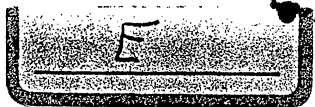


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STUDY FAILS TO LINK
AGENT ORANGE TO DEATHS
OF INDUSTRIAL WORKERS

ST. LOUIS, Oct. 9 -- Monsanto Company today reported that no apparent relationship exists between TCDD, the toxic dioxin contaminant in "Agent Orange," and the cause of death of 58 employees potentially exposed to it during 2,4,5-T herbicide production at the company's Nitro, W. Va., plant.

This finding was among those reached in a new study, co-authored by Monsanto epidemiologist Judith A. Zack and Raymond R. Suskind, M.D., of the University of Cincinnati Medical Center. Their investigation examined the cause of death of all hourly workers who had been active employees of the plant for one or more years between 1955 and 1977 and have since died from any and all causes. The entire group was successfully traced and all deaths verified by death certificate.

Monsanto produced 2,4,5-T at its Nitro plant from 1948 until 1969. It is currently the subject of widespread controversy centering on its use in the defoliant Agent Orange during the Vietnam War.

This is the second major effort undertaken to examine the mortality (cause of death) of Nitro plant workers, either exposed or potentially exposed to TCDD. Mrs. Zack and Dr. Suskind earlier this year co-authored a separate but related study of employees who had experienced high peak exposure

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to TCDD during an industrial accident at the plant in 1949. The results of that investigation, published in the January, 1980 issue of The Journal of Occupational Medicine, indicated no excess in total deaths or in deaths from cancer or cardiovascular disease.

In this larger, follow-up effort, the mortality experience of the total Nitro plant workforce was analyzed by the modified life-table method using the U.S. population as the standard. Of the 884 men identified for study, 721 (82%) were verified as still alive and 163 (18%) were confirmed dead by death certificates. The study found no statistically significant excess in total deaths or deaths due to cancer or disease of the nervous system, circulatory system, respiratory system or digestive system.

The study did confirm and quantify an apparent excess in bladder cancer among Nitro Plant workers (nine observed vs 0.91 expected) which has been known for many years. This finding reflects the established and previously documented association between exposure to Para-aminobiphenyl (PAB) and cancer in man. PAB was used at Nitro from 1941 through 1952, for use as a rubber antioxidant and dye intermediate. Its use was discontinued when its cancer-causing potential was confirmed.

The authors pointed out that an intensive screening program was instituted by the company about 1955 to examine, on a continuing basis, all workers exposed to this chemical.

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Seven PAB-related deaths from bladder cancer have occurred among Nitro Plant employees enrolled in this program over these 25 years. These seven deaths are included in this study.

A review of the work history records of the 163 decedents further revealed that 58 (35.6%) had been exposed to 2,4,5-T and potentially to TCDD. One hundred four (63.8%) were considered non-exposed and the exposure of one decedent was not determined. The mortality experiences of these two subgroups were then compared using the proportional mortality method. This was done to test whether any relationship existed between potential TCDD exposure and proportional mortality. No such relationship was observed nor were any unusual patterns of mortality found in this exercise other than the PAB-related deaths described earlier.

The expected number of deaths in the 2,4,5-T subgroup was calculated on the basis of the percentage of deaths from various causes in the U.S. general population. Specifically, cancer deaths among 2,4,5-T workers (nine observed versus 10.94 expected) were found to be lower than in the non-exposed group (25 observed versus 20.43 expected).

Deaths due to disease of the nervous system, respiratory system and digestive system were also found to be lower than one would expect to find in a group of this size.

While not statistically significant, deaths due to disease of the circulatory system (largely arteriosclerotic heart disease) were elevated at 31 versus 26.48 expected.

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The analysis of the total Nitro plant population found a similar excess in deaths from arteriosclerosis. In the discussion section, the authors pointed out that these excesses most likely reflect the higher mortality from heart disease which has been observed for Charleston and Kanawha County, W. Va.

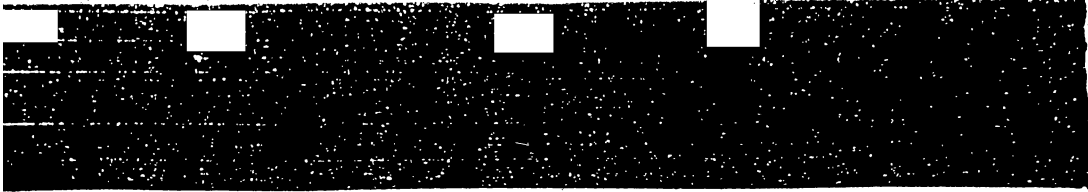
A third study, based on health information gathered from extensive physical examinations of over 400 present and former Nitro plant employees is currently being conducted solely by Dr. Suskind and his medical team from the University of Cincinnati's Institute of Environmental Health.

