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January 30, 1985

JAN 31 1985

George Roush, M.D.
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MONSANTO COMPANY GZWG
800 North Lindberg Boulevard
St. Louis, Missouri 63167

Dear Doctor Roush:

We are forwarding to you the revised protocol for the "Epidemiologic Investigation of the Health Status of Monsanto Employees with Past Exposure to Chlorophenols, Chlorphenoxy Acids, and Their Dioxin Contaminants at the W.G. Krummrich Plant in Sauget, Illinois". This revision incorporates many of the excellent suggestions of the Peer Review Committee.

We believe that each worker will look upon the examination as a valuable benefit provided by Monsanto. We also believe that this study will be a major contribution to the scientific literature on dioxins. The study is designed to answer many of the previously unresolved questions regarding the possibility of chronic health effects in workers with past exposure to dioxins.

The Peer Review Committee was unanimous in commending Monsanto for its sponsorship of this study. We appreciate your confidence in selecting us to design and carry out this important research. We wish to extend our personal thanks to you and your staff for your assistance and the courtesy you have shown us during the design of this study.

Sincerely,

James R. Webster, Jr., M.D.

Warren Wallace M.D

Warren Wallace, M.D.

JRW/WW:pjw

DSW 476038.0475

STLCOPCB4042638

EPIDEMIOLOGIC INVESTIGATION OF THE HEALTH STATUS OF MONSANTO EMPLOYEES WITH PAST EXPOSURE TO CHLOROPHENOLS, CHLORPHENOXY ACIDS, AND THEIR DIOXIN CONTAMINANTS AT THE W.G. KRUMMRICH PLANT IN SAUGET, ILLINOIS: STUDY PROTOCOL

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January, 1985

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EXECUTIVE SUMMARY OF THE STUDY PROTOCOL

The purpose of this study is to determine if workers at Monsanto's Krummrich Plant in Sauget, Illinois suffered any long term health effects as a result of their past exposure to chlorinated phenols, esters of 2,4-D and 2,4,5-T, and their chlorinated dioxin contaminants. The health status of the exposed employees will be compared to the health status of Krummrich employees who were not exposed to these compounds.

The exposed cohort will consist of all Krummrich employees who were engaged in the production of chlorinated phenols or chlorphenoxy herbicides for one or more days between January 1, 1938 and December 31, 1983. Maintenance employees who were assigned to these areas and who developed chloracne will also be included in the exposed cohort. One thousand and fifty-five employees meet the definition of exposure of whom 221 are deceased. Four hundred and four exposed workers are expected to participate in the study. This exposed cohort will be comprised of 221 active, 106 retired, 60 terminated, and 17 other workers whose employment status is as yet unknown.

One thousand seventy-seven Krummrich employees were considered to be non-exposed during this same time period. Four hundred and nine are expected to participate as internal controls. This group will be comprised of 218 active, 50 retired, and 141 terminated workers.

Study participants will undergo a comprehensive medical examination, including a medical history, occupational and environmental history, reproductive history, physical examination, dermatologic examination, neurologic examination, electrocardiogram, pulmonary function tests, chest

x-ray, quantitative sensory examination, nerve conduction velocity studies, neurobehavioral testing, blood tests, and urine tests. Questionnaire items will be confirmed by medical record review.

The health status of the exposed cohort will be compared to the health status of the internal controls. The strategy for statistical analysis will consist of 1) examination of crude associations, 2) stratified analysis, 3) tests for dose response, and 4) multivariate analysis.

1. PURPOSE OF THE STUDY

The purpose of this study is to determine if workers at Monsanto's Krummrich Plant in Sauget, Illinois suffered any long term health effects as a result of their past exposure to chlorinated phenols, esters of 2,4,-D and 2,4,5-T and their chlorinated dioxin and dibenzofuran contaminants.

2. BACKGROUND

2.1 Plant History

The plant was established in 1907 as the Commercial Acid Company. At that time it occupied 30 acres and employed 70-100 people. Monsanto purchased the plant in 1917 to insure a supply of mineral acids. The plant was referred to as "Plant B" until 1951, when it was renamed the William G. Krummrich Plant in honor of a former plant manager.

The Krummrich Plant currently occupies 329 acres and employs approximately 1100 people. The plant produces about 1 billion tons of material per year. The plant is administered by two of Monsanto's four operating companies: Monsanto Industrial Chemicals and its guest company, Monsanto Polymer Products. The Krummrich Plant is organized by the International Chemical Workers Union, Local 12. The plant is located in Sauget, Illinois, which is 3 miles southeast of downtown St. Louis.

Fifteen percent of the plant's total resources in manpower, time, and money are devoted to its environmental monitoring and control program. The plant employs 2 part-time physicians and several nurses in addition to a large staff of industrial hygiene, safety, and environmental personnel. Monsanto's Corporate Medical Program provides oversight and support of the plant program, including computerization of employee exposure and medical surveillance data.

2.2 Products

The Krummrich plant currently uses more than 75 different raw materials to produce approximately 20 different intermediate chemical products. The major raw materials include chlorine, phosphorus, benzene, sulfur, and salt. Major products include chlorinated benzenes, chlorophenols, orthonitrophenol, nitroanilines, PCl_3, $POCl_3$, P_2S_5, chlorine, sulfuric acid, chlorosulfonic acid, muriatic acid, chlorine bleaches and stabilizers, detergent materials, feed grade antioxidants, and elastomers.

The manufacture of chlorophenols began in 1938. Production of pentachlorophenol was discontinued in 1978; the production of mono- and di-chlorophenols was discontinued in 1983. Esters of 2,4-D and 2,4,5-T were produced between 1960 and 1970. This plant was a producer of PCBs until 1977 when production was discontinued.

2.3 Previous Studies of the Plant Population

2.3.1 Tillman, 1977

In 1977 Dr. Ernest Tillman reviewed the plant medical records of 60 employees in the Pentachlorophenol Unit at the W. G. Krummrich Plant. The study group included all persons who were working in Department 236 in 1977 and all persons who had worked in Department 236 for 1 year or more since 1951. The lengths of exposure ranged from 3 months to 13 years.

Forty-eight percent of the cases studied developed chloracne at some time while assigned to Department 236. In the majority of cases of active employees, chloracne appeared within 1 year of being assigned to Department 236. No difference in the frequency of occurrence was found on the basis of race or age. Chloracne occurred at all times between 1959 and 1977 with

no peak at any particular time.

Seventy-seven percent of the study group made repeated comments about weight variations from one periodic examination to the next. The review of the periodic health questionnaires and physical examinations failed to identify any other abnormalities.

2.3.2 Suskind, 1980

In 1979 Dr. Raymond Suskind conducted a medical survey to determine the health status of employees of the W. G. Krummrich Plant who had been exposed to chlorinated phenols. The study population included active employees who had worked in either Department 236 (pentachlorophenol) or Department 237 (chlorophenols). The total number of active employees who worked in these two areas was 157. One hundred fifteen persons volunteered for examination and 106 of these completed the physical examination.

The medical survey included the completion of an administered questionnaire, a medical history, a dermatologic examination, and examination of other organ systems if indicated by the clinical history. Skin biopsies were done when indicated. Clinical laboratory tests included: blood Ca, P, BUN, creatinine, BUN-creatinine ratio, uric acid, fasting blood sugar, total protein, albumin, globulin, total bilirubin, direct bilirubin, SGOT, SGPT, alkaline phosphatase, LDH, cholesterol, iron, magnesium, sodium, potassium, chloride, GGT, triglycerides and lipoprotein profiles; CBC and differential; urinalysis and urinary copro-porphyrin, uroporphyrins, and creatinine. Personal medical histories were comfirmed by reviewing plant medical and personnel records.

Sixty-six of 115 workers had a history of chloracne. Forty-three were found to have residual chloracne and of these cases 67.6% were mild and 32.5%

moderate. All of the residual cases were comedonal in type, and 32.5% of those had cystic lesions as well. Five of 106 persons were found to have malar hirsutism and 12 were found to have actinic elastosis.

In the analysis of laboratory data, test results were compared between employees with and without a history of chloracne or residual chloracne. While a small number of elevated total serum lipids were observed, there was no correlation between the serum lipids and the presence of chloracne. While persons with elevated triglycerides were found in both groups, there was no correlation between serum triglycerides and presence or absence of chloracne. No significant differences in levels of cholesterol, LDL, SGOT, SGPT, and GGT were found between the chloracne and non-acne groups. Urinary porphyrins could not be interpreted due to technical error.

The frequency of abnormal levels of VLDL was significantly increased in those persons with a history of chloracne or with residual chloracne as compared to those who never had chloracne. There appeared to be less residual chloracne in the group with HDL levels of 45 or more than those in the group with levels less than 45. There was also significantly less chloracne found in workers who did not smoke at the time of examination than those who did smoke.

2.3.3 Zack, 1980

In 1977, The Chemical Manufacturers Association contracted with Tabershaw Occupational Medicine Associates to conduct an industry-wide epidemiologic study of workers exposed to benzene. The W.G. Krummrich Plant was one of the nine plants chosen to participate in this study. Judith Zack conducted a separate Standardized Mortality Ratio analysis of the data from

the Krummrich population.

Her study cohort consisted of all male, hourly employees active on or after January 1, 1946 with six months or more of employment prior to December 31, 1977. Vital status was ascertained as of December 31, 1977. The population of the United States was used as the standard.

Three thousand twenty-two employees fit the cohort entrance criteria, but 114 were excluded because of incomplete data. Two thousand seventy-two of the 2908 member study cohort were verified as living, 736 were identified as deceased, 702 of these by death certificate.

The SMR's for white and non-white employees for specific causes of death are shown in Tables 1 and 2. There were no statistically significant elevations in SMR's observed among male Krummrich employees for any of the cause-of-death categories examined.

Re-analysis of this data by work area is currently being done by Monsanto epidemiologists. Past employees of Department 236 and Department 268 (agricultural esters) have been included in NIOSH's industry-wide mortality study of workers exposed to dioxin.

Table 1

Observed and Expected Deaths for Krummrich Plant Study Population

Non-white Males

Cause of Death	8th Rev. ICD Code	Observed	Expected	SMR
All causes of death	001-998	225	256.87	88*
All malignant neoplasms	140-209	42	44.54	94
Buccal cavity and pharynx	140-149	1	1.54	65
Digestive organs and peritoneum	150-159	9	15.34	59*
Respiratory system	160-163	17	13.20	129
Genitourinary organs	185-189	6	6.88	87
Lymphatic and hematopoietic tissue	200-209	6	3.02	199
Leukemia and aleukemia	204-207	2	1.09	183
Other lymphopoietic cancer	-	4	1.93	207
Other malignant neoplasms	-	3	4.56	66
Circulatory diseases	390-458	117	123.01	95
Arteriosclerotic heart disease	410-413	62	58.34	106
Cerebrovascular disease	430-438	25	28.01	89
Other circulatory diseases	-	30	36.66	82
Respiratory diseases	460-519	4	14.90	27*
All other diseases	-	19	47.79	40*
All external causes of death	800-998	31	25.47	122
Total Residual		12	1.16	

* $p < .05$

Number persons observed = 584

Number person-years observed = 12925.1

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Table 2

Observed and Expected Deaths for Krummrich Plant Study Population-White Males

Cause of Death	8th Rev. ICD Code	Observed	Expected	SMR
All causes of death	001-998	511	522.43	98
All malignant neoplasms	140-209	98	101.76	96
Buccal cavity and pharynx	140-149	2	3.54	56
Digestive organs and peritoneum	150-159	17	28.45	60*
Respiratory system	160-163	46	34.76	132
Genitourinary organs	185-189	6	11.01	54*
Lymphatic and hematopoietic tissue	200-209	7	10.58	66
Leukemia and aleukemia	204-207	2	4.14	48*
Other lymphopoietic cancer	-	5	6.44	78
Other malignant neoplasms	-	20	13.42	149
Circulatory diseases	390-458	273	261.06	105
Arteriosclerotic heart disease	410-413	201	188.14	107
Cerebrovascular disease	430-438	30	30.60	98
Other circulatory diseases	-	42	42.32	99
Respiratory diseases	460-519	20	27.90	72
All other diseases	-	41	69.49	59*
All external causes of death	800-998	57	59.62	96
Total Residual		22	2.60	

*p <.05

Number persons observed = 2324

number person-years observed = 54509.1

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3. LITERATURE REVIEW

3.1 Overview

The health effects of 2,3,7,8-TCDD, 2,4,-D, and 2,4,5-T have been studied extensively in recent years and are the subjects of several excellent reviews (Kimbrough, 1980; Esposito et al, 1980; Huff et al, 1980; HALTS, 1980; JRB, 1981; Clement, 1984). The occupational morbidity studies done to date suffer from inadequate characterization of exposure and lack of adequate controls. The occupational mortality studies are limited by small numbers. Very few studies have followed affected workers over time. Little is known about the health effects of exposure to PCDDs other than 2,3,7,8-TCDD.

The only human data on the health effects of exposure to PCDFs comes from the outbreaks of Yusho disease in Japan and Taiwan in the past two decades (Kuratsune et al, 1972). These observations are confounded, however, by the co-ingestion of PCBs and chlorinated quaterphenyls.

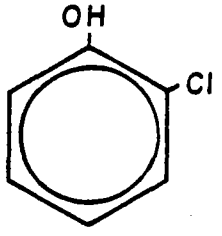
Acute poisoning from pentachlorophenol has been well described. Studies of chronic effects, however, have been limited to small numbers of active workers. There is very little animal data and no human data on the toxicities of the mono- and dichlorophenols.

The structures of the chemicals discussed in this review are shown in Figure 1. A description of the actual manufacturing processes and resulting exposures is provided in Sections 4.2.1 and 4.2.2.

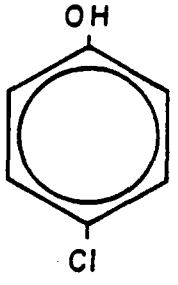
3.2 Ortho Chlorophenol

Ortho chlorophenol (O-CP) is a light amber liquid used as an intermediate in chemical synthesis. O-CP is prepared by the direct chlorination of phenol. It is soluble in water (2.85/100 parts water), alcohol, and ether; its vapor

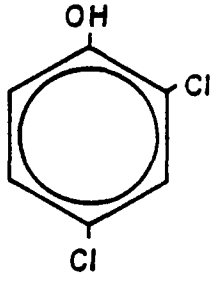
Fig.1 CHEMICAL STRUCTURES OF CHLOROPHENOLS, CHLORPHENOXY ACIDS, AND THEIR DIOXIN AND DIBENZOFURAN CONTAMINANTS



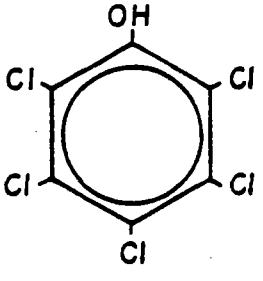
o-CHLOROPHENOL



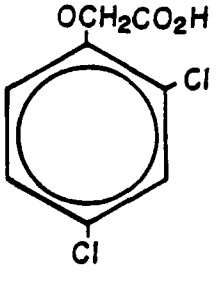
p-CHLOROPHENOL



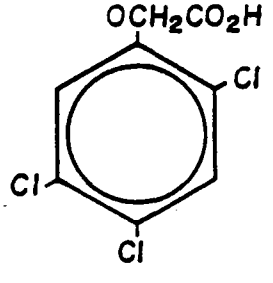
2,4-DICHLOROPHENOL



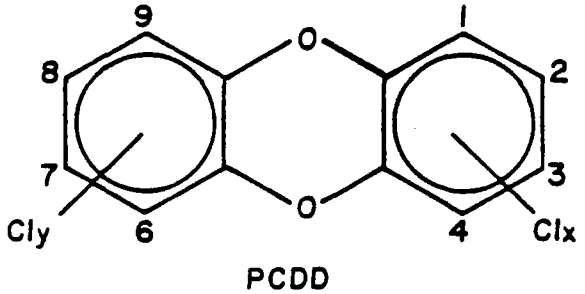
PENTACHLOROPHENOL



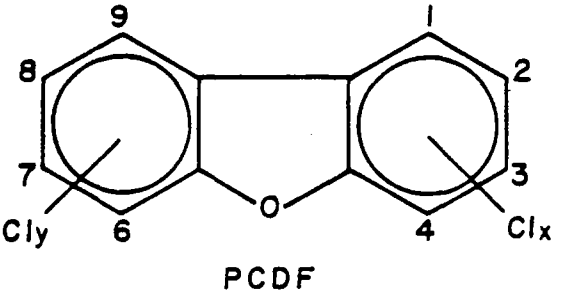
2,4-D



2,4,5-T



PCDD



PCDF

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pressure is 1 mm at 12.1° C.

The oral LD_{50} of O-CP is 670 mg/kg in rats (NIOSH, 1983) and 625-750 mg/kg in chickens (Bubnov et al, 1971). Toxic effects in rats include restlessness, increased respiratory rate, tremors, and clonic convulsions. Pathologic changes in chickens include inflammatory loci in the cerebral cortex and dystrophic changes in the liver and myocardium. O-CP decreased hemoglobin content; increased alkaline phosphatase, LDH, and glutamate-oxaloacetate; and produced pathologically evident liver tissue degeneration in rats (Chung, 1978). O-CP did not affect the immune system in rats at oral concentrations of 500 ppm (Exxon and Koller, 1983). O-CP is fetotoxic in rats and high doses (Exxon and Koller, 1982).

3.3 Parachlorophenol

Parachlorophenol (P-CP) is a white to straw-colored crystalline compound prepared by the direct chlorination of phenol. Solutions of P-CP are used as topical antiseptics. P-CP is soluble in water (2.71/100 parts water) and very soluble in alcohol and ether.

The oral LD_{50} of P-CP is 261 mg/kg in the rat (NIOSH, 1983). Toxic effects include restlessness, increased respiratory rate, tremors, and convulsions. P-CP is irritating to rabbit eye and skin.

3.4 2,4-Dichlorophenol

2,4-Dichlorophenol (2,4-DCP) is a colorless crystalline compound prepared by the direct chlorination of phenol. 2,4-DCP is used as an intermediate in the synthesis of 2,4-Dichlorophenoxy acetic acid. It is sparingly soluble in water. (.45/100 parts water) and very soluble in alcohol and ether.

Somani et al (1981) studied the kinetics of 2,4-DCP in rats. 2,4-DCP was conjugated to glucuronide and other conjugates. The kidney had the highest amounts of free compound, followed by the liver and fat.

The LD_{50} of 2,4-DCP is 580-4,500 mg/kg in rats and 1,630 mg/kg in mice (Kobayashi et al, 1972). Toxic effects in rodents include decreased spontaneous locomotor activity, loss of righting reflex, and sedation. The maximum chronic no-effect level in mice is 100 mg/kg/day (Kobayashi, 1972). 2,4-DCP in doses of .1 mg/kg is fetotoxic in rats (Konstantinova et al, 1976).

3.5 Pentachlorophenol

Pentachlorophenol (PCP) is the second most heavily used pesticide in the U.S. Its major application is wood preservation. PCP is a dark-colored crystalline compound which is produced in the U.S. by the direct liquid phase chlorination of phenol (Boehringer process). PCP produced by the Boehringer process may contain 4-12% tetrachlorophenol, 1-5% hydroxychloro-diphenyl ether, 0.1% trichlorophenol, and trace amounts of PCDDs and PCDFs. Very little is known about the toxicity of hydroxychlorodiphenyl ethers. One of these pre-dioxins, 2-hydroxy-2,4,4-trichlorodiphenyl ether, has a low acute toxicity in rats, with an LD_{50} of about 5000 mg/kg (Williams, 1982).

The sodium salt of PCP is produced by reacting pentachlorophenol with sodium hydroxide. While PCP and its sodium salt vary in their solubilities in different solvents, their toxicities are basically the same. PCP and its sodium salt are usually used as 1-5% solutions in organic solvents (PCP) or water (Na PCP).

The main routes of occupational exposure to PCP are inhalation and skin contact. Skin absorption is facilitated by the presence of organic solvents or by cuts and abrasions of the skin. PCP is bound to plasma proteins. Repeated

workday exposures to the TLV of 0.5 mg/m^3 results in a maximum steady state plasma concentration of 0.5 ppm (Wood, 1983). PCP is eliminated from the plasma via distribution to the tissues, metabolism via glucuronidation and oxidation to tetrachloro-p-hydroquinone, and excretion of PCP and its metabolites in the urine and, to a lesser extent, the feces. PCP may undergo enterohepatic circulation. Elimination follows a first order, single compartment model with a half life of 30.2±4 hours in healthy human volunteers. (Braun, 1979). Elimination half lives in workers may be longer.

Technical-grade PCP is irritating to the skin and mucous membranes of the eyes and upper respiratory tract. Skin irritation occurs with frequent contact to PCP solutions of 1% or stronger. Eye and respiratory tract irritation occur at PCP air levels greater than 1.0 mg/m^3. Skin contact with technical-grade PCP can produce chloracne, though this is most likely due to the HCDD (and perhaps other PCDD/PCDF) contaminants.

PCP produces its systemic toxicity by interfering with electron transport in mitochondria. The resulting uncoupling of oxidative phosphorylation results in an increase in metabolic heat production and hyperpyrexia.

The acute oral LD_{50} of PCP is 40-130 mg/kg in rabbits and 27-78 mg/kg in rats. PCP contaminated with HCDD, HeCDD, and OCDD has produced hepatic effects in rats, including hepatic porphyria and increases in aryl hydrocarbon hydroxylase (AHH) and glucuronyl transferase (GGT) activity (Goldstein, 1977). Pure PCP was not porphyrogenic and produced only a slight effect on GGT activity. Technical PCP has also produced hepatocellular degeneration and necrosis in rats (Kimbrough and Linder, 1978). PCP has not been shown to be carcinogenic in

animals. PCP with its HCDD contaminant, however, may be fetotoxic and teratogenic (Cirelli, 1978).

There are numerous case reports of acute PCP poisoning resulting from occupational exposures (Truhaut et al, 1952; Menon, 1958; Wood et al, 1983). Symptoms include hyperpyrexia, diaphoresis, tachycardia, tachypnea, weakness, nausea, vomiting, abdominal pain, anorexia, thirst, pain in the extremities, progressive coma, and death. Acute PCP poisoning may present with hepatic and renal dysfunction and metabolic acidosis with an increased anion gap. Skin absorption appeared to be the primary route of exposure in many of these cases. Sporadic cases of aplastic anemia, leukemia, Hodgkin's disease, and non-Hodgkin's lymphoma of the skin have been reported among PCP workers, but the association with PCP exposure is not conclusive (Roberts, 1983).

Chronic occupational exposure to PCP has been associated with an increased prevalence of conjunctivitis, chronic sinusitis, bronchitis, polyneuritis, and dermatitis (Baader and Bauer, 1951; Klemmer et al, 1980). Chloracne has occurred in PCP workers, but is most likely due to the PCDD and PCDF contaminants. Treibig et al (1981) found a significant decrease in sensory nerve conduction velocities in PCP production workers, but they could not demonstrate a dose response relationship. Zober et al (1981) found elevated GLDH-activities in workers producing and applying PCP. Begley et al (1977) demonstrated a significant improvement in creatinine clearance and phosphorus reabsorption in PCP wood treatment workers following a 20-day vacation. Bauchinger et al (1982) analyzed the chromosomes from peripheral lymphocytes from PCP production workers. They found a small, but significant, increase in the frequency of dicentrics and acentrics, but no significant increase of sister-chromatid exchanges.

3.6 2,4 Dichlorophenoxyacetic Acid

2,4-Dichlorophenoxyacetic acid (2,4-D) is a widely used post-emergent herbicide. 2,4-D is a white powder produced by reacting 2,4-dichlorophenol with chloroacetic acid in a solvent mixture of water and sodium hydroxide. The esters are produced by reacting 2,4-D with the appropriate alcohol. 2,4-D may be contaminated with Di-CDD, Tri-CDD, and 1,3,6,8-TCDD as well as with a variety of derivatives of phenoxyacetic acid and phenol, such as Bis (2,4-dichlorophenoxy) methane, Bis (2,5-Dichlorophenoxy) methane and 2,2,4,6- tetrachlorodiphenoxy methane. Most commercial 2,4-D preparations contain the ester or the salt rather than the free acid due to their better solubility characteristics. Alcohols are often used as solvents in 2,4-D formulations. The concentration of 2,4-D in commercial preparations is highly variable and may range from 1-80% (Halts, 1980).

2,4-D is rapidly absorbed from the gastrointestinal tract in healthy male volunteers with peak plasma levels occurring in 4-24 hours. The volume of distribution is .28-.29 1/kg. Elimination is first order with a plasma half life of 7-33 hours. 2,4-D is excreted in the urine as the free acid, though a small percent may appear in the urine as conjugates. (Kohli et al, 1974; Sauerhoff et al, 1977). Since 2,4 D is a weak organic acid, urinary excretion is pH dependent. Prescott (1979) increased renal clearance of 2,4-D in a case of accidental ingestion by alkalinizing the urine. Feldman and Maichbach (1974) found that 5% of 2,4-D applied to the forearm was absorbed and excreted.

2,4-D's mechanism of toxic action has not been well established. 2,4-D may produce its neuromuscular effects by interfering with organic acid anion transport in neuromuscular tissues. (Podolak, 1981 a,b; Kim, 1981). 2,4-D has also been shown to induce mixed function oxidases in animals (Rivieri and Bach, 1981).

The LD_{50} of 2,4-D in animals ranges from 100 mg/kg to a few thousand mg/kg depending on the form of 2,4-D and the species tested (IARC, 1977). Toxic effects are apparent after a latent period of 2-9 days and include loss of appetite, weight loss, myotonia, and muscle weakness progressing to paralysis, coma, and death. Pathological changes have been described in the gastrointestinal tract, liver, lungs, and kidneys. The free acid appears to be more toxic than the esters, and equal in toxicity to the sodium salt (HALTS, 1980).

