further illness.

b. Initial Medical Report

5-6 workers, locksmiths and chemical workers, came down with chloracne as a result of this refurbishing project. No other symptoms were reported in the references used.

4. Medical Follow-up of Exposed Group

No medical follow-up studies have been published for this small group.

X. Company: Thompson Hayward
Location: Kansas/U.S.A.
Date: 1975
References: 21, 29, 31, 86

1. Process Information

2,4,5-trichlorophenol was manufactured at this plant. No other process information has been reported in the literature.

2. Incident Description

Workers were reportedly occupationally exposed during normal operations, and as the result of an environmental release (probably contained within the plant) of the reaction products from overheating of the reactor.

3. Human Exposure and Illness

The number of persons reported to have been affected from these incidents varied in the literature, but was estimated to be about 5. No other information, eg. symptoms, industrial hygiene precautions, etc. was reported.

4. Medical Follow-up

No further information was available in the literature.

Y. Company: Monsanto Company
Location: South Wales/United Kingdom
Date: 1976
References: 28

1. Process Information

Pentachlorophenol was produced at Monsanto Company's Newport, South Wales plant between 1950 and August of 1978. At the time of closing, the plant's capacity was rated at 3000 tons per year. Detailed process information, eg., process design and equipment, chemicals used, reaction parameters, etc., was not given in the reference used. It was noted that hepta, hexa and octo chlorinated dibenzodioxins were present as impurities in the pentachlorophenol. (Out of these three groups of impurities, only the hexachlorodibenzodioxins are known to cause chloracne.)

2. Incident Description

All cases were attributed to occupational exposure during normal operations.

3. Human Exposure and Illness

a. Industrial Hygiene

No industrial hygiene information was provided in this reference whereby an assessment of worker exposure and dose to the various chemicals involved could be made.

b. Initial Medical Reports

According to a review written by Hay, 12 definite and 8 suspected cases of chloracne had occurred at this plant prior to its closure. No other symptoms were listed.

4. Medical Follow-up of Exposed Group

Hay's review also reported on a health study that had been conducted by Monsanto and the U.K. Health Safety Executive's Employment Medical Advisory Service (EMAS) on the workers of this plant. This study is summarized below. In regards to this study it should be noted that, no formal report on the results of this study was found in the published literature.

The health status of 40 male workers who were employed in the pentachlorophenol department (This included the pentachlorophenol and pentachlorophenate processes.) for more than three months and who were potentially exposed to hepta, hexa and octo chlorodibenzodioxins was compared to the health status of two internal comparison groups. The two control groups consisted of workers who may have had contact with the pentachlorophenol process (25 workers - control group 1) and workers who had no significant contact with the process (23 workers - control group 2).

The results, as reported by Hay, "show that in the dioxin-exposed group those with chloracne were at greater risk of developing ischaemic heart disease than any of the other groups". Those workers with chloracne exhibited higher blood cholesterol and triglyceride levels than their matched peers. In addition, the high density lipoprotein (HDL) levels for the chloracne group were more variable than in either of the control groups.

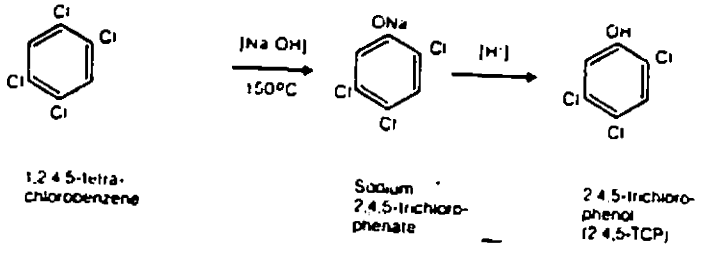
No other medical follow-up studies were found in the literature for this group.

Z. Company: ICMESA
Location: Meda/Italy
Date: 1976
References: 2, 11, 13, 20, 21, 23, 28, 29, 31, 34, 35, 38, 50, 61, 62, 67, 70, 71, 74, 81, 86, 90, 94, 96, 101

1. Process Information

2,4,5-trichlorophenol was manufactured at a small plant in Meda, Italy operated by the Industrie Chemiche Meda Societa, Anonima, (ICMESA), an Italian firm owned by the Swiss company Givaudan, which in turn was owned by Hoffman-LaRoch, a Swiss pharmacuetical company. Production began in this plant in 1969 after a new manufacturing process procedure had been worked out at the parent companies in Switzerland in 1967-1968. (Note, this infers that TCP was produced at this plant at an earlier date by a different process. This may be the same plant that resulted in 5 cases of chloracne in 1959. See Section L. It was noted by Reggiani that Givaudan had over 30 years experience with TCP production, and that after several accidents due to runaway reactions, they modified their process and equipment.) Production ceased in 1976 after an industrial accident. Although the annual yield of TCP represented only 5% of the total ICMESA production, 370 tons of TCP had been produced between 1969 and 1976. The end use of this product was intended exclusively for Givaudan in the manufacture of hexachlorophene.

TCP was synthesized at the ICMESA plant by the alkaline hydrolysis of 1,2,4,5-tetrachlorobenzene with sodium hydroxide in a solvent mixture of ethylene glycol and xylene, at 150°C and atmospheric pressure. Xylene was used solely to facilitate the azeotropic removal of water formed during the reaction. This step was followed by the distillation of the solvents and acidification of the NaTCP to yield crude TCP. The crude TCP was then further purified to remove process residues including 2,3,7,8-TCDD. The process chemistry scheme for this reaction is shown below.



A more detailed description of the process steps and operation was outlined by Reggiani in 1983. This description is presented verbatim as follows.

The principal steps of the ICMESA process for the manufacture of TCP were as follows (139):

1. Alkaline hydrolysis of tetrachlorobenzene (TCB) at 135°-160°C with NaOH in the presence of ethylene glycol as solvent and xylene as azeotropic agent.

2. Distillation of the water formed during the reaction in the form of an azeotrope with xylene at about 160°C.

3. Distillation of 45% of the charged ethylene glycol under reduced pressure (~20 Torr) at 150°-160°C.

4. Addition of cooling water.

5. Acidification with HCL, addition of water, formation of two liquid phases.

6. Recovery of TCP from the organic phase by distillation under reduced pressure (10-20 Torr) at 150°-170°C.

The main vessel used for the hydrolysis reaction had a 10,000 liter capacity. Ethylene glycol was selected as solvent in preference to the cheaper methanol primarily for safety reasons: it allows operating without pressure. Xylene was added to facilitate removal of water. Steam was used for heating in preference to oil, again because it is less likely to cause overheating, the inertia of the system is lower, and the coils can be used to circulate cooling water in case of an emergency.

The process operation was as follows: the various ingredients in the reactor vessel were heated at about 150°C and could be left indefinitely in the reactor before transfer to the next reactor for acidification and further stages of the process. Careful control of the temperature prevented the formation of TCDD. For the initial stages of the reaction the main protective device on the reactor was a vent directly into the atmosphere, with a rupture disk set at a pressure of 3.8 atm, which is approximately the vapor pressure of xylene at 180°C. Any temperature increase during the operational phases was to be controlled by manually adding a large quanitity of water to the reactor, thus cooling the mixture. The safe running of the operation depended on the promptness and efficiency of the staff controlling the installation.