Included in this ongoing study are both those workers exposed during the 1949 accident as well as those exposed during normal 2,4,5-T operations between 1948 and 1969 when the unit was shut down. A control group of employees who worked in other areas of the plant during that time frame is also being studied for comparative purposes. The results of this study are expected later this year and will be submitted for publication in an appropriate medical journal.

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Human and Environmental Risks of Chlorinated Dioxins and Related Compounds

Human and Environmental Risks of Chlorinated Dioxins and Related Compounds

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original
file: dioxin

MORTALITY STUDY OF WORKERS EMPLOYED AT THE
MONSANTO COMPANY PLANT IN NITRO, WEST VIRGINIA

Judith A. Zack and William R. Gaffey

Monsanto Company
St. Louis, Missouri USA

BACKGROUND

The compound 2,3,7,8-tetrachlorodibenzo-p-dioxin (TCDD) is a highly toxic impurity that is formed in trace quantities during the reduction of 2,4,5-trichlorophenoxyacetic acid (2,4,5-T). Exposure to TCDD can cause chloracne, a skin disorder characterized by comedones, cysts, and abscesses.¹ Outbreaks of chloracne have been reported among workers associated with the production of 2,4,5-T and 2,4,5-T based products. Such incidents resulting from both accidental and routine occupational exposures have been reported from several countries.²

The first reported industrial accident involving exposure to TCDD occurred in 1949 at the Monsanto Company plant in Nitro, West Virginia. A total of 122 employees developed symptoms of chloracne following a trichlorophenol (TCP) process accident. An undetermined number of other employees developed symptoms of chloracne resulting from exposure to the regular operations concerned with 2,4,5-T production over the period 1948-1969.

Between 1949 and 1953, Ashe and Suskind^{3,4} examined thirty-eight Nitro plant employees with chloracne. Twelve of these had developed symptoms of chloracne directly following the 1949 TCP accident; twenty-six other chloracne cases had resulted from exposure to the regular 2,4,5-T production operations. In addition to chloracne, other signs and symptoms were observed in this group. These included severe aches in the lower extremities, fatigue, nervousness and irritability, loss or decrease of libido, dyspnea, and vertigo. These findings are consistent with those that have been reported in other industrial incidents.⁵

To examine the chronic health effects of exposure to TCDD, a mortality study of the Nitro plant employees who had developed symptoms of chloracne following the 1949 TCP accident was conducted.⁶ The study cohort was comprised of 121 of the 122 chloracne cases; one female who was living as of the endpoint of the study was excluded from analysis. At the time of the incident, it was assumed that the symptoms were caused by exposure to unknown products of decomposition. From today's vantage point, these symptoms suggest exposure to TCDD. The 121-member study cohort, with a presumptive high-peak exposure to TCDD, was followed for mortality through 1978. The entire cohort was traced: thirty-two deaths were observed and eighty-nine persons were confirmed as living. Analysis indicated no excess in total mortality or in deaths from malignant neoplasms.

The study presented here examines the mortality of Nitro plant workers who were assigned to an area of TCP or 2,4,5-T production, with potential for exposure to TCDD. The mortality of these workers is examined in the context of the mortality experience of the total Nitro plant worker population.

The Monsanto Nitro plant began operations in 1922, when the Rubber Service Laboratories purchased the plant as war surplus and began production of chemicals and additives for the growing rubber industry. In 1929, Monsanto Company purchased the Nitro plant from the Rubber Service Laboratories and entered the rubber chemicals business. Over the years, the Nitro plant has diversified to where it now produces agricultural chemicals, paper chemicals, plasticizers, fine chemicals, and intermediates, in addition to rubber chemicals. The plant is situated in the Kanawha River Valley, an area containing one of the largest concentrations of chemical production facilities in the United States.

Of the many chemicals used over the years at the Nitro plant, one has an established association with the occurrence of cancer in man. Para-aminobiphenyl (PAB), used from 1941 through 1952 for use as a rubber antioxidant and dye intermediate, was shown in 1954 by Walpole et al.⁷ to induce bladder cancer in dogs. In 1955, Melick et al.⁸ confirmed the carcinogenicity of para-aminobiphenyl to man with the reporting of bladder tumors among workers exposed to this chemical at two Monsanto plants. Para-aminobiphenyl was produced at one plant and then transferred by tank car to the Nitro plant where additional processing was carried out. The minimum duration of exposure reported to have produced a bladder tumor is 133 days; the latent period has ranged from 15 to 35 years.⁹ An intensive screening program was instituted at Monsanto Company about 1955 to examine, on a continuing basis, all workers exposed to this chemical. Seven deaths from bladder cancer have occurred among Nitro plant employees enrolled in this program. These seven deaths are included in the present study.