2,4-D increased the frequency of tumors in rats (Hansen et al, 1971; but most other studies have not shown a carcinogenic effect in animals. 2,4-D is fetotoxic in high doses and may be a weak teratogen. Duffard et al (1981) demonstrated reduced hatchability and an increased frequency of malformations in chick eggs painted with 2,4-D. In a second study, painting eggs with 2,4-D resulted in postnatal alterations in the chemical composition of chick brain (Duffard et al, 1982)

The LD_{50} of 2,4-D in man is estimated at 80-800 mg/kg. Autopsy findings from two fatal human ingestions showed acute demyelination in the brain (patient with senile dementia), peripheral neuropathy, degenerative changes in the ganglion cells, hepatic necrosis, and congestion of most organs (Nielsen et al, 1965; Dudley and Thapar, 1972). Seven cases of peripheral neuropathy following dermal exposure to 2,4-D have been reported in the literature (Goldstein et al, 1959; Todd, 1962; Berkeley and Magee, 1963; Wallis et al, 1970; Halts, 1980). Signs and symptoms of a symmetric, "dying back," sensorimotor neuropathy began within 1-2 weeks after exposure. While nerve conduction times were at or slightly below the lower limit of normal, electromyography revealed denervation phenomena in the most severely affected patients. Recovery was slow with some residual deficits.

Epidemiologic studies of occupational exposure to the phenoxy herbicides are discussed under the section on PCDDs and PCDFs.

3.7 2,4,5-Trichlophenoxyacetic Acid

2,4,5-Trichlorophenoxyacetic Acid (2,4,5-T) was widely used as a post-emergent herbicide for controlling woody plant growth until 1979, when many of its uses were curtailed by the US EPA. 2,4,5-T is a light tan solid produced by reacting 2,4,5-Trichlorophenol with chloroacetic acid under alkaline conditions. The esters are produced by reacting 2,4,5-T with the appropriate alcohol. 2,4,5-T may be contaminated with 2,3,7,8-TCDD, HCDD, and perhaps some PCDFs. Most commercial preparations contain the ester or amine salt. The amine salts are soluble in water while the esters are emulsifiable in water and soluble in most oils.

2,4,5-T is rapidly absorbed from the gastrointestinal tract in healthy male volunteers (Matsumura, 1970; Gehring et al, 1973; Kohli et al, 1974). Rates of skin absorption vary from 0.22-1.13 mg/sq ft/hr for spray concentrations of 2-32 lb 2,4,5-T/100 gal (GRB, 1981). Elimination is first order with a plasma half life of 19-23 hours. Metabolites have been detected in animals but not in humans. 2,4,5-T propylene glycol butyl ether ester is rapidly hydrolyzed to the free acid in rats (Young et al, 1981).

The LD_{50} of 2,4,5-T and its derivatives ranges from 100 to 940 mg/kg in various species (JRB, 1981). The free acid appears to be more toxic than the salts or esters. Acute toxic effects in animals include anorexia, vomiting, diarrhea, locomotive disturbances, and depression. Histopathologic changes are nonspecific. The mechanism of toxic action of 2,4,5-T is unknown.

2,4,5-T with less than 1 ppm TCDD produced cleft palate and growth

retardation in mice (Roll, 1971; Hood et al, 1979). 2,4,5-T increased the incidence of tumors in C3Hf mice (Muranyi-Kovacs et al, 1976). Tumor incidence was not increased, however, in other strains of mice or in other animal species.

The health effects observed in humans after chronic exposure to 2,4,5-T are usually ascribed to the 2,3,7,8-TCDD contaminant. There are no reported cases of acute poisoning with pure 2,4,5-T in humans.

3.8 Polychlorinated Dibenzo-p-Dioxins (PCDDs) and Polychlorinated Dibenzofurans (PCDFs)

PCDDs and PCDFs are two series of tricyclic aromatic compounds which are inadvertantly formed during the synthesis of chlorinated phenols and their derivatives. The dibenzo-p-dioxin and dibenzofuran nuclei can hold from one to eight chlorine atoms. The numbers of possible positional PCDD and PCDF isomers are given in Table 3. Each of the 75 PCDD and 135 PCDF isomers may have different chemical, physical, and toxicological properties. As a general trend in both series, solubility in most solvents and volatility decrease with an increasing number of chlorine atoms.

Levels of PCDDs and PCDFs reported in mono-, di-, and pentachlorophenols are shown in Table 4. PCDDs do not appear to be common contaminants of mono- and di-chlorophenols. The levels of PCDFs in these compounds are unknown. Hexa, hepta, and octa-dibenzo-p-dioxins and dibenzofurans have been repeatedly detected in PCP. The tetra- and penta-dibenzofuran congeners have been detected in numerous samples of 2,4,5-T. 2,4-D is frequently contaminated with DCDD, tri-CDD, and 1,3,6,8-TCDD. (Table 5).

The various PCDD and PCDF isomers vary considerably in toxic potential. The LD_{50}s range from 0.6-2.0 mcg/kg for 2,3,7,8-TCDD in guinea pigs to over

TABLE 3. POSSIBLE NUMBER OF POSITIONAL ISOMERS OF PCDDs AND PCDFs.

Chlorine Substitution	Number of Isomers	
	PCDDs	PCDFs
mono-	2	4
di-	10	16
tri-	14	28
tetra-	22	38
penta-	14	28
hexa-	10	16
hepta-	2	4
octa-	1	1
	75	135

TABLE 4. PCDDs and PCDFs Reported in o-chlorophenol, 2,4-Dichlorophenol and Pentachlorophenol

Chlorophenol	PCDDs, ppm[a] mono-CDD	DCDD	tri-CDD	TCDD	penta-CDD	hexa-CDD	hepta-CDD	OCDD	Data Source
Monochlorophenol									
o-chlorophenol	ND	ND	ND	ND	ND	ND	ND	ND	Firestone et al, 1972
o-chlorophenol	--	--	--	0.037 (2,3,7,8)[b]	--	--	--	--	Esposito et al, 1972
Dichlorophenol									
2,4-dichlorophenol	ND	ND	ND	ND	ND	ND	ND	ND	Firestone et al, 1972
Pentachlorophenol									
PCP (Dowcide 7)	--	--	--	--	--	9	235	250	Buser, 1975
PCP	--	--	--	ND (0.5)	--	10-100	100-1000	100-1000	Woolson et al, 1972
Na-PCP (1967)	ND	ND	ND	ND	ND	14	14.5	3.8	Firestone et al, 1972
Na-PCP (1969)	ND	ND	ND	ND	ND	20	11.3	3.3	"
PCP (1970)	ND	ND	ND	ND	ND	39	49	15	"
PCP (1970)	ND	ND	ND	ND	ND	35	23	ND	"
PCP (1967)	ND	ND	ND	ND	ND	0.17	ND	ND	"
PCP (1969)	ND	ND	ND	ND	ND	13	47	ND	"
PCP (1970)	ND	ND	ND	ND	ND	0.19	2.1	5.3	"
PCP (1970)	ND	ND	ND	ND	ND	15	23	15	"
PCP (1978)	--	--	--	ND(0.1)	--	19	140	432	USEPA, 1978
Pentachlorphenate	--	--	--	--	--	--	+	+	Jensen and Renberg,1972
PCP formulation	--	--	--	--	--	--	870	50-3300	"
PCP (technical grade)	--	--	--	ND	--	33-42	19-24	7-11	Villanueva et al,
PCP (reagent grade)	--	--	--	ND	--	0.02-0.03	0.04-0.09	0.02-0.03	"
PCP (many samples	--	--	--	ND	--	9-27	90-135	575-2510	"
PCP's (17)	--	--	--	--	--	0-23	--	0-3600	"

(continue

Table 4 (cont.)

	PCDDs, ppm[a]								
	mono CDF	DCDF	tri-CDF	TCDFs	penta-CDFs	Hexs-CDFs	Hepta-CDFs	Octa-CDFs	Data Source
PCP or PCP-Na (7)	--	--	--	--	--	0.03-10	0.06-180	5.5-370	Buser and Bosshardt,1976
PCP (Dowcide 7 1970)	--	--	--	--	--	4	125	2500	USEPA, 1978
PCP (Dowcide 7 1970) (distilled)	--	--	--	--	--	1.0	6.5	15	"
PCP	--	--	--	--	--	9-27	--	575-2510	Johnson, 1973
Na-PCP(Dowcide G 1978)	--	--	--	--	--	ND-2	1-12	4-173	"
	PPDFs, ppm								
Pentachlorophenol									
PCP (USA)	--	--	--	0.9	4	32	120	130	Rappe, 1978
PCP (USA)	--	--	--	--	--	30	80	80	USEPA, 1978
PCP (USA)	--	--	--	$\leq$0.4	40	90	400	260	Goldstein, 1977
PCP (Germany)	--	--	--	--	--	0.03	0.8	1.3	Rappe, 1981
PCP	--	--	--	0.20	0.20	13	70	55	Buser and Bosshardt, 1976

[a]Key to abbreviations and symbols: ND = Not detected (minimum detection level, ppm). Other numbers in parentheses indicate year chlorophenol sample was obtained, or specific dioxin detected.
-- = Not analyzed or not reported.

[b]Presence of 2,3,7,8-TCDD confirmed but not quantitatively reported.

TABLE 5. PCDDs IN 2,4,5-T AND 2,4-D

Pesticide Sample	PCDDs ppm Mono-CDD	DCDD	Tri-CDD	TCDD	Penta-CDD	Hexa-CDD	Hepta-CDD	OCDD	Data Source
2,4,5-T (1973)	--[a]	--	--	10.0	--	10.0	--	--	Fishbein, 1973
2,4,5-T Acid (1952)	--	--	--	1.10[b]	--	--	--	--	Rappe and Buser, 1980
2,4,5-T Ester	--	--	--	0.50	--	--	--	--	"
2,4,5-T Ester	--	--	--	0.05	--	--	--	--	"
2,4,5-T Ester (1960)	--	--	--	0.40	--	--	--	--	"
2,4,5-T Ester (1962)	--	--	--	0.95	--	--	--	--	"
2,4,5-T Ester (1966)	--	--	--	0.10	--	--	--	--	"
2,4,5-T Ester (1967)	--	--	--	0.05	--	--	--	--	"
2,4,5-T Ester (1967)	--	--	--	0.22	--	--	--	--	"
2,4,5-T Ester (1967)	--	--	--	0.18	--	--	--	--	"
2,4,5-T Acid (1964)	--	--	--	4.8	--	--	--	--	"
2,4,5-T Acid (1969)	--	--	--	6.0	--	--	--	--	"
Herbicide Orange	--	--	--	0.12	--	--	--	--	"
Herbicide Orange	--	--	--	1.1	--	--	--	--	"
Herbicide Orange	--	--	--	5.1	--	--	--	--	"
2,4-D Ester (1980)	--	--	0.35	0.23[c]	--	--	--	--	Cochrane et al, 1982
2,4,-D Ester (1980)	--	2.72	2.08	0.72	--	--	--	--	"
2,4-D Ester (1980)	--	4.20	1.63	1.75	--	--	--	--	"
2,4-D Ester (1980)	--	0.10	0.64	0.32	--	--	--	--	"
2,4-D Ester (1980)	--	1.24	1.82	0.85	--	--	--	--	"
2,4-D Ester (1980)	--	0.11	0.93	0.49	--	--	--	--	"
2,4-D Ester (1980)	--	0.10	0.68	0.32	--	--	--	--	"
2,4-D Ester (1980)	--	--	--	--	--	--	--	--	"

TABLE 5 (cont.) PCDDs in 2,4,5-T and 2,4-D

Pesticide Sample	PCDDs ppm								Data Source
	Mono-CDD	DCDD	Tri-CDD	TCDD	Penta-CDD	Hexa-CDD	Hepta-CDD	OCDD	
2,4,-D Ester (1980)	--	0.20	0.16	0.21	--	--	--	--	Cochrane et al, 1982
2,4-D Salt (1980)	--	--	0.038	0.054	--	--	--	--	"
2,4-D Salt (1980)	--	--	0.58	0.28	--	--	--	--	"
2,4-D Salt (1980)	--	0.005	0.054	0.02	--	--	--	--	"
2,4-D Salt (1980)	--	--	--	--	--	--	--	--	"
2,4-D Salt (1980)	--	0.033	0.53	0.21	--	--	--	--	"
2,4-D Salt (1980)	--	--	--	--	--	--	--	--	"
2,4-D Salt (1980)	--	--	--	--	--	--	--	--	"
2,4-D (1972)	--	--	--	--	--	0.5-10	--	--	Woolson et al, 1972

[a]Not detected, not tested, or not reported.

[b]Levels of TCDD in this and subsequent 2,4,5-T formulations are of the 2,3,7,8 isomer.

[c]Levels of TCDD in this and subsequent 2,4-D formulations are of the 1,3,6,8 isomer.

4.0×10^6 mcg/kg for OCDD in mice. (Esposito et al, 1980). The LD_{50} for 2,3,7,8-TCDF in guinea pigs is 2 to 4-fold higher than that reported for 2,3,7,8-TCDD (More et al, 1979). Chemical structural requirements for toxicity in both series appear to be chlorine substitutions at positions 2,3, and 7 with at least one hydrogen remaining on the nucleus.

The mechanism of toxic action of PCDDs and PCDFs is still unknown. A cytosol receptor has been identified in mouse and rat liver which binds certain PCDDs and corresponds to their potency to induce aryl hydrocarbon hydroxylase activity (Huff et al, 1980). The ability of these compounds to induce aryl hydrocarbon hydroxylase correlates with their toxicity in animal studies. Iron deficiency protects mice from some of the toxic effects of 2,3,7,8-TCDD, but the mechanism of this interaction is unclear (Jones and Sweeney, 1982).

The toxicokinetics of 2,3,7,8-TCDD have been studied in several species including rats, guinea pigs, and monkeys (Piper et al, 1973; Rose et al, 1976; Nolan et al, 1979; Gasiewicz and Neal, 1978; Van Miller, et al, 1976). 2,3,7,8-TCDD is moderately well absorbed from the gastrointestinal tract in most species. There are significant differences in the tissue distribution of this compound among various animal species. Following a single administration of 14 C-2,3,7,8-TCDD, the largest percentage of the dose appears in the liver in rats and in the adipose tissue in guinea pigs and monkeys. Materials other than 2,3,7,8-TCDD constitute a significant fraction of the 14 C activity in the feces, but no metabolites have yet been identified. After repeated oral dosing in the rat, a fraction of the 14 C acivity may also appear in the urine. The excretion of a single oral dose of 14 C-2,3,7,8-TCDD in rats follows a one-compartment, open model with a half life of 31 days.

The toxicokinetics of other PCDDs can differ considerably from those of 2,3,7,8-TCDD. Norback (1975) studied the toxicokinetics of OCDD in the rat following chronic oral dosing: OCDD concentrated in rat liver and was excreted mainly by the urinary system with a half-life of about 3 weeks. Tulp and Hutzinger (1978) studied the rat metabolism of a series of PCDDs. They demonstrated that some PCDDs can be metabolized by hydroxylation at the lateral (2,3,7 and/or 8) positions in the molecule. When these positions are blocked by chlorine atoms, metabolism via epoxide formation is much less likely to occur.

Decad et al (1982) studied the toxicokinetics of 2,3,7,8-TCDF in guinea pigs, rats, and monkeys. Gastrointestinal absorption of 2,3,7,8-TCDF was nearly complete in rats and guinea pigs. The liver was the major initial depot for 2,3,7,8-TCDF in all three species with lesser amounts in adipose tissue, skin, and muscle. Rats, and to a lesser extent, monkeys were able to metabolize 2,3,7,8-TCDF whereas guinea pigs could not. The whole body half-life of TCDF in guinea pigs, monkeys, and rats was 20, 8, and 2 days respectively.

The metabolism of PCDF isomers in man may depend on the positions of the chlorine atoms on the dibenzofuran nucleus. Rappe analyzed liver samples for PCDFs from two patients with Yusho disease and compared the distribution of the isomers to that found in the ingested rice oil (Rappe et al, 1981). He found that the PCDF isomers which had apparently been excreted had two vicinal hydrogenated carbon atoms in at least one of the two rings; these unblocked positions are presumably involved in the metabolism by forming epoxides.

The toxic effects produced by PCDDs and PCDFs vary quantitatively and qualitatively among different species. Within a given species, the effects produced by the toxic PCDD and PCDF isomers are similar to those of 2,3,7,8-TCDD, differing mainly in the intensity of toxic effect. In all laboratory animals the lethal effect is slow and ensues days or weeks after a single dose. The spectrum of acute toxic effects of 2,3,7,8-TCDD in mice, guinea pigs, and monkeys is presented in Table 6. The most striking finding in most species is substantial loss of body fat. Involution of the thymus and testicular alterations have been observed in all species studied. Biochemical effects of 2,3,7,8-TCDD include induction and/or suppression of various enzyme systems, changes in porphyrin metabolism, and alteration of lipid profiles. 2,3,7,8-TCDD and HCDD have produced chloracne in animals. Rats fed TCDD were found to have decreased thyroxine, free thyroxine index, glucose, and insulin levels in the serum (Potter et al, 1983). Doses of 2,3,7,8-TCDD which do not produce overt clinical or pathological changes may still be capable of causing immunosuppression. (Thigpen et al, 1975).

Moore et al (1979) studied the toxicity of TCDF in mice, guinea pigs, and monkeys. The toxic effects in guinea pigs and monkeys were similar to those produced by 2,3,7,8-TCDD but required 2-20 fold higher doses of TCDF. Mice did not demonstrate clinical signs of toxicity at a dose of TCDF which was 23 fold higher than the TCDD $LD_{50/30}$. The interspecies variation in acute toxicity may be due to differences in detoxification metabolism (Decad et al, 1982).

2,3,7,8-TCDD increases the incidence of neoplasms in rats and mice. (Van Miller et al, 1977; Kociba et al, 1978; Toth et al, 1979). The data implicating 2,3,7,8-TCDD as a mutagen are conflicting, and it is unclear whether 2,3,7,8-TCDD acts as an initiator or a promotor. Carcinogenecity studies of other

Table 6. Summary of Acute Toxicity Effects of 2,3,7,8-TCDD[a]

	Mice	Guinea pigs	Monkeys (female)
Thymus involution	+++	+++	+++
Spleen reduction (white pulp)	+	+	+
Bone-marrow hypoplasia	±	++	+
Liver, megalocytosis/degeneration	+++	-	-
Bile-duct hyperplasia	±	±	+++
Testicular degeneration	++	+++	N/A
Renal-pelvis hyperplasia	-	++	+
Urinary-bladder hyperplasia	-	++	-
Adrenal-cortical atrophy (Zona Glomerulus)	-	++	-
Hemmorhage: Intestinal	+	+	-
Adrenal	-	++	-
Acites	++	-	+
Cutaneous lesions	-	-	+++

[a]Source: Esposito, Tiernan, and Dryden, 1980

Key as follows:
- - no effect
- + mildly affected
- ++ moderately affected
- +++ severely affected

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PCDDs are in progress. The carcinogenic potentials of PCDFs have not been studied.

2,3,7,8-TCDD is teratogenic in mice and hamsters. The threshold teratogenic dose in mice was estimated to be 0.1 mcg per day (Smith et al, 1976). 2,3,7,8-TCDD has been shown to be fetotoxic in a wide variety of species, including primates. HCDD was teratogenic in rats at a dose of 100 mcg/kg per day (IARC, 1977) There is as yet no data on the fetotoxic potentials of PCDFs in animals.

The toxic effects of 2,3,7,8-TCDD in man are summarized in Table 7. The toxic effects most consistently observed in occupational studies are chloracne, liver dysfunction, neuropsychiatric disturbances, and abnormalities in porphyrin metabolism. Table 8 summarizes the findings of the morbidity studies of workers exposed to 2,3,7,8-TCDD to date. The few follow-up studies which have been done show resolution of gross liver dysfunction and porphyrin abnormalities following removal from exposure. (Pazderova-Vijlupkova et al, 1981; Suskind, 1984).

Several of the occupational exposures occurred as the result of uncontrolled exothermic reactions during the production of trichlorophenol. A similar process accident at Seveso, Italy in 1976 resulted in widespread community exposure to 2,3,7,8-TCDD. Health effects included chloracne, primarily in children, and peripheral neuropathy in a small percent of those exposed (Pocchiari et al, 1979).

The epidemiologic studies on the carcinogenecity of TCDD are summarized in Table 9. While individual occupational mortality studies reveal no excess of cancer, the pooled data suggest an excess of soft tissue sarcoma (Honchar and Halperin, 1981).

Table 7. Toxic Effects of 2,3,7,8-Tetrachlorodibenzo-*p*-dioxin in Man.[a]

Effects
DERMATOLOGICAL
Chloracne
Porphyria cutanea tarda
Hyperpigmentation and hirsutism
INTERNAL
Liver damage[b]
Elevated serum hepatic enzyme levels
Disorders of fat metabolism
Disorders of carbohydrate metabolism
Cardiovascular disorders
Urinary tract disorders
Respiratory disorders
Pancreatic disorders
NEUROLOGICAL
Polyneuropathies (perpheral neuritis)
Lower extremity weakness
Sensory impairments (sight, hearing, smell, taste)
PSYCHIATRIC
Neurasthenic or depressive syndromes

[a]Source: Huff, Moore, Saracci, and Tomatis, 1980

[b]Mild fibrosis, fatty changes, hemofuscin deposition and parenchymal-cell degeneration were observed in a few cases.

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TABLE 8. REPORTED OCCUPATIONAL EXPOSURES IN CHLORINATED PHENOLS RESULTING IN HUMAN ILLNESS[a]

Year, Place, and chemical(s)	Type of exposure and no. of cases	Effects on the skin	Neurological effects	Effects on the liver and serum lipids	Other effects	References
1936 Michigan Tetrachlorophenol 2-(2-chlorophenyl) phenol	Production 21	Chloracne, hyperkeratosis			Fatigue, weight loss	Butler, 1937
1936 Mississippi Tetrachlorophenol	Wood treatment 300-400	Chloracne, facial erythema, vesiculation, ulceration, hyperkeratosis, hyperpigmentation			Fatigue, colored urine, urinary problems, venous thrombosis	Anonymous, 1936: Stingily, 1940
1949 West Virginia Trichlorophenol 2,4,5-T	Explosion 117 Production 111	Chloracne, facial erythema, hyperpigmentation, melanosis	Nervousness, irritability, insomnia, personality change, depression, headache, vertigo, pain and weakness lower extremeties, paresis, peripheral neuropathy, abnormal nerve biopsy (loss of myelin)	Hepatomegaly, abnormal liver function, toxic hepatitis, elevated triglycerides and cholesterol	Fatigue, weight loss, weakness, decreased libido, impotence, intolerance to cold, increased susceptibility to infection (especially respiratory)	Ashe and Suskind, 1949, 1950; Suskind, 1953; Suskind, 1977
1949 Germany Trichlorophenol Tetrachlorophenol Pentachlorophenol	Production, Industrial Laboratory 17	Chloracne, hyperpigmentation, scarring	Lower extremity pain and weakness, paresis without atrophy, paresthesia, polyneuritis	Abnormal liver function, cirrhosis	Fatigue, severe bronchitis, decreased libido, impotence, bursitis, myocardial damage	Baader and Bauer, 1951

1952 Germany Trichlorophenol	Production 31	Chloracne, hyperpigmentation	Lower extremity pain and weakness, paresthesia, memory and concentration deficits, sleep disturbances, hypersomnolence, abnormal psychological tests (apathy, dulled emotional response)	Toxic hepatitis, abnormal liver biopsy	Fatigue, chronic bronchitis, persistent blepharoconjunctivitis, myocardial damage, intolerance to alcohol	Suskind, 1977
1953 Germany Trichlorophenol	Explosion 55	Chloracne	Sensory impairment of smell, taste, hearing; tendency to orthostatic collapse, limited paresis, peripheral neuropathy, reading difficulties	Toxic hepatitis	Fatigue, drowsiness, bronchitis, laryngitis, blepharoconjunctivitis, hemorrhagic pleuritis, myocardial damage, increased susceptibility to infection	Goldman, 1973
1956 France Trichlorophenol 1966 France Trichlorophenol	Production 17 Explosion 21	Chloracne	Peripheral neuropathy	Toxic hepatitis, elevated tryglycerides and cholesterol		Dugois et al, 1956; Dugois et al, 1968
1956 New Jersey Trichlorophenol	Production 29	Chloracne, hyperpigmentation, hypertrichosis, acquired porphyria cutanea tarda	Clinical examination normal	Abnormal liver function, abnormal liver biopsies (parenchymal cell degeneration, fluorescence)	Right upper quadrant pain	Bleiberg et al, 1964
1963 Holland Trichlorophenol 2,4,5-T	Explosion 106	Chloracne, facial erythema	No information	Liver function normal	Fatigue	Vos et al, 1977

1964 USSR Trichlorophenol 2,4,5-T	Production 128	Chloracne	Headache, loss of memory, somnolence, sleeplessness, increased sweating		Fatigue, joint pain, stomach pain	Telegina and Bikbulatova, 1970
1968 England Trichlorophenol	Explosion 79	Cloracne, facial erythema		Abnormal liver function	Transient glycosuria, mild conjunctivitis	May, 1973; Jensen and Walker, 1965; Jensen et al, 1972
1965-1968 Czechoslovakia Trichlorophenol Pentachlorophenol 2,4,5,-T	Production 80	Chloracne, hyperpigmentation, hypertrichosis, scarring, acquired porphyria cutanea tarda	Lower extremity weakness and pain,somnolence, headache, insomnia, emotional and psychiatric disorders, peripheral neuropathy (confirmed by abnormal EMG)	Hepatomegaly, abnormal liver function, abnormal liver biopsies (mild steatosis, periportal fibrosis, fluorescence). Elevated triglycerides, phospholipids, and cholesterol	Fatigue, weight loss, abnormal blucose tolerance, no evidence of myocardial or renal damage or of increased eye inflammation or respiratory infection	Jiraskek et al, 1964; Pazderova-Vejlupkova et al, 1980; Pazderova-Vejlupkova et al, 1981
1969 New Jersey Trichlorophenol 2,4,5-T 2,4-D	Production 73 Followup of plant studied by Bleiberg (above)	Chloracne in 48, hypertrichosis in 16, hyperpigmentation in 30, no overt porphyria cutanea tarda	Lower extremity weakness, correlation between chloracne and hypomania scale on MMPI	No significant abnormalities	Eye irritation, mild uroporphyrinuria in one worker	Poland et al, 1971 (see Bleiberg et al, 1964)
1978 England Trichlorophenol no longer in production	Followup of 41 workers in 1968 explosion (above) 41	Chloracne		Elevated GGT, elevated triglycerides, elevated urinary D-glucaric acid		May, 1982

