clinical symptoms, in order of relative frequency,[4] 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 in 1949 and 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.[3,5,6]

In 1953, four of the six workers examined in 1949 and 1950 were re-examined and 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 which had been 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]

The findings of the examinations by Ashe and Suskind are consistent with those which have been reported in other industrial episodes which occurred subsequently.[1] The acute health effects of TCDD exposure are described in the literature,[7] but little is known of the chronic effects.

Several reports describe the occurrence of cancer and other deaths in workers exposed to TCDD which suggests an association between exposure and the subsequent development of a variety of neoplasms.[8-11] These reports, however, are generally of small groups of workers with relatively short periods of follow-up and are considered to be preliminary in nature. In a 25-year follow-up study, 17 deaths were observed among a cohort of 75 German workers who had been involved in a 1953 TCP process accident.[8] Of the 17 deaths observed (11-25 expected depending on the choice of a control population), six were from cancer (four or fewer expected), five from cardiovascular disease (as expected), two from suicide (fewer than one expected), one from liver cirrhosis, one from a urogenital tract disease, and two from external causes. Of the six cancer deaths, three were from stomach cancer in the age group 60-69, a number significantly higher than expected. Two other cancer deaths were from oat-cell carcinoma of the lung and one was from adenocarcinoma of the colon.

A similar accident occurred in the Netherlands in 1963 in a factory producing 2,4,5-T.[8] Eight deaths have been observed among 93 exposed workers. Five or six of these deaths were from cardiovascular disease. The proportion of deaths due to myocardial infarction was noted to be high.

Jirasek et al[9,10] and Pazderova[11] followed 55 of the 78 Czechoslovakian workers who were affected by chloracne resulting from occupational exposure to 2,4,5-T and pentachlorophenol. In this study, five deaths were observed. These included two deaths from bronchiogenic carcinoma (less than one expected), one from cardiovascular disease, one from liver cirrhosis, and one from an accidental industrial intoxication.

In 1976, a TCP process accident in Meda, Italy, resulted in the contamination of a large and densely populated area.[8] A preliminary mortality study has been conducted in two of the 11 towns affected. The overall mortality rate did not differ from that expected, but increases in deaths from liver cirrhosis and leukemia were suggested.

The chronic toxicity of TCDD exposure to animals has been more extensively studied. TCDD toxicity has been thoroughly reviewed.[7] Chronic toxicity to TCDD is manifested by liver necrosis, thymic atrophy, and depletion of the lymphoid organs. Two studies indicate that chronic administration of low levels of TCDD to rats is associated with an increased incidence of neoplasia. In one study, the oral administration of TCDD produced an increase in hepatocellular carcinomas and squamous cell carcinomas of the lung, hard palate/nasal turbinates, or tongue.[12] In another study, TCDD fed to rats produced tumors in 38% of the test animals.[13] Neoplastic nodules and cholangiocarcinomas of the liver were observed.

The study reported here will examine the mortality experience of a cohort of 121 employees involved in the 1949 trichlorophenol process accident, with special emphasis on cardiovascular disease and on neoplasms, particularly of the stomach, liver, lung, and skin.

Population and Methods

In this study, the development of chloracne, a hallmark of TCDD exposure, was used to identify employees for study. The study population consists of all persons with chloracne which could be attributed to the 1949 TCP process accident. One hundred and twenty-two employees who developed chloracne following this incident were identified from plant safety records dating to the time of the accident, and from workmen's compensation and plant medical records. One hundred and twenty-one white males were included in this study — one female who was living as of the endpoint of the study was not included in this mortality analysis. It is assumed that all of the skin disorders recorded in the plant records represent true cases of chloracne and not other types of occupational or nonoccupational dermatitis. An analysis of the chloracne cases and exposures not associated with this accident but rather with the normal TCP/2,4,5-T production processes will be the subject of a future paper.

The data were analyzed by the modified life-table method using the updated Monson program.[14] In this method of analysis, the age-, race-, time- and cause-specific mortality rates for a standard population (in this case, the population of the United States) are applied to the person-years lived classified by age, race, and time. A standardized mortality ratio was calculated as the ratio of the observed deaths to the expected deaths for 22 selected causes of death. The statistical significance of differences between observed and expected numbers was based on the Poisson distribution and statistical significance was determined at the 5% level of significance.

For the purpose of analysis, each member of the study cohort was assumed to have entered the study on March 8, 1949, the date of the accident. The vital status of each member was determined using standard follow-up techniques and ascertained as of December 31, 1978. For each person found to be deceased, a death certificate was ob-

Table 1. — Observed and Expected Deaths Among 121 Males Exposed to Tetrachlorodibenzodioxin in a Trichlorophenol Process Accident.

Cause	ICD No. (Eighth Revision)	Observed	Expected	SMR
All causes of death		32	46.41	0.69*
All malignant neoplasms	140-209	9	9.04	1.00
Buccal cavity and pharynx	140-149	0	0.30	†
Digestive organs and peritoneum	150-159	0	2.59	†
Stomach	151	0	0.50	†
Liver	155-156	0	0.18	†
All other digestive organs	—	0	1.91	†
Respiratory system	160-163	5	3.02	1.66
Lung	162,163	5	2.85	1.75
All other respiratory organs	—	0	0.17	†
Skin	172,173	1	0.15	†
Genitourinary organs	185-189	0	1.16	†
Lymphatic and hematopoietic tissue	200-209	3	0.88	†
Other sites	—	0	0.94	†
Diseases of the nervous system and sense organs	320-389	0	0.36	†
Diseases of the circulatory system	390-458	17	25.01	0.68
Arteriosclerotic heart disease, including coronary heart disease	410-413	13	17.74	0.73
All other disease of the circulatory system	—	4	7.27	†
Diseases of the respiratory system	460-519	1	2.78	†
Diseases of the digestive system	520-577	0	2.26	†
All other diseases	—	2	3.18	†
External causes of death	800-998	3	3.78	†

*$p < 0.05$
†Less than 5 observed deaths

tained. The underlying cause of death was coded to the 8th Revision of the International Classification of Diseases, Adapted[15] by an experienced nosologist.