Other chemicals with known health effects produced at the Nitro plant include methylparathion and carbon disulfide. The acute effects of exposure to each of these chemicals have been described^{9,10} while the chronic effects are less well understood. Besides p-aminobiphenyl, several other rubber chemicals are of potential health concern. For all of these, there is insufficient evidence to evaluate their carcinogenicity to man. Tetramethyl thiuram disulfide is considered an animal carcinogen¹¹ and there is some evidence, although not sufficient, that N-methyl-N,4-dinitrosaniline is also an animal carcinogen.¹² For several other rubber chemicals, there is insufficient evidence to evaluate the carcinogenicity to animals. However, these chemicals have the potential for forming nitrosamines, certain of which are known animal carcinogens.¹³ Zinc dimethyl dithiocarbamate, tetramethyl thiuram disulfide and tetramethyl thiuram monosulfide have the potential to form N-nitrosodimethylamine. N-Nitrosomorpholine has been found in product samples of 2-(morpholiniothio) benzothiazole and 4,4'-dithiodimorpholine (Frisone, G.J., The General Tire and Rubber Company, unpublished data).

Although several of the chemical compounds produced or used at the Nitro plant over the years have been associated with adverse health effects, no attempt has been made to relate chemical exposure to mortality with the exception of decedents exposed to the TCP or 2,4,5-T operations and potentially exposed to TCDD. As a result, the only specific hypothesis that can be tested is whether a relationship exists between potential TCDD exposure and proportional mortality, especially for malignant neoplasms. The mortality for this group is examined in addition to that of the total Nitro plant worker population.

POPULATION AND METHODS

A study cohort was developed from the Nitro plant consisting of employees active on or after January 1, 1955 with one or more years of employment on the hourly roll prior to December 31, 1977. Salaried personnel who had never worked on the hourly roll were excluded from study because many of these employees had no appreciable exposure to the plant environment and, for the most part, their exposure cannot be determined from plant records. Females and non-white males were also excluded because of their small numbers.

The cohort was assembled using government earnings reports, independent of the plant work history records. Annual earnings reports were available on a computer file from 1951 through 1977. Names and social security numbers were identified from this source. Work history records were used to supplement the earnings records. Information on race, sex, date of birth, date of hire, date of separation, and, if deceased, 2,4,5-T exposure was abstracted from these records. Ascertainment of 2,4,5-T exposure was confined to decedents only because it was too tedious to do for the entire cohort. The

information from the work history records was used to determine which names identified from the annual earnings records met the cohort entrance criteria. Employees identified from the earnings records who terminated prior to 1955 were not included in this study because work history records for all such employees were not retained prior to this date.

Exposure to 2,4,5-T was determined by assignment to a 2,4,5-T operation based on the work history records. 2,4,5-T exposure was determined for all but one decedent. Employees holding a job having plant-wide responsibilities with the potential for exposure to 2,4,5-T were, for the purposes of this study, considered to be non-exposed.

The vital status of each member of the study cohort was determined using standard follow-up techniques and ascertained as of December 31, 1977. Death certificates were coded by an independent nosologist for the underlying cause of death, according to the rules of the Eighth Revision of the International Classification of Diseases, Adapted.¹⁴

Data for the total Nitro plant study population were analyzed by the modified life-table method using the U.S. population as the standard. With this method of analysis, the age-, race-, time-, and cause-specific mortality rates for the U.S. general population are applied to the person-years lived classified by age, race, and time. A standardized mortality ratio (SMR) was calculated for 23 selected cause of death categories. Cause-specific SMR's for 15 selected cancer sites were calculated for subgroups of the total Nitro plant study population defined by date of death, age at death, and year of hire. The statistical significance of the deviation in a SMR from 100 was tested using the formula:

$$\text{standard error of SMR} = \frac{100 \sqrt{\text{no. observed deaths}}}{\text{no. expected deaths}}$$

If the observed SMR differed from 100 by 1.96 standard errors, it was regarded as significant at the 5% level. A SMR was tested for significance only when the observed number of deaths was five or greater.

Data for those deceased were also analyzed according to 2,4,5-T exposure using the proportional mortality method. In this case, the expected number of deaths is calculated on the basis of proportions of deaths observed in the U.S. general population. A proportional mortality ratio (PMR) was calculated for 23 selected cause-of-death categories. PMR's were calculated separately for those exposed to 2,4,5-T and for those not exposed. The statistical significance of the deviation of a PMR from 100 was tested by calculating the 95%

confidence interval for the PMR for a given cause k according to the formula:

$$\text{confidence interval for PMR}_k = \frac{N(\text{confidence limits for \% of observed deaths})}{\exp_k}$$

where N = number of observed deaths for all causes

Both the standardized and proportional mortality analyses were conducted using the computer program developed by Monson.¹⁵ The observed mortality was compared to that of the United States white male population for the time period of study.

RESULTS

A total of 884 men were identified for study and traced for deaths through 1977. The entire cohort was successfully traced. Death certificates were obtained for all deaths. Seven hundred twenty-one (82%) were verified as living and 163 (18%) were confirmed dead by death certificates.

Tables 1-3 characterize the total Nitro plant study population by age at hire, year of hire, and length of employment. The distribution of the study population by age at hire indicates that the workers were fairly young at first hire (Table 1). Seventy-two percent of the study cohort were hired by age 30. None were hired at age 50 or above.