1949 West Virginia Trichlorophenol 2,3,5-T	226 Followup of plant studied by Ashe and Suskind (above)	Chloracne 70-residual 47-by history	Abnormal sensory findings in those with chloracne	Elevated GGT in those with chloracne	Decreased libido, sexual dysfunction	Moses et al, 1984
1949 West Virginia Trichlorophenol 2,4,5-T	204 Followup of plant studied by Ashe and Suskind and Moses et al (above)	Chloracne in 107 Actinic Elastosis			History of GI ulcer Lower pulmonary function in exposed smokers	Suskind and Hertzberg, 1984
1976 Seveso Trichlorophenol	No. not given ICMESA workers follow-up five years after explosion			Elevated Alk. Phos.	Elevated urinary porphyrins	Ghezzi et al, 1984

[a] Source: Moses et al, 1984

Table 9 Epidemiologic Studies on the Carcinogenicity of TCDD.[a]

Type and Place of Exposure	Number of Cases	TCDD Level of Exposure	Time Elapsed Since Exposure	Frequency of Cancer Death	Reference
Accidental, Monsanto, USA	228	Unknown	30 years	No Excess	Zack, 1980
Accidental, Boehringer, RFG	24	Unknown	28 years	No Excess	Krause, 1978
Accidental, Basf, RFG	55	Unknown	27 years	Excess of Stomach Cancer	Theiss, 1982
Accidental, Philips, Netherland	50	10,000 ppb	17 years	No Excess	Vos, 1978
Accidental, Dow Chemical, USA	60	Unknown	16 years	No Excess	Cook, 1980
Accidental, Spolana, Czechoslovakia	78	24,200 ppb	15 years	No Excess	Jirasek, 1978
Accidental, Coalite, UK	79	400 ppb	12 years	No Excess	May, 1980
Accidental, Chemie Werke, Linz, Austria	50	140 ppb	7 years	----	----
Herbicide Spraying, Sweden, Backsprayers	348	0.00315 ppt	Over 10 years	Excess of Stomach Cancer	Axelson, 1979
Herbicide Spraying, Finland, Backsprayers	1960	0.00315 ppt	Over 10 years	No Excess No Lymphomas	Rihmaiki, 1980
Herbicide Contamination, Sweden	72	0.0001 ppb 0.1 ppt	Over 10 years	Excess of Lymphomas	Hardell, 1979
Agent Orange Spraying USAF, VietNam	1242	1.9 ppm	Over 13 years	No Excess	Lathrop, 1983

[a] Source: Reggiani, 1980

A review of these cases revealed that several were not true soft tissue sarcomas; moreover, exposure in a few of the cases was minimal (Fingerhut et al, 1984). Swedish case-control studies of soft tissue sarcoma found an association with previous exposure to phenoxy acids or chlorophenols (Hardell et al, 1979; Eriksson et al, 1979)

The Yusho cases provide our only data on the human toxicity of PCDFs. Yusho disease was caused by ingestion of rice oil accidentally contaminated with PCDFs, PCBs, and polychlorinated quarterphenyls; as such it is difficult to separate the effects of the various toxic principles. The clinical symptomatology of the Yusho cases is presented in Table 10. The Yusho oil was clearly fetotoxic. There is as yet no data on the carcinogenic potential of PCDFs in man.

Table 10. Clinical Symptomology of Yusho Cases, 1969-1972.[a]

Effects	Percent
Skin Acneform eruptions, distinctive hair follicles, red plaques on limbs, dark brown pigmentation of nail, skin and mucous membranes, itching, sweating of palms.	82-87%
Ocular manifestation Increased eye discharge, swelling of the upper eyelids, hyperemia of conjunctives, transient visual disturbance.	83-88
Jaunidce No abnormalities of liver functions in the majority of cases.	10
Numbness of the limbs, feeling of weakness, spasm of the muscles	32-39
Reduced sensory and motor nerve conduction velocity in few cases	9
Hearing difficulties	18
Headaches, vomiting, diarrhea	17-39
Chronic Bronchitis Lower serum Ig A and Ig M. PCB in the sputum	40
Irregular menstrual cycles	60
Dark brown skin pigmentation of newborn, which gradually faded away, retarded growth and abnormal teeth number and shape.	

[a]Source: Reggiani, 1980

4. DESIGN

4.1 Study Design

The design of this study combines elements of both cohort and cross-sectional designs. Two historical cohorts, exposed and non-exposed, will be identified and followed to ascertain their current vital and employment status. The health status of surviving members of both cohorts will be assessed by an in-depth medical survey to determine prevalence of clinical and sub-clinical disease states. Previous incidence of disease will be ascertained by subjects' self-reporting and verified by medical record review. Differences in health outcomes between the two cohorts will be compared statistically, after adjusting for the effects of confounding variables.

4.2 Ascertainment of Exposure

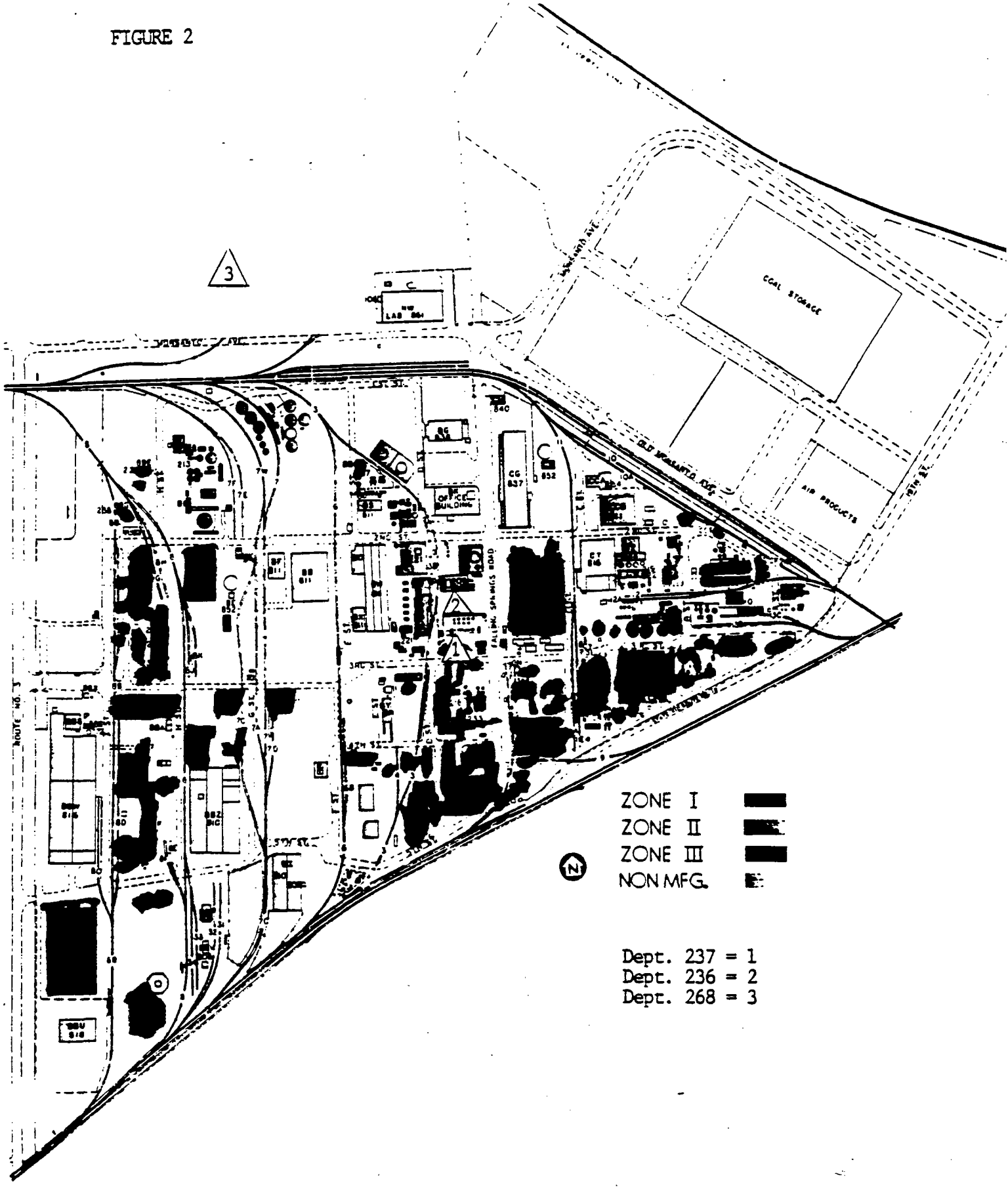
The departments where employees were most likely to be exposed to PCDDs include Departments 226 (Santobrite), 236 (Penta), 237 (chlorophenols) and Department 268 (agricultural esters). The locations of these departments within the plant are shown in Figure 2.

4.2.1 Processes

Departments 236 (Penta) and 226 (Santobrite)

The production of Pentachlorophenol (PCP) began at the Krummrich Plant in 1938. PCP was marketed in the flake form from 1939 to the late 1950's or early 1960's. At that time Penta (PCP)and Penta 60 (so called because it contained 60% PCP and 35% tetrachlorophenol) were offered in prilled form. From 1970, PCP was also offered in the 2000 lb. block form. The sodium salt of PCP (first called Santophen 20S and later Santobrite) was produced in powder, briquette, and 30% aqueous solution forms throughout its history.

FIGURE 2



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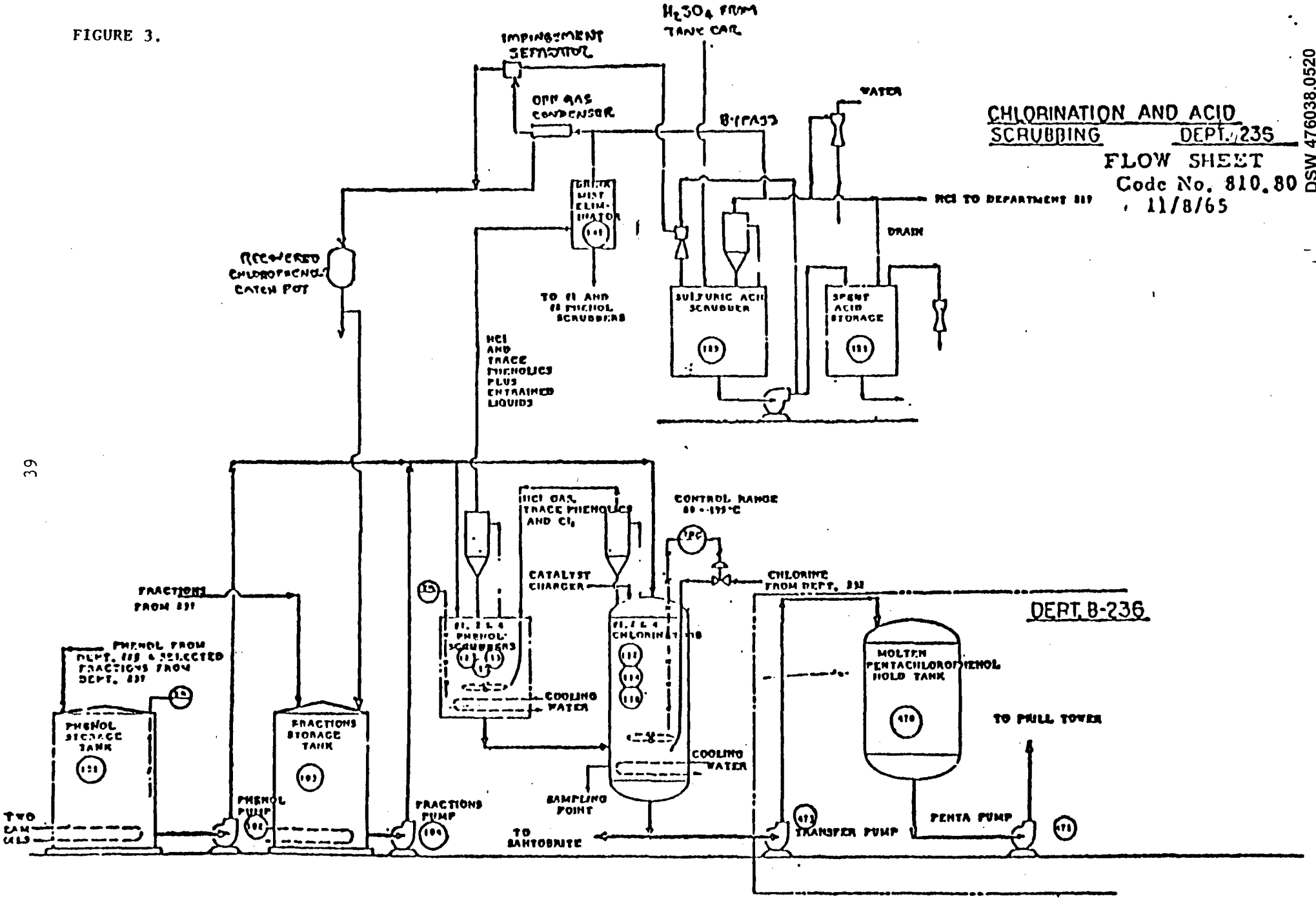
Santophen 20 P.A. (a PCP/pine oil/alcohol mixture) was only offered for a few years. The production of Na PCP was discontinued in 1972. The production of PCP and Penta 60 was discontinued in 1978. Over the years, the chemistry for the production of Penta and Santobrite remained essentially the same. The flow sheets for the process are shown in Figures 3 and 4. Department 236 was contained in a building which has since been dismantled.

Phenol, or chlorophenol fractions from the production of o-, p-, or 2,4-dichlorophenol were progressively chlorinated with subsequent increases in reaction temperature until the appropriate crystallization point was reached (for Penta, 174-182° C; for Penta 60, 145° C). Iron powder was first used as the catalyst; later, it was replaced by aluminum. Santobrite was simply the neutralization of Penta with sodium hydroxide.

Flaked Penta was produced by feeding molten Penta into a container from which it was picked up on the surface of a cold rotating drum. The material was flaked off the surface as the drum rotated against a stationary blade. The material was then mechanically conveyed to a packing area where it was bagged into cylindrical fiber backs or loaded into steel drums.

Prilled Penta was produced by dispersing molten Penta into fine streams using a shower head type prill plate. The molten streams would solidify by cooling with ambient air. The cooling chamber was an 8' diameter x 40' high prill tower. The prilled material would be further cooled in a Roto-Louvre cooler and would then be conveyed in a bucket elevator to a storage hopper to await packaging. The prills were packed into fiber packs or drums using a pneumatic packer. The air used for cooling passed through a Venturi scrubber where it was scrubbed with a dilute caustic solution.

FIGURE 3.



CHLORINATION AND ACID SCRUBBING DEPT. 235

FLOW SHEET

Code No. 810.80

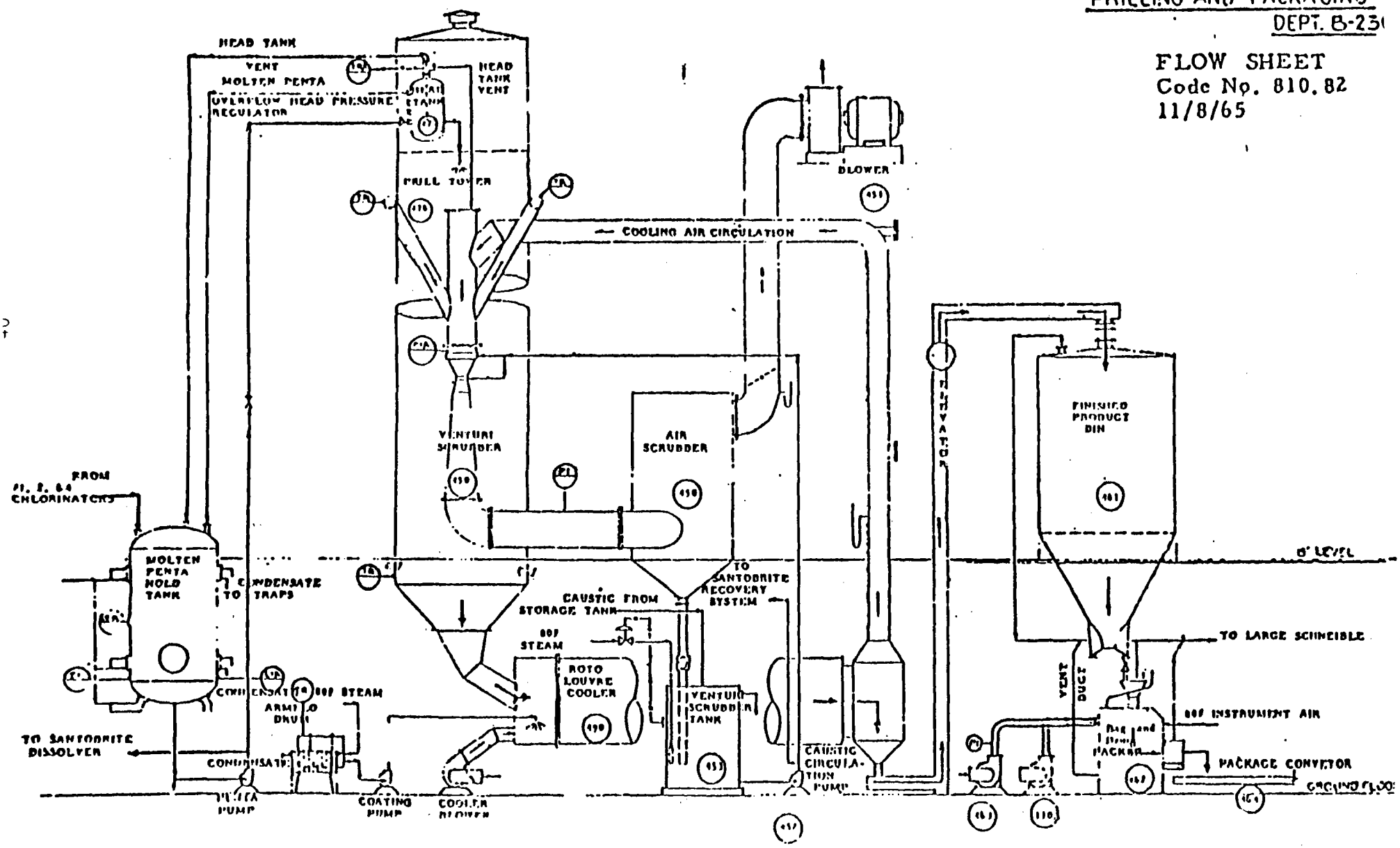
11/8/65

DEPT. B-236

DSW 476038.0520

STLCOPCB4042684

FIGURE 4.



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STLCOPCB4042685

Penta blocks were produced by pouring molten Penta into large tapered molds and allowing it to set. The material was removed from the mold by heating it with a welding torch.

Penta 60 was produced in the same way as molten Penta, except that the chlorination was terminated earlier (batch temperature 153-157° C; 145° crystalization point). It was prilled in the same manner as molten Penta.

A list of the job titles in Department 236 is given in Table 11.

Department 237 (Chlorophenols)

The production of chlorophenols began at the Krummrich plant in 1938 and continued through 1983. The principal products of this Department were o-chlorophenol, p-chlorophenol, and 2,4-dichlorophenol. P-chlorophenol was transferred to Department 239 where it was reacted with benzyl chloride to produce Santophen 1 (orthobenzyl p-chlorophenol). 2,4-dichlorophenol was transferred to Department 262 where it was reacted with chloroacetic acid to produce 2,4-dichlorophenoxyacetic acid. Chlorophenol fractions from Department 237 were also used as feedstock for production of pentachlorophenol in Department 236.

The flowsheets for the production of mono- and di-chlorophenols are shown in Figure 5. The overhead layout of the work area is shown in Figure 6. Department 237 was an open area located adjacent to Department 236.

The chemistry for the production of the chlorophenols appears to have remained unchanged over the years. Crude monochlorophenol was prepared by the batchwise chlorination of phenol at a temperature of 70-90° under a pressure of 2-5 psig in a Monel chlorinator. Crude mono contained 45%

TABLE 11. JOB DESCRIPTIONS LISTED IN THE MONSANTO COMPANY/ CHEMICAL WORKERS UNION WORKING AGREEMENTS

DEPT	JOB DESCRIPTION	YEARS																								
		37/38	38/39	39/40	40/41	41/42	42/43	43/44	44/45	45/46	46/47	47/48	48/49	49/51	51/52	52/53	53/54	54/55	55/56	56/58	58/59	59/61	61/63	63/65	65/68	68/71	71/74	74/77	77/80
226	Relief Foreman				X			X	X		X	X	X	X	X	X	X												
	Chief Operator	X			X		X	X	X		X	X	X	X	X	X	X												
	Operator	X			X			X	X		X	X	X	X	X	X	X												
	Helper Day	X			X			X	X		X	X	X	X	X	X	X												
	Repairman								X		X	X	X	X	X	X	X												
236	Relief Foreman				X			X	X		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
	Chief Operator						X	X	X		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
	Repairman								X		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
	Operator Building BD												X	X	X	X	X	X	X	X		X	X						
	Operator Building BO													X	X	X	X	X	X	X									
	Intermediate Op. Bldg. BD																X	X	X	X									
	B Operator - Oiler																X	X											
	Pelletizer Operator																X	X	X	X	X	X	X						
	Helper				X		X	X		X	X	X	X	X		X	X	X	X	X										
	Porter																X	X		X	X	X							
	A Operator Bldg. BD																			X	X	X		X	X				
	B Operator Bldg. BD											X	X	X	X	X				X	X	X	X	X	X				
	Briquette Operator Bldg. BD																			X	X	X	X	X	X				
	Premium Operator Bldg. BD																				X	X	X	X	X				
	Helper Porter																						X	X	X	X			
	Santobrite Operator																							X	X	X			
	Packer Helper																							X				X	X
	Operator				X			X	X		X	X	X																
	Premium Operator																									X			X

JOB DESCRIPTIONS LISTED IN THE MONSANTO COMPANY/ CHEMICAL WORKERS UNION WORKING AGREEMENTS

DEPT	JOB DESCRIPTION	YEARS																								
		37/38	38/39	39/40	40/41	41/42	42/43	43/44	44/45	45/46	46/47	47/48	48/49	49/51	51/52	52/53	53/54	54/55	55/56	56/58	58/59	59/61	61/63	63/65	65/68	68/71	ZI/74	74/77	77/80
236 (Cont'd)	A Operator																									X	X	X	X
	B Operator																									X	X	X	X
	Briquette Operator																									X	X	X	
	237 Operator																										X	X	X
237	Relief Foreman				X			X	X		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X			
	Operator	X			X			X													X	X	X	X	X	X			
	Helper Shift				X																								
	Operator New Dept.								X		X	X	X	X	X	X	X	X	X										
	Operator Old Dept.								X		X	X	X	X	X	X													
	Repairman										X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X			
	Helper Day										X	X	X	X	X	X	X	X	X	X	X	X	X						
	Chief Operator												X	X	X	X	X	X	X	X	X	X	X	X	X	X			
208	Premium Operator																						X	X	X	X			
	Intermediate Operator																						X	X	X	X			
	Utility Helper																								X				