The scheduled working times for each of these phases were: 1 hour for charging the reactor; 1 hour heating; 6-8 hour for reaction; 3-4 hour for distillation; and 15-30 min for quenching with water. Approximately 10 hours were then available for transfer to the next reactor for acidification, extraction, and washing, so that one full production cycle could be completed during a 24 hour day, and carried out in three working shifts.

A diagram of the process equipment used to produce TCP is shown in Figure Z-1.

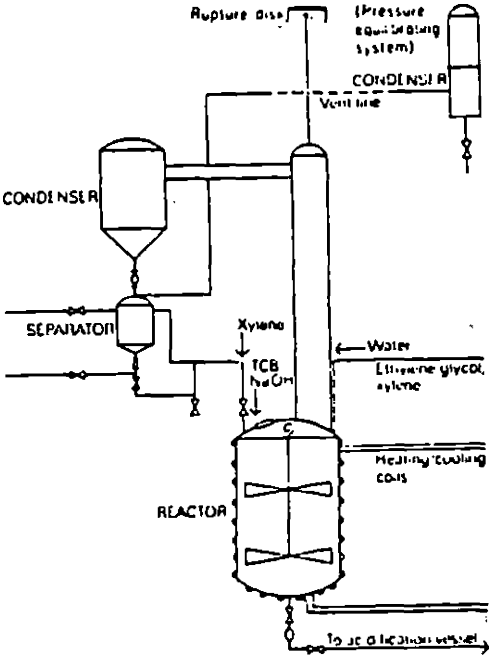


Figure Z-1: Equipment for the production of TCP.

The process followed by ICMESA during the 1969-1976 period was designed to limit the formation of the highly toxic byproduct 2,3,7,8-TCDD produced during the reaction so that the waste residues could be more easily disposed of. It was known that the formation of 2,3,7,8-TCDD from the thermal condensation of trichlorphenate was temperature dependent. Below 150°C little TCDD was formed. At 180°C, less than 1 mg TCDD was produced per kg of TCP (<1 ppm). If heating continued at 230°-260°C for 2 hours, about 1.6 g of TCDD per kg of TCP can be formed.

By operating the process at 150°C-170°C ICMESA controlled the formation of TCDD to about 5 g per batch. The crude TCP contained 1-2 ppm TCDD while the technically purified product contained 10 ppb TCDD. The distillation residues contained 10 ppm TCDD or roughly 99.9% of the TCDD was removed from the product via distillation.

2. Incident Description

On July 10, 1976 a severe accident occurred at the ICMESA, TCP plant which is often misappropriately described as an "explosion". This accident has been thoroughly investigated by Givaudan, the owner of ICMESA, and has been reported in the literature by J. Sambeth and G. Reggiani. Exerpts from Sambeth's report are presented below under Subsection 2a. Clarifications from Reggiani's report are included in parenthesis.

a. Description of the Accident

The events leading to the accident started the previous evening, Friday, July 9 at 4:00 P.M. when startup of the operation was scheduled. The production run itself ended the following morning at 6:00 A.M. - a time that coincided with the closing of the plant for the weekend.

TCP is manufactured by hydrolyzing 1,2,4,5-tetrachlorobenzene with sodium hydroxide in the presence of ethylene glycol at temperatures between 140° and 170°C. The equipment used at ICMESA (shown in Figure Z-1) consisted of a 10,000 liter chromium-molybdenum-steel jacketed vessel heated with 12 bar steam.

In this particular production run, the following quantities were used:

MATERIALS	KILOGRAMS
1,2,4,5-tetrachlorobenzene	2,000
Sodium hydroxide	1,050
Ethylene glycol	3,300
Xylene	600

The figure at the bottom right shows the various phases of what actually happened (solid line), and what should have happened had it been a normal run (dashed line). Thus, in the fourteen hours allotted to this production cycle the following operations were to be covered:

OPERATION	HOURS
Charging	1
Reaction	6-8
Solvent distillation	3-4
Quenching	0.25

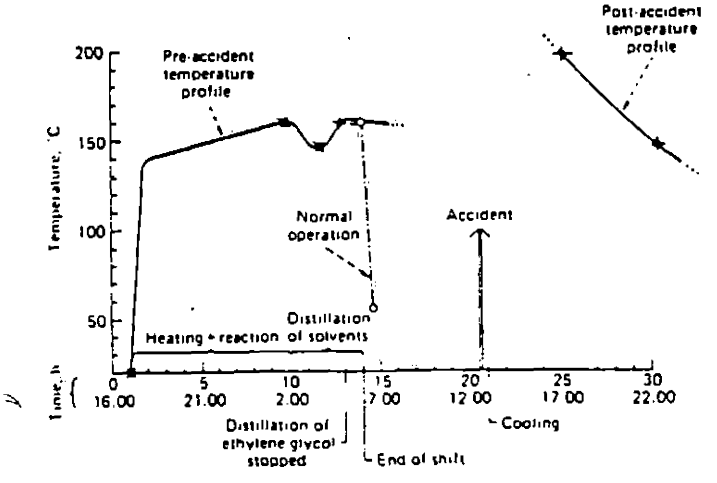
Normally, after completion of the reaction, approximately 50% of the ethylene glycol used would be distilled before the shift ended. The temperature of the reaction mixture would then be lowered to 50°-60°C thus halting any further reaction by quenching with 3,000 liters of water (dashed line).

However, the operating procedure on July 10th, 1976, was exceptional and did not conform to the company's prescribed instructions. For one thing, only 500 kg about 15% of the ethylene glycol was distilled, leaving the major portion of the solvent still in the reaction vessel. Further, at about 5:00 A.M., when the distillation was interrupted and heating discontinued, water was not added to cool the reaction mass. Stirring was also stopped 15 minutes after the distillation cycle had ended (solid line).

The last recorded temperature in the reaction vessel was 158°C. The temperture recorder was then switched off and the installation remained after the shift ended at 6:00 A.M. without supervision for about 6½ hours.

At 12:37 P.M. of the same day, pressure had built up sufficiently to break through the rupture disk and release an aerosol cloud from the reaction vessel. The accident was then contained and further accidental release of product stopped by cooling the reaction vessel with water. (Reggiani indicated that the rupture disk had blown and the contents of the reactor were vented through the pipe in the roof and spread over th surrounding area. The section foreman of the weekend watch shift and a chemist who had been called went into the shed protected by respirators and activated the cooling system. The emission of vapors ceased almost immediately.)

The reactor's contents returned to normal temperature in the course of several hours. The upper limit of the temperature recorder which had been switched on again after the accident showed that the vessel's contents had, in the interim, somehow been heated to above 200°C.



b. Accident Investigation

An investigation into the cause of this accident was conducted by the Italian authorities, Givaudan and Hoffman-LaRoche. Although the accident was unable to be reproduced on a laboratory bench scale basis, research on the thermal stability of sodium 2,4,5-trichlorophenate reaction mixtures clued the investigators to the probable cause of the accident.

