

Human Health Effects of 2,4,5-T and Its Toxic Contaminants

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• A clinical epidemiologic study was conducted to determine the long-term health effects of workplace exposure to the process of manufacturing the herbicide (2,4,5-trichlorophenoxy)acetic acid including contaminants such as 2,3,7,8-tetrachlorodibenzo-p-dioxin. The population consisted of two cohorts: 204 clearly exposed and 163 not exposed. Among the exposed, clinical evidence of chloracne persisted in 55.7%. None of the not exposed experienced chloracne development. An association was found between the persistence of chloracne and the presence and 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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THE HERBICIDE (2,4,5-trichlorophenoxy)acetic acid (2,4,5-T), first marketed in 1948, was used widely until 1970 in large-scale farming, family gardens, forest management, and weed control along roadsides and railroad rights-of-way.

The medical and scientific community was alerted to health problems arising from exposure to the manufacturing process of 2,4,5-T following a process accident (runaway reaction) that occurred in a plant in Nitro, WV, on March 8, 1949.¹ The accident involved a kettle in which the intermediate trichlorophenol was being synthesized. Those employees involved in the cleanup of the building and the repair of equipment experi-

enced acute symptoms characterized by skin, eye, and respiratory tract irritation, headache, dizziness, and nausea. 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.² An examination of the workers in 1949 revealed a severe and generalized acneform eruption (chloracne), hepatic enlargement, peripheral neuritis, delayed prothrombin time, and increased total serum lipid levels. By 1953, these symptoms and findings referable to the nervous system and liver had subsided. The chloracne, although much improved, persisted.³

In 1957, 2,3,7,8-tetrachlorodibenzo-p-dioxin (TCDD) was identified as a toxic and acnegenic contaminant of trichlorophenol synthesis.⁴ The sub-

acute effects of this agent, which have been repeatedly observed in humans, include chloracne,^{5,6} the most consistent clinical marker, liver function impairment,^{7,8} peripheral neuropathy,^{9,10} nervousness and irritability,¹¹ personality changes,¹² porphyria cutanea tarda,¹³ and hypertrichosis and hyperpigmentation.¹⁴ Elevation of levels of blood cholesterol,¹⁵ triglycerides,¹⁶ gamma-glutamyl transpeptidase (GGTP),¹⁷ and alkaline phosphatase have been reported.

Toxicologic studies of TCDD in animals have revealed hepatotoxic effects,^{18,19} teratogenic effects,²⁰ suppression of cell-mediated immunity in mice and guinea pigs,²¹ and the induction of hepatic carcinomas in rats.²²

Some of the clinical reports have been concerned with the association of cardiovascular disease²³ and an increased risk for cancer in populations exposed to TCDD.^{24,25} Several comprehensive reviews on this entire subject have been published.^{26,27}

A mortality analysis of workers exposed to the runaway reaction materials was conducted. As of 1979, the Standardized Mortality Ratio (SMR) for all causes of death was 0.69, with 32 deaths observed and 46.41 expected. For the categories of cancer and circulatory diseases, the SMRs were 1.00 and 0.68, respectively.²⁸

A CLINICAL STUDY

In June 1979, a clinical examination program was conducted that included the active and retired employees of the Nitro, WV, plant, who were exposed to the 2,4,5-T process between 1948 to 1969. The objective of the examination program was

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to determine possible increased risks, on a long-term basis, for adverse cutaneous, pulmonary, cardiovascular, gastrointestinal (GI), hepatic, renal, neurological, behavioral, and reproductive effects; effects on lipid metabolism and the possibility of increased risks for cancer. The population included those exposed to the process accident as well as those exposed to normal manufacturing processes and included chemical operators and service employees, such as pipefitters and mechanics. The control group consisted of current or former employees of the same plant who, according to interview work history and personal work records, were never associated with the 2,4,5-T process or its materials.

Subjects of the Study

The total number of subjects examined was 436. There were 419 white males, five black males, one male of Hispanic descent, one male of American Indian descent, and ten white females. One subject among the 419 was exposed to the runaway reaction residue in 1949 as a child. The seven nonwhite males, ten white females, and the white male exposed as a child were excluded from this analysis. There were also 51 subjects whose possible exposure was limited, poorly documented, and did not include work in the 2,4,5-T production process. They are not included in this analysis. The remaining 367 subjects were designated by exposure as follows: (1) exposure without qualification: 204 subjects who were involved in any aspect of the production of 2,4,5-T, including maintenance from 1948 to 1969; and (2) no exposure: 163 subjects currently or formerly employed at the same plant but never associated with any aspect of 2,4,5-T production or maintenance of the production facility.

All living employees, active, retired, or terminated, as determined from company records, were asked to participate. To constitute cohorts of the target sample size, all those who volunteered participation in the study were examined; thus, it was not possible to randomize the selection of participants. Of the living exposed personnel, approximately 61% voluntarily participated in the study, as did approximately 46% of the living not exposed personnel. The only mortality data available for analysis at the time of this study were for personnel who were exposed to the runaway reaction materials.¹¹

Clinical Examination

The interviews and clinical examination with informed consent were conducted during the week July 11 to 18, 1979, in Winfield, WV.