Table 2 shows the distribution of the study population by year of hire. The majority of workers (75.3%) were hired during the period 1940-1959, while smaller percentages of workers were hired prior to 1940 (10.8%) and after 1960 (13.9%).

An examination of the study population by length of employment indicates a fairly even distribution over the intervals less than 10 years, 10-19 years, 20-29 years, and greater than 30 years (Table 3).

Observed and expected deaths occurring during 1955-1977 among the total Nitro plant study population are shown by cause in Table 4. The SMR for all causes of death was 103 with 163 deaths observed and 158.10 expected. There were 35 deaths from malignant neoplasms with 30.92 expected, yielding a SMR of 113. Significantly elevated SMR's were seen for the categories of malignant neoplasms of the genitourinary organs and of the bladder. The SMR for bladder cancer was 989 with 9 deaths observed and 0.91 expected. This excess in bladder cancer deaths is reflected in the elevated SMR for malignant neoplasms of the genitourinary organs. A significantly elevated SMR is also seen for arteriosclerotic heart disease. There were 79 deaths from this cause with 59.40 expected (SMR = 133). The SMR for

Table 1. Distribution of Total Nitro Plant Study Population by Age at Hire

Age at Hire	Number	Percent
<20	122	13.8
20-29	518	58.6
30-39	191	21.6
40-49	53	6.0
50+	0	0.0
Total	884	100.0

Table 2. Distribution of Total Nitro Plant Study Population by Year of Hire

Year of Hire	Number	Percent
Prior to 1930	21	2.4
1930-1939	74	8.4
1940-1949	361	40.8
1950-1959	305	34.5
1960-1976	123	13.9
Total	884	100.0

Table 3. Distribution of Total Nitro Plant Study Population by Length of Employment

Length of Employment (yrs.)	Number	Percent
<10	225	25.5
10-19	213	24.1
20-29	204	23.1
30+	242	27.4
Total	884	100.1

Table 4. Observed and Expected Number of Deaths
Standardized Mortality Ratios (SMR'S)

Cause of Death

All causes of death

All malignant neoplasms

Buccal cavity and pharynx

Digestive organs and peritoneum

Stomach

Liver

All other digestive organs

Respiratory system

Lung

All other respiratory organs

Skin

Genitourinary organs

Bladder

All other genitourinary organs

Lymphatic and hematopoietic tissue

Other sites

Diseases of the nervous system and sense organs

Diseases of the circulatory system

Arteriosclerotic heart disease, including CHD

All other diseases of the circulatory system

Diseases of the respiratory system

Diseases of the digestive system

All other diseases

External causes of death

Number at risk: 884

Person-years at risk: 13968.7

*p < .05

During 1955-1977 by Cause Showing
for Total Nitro Plant Study Population

ICDA Codes

<u>8th Rev.</u>	<u>Observed</u>	<u>Expected</u>	<u>SMR</u>
	163	158.10	103
140-209	35	30.92	113
140-149	0	1.03	0
150-159	4	8.65	46
151	1	1.63	61
155-156	0	0.60	0
---	3	6.42	47
160-163	14	10.51	133
162-163	14	9.91	141
---	0	0.60	0
172-173	0	0.58	0
185-189	12	3.75	320*
188	9	0.91	989*
---	3	2.84	106
200-209	1	3.15	32
---	4	3.25	123
320-389	0	1.28	0
390-458	92	82.59	111
410-413	79	59.40	133*
---	13	23.19	56*
460-519	6	9.13	66
520-577	5	8.03	62
---	5	10.46	48*
800-998	20	15.69	127

MORTALITY STUDY OF WORKERS

other circulatory diseases was significantly low at 56. A significant deficit was also seen for the category of all other diseases where the SMR was 48 with 5 deaths observed and 10.46 expected.

Trends for malignant neoplasm deaths with calendar time are shown in Table 5. SMR's which increased consistently over the period 1955-1977 are seen for the categories of all malignant neoplasms and malignant neoplasms of the respiratory system. The SMR for all malignant neoplasms rose from 32 to 131. The SMR for malignant neoplasms of the respiratory system rose from 0 to 172 reflecting a SMR for lung cancer which increased from 0 to 181. Although based on very small numbers, the SMR for malignant neoplasms of the digestive organs and peritoneum consistently decreased over time from 99 to 24. The SMR for malignant neoplasms of the genitourinary organs peaked during the period 1960-1969. This is reflected in the SMR for bladder cancer which increased from 0 in 1955-1959 to a peak of 1471 in 1960-1969 and decreased to 833 in 1970-1977.

The analysis of observed and expected deaths from malignant neoplasms by age at death revealed little in terms of consistent trends with age (Table 6). For most of the cause-of-death categories, the SMR peaked at age 45-64 rather than continuing to rise with increasing age. Bladder cancer is one category where the SMR remained high at age 65 and over.