Mild exothermic reactions at about 180°C were found to take place in the NaTCP reaction mixture. It was found that, in contrast to classical theory, in the absence of stirring, residual heat from the reactor walls collected in the upper 1/10 layer (1/10 by height) of the vessel's contents.

In this particular incident, the NaTCP reaction mixture was stored in the vessel after the chemical reaction had ended. In the absence of stirring, localized overheating by residual superheated steam in the vessel's vapor space, and heat from the reactor's walls conceivably raised the surface temperature to 190°-200°C. At this temperature, the mild, lower temperature exothermic reactions were initiated. Localization of the heat generated by them then caused the stratum's temperature to further rise to 230°C, where known exothermic reactions, those described in the literature before 1976, took place. These later reactions caused the increase in pressure that finally resulted in breaking of the rupture disk and the escape of part of the reactor contents.

It should be noted, that this accident occurred despite various safeguards, eg., built in temperature cut off at 188°C to the reactor, rapid cooling systems, the reactor rupture disk and use of ethylene glycol as a solvent which had a lower boiling temperature and enabled the reaction to be carried out at lower temperatures, without pressure. These safeguards had taken into account the dangers cited in the literature at that time which were thought to be related to the reaction itself. However, they did not account for the dangers encountered during storage of NaTCP after the chemical reaction was terminated.

Reggiani also indicated that between 1975 and 1976 the operation was initiated on Friday 23 times in the morning and 11 times in the afternoon. Yet on these occasions the hydrolysis reaction was either already completed and quenched with water or no solvent had been removed. An accident did not occur when the reaction was shut down with only 15% of the solvent removed and without decreasing the temperature by cooling.

c. Extent of Exposure

An extensive amount of research has been conducted around the ICMESA plant in Meda, Italy to assess the severity of environmental contamination from the July 10,1976 TCP accident. The quantity of tetrachlorodibenzo-p-dioxins (TCDD's) released to the surrounding environment (although not agreed on by

researchers) has been estimated to be between 300 g-130 kg. The contents of the reactor were vented directly into the atmosphere, and were carried by a mild breeze in a south east direction over 11 towns and villages. (Seveso, whose town boundaries border the plant limits was the most seriously affected.) The chemical cloud condensed and fell into an area about 5 km long by 700 m wide.

The events which transpired over the week immediately following the accident were described in the EPA document Dioxin, reference 21:

> No emergency action was taken by plant personnel or local authorities, although several people reported to hospitals with chemical burns. Not until the next day, Sunday, was the mayor of Seveso notified of the accident, and officials of other affected towns were not told until Monday. The plant resumed normal operations Monday morning. No official emergency decree was issued until 5 days after the accident, and the possible presence of 2,3,7,8-TCDD was not announced to the local population until after 8 days (Carreri 1978). By then, hundreds of animals had sickened and died, and people with chloracne, prinicipally children, were being hospitalized. Dow Chemical Company has asserted that these deaths probably were due to chlorophenol exposure (Crummett 1980). The plant workers went out on strike, finally closing the plant. Since ICMESA had no suitable laboratory, samples of the contamination had to be sent to Switzerland for analysis; not until 10 days after the accident did Givaudan and Hoffman-LaRoche confirm that the contamination was 2,3,7,8-TCDD. Only then were organized steps taken to assess the damage and to safeguard the health of the people who had been exposed (Reggiani 1977); Peterson 1978; Bonaccorsi, Fanelli and Tognoni 1978; Carreri 1978).

Samples of vegetation and soil were collected from the surrounding areas. On the basis of soil analysis for contamination by TCDD's the affected area was divided up into three zones, as shown in Figure Z-3. Descriptions of these zones are as follows:

> Zone A. - 216 acres, 730 people. This zone was the most highly contaminated with the average soil concentration of TCDD for the area equal to 240 ug/m^2 or roughly 2.40 ppb. The highest concentrations were around 10-50 ppb.
>
> Zone B. - 666 acres, 4,737 people. This zone was considered to be moderately contaminated with an average soil concentration of TCDD for the area equal to 3 ug/m^2 or roughly 30 ppt.

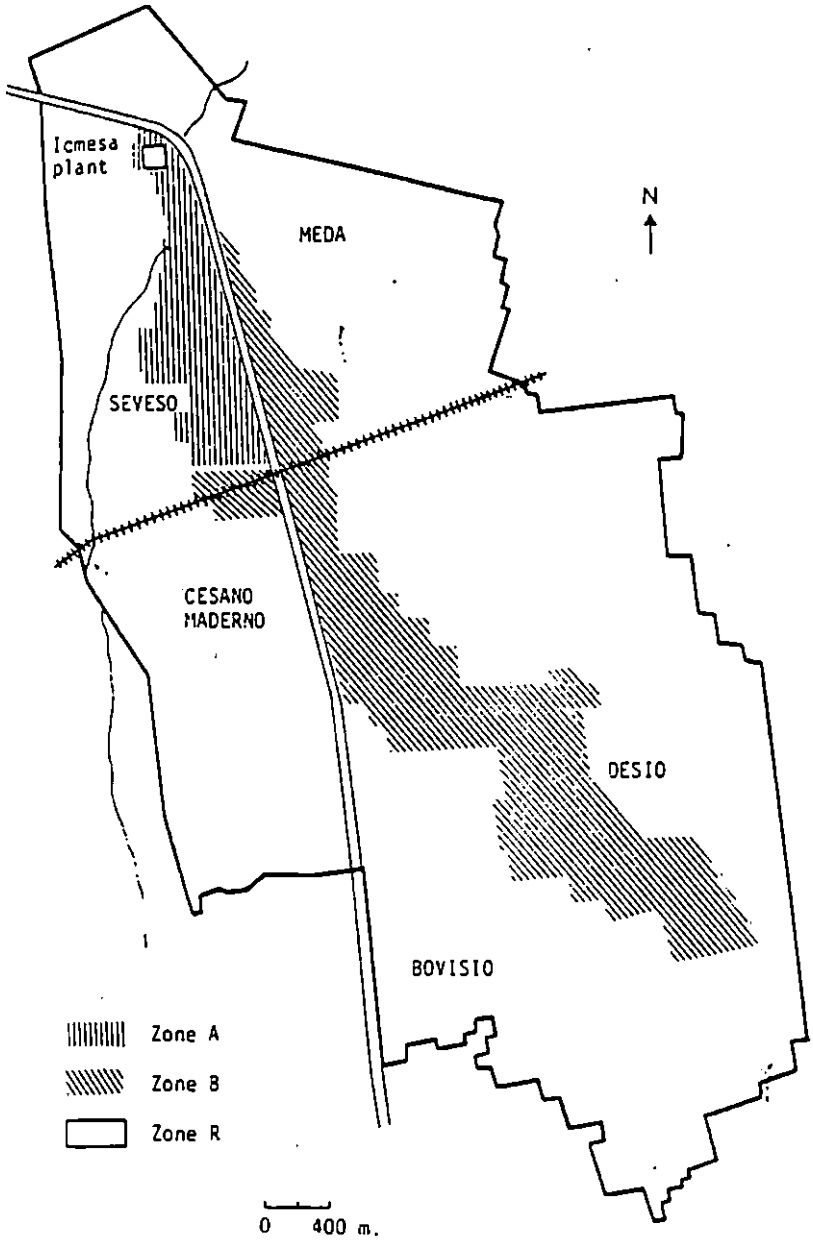


FIGURE Z-3: MAP OF THE SEVESO AREA OUTLINING ZONES, A, B AND R.

