

III. SUMMARIES OF INDUSTRIAL ACCIDENTS/INCIDENTS
RESULTING IN POTENTIAL HUMAN EXPOSURE TO
2,3,7,8-TCDD OR OTHER DIOXINS

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023523

A. Company: Lumber Company
Location: Mississippi/U.S.A.
Date: 1936
References: 5

1. Process Information

Treatment of wood with a fungicidal chlorophenol formulation, Dowicide H, which contained tetrachlorophenol. Specific process information/treatment methods were not reported.

2. Incident Description

All cases reported to be due to occupational exposure.

3. Human Exposure and Illness

a. Industrial Hygiene

No information was available whereby the exposure or dose received by the worker could be determined.

b. Initial Medical Report

Stingily reported that 300-400 workers were affected in this incident. Initial symptoms included erythema and ulceration of the skin. The development of chloracne followed, and was characterized by comedones, cysts, pustules and thickening of the skin. These lesions were found to be persistent, and sometimes lasted several years beyond the last exposure. Other symptoms included cases of leg cramps, thrombosis and highly colored urine.

4. Medical Follow-up of Exposed Group

No other medical reports on this group could be found in the literature.

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B. Company: Dow Chemical Company
Location Michigan/U.S.A.
Date: 1937
References: 5

1. Process Information

Process information for this plant was very scant. Various chlorinated phenols, "Dowicides", were manufactured at this plant. In this particular incident 2-(2-chlorophenyl)phenol and tetrachlorophenol were involved. The process specifics, eg. equipment, chemicals used, reaction parameters etc., were not given.

This plant was temporarily shut down after the chloracne incident in 1937. The length of time during which it was shutdown was not specified.

2. Incident Description

All cases were reported to have been due to occupational exposure from handling 2-(2-chlorophenyl)phenol and tetrachlorophenol.

3 Human Exposure and Illness

a. Industrial Hygiene

No industrial hygiene information was available from the reference whereby an assessment of worker exposure, and dose to the various chemicals could be made.

It is interesting to note that Butler had commented (possibly recommended to Dow) that the use of these chemicals as "biocides" should be stopped until more was known about their toxicity and mechanisms for causing chloracne. He even recommended that animal toxicity studies be carried out, however, these steps were not taken by the company at the time.

b. Initial Medical Report

Butler, of the Dow Chemical Company; reported that 21 workers had come down with chloracne after having handled the tetrachlorophenol and 2-(2-chlorophenyl)phenol. Hyperpigmentation, scar formation and persistence of the chlorance were also cited. No other symptoms were given.

4. Medical Follow-up of Exposed Group

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

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C. Company: Monsanto Chemical Company
Location: West Virginia/U.S.A.
Date: 1949
References: 2, 5, 16, 21, 28, 29, 31, 34, 38, 55, 67, 86, 89, 109,
114, 118, 125, 126

1. Process Information

The production of 2,4,5-trichlorophenol (TCP) and 2,4,5-T at Monsanto Chemical Company's Nitro, West Virginia plant began in the fall of 1948 and ended in 1969. In this process, TCP was synthesized by the alkaline hydrolysis of 1,2,4,5-tetrachlorobenzene with sodium hydroxide in a solvent of methanol under increased temperature and pressure. The temperature and pressure were not specified in the literature. Information pertaining to further processing of the crude TCP and its conversion to 2,4,5-T was not reported.

Other detailed process information, eg. capacity, process design and equipment, reaction parameters and chemistry, etc., was not reported in the published literature. It was inferred from one source, Hay, that the operation, at least in the early days, was a manual one and was said, "to have been extremely crude with workers removing the chemicals from the reactor by scraping it out with their hands."

2. Incident Description

The accident at Monsanto's Nitro, West Virginia plant occurred about six months after production start-up. On March 8, 1949 during a routine production run the reaction underwent an exothermic decomposition which resulted in a rapid increase in temperature and pressure in the vessel. The pressure rose rapidly and eventually blew the safety relief valve on the vessel and ruptured other nearby pipe connections. The contents of the vessel were violently expelled into the interior of the building and into the atmosphere. The ejected substances were described as thick, sticky, dark brown tars and a fine black powder.

Workers, who worked in the TCP production area or who were involved with the clean-up began to develop symptoms immediately following exposure to the tarry substances. 117 workers were affected by this incident with chloracne and other systemic symptoms. Another 111 were affected with similar symptoms as a result of occupational exposure during routine operations in the manufacture of TCP and 2,4,5-T.

3. Human Exposure and Illness

a. Industrial Hygiene

No detailed industrial hygiene information, eg., employee work history, exposure levels, exposure duration, protective equipment used, etc., was available in the published literature whereby an assessment of worker exposure and dose can be made. One review, written by Alistair Hay, did indicate that few safety precautions were taken by the workers who entered the building after the accident. Hay, however, did not cite his source of information.

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Dr. R. Suskind in a report given at the Joint Conference of NIEHS/IARC in Lyon, France on January 11, 1978, indicated that some of the intermediates and final products from the plant process were made available for biological/toxicological studies. (This was probably done in an effort to identify the chloracneogenic substance responsible for worker illness.) These materials included trichloroanisole, pentachloroanisole, 2,4,5-trichlorophenoxy acid, the sodium salt of 2,4,5-T and sodium 2,4,5-trichlorophenate. The samples were noted to have come from the process which resulted in over 200 cases of chloracne and systemic effects. Repeated skin exposure to 5% acetone solutions of these materials to rats and rabbits failed to produce follicular or pilosebaceous changes.

Three different samples of sodium 2,4,5-trichlorophenate (NaTCP) were used in human topical exposure experiments -- one from the plant process itself (pH 10.0, and contained 22.4% TCP); another by distilling trichlorophenol and taking it up in caustic to form the phenate (pH= 9.9 and contained 33.5% TCP); and a third sample was prepared by the procedure followed at Diamond Alkali Company which incorporated dilution and filtration of the NaTCP (pH = 9.9 and contained 31% TCP). Halowax 1014 was used as a positive control substance.

Small groups of persons (volunteers) were exposed to each sample in concentrations ranging from 2½ to 5% of each of the trichlorophenate, and to 20% Halowax 1014 (a mixture of hexa and penta chloronaphthalene). There were 12 persons in the test. Applications were made 5 days per week for 6 weeks. As to the concentration applied, we were guided by the level of irritation produced and tolerance to the application. Physical examinations, CBC, and liver function tests were performed prior to the start of this test, at the end of the 2nd, 4th and 6th week of the test, and at monthly intervals after the end of this test.

All of the materials induced an inflammatory reaction and itching which persisted for the duration of the exposure. The process NaTCP was found to be much more chloracneogenic than either the distilled or filtered TCP samples and that the distilled TCP sample was more chloracneogenic than the filtered NaTCP sample.

Under the conditions of the investigation, the application of the test materials, as well as the control, appeared to produce no systemic effects.

More detailed information on these human exposure studies can be found in references 125 and 126.

b. Initial Medical Reports

Employees who worked in the area of TCP production or who were involved with the clean-up developed symptoms from within hours to 3½ months after the accident. According to Suskind, when a final count was taken five years later 117 persons with chloracne and associated systemic symptoms were traced to the incident. An additional 111 persons who had not been associated with this 1949 incident, but who had been

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occupationally exposed during work activities involved with 2,4,5-T synthesis, developed the same clinical symptoms but at a lower level of severity. (Note: Suskind's report infers that these 111 cases had occurred prior to the date of the accident. This figure is often quoted in the published literature. However, in recent conversations with Monsanto, Dr. Suskind has stated that he was misquoted, and that the 111 cases due to occupational exposure occurred over the course of production at Nitro, not just before the incident.) The total number of persons affected was 228.

It should be noted that those affected were not only workmen in the TCP/2,4,5-T areas but included laboratory personnel who worked with the chloracnegenic materials, medical personnel who treated the workmen, safety professionals who investigated the accident, several wives of husbands who were affected, and a father and son who had purchased a truck which was parked in the vicinity of the accident at the time it occurred. All these people also contracted chloracne.

Several medical studies were conducted by Drs. Ashe and Suskind between 1949-1953 on the exposed workers at this plant. Moses (ref. 114), Zack (ref. 89) Hay (ref. 28) and Suskind (ref. 125) all refer to these studies, however, none of them have been published.

A summary of these earlier studies as provided by these references is presented below. Case studies of the four severely affected workers who were hospitalized and studied by Drs. Ashe and Suskind in 1949 are included.

Employees, who worked in the area of TCP production or were involved in the clean up, began to develop symptoms immediately following exposure to the material which was discharged from the autoclave. Acute symptoms included eye and respiratory tract irritation, headache, dizziness and nausea, and a severe irritant reaction of the exposed skin. These symptoms subsided within one to two weeks and were followed by an acneform eruption, severe muscle pain affecting the extremities, thorax, and shoulders, fatigue, nervousness and irritability, dyspnea, complaint of decreased libido, and intolerance to cold.

1949 Study

Four of the more severely affected workers were hospitalized in 1949 and examined by Drs. Ashe and Suskind: Ivan McClanahan, Paul Willard, Jesse Steele, and Jonathan Hurley. All four had severe cases of chloracne characterized by comedones, milia or pilosebaceous retention cysts, nodules, folliculitis, pustules and abscesses. The areas affected primarily were the face, neck, back, abdomen, forearms and scrotum. Three of the four cases showed palpable livers, while the initial clinical and laboratory findings for all four indicated transient liver dysfunctions. Serum lipid levels were elevated in all four cases, and the prothrombin concentration was decreased to about 50% of normal. All four exhibited manifestations of peripheral neuropathy including severe aches and pains and fatigability upon exertion which were later found to be the major causes of disability and time

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lost in the workers affected. One case exhibited muscle weakness and sensory changes of the lower limbs. Muscle biopsies in all 4 cases were normal, while a peripheral nerve biopsy in one case revealed destruction of myelin sheaths and nerve fibers. This latter case also had poor muscle strength, hyperactive deep tendon reflexes and a diminution-to-absent sensation to all modalities. Loss of libido was also noted. In addition, all four when placed in a closed room were found to produce an odor resembling a phenolic compound. Porphyrria was not reported.

Regarding the response of these workers to treatment, Suskind noted that state of the art dermatological therapy was not effective for treating chloracne; that chloracne regressed slowly only after removal from exposure; common analgesics were not effective for controlling pain; tranquilizers were effective for controlling nervousness and irritability; and after a few months hepatic dysfunction in all cases subsided.

Case 1 - Ivan McClanahan:

Case 1 was a 32 year old steamfitter who had been sent back into Building 41 less than 1 hour after the accident to repair damage. He was first exposed for about three hours. During that time, he experienced a burning sensation of the eyes, nose and throat. On the following day, he again worked in the same building before being transferred to another part of the plant. Several hours after his initial exposure, he developed a headache, nausea, dizziness, and he vomited. The headache persisted for 8 days, and has recurred after that at occasional intervals. Six (6) days after the initial exposure, he developed severe itching, redness and swelling of the face, which was most marked over the eyelids, nose and lips. Within the next few days after that, he developed inflamed nodules as well as pustules on the face, forearms, shoulders, neck and trunk. After two weeks he noticed comedones and cysts. During the first three (3) months, after the initial appearance of the acneform eruption, the skin became hyperpigmented. Just at about the time the eruption appeared, the patient noticed that he fatigued easily. About one (1) month after his initial exposure, he developed aching muscles, especially in the thighs and in the chest area, which was aggravated by exertion. He was unable to work or walk. He developed insomnia, extreme irritability, and complained of loss of libido. In all, the pain lasted for about six weeks, but continued to recur on occasions. Several months later, he still felt weak, fatigued upon exertion, had sleep disturbances, and felt nervous.

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Case 2 - Paul Willard:

Case 2 was a 36 year old chief operator in Building 41. Thirty-six year old Paul Willard, the chief operator in Building 41, had similar symptoms. Six weeks after resuming his post in the accident-damaged building Willard noted a rash on his right leg; this was followed by an aching pain. A few days later his left leg was similarly affected. Blackheads, cysts, and pustules began to appear on his face and neck. At first the lesions were mild but as the weeks passed the condition became much more severe.

Willard found it impossible to work in the contaminated building and not be covered in the explosion residue. The continuous exposure had severe consequences for his health. The pain in his legs became more intense and in early June, 1949 he was hospitalized; he was unable to walk. He remained there for 6 days until the pain subsided. A few months later he was readmitted to a hospital. Willard was now experiencing severe pain in the chest, back, and neck; his breathing was labored. With treatment the pain subsided and Willard returned home. He, too, when examined some eight months after the accident, complained of insomnia and feeling unduly nervous.

Case 3 - Jesse Steele:

No specific information was given other than he exhibited almost identical symptoms to Cases 1 and 2.

Case 4 - Jonathan Hurley:

Case 4 was 56 years old. No other specific information was given other than he exhibited almost identical symptoms to Cases 1, 2 and 3.

1949-1953 Studies (Taken from Zack's report, reference 89.)

Ashe and Suskind examined a total of 12 more severely affected workers on three occasions during the period of 1949-1953. Another 26 persons with chloracne, apparently not related to the accident, were also examined in 1953. The clinical symptoms in order of relative frequency included acneform lesions, severe pains in muscles of upper and lower extremities, shoulders and thorax on exertion, fatigue, nervousness and irritability, decrease in libido, dyspnea, vertigo and intolerance to cold. On examination, all of the cases had chloracne. Several were severely hyperpigmented, especially on the face. Of the six workers examined between 1949-1950, four had liver enlargement and one had sensory loss in one foot. Liver impairment, as indicated by hepatomegaly, tenderness and soreness in the right upper quadrant and epigastrium, and a delayed prothrombin time, was observed.

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In 1953, four of the six workers examined in 1949 and 1950 were reexamined; six additional workers involved in the accident were also examined. The findings in this later examination indicated a general regression of both the cutaneous and noncutaneous symptoms present earlier. All of the workers showed a marked improvement in their skin lesions; there were residua of the acne and a few active lesions. In a few cases, workers continued to complain of aches and pains of the lower extremities and back, nervousness, excessive fatigue, and dyspnea. No clinical explanation for these complaints could be made based on the results of the physical examination.

4. Medical Follow-up of Exposed Group

In an effort to assess the chronic effects of human exposure to 2,3,7,8-TCDD several epidemiology studies have been conducted on Monsanto's Nitro, West Virginia cohort. These are summarized below.

a. Zack and Suskind, 1980

Twenty-nine years after the March 8, 1949 TCP accident a standardized mortality analysis was conducted on the Nitro workers who had been exposed to 2,3,7,8-TCDD as a result of the accident. 121 male workers who developed chloracne as a result of the accident were selected for study. (1-female worker had been excluded.) The mortality experience of the cohort was analyzed by the modified life-table method using the Monson program, and comparing the results to that of the population of the U.S.A. Special emphasis was placed on the effects of exposure, cardiovascular disease, and cancer of the stomach, liver, lung and skin. Follow-up of the group was 100% complete.

The results of the standardized mortality analysis of this 121 member cohort are shown in Table C-1. The relative risk for all deaths was shown to be 0.69 with 32 observed deaths versus 46.41 deaths expected. This difference was the only statistically significant difference found at $\alpha = 0.05$.

There were 9 deaths from malignant neoplasms with 9.04 expected. There were no deaths from stomach or liver cancer. For the categories of lung and skin cancer, there were five lung cancer deaths versus 3.02 expected and one skin cancer death with 0.15 expected. The malignant tumor was a fibrous histiocytoma (soft tissue sarcoma) presumably of dermal origin; it is rare. Three other cancer deaths were from neoplasms of lymphatic and hematopoietic tissue with 0.88 expected.

There were 17 observed deaths from circulatory diseases with 25.01 expected. The relative risk for circulatory diseases was low at .68.

Case summaries for the cancer deaths are given in Table C-2.

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TABLE C-1

**OBSERVED AND EXPECTED DEATHS AMONG 121 MALES EXPOSED TO TETRACHLORODIBENZODIOXIN
IN A TRICHLOROPHENOL PROCESS ACCIDENT**

<u>ICD Number (Eighth Revision)</u>	<u>Cause</u>	<u>Observed</u>	<u>Expected</u>	<u>Relative Risk</u>
	All causes of death	32	46.41	.69*
140-209	All malignant neoplasms	9	9.04	1.00
140-149	Buccal cavity and pharynx	0	0.30	+
150-159	Digestive organs and peritoneum	0	2.59	+
151	Stomach	0	0.50	+
155-156	Liver	0	0.18	+
-	All other digestive organs	0	1.91	+
160-163	Respiratory system	5	3.02	1.66
162, 163	Lung	5	2.85	1.75
-	All other respiratory organs	0	0.17	+
172, 173	Skin	1	0.15	+

*Taken from Zack and Suskind's report, reference 89.

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TABLE C-1 (CONTINUED)

<u>ICD Number (Eighth Revision)</u>	<u>Cause</u>	<u>Observed</u>	<u>Expected</u>	<u>Relative Risk</u>
185-189	Genitourinary organs	0	1.16	+
200-209	Lymphatic and hematopoietic tissue	3	0.88	+
-	Other sites	0	0.94	+
320-389	Diseases of the nervous system and sense organs	0	0.36	+
390-458	Diseases of the circulatory system	17	25.01	.68
410-413	Arteriosclerotic heart disease, including coronary heart disease	13	17.74	.73
-	All other disease of the circulatory system	4	7.27	+
460-519	Diseases of the respiratory system	1	2.78	+
520-577	Diseases of the digestive system	0	2.26	+
-	All other diseases	2	3.18	+
800-998	External causes of death	3	3.78	+

* $p < .05$

+ Less than 5 observed deaths

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TABLE C-2**

CANCER DEATHS AMONG A COHORT OF 121 MALES EXPOSED TO
TETRACHLORODIBENZODIOXIN IN A TRICHLOROPHENOL PROCESS ACCIDENT

<u>Year of Birth</u>	<u>Year of Hire</u>	<u>Year of Death</u>	<u>Death Certificate Statement of Cause of Death</u>	<u>Smoking History*</u>
1909	1943	1962	Lung cancer (162.1)	Cigarettes
1910	1927	1970	Pulmonary carcinoma (162.1)	Cigarettes
1911	1939	1964	Bronchiogenic carcinoma (162.1)	Cigarettes
1922	1945	1973	Bronchiogenic carcinoma (162.1)	Non-smoker
1915	1939	1970	Lung cancer (162.1)	Cigarettes
1920	1946	1978	Malignant fibrous histiocytoma of soft tissue origin (173.9)	Cigarettes
1919	1943	1973	Hodgkin's disease (201.0)	Cigarettes
1907	1943	1971	Lymphatic leukemia (204.9)	Pipe
1910	1939	1978	Acute myelogenous leukemia (205.0)	Cigarettes

* Smoking history was obtained by interviews with former co-workers of the decedents

** Taken from Zack and Suskind's report, reference 89.

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Because of the small size of the cohort and the relatively small number of deaths observed, the results of this study cannot be conclusive. However, it is important that no apparent excess in total mortality or in deaths from malignant neoplasms or diseases of the circulatory system was observed in a group of workers with a high peak exposure to 2,3,7,8-TCDD followed over a period of nearly thirty years.

b. Suskind and Hertzberg, 1984

A clinical epidemiology study was conducted in 1979 to assess the long-term health effects of workplace exposure to the process of manufacturing 2,4,5-T including contaminants such as 2,3,7,8-TCDD formed during the synthesis of trichlorophenol. Special emphasis was placed on determining the possible increased risks, on a long-term basis, for developing adverse cutaneous, pulmonary, cardiovascular, gastrointestinal (GI), hepatic, renal, neurological, behavioral and reproductive effects, effects on lipid metabolism and the possibility for increased risks for cancer. The population studied consisted of two cohorts: (1) 204 clearly exposed workers who were involved in any aspect of the production of 2,4,5-T, including maintenance from 1948 to 1969. (This included workers exposed during the 1949 accident.), and (2) 163 non-exposed current or former workers who had worked in the same plant, but who were never associated with any aspect of the 2,4,5-T process or maintenance of the production facility. Data on both cohorts were obtained by clinical examination and examination via questionnaire of the worker's medical history. These data are summarized in Tables C-3 thru C-13.