FIGURE 5. PROGRESS FLOWSHEET FOR CHLOROPHENOLS

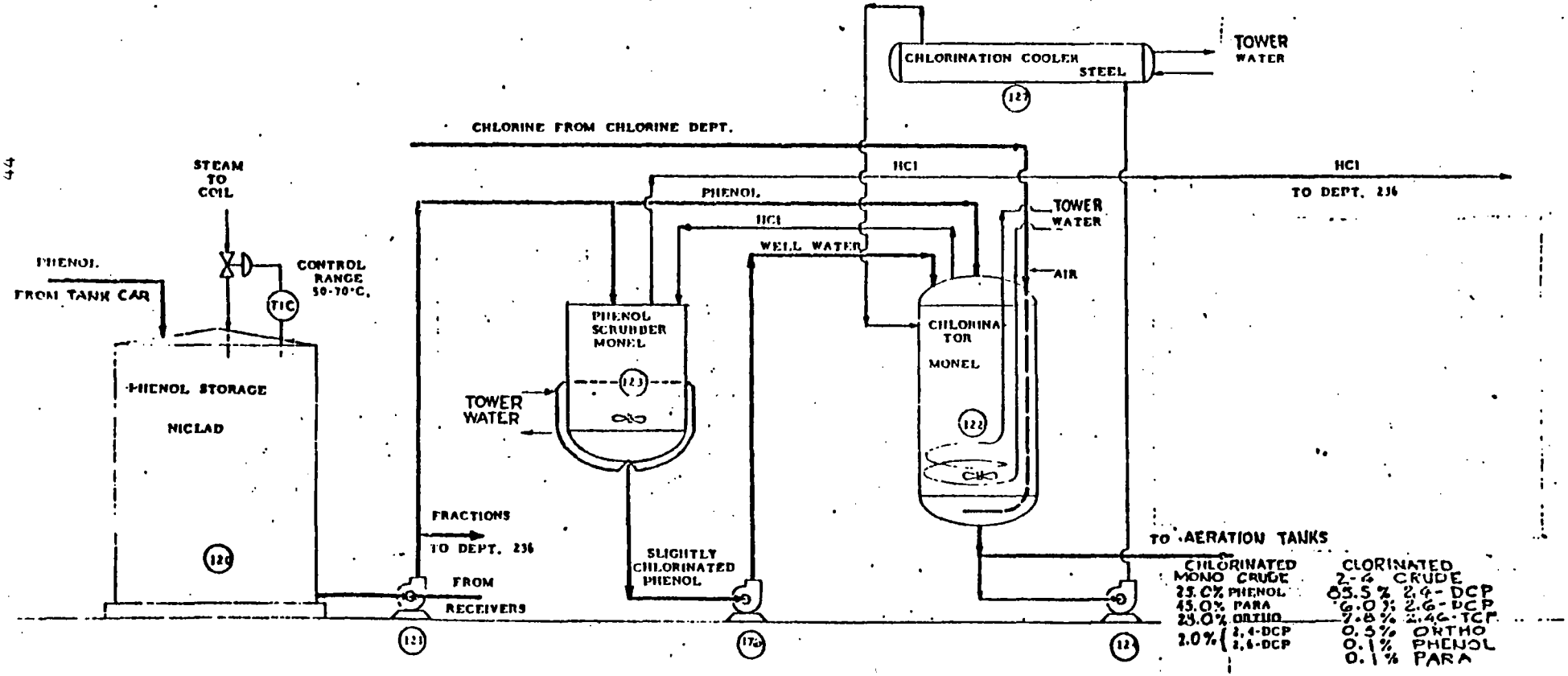
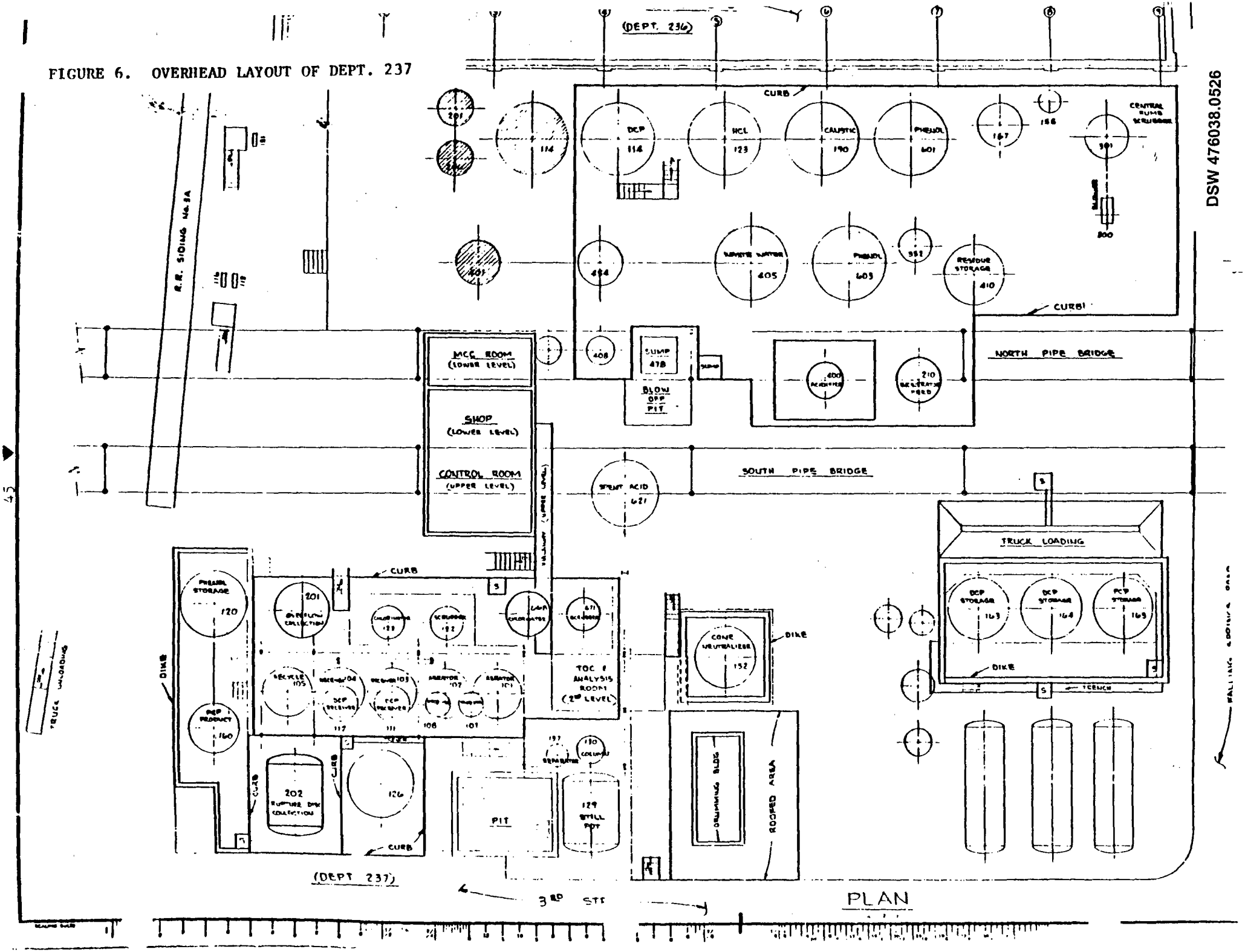


FIGURE 6. OVERHEAD LAYOUT OF DEPT. 237



parachlorophenol (P-CP), 28% orthochlorophenol (O-CP), and 2% dichlorophenol (DCP). The crude material was blown with air to remove dissolved HCl gas. The byproduct HCl gas was piped to Department 236's clean-up system.

The crude mono was neutralized with 50% caustic and distilled in a Linde tray fractionating column. Normal cuts from this batch distillation were water, wet fractions, O-CP, dry fractions, and P-CP. The dry fractions were transferred to Department 236 for use as raw materials in the production of molten pentachlorophenol.

Crude dichlorophenol was prepared by the batchwise chlorination of phenol at 80-90° C and at atmospheric pressure. The crude material contained 85.5% 2,4-DCP, 6.0% 2,6-DCP, 0.5% O-CP, 7.8% 2,4,6 trichlorophenol, 0.1% P-CP, and 0.1% phenol. The chlorinated crude material was blown with air to remove the bulk of dissolved HCl; the remaining HCl was neutralized with caustic.

The 2,4 isomer in the crude DCP was recovered by vacuum batch distillation in a Monel fractionating column. The remaining chlorophenol fractions stripped from the crude were transferred to Department 236 for use in pentachlorophenol production. The byproduct HCl was sent to Department 236's clean-up system.

A list of the job titles in Department 237 is given in Table 11.

Department 268 (Agricultural Esters)

The production of the butyl, isobutyl, and isooctyl esters of 2,4,5-trichlorophenoxyacetic acid (2,4,5-T) and 2,4-dichlorophenoxyacetic acid (2,4-D) began at the Krummrich plant in 1960 and continued through about 1970. The 2,4,5-T was shipped in from Monsanto's plant in Nitro, West Virginia. The 2,4-D was transferred to Department 268 from Department 262. The flow sheets for the pre-mix, reaction, and neutralization/filtration stages of the process are shown in Figures 7, 8, and 9, respectively.

FIGURE 7.

A. PRE-MIX (SLURRY)

DEPT. 268

BUTYL 2,4,5-T	894.12
ISO BUTYL 2,4,5-T	894.28

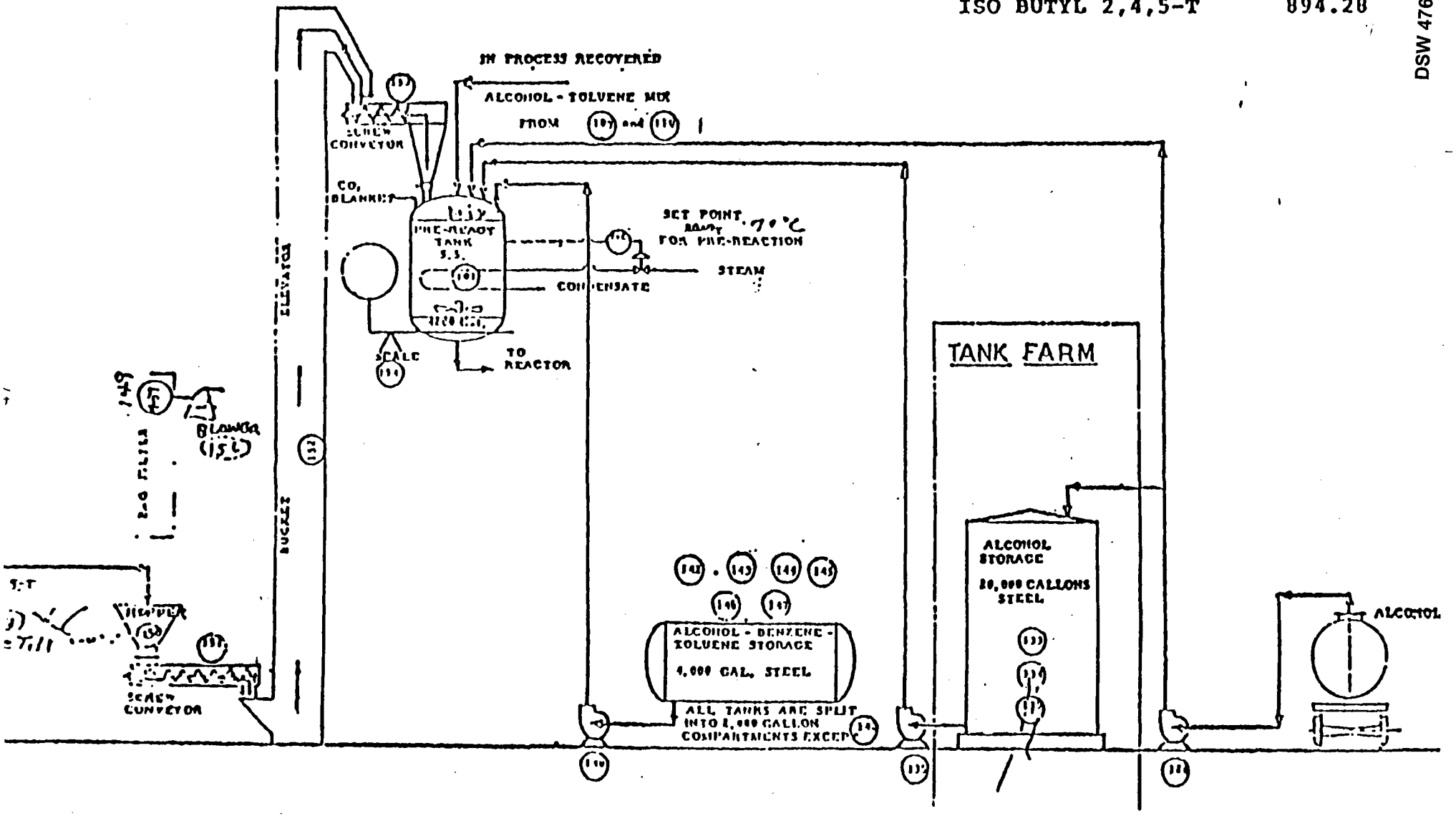


FIGURE 8.

B. REACTION

DEPT. 268

BUTYL 2,4,5-T 894.12

ISO BUTYL 2,4,5-T 894.28

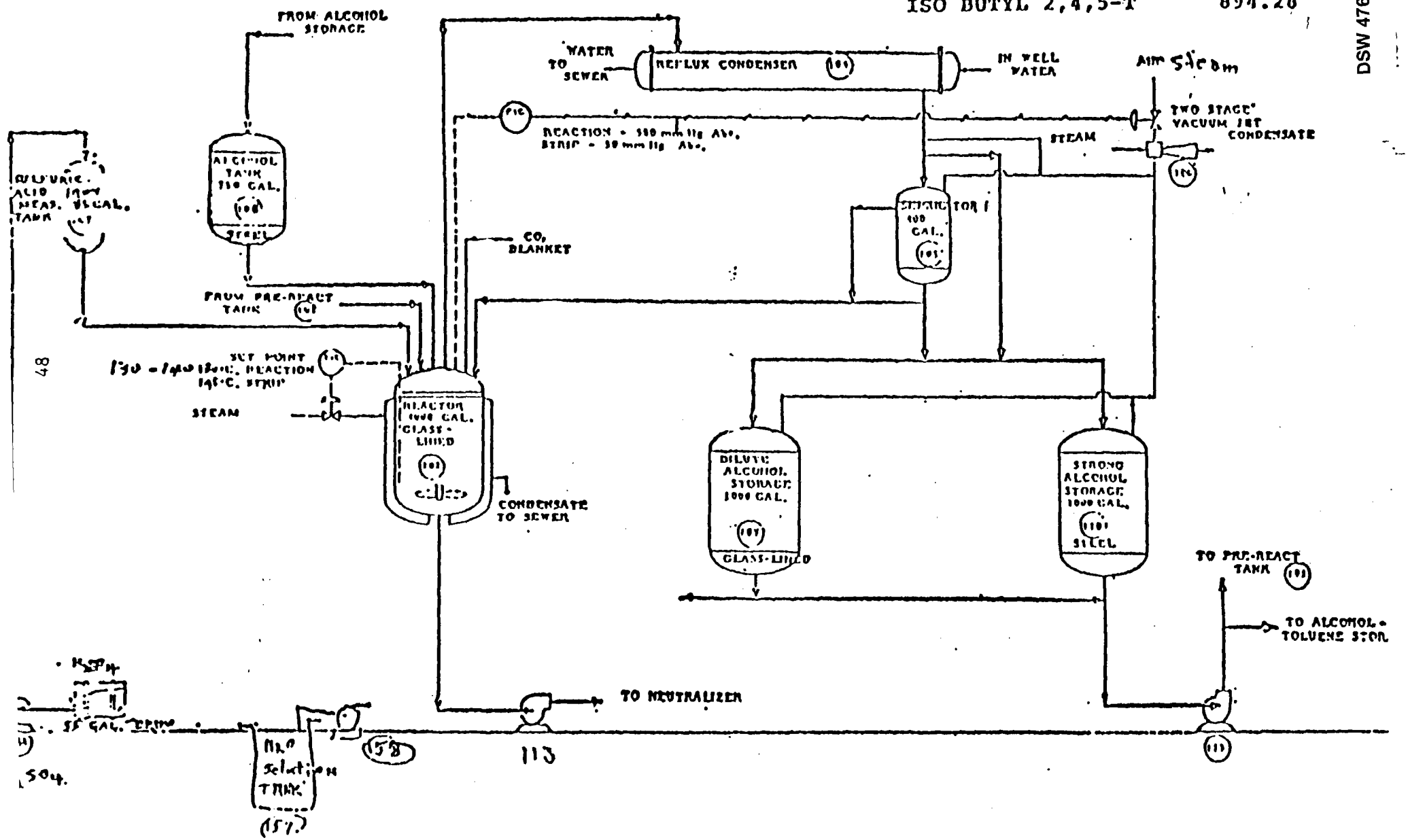
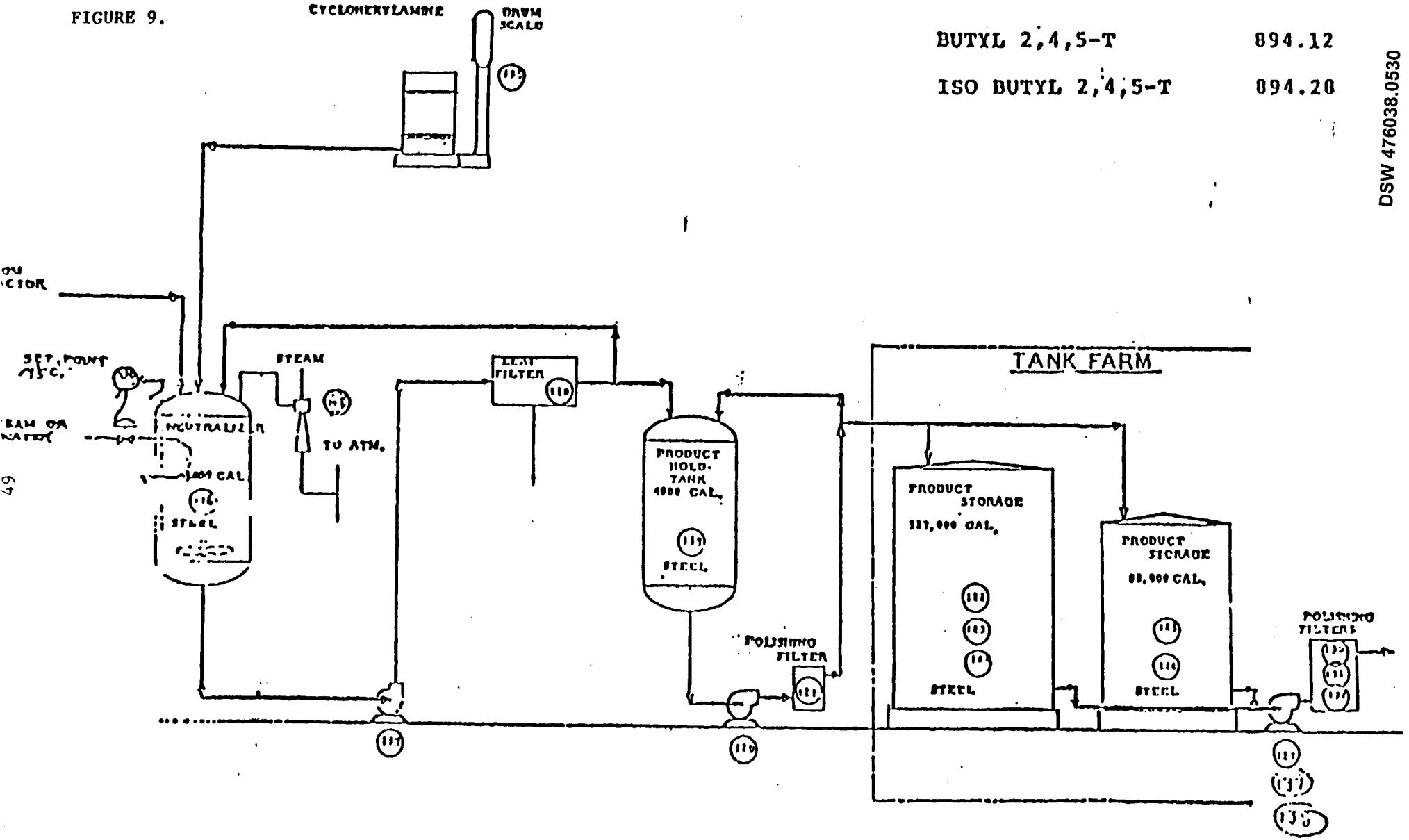


FIGURE 9.

BUTYL 2,4,5-T	894.12
ISO BUTYL 2,4,5-T	894.20



The esters were produced by reacting the chlorphenoxy acids with the appropriate alcohol using a small amount of sulfuric acid as a catalyst. The materials were pre-mixed in a slurry tank, then dropped into the reactor where the sulfuric acid was added. The reactor was then set at the appropriate temperature and pressure (butyl and isobutyl esters of 2,4,5-T; 130-140° C, 580 mm Hg; isooctyl ester of 2,4,5-T; 135-140° C, 200 mm Hg.) The reaction was originally driven to completion by removing the binary alcohol/water azeotrope and, on cooling and separating, recycling the alcohol. The 1969 processes for the butyl and isobutyl esters used toluene as a solvent for increased efficiency in driving the reaction to completion and in the water/alcohol separation.

When the reaction was complete, the alcohol and toluene were stripped off maintaining the reactor at 50 mm Hg and 140-150° C for two hours. The batch was then neutralized with cyclohexylamine. After filtration, the product was pumped to storage, tank cars, tank trucks, or 55 gallon drums.

A list of the job titles in Department 268 is given in Table 11.

4.2.2 Industrial Hygiene

Departments 226 and 236

Chemical exposures in Departments 226 and 236 included pentachlorophenol, tetrachlorophenol, phenol, chlorophenol fractions, chlorine, hydrochloric acid, sodium hydroxide, iron, aluminum and PCDDs/PCDFs. Repeated overexposure to phenol may result in chronic phenol poisoning. Symptoms include vomiting, difficulty in swallowing, diarrhea, lack of appetite, headache, fainting, dizziness, dark urine, mental disturbances, and possibly skin rash. Liver and kidney damage and discoloration of the skin may also occur. Chlorine, hydrogen chloride, and sodium hydroxide are irritating to the skin, eyes, and mucous membranes. Overexposure to chlorine and hydrogen chloride gas may result in tracheobronchitis and pulmonary edema (NIOSH, 1977). Exposures to the iron and aluminum powder catalysts are not likely to result in serious health effects. The toxicities of the chlorophenols have been reviewed in Section 3.

The earliest information regarding the industrial hygiene conditions in Department 236 comes from a report of an inspection conducted in 1947 by the State Department of Labor's Division of Factory Inspection. The report listed several conditions which needed improving: 1) the drum flakers on the first floor of Building BD (Dept. 236) emitted considerable fumes and dust under ordinary operating conditions; 2) maintenance personnel who handled the Draco Dust Collector System were exposed to the product when the Draco bags occasionally broke; 3) employees involved in the drumming and bagging operation which was connected to the Draco Dust Collection System bagged much of the material by hand; 4) the hopper which fed the Santobrite pelletizing system was frequently blocked and was dug out by hand; and 5) the ventilation system on the Penta briquette operation was poor. A 1954 company memo acknow-

ledges a chloracne problem in Department 236 which had existed for several years. In 1963 a Schneible Dust Collector System was installed in both the Penta and Santobrite operations.

On October 24, 1965 a fire broke out in one of the chlorinators. The batch in the chlorinator was in the trichlor-tetra stage. The cause of the fire was unknown. No material was lost from the chlorinator. The operators who were on duty did not appear to suffer any acute health effects.

In 1967 a central fume scrubber was installed for sample hoods, tank vents, and loading areas.

Monsanto began reviewing the literature on dioxins in 1970. That same year the Medical Department established a registry of employees at the Krummrich Plant who had developed chloracne or who worked in Departments where chloracne was prevalent. In 1972 Monsanto began monitoring the dioxin levels in PCP. The levels of PCDDs in PCP, PCP-cuts, and PCP residue from 1972 to 1979 are given in Table 12.

The production of Santobrite stopped in 1972. The same year special hygiene practices (showers, clothes changes, washing, cleansing housing with Seba-Nil Solution) were begun for employees who continued to produce PCP in Department 236.

Environmental monitoring for PCP began in 1977. Levels of PCP in air and wipe samples are given in Table 13. All of the air samples collected between April and October of 1977 were below the TLV of .5 mg/m^3.

In May of 1977, MIC staff personnel conducted an environmental audit of Department 236. The audit concluded that: 1) overchlorination of PCP could potentially cause major process accidents; 2) since 1975, 40% of the

TABLE 12 LEVELS OF PCDD IN PCP, PCP-CUTS, AND PCP RESIDUE (ppm)

DATE	SAMPLE	C_1	C_2	C_3	C_4	C_5	C_6	C_7	C_8
1972	PCP	"3000 ppm Total Dioxin"							
6/75	PCP	-	-	-	(<.01)	(<.07)	11	220-538	460
8/75	PCP	-	-		(<.01)	(<.07)	-	"	490
4/16/79	Blown Crude	(BDL)	(BDL)	(BDL)	(BDL)	(BDL)	(BDL)	(BDL)	(BDL)
	Dry Fraction	"	"	"	"	"	"	"	"
	Phenol Cut	"	"	"	"	"	"	"	"
	Para-Rich Cut	"	"	"	"	"	"	"	"
	PCP-Cut	"	"	"	"	"	"	"	"
2/28/79	PCP Residue with Caustic	63	59	15	3.1	6.7	1.3	2.2	.44
3/1/79	"	240	190	64	6.2	.1	.44	.08	.14
3/2/79		250	200	35	5.9	1.9	5.2	1.3	.16
3/11/79		240	1,400	1,600	410	4.7	.62	.81	.17
5/11/79	PCP Residue without Caustic	(<1)	(<1)	(<1)	(<1)	(<1)	(<1)	(<1)	(<1)
4/6 to 6/9/79	PCP with Caustic	2 -22	1 -5.4	.18 -1.4	(<.01)	(<.05)	(<.05)	(<.02)	(<.025)
4/25 to 6/9/79	PCP Without Caustic	(<.01) -.52	(<.01) -.47	(<.01) -.11	(<.01) -.016	(<.05)	(<.05)	(<.02)	(<.06)

TABLE 13.

PCP AIR (mg/m^3) AND WIPE ($mcg/100\ cm^2$) SAMPLES FROM DEPARTMENT 236

DATE	SAMPLE	PCP AIR	PCP WIPE
4/26/77	Personal, 8-Hour	.14	
	Operator	(<.001)	
	"		
	Area, 2nd Level		
	Outside Control Room	.026	
8/10/77	Personal, 8-Hour	.066	
	Operator	.034	
	"	.026	
10/7/77	"	.025	
3/77	(All Penta Control Room)		
	Sink Area		15.5
	Table		30.7
	Ice Box		24.5
	Cabinet		24.2
	Desk		13.0
	Table		216
	Bookshelf		39
8/77	Sink Area		6.14
	Table		11.10
	Ice Box		1.39
	Cabinet		15.1
	Desk		8.89
	Table		1.89
	Bookshelf		4.64

personnel in Department 236 had developed chloracne; 3) the TLV and STEL for PCP were at times exceeded during the block pouring, sawing of the 1000 pound molds, and chlorinator sampling operations; and 4) serious sources of direct operator contact with the dusty product included prilling, prill bagging, bulk loading, and routine cleaning.

In 1977 Monsanto instituted more stringent industrial hygiene practices (disposable dishes, midshift shower for dirty jobs). Wipe sampling (Table 13) showed a reduction in the levels of surface contamination in the Penta Control Room between March and August of 1977. Monsanto decided to shut down the Penta operation and to explore ways to further reduce the levels of product and workplace contamination.

