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A Mortality Analysis of Employees Engaged in the Manufacture of 2,4,5-Trichlorophenoxyacetic Acid

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There have been few published reports regarding surveillance of individuals occupationally exposed to 2,4,5-trichlorophenoxyacetic acid (2,4,5-T). The present study examined the mortality experience of 204 persons exposed to 2,4,5-T during its manufacture from 1950 to 1971. Length of employment in job assignments within the 2,4,5-T process area ranged from less than one year to a maximum of approximately ten years. Efforts to minimize 2,3,7,8-tetrachlorodibenzo-p-dioxin (TCDD) contamination of the product resulted in nondetectable concentrations using a method of detection developed in 1966 that was sensitive to 1 part per million. Within the scope of this mortality survey, no adverse effects were observed with respect to occupational exposure to 2,4,5-T or its feedstock, 2,4,5-trichlorophenol.

In 1976 Muranyi-Kovacs et al¹ published results of a bioassay of 2,4,5-trichlorophenoxyacetic acid (2,4,5-T) for carcinogenicity. The 2,4,5-T, which contained less than 0.05 parts per million (ppm) of 2,3,7,8-tetrachlorodibenzo-p-dioxin (TCDD), was found to produce a significant increase in non-incident tumors (diagnosed during life or causing the death of the animal) in C3HF mice, but not in XVIIC mice. Both groups of mice had been fed 80 ppm 2,4,5-T on a daily basis until death. Previously, considerable variation between species had been demonstrated in the kinetics of excretion of 2,4,5-T.² An earlier screening bioassay study by Innes et al³ was not positive for tumorigenicity in two hybrid strains of mice fed 60 ppm 2,4,5-T in their diets. The authors of the 1976 bioassay article, aware of the kinetic studies and paper by Innes, suggested that additional testing of 2,4,5-T was needed. A two-year feeding study in rats was conducted in Midland, Michigan (Kociba et al⁴). Concentrations of up to 30 mg of 2,4,5-T per kilogram per day did not induce any treatment-related tumors.

Only limited epidemiological investigations of employees exposed to 2,4,5-T have been conducted.⁵⁻⁶ In 1971, Poland et al⁶ reported results of a health survey of 73 male employees in a 2,4,5-T and 2,4-dichlorophenoxyacetic acid (2,4-D) manufacturing plant. This survey was a follow-up of studies published by Bleiberg et al⁷ in 1964 on 29 employees in the same plant. An important finding in the follow-up was evidence of varying degrees of acne in 48 of the 73 employees. The term "chloracne" was employed to describe the moderate to severe lesions observed for 13 (18%) of the individuals. No evidence of abnormal excretion of uroporphyrins was found in the follow-up study, in contrast to the findings of the original study. Also, in their summary the authors stated that markedly less evidence of toxicity was found in other organ systems, such as the liver, than was reported in previous studies. Although not judged to be explanatory of differences in toxicity seen from the earlier work, TCDD contamination of the process-starting material, 2,4,5-trichlorophenol (TCP), had been reduced from 10-25 ppm to 1 ppm six months before the second survey. No detailed industrial hygiene measurements of 2,4,5-T or TCDD levels in the work environment were provided.

The present study examines the mortality experience of a cohort of 204 employees engaged in the manufacture of 2,4,5-T. A review of health examination findings of phenoxy herbicide workers in this plant was discussed in a paper by Johnson.⁸ The current survey compares mortality due to specific causes with that of the corresponding U.S. white male population, and with results of other mortality studies conducted at this company location.

History of Process and Industrial Hygiene Measurements

The commercial production of 2,4,5-T in the company began in March 1950, with the original process being operated continuously until it was permanently shut down in May 1971. In 1967, a second operation was developed which employed different personnel and which has continued in production. Personnel from the

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second process were not included in the present study because of the shorter latency period, and because this more recent process is for the manufacture of esters of 2,4,5-T without isolation of the acid. 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.

The 2,4,5-T was manufactured by reacting sodium monochloracetate with the sodium salt of TCP, the salt being prepared by adding caustic to TCP. This was followed by conversion to the acid. An additional step, not considered part of the process but taking place in the same building, was esterification of 2,4,5-T with propylene glycol butyl ether or with isooctyl alcohol. 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 $\mu\text{g}/\text{sample}$, 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.

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 $< 0.1 \text{ mg}/\text{m}^3$ to $6.2 \text{ mg}/\text{m}^3$. Estimated time-weighted average (TWA) concentrations for the three compounds by job classification are shown in Table 1. Concentrations of these substances were relatively similar for three of the job classifications:

Table 1. — 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.

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 $0.1 \text{ mg}/\text{m}^3$ of 2,4,5-T or less than $4 \text{ mg}/\text{m}^3$ 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.

Method of Analysis

The employees included in the study were determined by a two-stage procedure. The first step was the identification, from annual census lists covering the period January 1951 through January 1971, of all persons who had worked in the department under which the process was organized. The second step was a review of the complete work history for each individual to determine those who had had experience on any of the four jobs of interest. These employees constituted the population of concern. This method of selecting the exposed population insured that all employees who worked continuously for at least one year in the 2,4,5-T work area were included, but could have missed some personnel who worked in the exposure area for shorter periods of time.

