INTER-OFFICE CORRESPONDENCE

Diamond Alkali Company

DATE: November 7, 1969

TO: Dr. R. W. McBurney
Mr. R. A. Guidi Mr. R. Chonoles

FROM: Mr. F. G. Steward - Newark

SUBJECT: U.S.P.H.S. --- NEWARK PLANT HEALTH SURVEY ---
MANUSCRIPT FOR PUBLICATION

REPLY REQUESTED BY (DATE)

Enclosed is a copy of the manuscript reporting results of the Newark Plant health survey made during February 1969, by the U. S. Public Health Service. Mr. William F. Barthel submitted the manuscript for Diamond's review and approval prior to publication per the agreement between Diamond and the P.H.S.

Since changes may be made by all (3) recipients of manuscript copies, Ray Guidi has asked that I compile the changes and coordinate the submission of the corrected manuscript to the P.H.S. Mr. Barthel in his letter to Diamond did not list any publication deadline; however, in deference to them, please make any changes you desire, and return the manuscript to me by November 24th --- this will permit a reply to the P.H.S. approximately 30 days after receipt of the manuscript.

F. Gordon Steward

F. GORDON STEWARD

FGS/nr

Enclosure

cc: F. R. Kennedy

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R W McBurney

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A HEALTH SURVEY OF WORKERS IN A 2,4-D AND 2,4,5-T PLANT: WITH SPECIAL ATTENTION TO CHLORACNE, PORPHYRIA CUTANEA TARDA AND PSYCHOLOGIC PARAMETERS

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INTRODUCTION

The herbicides 2,4-D* (2,4-dichlorophenoxyacetic acid) and 2,4,5-T* (2,4,5-trichlorophenoxyacetic acid) are widely used throughout the world. Several distinct medical problems have been described in workers involved in the production of these compounds. These problems can arbitrarily be subdivided into 1) chloracne and mucous membrane irritation, 2) hepatoxicity, neuromuscular symptoms, psychologic alterations and other systemic symptoms, and 3) porphyria cutanea tarda.

1. Chloracne and Mucous Membrane Irritation

Chloracne (Perna's disease, perchloronaphthalene disease) has been described as an extremely refractory acne seen in workers involved in the production of several chlorinated aromatic compounds[1]. Kimmig and Schulz[2,3,4] described this dermatologic condition in workers in a 2,4,5-T factory. The condition is characterized by inclusion cysts, comedones, pustules, and eventually scarring originating in the temple-zygomatic area with spread to the pinna, nape of the neck, back, upper chest and inguinal area. Many of these patients also had blepharoconjunctivitis. The investigators showed that purified 2,4,5-trichlorophenol (TCP) was not acnegenic, but that 2,3,6,7-tetrachlorodibenzodioxin (dioxin) isolated from the crude

* Abbreviations: 2,4-D, 2,4-dichlorophenoxyacetic acid; 2,4,5-T, 2,4,5-trichlorophenoxyacetic acid; DCP, 2,4-dichlorophenol; TCP, 2,4,5-trichlorophenol; dioxin, 2,3,6,7-tetrachlorodibenzodioxin; ALA, δ-aminolevulinic acid; PBG, porphobilinogen; PCT, porphyria cutanea tarda. MMPI - Minnesota Multiphasic Personality Inventory.

TCP reaction mixture was an extremely potent acnegenic agent when applied to rabbits' ears.[2] The dioxin is considered an important, but not necessarily the only acnegenic compound in 2,4,5-T production.

2. Hepatotoxicity, neuromuscular problems, psychologic alterations and other systemic symptoms.

In addition to chloracne, studies of workers in 2,4,5-T plants have frequently noted other signs and symptoms suggestive of systemic toxicity. These include: anorexia and weight loss, abdominal pains and post-prandial flatulence, headaches, weakness in the legs, and hepatic dysfunction.[4,5,6,7,8] Also noted were psychological alterations: lack of vigor, drive, and libido; easy fatiguability; emotional instability; and diminished ability to learn.

3. Porphyria Cutanea Tarda (PCT).

In 1964, Bliberg et al., reported on 29 workers in a 2,4-D and 2,4,5-T factory in which many of the workers had chloracne and eleven had abnormal excretion of urinary uroporphyrins. Many of the workers, with and without uroporphyrinuria, had hirsutism, hyperpigmentation and increased skin fragility. Liver dysfunction was noted in two hospitalized patients.

As a follow-up of Bliberg's observations of a toxic porphyria cutanea tarda in these factory workers,[9] we restudied all the employees in the same plant in February 1969 with particular emphasis on PCT, chloracne, hepatotoxicity, and neuropsychiatric symptoms.

METHODS

All volunteers submitted to a medical history and physical examination; special emphasis was placed on occupational, smoking, drinking, and medication histories and the detection of any neurologic or dermatologic signs and symptoms.