The routine laboratory analysis of blood and urine was completed by Metpath. Blood plasma lipid fraction examination

was carried out by the Lipid Research Division (a National Institutes of Health Center) of the University of Cincinnati Medical Center using methods of the National Lipid Research Project,¹² including determination of plasma cholesterol, plasma triglyceride, plasma high-density lipoprotein (HDL) cholesterol, and estimated plasma low-density lipoprotein (LDL) cholesterol values. Pulmonary function tests, ECG, chest roentgenogram, and nerve conduction velocity measurements, performed by the method described in Goodgold and Eberstein,¹³ were done at the time of the physical examination. The nerve conduction velocity measurements were obtained for most subjects from the peroneal nerve for motor and the sural nerve for sensory function.

Clinical laboratory analyses included blood calcium, phosphorus, blood urea nitrogen, creatinine, blood urea nitrogen/creatinine ratio, uric acid, glucose, total protein, albumin, globulin, albumin/globulin ratio, total bilirubin, direct bilirubin, SGOT, SGPT, alkaline phosphatase, iron, total lipids, sodium, potassium, chloride, GGTP, complete blood cell count and differential cell count, thyroxine radioimmunoassay, and thyroxine-binding globulins. Urinalysis included routine examination as well as determination of coproporphyrin and uroporphyrin values. (Values were determined from a single void sample; hence, the measurements cannot be regarded as valid.)

Analysis of Data

Data from questionnaires and the subject's medical history were coded by assigning numerical values to the responses given. The subject's medical history and findings were coded using the Systematized Nomenclature of Medicine¹⁴ System. Laboratory data were entered as received. Data were keypunched and verified. The computer data were compared with the original files for accuracy. The Statistical Analysis System¹⁵ computer package was used for data analysis. As the analysis progressed, editing continued to ensure the greatest possible accuracy. Multiple linear regression analysis¹⁶ was used to compare the exposed group with the not exposed group and to compare the three chloracne subgroups with respect to plasma lipid levels, pulmonary function values, clinical laboratory values, and nerve conduction measurements after adjustment for covariables. The covariables were age in the analysis of clinical laboratory values and nerve conduction measurements, age and smoking status (never, former, and current) in the analyses of pulmonary function values and age, and smoking status and alcohol status (never used, formerly used, and currently used) in the analyses of plasma lipid values. Fisher's exact test¹⁷ and the χ^2 test for indepen-

dence in contingency tables were used to compare the two exposure groups and the three chloracne categories with respect to frequency of abnormal findings on physical examination, pulmonary function test, and lipid analyses. Fisher's exact test was also used to compare the two exposure groups with respect to reproductive findings. Mantel-Haenszel analysis¹⁸ was used to compare the exposed group with the not exposed group with respect to frequency of abnormal findings on physical examination after adjustment for age group (<50 and ≥ 50 years) and with respect to frequency of abnormal findings on pulmonary function test or abnormal plasma lipid levels after adjustment for smoking status. Logistic regression analysis¹⁹ was used to detect associations of exposure with abnormal findings on pulmonary function test after adjustment for pack years smoked. Log linear models²⁰ were used to detect associations between the three chloracne groups and abnormal plasma lipid levels after adjustment for smoking status.

RESULTS

Demographic Information

Demographic data of the 367 white males were examined to determine potentially confounding variables. The mean ages of the exposed and not exposed groups were 56.7 ± 0.7 ($\bar{X} \pm SE$) years and 46.2 ± 1.0 years, respectively ($P < .0001$). The two groups were found to be significantly different with respect to employment status and highest educational level achieved ($P < .0001$). In the exposed and not exposed groups, 34.8% and 13.5% were retirees and 9.8% and 0.6% were terminated (left voluntarily or laid off), respectively. Among the exposed and not exposed groups, 9.4% and 1.2% reached no further than the eighth grade, respectively; 72.4% and 56.8% had some high school education, respectively. Among the not exposed, 42.0% attended college, some to completion, while among the exposed, only 18.2% attended college.

Alcohol and Smoking

History of alcohol consumption was not found to be significantly different in the two groups. When smoking status (current, former, or never) was used as the criterion, no differences were found. Among current smokers, the exposed group had smoked significantly longer than the not exposed by 19 pack-years ($.0001 < P < .001$). Among former smokers, the exposed

group had smoked longer than the not exposed group by seven pack-years ($.05 < P < .10$). This reflected the ten-year age difference between the exposed and the not exposed group.