The distribution of deaths from malignant neoplasms by year of hire is shown in Table 7. No deaths from malignant neoplasms were observed among workers hired after 1960. The SMR for all malignant neoplasms was similar for those hired prior to 1945 and for those hired in the period 1945-1959. The greatest difference in SMR's between those hired prior to 1945 and those hired from 1945-1959 occurs with bladder cancer. The SMR for bladder cancer is highest for those hired prior to 1945 with a SMR of 1111.

A subset of deaths identified from the total Nitro plant study population was studied separately. Table 8 characterizes the decedents according to 2,4,5-T exposure. Of the 163 decedents, 58 (35.6%) were considered to be exposed to 2,4,5-T based on their work history records, while 104 (63.8%) were considered to be non-exposed. The exposure of one decedent was unknown.

The results of the proportional mortality analysis by 2,4,5-T exposure classification are presented in Table 9. The proportion of cancer deaths among 2,4,5-T workers is lower than in the non-exposed group (PMR: 82 vs. 122). The PMR for lung cancer deaths is slightly higher in the exposed group (PMR: 159 vs. 117). The proportion of deaths due to bladder cancer is higher among the decedents not exposed to 2,4,5-T. There were 7 deaths from bladder cancer among these workers with 0.65 expected (PMR = 1077). The PMR for bladder cancer among decedents exposed to 2,4,5-T was 909 with 2 deaths observed and

Table 5. Observed and Expected Deaths from Malignant Neoplasms During 1955-1977 by Calendar Time Showing Standardized Mortality Ratios (SMR'S) for Total Nitro Plant Study Population

Cause of Death	Calendar Time								
	1955-1959			1960-1969			1970-1977		
	Observed	Expected	SMR	Observed	Expected	SMR	Observed	Expected	SMR
All malignant neoplasms	1	3.13	32	13	11.81	110	21	15.98	131
Buccal cavity and pharynx	0	0.11	0	0	0.41	0	0	0.50	0
Digestive organs and peritoneum	1	1.01	99	2	3.48	57	1	4.16	24
Stomach	0	0.25	0	0	0.70	0	1	0.69	145
Liver	0	0.09	0	0	0.28	0	0	0.23	0
All other digestive organs	1	0.67	149	2	2.50	80	0	3.24	0
Respiratory system	0	0.87	0	4	3.83	104	10	5.81	172
Lung	0	0.80	0	4	3.59	111	10	5.52	181
All other respiratory organs	0	0.07	0	0	0.24	0	0	0.29	0
Skin	0	0.07	0	0	0.23	0	0	0.28	0
Genitourinary organs	0	0.33	0	5	1.37	365	7	2.05	341
Bladder	0	0.09	0	5	0.34	1471*	4	0.48	833
All other genitourinary organs	0	0.24	0	0	1.03	0	3	1.57	191
Lymphatic and hematopoietic tissue	0	0.40	0	0	1.24	0	1	1.50	67
Other sites	0	0.34	0	2	1.25	160	2	1.68	119

*p < .05

Table 6. Observed and Expected Deaths from Malignant Neoplasms During 1955-1977 by Age at Death Showing Standardized Mortality Ratios (SMR'S) for Total Nitro Plant Study Population

Cause of Death	Age at Death								
	<45			45-64			65+		
	Observed	Expected	SMR	Observed	Expected	SMR	Observed	Expected	SMR
All malignant neoplasms	2	2.39	84	21	16.85	125	12	11.69	103
Buccal cavity and pharynx	0	0.06	0	0	0.67	0	0	0.31	0
Digestive organs and peritoneum	0	0.51	0	4	4.58	87	0	3.57	0
Stomach	0	0.10	0	1	0.85	118	0	0.68	0
Liver	0	0.03	0	0	0.32	0	0	0.24	0
All other digestive organs	0	0.38	0	3	3.41	88	0	2.65	0
Respiratory system	0	0.54	0	11	6.36	173	3	3.61	83
Lung	0	0.51	0	11	5.99	184	3	3.42	88
All other respiratory organs	0	0.03	0	0	0.37	0	0	0.19	0
Skin	0	0.13	0	0	0.31	0	0	0.14	0
Genitourinary organs	1	0.20	500	3	1.43	210	8	2.12	377*
Bladder	1	0.02	5000	2	0.39	513	6	0.50	1200*
All other genitourinary organs	0	0.18	0	1	1.04	96	2	1.62	123
Lymphatic and hematopoietic tissue	0	0.55	0	1	1.60	63	0	1.00	0
Other sites	1	0.40	250	2	1.90	105	1	0.94	106

*p < .05

Table 7. Observed and Expected Deaths from Malignant Neoplasms During 1955-1977 by Year of Hire Showing Standardized Mortality Ratios (SMR'S) for Total Nitro Plant Study Population