Zone R. - 3,530 acres, 31,800 people. This was considered a zone of respect or risk, and surrounded both Zones A and B. The average soil concentration of TCDD for this area was 0.9 ug/m^2 or roughly 9 ppt.

Zone A was completely evacuated and sealed off between July 24 - August 2, 1976. In Zones B and R only the children and pregnant women were evacuated. Zone B was restricted to residents only. The residents who remained in Zones B and R were instructed to follow a number of hygienic rules including not to start any pregnancies, and not to consume animals, fruit or vegetables which had been raised in the area. (The health status of the people within the affected areas are described in Section Z.3.) Four years later after Hoffman-LaRoche had bought up most of the heavily contaminated lands, and other areas were decontaminated, the former residents were permitted to return to the area.

As indicated above, many animals died as a direct consequence of the accident: 3,293 estimated deaths out of 81,131. The surviving 77,716 animals from Zones A, B and R were slautered before June 30, 1978 in an effort to keep their meat out of the food chain. Samples taken from these animals did indicate various levels of TCDD contamination.

TCDD contamination was also found in fruits and vegetables directly contaminated by the chemical cloud. According to Wipf, 1 year later in 1977 no traces of TCDD were found in the flesh of apples, pears, peaches, corn cobs or corn kernels. Traces of TCDD, however, were found in the skin of the fruit and in the sheaths of the corn cobs. This was suggestive of local contamination by dust and not plant uptake.

3. Human Exposure and Illness

a. Industrial Hygiene

Little information in the area of industrial hygiene could be found in the references used for the workforce at ICMESA. It was noted that respirators were used to reenter the area after the rupture disk had blown so that the cooling system could be turned back on to the reactor. No other information was available, eg., employee work history, exposure duration, exposure levels, protective clothing, etc., whereby an assessment of worker exposure and dose could be made.

The hygienic precautions taken for the populace, eg., evacuation, slaughter of animals to prevent their entry into the

food chain, discontinued use of fruits and vegetables grown in the contaminated area, etc., were presented previously in Subsection Z.2.c. Although the contaminant levels in the soil, water, foods, etc., have been extensively studied, the dose of the various chemicals received by the populace is impossible to determine.

b. Initial Medical Reports

- ICMESA Workers

Information in the published literature on the health effects of the 170-176 ICMESA plant workers after the accident is limited and conflicting. Reggiani, a company physician, indicated that immediately following the accident and one year later, the 10 workers who were in the plant at the time of the accident showed no signs of disease related to TCDD exposure. Zedda, however, reported that of the 176 plant workers who underwent medical examination 3 to 4 weeks after the accident, 1 suspected case of chloracne was found in the 12 workers who were in the plant at the time of the accident. Other findings included 29 cases of liver insufficiency, 28 cases of chronic bronchitis with functional disturbances, 17 cases arterial hypertension, 9 cases coronary insufficiency, 8 cases muscular asthenia, 3 cases of loss of libido, altered gama-GT levels in 37 cases, altered alkaline phosphatase in 32 cases, and 5 cases coproporphyrinuria (PCT). Zedda also indicated that since the occupational exposure of these workers included other irritating, neurotoxic and hepatotoxic agents the occurrence of these health findings could not be solely linked to TCDD. (Social factors were not mentioned.) Another report, included in reference 21, indicated that 91 of 141 of the workers suffered from liver problems and other complaints, and 79 of the 160 workers involved with the plant clean-up had chromosomal abnormalities.

- Population of Seveso

Several thousand people and animals were directly or indirectly exposed to the chemicals released from the ICMESA plant. Those closest to the source of contamination became ill almost immediately with headaches, nausea, vomiting, and chemical burns to the exposed skin. Similar symptoms occurred within a few days in those less severely affected. During July and August, 1976, 447 cases of dermatitis caused by contact with released chemicals were found in 1,600 persons examined. Most lesions were noted to be mild, and recovered fully within 2-3 weeks.

After the evacuation of Zone A, medical screening programs were set up for the populace within the affected zones. The first cases of chloracne appeared toward the end of August, 1976. By April of 1977, 187 cases of chloracne were found: 159 in children under 14 years of age, and 28 in adults. The distribution of these chloracne cases by zone is presented in Table Z-1.

TABLE Z-1

Chloracne Cases Related to Zones of Contamination

Zone	Chloracne cases, Sept. 1976–April 1977		Percentage of population	
	Total	Children 3–14 years	Total	Children 3–14 years
A	61	42	8.28	19.6
B	9	8	0.19	0.50
C	64	63	0.20	0.70
Territory outside contaminated zones	53	46	0.06	0.1
Total	187 (159 children and 28 adults)		0.18%	

Most of the chloracne cases were considered to be of mild severity which healed quickly. The more severe cases lasted for up to 2 years and resulted in some scar formation. A summary of the other health findings identified for this exposed cohort are outlined below.

- Nervous System: - No psychic disorders reported. Subclinical signs of peripheral nervous system damage were found in about 10% of persons living in the contaminated zones, with a greater proportion of cases in Zone A. Neurological studies were conducted on persons in Zone A (highest contamination) as compared to unexposed, age, and sex matched controls from other similar areas in Italy. The studies point out cases of isolated, doubtful and purely instrumental alterations of the peripheral nervous system that do not identify any definite neurological diseases and can not be associated with TCDD exposure.

- Hepatic System: - A study of urinary d-glucaric acid (UGA) excretion in children ages 6-8 was made in an effort to evaluate any changes in excretion of hepatic microsomal enzymes. 98 TCDD exposed children were compared with 86 non-exposed children. Children with chloracne showed significantly increased levels of UGA compared with children without chloracne. Ideo concluded that it is possible that TCDD, a potent enzyme inducer in animals, is responsible. Hepatomegaly of unknown etiology was found in the populations within the contamined areas. The percentage reported varied by author. Values of 20-39% for the total population and 8% for adults and 10% for children were reported.

  Out of 4,500 cases examined in the contaminated zones 27% showed abnormal liver function tests. However, compared to an unexposed control population in Italy, there was no difference in liver pathology.

- Immune System: - No increase in deficiency of the immune system found in children as compared to the Lombardy region.

- Reproductive System:

  - Cytogenic examinations carried out on 366 exposed adults revealed no chromosomal aberrations.

  - Data on birth defects and frequency of spontaneous abortions are inconclusive since the statistical data for previous years is poor.