In 1978 the Penta operation was shut down. In 1979 Monsanto developed the capability to measure PCDDs with greater analytical precision. Wipe sampling of the Department (Table 14) revealed surface contamination with trace amounts of higher chlorinator PCDDs. That same year, Monsanto discovered that the levels of PCDDs in PCP could be greatly reduced by removing sodium hydroxide from the process (Table 12). Department 236 was not re-opened, however, and the building was subsequently dismantled.

Department 237

Chemical exposures in Department 237 included phenol, o-chlorophenol, p-chlorophenol, 2,4-dichlorophenol, 2,6-dichlorophenol, 2,4,6-trichlorophenol, PCP (possibly from adjacent Dept. 236), chlorine, hydrochloric acid, and the lower-chlorinated PCDDs.

The earliest record of any problem in Department 237 dates back to April 25, 1952 when an explosion destroyed a 2,4-DCP transfer pump. The

TABLE 14.

LEVELS OF PCDDs IN WIPE SAMPLES FROM DEPARTMENT 236

DATE	SAMPLE	C_1	C_2	C_3	C_4	C_5	C_6	C_7	C_8
6/6/79	Blower (mcg/m^2)	(BDL)	(BDL)	(BDL)	(BDL)	(BDL)	400	8,000	58,000
	Office Wall (")	"	"	"	4.5	"	(BDL)	50	9,000
	Handrail (")	"	"	"	(BDL)	"	"	14	1,800
	Beam (")	"	"	"	10	"	60	140	47,000
	Wall (")	"	"	"	1	"	(BDL)	2	700
5/81	Penta Purification Column								
	3rd Level ($ng/100\ cm^2$)	-	-	-	1	44	112	34	36
	Top of Column (")	-	-	-	7	61	46	16	38
	Open Top Wall (")	-	-	-	19	74	46	10	36

pump overheated after it ran dry. The two operators who were in the vicinity did not appear to suffer any serious health effects.

Chloracne does not appear to have been prevalent in Department 237. Early company memos dealing with the chloracne problem do not identify Department 237 as a problem area. Only one of six employees who had worked exclusively in this Department was found to have questionable chloracne by Dr. Suskind in 1979.

Environmental monitoring for phenol and chlorophenols began in 1977. Air levels of these chemicals in Department 237 between 1977 and 1982 are given in Table 15. None of the air levels for phenol exceeds the TLV of 19 mg/m^3. TLVs for o-chlorophenol, p-chlorophenol, and 2,4-dichlorophenol have not been established. Air levels of PCP exceeded the TLV on several occasions.

Air samples for chlorine and hydrochloric acid were collected between September of 1979 and January of 1980. Air levels of HCl ranged from .06 - .32 mg/m^3, well below the 7 mg/m^3 ceiling value. Air levels of chlorine ranged from .02-.10 mg/m^3. One air sample collected near the chlorinator showed an unusually high chlorine level of 5.4 mg/m^3, which is above the 3 mg/m^3 TLV.

In 1979 Monsanto analyzed batches of o-chlorophenol and 2,4-dichlorophenol for PCDDs. (Table 16) O-chlorophenol was contaminated with ppb levels of mono-, di-, and tri-CDDs. 2,4-dichlorophenol was contaminated with mono-, di-, tri-, and tetra CCDs. Removal of the caustic addition resulted in a marked reduction in PCDD contamination. An OSHA inspection in 1979 found 300 ppb of PCDDs (>50% 2,3,7,8-TCDD) in an ortho-crude spill, but Monsanto questioned the validity of this analysis.

TABLE 15. AIR LEVELS OF CHLORINATED PHENOLS AND PHENOL IN DEPARTMENT 237 (mg/m^3)

DATE		PHENOL	O-CP	P-CP	D-CP	T-CP	PCP
3/15/77	Personal, 8-Hour	.15	.30	-	-	-	.05
	"	.12	.25	-	-	-	.55
3/16/77	"	.075	.19	-	-	-	.05
	"	.39	.93	-	.09	-	.50
	"	.13	.10	-	.04	-	.05
	"	.21	.57	-	.06	-	.32
	"	.53	.44	-	4.13	-	.48
3/31/77	"	.14	.34	-	.06	-	.04
	"	.06	.27	-	.06	-	.05
	"	-	-	-	-	-	.14
4/14/77	"	.16	.76	-	.12	-	.18
	"	.38	.20	-	.05	-	.14
	"	.28	.44	-	.23	-	.05
	"	.37	.40	-	.06	-	.15
	"	.03	.02	-	-	-	-
3/10/78	" (Operator)	.53	1.88	-	-	-	.57
	" "	1.70	12.66	-	-	-	.93
1980	" (Control Room)	.20	.18	.18	.09	-	-
	Personal, 8-Hour Samples	.21 -.66	.20 - .70	.12 -.18	.10 -.11	-	-
7/80	Personal, 8-Hour	.73	-	-	.15	-	2.35
	"	.75	-	-	.79	-	1.53
	Area, Analytical Shed	.90	-	-	.67	-	1.15
8/80	Personal, 8-Hour	.62	-	-	.37	-	4.88[a]
	"	.67	-	-	.19	-	5.17[a]
7/28/81	"	.18 -.31	.10 -.14	.07 -.14	.02 -.03	-	-
5/82	"	.40 -.53	.01 -1.5	.19 -1.2	.03 -.29	(<.01)	-
8/21/82	Area, Shift, Control Room	.59	.02	.24	.24	(<.01)	-
	GLC Room	.10	.05	.06	.50	(<.01)	-

TABLE 16.

LEVELS OF PCDDs IN O-CP AND D-CP (ppm)

DATE	SAMPLE	C_1	C_2	C_3	C_4	C_5	C_6	C_7	C_8
2/28 to 4/16/79	O-CP With Caustic	(<.05) -.89	(<.02) -.18	(<.03) -.45	(<.01)	(<.05)	(<.05)	(<.02)	(<.05)
4/25/79	O-CP Without Caustic	(<.01)	(<.02)	(<.01)	(<.01)	(<.05)	(<.05)	(<.07)	(<.08)
3/3 to 4/18/79	D-CP With Caustic	(<.02) -9.5	(<.01) -29	(<.02) -13	(<.02) -.19	(<.02)	(<.05)	(<.10)	(<.10)
5/15 to 5/31/79	D-CP Without Caustic	(<.01)	(<.01) -.04	(<.01) -.25	(<.01) -.04	(<.05)	(<.05)	(<.01)	-

Trace amounts of OCDD were found in surface wipes of the chief operators desk and the desk in the Department 237 Control Room. It is not known whether these samples were analyzed for other PCDDs.

PCDFs were not routinely measured in the samples collected for PCDD analysis.

Department 268

Chemical exposures in Department 268 included 2,4,5-T, n-butyl alcohol, isobutyl alcohol, isooctyl alcohol, toluene, sulfuric acid, and cyclohexylamine. Exposures to high concentrations of the alcohol vapors may cause headache, dizziness, and drowziness. Keratitis characterized by corneal vacuoles has been reported following exposure to the vapors of n-butyl and isobutyl alcohols. Toluene is a central nervous system depressant. Prolonged, heavy over-exposure may result in permanent encephalopathy. Cyclohexylamine and sulfuric acid are skin and eye irritants. Repeated inhalation of sulfuric acid mist may lead to chronic bronchitis.

The only information regarding industrial hygiene conditions in Department 268 comes from an internal industrial hygiene survey (undated) conducted in the 1960s. The report states that some dust was generated when 2,4-D was loaded into the fill hopper through the front end pay loader. 2,4,5-T was received from the Nitro plant in Lever packs; this was changed over to tote bins to reduce the amount of dust exposure during charging. The Drumming Station was not vented. The filter press was cleaned every three days. The operators who were not manually handling the material operated the equipment from an air-conditioned control room. The 2,4-D and 2,4,5-T esters were apparently not analyzed for PCDDs. The levels of PCDDs in these products were probably not much different from those reported in the literature (Table 5).

4.2.3 Chloracne Registry

In 1970 the Medical Department at the Krummrich Plant instituted a registry of current employees who had developed chloracne or who had worked in departments where chloracne was prevalent. Employees were examined for chloracne if they 1) worked in Department 236 or 237; 2) worked in Maintenance and had worked for more than 200 hours in the area containing Departments 236 and 237; or 3) were self-referred because of concern over chloracne.

One hundred forty-five employees appear on the Chloracne Registry. Fifty-five of these were noted to have chloracne on at least one visit. Thirty-three of the employees were working in Maintenance at the time of examination. Twenty of these were noted to have chloracne.

4.2.4. Maintenance Employees

In addition to the production workers in Departments 226, 236, 237, and 268, an unknown number of maintenance workers were exposed to chlorophenols, chlorphenoxy acids and dioxins in these work areas. One thousand nine hundred and forty employees held maintenance jobs between 1940 and 1980 and are presently alive according to company records. The demographic characteristics of these workers are shown in Table 17.

A review of personnel and payroll records and interviews with maintenance supervisors have revealed that there are no existing records of Department assignments for maintenance workers prior to 1976. Self-reporting was considered as a means for ascertaining maintenance worker exposure. Moses et al (1984) attempted this approach and found it unfeasible in their study of the Nitro plant. Fingerhut and her co-workers at NIOSH are not including Krummrich maintenance workers in the Dioxin Registry due to the difficulties in assigning exposure.

TABLE 17

DEMOGRAPHIC CHARACTERISTICS OF MAINTENANCE WORKERS EMPLOYED BETWEEN 1940 AND 1980.

CHARACTERISTIC	N (Total = 1940)	Percent
Employment Status		
Active/Temp. Inac.	741	38
Terminated	572	29
Retired	627	32
Payroll		
Hourly	1,629	84
Salaried	311	16
Sex		
Male	1,871	96
Female	68	4
Unknown	1	<1
Race		
White	1,602	83
Black	317	16
Unknown	21	1
Age		
<20	2	<1
20-24	2	<1
25-29	37	2
30-34	55	3
35-39	72	4
40-44	130	7
45-49	146	8
50-54	118	6
55-59	272	14
60-64	311	16
65-69	312	16
70+	483	25

We have decided to adopt the approach of Moses et al (1984) and use chloracne as a marker of exposure for maintenance workers. These workers will be identified through a review of plant medical records. In addition we will consider any maintenance worker who appears on the Chloracne Registry as exposed. This approach is expected to identify approximately 48 maintenance workers with the highest dioxin exposures.

4.2.5 Definition of Exposed Cohort

The exposed cohort in this study will consist of all past and present Krummrich employees who are alive and who meet one or more of the following criteria:

1) Hourly and salaried employees who had worked in Departments 226, 236, 237, or 268 for one or more days between January 1, 1938 and December 31, 1983.
2) Maintenance employees who appear on the Chloracne Registry.
3) Employees who were noted to have chloracne on plant medical records (with the exception of employees who were exclusively engaged in the production of PCBs or tetrachlorobenzene).

The first entry criterion encompasses most of the members of the exposed cohort. One thousand seven employees worked in Departments 226, 236, 237, and 268 between 1/1/46 and 1/1/75. The identification of employees who were hired and left before 1946 or between 1976 and 1980 has not yet been completed. Two hundred twenty-one of the 1007 employees are deceased, leaving 786 survivors. The distribution of 720 of these employees by length of employment in one or more of these departments and by employment status is given in Table 18.

TABLE 18. DISTRIBUTION OF EXPOSED COHORT BY LENGTH OF EXPOSURE AND EMPLOYMENT STATUS AS OF 1/1/84[a]

Employment Status	Length of Exposure (months)					Total
	<1	1-≤3	>3-≤6	>6-≤12	>12	
Active	55	42	48	39	82	266
Retired	33	24	22	33	65	177
Transferred within Monsanto	2	0	2	0	2	6
Leaves of Absence	4	7	5	5	8	29
Military Leave	9	10	11	14	9	53
Other Terminations	35	47	34	43	30	189
Total	138	130	122	134	196	720[b]

[a]Cohort limited to employees who had worked in Departments 226, 236,237, and 268 between 1/1/46 and 1/1/75.

[b]Sixty six additional employees have as yet not been classified by length of exposure

Thirty-three Maintenance personnel are included on the Chloracne Register indicating that they had either developed chloracne or had worked in Departments 226, 236, 237, or 268 for more than 200 hours after 1970. Company documents dated before 1970 contain lists of names of employees who had developed chloracne. An additional 15 names are expected to result from this entry criterion.

The current estimate of the total number of individuals in the exposed cohort is approximately 834.

4.2.6. Demographic Characteristics of the Exposed Cohort

At this time demographic information is available on the employees who had worked in Departments 226, 236, 237, and 268 between 1/1/46 and 1/1/76. These individuals comprise about 90% of the total exposed cohort. Eighty-five percent of these workers are white, 14% are black, and in 1% the race is unknown. Ninety-seven percent of these workers are male. The age distribution of these workers is given in Table 19. Fifty percent are 60 years of age or older. Ninety-three percent of the workers were hourly employees and 7% were salaried.

4.2.7. Follow-Up, Accessibility, and Participation of the Exposed Cohort

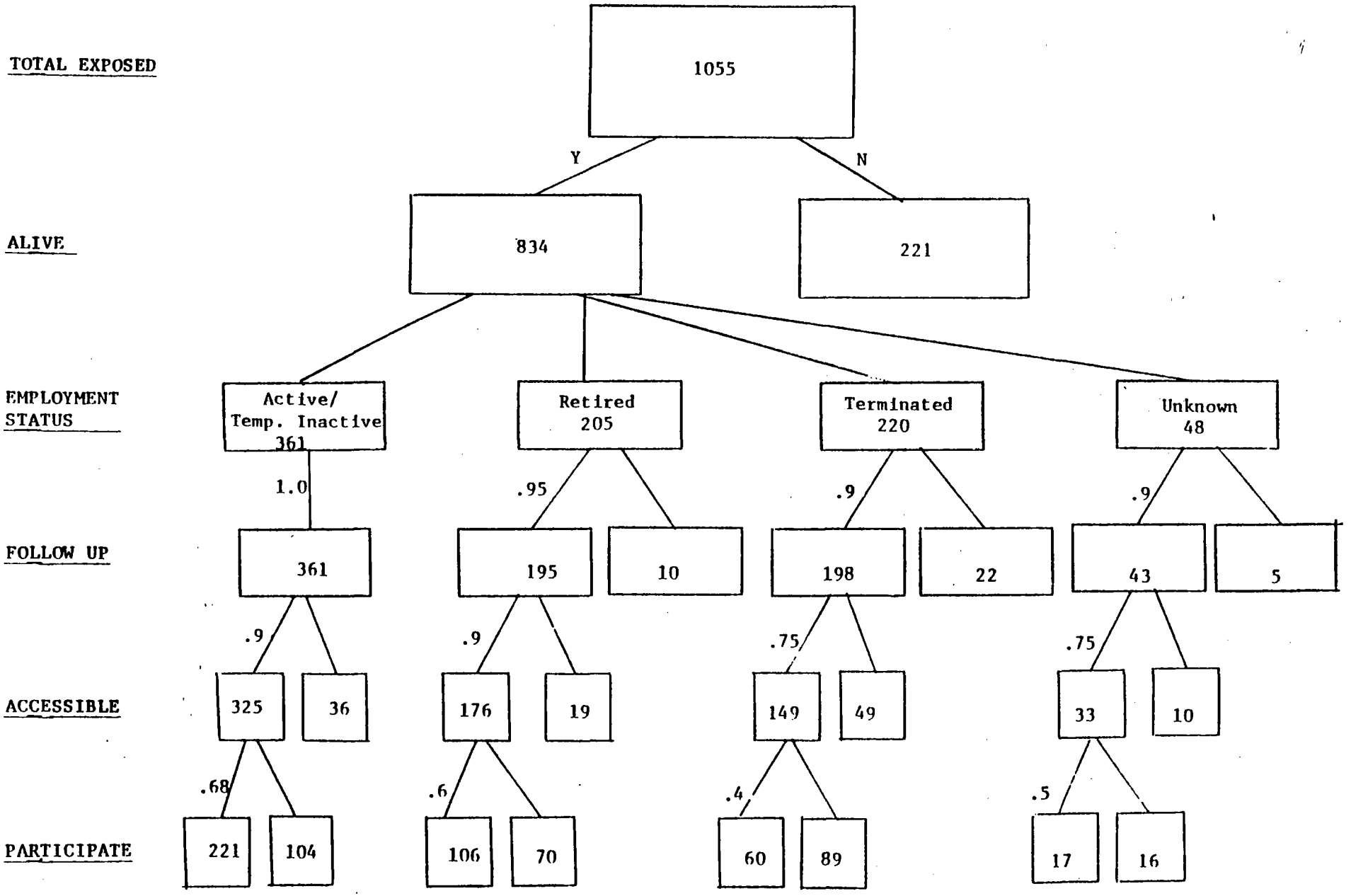
The size of the exposed population which will undergo medical examination will depend on the rates of follow-up, accessibility for examination, and participation. These rates are expected to vary by employment status. The effects of these rates in determining the size of the examined cohort are shown in Figure 10.

Follow-up is expected to be complete for active and temporarily inactive workers. An estimated 90% of these workers will be accessible for

TABLE 19. AGE DISTRIBUTION OF THE EXPOSED COHORT AS OF 1984

AGE	N	PERCENT
25-29	13	2%
30-34	9	1
35-39	14	2
40-44	60	8
45-49	74	9
50-54	64	8
55-59	160	20
60-64	145	18
65-69	115	15
70 +	132	17
TOTAL	786	100%

FIGURE 10. ESTIMATED FOLLOW-UP, ACCESSIBILITY, AND PARTICIPATION OF THE EXPOSED COHORT



tal Number Participating = 404

medical examination. In Suskind's 1979 survey of this same population, 68% of the active employees chose to participate. A similar participation rate in the present study would result in 221 active and temporarily inactive workers.

The follow-up rate for retirees is estimated at 95%, since these workers are traceable through pension records. Over ninety percent are known to be living within 300 miles of St. Louis and accessible for examination. A participation rate of 60% would result in 106 retirees.

The follow-up rate for terminated workers is projected at 90%. The locating of terminated workers will be performed by Equifax. An estimated 75% are still living within 300 miles of St. Louis. Approximately 30 employees who had worked in Department 268 terminated employment at the Krummrich Plant when their area of the plant was sold to the Edwin Cooper Company. This group of employees will be especially targeted for participation in the study. A participation rate of 40% would result in 60 terminated workers. Retired and terminated workers will receive a reasonable reimbursement for their time and travel.

The follow-up rate for employees whose employment status is as yet unknown is estimated at 90%. The accessibility and participation rates for these employees are estimated at 75% and 50% respectively, resulting in an additional 17 workers.

A total of 404 exposed employees are expected to participate in the medical examinations. Present and past employees who choose not to participate in the study will be surveyed as to their reasons for non-participation and general health status. This information will be useful in detecting and measuring non-responder bias.

4.2.8 Internal Control Group

The internal control group will consist of all present and past employees at the Krummrich Plant who are alive and meet all of the following entry criteria:

1) Never worked in Departments 226, 236, 237, or 268.
2) Did not appear on the Chloracne Registry.
3) Were not listed on company documents as having chloracne.
4) Never worked in Maintenance.
5) Never worked in Department 239 (Santophen).
6) Never worked in Department 224 (chlorinated benzenes).
7) Never worked in Department 262 (2,4-D).
8) Never worked in Department 218 (muriatic acid - chlorinated benzene).
9) Never worked in Department 246 (PCBs).
10) Never worked in Department 233 (chlorinated benzene).
11) Never worked in Department 861 (laboratory).

One thousand seventy-seven employees meet the entry criteria for the internal control group. Thirty-three percent are active workers, 59% are terminated, and 9% are retired. Ninety-five percent are hourly employees and 5% are salaried. Ninety-six percent are male. Seventy-eight percent are white, 11% are black, and in 11% the race is unknown.

The demographic characteristics of the exposed cohort and the internal controls, are compared in Table 20. The exposed and non-exposed groups are similar with respect to age, sex, race, and payroll. A larger percentage of the internal controls are terminated employees. A larger percentage of the exposed cohort are retired, regardless of whether the terminated employees

TABLE 20.

COMPARISON OF THE PERCENT DISTRIBTUIONS OF DEMOGRAPHIC CHARACTERISTICS BETWEEN THE EXPOSED COHORT AND THE INTERNAL CONTROLS

CHARACTERISTIC	Exposed (n=786)	Control (n=1077)
Employment Status		
Active/Temp. Inactive)	46	33
Terminated	28	59
Retired	26	9
Payroll		
Hourly	91	95
Salaried	9	5
Sex		
Male	97	96
Female	3	4
Unknown	<1	<1
Race		
White	85	78
Black	14	11
Unknown	1	11
Age		
<20	0	1
20-24	0	0
25-29	2	1
30-34	1	2
35-39	2	6
40-44	8	7
45-49	9	6
50-54	8	9
55-59	20	20
60-64	18	20
65-69	15	11
70+	17	17

are included or excluded. Overall, the two groups are acceptably comparable with respect to the major demographic variables.

If we assume similar rates of follow-up, accessibility, and participation,[1] an estimated 218 active, 50 retired, and 141 terminated workers are expected to comprise the internal controls. The 409 internal controls and 404 exposed result in a control:exposed allocation ratio of 1.01:1.

[1]Thirty-three percent of non-exposed terminated workers are expected to participate in the study as opposed to 40% of the exposed terminated workers.

4.3 Ascertainment of Health Status

The comprehensive medical examination will ascertain the subjects' present and past health status. The incidence of past health events will be determined through the medical questionnaire and validated through medical record review. The examiners will be blinded as to the exposure status of the exposed cohort and the internal controls. The components of the medical examination are summarized in Table 21.

4.3.1. Medical History Questionnaire

A trained medical interviewer will administer a standard medical history questionnaire which will be a modification of the questionnaire previously used by the U.S.A.F. School of Aerospace Medicine in their Ranch Handy Study (Lathrop et al, 1983). The questionnaire will contain the following elements:

1. Current health status including any chief complaints or medical problems.
2. Past medical history, including hospitalizations for medical illness, surgical procedures, or transfusions. Specific questions will be asked about the presence of hypertension, cardiovascular, cerebrovascular, pulmonary, hepatic, intestinal, urogenital, reproductive, neurologic, mental, and psychiatric diseases.
3. Family history including health status of all first degree relatives, causes of death, hospitalizations, etc.
4. Social history including marital status (current and previous spouses), habits of alcohol and tobacco use.

5. Review of systems including:

   a. Constitutional symptoms of weight change, energy level, etc.

   b. Headaches

   c. Eye (vision, pain, discomfort)

   d. Ear (hearing, pain, discharge)

   e. Nasal (congestion, discharge, sense of smell)

   f. Mouth (lesions, dental, dysphagia)

   g. Respiratory (sputum, cough, dyspnea, etc.)

   h. Cardiac (chest pain, palpitations, PND)

   i. Abdomen (pain, diarrhea, constipation, nausea, vomiting, etc.)

   j. Urogenital (dysuria, urgency, frequency, infection, nephrolithiasis, sexual dysfunction)

   k. Joints (pain, swelling, deformity)

   l. Neurologic (weakness, paresthesia, memory change, etc.)

   m. Psychologic (sleep disturbance, anxiety, depression)

   n. Dermatologic (rashes, blisters, sunburn, excess hair)

   o. Gynecologic (regularity of menses, character of flow, etc.)

6. Medication history which will include current as well as past use of prescription and over-the-counter preparations.

4.3.2 Reproductive History

At the time of the medical history, permission will be sought to conduct a phone interview with current and previous spouses concerning reproductive outcomes. The Ranch Hand spouse's questionnaire will be administered by trained, medical telephone interviewers and will include questions on the number of pregnancies, their outcomes, and any congenital

malformations in offspring of the subjects. Permission will be sought to verify reported congenital malformations in offspring through medical record review.

4.3.3 Dietary History

Participants will be asked to complete a three-day dietary history. They will be instructed in the completion of this diary by a trained nutritionist.

4.3.4. Physical Activity Assessment

Participants will be administered a seven-day activity recall questionnaire (Taylor et al, 1984) to determine their level of physical activity.

4.3.5. Occupational and Environmental History

A trained interviewer (other than those administering the other components of the medical examination) will administer a questionnaire designed to determine each of the following items as best remembered by the subject:

1. Job classification, duration, and duties for each position held at the Krummrich plant.
2. Job classification, duration, and duties for all employment other than at the Krummrich plant.
3. Description of any hobbies or other pursuits involving exposure to chemicals which might be confounding.
4. Military history (if any) with particular attention to service in Vietnam, especially Operation Ranch Hand.

4.3.6. Medical Records Review

Permission will be sought for review and release of medical records from treating physicians and hospitals for purposes of confirming the

previously obtained medical histories. The medical records will be reviewed by registered medical record technicians. Diagnoses and procedures will be classified into ICD-9.

4.3.7 Internist's Physical Examination

The general physical examination will be performed by an internist blinded to the exposure history of the worker.

The examination will consist of the following:

1. General appearance and vital signs: supine and sitting blood pressure and pulse, respiratory rate, height and weight.
2. Head: shape, evidence of trauma.
3. Eyes: pupillary response, presence of conjunctivitis, icterus.
4. Ears: hearing, appearance of tympanic membranes.
5. Nose: appearance of mucosa, purulent secretions, polyps.
6. Mouth: appearance of teeth, tonsils, mucous.
7. Neck: adenopathy, size and consistency of thyroid, range of motion.
8. Lungs: percussion, auscultation.
9. Heart: size and description of PMI, abnormalities of heart sounds, extra sounds and murmurs.
10. Abdomen: tenderness, masses, bowel sounds, liver and spleen size.
11. Genital (males): testicular size and consistency, hernias.
12. Rectal: mucosal surfaces, prostate size and consistency (males), stool hemocult.