The results indicated that among the exposed, clinical evidence of chloracne persisted in 55.7%. None of the non exposed experienced chloracne development. An association was found between the persistence of chloracne and the presence of severity of actinic elastosis of the skin. There is an association between exposure and the history of gastrointestinal tract ulcer. Pulmonary function values among those who were exposed and who currently smoked were lower than those who were not exposed and who currently smoked. The data assembled in the study indicate no evidence of increased risk for cardiovascular disease, hepatic disease, renal damage, or central or peripheral nervous system problems.

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TABLE C-3 - HISTORY OF MEDICAL PROBLEMS VS. EXPOSURE STATUS AND BY AGE

History	Age <50 yr. %		Age >50 yr. %			
	Exposed % (n=204)*	Not Exposed % (n=163)	Exposed (n=51)	Not Exposed (n=100)	Exposed (n=153)*	Not Exposed (n=63)
Chloracne † ‡	86.3	0.0	76.5	0.0	89.5	0.0
Acne Vulvaria §"q	9.9	29.5	17.7	42.0	7.2	9.5
Skin cancer	3.9	2.5	0.0	1.0	6.3	4.8
Hypertension ‡ #	34.5	24.5	21.6	16.0	38.8	36.1
Angina #	7.4	6.1	5.9	1.0	7.9	14.3
Coronary artery disease ‡ q	10.8	6.1	2.0	0.0	13.8	15.9
Upper Gastrointestinal tract ulcer §	20.7	5.5	13.7	5.0	23.0	6.4
Cancer of all sites ** (except skin)	3.0	1.2	0.0	0.0	3.9	3.2

* One of the 204 subjects did not complete the interview/physical examination program but had a documented workman's compensation claim for chloracne.

† $p < .0001$; p value for Mantel-Heenazal comparison of exposed vs. not exposed across age strata.

‡ $.01 < p < .05$: in exposed, young vs. old, by Fisher's exact test.

§ $.001 < p < .01$: p value for Mantel-Heenazal comparison of exposed vs. not exposed across age strata.

" $.05 < p < .10$: in exposed, young vs. old, by Fisher's exact test.

q $p < .0001$: in not exposed, young vs. old, by Fisher's exact test.

$.001 < p < .01$; in not exposed, young vs. old, by Fisher's exact test.

** In the exposed group, bladder cancer, two; colon, cancer, three; prostate cancer, one; in the not exposed group, bladder cancer, one; melanoma, one.

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TABLE C-4 - COMPLAINTS OF NERVOUSNESS AND SEXUAL PROBLEMS TO EXAMINING
PHYSICIAN OR INTERVIEWER

Complaint	Exposed % (n=203)	Not Exposed % (n=163)	Age <50 yr. %		Age >50 yr. %	
			Exposed (n=51)	Not Exposed (n=100)	Exposed (n=152)	Not Exposed (n=63)
"Nervousness"/ anxiety/depression*	16.3	11.7	7.8	15.0	19.0	6.4
Decreased libido † ‡ §	35.5	15.3	19.6	5.0	40.8	31.7
Impotence, not otherwise specified ‡ §	27.6	11.7	7.8	2.0	34.2	27.0

* .05<p<.10; in exposed, young vs. old, by Fisher's exact test.

† .001<p<.01; for Mantel-Heenzael comparison of exposed to not exposed across age strata.

‡ p<.001; in not exposed, young vs. old, by Fisher's exact test.

§ .001<p<.01; in exposed, young vs. old, by Fisher's exact test.

' .0001<p<.001; in exposed, young vs. old, by Fisher's exact test.

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TABLE C-5 - HISTORY OF MEDICAL PROBLEMS VS. CHLORACNE STATUS IN EXPOSED ONLY AND BY AGE

History *	Chloracne Status %								
	Age <50 yr.			Age >50 yr.					
	History Only (n=68)	Current (n=107)	No History (n=28)	History Only (n=16)	Current (n=23)	No History (n=12)	History Only (n=52)	Current (n=34)	No History (n=16)
Acne vulgaris	8.8	6.5	25.0	18.8	8.7	33.3	6.8	6.0	18.8
Skin cancer	5.9	2.8	3.6	0.0	0.0	0.0	7.7	3.6	8.3
Hypertension †	35.3	38.3	17.9	6.3	34.8	16.7	44.2	38.3	18.8
Angina	5.9	10.3	0.0	0.0	13.0	0.0	7.7	9.5	0.0
Coronary artery disease ‡	8.8	14.0	3.6	6.3	0.0	0.0	9.6	17.9	6.3
Upper gastrointestinal tract ulcer	16.2	25.2	14.3	6.3	21.7	8.3	19.2	26.2	18.8
Cancer of the sites (except skin)	4.4	2.8	0.0	0.0	0.0	0.0	5.8	3.6	0.0

* All comparisons of the three chloracne categories, both for the total group and for the two age groups, were found to be not significant by χ^2 test for independence in contingency tables.

† .01<p<.05 for history only, young vs. old by χ^2 test for independence in contingency tables.

‡ .05<p< 10 for current, young vs. old by χ^2 test for independence in contingency tables.

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TABLE C- 6 - SIGNIFICANT CLINICAL FINDINGS VS. EXPOSURE STATUS AND BY AGE

Findings	Exposed % (n=203)	Not Exposed % (n=163)	Age <50 yr. %		Age >50 yr. %	
			Exposed (n=51)	Not Exposed (n=100)	Exposed (n=152)	Not Exposed (n=63)
Chloracne *	52.7	0.0	45.1	0.0	55.3	0.0
Acne vulgaris † ‡ §	2.0	11.7	7.8	18.0	0.0	1.6
Actinic elastosis ¶ #	59.1	30.1	37.3	18.0	86.4	49.2
Basal cell epitheloma §	6.9	4.3	2.0	0.0	8.6	11.1
Peyronies's disease	1.5	0.0	0.0	0.0	2.0	0.0
Hirsutism	5.4	1.8	3.9	1.0	5.9	3.2

* $p < .0001$; p value for Mantel-Heenazel comparison of exposed vs. not exposed across age strata.

† $.05 < p < .10$; p value for Mantel-Heenazel comparison of exposed vs. not exposed across age strata.

‡ $.0001 < p < .01$; in exposed, young vs. old, by Fisher's exact test.

§ $.001 < p < .01$; in exposed, young vs. old, by Fisher's exact test.

|| $.0001 < p < .001$; p value for Mantel-Heenazel comparison of exposed vs. not exposed across age strata.

¶ $.0001 < p < .001$; in exposed, young vs. old, by Fisher's exact test.

$p < .0001$; in exposed, young vs. old, by Fisher's exact test.

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TABLE C-7 - SIGNIFICANT CLINICAL FINDINGS VS. CHLORACNE STATUS IN EXPOSED ONLY AND BY AGE

Findings	Age <50 yr.			Age >50 yr.					
	History Only (n=68)	Current (n=107)	No History (n=28)	History Only (n=16)	Current (n=23)	No History (n=12)	History Only (n=52)	Current (n=34)	No History (n=16)
Acne vulgaris *	1.5	0.0	10.7	6.3	0.0	25.0	0.0	0.0	0.0
Actinic elastosis * † ‡	47.1	74.8	28.8	31.3	56.3	8.3	51.9	79.8	43.8
Basal cell epitheloma	5.9	8.4	3.6	6.3	0.0	0.0	3.8	1.2	6.3
Hirsubam †	0.0	10.3	0.0	0.0	8.7	0.0	0.0	10.7	0.0

* .01<p<.05; for overall differences between the three chloracne categories in age 49 years or younger, by χ^2 test for independence in contingency tables.

† .0001<p<.01; .01<p<.05; for overall differences between the three chloracne categories in age 49 years or younger, by χ^2 test for independence in contingency tables.

‡ .01<p<.05; in exposed, young vs. old, by Fisher's exact test.

§ .05<p<.10; in exposed, young vs. old, by Fisher's exact test.

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TABLE C-8 - EXPOSURE VS. PLASMA LIPIDS

Plasma Lipids	n	Exposed $\bar{x} \pm SE$	% Out of Range	n	Not Exposed $\bar{x} \pm SE$	% Out of Range	p value
Cholesterol	200	211.15 $\pm$ 2.53	7.5	163	204.07 $\pm$ 2.97	10.4	NS
Triglycerides	200	149.88 $\pm$ 7.44	14.5	163	159.63 $\pm$ 7.73	19.0	NS
Low-density lipoprotein cholesterol	196	136.74 $\pm$ 2.40	7.7	159	127.06 $\pm$ 2.80	6.3	NS
High-density lipoprotein cholesterol	200	45.63 $\pm$ 0.91	9.5	163	44.22 $\pm$ 0.77	10.4	NS

* Reference ranges for plasma cholesterol, triglyceride, and low-density lipoprotein cholesterol were defined as less than the age-specific 90th percentile as determined by the National Lipid Research Project. Reference ranges for high-density lipoprotein cholesterol were defined as above the age-specific tenth percentile as determined by the National Lipid Project.

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TABLE C-9 - CHLORACNE STATUS IN EXPOSED ONLY VS. PLASMA LIPIDS

Plasma Lipid	History Only			Current			No History		
	n	$\bar{x} \pm SE$	% Out of Range	n	$\bar{x} \pm SE$	% Out of Range	n	$\bar{x} \pm SE$	% Out of Range
Cholesterol	67	215.18 $\pm$ 4.67	11.9	105	210.23 $\pm$ 3.17	4.8	26	204.95 $\pm$ 7.13	7.1
Triglycerides	67	144.00 $\pm$ 14.88	7.6	105	153.84 $\pm$ 9.39	19.1	26	149.11 $\pm$ 18.35	14.3
Low-density lipoprotein cholesterol †	96	142.64 $\pm$ 4.69	15.2	103	134.48 $\pm$ 2.98	2.9	27	130.96 $\pm$ 7.06	7.4
High-density lipoprotein cholesterol ‡	67	45.64 $\pm$ 1.17	3.0	105	44.93 $\pm$ 1.31	14.3	28	47.75 $\pm$ 3.31	7.1

* Reference ranges for plasma cholesterol, triglyceride, and low-density lipoprotein cholesterol were defined as less than the age-specific 90th percentile as determined by the National Lipid Research Project. Reference ranges for high-density lipoprotein cholesterol were defined as above the age-specific tenth percentile as determined by the National Lipid Project.

† $p < .015$; for comparing frequency of out-of-range levels in the three chloracne groups.

‡ $p < .05$; for comparing frequency of out-of-range levels in the three chloracne groups.

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TABLE C-10 —Exposure v Pulmonary Function Findings by Smoking Status

Pulmonary Function Parameter	Smoking Status	Exposed		Not Exposed		P Value	Results of Logistic Regression on Pack-Years Smoked	
		n	% Abnormal	n	% Abnormal		Odds Ratio	P Value
FEV ₁ *	Never	38	5.1	40	5.0	NS	...	...
	Former	88	11.2	77	8.2	NS	...	...
	Present	74	27.0	48	4.4	.0025	...	...
	Total†	200†	16.8	162	4.9	.0013	2.81	.0150
FVC*	Never	38	5.1	40	12.5	NS	...	...
	Former	88	15.7	77	8.5	NS	...	...
	Present	74	26.7	48	2.2	.0008	...	...
	Total†	200†	17.2	162	6.8	.0006	2.25	.0318
FEV ₁ /FVC %	Never	38	5.1	40	2.5	NS	...	...
	Former	88	12.4	77	5.2	NS	...	...
	Present	74	25.7	45	6.7	.0143	...	...
	Total†	200†	16.8	162	4.8	.0013	2.87	.0099
FEF ₂₅₋₇₅ *	Never	38	7.7	40	7.5	NS	...	...
	Former	88	18.1	77	13.0	NS	...	...
	Present	74	38.5	45	11.1	.0035	...	...
	Total†	200†	23.2	162	11.1	.0036	1.88	.0517

*FEV₁ indicates forced expiratory volume in 1 s; FVC, forced vital capacity; FEF₂₅₋₇₅, forced midexpiratory flow rate.
 †Unknown smoking status, two subjects, one whose pulmonary function test result was normal and is included in the total.

TABLE C-11 —Exposure Group Means of Percent-Predicted Pulmonary Function Parameters Adjusted for Smoking Status

Pulmonary Function Parameter	Smoking Status	Exposed $\bar{X} \pm SE$	Not Exposed $\bar{X} \pm SE$	P
FEV ₁ *	Never	107.12 $\pm$ 3.06	105.93 $\pm$ 3.03	NS
	Former	101.43 $\pm$ 2.03	104.98 $\pm$ 2.18	NS
	Present	89.63 $\pm$ 2.22	102.33 $\pm$ 2.85	0.0005
	Total	99.39 $\pm$ 1.43	104.42 $\pm$ 1.57	0.0184
FVC*	...	92.73 $\pm$ 1.17	97.80 $\pm$ 1.28	0.0054
FEV ₁ /FVC %	...	76.49 $\pm$ 0.83	79.83 $\pm$ 0.68	0.0002
FEF ₂₅₋₇₅ *	...	101.00 $\pm$ 4.02	109.16 $\pm$ 4.39	NS

*FEV₁ indicates forced expiratory volume in 1 s; FVC, forced vital capacity; FEF₂₅₋₇₅, forced midexpiratory flow rate.

TABLE C-12 —Mean Nerve Conduction Velocity* for the Exposure Groups and for the Chloracne Subgroups

Category	Nerve Tested		
	Ulnar	Peroneal	Sural
Exposed† $\bar{X} \pm SE$ (n)	55.90 $\pm$ 2.36 (9)	41.77 $\pm$ 0.47 (160)	42.06 $\pm$ 0.49 (150)
Not Exposed $\bar{X} \pm SE$ (n)	61.91 $\pm$ 2.36 (9)	42.62 $\pm$ 0.52 (134)	41.48 $\pm$ 0.54 (128)
Chloracne, history only† $\bar{X} \pm SE$ (n)	56.92 $\pm$ 5.02 (3)	40.68 $\pm$ 0.77 (50)	41.14 $\pm$ 0.90 (51)
Chloracne, current $\bar{X} \pm SE$ (n)	57.85 $\pm$ 4.11 (5)	41.32 $\pm$ 0.59 (86)	41.37 $\pm$ 0.75 (74)
Chloracne, never $\bar{X} \pm SE$ (n)	62.10 $\pm$ 0.00 (1)	40.81 $\pm$ 1.12 (24)	41.23 $\pm$ 1.30 (25)

*Adjusted for age.

†P equals not significant for comparison of exposed with not exposed with respect to ulnar, peroneal, and sural, and also for comparison of the three chloracne categories with respect to ulnar, peroneal, and sural.

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- Of the 25 subjects reporting a positive cancer history. 11(44%) reported bladder cancer; all had had occupational exposure to 4-aminobiphenyl. Skin cancer was reported by 12 subjects, none categorized as melanoma. (See Table C-19 for a summary of the reported cancer cases for this study cohort.)
- Statistically significant differences between those with and without chloracne were found for reported symptoms of muscle pain, insomnia, decreased libido, sexual dysfunction (difficulty with erection or ejaculation), and eyelid cysts.
No significant differences were found between those with and without chloracne for the following symptoms: joint pain, abdominal pain, nausea, vomiting, diarrhea, constipation, weakness, fatigue, irritability, nervousness, depression, numbness, vertigo, lightheadedness, or personality change. (See Table C-20 for a review of symptoms by age and chloracne status.)
- Neurological examination showed a statistically significant higher prevalence of abnormal sensory findings in those with chloracne.
- Increased prevalence of reported sexual dysfunction and decreased libido in those with chloracne compared to those without was statistically significant after age adjustment.
- No differences were found between those with and without chloracne in serum cholesterol, total urinary porphyrins, or in reproductive outcome. (See Table C-21 for a summary of reproductive outcome versus chloracne status.)

Moses concluded from the study results that, "Exposure to TCDD in 2,4,5-T production may result in apparently permanent changes in the skin. Sensory changes in peripheral nerves and possible changes in liver metabolism in those with current or past chloracne are suggested by the data as well. Based on worker histories, even severe acute toxicological effects of TCDD were reversible or markedly improved over time. While the cross-sectional nature of the study, the low participation rate, and the highly select nature of the population, limit the conclusions that can be drawn, it is unlikely that permanent, severe, and debilitating toxicological sequelae are inevitable after exposure to TCDD sufficient to produce chloracne. It must be noted, however, that individual susceptibility may make certain workers with heavy exposure more vulnerable."

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TABLE C-14- Duration of Employment in Years by Chloracne Status

No. of years employed	Chloracne	No chloracne	Total
1-10	5 (4%)	13 (13%)	18 (8%)
11-20	28 (24%)	37 (34%)	65 (29%)
21-30	39 (33%)	22 (20%)	61 (27%)
30+	45 (39%)	37 (34%)	82 (36%)
Total	117(100%)	109(100%)	226(100%)
Mean $\pm$ SD ^a	27.0 $\pm$ 8.9	22.9 $\pm$ 11.0	24.8 $\pm$ 10.2

^aStudent's t-test of difference between the two groups: t = 25.2, p < .001.

TABLE C-15- Age by Chloracne Status

Age in years	Chloracne	No chloracne	Total
20-39	12 (10%)	23 (21%)	35 (15%)
40-59	57 (49%)	49 (45%)	106 (47%)
60+	48 (41%)	37 (34%)	85 (38%)
Total	117(100%)	109(100%)	226(100%)
Mean $\pm$ SD ^a	55.9 $\pm$ 11	52.1 $\pm$ 14	54.1 $\pm$ 13

^aStudent's t-test of difference between the two groups: t = 16.6, p < .001.

TABLE C-16 - NUMBER OF CHLORACNE CASES BY DATE

Date of Occurrence	Number of Cases
1949 or before	45
1950 - 1954	35
1955 - 1959	7
1960 - 1964	14
1965 - 1969	12

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TABLE C-17 -

Prevalence of Abnormal Serum Chemistries and Abnormal Total Urinary Porphyrins and Mean Values by Chloracene Status*

Test	No. abnormal		χ^2	Chloracene (N = 105)		No chloracene (N = 101)		Student's t-test
	Chloracene (N = 105)	No chloracene (N = 101)		Mean $\pm$ SD	Min-Max	Mean $\pm$ SD	Min-Max	
GGT ^a			6.49					2.99
> 29 IU	22(23%)	9 (9%)	p < .025	26.3 $\pm$ 27	4- 196	17.4 $\pm$ 11	3- 70	p = .003
Triglycerides ^b			b					1.6
> 190 mg/dl	23(24%)	18(19%)	b	153.6 $\pm$ 114 ^c	35- 1002 ^d	132.3 $\pm$ 66	31-333	p = .056 ^e
Cholesterol			b					b
> 265 mg/dl	4 (4%)	4 (4%)	b	208.1 $\pm$ 34	141- 311	207.8 $\pm$ 33	117-297	b
SGPT			b					b
> 45 IU	4 (4%)	2 (2%)	b	15.9 $\pm$ 13	1- 93	15.7 $\pm$ 13	1-104	b
SGOT			b					2.96
> 41 IU	3 (3%)	0 (0%)	b	21.3 $\pm$ 9	6- 47	18.5 $\pm$ 5	10- 38	p = .002 ^d
Alkaline phos.			b					c
> 110 IU	3 (3%)	7 (7%)	b	75.8 $\pm$ 21	30- 182	77.8 $\pm$ 22	35-146	c
Urinary porp. ^f			b					c
> 300 nm/g creat.	2 (2%)	2 (2%)	b	97.1 $\pm$ 208 ^g	3-2,072 ^h	79.5 $\pm$ 67	17-104	c

*Twenty subjects whose weekly alcohol consumption was ≥ 9 oz (equivalent to 24 beers) or who were past or current problem drinkers were excluded, 12 with chloracene, 8 without.

^bBased on N = 97 chloracene, N = 97 no chloracene, excluding diabetics and subjects on drugs known to induce GGT.

^cNot statistically significant.

^dOne-tailed test.

^eNot significant by Wilcoxon rank test.

^fBased on N = 100 with chloracene and N = 96 without.