History of Medical Problems

The comparison of the exposed and not exposed cohorts for self-reported history of illness is given in Table 1. Chloracne was reported only in the exposed group: 86.3% in the exposed v 0.0% in the not exposed. The data about the history of chloracne were determined on the basis of statements from subjects that an acnelike eruption called "weed bumps" appeared after an assignment to a 2,4,5-T production area. Records of the medical department of the company and the state Workmen's Compensation Bureau stating that the person had chloracne confirmed many of these histories. In the not exposed group, a history of acne vulgaris was reported more frequently than in the exposed group. This information was based on the story of adolescent acne before employment at this plant. A history of upper GI tract ulcer was reported almost four times more frequently in the exposed group. When the medical history of the exposed and not exposed was compared for two age groups younger than 50 years v 50 years or older, a history of coronary artery disease and of hypertension were related to age, not exposure. Among the not exposed, angina was significantly related to age; in the history of upper GI tract ulcer, however, exposure, not age, appeared to be a factor.

Closer examination of onset of ulcer in relation to exposure revealed six subjects whose symptoms occurred before exposure. There were also four subjects whose symptoms occurred while they were receiving corticosteroid therapy or high doses of aspirin or that were attributed to chronic alcoholism. If these ten subjects were omitted from the analysis, there remained statistically significant differences between the exposed and not exposed groups (16.6% v 5.5%; $P \leq .01$ on age adjustment).

The complaint of loss of libido occurred more frequently in the exposed group than the not exposed group. When age was considered, the largest number of complaints of loss of libido or impotence were reported

History	Not		Age <50 yr, %		Age ≥60 yr, %	
	Exposed, % (n=204)*	Exposed, % (n=183)	Exposed (n=61)	Not Exposed (n=100)	Exposed (n=163)*	Not Exposed (n=63)
Chloracne†‡	86.3	0.0	78.5	0.0	89.5	0.0
Acne vulgaris§¶	9.9	29.5	17.7	42.0	7.2	9.8
Skin cancer	3.9	2.5	0.0	1.0	5.3	4.8
Hypertension	34.8	24.8	21.8	16.0	38.8	38.1
Angina§	7.4	6.1	5.9	1.0	7.9	14.3
Coronary artery disease	10.8	6.1	2.0	0.0	13.8	16.9
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 workmen's compensation claim for chloracne.

† $P < .0001$; P value for Mantel-Haenszel comparison of exposed v not exposed across age strata.

‡ $.01 < P < .05$; in exposed, young v old, by Fisher's exact test.

§ $.001 < P < .01$; P value for Mantel-Haenszel comparison of exposed v not exposed across age strata.

¶ $.05 < P < .10$; in exposed, young v old, by Fisher's exact test.

|| $P < .0001$; in not exposed, young v old, by Fisher's exact test.

§ $.001 < P < .01$; in not exposed, young v 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.

Complaint	Not		Age <50 yr, %		Age ≥60 yr, %	
	Exposed, % (n=203)	Exposed, % (n=183)	Exposed (n=61)	Not Exposed (n=100)	Exposed (n=162)	Not Exposed (n=63)
"Nervousness"/ anxiety/depression"	16.3	11.7	7.8	15.0	19.0	6.4
Decreased libido†‡	38.6	15.3	19.8	8.0	40.8	31.7
Impotence, not otherwise specified	27.8	11.7	7.8	2.0	34.2	27.0

* $.05 < P < .10$; in exposed, young v old, by Fisher's exact test.

† $.001 < P < .01$; for Mantel-Haenszel comparison of exposed to not exposed across age strata.

‡ $P < .0001$; in not exposed, young v old, by Fisher's exact test.

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

|| $.0001 < P < .001$; in exposed, young v old, by Fisher's exact test.

by the older age group (Table 2).

As noted in Table 1, the reported history of skin cancer, hypertension, angina, coronary artery disease, and cancer of all sites (except skin) was not found to be significantly associated with exposure. The sample size obtained was sufficient (at significance level of .05, power of .80 [probability of detecting a true difference]) to detect a fourfold increase in skin cancer, a twofold increase in hypertension, a threefold increase in angina and coronary artery disease, and a sixfold increase in cancer of all sites (except skin) for exposed over what was observed in the not exposed. As noted in Table 2, the complaint of nervousness/depression/anxiety and the complaint of impotence were not related to exposure. The sample size was sufficient to detect a twofold increase in complaint of nervousness/

depression/anxiety for exposed over not exposed. Although the sample size was sufficient to detect crude differences between the two groups with respect to complaint of impotence, the difference disappeared when age was considered.

The exposed population was categorized into three subgroups, ie, those who never had chloracne develop ($n=28$), those who had a history of chloracne only ($n=69$), and those whose chloracne persisted ($n=107$). When the histories of medical problems were examined in relation to chloracne status, hypertension and coronary artery disease were found to be age related, not chloracne related. Histories of skin cancer and angina were not statistically significant when related to chloracne or to age within the chloracne groups. While it would seem (Table 3) that skin cancer

Table 3.—History of Medical Problems v 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=18)	Current (n=23)	No History (n=12)	History Only (n=62)	Current (n=84)	No History (n=16)
Acne vulgaris	8.8	6.5	25.0	18.8	8.7	33.3	5.8	6.0	18.8
Skin cancer	6.8	2.8	3.6	0.0	0.0	0.0	7.7	3.8	6.3
Hypertension†	35.3	38.3	17.9	6.3	34.8	16.7	44.2	39.3	18.8
Angina	5.8	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	10.2	26.2	18.8
Cancer of all 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.