  - Of the 34 fetuses studied from therputic (30) and spontaneous abortions (4), there were no birth abnormalities; i.e., not mutagenic, teratogenic or embryotoxic. 1 case of fetal Down's syndrome was suspected, but was not attributed to TCDD exposure. Since the study of these fetuses was not a controlled study, no definite conclusion of the embryotoxic nature of TCDD in humans can be made.

  - The rate of spontaneous abortion in the Seveso area has been reported to have increased to twice the Italian national average since the incident. However, there were methodological problems in assessing the true rates of abortion for the area. Tuchmann-Duplesis reported the following spontaneous abortion rates for the zone A area: between 1973 and 1976 = 9.40 - 10.95%; third trimester of 1976 = 16.46%; fourth trimester of 1976 = 21.27%; and for 1977 = 11.33%. (Note, it was unclear as to whether the 1976, third and fourth trimester rates were all abortions or for spontaneous abortions only.) Tuchmann-Duplesis indicated that at first glance these figures could be interpreted to a cause/effect relationship between the increase in abortion rate and chemical contamination. However, two series of facts contradict this interpretation: in the first place the rate of abortions for the affected zones is lower than the typical European standard (20-25%), and, secondly of 600 pregnancies studied at the time of the release (mothers did not have chloracne) there was no increased rate of abortion verified nor was there any correlation between the degree of contamination and rate of abortions.

  - Post natal development of the children borne, was normal with no immune deficiency.

- Other: -

  - Comparison study made between 146 out of 164 chloracne cases under age 15 in comparison with 182 children without skin lesions from the same area. An overall positive association was found between the territorial distribution of chloracne cases and the differenct levels of said contamination in the affected area. Disturbances of the gastrointestinal tract (anorexia, nausea, vomiting, abdominal pain, gastritis) were more frequently observed in children affected with chloracne than those from the same area having no skin lesions. However, no clinically definable systemic disease has been diagnosed. (Caramaschi, 1981)

  - Other than chloracne no other systemic, pathological conditions affected by TCDD exposure were found after clinical, pediatric and hematological examination.

4. Follow-up Medical Studies

A summary of the more important medical studies on this exposed cohort was previously presented in Subsection Z.3. Other than chloracne, no other trends in systemic health effects attributable to TCDD exposure have been found. These results, however, should be considered preliminary since a sufficient latency period has not yet past whereby a determination of long-term health effects to low level TCDD exposure can be determined.

AA. Company: Vertac Inc.
Location: Arkansas/U.S.A.
Date: 1979
References: 21, 68, 79, 131

1. Process Information

Both 2,4-D and 2,4,5-T had been manufactured at this 93 acre plant site since about 1957 or 1958. According to Singer, more than 14 million pounds of Agent Orange (a 1:1 combination of the n-butyl esters of 2,4,5-T and 2,4-D) were produced at this site in the late 1960's. Since 1971 the manufacture of phenoxy herbicides had been the exclusive product of this plant. Production ceased in April, 1979.

Other process information, e.g., process used, chemicals used, reaction parameters, etc., for thisplant was not found in the published literature.

2. Incident Description

Worker exposure occurred as a result of both normal operations and from occasional accidental "blowouts" (probably released through the vessel's rupture disc). One such reactor "blowout" incident occurred in 1974, and resulted in 13 cases of chloracne in the workers assigned to do the clean up.

Another problem stems from the fact that the waste materials generated from this process were drummed into metal drums and buried on the plant site. Approximately 3,000 drums of waste containing as much as 40ppm 2,3,7,8-TCDD were found on the plant site in 1979.

The concern is in the deterioration of these drums, and eventual release of the 2,3,7,8-TCDD into the environment. Samples analyzed in 1980 indicated levels of 2 to 102ppb TCDD in bottom core samples from the Vertac cooling pond, and 400ppb TCDD in the bottom sediments of the equalization basin. Water samples from these same two sources showed no detectable levels of TCDD (detection limit of 0.05ppb and 0.010ppb respectively for each site). A composite sample of water and sediment from the city sewage treatment plant lagoon, to which Vertac's site effluent is sent, showed levels of 8ppb TCDD. In addition, 82ppt TCDD was found in the fish downstream of the plant in the two adjacent rivers. Leaking drums of Vertac waste were identified as the source.

3. Human Exposure and Illness

13 of 74 workers at the Vertac site were reported to have chloracne in 1979. No other symptoms were listed in the references used. No industrial hygiene information was reported.

4. Medical Follow-up of Exposed Group

The Mount Sinai Medical School, Laboratory for Environmental Sciences in July of 1979 conducted a health survey of 190 active, retired and former workers of the Vertac plant. Of the 88 workers who were currently employed at the plant 76 participated in the survey.

The primary diagnosist tool used to assess toxic changes in the workers as a result of exposure to the phenoxy herbicides and 2,3,7,8-TCDD was that of nerve conduction velocities (NCV). NCV assessment has been shown to be sensitive to toxic changes before other signs or symptoms become manifest. In addition, since NCV slowing is considered an early indicator of neuropathy, measurement of NCV is being increasingly used to assess subclinical dysfunction in studies of environmental and occupational toxic exposures.

Workers were selected for study and NCV assessment on the basis of screening interviews. Those workers with a positive history of diabetes, neurological disease, excess alcohol consumption or who had worked with other neurotoxic agents were excluded from the study group since these conditions would also affect NCV. Because of time constraints, NCV was measured in only 55 of the 190 workers (53 active employees, 2 retirees.). None of these workers had concurrent exposure to other neurotoxic agents.

The results of NCV assessments for this study group were compared against the results of a 25 membered control group. The control group was comprised of 17 Environmental Sciences Laboratory staff and 8 brake workers examined as part of a survey of asbestos exposed workers. All control group subjects were similarly screened for diabetes, stroke, other neurologic disease and alcohol use. None of them had significant exposure to any neurotoxic agent.

NCV assessments of the median motor, median sensory, and sural nerves were assessed. Median motor velocity was measured in 53 cases and 25 controls; median sensory velocity in 54 cases and 23 controls; and sural sensory velocity in 50 cases and 20 controls. A summary of the results of this medical survey is quoted below from Singer's report.

> "Conduction velocities (NCV) of the median motor, median sensory, and sural nerves were measured in 56 workers employed in the manufacture of 2,4,5-trichlorophenoxy acetic acid (2,4,5-T) and 2,4-dichlorophenoxy acetic acid (2,4-D). Mean age was 35 years and mean duration of employment was 7 years. The control group consisted of 25 subjects without exposure to neurotoxic agents. When compared with controls, slowing was noted in the sural nerve (mean = 34.0 vs 40.1 m/sec,$P<0.02$). All values were then adjusted for age and temperature and were transformed to Z values (mean = 0,standard deviation = 1), whereupon slowing was seen in the sural (-2.21 vs -0.52,$P<0.0001$) and median motor nerves (0.19 vs 0.91, $P<0.03$). Duration of employment was significantly correlated with slowing of sural velocity ($r = -0.40$, $P<0.004$). Altogether, 46% of the study group had one or more slowed nerve conduction velocity, versus 5% of the control group $P<0.001$)."