Results

All of the 121 members of the study cohort were traced. Eighty-nine were verified living and 32 were verified deceased by death certificate.

The results of the standardized mortality analysis of the 121-member study cohort are shown in Table 1. The standardized mortality ratio for all deaths is shown to be 0.69, with 32 observed deaths and 46.41 expected. This is the only statistically significant difference shown in this table. There were nine deaths from malignant neoplasms with 9.04 expected. There were no deaths from stomach or liver 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 presumably of dermal origin, which is rare. There were three deaths from neoplasms of lymphatic and hematopoietic tissue with 0.88 expected.

There were 17 observed deaths from circulatory diseases with 25.01 expected. The standardized mortality ratio for circulatory diseases was low at 0.68.

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

Discussion

Because the study cohort was small and only 32 deaths were observed, the results cannot be considered conclusive. Nevertheless, the analysis of the mortality experience of these workers indicated no apparent excess of total mortality or of deaths due to malignant neoplasms or circulatory diseases.

The TCDD-exposed workers in the present study represent the largest group ever investigated after long-term follow-up. The criteria for inclusion (presence of the workers at the 1949 accident and the subsequent occurrence of chloracne) limit the group to those with a significant exposure at that time. The latency period of 29 years

Table 2. — Cancer Deaths Among a Cohort of 121 Males Exposed to Tetrachlorodibenzodioxin in a Trichlorophenol Process Accident.

Year of Birth	Year of Hire	Year of Death	Death Certificate Statement of Cause of Death	Smoking History*
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)	Nonsmoker
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

is longer than that of any previous study, and the follow-up is complete. Therefore, although the cohort is small, it represents the best opportunity so far to study the long-term effects of TCDD on mortality. By augmenting these data with the results of comparable mortality studies, the long-term effects of TCDD may be more definitely evaluated.

The authors wish to thank Mrs. Janet Yung, Mr. Randy Picolet, and Mrs. Phyllis Korte for their assistance with the data collection.

References

1. International Agency for Research on Cancer. IARC Monographs on the Evaluation of the Carcinogenic Risk of Chemicals to Man. Vol. 15. Some Fumigants, the Herbicides 2,4-D and 2,4,5-T, Chlorinated Dibenzodioxins and Miscellaneous Industrial Chemicals. Lyon, IARC, 1977.

2. Kimmig J. and Schulz KH. Occupational acne (so-called chloracne) due to the chlorinated aromatic cyclic esters. *Dermatologica* **115**:540-546, 1957.

3. Ashe WF and Suskind RR. Reports on chloracne cases, Monsanto Chemical Company, Nitro, West Virginia. Reports of the Kettering Laboratory, December 1949 and April 1950.

4. Suskind RR. A clinical and environmental survey, Monsanto Chemical Company, Nitro, West Virginia. Report of the Kettering Laboratory, July 1953.

5. Suskind RR. Chloracne and associated problems. Report to the Conference of the National Institute of Environmental Health Sciences on Chlorinated Dibenzodioxins and Dibenzofurans, April 3, 1973.

6. Suskind RR. Chloracne and associated health problems in the manufacture of 2,4,5-T. Report to the Joint Conference, National Institute of Environmental Health Sciences, International Agency for Research on Cancer, Lyon, France, January 11, 1978.

7. Young AL, Calcagni JA, Thalken CE, et al. The toxicology, environmental fate, and human risk associated with herbicide orange and its associated dioxin. U.S. Air Force Occupational and Environmental Health Laboratory Report OEHL TR-78-92, Brooks Air Force Base, Texas, 1978.

8. International Agency for Research on Cancer. Long-term hazards of polychlorinated dibenzodioxins and polychlorinated dibenzofurans. IARC Internal Technical Report No. 78/001, Lyon, 1978.

9. Jirasek L, Kalensky J, and Kubec K. Acne chlorina and porphyria cutanea tarda during the manufacture of herbicides. *Cesk Dermatol* **48**:306-317, 1973.

10. Jirasek L, Kalensky J, Kubec K, et al. Acne chlorina, porphyria cutanea tarda, and other manifestations of general poisoning during the manufacture of herbicides. II. *Cesk Dermatol* **49**:145-157, 1974.

11. Pazderova J, Lukas E, Nemcova M, et al. Chronic poisoning by chlorinated hydrocarbons formed in the production of sodium 2,4,5-trichlorophenoxyacetate. *Prac Lek* **26**:332-339, 1974.

12. Kociba RJ, Keyes DG, Beyer JE, et al. Results of a two-year chronic toxicity and oncogenicity study of 2,3,7,8-tetrachlorodibenzo-p-dioxin in rats. *Toxicol Appl Pharmacol* **46**:279-303, 1978.

13. Van Miller JP, Lalich JJ, and Allen JR. Increased incidence of neoplasms in rats exposed to low levels of 2,3,7,8-tetrachlorodibenzo-p-dioxin. *Chemosphere* **6**:537-544, 1977.

14. Monson RR. Analysis of relative survival and proportional mortality. *Comput Biomed Res* **7**:325-332, 1974.

15. Eigth Revision, International Classification of Diseases, Adapted for Use in the United States. U.S. Department of Health, Education and Welfare, Public Health Service, PHS Publication No. 1693. Washington: U.S. Government Printing Office, 1977.