†0.01 < P < 0.05 for history only, young v old by χ^2 test for independence in contingency tables.

‡0.05 < P < 0.10 for current, young v old by χ^2 test for independence in contingency tables.

is related to age in the three chloracne groups, the number of persons in the age group younger than 50 years was too small to achieve statistical significance. There was no association between the history of upper GI tract ulcer and chloracne status (Table 3).

While the number of subjects reporting a history of cancer (other than skin) was small, all of them were found in the group aged 50 years or older, and the percentage in the exposed group was not significantly different from that in the not exposed group (Table 1). The three bladder cancers were reported by persons exposed to *p*-aminobiphenyl, a rubber additive that was also made in the plant.

Physical Examination Results

There seemed to be no difference in blood pressure findings between the exposed and not exposed group. The criteria for determining normal for combined systolic/diastolic values were less than 140/90 mm Hg for subjects aged 59 years or younger and less than 160/95 mm Hg for subjects aged 60 years or older. For diastolic alone, less than 80 mm Hg was considered normal. Diastolic values of 80 to 89 mm Hg for ages 59 years and younger and 80 to 94 mm Hg for ages 60 years and older were considered borderline. Diastolic values of 90 mm Hg or greater for ages 59 years and younger and diastolic values of 95 mm Hg or greater for ages 60 years and older were considered high.

The significant clinical examination findings as related to exposure status and age are found in Table 4. Of those who were clearly exposed,

Table 4.—Significant Clinical Findings v Exposure Status and by Age

Finding	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	1.8
Actinic elastosis*†§	59.1	30.1	37.3	18.0	66.4	49.2
Basal cell epitheliomas	8.9	4.3	2.0	0.0	8.6	11.1
Peyronie's disease¶	1.5	0.0	0.0	0.0	2.0	0.0
Hirsutism	6.4	1.8	3.9	1.0	5.9	3.2

*P < .0001; P value for Mantel-Haenszel comparison of exposed v not exposed across age strata.

†0.05 < P < 0.10; P value for Mantel-Haenszel comparison of exposed v not exposed across age strata.

‡0.0001 < P < 0.01; in exposed, young v old, by Fisher's exact test.

§0.01 < P < 0.01; in not exposed, young v old, by Fisher's exact test.

¶0.0001 < P < 0.001; P value for Mantel-Haenszel comparison of exposed v not exposed across age strata.

§0.0001 < P < 0.001; in exposed, young v old, by Fisher's exact test.

¶P < .0001; in not exposed, young v old, by Fisher's exact test.

52.7% still had chloracne, 62.6% were mild cases, 33.9% were regarded as moderate, and 3.8% were severe.

The diagnoses of chloracne and acne vulgaris were made by qualified dermatologists. The criteria for diagnosis of chloracne include the initial appearance of comedones, milia, or epidermal cysts on the malar, temple, and periorbital areas that may subsequently involve other areas of the face, the neck, forearms and arms, and scalp and genitalia. The scrotum and penis are commonly affected in persons whose clothing becomes heavily contaminated by the acnegenic material. Lesions may become secondarily infected, especially on the trunk, forearms, and genitalia. By contrast, acne vulgaris that usually starts in adolescence is seen as inflamed papules, pustules, and comedones, on the perinasal area, cheeks, chin, neck, and back. It rarely, if ever, starts on the malar or periorbital areas. The skin of the affected sites in

acne vulgaris is usually very oily or greasy. In the case of chloracne, the skin surface is usually dry. Persons with acne vulgaris, exposed to chloracnogens, may experience the development of chloracne. The lesions of acne vulgaris may increase in severity and lesions may develop in sites not usually or previously affected by acne vulgaris.

Among the exposed, 59.1% were found to have actinic elastosis in contrast to 30.1% among the not exposed. There was a significant difference in the occurrence of actinic elastosis between the exposed and not exposed in both age groups even though age is a factor in this clinical finding. Three cases of Peyronie's disease were observed among the 204 exposed. All of them had chloracne at some time and they were all older than 50 years. Peyronie's disease is characterized by induration and scarring of the corpus cavernosum of the penis, producing distortion on erec-

Finding	History Only, % (n=68)	Current, % (n=107)	No History, % (n=28)	Age <50 yr. %			Age ≥60 yr. %		
				History Only (n=16)	Current (n=23)	No History (n=12)	History Only (n=53)	Current (n=64)	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	28.6	31.3	56.3	6.3	51.9	79.8	43.8
Basal cell epithelioma	5.9	6.4	3.6	6.3	0.0	0.0	5.8	10.7	6.3
Payrson's disease	2.9	0.9	0.0	0.0	0.0	0.0	3.8	1.2	0.0
Hirsutism†	0.0	10.3	0.0	0.0	6.7	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; for overall differences between the three chloracne categories in age 60 years or older, by χ^2 test for independence in contingency tables.
‡.01 < P < .05; in current chloracne, young v old, by Fisher's exact test.
§.05 < P < .10; in no history of chloracne, young v old, by Fisher's exact test.