^gWith outlier removed, mean 77.9 $\pm$ 59, range 3-407.

^hWith outlier removed, mean 144.7 $\pm$ 73 range 35-445, p = .108.

TABLE C-18
Reported Myocardial Infarction and Angina* by Age and Chloracne Status

Age	Myocardial infarction (MI) ^a				Angina ^b				Total in age group
	Chloracne		No chloracne		Chloracne		No chloracne		
	MI	No MI	MI	No MI	Angina	No angina	Angina	No angina	
40-49	3	20	0	18	3	20	1	17	41
50-59	4	32	2	26	5	31	1	29	66
60-69	6	31	4	24	7	30	5	23	65
70+	4	6	1	8	2	8	0	9	19
Total	17	99	7	76	17	99	7	76	191

*Based on physician assessment if condition currently present.

^aMantel-Haenszel age adjusted $\chi^2 = 1.99$, $p > .10$.

^bMantel-Haenszel age adjusted $\chi^2 = .932$, $p = .35$.

TABLE C-19
History of Cancer Reported by 25 Subjects *

Subject No.	Site	Year of diagnosis	Age at diagnosis	Subject No.	Site	Year of diagnosis	Age at diagnosis
1	Bladder	1949	35	6 ^a	Skin	1953	52
2	Bladder	1959	35	16	Skin	1970	59
3 ^b	Bladder	1964	57	17	Skin	1974	45
4	Bladder	1971	76	18 ^c	Skin	1974	55
5	Bladder	1973	48	19	Skin	1976	54
6 ^d	Bladder	1975	64	20 ^d	Skin	1976	64
7	Bladder	1976	50	21	Skin	1978	43
8	Bladder	1976	43	3 ^a	Skin	1978	71
9	Bladder	1977	51	22	Kidney	1958	34
10	Bladder	1977	67	23	Larynx	1964	50
11	Bladder	1978	60	20 ^b	Larynx	1966	54
12	Skin	1958	48	18 ^b	Lymphoma	1973	54
13	Skin	1958	45	24	Bowel	1975	56
14	Skin	1958	45	25	Leukemia	1979	81
15	Skin	1959	41	25	Prostate	1979	81

^aSubject also had bladder cancer.

^bSubject also had skin cancer.

^cSubject also had lymphoma.

^dSubject also had laryngeal cancer.

* Note: bladder cancer was a result of exposure to 4-aminobiphenyl.

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TABLE C-20- Review of Symptoms by Age and Chlornene Status

Age	Muscle pain		Insomnia		Decreased libido		Sexual dysfunction ^a		Eyelid cysts		Total in age group	
	Chlor- acne	No chlor- acne	Chlor- acne	No chlor- acne	Chlor- acne	No chlor- acne	Chlor- acne	No chlor- acne	Chlor- acne	No chlor- acne	Chlor- acne	No chlor- acne
20-29	0	0	1	0	0	0	0	0	0	1	1	6
30-39	1	1	1	3	0	2	1	3	1	1	10	18
40-49	3	2	6	2	7	0	6	1	3	0	23	18
50-59	5	0	9	2	11	15	14	4	7	0	36	30
60-69	7	1	8	6	14	5	14	7	6	2	37	28
70+	3	1	4	1	5	1	4	2	1	0	10	19
Total	19	5	29	14	37	13	39	17	18	4	117	109
χ^2 ^b	7.39 p < .005		5.20 p > .025		8.24 p < .005		8.94 p < .005		7.59 p < .005			

^aPositive response to difficulty with erection and/or ejaculation currently or anytime in the past

^bMantel-Haenszel age adjusted test.

TABLE C-21- Reproductive Outcome by Chlornene Status Before and After 1948

	Pregnancies	Live births	Spontaneous abortions	Stillbirths	Birth defects	Male/female ratio
Prior to 1948						
Chlornene (N = 107)	185	170	9(1.86) ^a	6(1.24) ^a	3(1.76) ^b	1.3
No chlornene (N = 91)	94	89	4(4.26) ^a	1(1.06) ^a	2(2.25) ^b	1.1
1948 and after						
Chlornene (N = 107)	235	221	14(5.96) ^a	0	11(4.97) ^b	0.96
No chlornene (N = 91)	203	188	14(6.90) ^a	1(0.49) ^a	7(3.72) ^b	1.1
Total	717	668	41(5.72) ^a	7(1.12) ^a	23(3.44) ^b	1.1

^aRate per 100 pregnancies.

^bRate per 100 live births.

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 during their course of employment with Monsanto Company. Both workers were cigarette smokers.

Case 1 -

Case 1 was born in 1920 and died in 1978 of a malignant fibrous histiocytoma. He had hired into Monsanto in 1946 and was first exposed to 2,3,7,8-TCDD in 1948. He had developed a definite case of chloracne. (This case was identified by Zack to have occurred at Monsanto's Nitro, West Virginia plant.)

Case 2 -

Case 2 was born in 1923 and died in 1972 of a liposarcoma. He had hired into Monsanto in 1946 and was first exposed to 2,3,7,8-TCDD in 1950 while working in a plant producing 2,4,5-T (plant not identified). While no history of chloracne was reported, it cannot be discounted.

Dr. Cook, also noted in his report that 2 Dow workers who had been potentially exposed to 2,3,7,8-TCDD also developed soft tissue sarcomas (See Section P 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.

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D. Company: Not Available
Location: Nordrhein, Westfallen/W. Germany
Date: 1949
References: 4, 21, 28, 31, 34, 86, 112

1. Process Information

Both pentachlorophenol and trichlorophenol (experimentation only) were manufactured in this plant between August 1948 and February 1949.

The pentachlorophenol process used was described by Baader as follows:

"In the technical production of pentachlorophenol, chlorine and partially chlorinated benzol are vaporized and brought to reaction in a quartz tube. The reaction product is finely dispersed hexachlorobenzol, hydrogen chloride, and chlorine. Hexachlorobenzol is extracted and mixed with sodium hydroxide, with which it reacts at a temperature of 240°C to form the sodium salt of pentachlorophenol. Free pentachlorophenol is obtained by the reaction of the sodium salt with dilute hydrochloric acid. The final product is centrifugalized, dried, and filled into barrels."

No capacity information was cited.

The process followed for the experimental production of trichlorophenol was not reported. Production of pentachlorophenol and trichlorophenol ceased in February 1949. The equipment used was dismantled.

2. Incident Description

All cases were attributed to occupational exposure. The specifics were not given.

3. Human Exposure and Illness

a. Industrial Hygiene

Worker job descriptions, the duration and nature of their exposures, exposure concentration, and protective devices used by the workers (if any) were not available in the references used. Therefore, no assessment of the worker's exposure to the chemicals, and dose(s) received can be made.

b. Initial Medical Report

Brinkmann in 1950 and Baader in 1951 reported on 17 workers in this pentachlorophenol/trichlorophenol plant who had filed worker's compensation claims for illnesses acquired while on the job. All of the workers had been involved with the chemical processing and packaging of the pentachlorophenol, while only some of them were involved with the trichlorophenol experimentation.

The symptomology exhibited by these 17 workers upon examination included:

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- 17 cases had chloracne, almost all exhibited severe skin eruptions with pustular infections, furunculosis and in some hyperpigmentation. 4 cases were very severe; 8 severe; and 5 moderate to mild.
- 4 cases of bursitis at the elbow.
- 11 cases of bronchitis. Irritation to the upper respiratory tract, irritation of the nasal mucosae, coughing, sneezing and chest oppression was reported by all the men to have occurred during work. These symptoms usually subsided within a few hours after leaving work. 7 cases of chronic bronchitis were cited, but these, too, subsided in all but 2 cases within a few weeks after the process was shut down. Baader attributed these symptoms to occupational exposure to pentachlorophenol and hexachlorobenzene since they subsided when exposure ended.
- 5 cases myocardial damage.
- 2 cases liver cirrhosis (1 fatal).
- 9 cases exhibited symptoms of neuritis: 7 cases of strong pains and weakness in the lower extremities; 4 cases of sensibility disturbances; 2 cases of mild paresis without atrophy; and 2 cases weakening of the Achilles reflexes. (Baader in 1951 questioned whether these were indeed true cases of neuritis or neuralgia.)
- 7 workers complained of psychic difficulties such as tiredness, depression, decreased energy, nervousness, mild headaches, disturbances of sleep, and a decrease in libido and potency.

4. Medical Follow-up of Exposed Group

Dr. Brinkmann first examined these cases in 1950. A year later Drs. Baader and Bauer reviewed the case histories of the affected workers and conducted exams on 10 of them. The results of these studies were reported in Section 3 above.

No other medical follow-up studies, mortality or morbidity studies have been published on this group of workers.

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E. Company: Not Available
Location Nordrhein, Westfallen/W. Germany
Date: 1952
References: 21, 28, 31, 34, 86, 112

1. Process Information

2,4,5-trichlorophenol was manufactured in two plants in the Middle-Rhein by the saponification of 1,2,4,5-tetrachlorobenzene by treatment with alcoholic sodium hydroxide. Other process information was not reported in the literature.

It should be noted that although many references cite this incident as having occurred at Nordrhein, Westfallen/West Germany, Bauer cited it as having occurred at two works in the Middle-Rhein. The names of the companies were not identified.

2. Incident Description

All cases were reported as being a result of occupational exposure during normal production operations. No other information was available in the literature.

3. Human Exposure and Illness

a. Industrial Hygiene

No industrial hygiene information, eg., employee work history records, chemicals exposed to, duration of exposure, exposure levels, etc., was reported in the literature for this cohort. Therefore, an assessment of worker exposure and dose cannot be made.

b. Initial Medical Report

60 cases of chloracne were reported by Bauer (originally cited by Hergt) as having occurred as a result of this incident. Other health effects were reported to have appeared only a long time after the exposure at work was discontinued. These included delayed psychopathic illnesses and permanent damage (unspecified in reference used).

4. Medical Follow-up of Exposed Group

No other medical follow-up studies, morbidity studies or mortality studies could be found in the literature on this group of workers.

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F. Company: Boehringer
Location: Hamburg/West Germany
Date: 1952-1953
Reference: 21, 28, 29, 31, 41, 67, 83, 86, 97, 112, 118

1. Process Information

2,4,5-T was manufactured at Boehringer's Hamburg facility from technical grade 2,4,5-trichlorophenol (TCP) received from their main plant in Ingelheim. The process was basically a manual, and non-closed system with only basic hygienic precautions taken.

The flaked technical TCP received from the Ingelheim plant was manually charged by the workers into the reaction vessel (autoclave) by shoveling from open drums. Dust clouds were generated from this operation and often spread about the room.

According to Bauer, the 2,4,5-T was produced by heating the 2,4,5-TCP with sodium hydroxide and monochloroacetic acid in the autoclaves. After completion of the reaction the end product was purified by double recrystallization. The final solid product was centrifuged to remove it from the reaction mixture. One reference indicated that esters of 2,4,5-T were also manufactured in this plant.

Other detailed information, eg., capacity, process equipment, process design, reaction parameters, etc., were not given in the published literature.

2. Incident Description

All 31-37 cases of worker health problems were attributed to occupational exposure during normal operation. (Exact number of cases cited differed by the literature source used.)

3. Human Exposure and Illness

a. Industrial Hygiene

No detailed industrial hygiene information, eg. employee work history, exposure levels, chemicals exposed to, exposure duration, protective clothing used, etc., was identified by which an assessment of worker exposure and the dose received to various chemicals can be made. However, it is obvious from the process description given by Bauer (See Section 1 above.) that worker exposure throughout the various process steps must have been significant. Bauer also indicated that the workers with the more severe cases of chloracne were those who had significant contact with the technical 2,4,5-TCP.

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b. Initial Medical Reports

31 cases of chloracne, characterized by comedones, retention cysts, follicular hyperkeratosis, inflammatory nodules, pustules and furuncles, were reported to have occurred as a result of occupational exposure in this plant. 9 of the cases were severe and persisted for many years, even after exposure had ceased. 14 cases were moderately affected, and 8 were considered mild. The workers who had the most significant exposure also developed erythema and edema of the face prior to the onset of chloracne. The face, earlobes, throat, and neck were affected in all cases, while the chest, back, abdomen, the extensor sides of the arms and legs, and the genitals were often affected in the more severe cases.

Other symptoms included: blepharo-conjunctivitis, anorexia, weight loss, intolerance to certain foods and alcohol, increased perspiration, sleep disorders, dyspnea, forgetfulness, mood changes, tendency to collapse, fatigue, and weakness in the legs. Initial clinical exams indicated no internal damage to the liver, kidneys, central nervous system, or hematopoietic systems. However, liver damage was found in 3 patients several weeks later.

4. Medical Follow-up of Exposed Group

Two medical follow-up studies were found on this group. The first was conducted 5 years after onset of illness and includes medical examinations of 9 out of the 31 original cases. The other study, follows 10 of the 31 cases for a period of 15 years. The major findings of these reports are given below.

a. Five Year Follow-up Study

Five years after this incident the 9 workers with severe cases of chloracne out of the group of 31 were still under medical treatment. Their chloracne which was found difficult to treat extended over the face, neck, auricle area, back, chest, underarms, genitals and hips. Hyperpigmentation and scar-formation was also noted. Besides the dermatologic symptoms the following disturbances, to various degrees, were found.

- Neuro-muscular - All 9 cases complained of tiredness, weakness and pain in the lower extremities. 2 cases of paraesthesia was found. No cases of paresis or atrophy were found. No signs of neurogenous damage was detected by electro-myogram. The examiners concluded that from the results, the neuro-muscular complaints could not be classified as either polyneuritis or polyneuropathy.

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- Internal organs - Blood pressure was normal in all cases. 2 cases of myocardial damage. 5 cases indicated pain and pressure in the region of the stomach and liver. 4 cases of GI tract disturbances found: 3-subacidity, 1-hyperacidity and gastritis. (Also anorexia, intolerance to certain foods and alcohol.) 2 cases indicated abnormal liver function tests, and 3 showed abnormal liver biopsies. Vegetative over excitability was indicated in 5 cases (trembling hands, increased sweating, and increased dermographia).

- Psycho-vegetative syndrome -

Subjective disturbances - Headaches, dizziness, orthostatic collapse, disturbance of vital sensations, disturbance of psychic basic mood and affectivity, uneasiness, anxiety, lack of initiative, both physical and mental weakness, inability to concentrate, loss of memory, sleep disturbances, somnolence, decreased libido, decreased potency, lack of appetite, irritability, hypochondria, entdifferntiation of personality.

Objective-psychopathologic findings - Certain level of acquired mental defficiency evidenced by the Hamburg-Wechsler test. Results of the Rorschach psychogram indicated coartation of experience type, signs of weakened emotional reactivity, weakness of concentration, reduction of pace, slowness of the thinking process, and tendencies to perversion.

Concerning the psycho-vegetative syndrome, 2 of the 9 patients showed considerable psychopathic or neurotic structure elements. The others did not, and there appeared to be a tendency for improvement in their subjective and objective symptoms.

b. Fifteen Year Follow-up Study

Kleu and Goltz conducted medical case histories and examinations of the same 9 patients examined by Bauer (see Section 4.a. above) plus one additional worker from the plant who exhibited psycho-pathological symptoms for the first time in 1961. Although their report discusses the chronological development of symptoms for these workers over a period of 15 years, only the 15 year results will be presented here.

8 out of 10 workers were examined again in 1968 and 1969, 15 years after the onset of symptoms. One of these workers in the course of examination died at the age of 61 of a myocardial infarction. Substantial cerebral sclerosis was also detected upon autopsy. The symptoms exhibited by this worker were not substantially different immediately prior to his death than before. He complained of exhaustion, forgetfullness, depressive psychosis, paresthesia, low endurance, and headaches.

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His objective behavior was not depressive and lacking in drive, as the others were, but was euphoric, lacked distance and showed increased drive.

The symptoms exhibited by the other 7 workers examined were noted after 15 years to follow a uniform pattern. These symptoms are outlined below.

- Dermatological - No further information provided on the condition of the worker's chloracne.
- Neuro-muscular - 6 workers still complained of muscle weakness and 3 of paresthesia. Other symptoms in this category were considered insignificant and could be attributed to primary or age induced changes.
- Internal organs - Vegetative over excitability consisting of finger tremors, excessive sweating and dermatographia persisted in most cases. 3 cases of sexual dysfunction were noted. No other information was provided on the condition of the internal organ systems.
- Psycho-vegetative syndrome -

Subjective Complaints - Muscle weakness (6 cases), dyspnea (7 cases), impotency (4 cases), sexual dysfunction (3 cases), 3 cases complained of exhaustion, sleep disorders, irritability, nervousness, forgetfulness, loss of appetite, loss of drive and interest, hypochondria, and general anxiety. (These were much the same as indicated 10 years prior to this exam See Section 4.a. above).

Objective findings - An increase in psychiatric symptoms was noted. All cases showed depressive psychosis with loss of drive, lack of vital powers, restlessness and sometimes morose traits. Premature deterioration and forgetfulness were also reported.

Kleu and Goltz concluded that there appeared to be a chronological progression in the symptoms exhibited by workers exposed to TCP which can lead to permanent damage. Several objective conditions were noted, eg., cerebral organic characteristics including affect lability, decompensation, and slight signs of degeneration which resembled premature aging independent of the age of the worker.

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- G. Company: Badischer Anilin and Soda Fabrik (BASF)
Location: Ludwigshaven/West Germany
Date: November 17, 1953
References: 2, 5, 21, 24, 28, 29, 31, 34, 38, 67, 80, 83,
86, 106, 107, 108, 118

1. Process Information

2,4,5-trichlorophenol was produced at BASF by the high temperature/pressure method. 1,2,4,5-tetrachlorobenzene was hydrolized to 2,4,5-trichlorophenol by using sodium hydroxide in a solvent of methanol at 180°C and a pressure of roughly 20 atmospheres. Specific information on process design engineering, process chemistries and the production capacities at the BASF plant have not been published.

After the incident on November 17, 1953, production of the trichlorophenol was ceased. Approximately two years later, after major decontamination efforts had taken place, the manufacture of other chemical substances was started up in the same building. Some of the original equipment, including the autoclaves, were used in the new processes.

Production continued without any incidence of illness until 1958, when a mechanic who had worked in and around the autoclave fell seriously ill. Recognizing that decontamination efforts had not been successful, the building was closed. Ten years later in 1968, it was demolished.

2. Incident Description

The incident at BASF occurred on November 17, 1953. During a routine 2,4,5-trichlorophenol production run an exothermic reaction started in the contents of the autoclave. The temperature and pressure in the autoclave rapidly increased and exceeded the pressure limits of the safety relief valves on the vessel. Consequently, the contents of the autoclave were ejected. This occurred with such force that a nearby steam valve was broken, thereby releasing steam into the area, too. The autoclave room immediately filled with vapors, and thereafter all the rooms in the four story building, and the stairwell which connected the floors were also filled with vapors. After several minutes the vapors dissipated. Those vapors which were not exhausted from the building by the ceiling fans in the roof, condensed to form a whitish film on the instruments, walls, windows, and doors. After the vapors dissipated, workers entered the area to assess the damage and initiate clean-up.

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3. Human Exposures and Illness

Seventy-five (75) workers in all were exposed to the reaction products during the incident, and/or subsequent clean-up activities. Most of the 75 exposed workers developed chloracne in varying degrees of severity. The 42 who initially entered the building after the incident were the most severely affected. In addition to chloracne 14 out of the 42 exhibited internal organ damage, and 7 out of the 42 exhibited disturbances of the nervous system. These illnesses are further discussed in subsections 4 and 5 of this section.

As far as can be discerned from the literature, no industrial hygiene measures were followed by the 42 workers who initially entered the contaminated building after the incident, nor were protective devices used during the initial clean-up and repair of the area. It wasn't until after the first case of chloracne developed (According to the literature the first case developed within a few days after exposure, but was not reported to the medical department until December 3, 1953, 16 days after the incident.) and then repeated cases developed that the use of personal protective equipment was implemented. From this point on, full gas permeable protective suits and respiratory devices (Van Der Grinten masks) were used by all workers entering the building, and working on contaminated equipment.