The Minnesota Multiphasic Personality Inventory was administered to all employees, in a quiet atmosphere at work supervised by management. The only exceptions were a few plant administrators who completed the inventory at home. The individual tests were scored by computer, and the mean and standard deviations computed for each scale and compared with normative data.[10] In addition, the frequencies of high and low two point series were determined.

Each employee was given a bottle of Glucola(R) (75 gm carbohydrate) to drink, prior to which they were asked to fast for at least 3 hours. Two hours after ingestion, a blood sample was obtained and serum glucose and other biochemistry tests were performed by an automated clinical laboratory. In persons reporting after 135 minutes, the two-hour serum glucose was considered invalid and not included in statistical analysis. In addition to the glucose, a serum glutamic-oxalacetic acid transaminase (SGOT), lactic dehydrogenase (LDH), alkaline phosphatase, cholesterol, bilirubin, albumin, total protein, blood urea nitrogen, hemoglobin, hematocrit, red blood cell count, white blood cell count, serum iron and iron-binding capacity were performed on each employee.

A casual urine specimen was collected from each volunteer the pH adjusted to 7.0, and the specimen frozen until porphyri analysis. An attempt was made to shield the urine from ultraviolet light, but this was not entirely satisfactory in the industrial setting. Each urine was analyzed for δ-aminolevulinic acid (ALA) and porphobilinogen (PBG) by the method of Schenkler et al.[12] The porphyrin and porphyrin precursor levels were expressed per gram of creatinine.

For statistical analysis, employees were subdivided into several different groups according to location in the plant, exposure to chemicals, and educational level. All quantitative results are reported as mean ± one standard deviation, percent of incidence, or a correlation coefficient between two variables Significance was determined by the Student's test or X^2 test; results reported as nonsignificant are those with significance level (p value) >0.05. Where distribution of results on a given continuous variable were not normally distributed, logarithmic transformations were made before performing t-tests or calculatir correlation coefficients. Means and standard deviations are alwa reported as untransformed values.

RESULTS

Descriptive Data

Seventy-eight persons were studied in the plant. Five women employed in the office were excluded from analysis. The remaining 73 employees, all men, included one part-time worker, and 4 persons who had not worked in the plant for 1 to 6 months.

The group of 73 persons can be subdivided into 4 basic occupational subgroups. (1) Production Workers - 28 persons working in the production area. (2) Supervisors - 11 foremen spending most of their time in the production area. (3) Maintenance - 14 men with various occupations (plumbers, electricians, etc.) some confined to maintenance shop and others frequently in the production area. (4) Administrators and technical help - 20 men including engineers, business office workers, laboratory technicians, and janitorial help, all housed in a building separated from the production area and thus less exposed to production chemicals.

As seen in Table I, the average age of the 73 employees was 39.3± 11.1* years, the average years of schooling 11.9 ± 2.6 years and the average duration of employment 8.3 years ± 7.6 years (Table II). There were 18 Negro and 55 Caucasian employees. Of 64 workers questioned, 22 missed more than one day from work due to illness in the past year. The average number of days lost for 63 employees was 2.8 days/year. (This excludes one person hospitalized for almost 2 months with a urinary tract infection.)

Acne

A specific dermatologic history with special emphasis on acne and porphyria was taken from all the employees and all were examined by a dermatologist (PP).

The minimal acne lesion consisted of comedomes and inclusion cysts in the temple-zygomatic area and the pinna of the ear. In more severe cases, cysts and comedomes were accompanied by pustules on the face and ear, nape of the neck and back, and in the worst cases, the chest and inguinal area. With anatomic spread

* mean ± 1 s.d.

there was generally an increase in the severity of the lesions and in the scarring. There were no erythematous or edematous lesions as previously reported by some investigators of acute exposures[1].

"Active acne" was defined as the presence of cysts, comedomes and/or pustules (but not scarring). Cysts, comedomes and pustules were graded according to the severity (grade 0 to 4) in each location (face, neck, back, chest, and other - five possible areas). The severity grades for each lesion were summed over all five locations; finally these severity sums for each lesion (cysts, comedomes, pustules) were totaled to produce an overall "active acne" score (maximal possible score: grade 4 in all 5 locations = 20 for each of 3 lesions = 60). This arbitrary rating allowed us to deal with the degree of "active acne" in a statistical form. Scarring was scored separately by the same system (grade 0 - 4 times 5 possible areas = maximal score of 20).

Twenty-five persons had an "active acne" score of 0 (no lesions), 35 had a score of 1 - 8 (minimal), and 13 employees had a score of 9 or greater (moderate to severe).

Scarring was also a highly skewed parameter: 37 employees had a score of 0, 29 had a score of 1 - 8, and 7 had a score greater than 9.

As seen in Table III, with increasing "active acne" scores there was a greater prevalence of scarring, hyperpigmentation, hirsutism, complaints of eye irritation, and higher scores on the manic scale on the MMPI.

Another way of expressing the same data is to convert the skewed "active acne" scores to a more normal distribution by logarithmic transformation (see Methods) and compare these transformed scores with other parameters by correlation coefficients. Scarring, also a skewed parameter, was similarly transformed.