Plasma Lipids	Exposed			Not Exposed			P Value
	n	$\bar{X} \pm SE$	% Out of Range*	n	$\bar{X} \pm SE$	% Out of Range*	
Cholesterol	200	211.15 $\pm$ 2.53	7.5	163	204.07 $\pm$ 2.97	10.4	NS
Triglyceride	200	149.68 $\pm$ 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	127.08 $\pm$ 2.60	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 Research Project.

tion.

As noted in Table 4, there was no association of findings of basal cell epithelioma and hirsutism with exposure. The sample size was sufficient to detect a threefold increase in basal cell epithelioma and a fourfold increase in hirsutism for exposed over what was observed in the not exposed.

Table 5 identifies the clinical findings in the exposed population in relation to chloracne status. In these groups, actinic elastosis was found preponderantly in the subjects with persistent chloracne (74.8%), but it also occurred significantly in those with a history of chloracne only (47.1%). Of the exposed with persistent acne, 10.3% were found to have malar hirsutism: nine of these 11 cases occurred in the group older than 50 years.

Actinic elastosis is a problem found in persons of light coloration exposed over many years to sunlight (eg, farmers' skin and sailors' skin). It is characterized by swelling and fragmentation of the elastic tissue elements of the dermis. There was an association of actinic elastosis with chloracne. It seems that the percentage of persons with severe actinic elastosis was related to presence of chloracne and that it is more severe when found with chloracne.

Plasma Lipids

Plasma cholesterol, triglyceride, LDL cholesterol and HDL cholesterol were classified by age-specific percentiles as determined by the National Lipid Research Project data.¹⁹ Plasma cholesterol, triglyceride, and LDL cholesterol values were classified as out of range if they fell above the 90th percentile; HDL cholesterol values were classified as out of range if they fell below the tenth percentile. The frequency of out-of-range lipid findings was compared for exposed and not exposed groups (Table 6). No significant differences were noted. The sample size was sufficient to detect a twofold increase in the frequency of out-of-range cholesterol, triglyceride, LDL cholesterol, or HDL cholesterol values for exposed over what was observed in the not exposed. After adjusting for smoking status, no significant differences were found. The mean lipid values were also compared for the exposed and not exposed groups (Table 6), and no significant differences were found.

When the lipid levels of the exposed group only were examined in relation to chloracne status, there was a significantly greater number of subjects with low HDL cholesterol levels in those with persistent chloracne than in those with a history only of chlor-

acne or those who never had chloracne (Table 7). There was a greater number of persons with high LDL cholesterol levels among those who had a history only of chloracne than those who had chloracne currently or never. The mean lipid levels for these three chloracne groups were also compared (Table 7), and no significant differences were found.

After adjusting for age, height/weight, smoking status, and alcohol status, no significant differences were found between the two exposure groups with respect to mean lipid values. The interaction of smoking status and alcohol status was also added to the model, and no differences were found between the two exposure groups.

To detect differences between the chloracne groups with respect to mean lipid values, the same adjustments described previously were performed. No significant differences were found.

Log linear models were used to detect associations between frequency of out-of-range lipid values and chloracne status in the exposed group only, adjusting for smoking status. Findings are as follows: (1) Out-of-range cholesterol or triglyceride values were not associated with chloracne status. (2) Out-of-range HDL cholesterol values were associated

Table 7.—Chloracne Status in Exposed Only v 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	87	215.16 $\pm$ 4.87	11.9	106	210.23 $\pm$ 3.17	4.8	28	204.96 $\pm$ 7.13	7.1
Triglyceride	87	144.00 $\pm$ 14.88	7.5	106	163.84 $\pm$ 9.39	19.1	28	149.11 $\pm$ 16.35	14.3
Low-density lipoprotein cholesterol†	86	142.84 $\pm$ 4.69	15.2	103	134.48 $\pm$ 7.68	2.9	27	130.96 $\pm$ 7.06	7.4
High-density lipoprotein cholesterol‡	87	45.84 $\pm$ 1.17	3.0	106	44.93 $\pm$ 1.31	14.3	28	47.76 $\pm$ 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 Research Project.

† $P < .018$; 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.

with chloracne status ($.01 < P < .05$), and the degree of association did not vary significantly by smoking status. (3) Out-of-range LDL cholesterol values were associated with chloracne status ($.01 < P < .05$), and the degree of association did not differ significantly by smoking status.