13. Joints: range of motion, effusion, deformity.

14. Back: range of motion, tenderness.

15. Breasts (females): masses, discharge.

16. Pelvic (females): cervix, adnexal tenderness or masses.

17. Peripheral pulses.

4.3.8 Dermatologic Examination

The dermatologists will be trained in the diagnosis of chloracne by an internationally recognized expert in the field. The dermatologic examination will be performed and recorded in a standardized manner to permit quantitative assessment of the findings. Particular attention will be devoted to the detection and scoring of chloracne, porphyria cutanea tarda, and basal cell carcinoma.

4.3.9. Neurologic Examination

A neurologist will perform a mental status examination and examine the cranial nerves, motor, and sensory systems. Reflexes and cerebellar function will be tested.

4.3.10. Electrocardiogram

A trained technician will do a 12-lead, resting electrocardiogram.

4.3.11. Pulmonary Function Tests

A trained technicial will measure the subject's forced vital capacity and forced expiratory volume at one second.

4.3.12. Chest X-ray

A trained technician will take a standard PA and lateral film.

4.3.13. Quantitative Sensory Examination

A trained technician will quantitate the subject's perception of temperature and vibration.

4.3.14. Nerve Conduction Velocities

A trained technician, under the supervision of the neurologist, will measure the nerve conduction velocities of the median and sural nerves (one side only) using standardized methods.

4.3.15. Neurobehavioral Testing

A trained technician will administer an automated neurobehavioral test battery (Baker et al, 1984) using computer terminals, which will include the following tests:

1. Paired associate learning
2. Mood scales
3. Continuous performance
4. Vocabulary
5. Symbol-digest substitution
6. Hand-eye coordination
7. Visual retention
8. Digit span
9. Paired associate recall

4.3.16. Blood Tests

Venous blood will be drawn after a 12-hour fast and distributed in the following manner:

1. 5cc of EDTA anticoagulated blood for complete blood count, differential white cell count, and platelet count.
2. 5cc of EDTA anticoagulated plasma for total cholesterol, HDL and LDL cholesterol and triglycerides.

3. 5cc of serum for SMA 20 (albumin, alkaline phosphatase, bilirubin, calcium, chloride, bicarbonate, creatine, GGT, glucose, phosphorus, potassium, LDH, protein, GOT, GPT, sodium, BUN, acid.).
4. 5cc of serum for LH, FSH, testosterone.
5. 2cc of serum for T4, T3 resin uptake and free thyroid index, TSH.
6. 3cc of serum for IgA, IgG, IgM.
7. 1cc of frozen serum for CPK.
8. 4.5cc of blood drawn into blue-top tube and delivered on ice for prothrombin time.
9. 5cc of EDTA plasma for apoproteins AI, AII, B, and E (Dr. Schoenfeld's laboratory).
10. 20cc of heparinized blood for lymphocyte stimulation studies (concanavalin A, phytohemaglutin, and Poke week mitogen).
11. 20cc of heparinized whole blood, 3cc of EDTA anticoagulated blood and 2 slides will be drawn for T and B cell determinations, T helper and suppressor cell ratio.
12. 10cc of serum will be frozen and banked to permit future analyses.

4.3.17. Urine Tests

The subjects will be asked to provide a clean catch, mid-stream urine

specimen for urinalysis after which a 24-hour urine collection will be begun using a light-proof container. The 24-hour urine collection will be kept refrigerated and appropriate preservatives will be used.

Aliquots will be sent for:

1. Creatine (creatinine clearance)
2. Protein (24-hour protein excretion)
3. Quantitative porphyrins

TABLE 21. SUMMARY OF COMPREHENSIVE MEDICAL EXAMINATION

1. Medical History Questionnaire (trained interviewer)
    - Current medical problems
    - Past medical history
    - Family history
    - Social history
    - Review of systems
    - Medication
2. Reproductive History (telephone interview by trained interviewer)
3. Dietary History (nutritionist-instructed 3-day diary)
4. Physical Activity Assessment
5. Occupational and Environmental History (trained interviewer)
6. Medical Record Review (internist)
7. General Physical Examination (internist)
8. Dermatologic Examination (dermatologist)
9. Neurologic Examination (neurologist)
10. 12-lead EKG (EKG technician)
11. Pulmonary Function Tests (PFT technician)
12. Chest x-ray, PA and lateral (technician)
13. Quantitative Sensory Examination (technician)
14. Nerve Conduction Velocities (NCV technician)
15. Neurobehavioral Testing
    - Paired associate learning
    - Mood scales
    - Continuous performance
    - Vocabulary

TABLE 21 (continued)

Symbol-digest substitution

Hand-eye coordination

Visual retention

Digit span

Paired associate recall

16. Blood Tests

Complete blood count

Platelet count

Cholesterol

HDL and LDL cholesterol

Triglycerides

Apoproteins AI, AII, B, and E

Glucose

BUN

Creatinine

Electrolytes

Uric Acid

Protein

Albumin

Bilirubin

Alkaline phosphatase

LDH, GOT, GPT

GGT

LH, FSH, testosterone

CPK

TABLE 21. (continued)

T4, T3 resin uptake, free thyroid index, TSH

IgA, IgG, IgM

Prothrombin time

Lymphocyte stimulation studies

T and B cell populations, T helper and suppressor ratio

Banked serum.

17. Urine Tests

Urinalysis

Creatinine clearance

24-hour protein excretion

Quantitative porphyrins

5. DATA ANALYSIS

5.1. Data Entry, Processing, and Storage

Data management and analysis will be performed at the Northwestern University Medical School. The data management system will include quality control measures at each step of the process to ensure completeness and accuracy of data entry.

Data entry and quality control will be facilitated through the use of standardized data entry forms. Whenever possible, original data will be recorded on the data entry forms to minimize transcription errors. A list of the original data, initial records, and data entry forms is given in Table 22.

The data from each employee's health examination will be visually inspected on site for completeness, legibility, and obvious inaccuracies. Errors in data collection or recording will be corrected on site. The data will be transported by courier to the Northwestern University Medical School for processing and storage. Results of laboratory analyses will be mailed to the School and inserted in each employee's data file.

Recording of data will be performed by data entry clerks following specific procedures under the supervision of the Data Manager. Data contained in the data entry forms will be entered into intelligent terminals using an Intelligent Data Entry program. A screen image of the data entry form will appear on the CRT. Spaces will be included for entering values as they are reported on the data entry form. The Intelligent Data Entry program will have checks on range values and numeric types to trap transcription errors.

Transactions from a forms entry session will be transmitted from the mini computer to the main frame over a phone line. The entry will be checked against

TABLE 22. FORMS FOR COLLECTION, RECORDING, AND CODING OF DATA

Components of Health Survey	Original Data	Initial Record	Data Entry Form
Information for Follow-up	Personnel Record	Computer Printout	Recoded
Employment Record	Personnel Record	Computer Printout	Recoded
Medical History	Face to Face Interview	Questionnaire	Same
Occupational History	Face to Face Interview	Questionnaire	Same
Reproductive History	Phone Interview	Questionnaire	Same
Internist's Exam	Physical Exam	Exam Form	Same
Dermatologist's Exam	Physical Exam	Exam Form	Same
Neurologist's Exam	Physical Exam	Exam Form	Same
PFT's	Flow-Volume Loop Volume-Time Graph	Computer Printout	Recoded
CXR	Film	Radiologist's Report	Recoded
Quantitative Sensory	Sensory Exam	Exam Form	Same
EKG	EKG	Cardiologist's Report	Recoded
EMG/NCV	Tracing	EMG/NCV Form	Same
Automated Neuro-behavioral Test	Neurobehavioral Exam	Computer Printout	Same
Blood Tests	Blood Specimen	Lab Report	Recoded
Urine Tests	Urine Specimen	Lab Report	Recoded
Non-Participant Survey	Phone Interview	Questionnaire	Same

the full data base on certain data items to prevent duplicate and other invalid entry. The original data will be stored and archived in the Northwestern University Medical School. Entered data will be stored on disks with archive copies to prevent inadvertant loss of the data base.

5.2. Quality Control

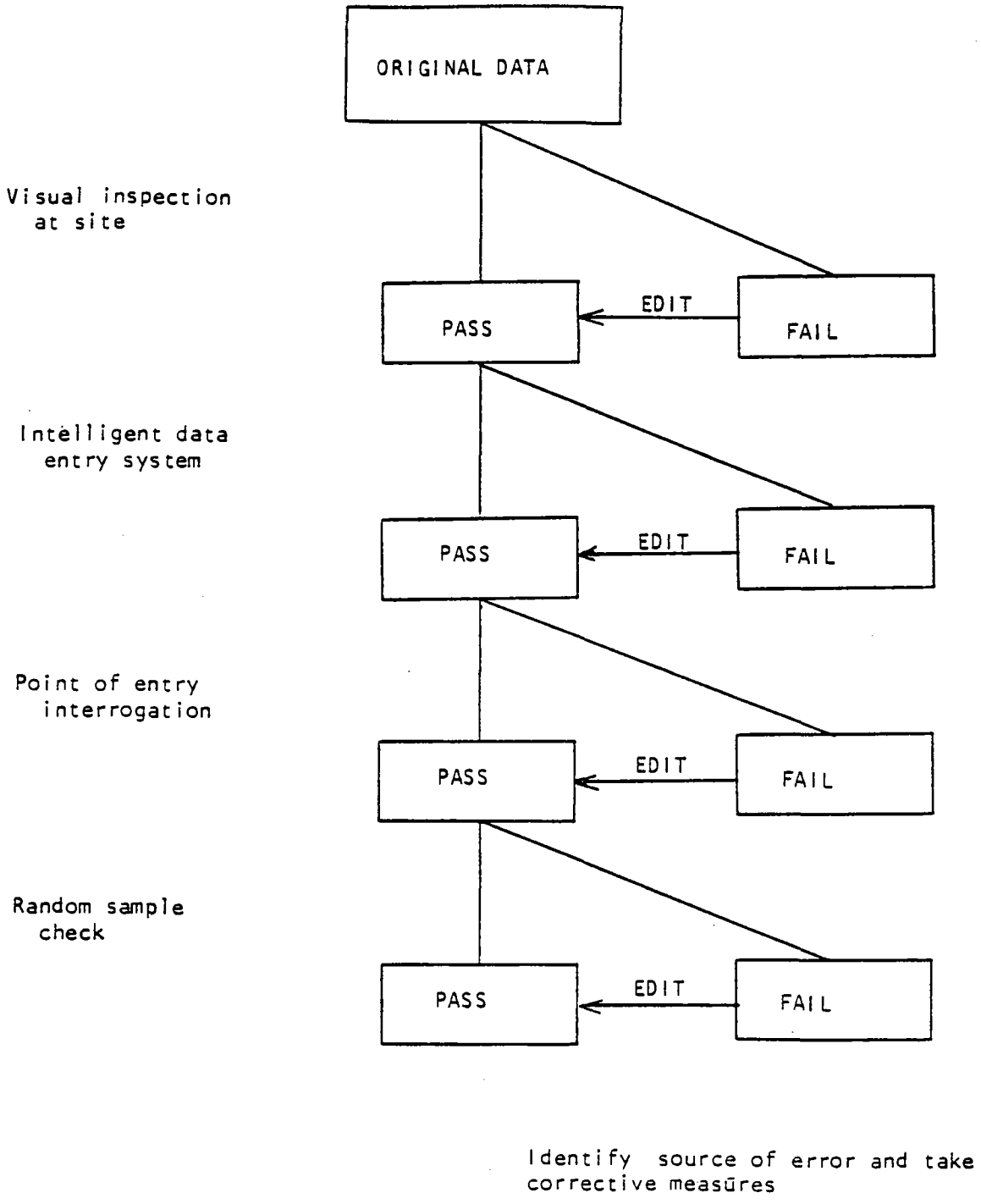
Personnel data on employment history which is supplied by Monsanto will be checked for accuracy by comparing a 10% random sample of this data to the original personnel records. The employee's occupational history will serve as a further check on the accuracy of the personnel data.

The most important step in the quality control of data management is the complete and accurate recording of data. Each employee's medical examination data will be visually inspected on site for completeness, legibility, and obvious inaccuracies.

Transcription errors during data entry will be minimized through the use of the previously described intelligent data entry system. Duplicate and other invalid entry will be prevented by comparing each entry against the full data base.

The final step in quality control will be an ongoing comparison of a 10% random sample of entries against the original data. Errors will be traced to their source and control measures taken to prevent their recurrence. Inaccurate or incomplete data will be corrected and re-entered. These quality control measures are summarized in Figure 11. Error tolerance will be set at .1%.

FIGURE 11. QUALITY CONTROL OF DATA ENTRY



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5.3 Analysis

5.3.1 Classification of Exposure

Each individual's exposure will be classified 1) dichotomously, 2) by length of exposure, and 3) by exposure score. All three exposure variables will be treated as categorical variables. The exposed cohort will be analyzed as a whole and, where sample size permits, by individual department.

In the dichotomous classification of exposure, individuals who meet one or more of the exposure criteria will be classified as exposed, and those who do not will be classified as non-exposed.

As an employee's length of employment in a department increases, his exposure to the chemicals in that department is expected to increase. The length of employment will be divided into the following four intervals: 1) 0 months, 2) >0-$\leq$3 months, 3) >3-$\leq$12 months, and 4) >12 months. Classification by length of exposure will permit analyses for dose-resonse.

NIOSH is currently developing a dioxin exposure score for the Dioxin Registry. The exposure score will be a numerical scale based on the department, job titles, length of exposure, and industrial hygiene data. The exposure score will be directly applicable to Krummrich employees, since employees from this plant are included in the Dioxin Registry. The exposure score is expected to be ready by March, 1985, and will be assigned to each employee without knowledge of the results of the medical examination. While the exposure score may be a continuous variable, we will treat it more conservatively as an ordinal varible with four exposure categories.

Our review of the industrial hygiene and process information leads us to conclude that analyses by individual departments are warranted. While

all four departments share the possibility of PCDD exposure, the mix of PCDDs was different for each department. Employees in Department 237 were exposed to the lower chlorinated dioxins, while employees in Departments 226 and 236 were exposed to the higher chlorinated dioxins. While no PCDD analyses were performed on the products from Department 268, historical information indicates that these employees were exposed to 2,3,7,8-TCDD. The departments will be categorized as 226/236, 237, 268, and Maintenance/Other.

5.3.2. Classification of Disease

The comprehensive health status evaluation, which includes a medical history, reproductive history, medical record review, physical examination, and laboratory tests, will generate a large number of categorical and continuous health outcome variables. The details of the medical survey are given in Section 4. The problem of repeated measures is discussed in Section 7.8.

5.3.3. Confounders and Effect Modifiers

5.3.3.1. Demographic Characteristics

The potential demographic confounders in this study include age, sex, race, socio-economic status, employment status, and urban/rural residence. The internal controls are similar to the exposed cohort with respect to age, sex, race, and payroll class. The effects of confounding will be controlled through stratified and multivariate analysis.

5.3.3.2. Lifestyle Characteristics

The potential lifestyle confounders in the study include smoking, alcohol consumption, physical activity, and diet. These variables will be ascertained through the medical history and controlled for in the statistical analysis.

5.3.3.3. Chemical Exposures

Employees at the Krummrich Plant are potentially exposed to chemicals other than the chlorophenols, phenoxy acid esters, and their contaminants. The major chemical products and intermediates are discussed in Section 2.2. The average Krummrich employee rotates from between 10 to 20 departments prior to retirement. The Krummrich Plant contains approximately 110 active and discontinued departments. Each employee will be dichotomously classified as having worked or not worked in each department. An employee will be considered as having worked in a department if he had worked in that department for a total of more than 3 months during his term of employment. A list of the chemical exposures in each department is available through Monsanto's MEHI computer system.

Each significant health finding in the comparison with the internal controls will be reviewed to determine if it could be associated with chemical exposures in a department where the employee had previously or subsequently worked (e.g. tremor on neurologic exam and exposure to mercury in the Denora Cell House). If the potential for confounding exists, the extent of confounding will be determined by cross-tabulating the confounding exposure with the abnormal health finding. If confounding is present, we will re-examine the original association after adjusting for confounding using Mantel-Haenszel methods. Major abnormal findings may warrant nested case-control study.

The Krummrich employees may have had exposure to chlorophenols, chlorphenoxy herbicides, and dioxins outside of their employment. These outside exposures will be ascertained through the administered questionnaire (e.g. history of farm use of chlorphenoxy herbicides). Confounding by

outside exposures will be controlled through the use of the aforementioned methods.

5.3.3.4. Effect Modifiers

A factor which will influence the prevalence of residual health effects is the time since last exposure. The few longitudial morbidity studies of dioxin-exposed occupational cohorts have shown that several acute health effects improve with time. The time since last exposure will be considered in the multivariate analysis.

Another factor which may influence our measurement of exposure is the calendar time of exposure. The industrial hygiene information suggests that the chemical exposures in Departments 226 and 236 were higher before 1970 than after 1970. There is no information to suggest a similar variation in exposure in Departments 237 or 268. The temporal variation in exposure will probably be factored into the NIOSH Exposure Score. If not, we will include it as a variable for study in the analysis of the data from Departments 226 and 236.

5.3.4. Statistical Tests

The strategy for statistical analysis of parametric data will consist of 1) examination of crude associations; 2) stratified analysis; 3) tests for dose-response; and 4) multivariate analysis using SAS statistical packages.

Crude associations between dichotomous variables will be examined by cross-tabulation, calculation of prevalence odds ratios, and testing for significance using Fisher's Exact or Chi Square Tests. Differences in means between continuous variables will be tested using the Student T Test.

In the next step of the analysis, we will stratify on major confounding variables and calculate factor-adjusted odds ratios using

Mantel-Haenszel methods. Differences in means between continuous variables will be adjusted for confounding and tested for significance using analysis of covariance.

Dose-response relationships between the ordinal exposure variables and dichotomous dependent variables will be examined using the test for trend. Confounding variables will be controlled using the Mantel extension. Multivariate analysis of dichotomous dependent variables will be performed using multiple logistic regression. Multivariate analysis of continuous dependent variables will be performed using multiple linear regression. Multivariate analysis of categorical dependent variables will be performed using log linear analysis.

6. IMPLEMENTATION

6.1 Identification and Recruitment of the Study Populations

The exposed and non-exposed employees at the Krummrich Plant will be identified through 1) Monsanto's MEHI computer system; 2) the chloracne register; and 3) a review of company memoranda dealing with chloracne at the Krummrich Plant prior to 1970. The addresses of active employees are available through current personnel records. The present addresses of retirees are available through the company's pension plan. Terminated workers will be located through Equifax.

Northwestern University will work together with Monsanto's Public Relations Department, and the international Chemical Worker's Union, and in recruiting Monsanto employees for the study. Active workers will be approached through the individual plants. Northwestern researchers will meet with the workers at the plants to discuss the purpose, scope, and implementation of the study. Retirees will be contacted by mail and also through existing retiree associations. Terminated workers will be contacted by mail.

6.2 Development of Survey Instruments

The medical history, occupational and environmental history, and non-participant questionnaires will be developed in conjunction with the Survey Research Laboratory. The Survey Research Laboratory will also provide trained medical interviewers to administer these instruments.

6.3 Medical Examinations

Northwestern University will place a team of health professionals at the plant sites to conduct the medical examinations. An examination is expected to take 8 hours of an employee's time, including breakfast and lunch. The examination will be completed during a single 8-hour shift with

the exception of the 24-hour urine collection, 3-day dietary history, and spouse's reproductive history. The team will be able to examine 18 employees per day by using a rotating-station examination system. Blood and urine samples will be processed and sent to the appropriate laboratories in daily batches.

Consent for medical record review will be sought at the time of examination. The medical records will be mailed to the Department of Medicine for review by medical record technicians after the examinations have been completed. The female spouses of the study participants will be asked to consent to a telephone interview to obtain pertinent reproductive history. The telephone interviews will be conducted by trained interviewers from the Survey Research Laboratory.

6.4 Data Analysis

Data analysis is discussed in detail in Section 5.

6.5 Report

6.5.1. Reports to Individual Participants

Each participant will be debriefed as to available medical findings on site upon completion of the medical examination. In addition, each participant will receive a report summarizing the results of his medical examination. The report will be prepared by the internist who examined the participant. The report will contain recommendations for further medical follow-up by the participant's personal physician when appropriate. If the participant so desires, the results of individual tests will be forwarded to the participant's physician.

6.5.2. Final Report

Northwestern University will submit a final report to Monsanto upon completion of the study. A draft of the final report will be reviewed by the

Peer Review Committee prior to submittal to Monsanto. The report will contain an introduction, presentation of methods, results of analyses, discussion, and conclusions.

6.6 Timetable

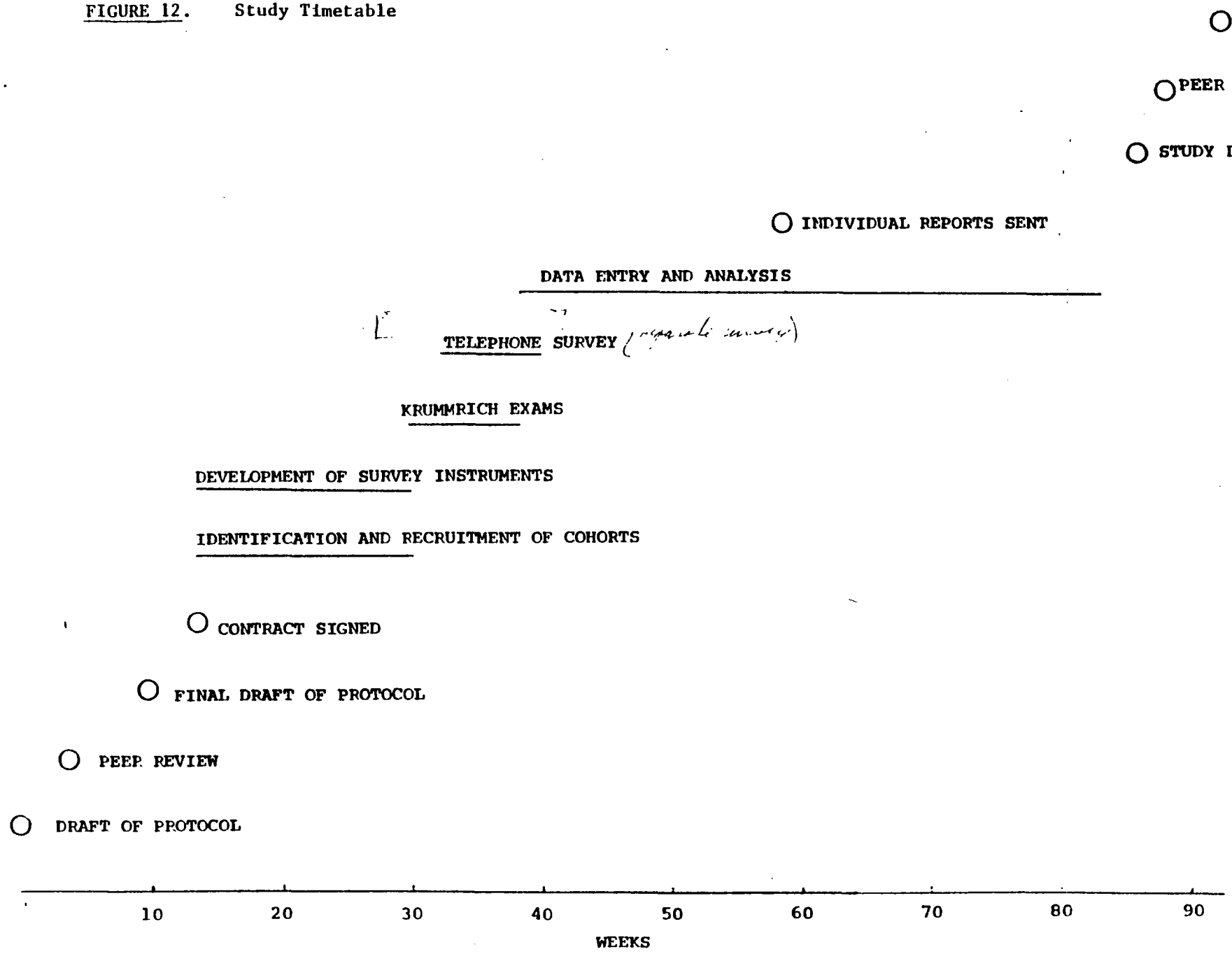
The study is expected to take 78 weeks to complete. The duration and timing of specific tasks are presented in Figure 13.

6.7 Human Subjects Review

The study is contingent upon approval by Northwestern University's Human Subjects Review Board. The major risks to participants are the discomfort of the medical examination and breach of confidentiality. The medical examination is by design non-invasive, with the exception of venopuncture. Venopuncture will be performed by a certified technician under the supervision of the examining physician.

Each participant's examination results will be confidential and will not be released to other parties without the participant's signed consent. Each participant will receive a study code number which will serve as his identifier. No personal identifiers will be entered into the computer or included in the group data file. A participant may elect to have his test results sent to his personal physician. A Monsanto employee may also elect to have his test results sent to the Monsanto Medical Department in lieu of his annual medical surveillance examination.

FIGURE 12. Study Timetable



7. Study Limitations and Corrective Measures

7.1 Loss to Study

Losses to the study may occur through 1) incomplete follow-up, 2) inaccessibility for examination, and 3) non-participation. If the losses are not random, then the study sample may not be representative of the entire exposed cohort. Losses will be especially damaging to the validity of the study if they are due to exposure and disease. For example, if exposure leads to illness, and illness results in termination, then losses due to terminations will bias the study in the negative direction.

Less than 10% of the exposed cohort are expected to be lost due to incomplete follow-up. These losses should not result in serious bias. Losses due to inaccessibility for examination are expected to be low, since 90% of the retirees and 75% of the terminated employees are estimated to be living within 300 miles of St. Louis. Non-participation is expected to result in substantial losses despite intensive recruitment efforts. We will compare the study sample with the entire exposed cohort on the basis of age, sex, race, payroll, work area, length of employment, and hospitalization rates while employed (available through the health insurance carrier) to determine if the sample is representative of the target population. We will also survey non-participants as to their reasons for non-participation and general health status.