The use of biological monitors (animals) to assess the extent of contamination in the building was also initiated after the first appearance of dermatitis (chloracne) in the workers. Initial experimentation involved housing caged rabbits in the autoclave room. Since no signs of illness were found in the animals, the hazardous condition caused by the vapors from the explosion was assumed to be gone, and that it was safe to resume repair activities in the building. With the incidence of chloracne in workers who had not been involved with the autoclave room right after the incident, the company recognized that the source of toxic exposure was not just due to vapors but also to a sublimate which had coated the interior of the building. Subsequent tests with rabbits exposed to the interior of the autoclave resulted in the death of some of the animals within 5 days after exposure. Death was attributed to liver necrosis.

After the gravity of the situation was understood extensive decontamination efforts were undertaken. The methods for decontamination and frequency of repeated use varied and continued for several years. These included: whitewashing of walls and equipment; spraying walls and equipment with chlorinated lime solutions; painting instruments and walls with a rust solvent and ferric oxide; covering floors and walls with coats of plastic and/or silicones; washing the autoclaves with sodium hydroxide and water; and boiling the autoclaves, pipes and instruments with benzene, and carbon tetrachloride. These efforts were later found to be insufficient.

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None of the references used in this report indicate whether or not the composition of the reaction mixture released was ever qualitatively or quantitatively identified. Since the contaminant(s) responsible for the worker's health effects were/was not known at the time of the incident, no worker exposure data was collected. Likewise, no detailed work history information for the workers and/or contractors, i.e., job descriptions, exposure duration, time in area, location of task in relation to the autoclave (theoretically highest area of contamination), etc., has been reported. Therefore, no assessment of worker exposure and thereby the dose received for each chemical can be made.

4. Medical Follow-up of Exposed Group

a. Case Studies

Case studies on the 42 severely affected workmen have been described in detail by Goldmann. He divided the cases into three categories exhibiting the same symptoms: i.e., cases only exhibiting chloracne (21 cases); cases with chloracne and internal organ damage (14 cases); and, cases with chloracne and lesions to the central nervous system (7 cases).

Eighteen of these case studies were published by Goldmann in 1972. These case studies are presented below, and for the most part are verbatim from Goldmann's report.

Cases Only Exhibiting Chloracne

There were 21 cases in this category. Chloracne started as an initial facial dermatitis in the area of the ears and cheeks. There was irritation of the conjunctivae with acne slowly developing predominantly in the face but also on the neck, shoulder, trunk, penis, scrotum, and other areas. Almost all cases developed the following symptoms, but to various degrees: comedones, retention cysts, nodules, pustules, furuncles, and abscesses. In addition, two cases exhibited chronic conjunctivitis and blepharitis.

Case A

Case A. had never entered the autoclave room in which the accident had occurred. Occasionally, however, he had sat in the dining room next to fellow workers. He was wearing workclothes and there was no particularly close physical contact. He developed acne on the face and on the forearms. All test results, including a liver test, were negative.

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Case B

The son of a severely affected worker suffered from the facial skin alterations typical of chloracne even though he had never been in the plant. The only cause for his disease was through contact in the home environment with his father and articles his father had used. (His father suffered from severe chloracne and toxic polyneuritis and was hospitalized.)

After the father had entered the hospital the son had slept in his father's bed. He had used handkerchiefs already used by his father and at the onset of the winter colds he had worn several of his father's scarves, one of which had already been washed three times.

Case C

Case C. was afflicted with a great variety of diseases apart from minor blushes in the face and digestive trouble: alcoholism with anacid gastritis, refractory to histamine treatments, sinusitis max. chron., laryngitis, bronchiectasis, cholecystitis, hypothyreosis with myxedema and apoplexia. However, none of the aforementioned diseases was a consequence of the intoxication. Case C and later Case N demonstrate once again that post hoc does not always mean propter hoc.

Case D

The only important aspect of Case D is that extensive and tenacious skin alterations caused by acne vermiculate and cornedosa did cause 2 [illegible] years of work disablement. There were no further internal damages.

Case E

Tenacious abscesses which could reach the size of chicken eggs kept developing, on the penis and scrotum as well as other sites. Comedones and sebaceous cysts could still be found after 18 years.

Case F

Apart from a severe pyretic skin inflammation which left this person incapable of being gainfully employed for five years, case F is remarkable for a chronic conjunctivitis and blepharitis. Since the Meibomian glands which lubricate the margin of the eyelid are related to the sebaceous glands in the skin with respect to the history of their development, their dysfunction had to be considered as another symptom of the chloracne.

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Cases with Dermatitis and Lesions of Internal Organs

Fourteen cases had disorders of internal organs in addition to the skin symptoms. There were four cases of hepatic damage. A characteristic microscopic finding of the biopsy was the storage of an iron-free gray pigment. Furthermore, there were temporary lesions of the heart muscles and toxic nephrosis. Inflammations of the upper air passages with laryngitis, tracheitis and bronchitis were diagnosed in five cases, one of which was complicated by a severe hemorrhagic pleurisy, another one by a tenacious pyretic gingivitis and stomatitis. A number of cases were generally sensitive to infections as a consequence of the diseases, sometimes this was shown as a significant decrease in blood serum gamma globulin. One case died of a typical pancreatitis.

Please note: In regards to this later case, designated below as Case I, current toxicological evidence refutes this death as having been caused by TCDD poisoning. Acute pancreatitis has not been associated with dioxin exposure experiments among lab animals, nor have any of the epidemiologic studies on TCDD exposed humans linked pancreatitis as a symptom of dioxin exposure. This case is considered an incidental finding and can not be verified by current toxicological or epidemiological findings.

Case G (Summary. More complete description in reference.)

Case G was a 20 year old mechanic who had worked in the autoclave room for 3 days. On the second day of work he had headaches, pains in the small of his back, and inflammatory swellings on his face and ears which developed into a typical case of chloracne with perpetually, recidivating finger tip size abscesses.

Furthermore, he suffered from temporary lesions of the heart muscle and the liver, bronchitis and residual damages due to toxic nephrosis. After a latency period of ten years, a rheumatic mitral stenosis developed. Hepatitis accompanied by thrombophlebitis of the lower leg and a pulmonary embolism, led to G.'s death at the age of 30. The mitral stenosis which was developed after a long latency period and the new hepatitis could not be recognized as consequences of the accident.

Case H (Summary. More complete description in text of reference.)

Case H was a 19 year old trained mason who had a history of "vegetative dystonia" prior to his exposure. As a result of working in the autoclave room for two hours walling up a hole in the autoclave enclosure, he developed chloracne.

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Eleven months after his exposure which he had overcome, he suffered a severe hemorrhagic pleurisy, a consequence of the poisoning. Subsequently he recovered completely. The schizophrenia and the suicide, 5½ years later, were not related to the intoxication.

The question of whether the schizophrenia which brought about his tragic end was causally related to his occupational disease is answered negatively in detailed medical reports.

Case I

Please note: This case is presented verbatim from Goldmann's article since it is frequently quoted (or misquoted) as being the first death attributed to dioxin exposure.

In 1958 a 57 year old employee and a colleague of his did some installation work on the autoclave agitator in the same part of the plant where 5½ years earlier an accidental reaction had occurred. In order to lift a cover and put in a new seal he had to burn the screw away with a blowpipe. During the replacement of the agitating mechanism a ball bearing was heated. This lead to the development of vapors. In compliance with the regulations he was wearing protective clothing consisting of a rubber outfit and a gas mask, but he had taken off the mask several times to wipe the sweat off his face. Four days later: burning facial skin, follicular dermatitis, headaches and hearing problems. The liver test was negative. One month later he was hospitalized on ground of a stenocardia. Six months later he had to stay in bed to be treated for pancreatitis. The size of the liver had increased: 1-20F. Temperature: 38.2°C; BSR 35:56 to 82:104; diastasis: 256 to 512 WE. Later a firm tumor in the left epigastral area caused great pain, growing to the size of a child's head. Leuko 18,000, an anacidity which was refractory to histamine treatment, obstinate constipation. 1959: reduced E and A2, somnolence, chills,- maximum temperature 41.0°C, Leuko 21,000. Exitus.

The autopsy showed that the necroses were numerous after the pancreatitis and there were perforations the size of a bean in both stomach and bulbus duodeni. Macroscopy could not determine if calculi had grown in the stomach and the duodenum had occurred. Furthermore, there had been a widespread formation of abscesses on the lower surface of the liver, general cachexia and chloracne on the stem of the liver.

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Summary: The first time patient I. had been exposed to the products of the trichlorophenol decomposition was in 1958, 5 years after the accident had occurred. He was so unprotected from the exposure that he developed an acute skin disease with skin alterations which were typical of the perna disease. It was a sign of the gravity of the primary exposure that these alterations spread to other parts of the body and were still present at the patient's death, 9 months after the contact with the toxin. The patient died of a pancreatitis which the autopsy confirmed. Apart from numerous necroses of adipose tissue, there was a double pea-sized perforation in the middle of the stomach and a duodenal ulcer with penetration into the pancreas. The point of perforation covered the pancreas thus establishing a direct communication between both.

Oettel and colleagues of his had conducted experiments on animals which showed that one single administration of the toxin (5 micrograms kg body weight) was sufficient to cause necrosis of the liver and after weeks or months, brought about the death of the animals. Furthermore, it is known specifically that the products of a trichlorophenol decomposition affect the lipase metabolism which is related physiologically to the pancreas. These considerations lead to the conclusion that the necrosis of the pancreas was most probably a late consequence of the poisoning caused 9 months earlier by the products of the trichlorophenol decomposition. The trade union paid an appropriate indemnity for the necrosis of the pancreas.

Case J

Case J. was an elderly employee with a chronic interstitial cirrhosis of the liver in his medical history. An exposure to the toxic products caused only laryngitis and tracheitis. After an operation on the upper jaws the trade union withdrew the temporary pension of 20% it had been paying for the sinusitis.

Case K

In 1953, Case K had taken a dirty chain hoist from the autoclave room and had worked on it. After that skin eruptions occurred. Lab results: (1954) Takata 30; Gros (illegible); Wuhrmann (illegible); electrophoresis: alph-, beta- and gamma- globulin very high; BSR on March 22, 1954: 22:44. The patient complained of fatigue and dyspepsia. He was disabled until August, 1955. In 1954 he was treated for a hepatolienal syndrome, hepatitis and splenitis, jaundice, fully compensated cirrhosis of the liver, hyperacidic gastroduodenitis and dysfunction of the auditory nerve on the left side.

Two and one-half years after the accident liver dysfunction could no longer be detected.

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Case L

In 1953 L. had spent a very short time loosening screws on the cover of a manhole. Two days later L. displayed dermatitis (chloracne).

L. had lesions of the liver cells and laryngitis. He received compensation for complete disablement. The laryngitis corresponded to a 10% decrease in income. According to experts, in 1967 the liver dysfunction was still responsible for a 20% decrease in earning capacity. The following were not classified as recognized occupational diseases: pneumonectasia, gastritis affecting the esophagus, vegetative dystonia and hardness of hearing on the right side.

Case M

Eight months after the accident, the 43 year old employee M. suffered an acute sinusitis maxillaris on the left side accompanied by a purulent rhinitis. In 1963, the sinusitis maxillaris on the left side chronically recurred. This recidivation could not be considered a consequence of the intoxication. The same holds for the 1963 angiosteosis of the tibialis anterior and posterior arteries. In 1966, there occurred a trophic decalcification of the right wrist. Like M. Sudcek's disease exhibited a wrist sclerosis syndrome and pronounced sclerosis of the blood vessels.

Cases with Dermatitis and Lesions of the Central Nervous System

Seven cases were included in this category. Besides chloracne, the central nervous system was unequivocally affected: i.e., 3 cases diagnosed with peripheral toxic polyneuritis; 2 cases diagnosed with peripheral toxic damage to the auditory, olfactory and gustatory organs; and, 2 cases diagnosed with toxic disseminated encephalomyelitis with a hemisyndrome.

Case N

The clinical findings were as follows: four days after exposure, dermatitis of the thighs, the legs and the feet. There were no dysfunctions of the bladder or the rectum. After seven weeks all neurological symptoms had disappeared. At the end of September, 1954 a toxic polyneuritis started developing.

In N's case there was a neurasthenic syndrome and skin alterations caused by chloracne on the legs, the buttocks and the penis. In addition, there were dysfunctions symptomatic of a toxic polyneuritis with hyporeflexia, hypotonia of the muscular system and hyperalgesia in the saddle block region. For years the results of repeated liver check-ups were negative. A vegetative dystonia and a fixation neurosis were not at all connected with the accident.

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Case O

This 24 year old employee assisted once at a dismantling about six weeks after the faulty reaction. He was wearing appropriate protective clothing. He suffered mild nondisfiguring skin alterations and, most of all, nervous dysfunctions with fatigued legs and irritation of the upper air passages. Fourteen years after the intoxication a subarachnoid hemorrhage occurred. The appraisal determined that this bleeding was independent of the accident, since in 1953 there had been only functional disorder.

Case P

An initial dermatitis on the face, ears, throat, neck, breast and back was later aggravated by the formation of abscesses. A temporary anosmia caused by a peripheral toxic lesion of the nervous olfactorius lasted one year. A pyretic stomatitis and gingivitis recidivated. An organic psychosyndrome with neurosis was diagnosed. Five years after the intoxication of duodenal ulcer had formed, it recurred for 10 years.

Case Q

Q's first skin alterations (chloracne) occurred four days after the accident. Apart from the skin alterations, which in the case of seborrhea led to cheloids on the breast and throat, Q had chronic conjunctivitis and blepharitis as well as a toxic disseminated encephalomyelitis with a spastic hemisyndrome on the left side. In 1971, a hydrops of the right knee joint and a bilateral Dupuytren's contracture occurred, both consequences of the accident.

Case R

R spent a short time working in the autoclave room. After seven weeks R suffered from facial paresis with ageusia of the left side; both were unrelated to the accident. The rest of the findings were of no importance.

b. Mortality Studies

Theiss has conducted two mortality studies on the exposed population at BASF. The first, conducted 24 years after the incident had occurred, was reported in 1977. The second conducted 27 years after the incident, and was reported in 1982. Both studies were 100% successful in their follow-up of the exposed cohort, with 74 persons participating. Since the overall results of these two studies were not appreciably different, only the results of the more recent study will be discussed in this report.

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Of the 74 persons exposed as a result of the 1953 incident; 70 were exposed in 1953, and 4 were exposed for short durations of time a couple years later as a result of the cleaning and testing of equipment which had been involved in the incident. (66 of the 74 exposed persons had developed chloracne.) The observed deaths in the exposed cohort were compared to the expected number of deaths in 3 external comparison groups, and to the number of deaths observed in 2 internal comparison groups.

The external comparison groups included:

- Total population of the town of Ludwigshaven (180,000 persons).
- Total population of the governmental district of Rhinehessia-Palatinate (1.8 million persons).
- Total population of the Federal Republic of Germany (60.5 million persons).

The internal comparison groups were selected at random after having been matched by age and date of entry into the factory. 74 persons were included in each of the internal control groups.

Table G-1 shows a comparison of observed deaths among the TCDD exposed cohort and the two internal control groups by category, along with those expected on the basis of the external comparison groups. The key results from this study are listed below.

- Overall mortality for the TCDD exposed group (21 deaths) did not differ from the rate expected in the three external reference populations or from that observed in the internal comparison groups where 18-20 deaths were observed.
- Of the 21 deaths observed in the TCDD exposed group 7 were from malignant neoplasms, as compared with 4.1 expected.
In addition, two other cases of cancer (one bronchial carcinoma, and one carcinoma of the prostate) were still alive at the time of the study. 5 deaths from malignant neoplasms were observed in each of the internal comparison groups.

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Table G-1: Observed and Expected Deaths in the TCDD Exposed Cohort, Internal Control Groups, and External Comparison Groups

CAUSE OF DEATH	OBSERVED DEATHS			EXPECTED DEATHS ON THE BASIS OF MORTALITY STATISTICS		
	TCDD EXPOSED COHORT	INTERNAL CONTROL GROUP 1	INTERNAL CONTROL GROUP 2	FED. REP. OF GERMANY 1971-1974	RHINEHESIA-PALATINATE 1970-1975	LUDWIGSHAVEN 1970-1975
Malignant Neoplasms	7	5	5	4.09 (p=0.12)	4.12 (p=0.12)	4.22 (p=0.14)
Stomach	3 (64,69,66) ^b	0	1 (61)	0.70 (p=0.034)	0.64 (p=0.027)	0.61 (p=0.024)
Colon	1 (70)	1 (49)	0	0.42 (p=0.34)	0.29 (p=0.25)	0.29 (p=0.25)
Bronchial/lung	3 (56,64,46)	0	1 (55)	1.26 (p=0.13)	1.30 (p=0.14)	1.36 (p=0.16)
Rectum	0	1 (47)	0	N.A. ^a	N.A.	N.A.
Gall Bladder	0	0	1 (73)	N.A.	N.A.	N.A.
Pancreas	0	1 (63)	0	N.A.	N.A.	N.A.
Prostrate	0	0	1 (62)	N.A.	N.A.	N.A.
Urinary tract	0	1 (64)	0	N.A.	N.A.	N.A.
Unknown primary site	0	1 (66)	1 (59)	N.A.	N.A.	N.A.
Soft tissue sarcoma	0	0	0	N.A.	0.02	0.03
Neoplasms of the lymphatic and hematopoietic tissue	0			N.A.	0.29	0.30
Cardiovascular diseases	7	7	6	7.88	7.43	N.A.
All other natural deaths	3	5	5	N.A.	5.41	5.06
Traffic Deaths	2	1	0	7.45 (p=0.17)	0.80 (p=0.19)	0.69 (p=0.15)
Suicide	2	0	3	0.65 (p=0.14)	0.68 (p=0.15)	0.62 (p=0.13)
Natural Deaths	17	17	16	17.64	17.01	16.64
Violent Deaths	4	1	3	1.99 (p=0.14)	2.02 (p=0.15)	1.82 (p=0.11)
Total Deaths	21	18	19	19.64 (p=0.43)	19.03 (p=0.37)	18.46 (p=0.32)

a. N.A. = Not available

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- Although based upon comparatively few deaths, the malignant neoplasms were found to be consistently above expectation. The effect, however, is shown to be beyond chance only for stomach cancer. The observed number of carcinomas of the stomach in the TCDD cohort was significantly higher ($p < 0.05$) compared to that expected in all three reference populations. Two out of three cases were in the age group 65-69, where only 0.20 deaths were expected. Only 1 stomach cancer occurred among 148 individuals in the two internal comparison groups.

Thiess also included in his report a discussion on the limitations of the study. He concluded: "Because of the small size of the cohort and the small absolute number of deaths from any particular cause, the results of this study do not permit any definite conclusions concerning the carcinogenic effects of dioxin exposure. Thus, it would be desirable to identify and study other, larger groups of persons unintentionally exposed to dioxin in order to ascertain the meaning of these results. Nevertheless, the observed incidence of malignant neoplasms, especially of stomach cancer, in the BASF cohort was considerably greater than expected and cannot be adequately explained as a mere chance event."

c. Morbidity Studies

No morbidity studies on this cohort were found in the literature.

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H. Company: Rhone Poulenc
Location: Grenoble/ France
Date: 1953-1971
References: 5, 21, 28, 29, 31, 34, 67, 86, 114, 117, 120, 123

1. Process Information

2,4,5-trichlorophenol was manufactured at the Rhone Poulenc plant between 1953 and 1971. The end use of the trichlorophenol, eg., synthesis of 2,4,5-T herbicides, or hexachlorophene germicides, was not specified in the literature. Detailed information on the process used, eg., chemicals used, conditions of reaction, equipment used, process capacities, etc., were not cited in the literature.

2. Incident Description

Worker exposure to the chloracnegen, 2,3,7,8-TCDD, and other reaction chemicals involved in the manufacture of 2,4,5-TCP at Rhone Poulenc occurred as a result of both occupational exposure during normal production, and as a result of two accidents often referred to as "explosions" in 1956 and 1966. Whether these incidents were indeed actual "explosions" in which the reactor blew apart or were releases of the reactor contents through the vessel's rupture disc as a result of an overpressurization was unclear from the literature sources. Dugois in describing the October 4, 1966 incident did state, "excess pressure caused explosion of piping resulting in pollution of the atmosphere."