Pulmonary Function Examination

Both forced expiratory volume in 1 s (FEV₁) and forced vital capacity (FVC) were considered abnormal if the observed value was less than 80% of the predicted value of Morris. A FEV₁/FVC percentage less than 70% was considered to be abnormal. The forced midexpiratory flow rate (FEF₂₅₋₇₅) was considered abnormal if the observed value was less than 70% of the predicted value of Morris.

Consistent differences in abnormal pulmonary function values (FEV₁, FVC, FEV₁/FVC, and FEF₂₅₋₇₅) were found when the exposed and not exposed groups were compared (Table 8). Among current smokers, there was a significant difference in frequency of abnormal pulmonary function values between the exposed and not exposed groups, but there were no differences among persons who have formerly smoked or among persons who have never smoked (Table 8).

Logistic regression was performed to evaluate the relationship between frequency of abnormal pulmonary function values and exposure after adjusting for pack years smoked. Odds ratios are given for these parameters in Table 8. Exposure significantly increased the odds for abnormal pulmonary function values even after adjustment for pack years smoked.

The means of the percent-predicted values were compared between the

two exposure groups after adjusting for the effect of smoking (Table 9). No difference was found between the two exposure groups with respect to FEF₂₅₋₇₅ percent predicted. Percent-predicted values for FEV₁/FVC and FVC were significantly lower in the exposed group. Furthermore, there was a significant interaction between smoking status and exposure with respect to FEV₁ percent-predicted values. When adjusted group means for each smoking status exposure combination (Table 9) were examined to determine the nature of the relationship, no significant differences were found between exposed and not exposed workers who never smoked or who formerly smoked. Among current smokers, however, there was a significant difference between exposed and not exposed workers with respect to FEV₁ percent-predicted values.

Clinical Laboratory Findings

With regard to clinical laboratory determinations other than plasma lipids, no significant differences were detected between exposed and not exposed groups. There have been reports of abnormal levels of alkaline phosphatase, SGOT, SGPT, and GGTP in other populations exposed to TCDD for short or long periods; however, no differences were found in these cohorts ten to 30 years after the last date of exposure.

ECG and Roentgenographic Findings

No differences were observed in the ECG findings when the exposed and not exposed groups were compared. When the chest x-ray film findings in the exposed group were compared with those in the not exposed group and separated by age, the arterioscle-

rotic changes and pleural thickening differences between the groups seemed to be age related, not exposure related.

Neurological Findings and Nerve Conduction Velocity Measurements

When exposed and not exposed groups were compared for frequency of abnormal findings on neurological examination, no differences were found.

Nerve conduction velocity measurements require controlled atmospheric conditions and uniform conditions of testing. Ambient and body temperatures were recorded. With the technology employed, it was at best a screening procedure.

All subjects reporting diabetes or reporting a high weekly alcohol intake (≥ 35 oz. of alcohol per week) were eliminated from the data analysis. After these deletions, there were 278 with complete sural and 294 with complete peroneal examinations remaining. The data from the nerve conduction velocity studies were corrected for body temperature according to the deJesus¹¹ method. The age-adjusted values are presented in Table 10. No significant differences were found when the two exposure groups were compared or when the three chloracne groups were compared.

Reproductive Effects

Information on reproductive factors and birth defects was elicited from the male participants. Neither physician nor hospital records were available to confirm the information.

A comparison between the exposed and not exposed groups for pregnancies, live births, infant deaths, mis-

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	39	5.1	40	5.0	NS	...	...
	Former	89	11.2	77	5.2	NS	...	...
	Present	74	27.0	45	4.4	.0025	...	...
	Total†	203†	15.8	162	4.9	.0013	2.81	.0159
FVC*	Never	39	5.1	40	12.5	NS	...	...
	Former	89	15.7	77	6.5	NS	...	...
	Present	74	26.7	45	2.2	.0008	...	...
	Total†	203†	17.2	162	6.8	.0038	2.28	.0319
FEV ₁ /FVC %	Never	39	5.1	40	2.6	NS	...	...
	Former	89	12.4	77	5.2	NS	...	...
	Present	74	25.7	45	6.7	.0143	...	...
	Total†	203†	15.8	162	4.9	.0013	2.97	.0099
FEF ₇₅₋₇₅ *	Never	39	7.7	40	7.6	NS	...	...
	Former	89	19.1	77	13.0	NS	...	...
	Present	74	36.5	45	11.1	.0035	...	...
	Total†	203†	23.2	162	11.1	.0038	1.86	.0617

*FEV₁, indicates forced expiratory volume in 1 s; FVC, forced vital capacity; FEF₇₅₋₇₅, forced midexpiratory flow rate.

†Unknown smoking status, two subjects, one whose pulmonary function test result was normal and is included in the total.

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 $\pm$ 2.86	0.0006
	Total	99.39 $\pm$ 1.43	104.42 $\pm$ 1.57	0.0184
FVC*	...	92.73 $\pm$ 1.17	97.80 $\pm$ 1.28	0.0064
FEV ₁ /FVC %	...	76.49 $\pm$ 0.63	79.93 $\pm$ 0.68	0.0002
FEF ₇₅₋₇₅ *	...	101.00 $\pm$ 4.02	109.16 $\pm$ 4.39	NS

*FEV₁, indicates forced expiratory volume in 1 s; FVC, forced vital capacity; FEF₇₅₋₇₅, forced midexpiratory flow rate.