"Active acne" was correlated with the degree of scarring ($r=.80$), and the presence of hyperpigmentation ($r=.38$), hirsutism ($r=.44$), and complaints about eye irritation ($r=.39$). All the above correlations have a significance level of $p < .001$. The "active acne" scores were not significantly correlated with the duration of employment nor with the excretion of coproporphyrins per gram creatinine.

There was no significantly greater occurence of acne in Negro employees compared with Caucasian workers (X^2 test). If one considers the entire population employed in the plant for greater than 14 months, the prevalence of acne is not statistically greater in those persons with a history of "teenage acne" (X^2 test). However, all 6 individuals who stated they had had "teenage acne" and who had worked in the plant for more than 14 months, did have "active acne."

The 73 male employees were subdivided into groups with respect to present work location in the plant: (TCP formation, DCP formation, phenoxyacetic acid production, esterification, formulation and storage tanks, maintenance, supervisory, laboratory help, administration). Often one man might work in several locations (e.g. supervisors might work in TCP and DCP production, and phenoxyacetic acid production and esterification). Then

each area was compared (by X^2 test) to see if the severity of the "active acne" of the employees might be worse in certain locations in the plant. There were no statistically significant differences, perhaps because of the small size of each group, and the mobility of the workers. However, as might be expected, the maintenance men tended to have the most acne (having to clean and repair vats and pipelines) and the administrative people (housed in a separate building) tended to have the least acne.

Mucous membrane irritation

By history, 7 employees complained of itching of the eyes, 14 of frequent tearing, 5 of "blood shot eyes", and 7 of styes. On physical examination, however, only 3 (4.1%) were found to have appreciable conjunctival infection. Twenty-three (31.5%) employees had hypermia of the nasal mucosa and 8 (10.9%) had inflammation of the buccal mucosa.

Hyperpigmentation and Hirsuitism

Hyperpigmentation, usually most prominent on the face, consisted of a grayish or brownish tome to the complexion. Hirsuitism was most notable in the area between the outer edge of the eyebrow and the temple hair margin. Both characteristics were recorded only as being present or absent. As seen in Table III, there were 16 subjects with facial hypertrichosis and 30 with hyperpigmentation. There is a significant correlation between hirsutism and increased hyperpigmentation ($r=.25$, $p < .05$). As previously mentioned, hirusitism and hyperpigmentation are significantly correlated with the severity of active acne. Neither is significantly correlated with coproporphyrin excretion.

Urinary excretion of porphyrins and porphyrin precursors

The average values of ALA, PBG, and coproporphyrin found in casual urine specimens of plant workers are shown in Table IV along with the normal values from the literature.[13] There was no abnormally elevated excretion of ALA, PBG, or coproporphyrin. One employee, hospitalized several years ago with severe PCT, still has mild uroporphyrinuria (107 ug/gm creatinine). No overt cases of porphyria, however, were found during this study. Only four of the eleven workers with uroporphyrinuria originally described by Blåberg et al[9] were still working in the plant. Several of the seven employees with uroporphyrinuria, who had left the plant, had been retested by Dr. Blåberg prior to leaving and had been found to have no elevation in urinary porphyrin excretion.

Several pertinent observations can be made about these urinary porphyrin values. The excretion of ALA, PBG and coproporphyrin were all elevated in the 15 maintenance men versus the other 56 workers; the coproporphyrin excretion/gm creatinine was significantly elevated (48.3 ± 14.4 vs 36.7 ± 19.6, $p < .025$). Persons with higher values for coprophorphyrin excretion (≥ 50 mg/gm creatinine, $n = 15$) did not show any greater duration of employment in the plant than those with lower values (X^2 test). There was a significant correlation ($r=.42$, $p < .001$) between ALA excretion and coproporphyrin excretion. There was a significant correlation between ALA excretion and age ($r=.42$, $p < .001$) and a significant negative correlation between ALA excretion and serum bilirubin concentration ($r=-.26$, $p < .05$).

Cardiovascular Findings

Casual recording of the pulse and blood pressure was performed by a nurse. The average pulse was 85.1 ± 10.2/min; systolic blood pressure was 126.6 ± 12.8 mm Hg; and diastolic blood pressure was 75.4 ± 7.8 mm Hg. Only four persons had a diastolic pressure greater than 90 mm Hg. Cardiac evaluation was unremarkable except in 3 employees who reported myocardial infarctions.

Pulmonary Findings

Twenty of 73 employees (27.4%) gave a history of a chronic cough, emphysema, and/or fairly consistent raising of early morning sputum. Of these twenty workers, 16 (80%) currently smoked cigarettes, and the other 4 had smoked considerably in the past. In the entire plant, 42 employees (57.5%) currently smoked cigarettes and another 15 (20.6%) gave a history of smoking in the past. The group of current smokers averaged 25.6 pack-years.