7.2 Survival

If exposure results in the death of the most susceptible individuals, then a morbidity survey of survivors will underestimate the strength of the association between the exposure and disease. The mortality study conducted by Zack (1980) suggests that exposures at the Krummrich Plant are not resulting in excessive mortality.

7.3 Incidence-Prevalance Bias

Medical surveys are designed to measure the prevalence of disease at the time of the survey; they are much less sensitive at detecting incident events that may have occurred many years before. The present study is aimed at measuring long-term health effects; as such, prevalence is an appropriate measure of disease frequency.

The incidence of past events remains of interest, however, and will be measured by 1) asking incidence-type questions on the medical history (e.g. "Have you ever been hospitalized for an ulcer"), and by 2) medical record review.

7.4 Recall Bias

The exposed employees will know the purpose of the study and may be more likely to recall information on the medical history than non-exposed employees. This source of bias will be controlled by 1) medical record confirmation of major health events and 2) correlating physical and laboratory findings with medical history findings.

7.5 Interviewer/Examiner Bias

The medical interviewers and examiners may be biased in their measurement of health status if they know the subject's exposure history. This source of bias will be eliminated through 1) blinding the interviewers and examiners with respect to the subject's exposure status; 2) training of interviewers and examiners; and 3) use of standardized questionnaires and physical examination protocols.

7.6 Misclassification of Exposure

Employees at the Krummrich Plant may be misclassified with respect to their degree of exposure due to 1) temporal changes in exposure; 2) personal

differences in work practices; and 3) non-documented exposures. Misclassification of exposure will bias the study in the negative direction. Our chief concern is the frequent and undocumented assignment of employees to the Utility work force which may briefly place them in an exposed work area. These exposures will be ascertained through the occupational and environmental history questionnaire.

7.7 Confounding Chemical Exposures

Differences in health status between the exposed cohort and the internal controls may be due to the confounding effect of chemical exposures incurred in other departments. We will code the employment histories of Krummrich employees to allow for statistical search for confounding. Exposures incurred outside the Krummrich Plant will be analyzed in a similar manner. If confounding appears to be present for major health outcomes, a nested case-control approach may be warranted.

7.8 Repeated Measures

The comprehensive medical survey will provide data on a large number of health outcomes. If we set out alpha error at .05, one out of twenty will be significant by chance alone. A reduction of the alpha error would result in an unacceptably high beta error for low frequency events. The judgement of causality will not rely on statistical significance alone

Associations will be judged for causality on the following criteria:

1. Statistical significance
2. Temporal Sequence: The exposure must have preceded the disease.
3. Consistency: The association should be consistent with findings from previous studies.

4. Strength of Association: The larger the value of the prevalence odds ratio or the greater the difference in means, the less likely the association is to be spurious.
5. Dose-Response: The frequency and severity of disease should increase as the exposure increases.
6. Specificity: Alternative causes, such as confounding by demographic, lifestyle, or outside exposure variables, have been ruled out.
7. Biological Plausibility: The association is plausible in light of existing toxicological and epidemiological data.

7.9 Statistical Power Limitations

The study is limited in its statistical power to detect some associations by the size of the exposed cohort. Power analyses for dichotomous variables by size of the prevalence odds ratio are given in Table 25. Power analyses for continuous variables by the difference in means is given in Table 26. As is clear from these Tables, the sample size is adequate to detect mean differences of 10% for most of the continuous variables and prevalence odds ratios of 2 for many of the important dichotomous variables.

These estimates are conservative in that they are based on a total sample size of only 600 participants. A sample size of 800 would provide an additional 10-30% increase in power for many of the study variables.

TABLE 23

POWER ANALYSIS FOR DICHOTOMOUS VARIABLES BY SIZE OF THE ODDS RATIOS
(EXPOSED = 328; CONTROLS = 283; α =.05)

Variable	Control	Prevalence(%)	Power by ψ							
			1.1	1.25	1.5	1.75	2	3	4	5
History										
Acne	RH[a]	35.2	.14	.37	.78	.96	.99	.99	.99	.99
"	S[b]	29.5	.13	.35	.76	.95	.99	.99	.99	.99
Chloracne	S	0.0								
Skin Cancer	S	2.5	.07	.11	.20	.32	.54	.87	.99	.99
Other Cancer	S	1.2	.06	.09	.14	.20	.27	.59	.85	.97
Any Cancer	RH	40	.08	.14	.27	.44	.61	.97	.99	.99
Hepatitis	RH	4.1	.08	.14	.28	.45	.62	.97	.99	.99
Jaundice	RH	4.5	.08	.14	.29	.48	.66	.98	.99	.99
Cirrhosis	RH	.4	.06	.07	.09	.11	.13	.25	.39	.55
UGI Ulcer	S	5.5	.08	.16	.33	.54	.72	.99	.99	.99
Heart Disease	RH	17.6	.12	.28	.64	.89	.98	.99	.99	.99
" " Verified	RH	14.1	.11	.25	.58	.84	.95	.99	.99	.99
Myocardial Infarction	RH	.5	.06	.07	.10	.12	.15	.30	.48	.66
" " Verified	RH	.4	.06	.07	.09	.11	.13	.25	.39	.55
Coronary Artery Disease	S	6.1	.09	.16	.36	.58	.77	.99	.99	.99
Angina	S	6.1	.09	.16	.36	.58	.77	.99	.99	.99
Hypertension	S	24.5	.13	.33	.73	.94	.99	.99	.99	.99
Psychosis	RH	.5	.06	.07	.10	.12	.15	.30	.48	.66
Anxiety	RH	.5	.06	.07	.10	.12	.15	.30	.48	.66
Other Neuroses	RH	.8	.06	.08	.12	.16	.20	.44	.69	.87

TABLE 23 (continued)

Variable	Control	Prevalence(%)	Power by Ψ 1.1	1.25	1.5	1.75	2	3	4	5
Alcohol Dependence	RH	.3	.06	.07	.08	.10	.11	.19	.30	.42
Nervousness/Anxiety/ Depression	S	11.7	.10	.23	.53	.79	.93	.99	.99	.99
Decreased Libido	S	15.3	.11	.26	.60	.86	.97	,99	.99	.99
Impotence	S	11.7	.10	.23	.53	.79	.93	.99	.99	.99
Chronic Sinusitis and Upper Resp. Disease	RH	55.7	.14	.38	.79	.96	.99	.99	.99	.99
Kidney Disease	RH	3.5	.08	.13	.25	.40	.57	.95	.99	.99
Miscarriage	RH	13.6	.17	.49	.92	.99	.99	.99	.99	.99
"	S	11.8	.16	.46	.89	.99	.99	.99	.99	.99
Stillbirth	RH	.8	.07	.11	.19	.30	.43	.85	.98	.99
"	S	1.3	.08	.13	.26	.57	.60	.97	.99	.99
Birth Defects	RH	6.5	.12	.32	.72	.94	.99	.99	.99	.99
"	S	2.9	.09	.20	.45	.71	.88	.99	.99	.99
Physical Exam										
Appears Ill	RH	.1	.05	.06	.06	.07	.07	.09	.11	.14
Chloracne	S	0.0								
Acne Vulgaris	S	11.7	.10	.23	.53	.79	.93	.99	.99	.99
Hirsutism	S	1.8	.07	.10	.17	.26	.36	.76	.96	.99
Comedones	RH	20.7	.12	.31	.69	.92	.99	.99	.99	.99
Acneiform Lesions	RH	17.5	.12	.28	.64	.89	.98	.99	.99	.99
Acneiform Scars	RH	10.4	.10	.22	.49	.76	.91	.99	.99	.99
Cysts	RH	10.5	.10	.22	.50	.76	.91	.99	.99	.99
Hyperpigmentation	RH	7.1	.09	.18	.39	.63	.81	.99	.99	.99

TABLE 23 (continued)

Variable	Control	Prevalence (%)	Power by Ψ 1.1	1.25	1.5	1.75	2	3	4	5
Hepatomegaly	RH	.8	.06	.08	.12	.16	.20	.44	.69	.87
Pinprick	RH	9.6	.10	.21	.47	.73	.89	.99	.99	.99
Light Touch	RH	7.5	.09	.18	.41	.65	.83	.99	.99	.99
Muscle Status	RH	3.6	.08	.13	.25	.41	.57	.95	.99	.99
Vibration	RH	8.8	.09	.20	.45	.70	.87	.99	.99	.99
Patellar	RH	.6	.06	.07	.12	.16	.17	.34	.56	.75
Achilles	RH	3.4	.08	.13	.25	.40	.56	.95	.99	.99
Biceps	RH	.5	.06	.07	.10	.12	.15	.30	.48	.66
Babinski	RH	.3	.06	.07	.08	.10	.11	.19	.30	.42
Tremor	RH	4.0	.08	.14	.27	.44	.61	.97	.99	.99
Coordination	RH	3.9	.08	.14	.27	.43	.60	.97	.99	.99
Romberg	RH	19.1	.12	.30	.67	.90	.98	.99	.99	.99
Gait	RH	1.8	.07	.10	.17	.26	.36	.76	.96	.99
Lab										
Sed Rate										
≤40 y.o.	RH	4.2	.07	.10	.18	.28	.39	.80	.97	.99
>40 y.o.	RH	5.4	.07	.11	.21	.33	.46	.87	.99	.99
RBCs on U/A	RH	1.3	.06	.09	.14	.21	.28	.63	.88	.98
Protein on U/A	RH	2.6	.07	.11	.21	.33	.46	.87	.99	.99
ECG										
<40 y.o.	RH	23.1	.10	.21	.46	.71	.87	.99	.99	.99
≥40 y.o.	RH	28.4	.10	.22	.50	.75	.90	.99	.99	.99

TABLE 24

POWER ANALYSIS FOR CONTINUOUS VARIABLES BY DELTA %

(Exposed=300: Controls==300)

VARIABLE	Power by Delta %								
	5	10	15	20	30	40	50	75	100
Alk. Phosphatase	.59	.99	1	1	1	1	1	1	1
GGT Males	.17	.53	.86	.98	1	1	1	1	1
LDH Males	.99	1	1	1	1	1	1	1	1
SGOT (AST)	.38	.91	1	1	1	1	1	1	1
SGPT (ALT) Males	.25	.73	.97	1	1	1	1	1	1
Triglycerides	.44	.95	1	1	1	1	1	1	1
Glucose	1	1	1	1	1	1	1	1	1
Urea Nitrogen	.74	1	1	1	1	1	1	1	1
Creatinine Males	.98	1	1	1	1	1	1	1	1
Total Protein	1	1	1	1	1	1	1	1	1
Total Bilirubin	.31	.84	.99	1	1	1	1	1	1
LDL	.92	1	1	1	1	1	1	1	1
HDL	.7	1	1	1	1	1	1	1	1
LH Males	.43	.73	.94	1	1	1	1	1	1
FSH Males	.26	.74	.98	1	1	1	1	1	1
Testosterone Males	.54	.98	1	1	1	1	1	1	1
T-4 by RIA	.84	1	1	1	1	1	1	1	1
T-3 Uptake Ratio	1	1	1	1	1	1	1	1	1
Free Thyroxine Index	1	1	1	1	1	1	1	1	1

Table 24 (continued)

	Power by Delta %								
	5	10	15	20	30	40	50	75	100
WBC	.85	1	1	1	1	1	1	1	1
Hemoglobin	1	1	1	1	1	1	1	1	1
HCT	1	1	1	1	1	1	1	1	1
Platelet Count	.66	1	1	1	1	1	1	1	1
Ferritin	.09	.22	.43	.67	.95	1	1	1	1
Creatinine Clearance	.98	1	1	1	1	1	1	1	1
Delta Ammino Levulinic Acid	.13	.37	.69	.91	1	1	1	1	1
Porphobilinogen	.4	.93	1	1	1	1	1	1	1
Copropophyrin	.2	.6	.91	.99	1	1	1	1	1
IgG	.86	1	1	1	1	1	1	1	1
IgA	.28	.8	.99	1	1	1	1	1	1
IgM	.4	.93	1	1	1	1	1	1	1
Total Protein-Urine	.86	1	1	1	1	1	1	1	1
T-Pan	.67	1	1	1	1	1	1	1	1
T-Helper	.38	.91	1	1	1	1	1	1	1
T-Suppressor	.36	.97	1	1	1	1	1	1	1
T-Helper/T-Suppressor	.56	.99	1	1	1	1	1	1	1

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9. PEER REVIEW COMMITTEE

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Robert Waldman, M.D.
Chairman, Department of Medicine
University of West Virginia
Morgantown, West Virginia

PRELIMINARY BUDGET ESTIMATES FOR KRUMMRICH PROJECT

1) Data Gathering - 18 subjects per day by a team of 6 physicians (3 internists, 2 neurologists, 1 dermatologist) working 5 days per week and communting from chicago on a weekly basis. (All figures assume 813 subject examination.)

Physician Fees	585,360
Physician Expenses	65,800
Blood & Urine Test	654,000
Paramedical Salaries	78,750
Equipment Lease/Purchase	46,300
Survey Research Lab	170,000
Neuro Behavioral Exam	12,810
Subject Reimbursement	54,000
	1,667,020

2) Data analysis - assumes 18 month required for data analysis and generation of individual reports.

Salary of Investigators	156,000
Salary for Support Personel	356,134
Office Equipment, Supplies	45,465
Equifax Cohort Search	45,150
Data Coding Service	31,150
Consultation Fees & Expenses	13,632
Peer Review	10,000
	657,531

Totals:	
I	1,667,020
II	657,531
University Overhead	53,250
	2,377,801

DSW 476038.0597

Julie,
File Dorthmeschen Study
Jim

DEC 1 9 1989

Monsanto

ENVIRONMENT, SAFETY & HEALTH

Monsanto Company
800 N. Lindbergn Boulevard
St. Louis, Missouri 63167
Phone: (314) 694-1000

December 11, 1989

Daniel O. Hryhorczuk, M.D.
1515 N. Keystone Avenue
River Forest, Illinois 60305

Dear Drs. Hryhorczuk and Wallace:

Thanks for your presentations to our workforce at the Krummrich plant last Friday the 1st. It appeared to us that you were successful in communicating both your findings and conclusions to the attendees at each meeting. We appreciate your efforts and are certain the plant and all of our employees feel the same.

We look forward to seeing you both again in a year or so, if not sooner. Until then have a joyous holiday season and fruitful new year.

Yours truly,

J. J. Collins, Ph.D.

P. R. Conner, M.D.

PRC/kg

DSW 476038.0598

STLCOPCB4042762

FB Hryhorczuk Friedlander

SEP 29 REC'D

Monsanto

ENVIRONMENT, SAFETY & HEALTH

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800 N. Lindbergh Boulevard
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Phone: (314) 694-1000

September 28, 1988

Daniel O. Hryhorczuk, M.D., MPH
Department of Preventive Medicine
and Community Health
Northwestern University Medical School
Chicago, IL 60611

Dear Dan:

Everybody and his brother (that is to say, Friedlander, Gaffey, Garrett, Haselhorst and Leet) has reviewed the preliminary draft report, each of us taking the sections that he or she was best qualified to review. Our comments are attached.

Some of the comments are editorial, some are matters of fact, and some represent our opinions or questions about the text. I hope they will be helpful to you. Some of them may affect the tables that will go into the final report.

Yours sincerely,

William R. Gaffey, Ph.D.
Epidemiology Director

/jf

cc: B.R. Friedlander w/copy of comments
J.T. Garrett " " "
B.L. Haselhorst " " "
T.L. Leet " " "

DSW 476038.0599

STLCOPCB4042763

Comments on Preliminary Draft Report Titled

"Epidemiologic Investigation of the Health Status of Monsanto Employees with Past Exposure to Chlorophenols, Chlorphenoxy Acid Esters and Their Dioxin Contaminants at the W.G. Krummrich Plant in Sauget, Illinois"

Pages 1-4.

Acronyms are given for a number of substances (e.g. 2,4-D) and tests (e.g. BUN). They should be spelled out the first time they are used, followed by the acronym in parentheses.

Page 3, first paragraph.

Dr. Tillman said that these weight variations did not seem to him to be unusual.

Page 4, Sec. 2.3.3.

The first two sentences are a nonsequitur and should be removed.

Page 5, Sec. 2.4.2.

Second line. "1982" should be "1986".

Third line. Something should be added to the effect that no adjustment was made for smoking because the data were not easily available.

Fourth line. "investigating" should be "investigated".

Sixth line. "selected" should be inserted between "with" and "subcohort".

Page 6.

After first sentence put (MEHI) in parentheses.

Page 7, Sec. 4.2.1.

No rationale for why some hypotheses are "primary" and some are "secondary".

Page 9, Sec. 4.3.

Here and elsewhere, proprietary names like Santobrite should be followed by TM the first time they are used, with a footnote saying that it is a registered trade mark of the Monsanto Company.

Page 15, Table 4.1.

1931. S-036 should be in parenthesis.
1964. S.G. should be spelled out.

Page 17, first line.

The term "snift gas" should be replaced by "revaporized chlorine (known in the plant as "sniff gas")."

Page 22, Table 4.2.

Did the A and B operator also assist the Premium Operator?
Replace question marks with an asterisk and explanatory footnote.

Pages 37 and 51.

The word "fines" is a generic term used here in specific senses that are not appropriate. On page 37, next to last line, replace "fines" with "materials" and on page 51, Table 4.10, in 1961, replace "fines" by "particulate products". The usage elsewhere is correct.

Page 83, Sec. 4.4.1.1.

Title and first sentence. Since cohorts are identified independently of outcome, and these people had to be alive to get into the study, the term "group" may be more appropriate.

Definition of exposed cohort. The implication here is that chloracne alone did not qualify a person as being exposed. On page 94, Sec. 4.5.2, the opposite is implied. On page 136, Sec. 5.6, it is apparent that people were called exposed if they worked in the appropriate departments according to their work histories or if they had chloracne and stated that they had worked in the appropriate departments. In other words, the criterion for exposure appears to be different for those with chloracne and those without. Some clarification is needed here and in the other cited sections.

Last paragraph. Salaried controls were not included in the main study. It might be appropriate here to explain why salaried people were included only in the pilot study. In the last sentence MEHI does not have to be spelled out.

Page 85a, Table 4.17.

The age ranges go over 100. In some comment needed?

Page 86, first complete paragraph.

We studied the mortality experience of the whole plant, so this could not explain the difference in the percents whose vital status is unknown in the exposed and controls. The explanation seems to be that one way not to be exposed was to work for a shorter time. Therefore there were more terminations in the control group who had to be followed, therefore more persons with unknown vital status.

Tables 4.17 and 4.18 vs. Tables 8.1, 8.2, 8.3. The labels "Exposed" and "Control" are used in both sets of tables, but it is clear that Tables 4.17 and 4.18 deal with "potential" or "eligible" persons while Tables 8.1 etc. deal with those who were actually examined. The labels should be different in the first set of tables.

Page 91, Sec. 4.5.1, first paragraph.

There were actually four sources. One was hard copies of employment records prior to MEHI.

Page 96, Sec. 4.5.1.1, first sentence.

No need to define the acronym MEHI. "hourly" should precede "worker" and "after 1935" should precede "at".

Page 92, first five lines.

Is the statement about Dr. Davis correct?

Page 93, fifth line.

"assigned" should replace "misclassified"

Page 94, third line from bottom.

Why capitalize "Department"?

Page 95, Sec. 4.5.2.2.

The classification by exposure department needs clarification. First, the implication is that there was no one with a mixed exposure. We know this is not true because in the succeeding tables the numbers of people in each of these categories do not add up to the "Total Exposed" given in the tables.

Second, the category "maintenance workers on the chloracne registry" must include some people (perhaps all of them) with chloracne. Therefore, in the succeeding tables, almost all of which show a fifth category called "chloracne", that category must overlap the other categories. A table showing the numbers in each group, and the numbers with mixed exposures, would be helpful.

Page 96, first complete paragraph.

Reliance in self-reporting was necessary because plant records were not available for those terminated before 1970.

Page 97, Sec. 4.6, last line.

There is no Table 19.

Page 100, Sec. 4.6.2, second line.

Delete "b".

Page 103, Sec. 4.6.9, third line

"Sensortec" should be "Sensortex".

Page 104, third line.

There is no Table 4.19.

Page 107, sec. 4.8.2.1, first paragraph.

In item (3), should it be pointed out that the subjects, when asked, did not recall any such discrepancies?

Page 108, Sec. 4.8.2.3.

Should it be pointed out that the groups were randomized with respect to time of examination in order to eliminate time-of-day bias?

Page 109, Sec. 4.9.

If there are to be power calculations after the fact, they should be done for tests of means as well as for tests of prevalence. However, after a test has been done the power is not relevant. What is relevant are the confidence intervals that were obtained. It can happen that a test which is a priori not powerful can give a confidence interval that rules out the alternative.

Page 117, second full paragraph, second and third lines.

Johns, not John's and Holmes, not Homes.

Page 122, last paragraph, fifth line.

Insert after "to" the phrase "a six digit job class code beginning with"

Page 148, Sec. 6.5.8, third line

One "n" in Marilyn.

Page 122, last paragraph, eighth line.

Add to the end of the sentence the parenthetical expression (this accounted for about two percent of the sample).

Page 125, Sec. 5.4.1, fourth line.

(83.2%) should be (83.3%)

Page 136, second line.

"that" should be "than".

Page 142, second paragraph, fifth line.

"of" should be "or".

Page 143, last line.

"coordinator" should be "manager".

Page 145, second line.

Insert the sentence - The van was also inspected by Mr. Paul Kalicki from the Illinois Department of Nuclear Protection.

Page 145, Sec. 6.5.3.

second line - change "coordinator" to "manager"
third line - change "electrocardiogram" to "electrocardiogram/ blood pressure".

Page 146, third line.

After first sentence insert - At that time each one was given an ID bracelet with a 4 digit study number and the first 4 letters of the last name for purposes of quality control, but which included no indication of exposure status.

Page 146, first paragraph, last line.

Change "coordinator" to "manager". Add the sentence - All participants completed a final exit interview prior to leaving the examination site.

Page 146, Sec. 6.5.6, fifth line.

Remove "ed" from "administered".

Page 148, Sec. 6.5.8, second line.

Date is April 7, 1986.

Page 149, Sec. 6.5.10, sixth line.

"At" should be "A".

Page 151.

Should be some comment on which records were lost. Were they for people who terminated before some date?

Page 154, Table 7.1.

What do the initials mean?

Page 157, Sec. 7.6, third paragraph.

Fisher's Exact test is usually a one-sided test. Chi-square is a two-sided test. For these associations and the p-values in the regression tables, was a one-sided or a two-sided test used?

Page 158, Sec. 7.6.1, first paragraph.

The exposure classification, except for the chloracne category, is redundant with Sec. 4.5.2.2 and needs clarification.

Page 161, Sec. 7.6.4.

Chloracne as defined here is a mixture of cumulative incidence and prevalence. This implies that the investigators consider chloracne a marker for relatively heavy exposure. This is perfectly proper, but should be mentioned so that readers will not interpret the chloracne figures as being incidence or prevalence.

Page 194, Sec. 8.3.1, second paragraph, third line.

Phrase (2) does not seem to make sense.

Page 197, Table 8.17.

The number in Maintenance cannot be greater than the corresponding number in Table 8.16. One of the two entries must be incorrect.

Tables 8.19, 8.20, 8.21, 8.22.

Apparently Table 8.19 includes people who worked in more than one production department and therefore do not appear in Tables 8.20, 8.21, or 8.22. It would be helpful to restate in the text that Tables 8.20, 8.21 and 8.22 do not add up to Table 8.19. (The pages for these tables are misnumbered.)

Tables 8.30-8.32.

Pages are misnumbered.

Page 232, Table 8.40

The number in "Only 236" is 278. It was never more than 260 in previous tables of the examined group. Is this an error?

Table 8.50 and text.

In several places in this table (Pattern Memory is one example) Department 236 did significantly worse than the controls while the other three exposure groups did very well. Because the people in 236 were a majority of the "All exposed" group the latter group also was significantly worse than the controls. The results for Department 236 and for "All exposed" are presented as if they were two independent conclusions, when in fact the latter is caused by the former. As stated, the findings for "All exposed" falsely imply that the result is pervasive in the exposed group, which it generally is not.

Tables 8.51 to 8.69.

What are the numbers in square brackets in the left column?

Jules,
File under Krummrich Study

DANIEL O. HRYHORCZUK, M.D., M.P.H.
1515 North Keystone Avenue
River Forest, Illinois 60305
(312) 366-1064

March 26, 1990

APR 6 REC'D

Dr. Barry Friedlander
Medical Director
Monsanto Company
800 N. Lindbergh Boulevard
St. Louis, Missouri 63167

Dear Dr. Friedlander:

My colleagues and I wish to thank you and your staff for your careful review of our first report on the Krummrich morbidity study. Several of your suggestions regarding an executive summary, critical literature review, and choice of emphasis and wording were excellent and would indeed improve the clarity of our report. While I had taken notes regarding your suggestions at our last meeting, I would be grateful if you could transmit them to me in writing. This way I can assure that we have the opportunity to address each of your suggestions.

We have sent the original version of our report to the Peer Review Committee to keep them abreast of our updates. We will similarly send them updated versions of our report as they become available.

We are eager to proceed with the preparation of manuscripts for publication in peer-reviewed journals. We will of course give you the opportunity to review these articles before they are submitted.

I know that we are all committed to completing this work as carefully and expeditiously as possible. I look forward to your reply at your earliest convenience. If need any additional information or have any questions, please feel free to call.

Sincerely,

Daniel Hryhorczuk, M.D., M.P.H.

DSW 476038.0607

NORTHWESTERN MEDICAL FACULTY FOUNDATION, INC.