Cause of Death	Observed	Expected	SMR	Observed	Expected	SMR	Observed	Expected	SMR
All malignant neoplasms	25	21.30	117	10	8.63	116	0	0.99	0
Buccal cavity and pharynx	0	0.70	0	0	0.31	0	0	0.03	0
Digestive organs and peritoneum	2	6.27	32	2	2.19	91	0	0.19	0
Stomach	0	1.21	0	1	0.39	256	0	0.03	0
Liver	0	0.45	0	0	0.14	0	0	0.01	0
All other digestive organs	2	4.61	43	1	1.66	60	0	0.15	0
Respiratory system	10	7.14	140	4	3.09	129	0	0.27	0
Lung	10	6.73	149	4	2.93	137	0	0.26	0
All other respiratory organs	0	0.41	0	0	0.16	0	0	0.01	0
Skin	0	0.31	0	0	0.22	0	0	0.05	0
Genitourinary organs	9	2.90	310*	3	0.76	395	0	0.09	0
Bladder	8	0.72	1111*	1	0.18	556	0	0.01	0
All other genitourinary organs	1	2.18	46	2	0.58	345	0	0.08	0
Lymphatic and hematopoietic tissue	1	1.95	51	0	1.00	0	0	0.20	0
Other sites	3	2.03	148	1	1.06	94	0	0.16	0

*p < .05

Table 8. 2,4,5-T Exposure Classification for Decedents During 1955-1977 Among Total Nitro Plant Study Population

2,4,5-T Exposure Classification	Number of Deaths	Percent
Exposed	58	35.6
Non-exposed	104	63.8
Unknown	1	0.6
Total	163	100.0

Table 9. Observed and Expected Number of Deaths During 1955-1977 by Cause and 2,4,5-T Exposure Category Showing Proportional Mortality Ratios (PMR'S)

Cause of Death	2,4,5-T Exposure Category					
	Exposed			Non-exposed		
	Observed	Expected	PMR	Observed	Expected	PMR
All malignant neoplasms	9	10.94	82	25	20.43	122
Buccal cavity and pharynx	0	0.38	0	0	0.64	0
Digestive organs and peritoneum	0	2.80	0	3	5.74	52
Stomach	0	0.52	0	0	1.06	0
Liver	0	0.19	0	0	0.39	0
All other digestive organs	0	2.09	0	3	4.29	70
Respiratory system	6	3.78	159	8	6.81	117
Lung	6	3.57	168	8	6.42	125
All other respiratory organs	0	0.21	0	0	0.39	0
Skin	0	0.29	0	0	0.35	0
Genitourinary organs	2	0.96	208	10	2.70	370*
Bladder	2	0.22	909	7	0.65	1077*
All other genitourinary organs	0	0.74	0	3	2.05	146
Lymphatic and hematopoietic tissue	0	1.35	0	1	2.07	48
Other sites	1	1.38	72	3	2.12	142
Diseases of the nervous system and sense organs	0	0.61	0	0	0.83	0
Diseases of the circulatory system	31	26.48	117	61	55.34	110
Arteriosclerotic heart disease, including CHD	27	19.72	137	52	39.68	131*
All other diseases of the circulatory system	4	6.76	59	9	15.66	57
Diseases of the respiratory system	2	2.67	75	4	6.49	62
Diseases of the digestive system	1	3.70	27	4	4.93	81
All other diseases	3	4.31	70	2	6.70	30
External causes of death	12	9.29	129	8	9.28	86
Total number of deaths:	58	58.00		104	104.00	
*p < .05						

0.22 expected. PMR's for both exposure groups are quite similar for diseases of circulatory and respiratory system. Slight differences appear in the PMR's between the two groups for diseases of the digestive system and all other diseases. However, the PMR's for both groups are quite low. The PMR for external causes of death is slightly higher in the exposed group (PMR: 129 vs. 86).

A listing of the cancer deaths among the 2,4,5-T exposed is given in Table 10. Table 11 listed the cancer deaths among the non-exposed group.

DISCUSSION

The observation made many years ago of an apparent excess in bladder cancer among Nitro plant workers was confirmed and quantified in the mortality analysis of the total Nitro plant population presented here. The SMR for bladder cancer was 989 and was the only statistically significant SMR among those for malignant neoplasms. The excess in mortality is not seen until 1960. The SMR peaked in the 1960's and declined somewhat in the 1970's. The excess also appeared to be clustered in those decedents aged 65 years and older at death and in those hired prior to 1945. This would suggest that we should see a further decline in the SMR for bladder cancer over time.

Although not statistically significant, the SMR for lung cancer appears to be elevated. The SMR increased with calendar time and was highest in those hired prior to 1945. The elevation appears to be clustered in those aged 45-64 years of age at death (SMR = 184) and does not show a gradient with age. Further analyses to evaluate trends in lung cancer deaths as they relate to occupation cannot be carried out due to limitations in the data collected in this study.

The SMR for diseases of the circulatory system was elevated at 11. This is most likely a reflection of the higher mortality from heart disease which has been observed for Charleston, West Virginia and Kanawha County, West Virginia (unpublished data, Neas LM, 1979 and Sterline PE, 1979). For the total Nitro plant study population, there was a statistically significant excess in deaths from arteriosclerotic heart disease and a deficit in deaths from other circulatory diseases. This variation in the distribution of deaths from that of the U.S. may be due to risk factor or medical care differences in the plant population and the local area. These may include differences in smoking habits, the availability and use of medical services and the specificity of diagnoses.