One source of occupational exposure resulting in chloracne cases was described by Dugois and Colomb in 1957. They indicated that the process operated without incidence of health problems for many months, until some technical process modifications were made. The changes concerned the method of elimination of the tars and sodium chloride from the 2,4,5-TCP end product. In the original procedure, the tars and salt were drawn off (method not specified; could have been by filtration, phase separation, etc.) when the reaction solution was cold. Since this was a slow method and time consuming, it was modified to use hot water and pressurized steam. While this decreased the time required to perform this task, it also increased worker exposures to vapors, which according to Dugois and Colomb, "bothered the workmen". Apparently the chemists at the plant tried to identify the components of the tar, but failed. Recognizing that K. H. Schultz had identified the chloracnegen (2,3,7,8-TCDD) in the tars from TCP manufacture, Dugois and Colomb commented, "it would seem appropriate to modify the system for removing the residual tars so that it can be done in the open air and the workmen will not be obliged to come near". According to one source, modifications were made in the process which proved to be successful in preventing new cases of chloracne.

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3. Human Health and Illness

a. 1956 Incident

17 workers were exposed and effected in this incident. The duration of exposure, exposure levels (probably not measured), job descriptions of the workers and protective equipment used were not indicated in the literature. Without this information it is impossible to assess the exposures and dose(s) of the chemicals that the workers received.

Although the severity of chloracne varied among the 17 cases, all were characterized by the formation of follicular keratin cysts, atrophied sebaceous glands and comedones. Hyperpigmentation was also noted. It manifested itself on the face (especially around the eyes), around the ears, on the back of the neck and shoulders, around the waist and on the external genitalia. Although various treatments were used, the moderate and severe cases were found not to be completely curable because upon evacuation of the cysts atrophic scars were formed. The severe cases, after having developed over the course of 6 months or more, were even found to go through periods of partial remission, followed by recurrent outbreaks. The cysts were also reported to give off an "intense odeur chlofee".

Besides chloracne, various internal disorders were reported in the workmen. These symptoms were found to correlate with the onset of the cutaneous symptoms, and sometimes also by their severity. These symptoms included: general digestive disorders such as anorexia, weight loss, vomiting and flatulence after eating; hepatic disorders such as liver tenderness and increased lipid levels (These were noted to have returned to normal within a few days to a week.); peripheral neuritis (weakness in limbs, headache); and conjunctivitis in about 50% of the cases. The renal and endocrine systems were noted not to have been affected.

b. 1966 Incident

Dugois also reported on the symptoms exhibited by workers in the 1966 incident. He noted, that prior to the incident there had been no signs of cutaneous lesions in the workers. However, after the incident individuals within the 2,4,5-TCP area and neighboring areas came down with chloracne. The exact number of cases which developed was not cited, however, 21 cases were examined.

Initial symptoms of exposure included erythema, edema and a burning sensation to the face. These lasted but a few days and were probably due to the irritant nature of the released chemicals. Within a few weeks, the typical lesions of chloracne evolved on the face, the chest, sometimes on the shoulders and on the limbs. Although the infected lesions responded well to treatment, the chloracne lesions persisted one year after the incident.

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In addition to chloracne, pain in the region of the right hypochondrium (area of the liver) was reported in many cases.

Little information was presented in the literature on either the industrial hygiene conditions which existed in the plant at the time of this incident. The parameters required to determine worker exposure and dose were also not available. No mention was made as to the use of protective equipment by the workers who reentered the area for clean-up activities. Likewise, no worker exposure measurements to the released chemical, if any were taken, were published. Work history information was also scant. It was mentioned that some of the workers who entered the area a few days after the incident were maintenance men and painters, and that most of the men had only remained in contact with the chemicals in the area for a short duration of time, up to several hours.

c. Occupational

According to Hay the poor industrial hygiene conditions in the plant between 1953 and 1971 increased the number of workers affected by dioxin exposure to around 100. No other details were given.

4. Medical Follow-up of Exposed Group

There has been no further studies published on this group concerning their mortality and/or morbidity experience, or medical follow-up.

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- I. Company: Boehringer
Location: Ingelheim/West Germany
Date: 1954
References: 21, 28, 31, 34, 67, 83, 86, 104, 112

1. Process Information

2,4,5-trichlorophenol was produced at Boehringer's Ingelheim plant by the alkaline hydrolysis of 1,2,4,5-tetrachlorobenzene with sodium hydroxide in a solvent of methanol at approximately 180°C and 19.5 atmospheres pressure. The 2,4,5-TCP product was drummed and sent to the Hamburg plant for further processing to make 2,4,5-T and its esters.

In around 1957, the process was modified to accommodate a lower reaction temperature, 157°C. This came about by experimentation and collaboration between Sorge, a chemist at Boehringer, and Schulz, of the department of dermatology at Eppendorfer Krankenhaus. Schulz had determined that 2,3,7,8-TCDD was responsible for the incidence in chloracne cases. Sorge recognized that TCDD could be a contaminant formed during TCP production, and that its formation was temperature dependent. Reportedly, since the low temperature method was initiated no new cases of chloracne occurred.

Other detailed process information, eg., process design, process equipment, reaction parameters, capacity, etc., for this time frame was not cited in literature. For additional process information after the low temperature method took effect in 1957, see reference 83 by Varhenholt.

2. Incident Description

All cases of worker illness were attributed to occupational exposure during normal operations.

3. Human Exposure and Illness

a. Industrial Hygiene

Somewhere between 24 and 31 workers became ill from working on this process (number varies by reference). All were involved with the synthesis of the trichlorophenol, and worked either in the plant at the mixing unit or in the laboratory analyzing samples. The average length of employment in the TCP department for these workers was 2 years, with a range between 3 months and 6 years.

Other detailed industrial hygiene information, eg., employee work history, exposure levels, chemicals exposed to, exposure duration, protective clothing used, etc., from which an assessment of worker exposure and dose to the various substances involved could be made, was not found in the published literature.

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b. Initial Medical Report

In 1954/1955, 24 workers at this plant were diagnosed to have chloracne which primarily involved the face, neck and arms. Other initial symptoms included: epigastric disorders in the form of nausea, anorexia, a feeling of pressure and intolerance of certain foods (12 cases); conjunctivitis (5 cases); liver enlargement (4 cases); abnormal liver functions (5 cases); and fibrous reconstruction of the liver as noted by laparoscopy (4 cases). About one year after the onset of chloracne 8 individuals developed central nervous system disorders as noted by a general feeling of fatigue, weakness in the arms and legs, loss of libido and EEG changes (2 cases). These eight were also found to have psycho-neurologic symptoms with MdE levels of overall 20-50%. These, too, were attributed to the worker's exposure in the TCP plant as occupational illness. The results of this initial study as taken from Krause's report are presented in table I-1.

4. Medical Follow-up of Exposed Group

20 years after the incident 11 of the 24 original workers with chloracne were reexamined. Many of them still exhibited pathological symptoms. The disappearance of chloracne was noted in only 2 cases, while 3 cases indicated only an occasional flare-up, and 6 cases still persisted. 7 of the 11 still complained of epigastric disorders including nausea, intolerance to certain foods, and pressure in the stomach/right rib arch area. 6 also noted alcohol intolerance. All evidence of conjunctivitis had disappeared. In 6 workers, those still with chloracne, psycho-neurologic symptoms were still present, as was a feeling of fatigue, weakness in the arms and legs and loss of libido. (These 6 received some worker's compensation for their disabilities.) Six new cases of liver enlargement was found, and in 8 cases at least one liver function test was abnormal. The results of this study as taken from Krause's report are tabulated in Table I-2.

It should also be noted that 2 of the original 24 cases had died by the time of this study in 1976. Both were age 61. One died of unnatural causes. The other died of arteriosclerosis.

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TABLE I-1: Distribution of Medical Symptoms in 24 Workers Exposed During the Manufacture of 2,4,5-TCP at Boehringer's Ingleheim Plant, 1954.*

	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23	24
Acne	+	+	+	f	+	+	+	+	f	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Conjunctivitis	+		+	f				+	f							+		+			+			
Bronchitis		+	+	f					f															
Subjective epigastric symptoms	+	+	+	f		+		+	f			+		+	+	+		+		+			+	+
Hypoacidity	+	-		f		+		+	f					+	+					+	+			
Liver hypertrophy	+			f					f		0	0		0		0	0	0	0	+		0	0	0
Liver test	+			f		+	0		f		0	0		0	+	0	0	0	0	0	0	0	0	0
Laparoscopy	+	+	-	f					f						+			-		0				-
EKG	+			f					f									0				-		
Fatigue	+	+		f					f		+			+	+	+				+				+
Limb weakness	+			f					f					+	+	+		+		+				+
Loss of libido		+		f				+	f		+			+		+		+		+				+
Loss of vitality	+			f					f		+			+	+	+		+		+				+
EEG	0			f					f						+			0		+		-		
Kidney	0	0	+	f	0				f			0					0	0	0	0	0	0	0	0
MdE	+	+	+	f					f		+			+	+	+		+		+	(+)	(+)		+
	40	20	30								30			30	40	40		30		50				

(+) = transient, + = pathological condition, 0 = no path. condition, f = no records available,
- = not tested

* Taken from Krause's Report, reference 104.

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TABLE I-2: 20 Year Medical Follow-up of Worker's Exposed During the Manufacture of 2,4,5-TCP at Boehringer's Ingelheim Plant, 1954.***

Patient number
Acne in the face
Other body parts
Conjunctivitis
Subj. epigastrium
Alcohol incompatibility
Fatigue
Limb weakness
Loss of libido
Liver hypertrophy
Liver hardening
palmar erythema
Thymol
y-GT
SGOT
SGPT
Electrophoresis
Bromothalein
Creatinine in serum
Albumin in urine
Urine sediment
MdE

3	5	6	8	12	14	15	18	20	23	24	N.W.†
+	+	0	(+)	+	+	+	+	+	0	(+)	
0	0	0	0	+	0	0	+	0	0	0	
0	0	0	0	0	0	0	0	0	0	0	
+	+	+	+	0	0	+	+	+	0	+	
+	+	0	0	+	0	+	0	+	0	+	
+	0	0	0	+	0	+	+	+	0	+	
0	0	0	0	0	+	0	+	+	0	+	
0	0	0	0	0	0	0	+	+	0	+	
+	+	(+)	(+)	0	+	0	+	0	0	0	
0	0	0	0	0	+	0	+	0	0	0	
0	0	+	0	0	0	0	0	0	0	0	
1.8	2.4	3.5	0.8	0.4	1.5	0.8	0.7	1.4	0.8	0.8	bis 3.0**
8	9	34	9	—	7	18	17	9	8	11	6-28
10 10	9 10	18 30	10 13	7 7	9 9	7 13	7 15	10 12	10 10	10 13	bis 15** bis 18
norm	γ-Glob. 28	norm	norm	norm	norm	norm	norm	α-Glob. 7	γ-Glob. 23	0	
2.7	2.5	6.9	6.2	—	2.6	6.4	6	2.1	3.5	6	bis 5%/**
0.8	0.7	—	0.8	0.7	0.8	0.9	—	0.8	0.8	1.0	0.9-1.5
0	0	0	0	0	0	0	0	0	0	0	
E: 8 L: 5	E: 2 L: 3	E: 2 L: 20	0	0	0	0	0	E: 2 L: 4	0	E: 5 L: 6	
30	0	0	0	0	30	30	30	50	0	20	

* Normal values of our laboratory

**bis = up to

*** Taken from Krause's Report, reference 104.

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J. Company: Diamond Alkali/Diamond Shamrock
Location: New Jersey/U.S.A.
Dates: 1956, and 1960
References: 17, 21, 28, 29, 31, 34, 67, 86, 116, 118, 119, 127

Two worker exposure incidents, dated 1956 and 1960, were reported to have occurred at a plant in New Jersey/U.S.A. owned by Diamond Alkali, later changed to Diamond Shamrock. The literature reports on medical studies conducted on the exposed workers at this plant, are unclear as to which incident (or both) the workers studied were exposed to. For this reason, these two incidents have been grouped together for discussion.

1. Process Information

Both 2,4-D and 2,4,5-T were manufactured at this plant. Poland, in his 1971 report, described the process synthesis for these two products as of the 1969 era. Although, the process design probably differed from the late 1950's to 1969, the process chemistry would basically have been the same. Poland's description of these processes are quoted verbatim below.

- 2,4,5-T Process

"The starting product for 2,4,5-T is 1,2,4,5-tetrachlorobenzene which reacts with methanol and aqueous sodium hydroxide to form 2,4,5-trichlorophenate, 2,4,5-trichloroanisole, and small amounts of several unwanted side products, eg, TDCC. The reaction product is steam-stripped to remove the anisole. At this point, sampling of various batches shows the TCDD to be present in 10 to 25 ppm. About six months before our survey, the company installed a device which removed most of the TCDD. The TCP thus produced contained less than 1 ppm TCDD.

The TCP reacts with monochloroacetic acid (MCA) to form 2,4,5-T. The latter is esterified with various alcohols or allowed to react with dimethylamine, and then formulated and packaged. Some 2,4,5-T and 2,4-D is sold as the unesterified acid in solid form."

Note: The analysis for TCDD in process stream samples probably did not start until after Dow's analytical method came out in 1966.

- 2,4-D Process

"The starting materials for 2,4-D are phenol and chlorine(gas) which react in an exothermic process to form DCP. Subsequent reactions with MCA to the phenoxyacetic acid are similar to 2,4,5-T. In 2,4-D production there is no formation of the TCDD."

According to Poland, "almost all operations were carried out in closed processes (eg. tank car to pipeline to reaction vessel to next pipeline to next reaction vessel)." This, again, referred to the 1969 process. To what extent the earlier processes were operated under closed conditions is unknown from the available published information.

Other detailed process information, eg. process design, process equipment, capacity, reaction parameters, etc., was not cited in the literature.

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2. Incident Description

As previously mentioned, two incidents were reported to have occurred at this plant. The first, in 1956, was attributed to occupational exposure during normal operating conditions. The second, in 1960, occurred as the result of both occupational exposure and from an accidental release of the trichlorophenol reaction chemicals from overheating of the reactor.

Specific details on either of these incidents could not be found in the published literature.

Note: A. Hay in reference 28 indicates that 1 death occurred in a worker exposed as a result of the 1960 accident at Diamond Shamrock. However, he gives no further explanation or a reference from which the death was cited. On July 9, 1984, Dr. W. McCarville, of Monsanto, contacted Dr. J. Worthington of Diamond Shamrock to confirm this death and to obtain the cause of death. 1 death did result from this accident. However, the cause of death was attributed to asphyxiation with vapors from the reactor as a result of the accident, and serious burns from a flash fire which also resulted from the accident. Which of the above causes or both were actually responsible for the death is still in question.

3. Human Exposure and Illness

a. Industrial Hygiene

Detailed industrial hygiene information, eg., employee work history records, exposure levels, exposure duration, protective equipment used, etc., could not be found in the published literature. Therefore, an assessment of worker exposure to the various chemicals involved, and dose received by the worker can not be made.

Poland and Bleiberg in their respective medical studies, identified some of the raw materials, intermediates, by-products and final products to which workers were potentially exposed. These included: acetic acid, phenol, monochloroacetic acid, sodium hydroxide, 1,2,4,5-tetrachlorobenzene, methanol, 2,4,5-trichlorophenolate, 2,4,5-trichloroanisole, TCDD, dimethylamine, chlorine, dichlorophenolate, various alcohols, 2,4-D and esters, and 2,4,5-T and esters. In addition, Poland identified some of the industrial hygiene practices followed by plant workers around 1969 in an apparent effort to control chloracne cases. These included: daily changes of work clothes; clean room facilities; showering; improved ventilation; elimination of TCDD; and medical follow-up by dermatologist. Whether similar practices were followed around the time of these two incidents was not identified, although it is doubtful.

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Table J-1: Summary of Clinical Symptoms Found in 29 Workers Exposed During 2,4-D and 2,4,5-T Manufacture¹

PATIENT	CHLORACNE ^a	HYPERPIG- MENTATION	HIRSUTISM	URINE UROPOR- PHYRINS	CHEMICAL ^b CONTACT	SKIN FRAGILITY
1	Severe	Mild	Moderate	Pos.	Moderate	Pos.
2	Mild	None	None	None	Severe	Neg.
3	Mild	Mild	None	None	Severe	Neg.
4 ^c	Severe	Mild	Mild	None	Severe	Pos.
5	Mild	None	Mild	Pos.	Severe	Pos.
6	Mild	None	None	None	Moderate	Neg.
7	Mild	Mild	None	Pos.	Moderate	Neg.
8	Severe	Moderate	Severe	None	Moderate	Neg.
9	Mild	Mild	Mild	None	Moderate	Neg.
10	Moderate	Moderate	Moderate	None	Severe	Neg.
11	Severe	Moderate	Moderate	None	Moderate	Neg.
12	None	None	None	None	Severe	Neg.
13	None	None	None	None	Severe	Neg.
14	None	None	None	Pos.	Moderate	Neg.
15	Moderate	Mild	Moderate	None	Moderate	Pos.
16	Moderate	Moderate	Marked	None	Severe	Pos.
17	Mild	Mild	None	None	Mild	Neg.
18	Moderate	Moderate	Marked	None	Mild	Neg.
19	Severe	Marked	None	Pos.	Mild	Neg.
20	Mild	Mild	Moderate	Pos.	Mild	Neg.
21	None	None	None	None	Mild	Neg.
22	None	None	None	None	Mild	Neg.
23	Mild	None	None	None	Mild	Neg.
24	None	None	None	None	Mild	Neg.
25	None	None	None	Pos.	Mild	Neg.
26	None	None	None	Pos.	Mild	Neg.
CS-1 ^d	Pos.	Pos.	Pos.	Pos.	NI ^e	Pos.
CS-2	Pos.	Pos.	Pos.	Pos.	NI	Pos.
CS-3	Pos.	Pos.	Pos.	Pos.	NI	Pos.
	(Severe)					

- a. Severity of chloracne is judged on the presence of comedones, epidermoid cysts, and furuncles and pustules.
- b. The extent of exposure is difficult to truly judge because of such variables as personal hygiene and work habits.
- c. Brief period of employment.
- d. CS = case study
- e. NI = not indicated
- f. Adapted from Bleiberg's report, reference 116.

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b. Initial Medical Reports

In 1964, Bleiberg reported on the medical symptoms of 29 workers who had been exposed at his plant while manufacturing 2,4,-D and 2,4,5-T. Three of these workers were severely affected and were admitted to the hospital for examination. The case studies of these workers are summarized below in subsection 3.c. The other 26 workers were examined on an ambulatory basis. The clinical symptoms exhibited by these workers included: chloracne (21 cases), hyperpigmentation (17 cases), hirsutism (14 cases), fragility of the skin (8 cases) and porphyria cutanea tarda (PCT)(11 cases) as evidenced by an increase in the levels of urinary uroporphyrins. A summary of the medical symptoms for these 29 workers is presented in Table J-1.

Although the severity of symptoms varied from individual to individual, Bleiberg noted the following correlations:

- The degree of hyperpigmentation was roughly proportional to the severity of chloracne.
- The degree of hirsutism was proportional to the severity of chloracne.
- The severity of chloracne did not usually correspond to the degree of chemical exposure.
- The severity of porphyria did not usually correspond to the degree of chemical exposure.
- The severity of chloracne did not usually correspond to the presence of porphyria.