On physical examination 18 workers were judged to have some impairment of maximal diaphragmatic excursion. Eight of these gave a history of chronic cough or frequent early morning sputum and one gave a history of asthma.

Although there appears to be an appreciable incidence of chronic pulmonary disease in the plant, it is impossible to attribute this to any industrially related cause as suggested by the report of Bauer[5] because 78% of the employees now smoke or have smoked cigarettes previously.

Hepatic Function

All serum total bilirubin tests (normal range 0.3 to 1.2 mg/100 ml) and albumin concentrations (normal range 3.7 to 5.5 gm/100 ml) were normal. Two employees had elevated serum glutamic-oxalacetic acid transaminase levels (normal range 7 - 45 U) and two others had abnormal alkaline phosphatase concentrations (normal range 7 - 18 KA U). Six persons had a palpable liver edge (only one of these had an abnormal liver chemistry).

Neurological Findings

Several German authors noted lower extremity weakness and fatigue in many of the patients with choracne in 2,4,5-T factories.[2,5] Only 7/73 (9.6%) employees in our study complained of lower extremity fatigue or difficulty climbing stairs. Five of these workers gave a history of arthritis in the lower extremities or heart disease with dyspnea. Thus, only 2/73 (2.7%) employees experienced leg fatigue totally unexplained by other concomitant disease. In no subject was lower extremity weakness detected on neurologic examination.

Ten workers had decreased auditory acuity, four of these had typanic membrane disease. No discrimination was made between nerve or bone conduction defects. A decrease in olfactory discrimination was observed in only one employee and this was most likely due to nasal obstruction. Two persons had decreased sense of proprioception and three had absent Achilles tendon reflex without other neurologic deficits. Tremors were observed in three employees. We found no abnormalities of cranial nerves other than noted above, no clonus, no alterations in deep tendon

reflexes of the biceps or triceps brachii or quadriceps femoris and no alteration in pain sensation.

Results of Laboratory Determinations

As mentioned in the section on hepatic function, all employees had normal serum bilirubin and albumin concentrations. Two persons had elevated SGOT concentrations, and another two employees had abnormal alkaline phosphatase determinations.

Only one employee had an elevated blood urea nitrogen (normal range 6-24 mg/100 ml) and only one had an elevated uric acid (normal range 3.0-7.9 mg/100 ml). The serum cholesterol (normal range 133-294 mg/100 mg) was elevated in 7/71. There was a surprising and unexplainable elevation in the serum lactic dehydrogenase (normal range 50-160) in 20/70 (28.6%) employees; this may have been due to centrifuging clinical chemistry blood specimen more than two hours after sampling.

The 2-hour serum glucose determination after an oral carbohydrate load was judged satisfactory in 58 employees (see Methods). Six employees (10.4%) had a 2-hour serum glucose of $\geq$ 140 mg% after 75 gm of carbohydrate. The average age of these six individuals was 50.6 years; four had chloracne; none gave a family history of diabetes; and one was obese.

Only 2/72 employees had a hemoglobin of less than 13 gm/100 ml of blood, 16 employees (22%) had a serum iron of less than 75 ug/100 ml. The mean serum iron was 96 $\pm$ 32 ug/100 ml and only two employees had a serum iron of 160 ug/100 ml or greater. The average percent saturation of the iron binding capacity was 27.4 $\pm$ 9.0%, with 27 persons (37%) having a percent saturation Fe/IBC of less than 25%. Seven persons had a white

blood cell count of less than 5000/mm^3, but in only two employees was it 4000/mm^3 or less. None of the seven had an absolute granulocytopenia (< 1500 neutrophils/mm^3)[15] and only one worker had a lymphopenia (< 1000 lymphocytes/mm^3).[15] The red cell morpholcgy platelets, determined by scan of the peripheral blood smear, were normal in all subjects.

MMPI Results

The MMPI scores of the production workers (N=52) and the administrative staff (including laboratory technicians) (N=17) were analyzed separately because of the difference between the two groups in environmental exposure and educational level. Two janitors, currently working in the administration building, were eliminated from the analysis of the administrative staff because of a different educational background and previous exposure as production workers.

MMPI results are based on an analysis of scores of all subjects on 13 separate scales. Ten of these scales are designed by common clinical terms and are thus self-explanatory (see Table V). The remaining three scales, the L, F, and K scales, measure the validity of the test results as an accurate profile of the subject. A high L score indicates that the subject answered most questions according to socially desirable standards rather than according to individual preferences. More highly educated subjects tend to have lower L scores; this is consistent with our finding of significantly lower L scores in the administrative staff. A high F score may be obtained if a subject answers in a prankish way, if he has a poor ability to read or comprehend the items, or if he is severely mentally

disturbed. Since only one subject out of 69 had a high F score (F > 15), the test seems to have been both understood and taken seriously by the workers.