The proportional mortality analysis of decedents by 2,4,5-T exposure classification indicated no unusual patterns of mortality in the 2,4,5-T exposed. The proportional mortality ratio (PMR for malignant neoplasms was low (PMR = 82) in the exposed group. Lung cancer was the only site among the malignant neoplasms which was somewhat higher in the exposed group.

Table 10. Deaths Due to Malignant Neoplasms Among
Nitro Plant Workers Exposed to 2,4,5-T

<u>Year of Birth</u>	<u>Year of Hire</u>	<u>Year of 1st Exposure</u>	<u>Year of Term.</u>	<u>Year of Death</u>	<u>Smoking History*</u>	<u>Cause of Death as Given on Death Certificate</u>
1917	1946	1951	1972	1972	Cigarettes	Carcinoma left lung with metastases (162.1)
1911	1948	1955	1972	1972	Cigarettes	Metastatic carcinoma of the lung (162.1)
1916	1946	1959	1968	1968	Cigarettes	Bronchiogenic carcinoma of right upper lobe (162.1)
1901	1944	1956	1963	1973	Cigarettes	Carcinoma lung with metastases (162.1)
1911	1941	1948	1971	1975	Cigarettes	Bronchiogenic carcinoma with cerebral metastases (162.1)
1922	1945	1948	1972	1973	Non-smoker	Bronchiogenic carcinoma with metastases (162.1)
1923	1946	1950	1972	1972	Cigarettes	Generalized liposarcoma (171.9)
1902	1922	1948	1966	1966	Non-smoker	Metastatic carcinoma urinary bladder (188.0)**
1910	1944	1948	1968	1968	Non-smoker	Carcinoma of the urinary bladder (188.0)**

* Obtained by interview with former coworkers of decedents.

** Included on the Nitro plant PAB roster.

Table 11. Deaths Due to Malignant Neoplasms Among
Nitro Plant Workers Not Exposed to 2,4,5-T

Year of Birth	Year of Hire	Year of Termin.	Year of Death	Smoking History*	Cause of Death as Given on Death Certificate
1911	1945	1966	1968	Cigarettes	Carcinoma of colon (153.8)
1904	1935	1957	1957	Cigarettes	Carcinoma of liver (157.9)
1899	1929	1959	1960	Pipe	Intraperitoneal carcinoma (158.9)
1905	1944	1970	1972	Cigarettes	Carcinoma of lung (162.1)
1909	1943	1962	1962	Cigarettes	Carcinoma of left lung (162.1)
1910	1927	1966	1970	Cigarettes	Pulmonary carcinoma (162.1)
1912	1944	1965	1965	Cigarettes	Carcinoma of apex of right lung (162.1)
1915	1937	1977	1977	Cigarettes	Carcinoma of lung (162.1)
1915	1939	1969	1970	Cigarettes	Carcinoma of lungs (162.1)
1894	1944	1960	1964	Non-smoker	Carcinoma of lung (162.1)
1912	1937	1973	1974	Cigarettes	Carcinoma of lung (162.1)
1919	1946	1963	1964	Cigarettes	Carcinoma of urinary bladder (188.0)**
1901	1933	1962	1977	Cigarettes	Carcinoma of bladder (188.0)**
1897	1941	1962	1965	Cigarettes	Carcinoma of urinary bladder (188.0)**
1898	1933	1962	1965	Smoked years ago	Carcinoma of urinary bladder (188.0)**
1905	1943	1971	1975	Cigarettes	Carcinoma of bladder (188.0)
1898	1943	1963	1970	Cigarettes	Bladder tumor (188.0)**
1888	1944	1956	1970	Unknown	Carcinoma of bladder (188.0)
1905	1933	1969	1977	Cigars	Prostatic carcinoma (185.0)
1906	1946	1968	1977	Cigarettes	Carcinoma of prostate (185.0)
1925	1945	1973	1974	Smoked years ago	Carcinoma of prostate (185.0)
1919	1943	1972	1973	Cigarettes	Hodgkin's Disease (201.0)
1901	1941	1964	1965	Cigars	Osteosarcoma arising from left arm (170.4)
1901	1943	1966	1977	Cigarettes	Carcinoma of liver & pancreas (197.8)
1922	1944	1964	1964	Cigarettes	Adenocarcinoma (199.0)

* Obtained by interview with former coworkers of decedents.

** Included on the Nitro plant PAB roster.

The PMR analysis is limited in that an assessment of the total force of mortality cannot be made. The cause-specific PMR's only approximate what an SMR analysis would have produced.¹⁶ The PMR analysis presented here estimates the cause-specific risks associated with 2,4,5-T exposure and potential TCDD exposure.