Bleiberg concluded that the occurrence of disease in these exposed workers was in part due to individual susceptibility which was influenced by prior damage to the same organ system (For example, prior liver damage from alcoholism predisposes to PCT.). The incidence of PCT as determined by disturbed porphyrin metabolism was believed to be the direct hepatotoxic effect of exposure to the chemicals in the plant and/or synergistic action with drugs taken by the workers. In addition, although the relationship between the occurrence of chloracne and PCT was not quantitative with each other, their occurrence appeared to be the result of the same etiologic factors, ie., exposure to either the finished product chemicals or intermediates formed during the manufacturing process.

c. Case Studies

Case 1- Case 1 was a 48 year old male. He was employed at the plant for 3 years as a chemical operator and came into intimate contact with the suspected chemicals. Prior to his coming to work at this plant (after 1953) he had had attacks of biliary cholic which eventually led to a cholecystectomy in 1953. He was not a heavy alcohol user. In 1956 he developed hyperpigmented skin,

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darkly colored urine, and right upper quadrant pain. A diagnosis of common duct obstruction was made, and an unsuccessful surgical attempt to probe the duct was conducted in January of 1957. That same spring he developed chloracne, progressive darkening of the skin, and marked hirsutism, especially around the temples. Analysis of his urine indicated elevated excretion of urinary porphyrins including uroporphyrins, coproporphyrins and prophobilinogen...acquired PCT.

Bleiberg indicated in his 1964 report that this man was alive and well, and was suffering little, if at all from PCT. His work no longer involved use of chemicals.

Case 2- Case 2 was a 60 year old white male who was employed at the plant for 7 years as a welder. As is typical for maintenance type professions, his work took him throughout the plant and into frequent and prolonged contact with various chemicals. At some point in time (date not specified) he developed chloracne, hyperpigmentation, hirsutism and a darkening of his urine. He was admitted to the hospital for examination. It was noted that his past medical history was unrevealing, except for moderately heavy alcohol intake.

Besides the above mentioned symptoms clinical examination revealed a palpable but smooth and non tender liver. The remainder of the physical exam was normal.

Laboratory tests indicated elevated urinary uroporphyrin, coproporphyrin and urobilinogen levels; and the feces showed increased uroporphyrins and coproporphyrin levels. Most other diagnostic tests were normal. Liver biopsy revealed parenchymal cell regeneration and hemofuscin deposition. The patient was diagnosed as having acquired PCT.

Case 3- Case 3 was a 48 year old white male employed in the plant for 8 years mixing batches of chemicals. At some point in time (date not specified) he developed a severe case of chloracne; hyperpigmentation of the exposed skin of the face and hands; marked hirsutism, especially around the temples, eyelids and eyebrows; and darkened urine. His family history was non-contributory. The above symptoms were confirmed upon physical examination. Most laboratory tests were within normal limits including urine porphyrin levels. Liver biopsy revealed slight dysfunction in porphyrin metabolism...PCT. The failure to produce increased porphyrin levels in the urine was believed to be due to the fact that the examination was conducted two years after the worker had been removed from contact with the chemicals at the plant. This was felt to indicate the possibility of acquired PCT being reversible. The remainder of his examination was normal except for prolapsed hemorrhoids.

4. Medical Follow-up of Exposed Group

As a follow-up to Bleiberg's study in 1963 (reported in 1964), Poland conducted a medical study on all employees in this plant. Special emphasis was placed on the occurrence of chloracne, hepatotoxicity, PCT and neuropsychiatric symptoms.

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78 employees volunteered to participate in the study which was composed of detailed medical history and physical examinations. 5 women office workers were excluded, which resulted in a cohort of 73 male workers: 55 white and 18 black; average age = 39.3 ± 11.1 years; education = 11.0 ± 2.6 years; and employment = 8.3 ± 7.6 years. The group was divided into 4 occupational subgroups: maintenance workers (14); on-line production area workers (28); production supervisors/foremen (11); and other persons unrelated to the production area (20). A study of the key findings from Poland's study are listed below.

Dermatological

- 48 out of 73 employees (66%) exhibited some degree of chloracne, however, only 13 had moderate to severe lesions (18%).
- The severity of active chloracne correlated with the presence of scarring, hyperpigmentation, hirsutism and complaints of eye irritation (only 3 cases of conjunctivitis found).
- The presence of hyperpigmentation and hirsutism correlate significantly with chloracne but not with coproporphyrin excretion. This suggests that these 2 symptoms, usually thought to be associated with PCT, may be more closely related to chloracne in 2,4,5-T plants.
- Individuals varied in their susceptibility to acquire chloracne.
- Of the 4 groups, the maintenance workers had the highest incidence of chloracne cases and a greater tendency for severe chloracne. The incidence of chloracne cases throughout the plant did not correlate to any specific location.
- Chloracne in some of the workers examined by Bleiberg persisted and still existed at the time of this study.

Porphyria Cutanea Tarda

- No clinical cases of PCT were found, and only 1 employee had a case of mild persistent uroporphyrinuria. This worker was one of Bleiberg's case studies in 1964 who exhibited PCT.
- Only 4 of the 11 workers identified by Bleiberg in 1964 as having PCT as evidenced by uroporphyrinuria were still working in the plant at the time of this study. However, several of the other seven cases who left the plant were reexamined by Bleiberg prior to their leaving, and showed no elevation in urinary porphyrin excretion.
- Even though the etiologic agent(s) responsible for chloracne and PCT in these workers may be the same, the symptom complex is distinct for each, can occur independently, and has different clinical courses.
- A statistically higher coproporphyrin excretion level in the maintenance men suggests they have a higher toxic exposure.

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Hepatotoxicity

- Bleiberg's study showed that of the workers with chloracne and PCT, 2 had abnormal liver function tests and abnormal liver biopsies. In this study, only 4 workers exhibited elevated liver function values (bilirubin, SGOT, albumin, alkaline phosphatase). Three of these cases were mild and the fourth was accompanied by no other abnormal values.
- Of the 6 workers with palpable livers, only one had a mildly elevated liver function test.
- Although TCDD and other chemicals produced by 2,4,5-T manufacture may be hepatotoxic in humans, the prevalence of significant hepatotoxicity in the workers of this plant are minimal.

Systemic Toxicity

- Evidence of toxicity in other organ systems was markedly less than that reported in previous studies and could not be shown to differ from normal populations in most cases.

Neuropsychiatric Symptoms

- Severity of chloracne correlated significantly with a high score on the manic scale of the Minnesota Multiphasic Personality Inventory.

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K. Company: Hooker Chemical Company
Location: New York/U.S.A.
Date: 1956
References: 21, 28, 29, 31, 66, 86

1. Process Information

2,4,5-trichlorophenol was manufactured at the Hooker plant in Niagra Falls, New York by use of the ethylene glycol procedure, e.g., TCP was produced by hydrolysis of 1,2,4,5-tetrachlorobenzene with sodium hydroxide in a solvent of ethylene glycol at increased temperature (not specified) and atmospheric pressure. No other process information was reported in the references used.

2. Incident Description

Worker exposures reportedly resulted from both normal operations, and accidental releases.

Another concern, was due to environmental pollution as a result of the 2,4,5-trichlorophenol waste disposal practices followed by the Hooker Chemical Company. Between 30-200 tons of trichlorophenol wastes, along with many other chemicals were buried between 1942-1952 in what has become known as the Love Canal. A rising water table and violation of the burial site by construction has resulted in environmental contamination, and potential exposure to the populace. TCDD's have been found at the Love Canal site, in the ppm range and have also been detected at the Hooker used Hyde Park dump site in Niagra Falls, New York and the Montague, Michigan dump site.

3. Human Exposure and Illness

Although "many workers" have been reported to have been affected by exposure during the manufacturing of 2,4,5-trichlorophenol at the Hooker plant in New York, the exact number affected and nature of their illness have not been reported.

Studies have been conducted on the populace of the Love Canal. However, direct correlation of adverse health affects due to TCDD or the other various chemicals present has not been established.

4. Medical Follow-up of Exposed Group

No medical reports on the workers exposed and affected at the Hooker Chemical Company site in Niagra Falls, New York could be found.

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- L. Company: Industrie Chimiche Melegnanesi Saronio
Location: Saronno, Milan/Italy
Date: 1959 (Note: This incident occurred in 1959, but was not reported by Hoffman until 1962. It is often misquoted as having occurred in 1962.)
References: 21, 28, 31, 67, 86, 122

1. Process Information

No specific process information has been reported in the literature for this plant and incident. The only information cited, indicated that trichlorophenol was produced from tetrachlorobenzene.

2. Incident Description

This incident has been described by Hoffman as follows:

"Following a breakdown in the boiler used for preparing the final product in the department where the patients worked, a rise in the temperature caused the development of intense blackish vapors from the active substance; they were deposited on all the surfaces in the environment as a tarry blanket. The patients then cleaned the department and the boilers."

It is assumed that the "boilers" referred to here, were the reaction vessels (autoclaves) used to manufacture the 2,4,5-trichlorophenol. Exposure occurred as the result of clean-up operations from an accidental release of the reaction products into the work environment.

3. Human Exposure and Illness

a. Industrial Hygiene

No specific industrial hygiene information, eg., exposure levels, identification of substances to which workers were exposed, exposure duration, etc., were identified by which an assessment of worker exposure and dose received could be made.

b. Initial Medical Reports

5 workers from this plant were examined by Hoffmann, after the incident and clean-up, and were all determined to have chloracne. One case was rather severe and developed hyperpigmentation and later, scars. The other four were less intense and covered a lesser area of the body. No other organ changes or symptoms were noted in these workers. Case studies of these workers are described below in Section 4.

NOTE: This incident is sometimes misquoted as having 13 affected workers. This stems from the fact that Hoffmann's report discusses 13 cases, however, only 5 were due to exposure from the manufacture of 2,4,5-trichlorophenol. The other cases were due to exposure to arochlors (Polychlorinated biphenyls) and other aromatic hydrocarbons.

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4. Medical Follow-up

a. Case Studies - The following case studies are presented verbatim from a translation of Hoffmann's report.

Case No. 1: G.E., age 16, worker in a chemical plant employed in preparing trichlorophenol from tetrachlorobenzene. Following a breakdown in the boiler used for preparing the final product in the department where the patient worked, a rise in the temperature caused the development of intense blackish vapors from the active substances; they were deposited on all of the surfaces in the environment as a tarry blanket. The patient then cleaned the department and the boilers. A few days after the cleaning period began, the subject observed many blackish blackheads, folliculitis and superficial nodular elements on the face, forearms, and neck. A slow but progressive generalization of the dermatosis to the trunk, scalp, and lower extremities (to a lesser degree) then followed. Several months after the onset of the first symptoms, the patient was hospitalized in this Clinic.

There were no data of particular importance in the remote history. He had had a mild seborrheic condition since puberty.

The following was found on general examination: normal type in good general physical and mental condition. No particular organic changes. Current laboratory tests revealed no damage to the renal and hepatic parenchyma.

On objective dermatological examination, the skin on the face and upper parts of the trunk was intensely brownish-grey either due to the pronounced density of large blackish comedones or because of dirty brown hyperpigmented zones with blurred margins. Yellowish-grey color of much less intensity on the remaining skin. The follicular openings seemed dilated. Diffuse follicular hyperkeratosis was found on almost the entire surface of the skin except for the palmar and plantar regions; the density was greater in the seborrheic sites. Hyperkeratosis in the follicular and perifollicular site (Figure 1 - omitted) on the scalp.

Most blackish comedones were present everywhere; on pressure, they exuded a slightly oily substance which was granular to the touch. Small yellow-white elements of a cystic-nodular appearance, mobile in the profound levels, frequently with an inflammatory component were observed here and there on the face (Figure 2 - omitted), neck, upper parts of the trunk, forearms, and to a lesser degree in other regions (there were none on the palms of the hands and soles of the feet). On cutting the largest cystic-nodular elements, which occasionally were the size of a lentil, a dense, ropy, yellow-white fluid came out.

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Predominantly, localized on the face, neck and forearms, follicular and perifollicular reactions and pustular folliculitis. Retracted varioloid scars were scattered here and there, especially on the face and neck.

The elements were relatively typical on the whole, and could be differentiated from acne vulgaris at first glance. The differential diagnosis with folliculitis from naphtha and carbon derivatives, which usually occupy much more limited skin surface, mainly only exposed sites or sites directly subject to the friction of clothing saturated with the causal agent, was very simple.

On the final examination of the patient approximately one year after hospitalization, most of the inflammatory-nodular, hyperkeratotic, follicular and folliculitic elements had regressed (Figure 3 - omitted) with sometimes varioliform scars. The latter, especially on the forehead, gave the skin the appearance of worm-eaten wood. Isolated microcystic elements persisted, particularly at the seborrheic sites, and blackish comedones were scattered everywhere. The scalp still exhibited some hyperkeratosis.

Cases 2, 3, 4 and 5

It is interesting to note that four other people (45, 53, 56 and 38 years of age, respectively) employed in cleaning the boiler in the same department successively became ill with the same skin disease within a somewhat shorter time. The dermatological symptoms were less intense and diffuse than in case 1 and affected the neck, face (Figures 4, 5, 6, 7 - omitted), extensor surface of the thighs and the ulnar surface of the forearm (site placed against the internal walls of the boiler during the cleaning operation). One of these cases merits description due to its clinical peculiarities.

Case No. 5: C.A., 38-year-old male employed in repairing and cleaning the mechanical equipment in the trichlorophenol production department. Had repeatedly worked (later than case 1) with mechanical material saturated with the tarry residue described above. A few months later, the patient observed the onset of small rounded yellow-white spots in the mandibular submandibular regions, in addition to the existence of numerous "blackheads" particularly scattered on the face, edges of the scalp, the concha of the ear auricles, the tensor surface of the thighs and the ulnar surface of the forearm.

The objective examination of the subject, in good physical and mental condition, showed no changes in the various organs and systems. The results of the various routine laboratory tests were normal.

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On objective dermatological examination, the following was observed: numerous hemispheric manifestations varying from a grain of millet to a large pea in size, sometimes slightly ovoid, isolated, smooth, non-inflammatory, whitish-yellow, hard in consistency were observed in the mandibular, submandibular and submastoid regions. Their appearance was manifestly cystic. These manifestations were accompanied by numerous large blackish comedones in the center of the face, the margins of the scalp, the ear auricles, extensor surface of the thighs and ulnar surface of the forearms. (Illegible - word form translation) follicular hyperkeratosis was particularly evident at the last two sites. There were small cystic formations (much smaller and less raised than those described above) on the skin on the penis, on the abdomen corresponding to the region of the waist. No signs of inflammatory and pustular folliculitis.

The evolution of the dermatosis over a year showed almost no regression of the symptoms (Figure 4 - omitted). No new elements appeared. The clinical picture was almost unchanged on the present examination.

b. Other studies - No other medical follow-up studies could be found in the literature on this small cohort.

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M. Company: Thompson Hayward
Location: Kansas/U.S.A.
Date: 1959
References: 28

1. Process Descriptions

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 exposed during normal operations...occupational exposure.

3. Human Exposure and Illness

The number of persons exposed and effected by illness at this plant has not been reported in the literature. No other information has been published on this incident.

4. Medical Follow-up of Exposed Group

No information available in the literature.

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N. Company: Phillips Duphar
Location: Amsterdam/Netherlands
Date: 1963
References: 21, 28, 29, 31, 34, 38, 67, 86, 113

1. Process Information

2,4,5-T was produced at the Phillips Duphar plant through the use of the intermediate sodium trichlorophenate. The sodium trichlorophenate was manufactured by the alkaline hydrolysis of 1,2,4,5-tetrachlorobenzene using sodium hydroxide in a solvent of methanol at a temperature of approximately 170°C and pressure of approximately 22 atmospheres. Other detailed information on the process, eg., process design and equipment, capacity, etc., was not given.

After the run-away reaction on March 6, 1963 the process was discontinued.

2. Incident Description

On March 6, 1963, at the start of a normal sodium trichlorophenate production run, an uncontrollable exothermic reaction started in the contents of the reaction vessel. The temperature and resulting pressure rapidly increased until it exceeded the pressure limits of the safety relief valves on the vessel. The increased pressure was so great that not only did the safety relief valves blow, the lid of the autoclave was also blown off. The contents of the autoclave were ejected into the area but were contained within the building. The final temperature and pressure of the vessel before it blew was estimated to be 400-450°C and >80 atmospheres. It was later estimated that somewhere between 200-500 g. of 2,3,7,8-TCDD had been liberated. Upon investigation, no cause due to mechanical failure could be found, however, operator error could not be ruled out. At the time of the incident, only two workers were in the building. No direct injuries or deaths were reported.

Recognizing the serious nature of this incident, as the company was aware of similar accidents in the U.S.A. and Germany, the building was closed to production activities until it could be thoroughly decontaminated. Efforts to assess the extent of contamination, both before and after decontamination efforts were undertaken, included animal tests and chemical analysis of the residues.

Rats and rabbits were used for testing over a period from March to July 1963. The animals were either exposed by placing them in cages inside the contaminated building, by feeding the animals food dosed with the contaminated residues or chipped paints, or by applying the residues to the skin of the animals. Under certain of these conditions the animals showed lipid accumulation in the liver, atrophy of the thymus, enlargement of the testes, and death. The results of the animal tests showed that the decontamination efforts were not effective.

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In 1963, the company was unaware of the presence of 2,3,7,8-TCDD in the reaction residue. Their efforts to use spectrophotometric analysis of the residue, which was state of the art at that time, was unsuccessful for identifying the crucial contaminant. It was not until 3 years later when Dow Chemical Company issued a method to detect 2,3,7,8-TCDD, that Phillips Duphar was able to measure the contaminant levels in the building. Levels up to 1000ppm were found in contaminated paint/residues. From this it was estimated that between 200-500 g. of 2,3,7,8-TCDD had been released.

Despite the extensive decontamination efforts followed, including the removal of paint from various contaminated surfaces and washing the area down with a weak solution of sodium hydroxide, and despite the reconstruction efforts undertaken including removal and replacement of equipment, the company's hopes to reopen the building in 1973 proved to be futile. Animal tests and analytical tests still showed the building to be contaminated. Later in 1973 the building was demolished and disposed of into the Atlantic Ocean.

3. Human Exposure and Illness

a. Industrial Hygiene

Reports of up to 145 men were involved over the years in the clean-up of this plant. 44 were factory workers involved in all stages of the clean-up and reconstruction. 62 were outside contractors involved between March to July of 1963: 18 involved with clean-up; 44 were plumbers, carpenters, painters, insulators, etc. The involvement of the other 37 was not clarified.

The hygienic practices followed by these workers during clean-up/reconstruction activities were not reported. Extensive hygiene controls, however, were implemented during the demolition. These included the use of air supplied, gas tight, full protective suits, and the use of clean-room facilities for wash-up and personal decontamination.

No other industrial hygiene information, eg., specific job tasks, exposure duration, and evaluation of exposure levels, etc., has been published. Therefore, no assessment of the worker's exposure and dose received to the various chemicals can be made.

b. Initial Medical Reports

Chloracne, characterized by comedones, pustules and cysts on the face and other body parts and a latency period of 4-6 weeks after exposure was found to be the most prominent clinical lesion of those examined. (44 plant employees examined: 26 cases chloracne. 16 of the 18 outside contractor cleaners examined: 10 cases chloracne, 16 of 44 outside contractors examined: 8 cases chloracne.) Liver function tests for thymol turbidity, serum glutamic pyruvic transaminase and serum glutamic oxaloacetic transaminase were all normal. Other symptoms included dermal erythema and edema shortly after exposure (probably due to the irritant nature of the substances exposed to), and some workers showed fatigue.

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4. Medical Follow-up of Exposed Group

a. Mortality Studies

The only mortality study results on this cohort of workers was conducted by Dr. L. M. Dalderup, physician for Phillips Duphar. Unfortunately only a summary of his work, and not the full study has been published.

According to this summary 141 out of 145 potentially exposed workers (plant and outside contractors) were studied 20 years after exposure for their mortality experience. The cohort of 141 men were divided into two groups: those with chloracne (69) and those without clear signs of chloracne (72). The mortality experience of these two groups is shown in Table N-1 (extracted from Dalderup's summary).

The results of the study indicated there was no apparent excess in total deaths or in deaths due to cancer. The standard mortality rating (SMR) for all deaths was 1.19 (25 deaths observed vs. 21 expected). The SMR for cancer deaths was 1.15 (8 observed vs. 6.94 expected). The cancers did not show an organ related pattern. The proportion of overall deaths due to myocardial infarction was noted to be high. 7 of the 8 deaths due to sudden death/myocardial infarction had chloracne. 4 of these were severe chloracne cases from the group of contract cleaners who had exposure to various chemicals both before and after their involvement at Phillips Duphar and, who, also, as a group showed relatively high alcohol consumption. Since the overall exposure picture for the contract cleaner group was so complex, and involved many more substances than 2,3,7,8-TCDD, it would be difficult to conclude that dioxin was the causative agent for this increase in myocardial infarction.