The only significant differences in means on all scales between administrative staff and production workers were on the F and Hypochondriasis scales, the production workers presenting a more hypochondriacal picture than the administrative staff. When scores of both groups of employees were compared with the normal values given for the MMPI Test scales (mean=50, standard deviation=10), administrative staff and production workers varied significantly from normal on a total of 6 and 9 scales respectively (see Table V). The normal values for the MMPI, however, were based on scores of a small population of Minnesota males who took the test just prior to World War II.[10] Since many obvious demographic differences exist between the plant population and the "normal population", it was thought that a more meaningful definition of the plant population would be obtained by searching for personality patterns appearing in high frequencies within the plant. A high point code system was used which grouped subjects according to the two scales in which they scored the highest. The following high point codes had the greatest frequency: administrative staff, hypomanic-hysterical, f=23%; production workers, hypomanic-psychopatic, f=12%. It is apparent from these frequencies that no one personality pattern tended to dominate either administrative or productive group.

Correlation coefficients were calculated for each MMPI scale with other parameters such as porphyrin excretion, chloracne, job history, and several biochemical tests. The only significant

correlation was between the score of severity of "active acne" and the hypomanic scale ($r=.33$, $p<.01$). Furthermore, the mean manic scale score for the group with the most severe chloracne was significantly higher than the means of the two groups with lesser acne ($p<.05$) (see Table III).

DISCUSSION

Acne, developing from occupational exposure has been reported in persons working with a variety of chlorinated aromatic compounds (e.g. chloronaphthalenes, chlorodiphenyls, chlorbenzols, chlorodibenzodioxanes).[1,16,17] In a series of papers, Kimmig and Schulz,[2,3] and Schulz[4] described the occurrence of chloracne in a 2,4,5-T factory in Germany. They showed that 2,3,6,7-tetrachlorodibenzodioxin, (dioxin), an unwanted side product formed in the conversion of tetrachlorobenzene to 2,4,5-trichlorophenate, is an extremely potent acnegen when applied to rabbit's ears or human skin. Purified 2,4,5-trichlorophenol and its closely related reaction products (sodium 2,4,5-trichlorophenate, 2,4,5-trichloroanisole, etc.) do not produce acne when applied to rabbit's ears.[4] The authors conclude that the dioxin is an important, if not the only, acnegenic agent produced in the manufacturing of 2,4,5-T.

Thirty-eight of seventy-three (52%) employees in our study had some degree of acne, but only 13 (18%) had moderate to severe lesions. Most previous investigations of acne occurring in 2,4,5-T plants have selectively presented clinical and pathologic findings in severely affected workers. In contrast, the present study surveyed the prevalence of acne in the entire

employee population and found the acne absent or minimal in 82% of the workers.

The severity of "active acne" correlated with the presence or absence of scarring, hyperpigmentation, hirusitism and complaints about eye irritation (Table III). Dugois and Colomb[8] reported a 50% incidence of conjunctivitis in 2,4,5-T workers with acne. Although we had many complaints about eye irritation, only 3 workers were observed to have conjunctivitis. However, 23 (32%) of the employees had hyperemia of the nasal mucosa and 8 (11%) had hyperemia of the buccal mucosa.

Hyperpigmentation and hirusitism were described in the toxic porphyria caused by hexachlorobenzene, in the study of this plant by Bleiberg et al., and in our study. There are reasons to believe that these signs which are ususally thought of as a part of the PCT syndrome may be more closely related to chloracne in 2,4,5-T plants: (1) The findings of Bleiberg et al[9] that the degree or presence of hirusitism and hyperpigmentation do not correlate well with the presence of uroporphyrinuria, (2) our findings that the presence of the two characteristics correlate quite significantly with the severity of acne and not at all with coproporphyrin excretion, and (3) the findings of other studies of 2,4,5-T factories[5,18] in which workers were noted to have chloracne and hyperpigmentation, but no mention was made of skin fragility, vesicular eruptions, or red urine.

Porphyria cutanea tarda (PCT) is an acquired porphyria, generally occurring in men after age 40, in which one finds significant liver dysfunction and usually a history of alcholic

abuse. The syndrome consists of vesiculobullous lesions on areas of the body exposed to light, hirsutism, excessive mechanical fragility of the skin, hyperpigmentation, and excretion of red urine containing an increased amount of uroporphyrin and/or coproporphyrin, but not a large increase in urinary ALA or PBG.[19,20] Frequently these patients have hyperferremia and hemosiderosis, and phlebotomy often reverses the clinical picture and decreases porphyrin excretion.[21,22]

In 1956, Cam[23] described a large outbreak of PCT in Turkey due to the accidental ingestion of hexachlorobenzene. This was the first clear demonstration of a toxic porphyria in humans. Although many medications (Sedormid(R), grisiofulvin, etc.) have precipitated PCT in individuals, Watson[24] argued this was merely overt expression of a latent genetic tendency for porphyria. The epidemiologic investigations of the hexachlorobenzene epidemic involving thousands of persons[23,25-27] and the outbreak of PCT described by Bliberg et al., in the 2,4,-D and 2,4,5,-T plant, however, support a direct toxic etiology of many cases of PCT.