Although slowed NCV were found to be more prevalent in the exposed cohort, this effect can not be solely attributed to dioxin since the workers were also exposed to 2,4-D and 2,4,5-T.

IV. SUMMARY AND CONCLUSIONS

IV. Summary and Conclusions

Of the twenty-nine industrial incidents resulting in potential human exposure to 2,3,7,8-TCDD and/or other dioxins, ten have occurred as a result of process accidents, and nineteen have occurred as a result of occupational exposure. In addition, five of the companies who had process accidents also reported cases due to occupational exposure.

Twenty-six of these industrial incidents involved the manufacture of 2,4,5-trichlorophenol (TCP), and/or used TCP to further process 2,4,5-trichlorophenoxy acetic acid (2,4,5-T), 2,4,5-T esters, or hexachlorophene. TCP was produced in these plants by one of two basic procedures. The first involved the alkaline hydrolysis of 1,2,4,5-tetrachlorobenzene to TCP using sodium hydroxide in a solvent of methanol at increased temperature (~180°-190°C) and pressure (20-45 atmospheres). The second method also involved the alkaline hydrolysis of 1,2,4,5-tetrachlorobenzene to TCP, but used ethylene glycol as the solvent, lower temperatures (150°C-180°C) and no pressure. Minor differences in process paramaters, i.e., temperature, pressure, the use of an additional solvent in with ethylene glycol, were followed by the different plants. Those companies using the methanol and ethylene glycol processes for synthesizing TCP are listed below. The process followed by thirteen of the companies for manufacturing TCP was not identified in the literature.

Companies Using Methanol as the Solvent in TCP Manufacture	Companies Using Ethylene Glycol as the Solvent in TCP Manufacture
* Monsanto Chemical Co.	* Hooker Chemical Co.
Boehringer	* Coalite and Chemical Products
* BASF	* ICMESA
* Phillips Duphar	
Dow Chemical Co.	
Spolano	
Linz Nitrogen Works	
Bayer	

* Indicates company had an industrial accident involving their TCP process.

Concerning the 10 industrial accidents, 9 of them, including Monsanto's in Nitro, West Virginia occurred as a result of an uncontrollable exothermic reaction during the processing of routine batches of TCP. The tenth, at ICMESA, occurred as the result of an exothermic reaction in the process intermediate sodium trichlorophenol which was being stored.

All totaled, greater than 1,872 persons have been potentially exposed to and affected by 2,3,7,8-TCDD or other dioxins as a result of industrial incidents: greater than 669 from accidents, and greater than 1,203 from occupational exposure. Although the

acute and subchronic health effects exhibited by human exposed during the various industrial accidents and/or occupational exposure incidents are relatively similar, the long-term health effects are still questionable and inconclusive. (See Table 4 for a summary of the health effects exhibited by the various cohorts exposed during industrial incidents.) Several epidemiology studies of these exposed cohorts have been conducted and have resulted in tenative conclusions of the long-term health effects due to 2,3,7,8-TCDD exposure. (See Table 4 for summary.) However, all of these studies have statistical limitations imposed by small sample size and study power. Other factors which weaken the conclusions of these studies include:

- Most, if not all persons, were exposed to a chemical mixture and not just 2,3,7,8-TCDD.

- The exposure levels at which the workers and other persons were exposed were not measured. Therefore, the doseage(s) received can not be determined. No dose-response relationship can be made.

- Some studies did not have complete follow-up of the exposed cohort. This could weaken or strengthen the study results based upon the medical experience of those not included.

- The control groups selected for comparison of the incidence of disease, in some cases were not well selected, i.e., poorly matched by demographic factors.

- The conclusions drawn from certain studies did not coincide with the study design, i.e., conclusions on the incidence of cancer were drawn when the latency period between the time of exposure and when the study was conducted was too short.

It appears from these studies that the only definite long-term health effect in humans due to 2,3,7,8-TCDD exposure is chloracne. The occurence or lack of other long term health effects cited from these studies are not conclusive, but are suggestive.

V. REFERENCES

V. REFERENCES

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VI. GLOSSARY

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A. Chemical Acronyms

1. DCP = dichlorophenol
2. 2,4-D = 2,4-dichlorophenoxy acetic acid
3. MCA = monochloroacetic acid
4. NaOH = sodium hydroxide
5. NaTCP = sodium trichlorophenate
6. PCP = pentachlorophenol
7. TCB = 1,2,4,5-tetrachlorobenzene
8. 2,3,7,8-TCDD = 2,3,7,8-tetrachlorodibenzo-p-dioxin
9. TCP = trichlorophenol
10. 2,4,5-T = 2,4,5-trichlorphenoxy acetic acid

B. DEFINITIONS

1. Acute symptoms - Those symptoms that occur or develop rapidly after a single administration of a substance.
2. Adenocarcinoma - A malignant neoplasm of epithelial cells in glandular or glandlike pattern, frequently with infiltration of adjacent tissue, metastases, recurrence after removal, etc. a malignant adenoma.
3. Ageusia - Loss of the sense of taste.
4. Angina - A severe constricting pain.
5. Angiosteosis - Calcareous degeneration of the walls of the arteries.
6. Anorexia - Loss of appetite.
7. Anosmia - Loss of the sense of smell.
8. Apoplexy - Apoplexia. 1) A sudden loss of consciousness followed by paralysis, due to cerebral hemorrhage or blocking of an artery of the brain by an embolus or thrombus. 2) An effusion of blood into the lungs or other organs.
9. Arteriosclerosis - Arterial sclerosis; hardening of the arteries; three types are recognized: intimal sclerosis (atherosclerosis), medial sclerosis (Monckeberg), and arteriolar sclerosis.

10. Ascites - An accumulation of serous fluid in the peritoneal cavity; hydroperitoneum; abdominal dropsy.

11. Atheroma - Focal deposit or degenerative accumulation of soft, pasty, acellular, lipid-containing material frequently found in intimal and subintimal plagues in arteriosclerosis especially in certain phases or examples of the condition.

12. Atrophy - Atrophia. A wasting of tissues, organs, or the entire body.

13. Autoclave - A reaction vessel which uses a heat source, and is capable of acheiving high pressures.

14. Azeotrope - A liquid mixture that is characterized by a constant minimum or maximum boiling point which is lower or higher than any of the components.

15. Blepharitis - Inflammation of the eyelids, especially of the margins of the eyelids.

16. Blepharo-conjunctivitis - Inflammation of the palpebral conjunctiva.

17. Bronchiecstasis - Dilation of a bronchus or of the bronchial tubes.

18. Bronchitis - Inflammation of the mucous membranes of the bronchial tubes.

19. Bursitis - Inflammation of the bursa.

20. Cachexia - A general lack of nutrition and wasting occuring in the course of a chronic disease.

21. Carcinogen - Any cancer producing substance.

22. Catarrhal otitis - Inflammation of the mucous membranes of the ear.

23. Cheloid - A nodular, frequently lobulated, unusually firm, moveable, nonencapsulated, generally linear mass of peculiar hyperplastic fibrous connective tissue, consisting of relatively large and fairly parallel bands of densely collagenous material separated by irregular bands of cellular fibrous tissue; occur in the dermis and adjacent subcutaneous tissue, usually after a traumatic injury or a burn, especially in Negro and yellow races, and frequently recur in the scar after surgical removal.