Category	Nerve Tested		
	Ulnar	Peroneal	Sural
Exposed† $\bar{X} \pm SE$ (n)	58.90 $\pm$ 2.36 (9)	41.77 $\pm$ 0.47 (160)	42.06 $\pm$ 0.49 (160)
Not Exposed $\bar{X} \pm SE$ (n)	61.91 $\pm$ 2.39 (9)	42.62 $\pm$ 0.62 (154)	41.49 $\pm$ 0.64 (126)
Chloracne, history only† $\bar{X} \pm SE$ (n)	58.92 $\pm$ 6.02 (3)	40.68 $\pm$ 0.77 (50)	41.14 $\pm$ 0.90 (51)
Chloracne, current $\bar{X} \pm SE$ (n)	67.68 $\pm$ 4.11 (5)	41.38 $\pm$ 0.69 (86)	41.37 $\pm$ 0.76 (74)
Chloracne, never $\bar{X} \pm SE$ (n)	52.10 $\pm$ 0.00 (1)	40.81 $\pm$ 1.12 (24)	41.23 $\pm$ 1.30 (26)

*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.

carriages, birth defects, and stillbirths is listed in Table 11. There were no significant differences in these parameters between the exposed and not exposed cohort. No data were available on age of wives of workers.

Other Work Exposures of the Study Population

Other than 2,4,5-T and its intermediates and/or contaminants, all of the workers in the study were exposed to multiple chemicals and industrial processes under varying working con-

ditions, at the same plant and/or other plants, between the late 1930s and 1979.

Rubber processing chemicals identified by the subjects as other exposures included diphenylguanidine, the benzothiazolesulfenamides, derivatives of *m*-cresol, *p*-phenylenediamine derivatives, and 4,4-dithiodimorpholine. Additional chemicals named were ethyl parathion and methyl parathion, phthalic anhydride, σ - and p -dichlorobenzene, σ - and p -nitrophenol, toluene and mercaptobenzothiazole derivatives of tetramethylthiuramdisulfide, and trimethylquinoline components.

Seventy-nine subjects, or 21.5% of the 367, reported in-plant exposure to *p*-aminobiphenyl, a known bladder carcinogen, during the course of their employment. These subjects are periodically examined in a clinical surveillance program established by the medical department of the company. Subjects reported the exposure and the monitoring program during the interview and to the examining physician. The data relating this exposure to 2,4,5-T are described in Table 12.

COMMENT

In any interpretation of the medical significance of data elicited from this study, it is essential to consider the characteristics of the cohorts as well as the strengths and weaknesses of the design of the study. With all industrial populations at risk in the

Table 11.—Exposure v Reproductive Findings			
Reproductive History	Exposed* (n=1804)	Not Exposed† (n=1653)	Probability
Pregnancies	658	479	...
Miscarriages	69	61	...
rate per 1,000 pregnancies	105.34	118.86	NS
Live births	576	373	...
Stillbirths	11	8	...
rate per 1,000 fetuses to term	18.77	13.23	NS
Dead in 4 weeks	17	8	...
rate per 1,000 live births	29.58	18.09	NS
Children with birth defects	18	11	...
rate per 1,000 live births	31.30	29.48	NS

*In the exposed, reported birth defects include spine bifida, unspecified cardiac anomalies, pyloric 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 spine bifida, congenital anomalies of eye, polycystic kidney disease, atrial web, obstructive defects of urinary tract, club foot, absence of fingers, congenital dislocation of hips, cystic hygroma, Down's syndrome, and hernia.

‡The difference in number (189 v 204 for exposed and 165 v 163 for not exposed) were due to men who were childless or men who did not respond (two nonresponders in the not exposed, three in the exposed).

Table 12.—History of Exposure to <i>p</i> -Aminobiphenyl (pAb) and (2,4,5-Trichlorophenoxy)acetic Acid (2,4,5-T) v History of Bladder Neoplasms								
History*	No Exposure to Either 2,4,5-T or pAb		2,4,5-T Exposure		pAb Exposure		pAb and 2,4,5-T Exposure	
	No.	%	No.	%	No.	%	No.	%
Bladder tumor†	0	0.0	0	0.0	1	12.5	7	9.9
Bladder cancer†	0	0.0	0	0.0	1	12.5	2	2.8

*History as determined from interview and report to examining physicians.

†Figures are mutually exclusive.