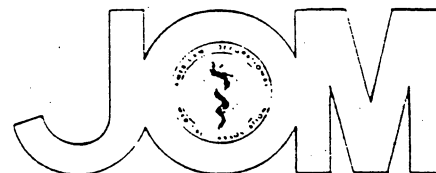
It is interesting to compare the results of this study of Nitro plant workers potentially exposed to TCDD with the results of the study of Nitro workers involved in the 1949 TCP accident. The workers involved in that incident had presumed TCDD exposure as evidenced by chloracne. The results of the two studies are similar in that neither shows an excess in deaths from any site among malignant neoplasms.

A recent study of Ott et al.¹⁷ found no excess in total mortality or in deaths from malignant neoplasms among workers exposed to 2,3,5-T. These workers were probably exposed to very low levels of TCDD since no cases of chloracne were observed. Other studies of workers who developed chloracne resulting from TCDD exposure have been conducted and have been reviewed.⁶ At the present time, data from these various studies do not constitute corroborative evidence of a cancer risk to man for any particular cancer site.

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The Mortality Experience of Workers Exposed to Tetrachlorodibenzodioxin in a Trichlorophenol Process Accident

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A standardized mortality analysis was conducted on workers exposed to tetrachlorodibenzodioxin in a trichlorophenol process accident at the Monsanto Company plant in Nitro, West Virginia. One hundred and twenty-one workers who developed chloracne resulting from this accident on March 8, 1949, were selected for study. Follow-up of this group was 100% complete. The standardized mortality ratio for all causes of death was shown to be 0.69, with 32 deaths observed and 46.41 expected. For the categories of malignant neoplasms and circulatory diseases, the standardized mortality ratios were 1.00 and 0.68, respectively. Because of the small size of the cohort and the relatively small number of deaths observed, the results of this study cannot be considered 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 tetrachlorodibenzodioxin who were followed over a period of nearly 30 years. The results of this study will be incorporated with those of a larger study which will include plant workers exposed in the course of 2,4,5-trichlorophenoxyacetic acid production during the period 1948 to 1969.

A wide variety of acute and sub-acute health effects has been reported in workers involved in the manufacture of 2,4,5-trichlorophenoxyacetic acid (2,4,5-T) from 2,4,5-trichlorophenol (TCP). The most consistent clinical finding is chloracne, a skin disease characterized by com-

edones, cysts, pustules, and abscesses. Hepatic dysfunction, peripheral neuritis, disorders of fat metabolism, and porphyria cutanea tarda are other frequently reported findings in these workers.¹ Chloracne has been shown to be essentially due to 2,3,7,8-tetrachlorodibenzodioxin (TCDD),² a byproduct in the synthesis of 2,4,5-T. The subject of this paper is the chronic health effects of exposure to TCDD, as reflected in the mortality experience of a cohort of Monsanto Company workers who developed symptoms of chloracne following a trichlorophenol process accident at the Nitro, West Virginia, plant in 1949.

Production of trichlorophenol began in the fall of 1948 at the Nitro plant. In this process, the reactants 1,2,4,5-tetrachlorobenzene, sodium hydroxide, and methanol were all added to the autoclave. Heat was applied and, when the pressure reached the desired point, the autoclave was vented. On March 8, 1949, about six months after production start-up, a violent reaction and decomposition occurred when temperature and pressure within the autoclave became excessive. The relief valve opened and the fumes and tarry residues from the decomposed contents of the autoclave were discharged into the atmosphere and into the interior of the building.

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. Symptoms included eye and respiratory tract irritation, headache, dizziness and nausea, and a severe irritant reaction of the exposed skin. After these initial symptoms subsided, the chloracne and other symptoms became evident. Ashe and Suskind^{3,4} examined a total of 12 more severely affected workers on three occasions during the period of 1949 to 1953. Another 26 persons with chloracne, apparently not related to the accident, were also examined in 1953. The

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clinical symptoms, in order of relative frequency,⁴ included skin 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.^{1,5,6}

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.⁹ 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.¹⁰ and Pazderova¹¹ 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.⁹ 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 oropharynx	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	2.25	†
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, Adapted¹⁵ 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.

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Future Risk

In the industrial countries we have grown rich during the age of hierarchical business corporations, in which each executive arranges what the man below him will do with his hands, all the way down to the man turning a screw on the assembly line. Now, two rather fundamental things have happened. First, we have begun to realize that workers in rich countries don't like working in such places. Secondly, the rich countries are moving out of the postmanufacturing age, but they still have great hierarchical corporations in which executives sit behind their desks trying to arrange what the man below will do with his imagination. This no longer works. New forms of business organization will have to be found, probably changing big corporations into confederations of entrepreneurs. The firms and countries that will go bust in these circumstances are those that try to replace hierarchical corporations by even more ossified forms of hierarchy — say, by deciding that you mustn't have a boss trying to arrange what free men do with their imaginations, but can have a trade union committee doing so instead.

— From "United States Can Keep Growing — And Lead — If It Wishes" by Norman Macrae, in *Smithsonian*, July 1976.