This study appears to be lacking a control population. As such, the results are questionable.

b. Morbidity Studies

According to Dalderup a morbidity study of 35 of the 145 potentially exposed workers, mostly plant employees, is currently being conducted (has not been published). The data are being compared to a matched control group. To date no significant differences have been found.

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Table N-1: 20 Year Mortality Experience of 141 Workers Potentially Exposed to 2,3,7,8-TCDD during the Phillips Duphar Incident in 1963**.

COHORT MORTALITY, 20 YEAR FIGURES						
			WITH CHLORACNE		WITHOUT CHLORACNE	
	TOTAL (141)	DIED (25)	TOTAL (69)	DIED (14)	TOTAL (72)	DIED (11)
BIRTH YEAR						
1910	12	5	2	0	10	5
1911-1920	29	13	12	9	17	4
1921-1930	51	5	32	4	19	1
1931-1940	41	2	22	1	19	1
1941	8	0	1	0	7	0
Recorded cause of death*						
Myocardial infarction, including sudden death (40-69)	--	8	--	7	--	1
Neoplasms(44-68)†	--	8	--	3	--	5
Congestive cardiac failure with generalized arteriosclerosis and emphysema(69)	--	1	--	1	--	0
Cerebrovascular accident with lung embolism(69)	--	1	--	1	--	0
Chronic bronchitis and emphysema(69)	--	1	--	1	--	0
Chronic asthmatic bronchitis, emphysema & bronchus carcinoma(73)‡	--	1	--	0	--	1
Chronic nephritis(63)	--	1	--	0	--	1
Thyrototoxic crisis(52)	--	1	--	0	--	1
Latrogenic gold intoxication following therapy for chronic back complaints of unknown nature(44)	--	1	--	1	--	0
Road traffic accidents (43-76)	--	2	--	0	--	2

* Age range in parentheses

† 1 each of mesothelioma (asbestos exposure), melaniosarcoma, stomach, pancreas, rectosigmoid, bronchus (heavy smoker), bladder & kidney, brain.

‡ Bronchial neoplasm in 1978, had radiotherapy, but was free of recurrence and metastases June 1982, died October 1982.

** Taken from Dalderup's summary published in The Lancet, November 12, 1983, reference 113.

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O. Company: Not Available
Location: Ufa, U.S.S.R.
Date: 1964
References: 21, 28, 29, 31, 34, 86, 115

1. Process Information

The butyl ester of 2,4,5-T was manufactured at this plant by the esterification of 2,4,5-T with butyl alcohol. Specific process information, eg., capacity, process design, process equipment, chemicals used, and reaction parameters, were not cited.

It was not clear from the main reference used, Telegina and Bikbulatova, which other herbicides were manufactured at this plant, and which were shipped in from other plants for use as raw materials or intermediates. The mention was made of operators coming in contact with 2,4,5-trichlorophenol and 2,4,5-T, in the presence of butyl alcohol, alkali, and hydrochloric acid.

Production of the 2,4,5-T butyl ester at this plant ceased somewhere around 1967 in an effort to eliminate the health problems of the workers.

2. Incident Description

All cases were attributed to occupational exposure during normal operation.

3. Human Exposure and Illness

a. Industrial Hygiene

54 operators, 11 machinists, 9 engineering/technical workers, 5 lab workers and 4 other workers constituted the various job functions held by the 83 workers who were later examined. Other specific information on industrial hygiene parameters, eg., measured exposure levels, use of protective equipment, exposure duration, etc., were not reported. Therefore, there is no way to assess the exposure and dose received by the worker to the various compounds.

b. Initial Medical Reports

All workers engaged in the production of the phenoxy herbicides were given medical exams approximately one year after production had begun. 128 of these workers were found to have occupationally related skin diseases.

Out of this group of 128 workers, 83 were given a more thorough examination. The pathological conditions found in these workers are presented in Table O-1. A summary of the results of laboratory tests conducted on the blood, liver and skin are listed below.

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TABLE C-13 - EXPOSURE VS. REPRODUCTIVE FINDINGS

Reproductive History	Exposed* (n=190)	Not Exposed† (n=155)‡	Probability
Pregnancies	955	429	...
Miscarriages	69	81	...
rate per 1,000 pregnancies	106.34	118.86	115
Live births	575	373	...
Stillbirths	11	6	...
rate per 1,000 fetuses to term	18.77	13.23	115
Dead in 4 weeks	17	6	...
rate per 1,000 live births	29.56	18.09	115
Children with birth defects	18	11	...
rate per 1,000 live births	31.30	29.49	115

* In the exposed, reported birth defects include spina bifida, unspecified cardiac anomalies, pytonic stenosis, undescended testicle, congenital hydrocele, obstructive defects of urinary tract, club foot, congenital short leg, anomalies of sternum, Down's syndrome, hernia and angioma.

† In the not exposed, reported birth defects include spina bifida, congenital anomalies of eye, polycystic kidney disease, antrla web, obstructive defects of urinary tract, club foot, absence of fingers, congenital dislocation of hips, cystic hygroma, Down's syndrome and hernia.

‡ The differences in number (189 vs. 204 for exposed and 155 vs. 163 for not exposed) were due to men who were children of men who did not respond (two nonresponders in the not exposed, three in the exposed).

c. Moses, et. al., 1984

In April, 1979, at the request of the United Steel Workers of America, AFL-CIO, a health study of current and retired workers at Monsanto's Nitro, West Virginia plant was conducted by the Environmental Sciences Laboratory of the Mount Sinai School of Medicine. The initial purpose of the survey was to determine if long-term health effects related to duration and/or intensity of past exposure to 2,3,7,8-TCDD could be demonstrated in the workers. However, since worker exposure levels to 2,3,7,8-TCDD had not been measured, it was not possible to establish a reliable exposure classification whereby the data could be analyzed for a dose-response relationship. The presence of chloracne

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was therefore used as an indicator of exposure. It was recognized, however, that those workers without chloracne, but with appropriate work-exposure history, might also have had exposure to 2,3,7,8-TCDD and were not, therefore, "unexposed controls".

425 persons hired prior to 1977 were invited to participate in this study: 131 workers who according to union records had worked in 2,4,5-T production; 161 retirees listed in the union records; and, 133 workers who had no known 2,4,5-T exposure were selected on a random systemic basis from the most recent union seniority list. Of the 425 invited, 226 of the volunteers were used in the study: 137 active Monsanto employees; 4 actively employed elsewhere; and 85 retirees. All but 3 were white. The mean age of the population was 54.1 years. The mean duration of employment was 24.8 years. 114 of the population also reported exposure to 4-aminobiphenyl, a known bladder carcinogen, and 18 were uncertain about exposure to this compound.

All 226 participating subjects were clinically examined and examined by questionnaire for past medical history. The results of the study are outlined below.

- Chloracne was found in 117 of the subjects: 70 current cases with a mean duration of persistence equal to 26.1 ± 5.9 years; and 47 with a past history of chloracne but no current evidence of it. (See Tables C-14 through C-16 for breakdown of chloracne cases by duration of employment, age and date of occurrence.)
- Increased prevalence of actinic elastosis in those with chloracne (23 cases) versus those without chloracne (12 cases) was not statistically significant when age adjusted.
- Except for gamma-glutamyl transpeptidase (GGT), no statistically significant differences were found between those with and without chloracne for any of the biochemical and hematological variables. No significant differences were found between chloracne and no chloracne groups with respect to gallbladder, liver, or peptic ulcer disease. (See Table C-17 for a summary of serum chemistries for both groups.)
- Increased prevalence of angina and reported myocardial infarction in those with chloracne was not significant when age-adjusted. (See Table C-18 for a summary of the incidence of myocardial infarction and angina by age and chloracne status.)

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TABLE O-1: Pathological Conditions Found in 83 Workers
Occupationally Exposed During Production of the
Butyl Ester of 2,4,5-T

<u>ORGAN SYSTEMS</u>	<u>NO. WORKERS</u> <u>AFFECTED</u>	<u>DESCRIPTION</u>
Skin	13	Severe chloracne cases- folliculitis, comedones, atheromas and cysts located on face, auricle of ears, neck, shoulders, back, chest and genitalia: mild hyperpigmentation: scar formation from cyst evacuation.
	24	Moderate chloracne cases- characteristics same as in severe cases, however, concentrated primarily on face and to lesser degree.
	32	Mild chloracne cases- small number of fine comedones on face.
	14	Non-chloracne, but considered occupational skin disease.
Nervous System	18	Neurasthenic syndrome
	14	Vasovegetative dystonia
Internal organs: Gastrointestinal	10	Chronic gastritis with elevated acidity in 6, and lowered acidity in 4.
	1	Duodenitis
	1	Chronic colitis
	1	Duodenal ulcer
Cardiovascular system	2	Dystrophic myocarditis

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TABLE O-1: Pathological Conditions Found in 83 Workers
Occupationally Exposed During Production of the
Butyl Ester of 2,4,5-T (cont.)

<u>ORGAN SYSTEMS</u>	<u>NO. WORKERS</u> <u>AFFECTED</u>	<u>DESCRIPTION</u>
Respiratory system	1	Emphysema
	1	Chronic bronchitis
Liver	3	Pain upon palpitation and change in consistency and size of liver. (1 case from severe chloracne group, 2 from moderate chloracne group)
ORL	17	Rhinitis (subatrophic, hypertrophic, vasomotor)
	17	Chronic tonsillitis
	21	Pharyngitis (granulous, atrophic, subatrophic)
	2	Hypertrophy of faucial tonsils
	5	Eustachitis
	16	Catarrhal otitis and mesotympanitis
	6	Naso pharyngitis
	3	Frontal sinusitis metapantiritis and maxillary sinusitis

NOTE: The workers also complained of headache; sleepiness; pain in the stomach; nausea or heartburn; irritability; susceptibility to fatigue; memory loss; pains in the heart; pains in the right hypochondrium; pains in the small of the back; joint pain; insomnia; excessive perspiration and loss of potency.

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- The average red blood cell counts, white blood cell counts, platelet counts and hemoglobin levels for all workers were within normal limits. Certain white cell factors were found to deviate more within the severe chloracne group, but were still within the normal range.
- Serum billirubin was normal in all workers.
- Although the average cholesterol levels were within normal limits for all groups, the levels tended to be on the lower end of the range. (Note - A. Hay refers to this report as indicating there having been high cholesterol levels in the severe chloracne group. The opposite was stated in this translation.)
- Colloid stability of the blood serum was normal in all workers. This indicated that protein metabolism was not inhibited.
- Results of the liver function tests indicated slight deviations from normal in the "antitoxic" function of the liver and lipid metabolism. However, pigment formation, carbohydrate and protein metabolism were not affected.
- There appeared to be a decrease in sensitivity of the skin to ultra violet light with an increase in severity of the chloracne.

According to Telegina and Bikbulatova the skin disorders started to develop within 6 months to 1½ years after beginning work in the plant. The disorders were wide spread among the work force and of the 83 workers thoroughly examined included: 54 operators, 11 machinists, 9 engineering/technical workers, 5 lab workers, and 4 other workers. Those operators who came in contact with 2,4,5-T and 2,4,5-trichlorophenol in the presence of butyl alcohol, alkalai or hydrochloric acid were noted to have had a significantly pronounced, early susceptibility to the skin disorders (chloracne).

In regards to the high incidence of respiratory and ORL disorders, Telegina commented that "it is difficult to attribute the damage to the mucous membranes and upper respiratory tract to random coincidence, and, obviously, one must take into account the result of the irritant effect of the complex of vaporous and gaseous chemical substances in the plant and the unfavorable effects of temperature change."

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4. Medical Follow-up of Exposed Group

Approximately one year after the first thorough examination was conducted on the 83 workers of this plant, 63 of the same workers were reexamined. 12 came from the severe chloracne group; 19 from the moderate chloracne group; 24 from the mild chloracne group; and 8 from the non-chloracne group.

A summary of the results of this examination are presented below:

- No clinical symptoms of hepatic disease (eg. pain upon palpitation, change in liver size) were found in the second examination as compared to 3 cases in the initial examination. (It was not stated whether the 3 cases reported in the first study were part of the reexamined group.)
- Serum billirubin levels remained normal.
- Average cholesterol levels remained normal.
- The slight deviations from normal of the liver function tests were found to be less noticeable upon second examination.
- Clinical recovery of these workers was manifest in 9 of the moderate cases of chloracne.
- Improvement in the clinical symptoms were found in 37 workers: 10 from the severe chloracne group; 14 from the moderate chloracne group; and 13 from the mild chloracne group.

The success in improving the affected workers conditions was attributed to two factors. The first was the rigorous medical treatment program followed which included the use of vitamins, antibiotics, lotions, cleanings and ultra violet light. The second, and more important as noted by Telegina and Bikbulatova, was the closing down of the 2,4,5-T butyl ester plant and conversion of the facility to make another herbicide.

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P. Company: Dow Chemical Company
Location: Michigan/U.S.A.
Date: 1964
References: 16, 17, 21, 28, 29, 31, 67, 86, 92, 93

1. Process Description

2,4,5-T was produced by Dow at their Midland, Michigan plant between 1950 and 1971. Although capacity figures were not cited, it has been noted that Dow was the largest producer of 2,4,5-T in the world.

2,4,5-T was produced through the use of the intermediate trichlorophenol (TCP). TCP and 2,4,5-T were made in two separate buildings on the plant site.

It was unclear from the published literature which method was used for the synthesis of TCP. Holmstead indicated that Dow produced its TCP by the alkaline hydrolysis of 1,2,4,5-tetrachlorobenzene by using sodium hydroxide in a solvent of ethylene glycol, at a temperature around 200°C, and at atmospheric pressure. Bond, on the other hand indicated that methanol was used as the solvent, and that the reaction took place at both high temperatures and pressure.

With the frequent occurrence of chloracne in 1964, however, Dow modified its process and adapted the low temperature (157°C) method used by Boehringer. In addition, continued efforts to minimize the contamination of TCDD in the TCP were made, and from about 1966 on process samples were analyzed for TCDD.

2,4,5-T was synthesized by reacting sodium monochloroacetate with the sodium salt of TCP. The salt was prepared by adding caustic to the TCP. The sodium 2,4,5-T was then converted to the acid. In the 2,4,5-T building esters of 2,4,5-T were also made by esterification of the 2,4,5-T with propylene glycol butyl ether or with isooctyl alcohol. The 2,4,5-T plant operated under the original process from start up in 1950 to shut down in 1971.

Other detailed process information, eg., process design, process equipment, reaction parameters, etc., were not cited in the published literature.

2. Incident Description

In 1964, workers within the TCP production facility contracted chloracne. All cases were attributed to occupational exposure during normal operations. The industrial hygiene and toxicology departments at the plant determined that the cause of this health problem was due to skin absorption of the process contaminant 2,3,7,8-TCDD.

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3. Human Exposure and Illness

a. Industrial Hygiene

2,4,5-TCP plant: Approximately 61 employees were exposed to 2,3,7,8-TCDD via percutaneous absorption during the 1964 incident. According to Dr. Ralph Cook, Director of Epidemiology at Dow, the dose of TCDD received by the employees was unknown, and impossible to calculate based upon the route of absorption. A qualitative assessment of worker exposure was made by the site industrial hygienist. Through his working knowledge of the process, and worker job tasks he divided the cohort into high and low exposure groups. The high exposure group included production workers who worked in the area of highest TCDD contamination, employees engaged in sampling operations and maintenance workers who were responsible for the production equipment. The low exposure group included workers who worked in areas away from the high TCDD areas, and other maintenance workers who were not directly responsible for the production equipment. Through work history records the time in area for each worker was also determined. A breakdown of the workers in each exposure group and date of time in the area is presented in Table P-1.

In addition to this professional assessment of exposure the areas were also assessed by biological monitoring with the classic rabbit ear test. Wipe samples taken from various areas in the plant showed positive results and thereby contamination. Samples collected after process modifications were made reduced the number of positive biological tests and also the degree of response in those that were positive. These changes together with the implementation of stricter hygiene practices were noted by Cook to have reduced employee exposure and eliminated the outbreak of chloracne.

Other detailed industrial hygiene information, eg., protective devices used, other chemicals involved and exposed to, etc., was not found in the published literature for this incident.

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TABLE P-1: - AGE DISTRIBUTION OF 61 EMPLOYEES POTENTIALLY EXPOSED TO TCDD DURING 1964 BY JOB CATEGORY AND BY DATE FIRST EMPLOYED IN PROCESS AREA. ^a

Exposure Group and Age Distribution	First Employed in Process Area:		
	Total	Prior to June 1964	July to December 1964
Group 1. (High potential exposure)			
Total	39	34	5
20-24	3	2	1
25-34	13	12	1
35-44	10	8	2
45-54	8	7	1
55-64	5	5	0
Group 2. (Low potential exposure)			
Total	22	16	6
20-24	4	0	4
25-34	6	5	1
35-44	9	9	0
45-54	3	2	1
55-64	0	0	0

a. Taken directly from Cook's report, reference 17.

2,4,5-T plant - In his 1980 report on the mortality experience of Dow's Midland, Michigan 2,4,5-T plant, Ott presented what has to be the most complete representation of the worker exposure experience published in the literature. The process information, also, discussed by Ott, has been pulled out separate and presented above in Section 1. Excerpts from his discussion on industrial hygiene are presented below and are quoted verbatim.

"The departmental unit under which the original process was first organized also was responsible for manufacturing a variety of other products, ranging from styrene-butadiene latex to herbicides such as 2,4,5-trichlorophenoxypropionic acid and 2-methyl-4-chlorophenoxyacetic acid. Thus, many of the individuals included in the present study were potentially exposed to numerous other substances during their employment with this unit.

Continuing efforts were made to minimize TCDD contamination in the 2,4,5-T plant by proper control of a separate plant which produced the TCP later used in the 2,4,5-T process. In 1970 wipe testing, using a combined gas chromatography and mass spectrometry method sensitive to approximately 1 µg/sample, depending upon interferences, failed to detect TCDD in the 2,4,5-T work area. The 2,4,5-T process was specifically run by a crew of four operators: a reactor operator, a salt wheel operator, an acid wheel operator, and a dryer operator.

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The reaction portion of the process in which the sodium salt of 2,4,5-T was produced was nearly a closed system. During the subsequent wheeling operations, the sodium salt was converted to the acid. The 2,4,5-T dust levels found in the plant were believed to have resulted primarily from finishing operations where the end product was dried and fed through a hammer mill.

An industrial hygiene survey of the process was conducted in 1969, at which time 50 area and breathing zone samples were collected, using a midjet impinger containing isooctane, at a flow rate of 2.2 liters per minute. The samples were subsequently analyzed by gas chromatography for TCP, 2,4,5-T and 2,4-D. Concentrations of 2,4,5-T or its sodium salt ranged from $<0.1 \text{ mg/m}^3$ to 6.2 mg/m^3 . Estimated time-weighted average (TWA) concentrations for the three compounds by job classification are shown in Table 1 (Table P-2 of this report). concentrations of these substances were relatively similar for three of the job classifications: reactor operator, dryer operator, and salt wheel operator. The acid wheel operator was exposed to lower 2,4,5-T levels and higher TCP concentrations. The 2,4-D measurements are maximum levels. This product was dried occasionally in the building where 2,4,5-T was made.

Dust levels in the finishing area often were high enough to be noticeably irritating. Unacclimated industrial hygienists reported sensory responses such as nasal irritation, sneezing, and a bitter taste from exposure levels of approximately 0.1 mg/m^3 of 2,4,5-T or less than 4 mg/m^3 of TCP, or both. A review of medical visits from 1954 to 1970 among the 204 men in this study revealed 19 episodes associated with acute exposure to 2,4,5-T or its esters. All exposure reported involved eye or skin contact, with the mild to moderate responses apparently resulting from the irritating effects of the materials. Six of the exposure episodes occurred while the men were working as ester operators rather than directly on the 2,4,5-T process. The esters of 2,4,5-T are believed to exert toxicological effects similar to those of the acid, after adjustments for the molecular weight of the ester itself."