United States, particularly for long-term follow-up, randomization and participation requirements for pristine epidemiological protocols are rarely satisfied. In this study it was not possible to match the exposed and not exposed groups demographically on basis of age, employment status, and education level. Although the two groups were defined on the basis of definite exposure to 2,4,5-T process and no evidence of exposure to 2,4,5-T anywhere in the plant, no information was available about levels of 2,3,7,8-TCDD in the work environment or in the trichlorophenol that was produced or in the final product, 2,4,5-T. Since 2,4,5-T was used ubiquitously as a weed killer in many gardens and farms, the possibility of exposure to some TCDD between 1948 and 1969 exists for both groups. There is current analytical information demonstrating that dioxins including 2,3,7,8-TCDD may also be present in the community environment in fly ash and flue gases^{13,14} from incineration of domestic garbage and industrial chemical wastes.^{15,16}

The degree to which each subject

may have been exposed to 2,4,5-T, the contaminant TCDD, and other chemicals varied markedly. Subjects reported exposure to the 2,4,5-T process for as little as one month to as long as 20 years, and exposure was often intermittent over a period of years. It was difficult to accurately designate the duration of exposure for many of these persons. The data do not provide characterization of incidence or dose-response relationship.

Data obtained from interviews and clinical examinations conducted by different physicians have inherent biases. Nevertheless, the available populations provide useful information on the prevalence of biologic effects in the population exposed, as compared with those who were not exposed to the 2,4,5-T production.

A comparison of manifestation of effects to TCDD toxicity in humans as observed in this population with those observations made in experimental animals must also consider the acute, subacute, and chronic effects in humans already reported.^{14,22}

The subacute effects of TCDD tox-

icity in the group of exposed persons as described in the reports cited in the references were characterized by cutaneous, hepatic, and peripheral nerve damage. In other populations, where hepatic changes were observed as a clinical subacute effect, elevated levels of SGOT, SGPT, and GGT were reported.^{14,22} Doses of 1.0 µg/kg/day in rats will induce altered liver function, elevation of alkaline phosphatase, lymphoid depletion of the thymus, and increased excretion of urinary porphyrins and Δ -amino-levalulinic acid.²³ The effects on the thymus have not been noted in humans, although there have been some reports of elevation of alkaline phosphatase and Δ ALA levels in long-term exposure.²⁴ Elevation of alkaline phosphatase levels was not observed in those who were examined in 1949, 1950, or 1953¹ or in this study population ten to 30 years after exposure.

Tetrachlorodibenzo-*p*-dioxin was found to induce cancer of the liver, lung, palate, and nasal turbinates in rats.²⁵ An excess of cancer of all sites was not observed in the mortality analysis of the group exposed to the runaway reaction materials,²⁶ nor was an increased prevalence of cancer of all sites observed in this study population. Cancer of the liver was not observed in this study population, nor was an excess of cirrhosis noted.

High doses of TCDD (30 ppm), administered orally or subcutaneously, in pregnant mice and rats may increase the incidence of cleft palate in mice and cystic kidney in rats.²⁷ No teratogenic effects were observed in rabbits receiving 10 to 40 mg/kg of 2,4,5-T containing 0.5 ppm of TCDD or in rats receiving 1 to 24 mg/kg of 2,4,5-T with the same TCDD content.²⁸ It has been demonstrated that hyperplasia and ulceration of the gastric mucosa occur in monkeys after lethal doses are administered.²⁹ In this study population, a statistically significant increase in the history of upper GI tract ulcer was found when the exposed were compared with the not exposed.

Birth defects as reported by participants in this study showed no differences statistically between the exposed and not exposed groups. In rhesus monkeys receiving 500 parts per trillion of TCDD, early abortions and inability to conceive were observed.^{30,31} These effects have not been

observed in this study population.

This study indicates that the pilosebaceous effects of exposure to the 2,4,5-T process were persistent in 53% of those exposed. The effects of the kind of care received by the various subjects may be a factor in persistence. Since biopsies of the size required to identify and measure TCDD were not available, the presence of TCDD or its metabolites as a factor in persistence could not be ascertained. There was an association of actinic elastosis with the occurrence and persistence of chloracne. This can be interpreted as increased susceptibility to UV radiation damage.

There was an association of history of upper GI tract ulcer with exposure. It was not possible to ascertain a designation of ulcer by site without GI roentgenography or endoscopic information. Among the exposed group, ten subjects reported surgical treatment of the ulcer, while none of the not exposed group reported surgical treatment of ulcer. These data are suggestive of association with exposure; no definite conclusion can be drawn because of the qualified nature of the data. The association of upper GI tract ulcer with exposure warrants additional study with an appropriately designed protocol.

Among those whose chloracne persisted, there was a higher frequency of low HDL cholesterol values. Among those with only a history of chloracne, there was a higher frequency of high LDL cholesterol levels. There were no differences found between the two exposure groups with regard to plasma lipid and lipoprotein values.

There was an association of altered pulmonary function values, especially FEV₁, in those who were exposed and who currently smoke. This suggests the influence of the number of pack years smoked as well as exposure.

There was no evidence in this study that exposure to the 2,4,5-T process is associated with an increased prevalence of cardiovascular disease, hepatic disease, renal damage, CNS or peripheral nerve problems, reproductive problems, or birth defects.

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