24. Chemical fume cupboard - British term for a laboratory chemical hood, a ventilated enclosure usually with sliding door access, the purpose of which is to contain and carry away chemical vapors and fumes from the laboratory worker as they are working on experimentation.

25. Chloracne - A chemically induced skin condition characterized by acne-form eruptions similar to adolescent acne, and which may persist for long periods of time. Keratinous plugs (comedones) form in the pilosebaceous orifices. Variously sized small (2-4 mm.) papules develop. Cystic lesions may form.

26. Chloracnegen - Any chemical which can cause chloracne: 2,3,7,8-tetrachlorodibenzo-p-dioxin, chlorinated napthalenes.

27. Cholecystectomy - Surgical removal of the gall bladder.

28. Cholecystitis - Inflammation of the gall bladder.

29. Chronic symptoms - Those symptoms that are manifest after the elapse of some time.

30. Coarctation - A narrowing, a compression.

31. Comedones - Blackheads; a plug of sebaceous matter, capped with a blackened mass of dust and epithelial debris, filling the pilosebaceous orifice.

32. Conjunctivae - The mucous membrane covering the anterior surface of the eyeball and lining the eyelids.

33. Cyst - An abnormal sac containing gas, fluid or a semi solid material.

34. Dermographia - A form of uticaria in which wheals follow the mark made by a pencil or stylus on the skin; skin writing.

35. Disseminated encephalomyelitis - Wide spread, acute, inflammation of the brain and spinal cord.

36. Dyspepsia - Indigestion or upset stomach.

37. Dyspnea - Subjective difficulty or distress in breathing, frequently rapid breathing, usually associated with serious disease of the heart or lungs.

38. Dystrophic myocarditis - Inflammation of the muscular walls of the heart due to a defect in nutrition.

39. Edema - A perceptible accumulation of excessive clear watery fluid in the tissues.

40. Embryotoxic - Relating to any agent which would result in the death of a fetus upon exposure to the agent.

41. Epigastrium - The epigastric region; pit of the stomach; the upper central region of the abdomen.

42. Erythema - Redness of the skin, inflammation.

43. Eustachitis - Inflammation of the mucous membrane of the Eustachian tube.

44. Exothermic - Denoting a chemical compound, the formation of which is attended by the development of heat.

45. Fibrosarcoma - A malignant neoplasm derived from fibrous connective tissue, characterized by immature, proliferating fibroblasts or undifferentiated, anaplastic spindle cells; they tend to invade locally and metastasize widely, although some forms manifest a relatively low degree of malignancy.

46. Fibrous histiocytoma - One of the forms of rare soft tissue sarcomas.

47. Flatulence - The presence of an excessive amount of gas in the stomach and intestines.

48. Follicular hyperkeratosis - The formation and buildup of excess keratin in the follicles.

49. Folliculitis - An inflammatory reaction of hair follicles. The lesions may be papules or pustules.

50. Furunculosis - A condition marked by the presence of furuncles or boils.

51. Gastritis - Inflammation of the stomach.

52. Gastroduodenitis - Inflammation of both the stomach and duodenum.

53. Gingivitis - Inflammation of the gums.

54. Glioma - Any neoplasm derived from one of the various types of cells that form the parenchyma of the brain. They rarely metastasize to sites outside the central nervous system, but occasionally spread by means of implantation on the meninges of the brain and spinal cord. Most are malignant as a result of their location or their invasive and destructive tendencies.

55. Glycosuria - The excretion of sugar (glucose) in the urine.

56. Gustatory - Relating to the sense of taste.

57. Hematological - Pertaining to the anatomy, physiology, pathology, symptomatology and therapeutics related to the blood and blood forming tissues.

58. Hematopoietic - Pertaining to or related to the formation of blood cells.

59. Hemofuscin deposition - A brown pigment derived from hemoglobin, that occasionally occurs in the urine.

60. Hepatic - Relating to the liver.

61. Hirsutism - Abnormal presence of excessive hair.

62. Hydronephrosis - Dilation of the pelvis and calyces of one or both kidneys in consequence of obstruction to the flow of urine.

63. Hydrops - Dropsy. An excessive accumulation of clear watery fluid in any of the tissues or cavities of the body.

64. Hyperalgesia - Extreme sensitiveness to painful stimuli.

65. Hypercholesterolaemia - The presence of an abnormally large amount of cholesterol in the cells and plasma of the circulating blood.

66. Hyperlipidemia - An abnormally large quantity of total lipids in the blood.

67. Hyperlipoproteinaemia - An abnormally large quantity of lipoproteins in the blood.

68. Hyperpigmentation - An excessive amount of pigment in the skin or other part of the body.

69. Hyperplasia - An increase in number of the individual tissue elements, excluding tumor formation, whereby the bulk of the part or organ is increased.

70. Hypochondria - Abdomen, regarded as the site of hypochondria. A morbid concern about the health and exaggerated attention to any unusual bodily or mental sensations; an unfounded belief that one is suffering from some disease.

71. Hypoplasia - Defective formation or incomplete development of a part. Atrophy due to destruction of some of the elements and not merely to their general reduction in size.

72. Hyporeflexia - A condition in which the reflexes are weakened.

73. Hypothyreosis - Diminished production of thyroid hormone, leading to thyroid insufficiency.

74. Hypotonia - 1) Reduced tension in any part, as in the eyeball. 2) Relaxation of the arteries. 3) A condition in which there is diminution or loss of muscular toxicity in consequence of which the muscles may be stretched beyond their normal limits.

75. Ischaemic Heart Disease - Heart disease brought about by local anemia due to mechanical obstruction (mainly arterial narrowing) to the blood supply.

76. Laparoscopy - Examination of the abdominal cavity.

77. Laryngitis - Inflammation of the mucous membrane of the larynix.

78. Libido - Conscious or unconscious sexual desire, creative energy; any passionate interest or form of life force.

79. Liposarcoma - A malignant neoplasm that may occur in any site in the body, but especially in the retroperitoneal tissues, the thigh, popliteal space, and gluteal region, usually deep in the intermuscular or periarticular planes; histologically, they consist chiefly of immature, anaplastic lipoblasts of varying sizes (including giant forms), with bizarre nuclei and vacuoles of varing sizes in the cytoplasm, usually in association with a rich network of capillaries. They may include foci of fully developed fat cells, as well as relatively undifferentiated, immature mesenchymal tissue; the demonstration of droplets and globules of fat (by menas of special stains) is helpful in recognizing the nature of the neoplasm. Termed also lipoblastoma, lipomyxoma, myxoma lipomatodes, myxolipoma, embryonal cell lipoma, fetal-fat cell lipoma, lipoblastic lipoma, primative cell lipoma, and Abernethy's sarcoma.