In the report of Bliberg et al.[9] in 1964 of this same plant, eleven employees had uroporphyrinuria and several had hirusitism, hyperpigmentation and/or skin fragility. In the three case histories presented, two patients had vesicular eruptions on exposed areas of the body, two had hepatic dysfunction and the two reported liver biopsies fluoresced intensely with ultraviolet irradiation. These three case histories unquestionably fulfilled the criteria for the diagnosis of PCT.

Our reexamination of the same plant 6 years later revealed no clinical PCT; and only one employee had mild persistent uroporphyrinuria.

We have administered reagent grade 2,4-dichlorophenol to rats and observed oral dose of 2,4-dichlorophenol caused a 3-fold increase in hepatic ALA synthetase activity, the rate limiting enzyme in porphyrin biosynthesis. Rimington and Ziegler[29] reported a series of structurally similar chlorinated benzene compounds which cuased experimental porphyria in rats. The dioxin, a potent hepatotoxin and acnegen, has not been examined for its ability to cause porphyrinuria in experimental animals.

Porphyria cutanea tarda (i.e., uroporphyrinuria, skin fragility, vesicular eruptions on the skin) appears to be a symptom-complex distinct from that of chloracne (i.e., cysts, pustules, comedomes, and scarring of the skin); both were found in this 2,4-D, 2,4,5-T plant. The independence of these syndromes is supported by (1) the lack of correlation between the severity or even presence of chloracne and uroporphyrinuria in Bleeberg's study, and (2) the persistence of chloracne in the factory six years later, despite the disappearance of the uroporphyrinuria and skin fragility.

The finding of statistically higher coproporphyrin excretins in the maintenance men suggests a higher toxic exposure in this group. There is also a tendency towards more severe acne in this group. These men repair the inside of reaction vessels and leaking pipelines and although their exposure is sporadic it is apparently more intense.

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The significant negative correlation between the serum bilirubin concentration and ALA excretion is consistent with the recent findings of Hayashi et al.[30] that parenterally administered bilirubin inhibits the induction of ALA synthetase and hence hepatic ALA formation.

Recently, much attention has been directed towards the finding of hemosiderosis and hyperferremia in patients with PCT, often with an alcoholic history.[30,31,32] Although iron metabolism was not reported in the patients with hexachlorobenzene intoxication, chelating agents did appear to reverse the clinical symptoms and porphyrin excretion.[34] In our study, despite the absence of uroporphyrinuria in the workers at the present time, one might expect a tendency towards hyperferremia. On the contrary, we found an unexplainable trend towards hypoferremia and a lower iron-binding saturation, with little demonstrable anemia.

Hepatotoxicity: Dioxin, which has been incriminated as a potent acnegenic agent, has also been shown to be very hepatotoxic. A single oral dose of 0.05 to 0.1 mg/kg resulted in death (of rabbits) in one to two weeks. Autopsy revealed extensive necrosis and enlargement of the livers.[3] Similarly dermal application of the tarry residues in 2,4,5-T synthesis caused rapid death in guinea pigs with gross hepatic lesions.[8] Clinically, several investigators have looked for evidence of hepatotoxicity in workers in 2,4,5-T plants affected with chloracne. Bauer et al.[5] noted 2/9 cases with slightly delayed BSP excretion and three with abnormal liver biopsies. In the report of Bliberg

et al.[9] of patients with chloracne and porphyria, 2 subjects were noted to have hepatic dysfunction and 2 patients had abnormal liver biopsies. Dugois and co-workers[6,8] have noted hyperlipemic and hypercholesterolemic sera in their subjects. Hoffman and Meneghini[18] state they found no hepatic damage in 6 patients with chloracne. We found only 2 persons with an elevated SGOT and 2 others with an elevated alkaline phosphatase. Serum bilirubin and albumin concentrations were normal in all employees tested. Although dioxin, and other chemicals produced in 2,4,5-T synthesis may be hepatotoxic in humans, the prevalence of demonstrable liver dysfunction in this plant is minimal.

Systemic Toxicity: A variety of other signs and symptoms and disease processes have been noted in various studies of 2,4,5-T workers with acne. Several studies above mentioned anorexia and weight loss, post prandial flatulence, nausea and vomiting, abdominal pain, and documented cases of gastritis and ulcers.[2,4.5,6,8] Although we searched for these signs and symptoms in our subjects, their occurrence was infrequent and unrelated to the presence or severity of chloracne. In addition, a wide variety of neurological signs and symptoms have been reported: headache, lower extremity weakness and fatigue, paresthesia, loss of coordination, and nonspecific EEG changes.[2,4,5,7,8] We found only 8/73 subjects with nonspecific headaches. Two of 73 subjects experienced unexplained lower extremity weakness but in neither was this weakness demonstrable on testing. A few subjects complained of paresthesias; however, we observed no demonstrable alteration in sensory perception except for two

workers with decreased proprioception and one with findings consistent with carpel tunnel syndrome. Six subjects were found to have an unexplained hearing deficit. It is obvious from the above frequencies, that the prevalence of objective neurologic abnormalities among these workers was quite small.