A crew of eight to 12 men operated the 2,4,5-T process on a daily basis. The flow of employees in and out of the department over the 21-year period resulted in 204 men having worked for one or more months on at least one of the four jobs involved. The mortality experience of these men was compared, by the indirect method, with that of the U.S. white male population (five-year age intervals) for the years 1952, 1957, 1962, 1967 and 1971. The vital status of former employees was traced initially through the Social Security Administration. Subsequently, verification of vital status has been obtained through contact with the individual or with relatives who could account for the former employee's vital status.

Table 2. — Vital and Employment Status of 204 Workers Exposed to 2,4,5-T as of December 31, 1976.

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

Table 3. — 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.

In this analysis, exposure is expressed only in terms of length of employment on the four jobs of primary concern. Exposure durations do not take into account the unmeasured exposures to 2,4,5-T or to esters of 2,4,5-T encountered on other jobs within the production department. One job did involve exposure to esters of 2,4,5-T, and several other jobs may have required filling in on a day-to-day basis for the operators in the four classifications of interest, as well as other duties with minimal exposure. Since many of the employees in the 2,4,5-T study worked on a number of jobs within the department, the durations of exposure are conservatively estimated. Sixty of these employees are also known to have worked in a styrene-butadiene latex plant organized within the production department. Thus, the persons included in the present study have been exposed to a variety of chemical compounds during their employment.

Results

The vital and employment status of the 204 workers exposed to 2,4,5-T and its sodium salts are shown in Table 2. Fifty-three of the 56 former employees have been traced through personal contact with the individual or with someone who currently knows him. For three persons vital status was verified at least through 1973, but not through 1976, by personal contact or by social security checks. Two former employees had died as of the end of 1976 and nine deaths were observed among individuals followed through employment and retiree records.

The distribution of employees by duration of exposure and by date first exposed is shown in Table 3. More than 75% of the men had worked for less than 12 months in jobs involving defined exposure. None of the men were exposed to 2,4,5-T over a working lifetime.

Medical records of employees were reviewed for evidence of chloracne or of porphyria cutanea tarda, which might indicate exposure to TCDD. No case of chloracne or of porphyria cutanea tarda was found.

Tables 4 and 5 summarize mortality by duration of exposure and by interval since first exposure. In Table 4, observed deaths were increased over expected only for the cause of death category "external causes" (6 observed vs. 3.7 expected). Three deaths in this category were due to separate automobile accidents, none of which took place while the individuals were employed on jobs involving 2,4,5-T exposure. One death was the result of a non-industrial fire, and the remaining two deaths were suicides of former employees which occurred more than ten years after exposure had ceased. The single observed malignancy death in the cohort to date was due to a respiratory malignancy which was discovered in a 63-year-old retiree who had been exposed to 2,4,5-T for eight years and who had a past history of smoking up to two packs of cigarettes per day.

The trend of deaths with respect to interval since first exposure follows a pattern which we have observed in other studies at this company location.⁹ The most favorable mortality experience occurs in the early years after first exposure, followed by a relative increase compared to general population mortality. We have interpreted these findings to indicate a preselection effect due to initial employment or transfer of individuals in a state of good health, which becomes less important both as the interval since employment increases and as the employees become older.

Comment

At the exposure concentrations of TCP and of 2,4,5-T (1966 product specification called for <1 ppm TCDD in the final product) experienced by the workmen in this study, no adverse mortality effects have been observed in association with the work environment. Within the scope of this limited survey, mortality has been favorable compared to that of U.S. white males, and also compares well with the background mortality experience at this manufacturing location.⁹ The mortality comparisons

Table 4. — 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 deaths based on U.S. white male mortality rates.

Table 5. — 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 Years		10-14 Years		15-19 Years		20+ Years	
	Observed	Expected	Observed	Expected	Observed	Expected	Observed	Expected
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	2.0	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 deaths based on U.S. white male mortality rates

presented in Tables 4 and 5 are point estimates and, as such, do not directly reflect imprecision in the estimates due to small sample size. Confidence interval and power calculations may be carried out using the data provided in the tables and tabulations of the Poisson distribution. Alternately, the largest SMR or relative risk that is consistent with the observations may be stated. For example, the probability of observing less than two deaths due to malignant neoplasms 15 or more years after first exposure (one actually observed), when, in fact, the true relative risk is two, is about 15%. If the true relative risk were four, the probability of observing less than two deaths would be 0.01. Because of questions raised by recent animal toxicological studies, mortality surveillance of this limited employee population will be continued. The mortality surveillance of other populations which have had past exposure to 2,4,5-T is recommended.

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Skills Productive Capital

The 1979 recipients of the Nobel Prizes for economics are W. Arthur Lewis, of Princeton University, and Theodore W. Schultz of the University of Chicago.

Schultz revived interest in human capital. He emphasized the extent to which the welfare of nations and individuals is determined by the amount of capital they have in the form of the productive skills of human beings, which has been acquired by investment in education, training, research and experience.

The second main idea associated with Schultz is the insistence, based on observation, that the behavior of people of all kinds, not only graduates of the Harvard Business School but also Indian villagers, can be explained on the assumption that they make rational and efficient use of the resources and information they have.

— From "Nobel Winner Deal With People, Not Theory" by Herbert Stein, in *The Pittsburgh Press*, October 28, 1979.