80. Lymphatic - Pertaining to lymph, a vascular channel that transports lymph or a lymph node.

81. Malar - Relating to the mala, the cheek or cheek bone.

82. Malignant - Resistant to treatment; occuring in severe form, and frequently fatal; tending to become worse and lead to an ingravescent course; in the case of a neoplasm, having the property of uncontrollable growth and dissemination, or recurrence after removal or both.

84. Melanoma - A malignant neoplasm derived from cells that are capable of forming melanin; may occur in the skin of any part of the body, or in the mucous membranes of the genitalia, anus, or oral cavity, or in other sites, but most frequently on the hands or feet. In the early phases, the lesion is characterized by proliferation of cells at the dermal-epidermal junction, and the neoplastic cells soon invade adjacent tissue extensively. The cells manifest a lack of cohesiveness, and the rather abundant, eosinophilic cytoplasm tends to resemble ground glass; the nuclei are relatively large, vacuolated, and frequently bizarre in shape, with prominent acidophilic nucleoli; mitotic figures tend to be numerous. Melanomas usually metastasize widely, and the liver, lungs, and brain are likely to be involved. Most examples of this neoplsam occur in patients who are more than 30 years of age, and approximately 60 per cent originate in a pigmented mole. For emphasis in distinguishing them from benign pigmented lesions, melanomas are usually termed **malignant m.**; they are also known as melanoblastoma, melanocarcinoma, melanosarcoma, nevocarcinoma, nevomelanoma, melanotic malignant tumor, and so on.

84. Metastasize - To pass into or invade, spread.

85. Mg/m^3 - A measurement of the concentration of a contaminant in air. Milligrams of a substance contained in a cubic meter of air.

86. Morbidity - A deceased state: the ratio of sick to well in a community.

87. Mortality - The ratio of the number of deaths to the total population. The ratio of the fatal cases to the total number of cases of any disease.

88. Mutagen - Any agent which causes the production of a mutation.

89. Myelin - 1) Medullary substances. 2) Droplets of lipid formed during autolysis and postmortem degeneration.

90. Myocardial infarction - Necrosis of the myocardium (heart muscle) resulting from obstruction of the local circulation by a thrombosis (blood clot).

91. Myxedema - Advanced deficiency of thyroid hormone, characterized by a relatively hard edema of the subcutaneous tissue, dryness and loss of hair, subnormal temperature, hoarseness, muscle weakness and slow return of the muscle after a tendon jerk to the neutral position; caused by removal of loss of functioning thyroid tissue.

92. Necrosis - Pathologic death of one or more cells or of a portion of tissue or organ resulting from irreversible damage to the nucleus.

93. Neoplasm - In a more literal sense, any new growth of cells or tissues, but the term is customarily used with rather specific reference to a focus (or a relatively large mass or region) of intermittently or constantly progressive comparatively unlimited or uncontrolled new growth that manifests varying degrees of autonomy.

94. Nephrosis - Degeneration of the epithelial lining of the renal tubules (part of the kidney) in which marked edema occurs, nonimflammatory disease of the kidneys.

95. Neuralgia - Nerve pain; pain of a severe, throbbing, or stabbing character in the course or distribution of a nerve.

96. Neurasthenia - Nervous exhaustion, a functional neurosis marked by intense nervous irritability and weakness.

97. Neuritis - Inflammation of a nerve, marked by neuralgia, hyperesthesia, anesthesia or paresthesia, paralysis, muscular atrophy in the region supplied by the affected nerve, and by abolition of the reflexes.

98. Neuropsychiatry - Combined neurology and psychiatry, the specialty dealing with both organic and functional diseases of the nervous system.

99. Orthostatic - Relating to or caused by the erect posture.

100. Palmar - Referring to the palm of the hand.

101. Palpable - Perceptible to touch.

102. Paresis - Partial or incomplete paralysis.

103. Paresthesia - An abnormal spontaneous sensation, such as the burning, pricking, numbness, etc.

104. Peripheral neuropathy - Any disease of the nervous system affecting the peripheral nerves.

105. Periportal fibrosis - The formation of fibrous tissue, usually as a reparative or reactive process, around the portal vein.

106. Pilosebaceous - Relating to the hair follicles and sebaceous glands.

107. Pinnae - The external ear exclusive of the meatus; auricle, concha, auricula.

108. Plantar - Relating to the sole of the foot.

109. Pleurisy - Inflammation of the pleura, the serous membrane enveloping the lungs and lining the walls of the thoracic cavity.

110. Pneumonectomy - Operative removal of a portion of lung tissue.

111. Polyneuritis - Inflammation of many nerves (See Neuritis).

112. Polyneuropathy - Multiple diseases of the nervous system.

113. Porphyrinuria - The excretion of porphyrin in the urine.

114. PPB - Parts Per Billion, a measurement of the concentration of a contaminant in a substance (gas, liquid, solid). 1PPB indicates that there is 1 part of the contaminant contained within 1 billion parts of the substance.

115. PPM - Parts Per Million, a measurement of the concentration of a contaminant in a substance (gas, liquid, solid). 1PPM indicates that there is 1 part of the contaminant contained within 1 million parts of the substance.

116. Prothrombin - One of the factors in the blood which aids in clotting of the blood.

117. Psychopathic - Relating to mental disease; a delirious or psychotic person.

118. Pustules - A small circumscribed elevation on the skin, containing pus.

119. Pyretic - Feverish.

120. Renal - Relating to the kidneys.

121. Rhinitis - Inflammation of the nasal mucous membrane.

122. Rupture disc - A pressure relief disc usually installed on a line from a reaction vessel and which is rated to withstand a certain set pressure. If the pressure in the vessel builds up and exceeds that of the rupture disc, the rupture disc will blow out, thereby relieving the pressure on the vessel and protecting the vessel from explosion.

123. Saponification - conversion into soap; denoting the hydrolytic action of an alkalai upon fat.

124. Sclerosis - Induration or hardening of chronic inflammatory origin; especially induration of nervous and other structures by a hyperplasia of the intestinal fibrous connective tissue.

125. SMR - Standard Mortality Ratio - ratio of the actual incidence of death to the expected number of deaths in a reference population.

126. Somnolance - 1) Drowsiness, sleepiness. 2) A condition of semiconsciousness approaching coma.

127. Steatosis - 1) Adiposis. 2) Fattty degeneration. 3) Any disease of the sebaceous glands.

128. Stenocardia - constriction of the heart; angina pectoris.

129. Stomatitis - Inflammation of the mucous membrane of the mouth.

130. Subarachnoid - Beneath the arachnoid membrane.

131. Systemic - Relating to a system; specifically somatic, relating to the entire organism as distinguished from any of its individual parts.

132. Teratogen - Any agent upon which exposure to results in developmental malformations of the fetus.

133. Thrombophlebitis - Inflammation of a vein with secondary thrombus formation.

134. Thrombosis - The formation of a thrombus (clot).

135. Tracheitis - Inflammation of the lining membrane of the trachea.

136. U.V. - Ultraviolet light.

137. Vertigo - dizziness.