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TABLE P-2: TIME-WEIGHTED AVERAGE EXPOSURE ESTIMATES FOR 2,4,5-T PROCESS BASED ON 50 SAMPLES OF UP TO FIVE MINUTES DURATION AND TIME STUDIES FOR EACH JOB, 1969.

JOB	TCP (mg/m ³)	2,4,5-T (mg/m ³)	2,4,-D (mg/m ³)†
Reactor operator	2.1	0.8‡	<0.4
Salt wheel operator	2.1	0.5‡	<0.4
Acid wheel operator	9.7	0.2	<0.4
Dryer operator	1.6	0.5	<0.4

* Product specifications for 2,4,5-T in 1966 called for a maximum of 1 ppm TCDD the sensitivity of the method of detection. In 1972, the maximum was lowered to 0.1 ppm TCDD.

† Highest possible values using levels of detection as real values.

‡ Present in work environment as sodium salt.

4. Medical Follow-up of Exposed Group

Two mortality studies and one morbidity study have been conducted on the workers involved with the manufacture of 2,4,5-trichlorophenol and 2,4,5-T at Dow's Midland, Michigan plant. The first mortality study was conducted on the 61 employees exposed to 2,3,7,8-TCDD in the 1964 TCP incident. The second mortality study dealt with 204 workers employed between 1950 and 1971 in the 2,4,5-T plant. The morbidity study considers both of the above groups.

Since both of these groups had the potential for exposure to 2,3,7,8-TCDD through contact with TCP and/or 2,4,5-T, all three studies will be summarized in this section.

a. 14 Year Mortality Study on 1964 TCP Incident Cohort

A mortality study was conducted on 61 male workers who were identified from plant records to have worked in the TCP department during the 1964 exposure incident.

The objectives of the study were to determine whether the 14 year mortality experience for a cohort with subacute, relatively high exposures was greater than expected, and whether unique patterns of exposure or mortality were observed among the deceased. The results were compared to cause-specific and age-specific mortality rates for the United States white male population.

For the purpose of the study, the cohort of 61 was divided into two exposure categories, high and low (See Section 3a. above for further explanation.). They were further subdivided according to the dates in which they were involved with the TCP department, between November 1963 to June 1964 when the exposure problem was identified or between July 1964 and December 1964 after the problem was solved through process modifications and increased hygiene efforts. The distribution of these 61 employees by age, exposure group, and date employed in the area are presented in Table P-1.

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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 trichlorophenol 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.

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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 from 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

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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 from 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.

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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	Duration of Exposure					
	Total Exposed Group		<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.

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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 $\pm$ 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.

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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 $\pm$ SD	45.4 $\pm$ 7.6	45.4 $\pm$ 7.8	42.8 $\pm$ 8.2	42.8 $\pm$ 8.3
Year of hire	1953.6 $\pm$ 7.9	1953.3 $\pm$ 9.2	1957.1 $\pm$ 8.5	1956.6 $\pm$ 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 $\pm$ SD	49.2 $\pm$ 9.5	49.2 $\pm$ 9.6	45.3 $\pm$ 10.2	45.3 $\pm$ 10.2
Year of hire	1951.4 $\pm$ 8.0	1951.7 $\pm$ 10.5	1956.7 $\pm$ 7.9	1955.0 $\pm$ 10.6
Salaried	5	20	17	68
Paid by the hour	43	172	118	472

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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% CI = 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.

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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.

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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 trichlorophenoxyacetate 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.

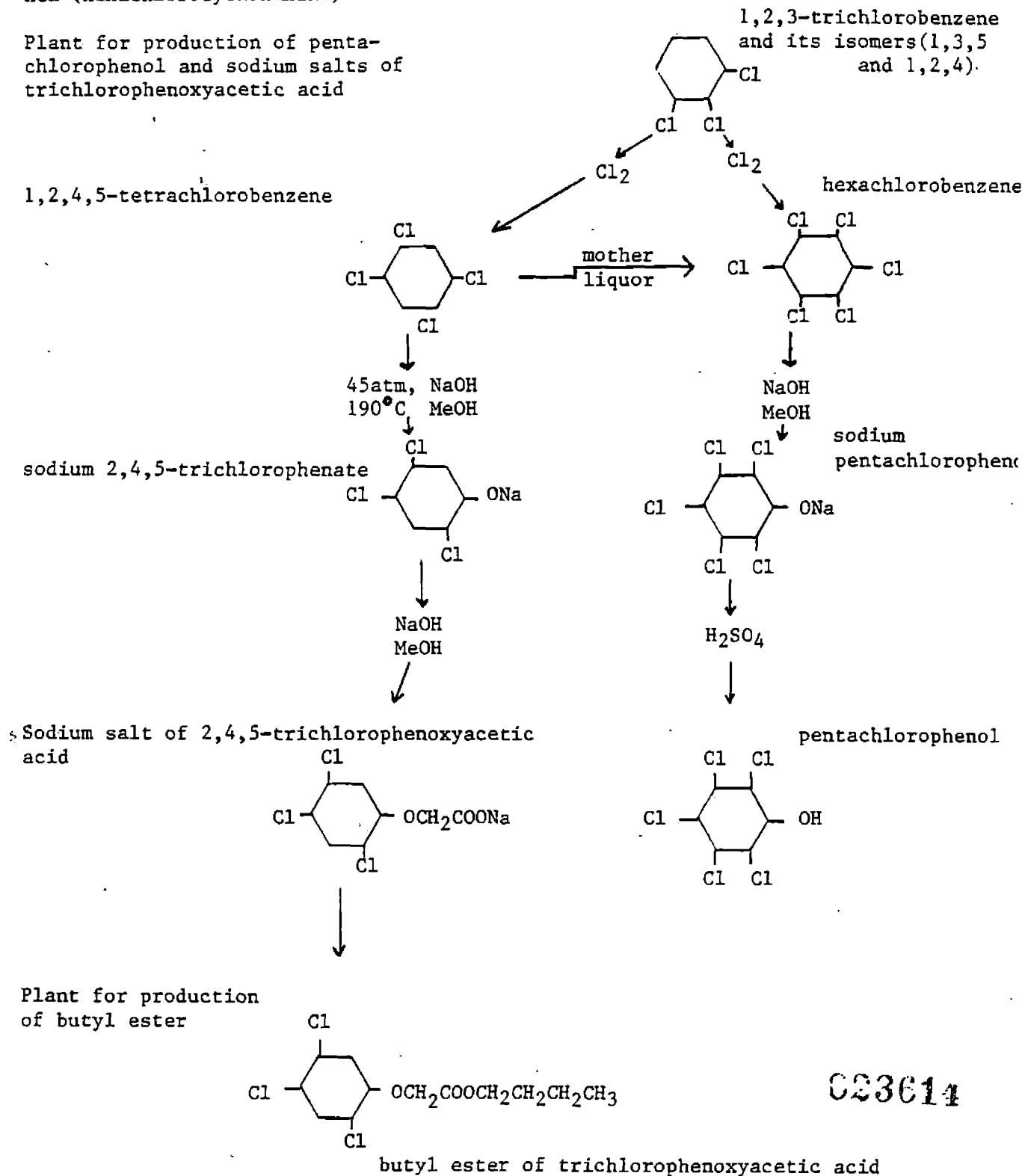
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TABLE Q-1: PRODUCTION SCHEME

Plant for production of
HCH (hexachlorocyclohexane)

Plant for production of penta-
chlorophenol and sodium salts of
trichlorophenoxyacetic acid



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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.

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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.

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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
α 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.	

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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

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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% originally). 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-comminuted 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.

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R. Company: Coalite and Chemical Products
Location: Derbyshire/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.

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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 monochloroacetic 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.

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FIGURE R-1:

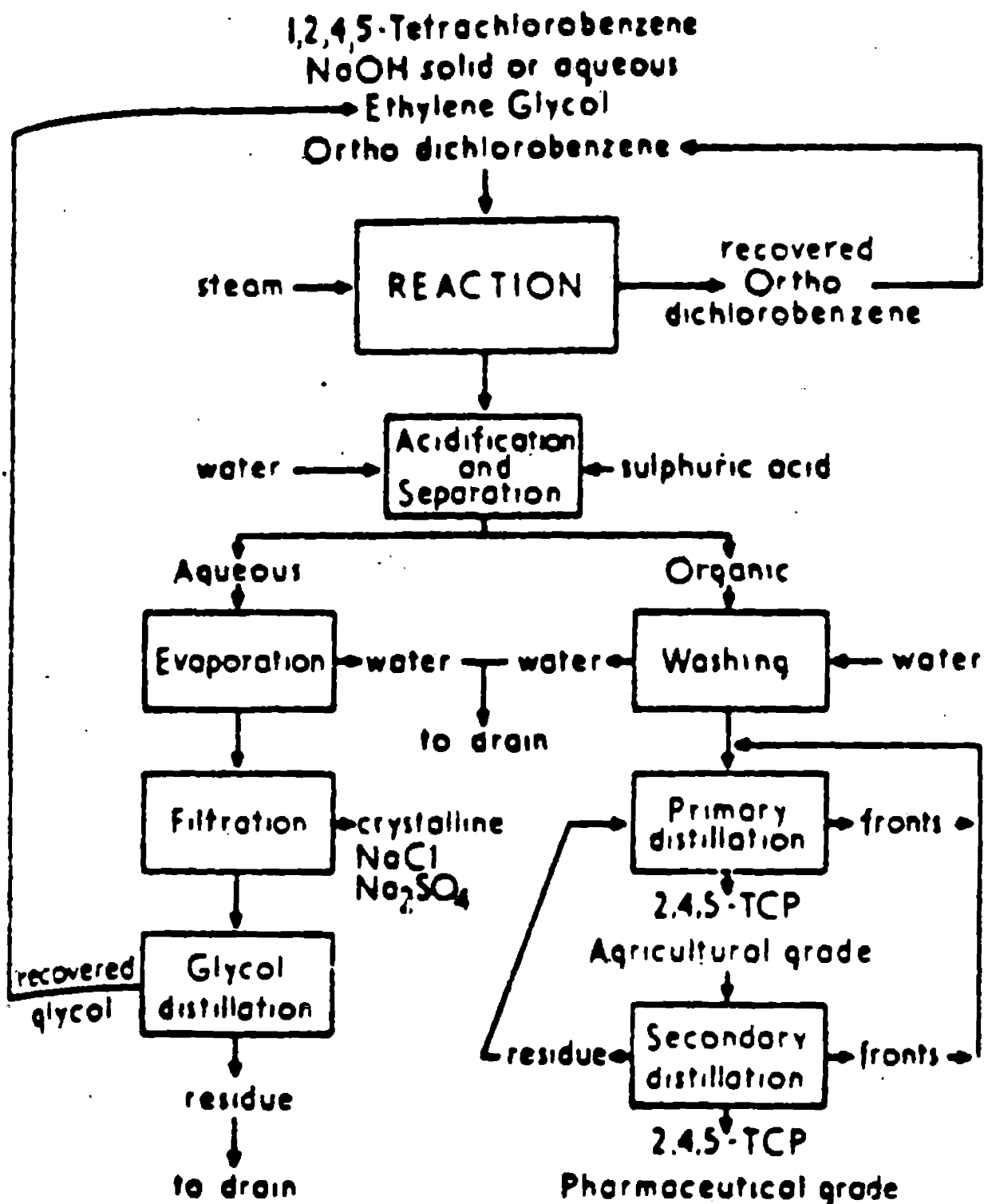


FIG. 1. Schematic representation of the reaction in 1,2,4,5-trichlorophenol production.

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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 trichlorophenol 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 quantity 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.

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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.

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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 develop 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.

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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

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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 congenital 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.

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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	Bilirubin	10.6	9.9	9.6 mmoles

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.

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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 statistically 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 chloracne 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.

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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 orthodichlorobenzene or orthochlorobenzene 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.

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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.

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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.

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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).

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- 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.

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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.

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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-tetrachlorobenzene to 2,4,5-trichlorophenol by using sodium hydroxide, in a solvent of methanol at 180°C, and increased pressure.) In 1975, the process technology was purchased from Boehringer to modify the process to the low temperature method, i.e., alkaline hydrolysis of 1,2,4,5-tetrachlorobenzene 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.

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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.

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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.

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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.

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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.

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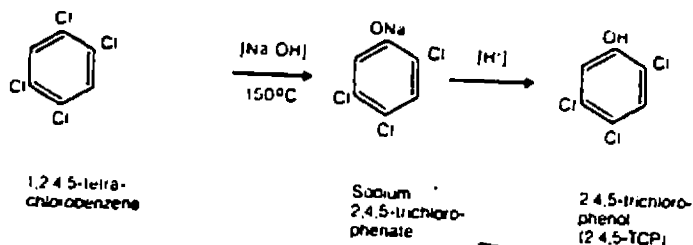
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Z. Company: ICMESA
Location: Meda/Italy
Date: 1976
References: 2, 11, 13, 20, 21, 23, 28, 29, 31, 34, 35, 38, 50,
61, 62, 67, 70, 71, 74, 81, 86, 90, 94, 96, 101

1. Process Information

2,4,5-trichlorophenol was manufactured at a small plant in Meda, Italy operated by the Industrie Chimiche Meda Societa, Anonima, (ICMESA), an Italian firm owned by the Swiss company Givaudan, which in turn was owned by Hoffman-LaRoch, a Swiss pharmaceutical 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.



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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 quantity 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.

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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.

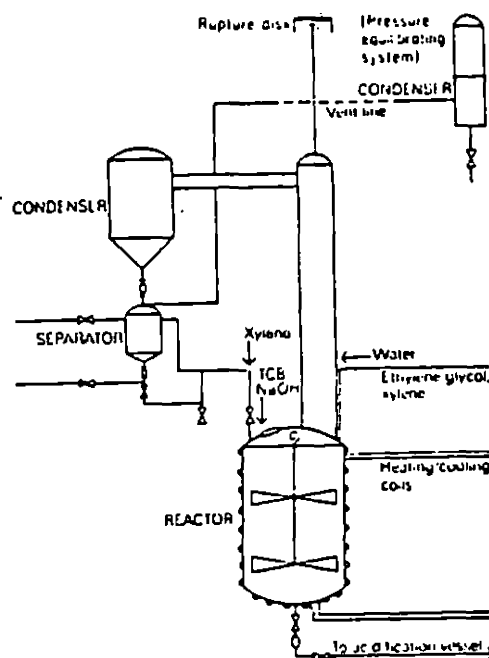


Figure Z-1: Equipment for the production of TCP.

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 trichlorophenolate 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.

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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

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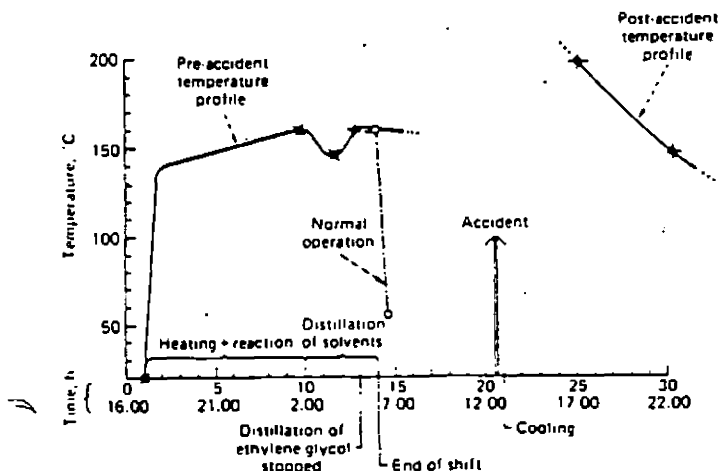
Normally, after completion of the reaction, approximately 50% of the ethylene glycol used would be distilled before the shift ended. The temperature of the reaction mixture would then be lowered to 50°-60°C thus halting any further reaction by quenching with 3,000 liters of water (dashed line).

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 temperature 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 the 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.



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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

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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, principally 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/m² 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/m² or roughly 30 ppt.

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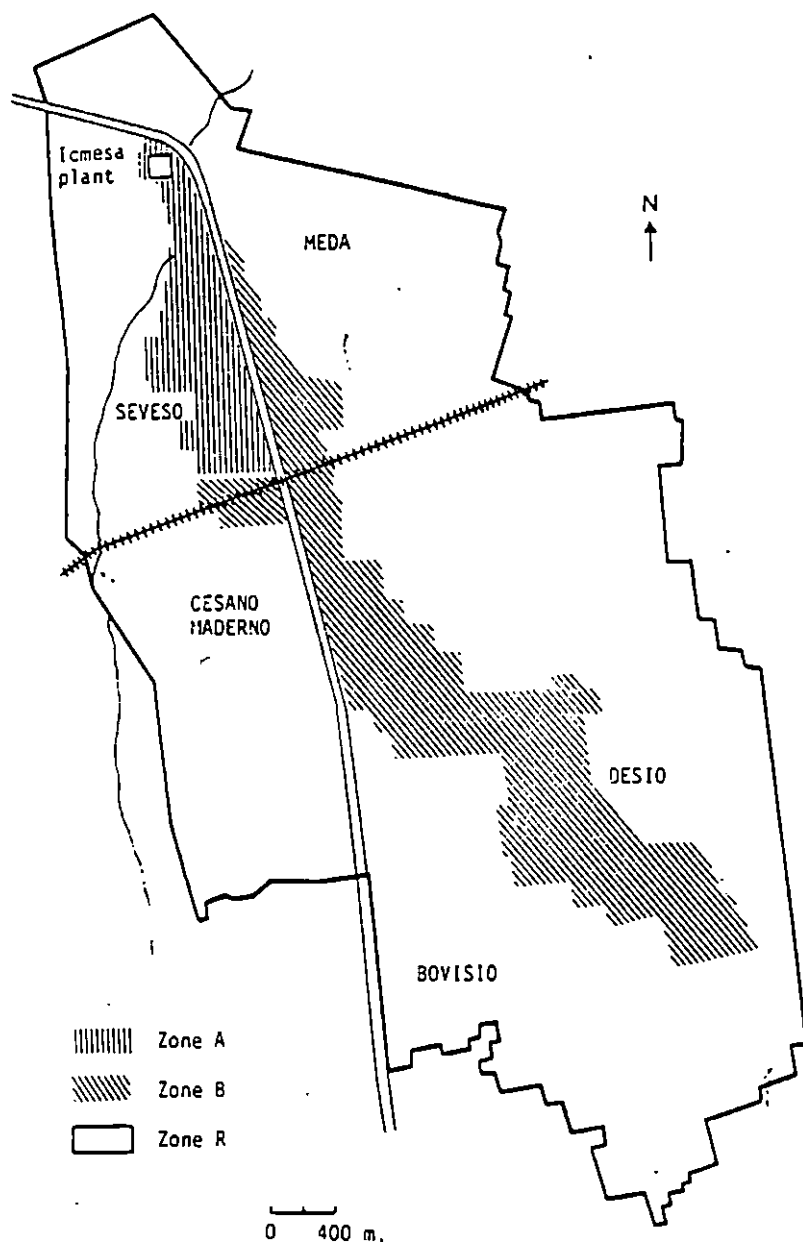


FIGURE Z-3: MAP OF THE SEVESO AREA OUTLINING ZONES, A, B AND R.

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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/m² 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 2.3.) 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 slaughtered 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

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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.

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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		0.18%	
	(159 children and 28 adults)			

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-glucuric 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 contaminated 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 therapeutic (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-Duplessis 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-Duplessis 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.

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- 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 different 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.

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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 this plant 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.

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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 diagnosis 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.

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IV. SUMMARY AND CONCLUSIONS

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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 parameters, 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

- * Monsanto Chemical Co.
Boehringer
- * BASF
- * Phillips Duphar
Dow Chemical Co.
Spolano
Linz Nitrogen Works
Bayer

Companies Using Ethylene Glycol as the Solvent in TCP Manufacture

- * Hooker Chemical Co.
- * Coalite and Chemical Products
- * ICMESA

* 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

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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 tentative 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 dosage(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 occurrence or lack of other long term health effects cited from these studies are not conclusive, but are suggestive.

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