MMPI: The MMPI results are important in that they offer an objective profile of the workers in one herbicide synthesizing plant. Conclusions about personality changes secondary to chronic exposure in a 2,4-D, 2,4,5-T plant can only be tenuous, however, because we have no suitable group with which to compare these results. The comparison of MMPI results of these factory workers with the "normal population" of pre-World War II, Caucasian subjects from Minnesota was inescapable since the scoring system for the test is based upon this "norm."[10] Nonetheless, we consider these groups incomparable. The only evidence we find to suggest any environmental effect of this herbicide plant on personality is the significant correlation between severity of chloracne (a known toxic effect), and the score on the hypomanic scale. This is an interesting finding and somewhat contradictory to the apathy and psychomotor retardation reported by Bauer.[5]

Many prior investigations of both acute and chronic poisoning in 2,4,5-T plants have reported the symptoms of anorexia with weight loss, fatigue, debility, and asthenia[2,5] However, only one author has described in detail personality changes thought to be associated with chemical exposure. Bauer et al[5] studied nine workers with severe chloracne which still persisted 5 years after termination of their exposure in a 2,4,5-T plant.

He describes a syndrome of general weakness, fatigue, apathy, and decreased libido alternating with fits of anger and irritability. Rorschach Tests performed on the nine workers showed a weakened emotional reaction, a lack of concentration, slowed thought processes, and perseveration. This whole syndrome was designated by the term "psychovegatative disorder."

The inconsistency of our finding of a significant correlation between hypomania and chloracne and Bauer's description of lethargy, dulled emotional response, and apathy remains to be adequately explained. Possible reasons include a basic difference in methodologies and a difference in testing period with relation to the time of exposure. Additionally, the severity and chronicity of the organic disease in Bauer's subjects may have induced personality change which mask any manic effects found with less severe disease.

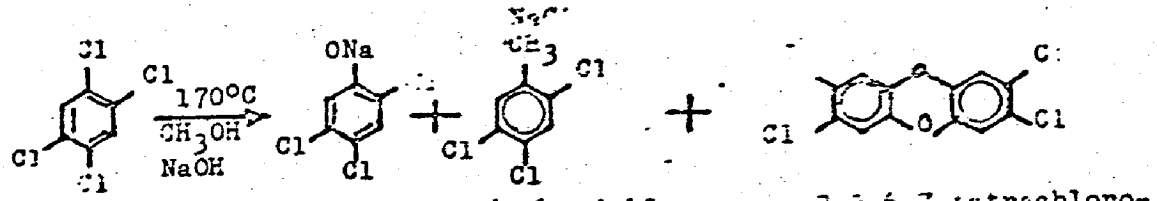
SUMMARY

An intensive medical study of 73 male employees in a 2,4,5-T factory was made. Moderate to severe chloracne was found in 18% of workers and the severity of the chloracne correlated significantly with the presence of hyperpigmentation, hirsutism, and eye irritation, and with a high score on the manic scales of the MMPI. Chloracne was not, however, correlated significantly with job location within the plant, duration of employment, or coproporphyrin excretion. Although eleven subjects with uroporphyrinuria and at least three with overt porphyria cutanea tarda had been found in a study of the same plant 6 years ago, no clinical porphyria could be currently documented and only one worker was found to have persistent uroporphyrinuria.

Evidence of systemic toxicity in other organ systems was markedly less than that reported in previous studies of 2,4,5-T plants.

Appendices

I. Chemistry



1,2,4,5 tetrachlorobenzene | 2,4,5 trichlorophenate | 2,4,5-trichloroanisole | 2,3,6,7 tetrachlorobenzodioxin

Although the structures of 2,4-D and 2,4,5-T differ only by one chlorine, the commercial synthesis of the two compounds are dissimilar. The starting product for 2,4,5-T is 1,2,4,5 tetrachlorobenzene which is reacted with methanol and aqueous sodium hydroxide to form 2,4,5 trichlorophenate, 2,4,5-trichloroanisole and small amounts of several unwanted side products, e.g., 2,3,6,7 tetrachlorobenzodioxin. The reaction product is steam stripped to remove the anisole. At this point, sampling of various batches shows the dioxin to be present in 10 to 25 ppm. About six months prior to our survey the company installed a ~~charcoal column to pass all the TCP through prior to further reaction. This column~~ DEVICE WHICH removed most of the dioxin. ~~and column effluents had~~ CONTAINED less than 1 ppm dioxin.

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

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The starting materials for 2,4-D are phenol and Cl_2 which react in an exothermic process to form the 2,4-dichlorophenol (DCP). Subsequent reactions with MCA to the phenoxacetic acid is similar to 2,4,5-T. In 2,4-D production there is no formation of the dioxin.

II. The Plant

The plant employs several measures in an attempt to improve industrial hygiene. Clean work clothes are issued daily. There are separate lockers for street and work clothes. All production workers said they showered daily before leaving the plant. The DCP and TCP are made in one building and the 2,4-D and 2,4,5-T (acids) and their esters in another. Attempts have been made to improve ventilation, and recently the company has been successful in removing most of the dioxin before the TCP leaves the area in which it is synthesized. A dermatologist employed by the company visits the plant at least weekly, largely to treat the chloracne.

Almost all operations are carried out in closed processes (e.g. tank car to pipeline to reaction vessel to next pepeline to next reaction vessel, etc.). There is of course some leakage, and frequently men working in maintenance have to clean the inside of the reaction tanks of open pipelines.

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TABLE I

Distribution, Age, and Educational Level of Employees According to Joo Category

Group	Number of Employees	Age	Years Of Schooling
1. Administrators, Lab Technicians, Janitors	20	34.0 ± 12.2	13.8 ± 2.3
2. Supervisors	11	46.8 ± 7.4	12.7 ± 3.0
3. Production	28	40.1 ± 10.0	10.6 ± 1.7
4. Maintenance	14	39.1 ± 10.5	10.6 ± 1.8
Total Plant	73	39.3 ± 11.1	11.9 ± 2.6

* mean ± 1 standard deviation

TABLE II

Duration of Employment in Plant

Number of Years	Number of Employees
0 - 4	33
4 - 8	10
9 - 12	1
>13	29

mean $\pm$ 1 S.D. = 8.3 $\pm$ 7.6 years

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TABLE III

Distribution of Certain Signs, Symptoms, and Test Scores Among Three Categories of "Active Acne" Severity

"Active Acne" Score	0	1-8	>9
Number of Employees	25	35	9
Hirusitism	3/25 (12%)	4/35 (11%)	9/13 (69%)
Hyperpigmentation	5/25 (20%)	15/34 (44%)	10/12 (83%)
Scarring	1/25 (4%)	22/35 (63%)	13/13 (100%)
Eye Irritation (History of tearing, itching, styes, "blood shot")	1/25 (4%)	8/35 (23%)	6/13 (46%)
Mean Score on Mania Scale of MMPI	55.4 ± 7.7	58.8 ± 10.2	64.9 ± 10.5*

* The persons with acne scores of >9 had significantly higher scores on the Mania Scale of the Minnesota Multiphasic Personality Inventory.

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TABLE IV

Urinary Porphyrin Excretion

	Plant Values + ug/gm creatinine	Normal Values[13]	Upper limit of normal ug/gm creatinine
δ-aminolevulinic acid	1021 ± 406	1900 ± 600 ug/gm creatinine	3100
prophobilinogen	444 ± 237	700 ± 400 ug/gm creatinine	1500
coproporphyrin	39.3 ± 19.0	0 - 175 ug/L	175*
uroporphyrin	trace++	0 - 15 ug/L	15*

+ = mean ± S.D., n = 72

* Values derived from normal by assuming a 70 kg man puts out 1.5 gm creatinine/day and 1500 ml of urine.

++ Measurable in only one person.

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TABLE V

Scale Scores on the Minnesota Multiphasic Personality Inventory

	52 Production Workers			17 Administration Worker		
	Mean	S.D.	p*	Mean	S.D.	p
L	52.5	8.2	NS	46.1	5.8	NS
F	54.6	7.4	<.0025	54.4	8.8	NS
K	53.2	8.9	<.025	55.4	6.3	<.025
Hypochondriasis	55.5	9.8	<.00025	48.8	8.5	NS
Depression	59.5	11.2	<.0001	56.7	11.5	<.01
Hysteria	59.0	8.8	<.0001	58.9	6.7	<.001
Psychodeviance	59.8	12.1	<.0001	55.5	12.1	<.025
Masculinity	57.4	7.6	<.0001	60.7	6.1	<.00025
Paranoia	52.9	8.3	<.05	52.6	9.6	NS
Psychasthenia	52.1	10.4	NS	50.8	8.9	NS
Schizophrenia	51.2	9.8	NS	51.2	10.0	NS
Mania	60.0	9.0	<.0001	56.8	12.4	<.01
Social Introversion	51.4	8.4	NS	50.1	9.8	NS
Years of Schooling	10.9 ± 2.1			15.2 ± 1.5		p <.001+
Coproporphyrin excretion ug/gm creatinine	38.8 ± 16.0			37.9 ± 24.7		NS+
Number of Persons with some degree of acne	36/52			10/17		NS++
"Active Acne" Score	6.2 ± 9.6			2.5 ± 3.2		NS+

* Significance values by Student's t test, comparing the above populations to the "normal" population.

\+ Significance by Student's t test.

++ Significance by X^2 test.

N.B. The significant differences between the plant groups are found in the L scale ($p < .005$) and the hypochondriasis scale ($p < .01$). The first would be expected on an education basis.

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