222 East Superior Street
Chicago, Illinois 60611
(312) 649-6940

January 30, 1985

File
Northwestern
Study

JAN 31 1985

George Roush, M.D.
Medical Director
Department of Medicine and Environmental Health
MONSANTO COMPANY G2WG
800 North Lindberg Boulevard
St. Louis, Missouri 63167

Dear Doctor Roush:

We are forwarding to you the revised protocol for the "Epidemiologic Investigation of the Health Status of Monsanto Employees with Past Exposure to Chlorophenols, Chlorphenoxy Acids, and Their Dioxin Contaminants at the W.G. Krummrich Plant in Sauget, Illinois". This revision incorporates many of the excellent suggestions of the Peer Review Committee.

We believe that each worker will look upon the examination as a valuable benefit provided by Monsanto. We also believe that this study will be a major contribution to the scientific literature on dioxins. The study is designed to answer many of the previously unresolved questions regarding the possibility of chronic health effects in workers with past exposure to dioxins.

The Peer Review Committee was unanimous in commending Monsanto for its sponsorship of this study. We appreciate your confidence in selecting us to design and carry out this important research. We wish to extend our personal thanks to you and your staff for your assistance and the courtesy you have shown us during the design of this study.

Sincerely,

James R. Webster, Jr., M.D.

Warren Wallace M.D.

Warren Wallace, M.D.

JRW/WW:pjw

DSW 476038.0608

EPIDEMIOLOGIC INVESTIGATION OF THE HEALTH STATUS OF MONSANTO EMPLOYEES WITH PAST EXPOSURE TO CHLOROPHENOLS, CHLORPHENOXY ACIDS, AND THEIR DIOXIN CONTAMINANTS AT THE W.G. KRUMMRICH PLANT IN SAUGET, ILLINOIS: STUDY PROTOCOL

Principal Investigators

Daniel O. Hryhorczuk, M.D., M.P.H. Warren H. Wallace, M.D.

Co-Investigators

James R. Webster, Jr., M.D. Victoria Persky, M.D.

Department of Medicine
Department of Preventive Medicine and Community Health
Northwestern University Medical School
Chicago, Illinois

January, 1985

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EXECUTIVE SUMMARY OF THE STUDY PROTOCOL

The purpose of this study is to determine if workers at Monsanto's Krummrich Plant in Sauget, Illinois suffered any long term health effects as a result of their past exposure to chlorinated phenols, esters of 2,4-D and 2,4,5-T, and their chlorinated dioxin contaminants. The health status of the exposed employees will be compared to the health status of Krummrich employees who were not exposed to these compounds.

The exposed cohort will consist of all Krummrich employees who were engaged in the production of chlorinated phenols or chlorphenoxy herbicides for one or more days between January 1, 1938 and December 31, 1983. Maintenance employees who were assigned to these areas and who developed chloracne will also be included in the exposed cohort. One thousand and fifty-five employees meet the definition of exposure of whom 221 are deceased. Four hundred and four exposed workers are expected to participate in the study. This exposed cohort will be comprised of 221 active, 106 retired, 60 terminated, and 17 other workers whose employment status is as yet unknown.

One thousand seventy-seven Krummrich employees were considered to be non-exposed during this same time period. Four hundred and nine are expected to participate as internal controls. This group will be comprised of 218 active, 50 retired, and 141 terminated workers.

Study participants will undergo a comprehensive medical examination, including a medical history, occupational and environmental history, reproductive history, physical examination, dermatologic examination, neurologic examination, electrocardiogram, pulmonary function tests, chest

x-ray, quantitative sensory examination, nerve conduction velocity studies, neurobehavioral testing, blood tests, and urine tests. Questionnaire items will be confirmed by medical record review.

The health status of the exposed cohort will be compared to the health status of the internal controls. The strategy for statistical analysis will consist of 1) examination of crude associations, 2) stratified analysis, 3) tests for dose response, and 4) multivariate analysis.

1. PURPOSE OF THE STUDY

The purpose of this study is to determine if workers at Monsanto's Krummrich Plant in Sauget, Illinois suffered any long term health effects as a result of their past exposure to chlorinated phenols, esters of 2,4,-D and 2,4,5-T and their chlorinated dioxin and dibenzofuran contaminants.

2. BACKGROUND

2.1 Plant History

The plant was established in 1907 as the Commercial Acid Company. At that time it occupied 30 acres and employed 70-100 people. Monsanto purchased the plant in 1917 to insure a supply of mineral acids. The plant was referred to as "Plant B" until 1951, when it was renamed the William G. Krummrich Plant in honor of a former plant manager.

The Krummrich Plant currently occupies 329 acres and employs approximately 1100 people. The plant produces about 1 billion tons of material per year. The plant is administered by two of Monsanto's four operating companies: Monsanto Industrial Chemicals and its guest company, Monsanto Polymer Products. The Krummrich Plant is organized by the International Chemical Workers Union, Local 12. The plant is located in Sauget, Illinois, which is 3 miles southeast of downtown St. Louis.

Fifteen percent of the plant's total resources in manpower, time, and money are devoted to its environmental monitoring and control program. The plant employs 2 part-time physicians and several nurses in addition to a large staff of industrial hygiene, safety, and environmental personnel. Monsanto's Corporate Medical Program provides oversight and support of the plant program, including computerization of employee exposure and medical surveillance data.

2.2 Products

The Krummrich plant currently uses more than 75 different raw materials to produce approximately 20 different intermediate chemical products. The major raw materials include chlorine, phosphorus, benzene, sulfur, and salt. Major products include chlorinated benzenes, chlorophenols, orthonitrophenol, nitroanilines, PCl_3, $POCl_3$, P_2S_5, chlorine, sulfuric acid, chlorosulfonic acid, muriatic acid, chlorine bleaches and stabilizers, detergent materials, feed grade antioxidants, and elastomers.

The manufacture of chlorophenols began in 1938. Production of pentachlorophenol was discontinued in 1978; the production of mono- and di-chlorophenols was discontinued in 1983. Esters of 2,4-D and 2,4,5-T were produced between 1960 and 1970. This plant was a producer of PCBs until 1977 when production was discontinued.

2.3 Previous Studies of the Plant Population

2.3.1 Tillman, 1977

In 1977 Dr. Ernest Tillman reviewed the plant medical records of 60 employees in the Pentachlorophenol Unit at the W. G. Krummrich Plant. The study group included all persons who were working in Department 236 in 1977 and all persons who had worked in Department 236 for 1 year or more since 1951. The lengths of exposure ranged from 3 months to 13 years.

Forty-eight percent of the cases studied developed chloracne at some time while assigned to Department 236. In the majority of cases of active employees, chloracne appeared within 1 year of being assigned to Department 236. No difference in the frequency of occurrence was found on the basis of race or age. Chloracne occurred at all times between 1959 and 1977 with

no peak at any particular time.

Seventy-seven percent of the study group made repeated comments about weight variations from one periodic examination to the next. The review of the periodic health questionnaires and physical examinations failed to identify any other abnormalities.

2.3.2 Suskind, 1980

In 1979 Dr. Raymond Suskind conducted a medical survey to determine the health status of employees of the W. G. Krummrich Plant who had been exposed to chlorinated phenols. The study population included active employees who had worked in either Department 236 (pentachlorophenol) or Department 237 (chlorophenols). The total number of active employees who worked in these two areas was 157. One hundred fifteen persons volunteered for examination and 106 of these completed the physical examination.

The medical survey included the completion of an administered questionnaire, a medical history, a dermatologic examination, and examination of other organ systems if indicated by the clinical history. Skin biopsies were done when indicated. Clinical laboratory tests included: blood Ca, P, BUN, creatinine, BUN-creatinine ratio, uric acid, fasting blood sugar, total protein, albumin, globulin, total bilirubin, direct bilirubin, SGOT, SGPT, alkaline phosphatase, LDH, cholesterol, iron, magnesium, sodium, potassium, chloride, GGT, triglycerides and lipoprotein profiles; CBC and differential; urinalysis and urinary copro-porphyrin, uroporphyrins, and creatinine. Personal medical histories were comfirmed by reviewing plant medical and personnel records.

Sixty-six of 115 workers had a history of chloracne. Forty-three were found to have residual chloracne and of these cases 67.6% were mild and 32.5%

moderate. All of the residual cases were comedonal in type, and 32.5% of those had cystic lesions as well. Five of 106 persons were found to have malar hirsutism and 12 were found to have actinic elastosis.

In the analysis of laboratory data, test results were compared between employees with and without a history of chloracne or residual chloracne. While a small number of elevated total serum lipids were observed, there was no correlation between the serum lipids and the presence of chloracne. While persons with elevated triglycerides were found in both groups, there was no correlation between serum triglycerides and presence or absence of chloracne. No significant differences in levels of cholesterol, LDL, SGOT, SGPT, and GGT were found between the chloracne and non-acne groups. Urinary porphyrins could not be interpreted due to technical error.

The frequency of abnormal levels of VLDL was significantly increased in those persons with a history of chloracne or with residual chloracne as compared to those who never had chloracne. There appeared to be less residual chloracne in the group with HDL levels of 45 or more than those in the group with levels less than 45. There was also significantly less chloracne found in workers who did not smoke at the time of examination than those who did smoke.

2.3.3 Zack, 1980

In 1977, The Chemical Manufacturers Association contracted with Tabershaw Occupational Medicine Associates to conduct an industry-wide epidemiologic study of workers exposed to benzene. The W.G. Krummrich Plant was one of the nine plants chosen to participate in this study. Judith Zack conducted a separate Standardized Mortality Ratio analysis of the data from

the Krummrich population.

Her study cohort consisted of all male, hourly employees active on or after January 1, 1946 with six months or more of employment prior to December 31, 1977. Vital status was ascertained as of December 31, 1977. The population of the United States was used as the standard.

Three thousand twenty-two employees fit the cohort entrance criteria, but 114 were excluded because of incomplete data. Two thousand seventy-two of the 2908 member study cohort were verified as living, 736 were identified as deceased, 702 of these by death certificate.

The SMR's for white and non-white employees for specific causes of death are shown in Tables 1 and 2. There were no statistically significant elevations in SMR's observed among male Krummrich employees for any of the cause-of-death categories examined.

Re-analysis of this data by work area is currently being done by Monsanto epidemiologists. Past employees of Department 236 and Department 268 (agricultural esters) have been included in NIOSH's industry-wide mortality study of workers exposed to dioxin.

Table 1

Observed and Expected Deaths for Krummrich Plant Study Population

Non-white Males

Cause of Death	8th Rev. ICD Code	Observed	Expected	SMR
All causes of death	001-998	225	256.87	88*
All malignant neoplasms	140-209	42	44.54	94
Buccal cavity and pharynx	140-149	1	1.54	65
Digestive organs and peritoneum	150-159	9	15.34	59*
Respiratory system	160-163	17	13.20	129
Genitourinary organs	185-189	6	6.88	87
Lymphatic and hematopoietic tissue	200-209	6	3.02	199
Leukemia and aleukemia	204-207	2	1.09	183
Other lymphopoietic cancer	-	4	1.93	207
Other malignant neoplasms	-	3	4.56	66
Circulatory diseases	390-458	117	123.01	95
Arteriosclerotic heart disease	410-413	62	58.34	106
Cerebrovascular disease	430-438	25	28.01	89
Other circulatory diseases	-	30	36.66	82
Respiratory diseases	460-519	4	14.90	27*
All other diseases	-	19	47.79	40*
All external causes of death	800-998	31	25.47	122
Total Residual		12	1.16	

* $p < .05$

Number persons observed = 584

Number person-years observed = 12925.1

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Table 2

Observed and Expected Deaths for Krummrich Plant Study Population-White Males

Cause of Death	8th Rev. ICD Code	Observed	Expected	SMR
All causes of death	001-998	511	522.43	98
All malignant neoplasms	140-209	98	101.76	96
Buccal cavity and pharynx	140-149	2	3.54	56
Digestive organs and peritoneum	150-159	17	28.45	60*
Respiratory system	160-163	46	34.76	132
Genitourinary organs	185-189	6	11.01	54*
Lymphatic and hematopoietic tissue	200-209	7	10.58	66
Leukemia and aleukemia	204-207	2	4.14	48*
Other lymphopoietic cancer	-	5	6.44	78
Other malignant neoplasms	-	20	13.42	149
Circulatory diseases	390-458	273	261.06	105
Arteriosclerotic heart disease	410-413	201	188.14	107
Cerebrovascular disease	430-438	30	30.60	98
Other circulatory diseases	-	42	42.32	99
Respiratory diseases	460-519	20	27.90	72
All other diseases	-	41	69.49	59*
All external causes of death	800-998	57	59.62	96
Total Residual		22	2.60	

*p <.05

Number persons observed = 2324

number person-years observed = 54509.1

DSW 476038.0622

3. LITERATURE REVIEW

3.1 Overview

The health effects of 2,3,7,8-TCDD, 2,4,-D, and 2,4,5-T have been studied extensively in recent years and are the subjects of several excellent reviews (Kimbrough, 1980; Esposito et al, 1980; Huff et al, 1980; HALTS, 1980; JRB, 1981; Clement, 1984). The occupational morbidity studies done to date suffer from inadequate characterization of exposure and lack of adequate controls. The occupational mortality studies are limited by small numbers. Very few studies have followed affected workers over time. Little is known about the health effects of exposure to PCDDs other than 2,3,7,8-TCDD.

The only human data on the health effects of exposure to PCDFs comes from the outbreaks of Yusho disease in Japan and Taiwan in the past two decades (Kuratsune et al, 1972). These observations are confounded, however, by the co-ingestion of PCBs and chlorinated quaterphenyls.

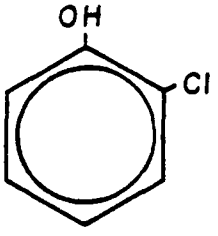
Acute poisoning from pentachlorophenol has been well described. Studies of chronic effects, however, have been limited to small numbers of active workers. There is very little animal data and no human data on the toxicities of the mono- and dichlorophenols.

The structures of the chemicals discussed in this review are shown in Figure 1. A description of the actual manufacturing processes and resulting exposures is provided in Sections 4.2.1 and 4.2.2.

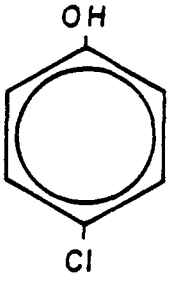
3.2 Ortho Chlorophenol

Ortho chlorophenol (O-CP) is a light amber liquid used as an intermediate in chemical synthesis. O-CP is prepared by the direct chlorination of phenol. It is soluble in water (2.85/100 parts water), alcohol, and ether; its vapor

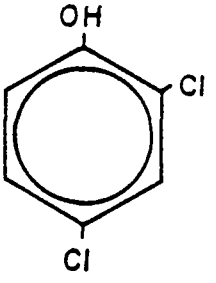
Fig.1 CHEMICAL STRUCTURES OF CHLOROPHENOLS, CHLORPHENOXY ACIDS, AND THEIR DIOXIN AND DIBENZOFURAN CONTAMINANTS



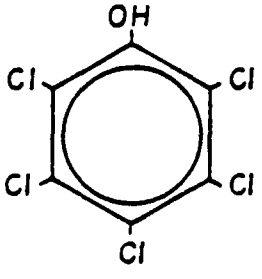
o-CHLOROPHENOL



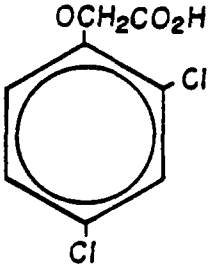
p-CHLOROPHENOL



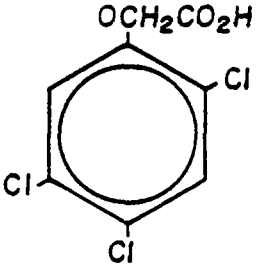
2,4-DICHLOROPHENOL



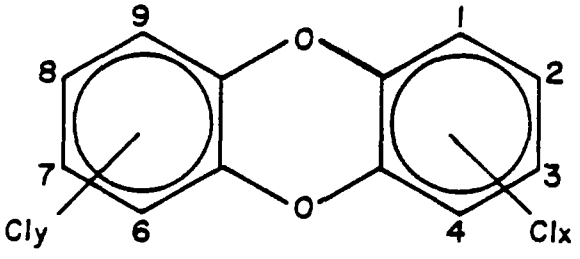
PENTACHLOROPHENOL



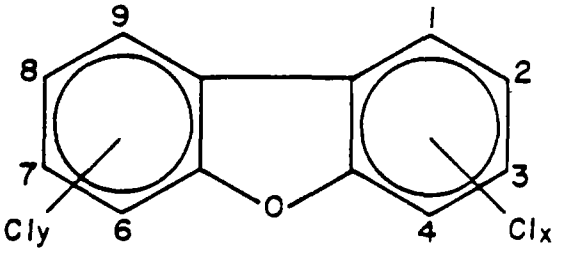
2,4-D



2,4,5-T



PCDD



PCDF

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pressure is 1 mm at 12.1° C.

The oral LD_{50} of O-CP is 670 mg/kg in rats (NIOSH, 1983) and 625-750 mg/kg in chickens (Bubnov et al, 1971). Toxic effects in rats include restlessness, increased respiratory rate, tremors, and clonic convulsions. Pathologic changes in chickens include inflammatory loci in the cerebral cortex and dystrophic changes in the liver and myocardium. O-CP decreased hemoglobin content; increased alkaline phosphatase, LDH, and glutamate-oxaloacetate; and produced pathologically evident liver tissue degeneration in rats (Chung, 1978). O-CP did not affect the immune system in rats at oral concentrations of 500 ppm (Exxon and Koller, 1983). O-CP is fetotoxic in rats and high doses (Exxon and Koller, 1982).

3.3 Parachlorophenol

Parachlorophenol (P-CP) is a white to straw-colored crystalline compound prepared by the direct chlorination of phenol. Solutions of P-CP are used as topical antiseptics. P-CP is soluble in water (2.71/100 parts water) and very soluble in alcohol and ether.

The oral LD_{50} of P-CP is 261 mg/kg in the rat (NIOSH, 1983). Toxic effects include restlessness, increased respiratory rate, tremors, and convulsions. P-CP is irritating to rabbit eye and skin.

3.4 2,4-Dichlorophenol

2,4-Dichlorophenol (2,4-DCP) is a colorless crystalline compound prepared by the direct chlorination of phenol. 2,4-DCP is used as an intermediate in the synthesis of 2,4-Dichlorophenoxy acetic acid. It is sparingly soluble in water. (.45/100 parts water) and very soluble in alcohol and ether.

Somani et al (1981) studied the kinetics of 2,4-DCP in rats. 2,4-DCP was conjugated to glucuronide and other conjugates. The kidney had the highest amounts of free compound, followed by the liver and fat.

The LD_{50} of 2,4-DCP is 580-4,500 mg/kg in rats and 1,630 mg/kg in mice (Kobayashi et al, 1972). Toxic effects in rodents include decreased spontaneous locomotor activity, loss of righting reflex, and sedation. The maximum chronic no-effect level in mice is 100 mg/kg/day (Kobayashi, 1972). 2,4-DCP in doses of .1 mg/kg is fetotoxic in rats (Konstantinova et al, 1976).

3.5 Pentachlorophenol

Pentachlorophenol (PCP) is the second most heavily used pesticide in the U.S. Its major application is wood preservation. PCP is a dark-colored crystalline compound which is produced in the U.S. by the direct liquid phase chlorination of phenol (Boehringer process). PCP produced by the Boehringer process may contain 4-12% tetrachlorophenol, 1-5% hydroxychloro-diphenyl ether, 0.1% trichlorophenol, and trace amounts of PCDDs and PCDFs. Very little is known about the toxicity of hydroxychlorodiphenyl ethers. One of these pre-dioxins, 2-hydroxy-2,4,4-trichlorodiphenyl ether, has a low acute toxicity in rats, with an LD_{50} of about 5000 mg/kg (Williams, 1982).

The sodium salt of PCP is produced by reacting pentachlorophenol with sodium hydroxide. While PCP and its sodium salt vary in their solubilities in different solvents, their toxicities are basically the same. PCP and its sodium salt are usually used as 1-5% solutions in organic solvents (PCP) or water (Na PCP).

The main routes of occupational exposure to PCP are inhalation and skin contact. Skin absorption is facilitated by the presence of organic solvents or by cuts and abrasions of the skin. PCP is bound to plasma proteins. Repeated

workday exposures to the TLV of 0.5 mg/m^3 results in a maximum steady state plasma concentration of 0.5 ppm (Wood, 1983). PCP is eliminated from the plasma via distribution to the tissues, metabolism via glucuronidation and oxidation to tetrachloro-p-hydroquinone, and excretion of PCP and its metabolites in the urine and, to a lesser extent, the feces. PCP may undergo enterohepatic circulation. Elimination follows a first order, single compartment model with a half life of 30.2±4 hours in healthy human volunteers. (Braun, 1979). Elimination half lives in workers may be longer.

Technical-grade PCP is irritating to the skin and mucous membranes of the eyes and upper respiratory tract. Skin irritation occurs with frequent contact to PCP solutions of 1% or stronger. Eye and respiratory tract irritation occur at PCP air levels greater than 1.0 mg/m^3. Skin contact with technical-grade PCP can produce chloracne, though this is most likely due to the HCDD (and perhaps other PCDD/PCDF) contaminants.

PCP produces its systemic toxicity by interfering with electron transport in mitochondria. The resulting uncoupling of oxidative phosphorylation results in an increase in metabolic heat production and hyperpyrexia.

The acute oral LD_{50} of PCP is 40-130 mg/kg in rabbits and 27-78 mg/kg in rats. PCP contaminated with HCDD, HeCDD, and OCDD has produced hepatic effects in rats, including hepatic porphyria and increases in aryl hydrocarbon hydroxylase (AHH) and glucuronyl transferase (GGT) activity (Goldstein, 1977). Pure PCP was not porphyrogenic and produced only a slight effect on GGT activity. Technical PCP has also produced hepatocellular degeneration and necrosis in rats (Kimbrough and Linder, 1978). PCP has not been shown to be carcinogenic in

animals. PCP with its HCDD contaminant, however, may be fetotoxic and teratogenic (Cirelli, 1978).

There are numerous case reports of acute PCP poisoning resulting from occupational exposures (Truhaut et al, 1952; Menon, 1958; Wood et al, 1983). Symptoms include hyperpyrexia, diaphoresis, tachycardia, tachypnea, weakness, nausea, vomiting, abdominal pain, anorexia, thirst, pain in the extremities, progressive coma, and death. Acute PCP poisoning may present with hepatic and renal dysfunction and metabolic acidosis with an increased anion gap. Skin absorption appeared to be the primary route of exposure in many of these cases. Sporadic cases of aplastic anemia, leukemia, Hodgkin's disease, and non-Hodgkin's lymphoma of the skin have been reported among PCP workers, but the association with PCP exposure is not conclusive (Roberts, 1983).

Chronic occupational exposure to PCP has been associated with an increased prevalence of conjunctivitis, chronic sinusitis, bronchitis, polyneuritis, and dermatitis (Baader and Bauer, 1951; Klemmer et al, 1980). Chloracne has occurred in PCP workers, but is most likely due to the PCDD and PCDF contaminants. Treibig et al (1981) found a significant decrease in sensory nerve conduction velocities in PCP production workers, but they could not demonstrate a dose response relationship. Zober et al (1981) found elevated GLDH-activities in workers producing and applying PCP. Begley et al (1977) demonstrated a significant improvement in creatinine clearance and phosphorus reabsorption in PCP wood treatment workers following a 20-day vacation. Bauchinger et al (1982) analyzed the chromosomes from peripheral lymphocytes from PCP production workers. They found a small, but significant, increase in the frequency of dicentrics and acentrics, but no significant increase of sister-chromatid exchanges.

3.6 2,4 Dichlorophenoxyacetic Acid

2,4-Dichlorophenoxyacetic acid (2,4-D) is a widely used post-emergent herbicide. 2,4-D is a white powder produced by reacting 2,4-dichlorophenol with chloroacetic acid in a solvent mixture of water and sodium hydroxide. The esters are produced by reacting 2,4-D with the appropriate alcohol. 2,4-D may be contaminated with Di-CDD, Tri-CDD, and 1,3,6,8-TCDD as well as with a variety of derivatives of phenoxyacetic acid and phenol, such as Bis (2,4-dichlorophenoxy) methane, Bis (2,5-Dichlorophenoxy) methane and 2,2,4,6- tetrachlorodiphenoxy methane. Most commercial 2,4-D preparations contain the ester or the salt rather than the free acid due to their better solubility characteristics. Alcohols are often used as solvents in 2,4-D formulations. The concentration of 2,4-D in commercial preparations is highly variable and may range from 1-80% (Halts, 1980).

2,4-D is rapidly absorbed from the gastrointestinal tract in healthy male volunteers with peak plasma levels occurring in 4-24 hours. The volume of distribution is .28-.29 1/kg. Elimination is first order with a plasma half life of 7-33 hours. 2,4-D is excreted in the urine as the free acid, though a small percent may appear in the urine as conjugates. (Kohli et al, 1974; Sauerhoff et al, 1977). Since 2,4 D is a weak organic acid, urinary excretion is pH dependent. Prescott (1979) increased renal clearance of 2,4-D in a case of accidental ingestion by alkalinizing the urine. Feldman and Maichbach (1974) found that 5% of 2,4-D applied to the forearm was absorbed and excreted.

2,4-D's mechanism of toxic action has not been well established. 2,4-D may produce its neuromuscular effects by interfering with organic acid anion transport in neuromuscular tissues. (Podolak, 1981 a,b; Kim, 1981). 2,4-D has also been shown to induce mixed function oxidases in animals (Rivieri and Bach, 1981).

The LD_{50} of 2,4-D in animals ranges from 100 mg/kg to a few thousand mg/kg depending on the form of 2,4-D and the species tested (IARC, 1977). Toxic effects are apparent after a latent period of 2-9 days and include loss of appetite, weight loss, myotonia, and muscle weakness progressing to paralysis, coma, and death. Pathological changes have been described in the gastrointestinal tract, liver, lungs, and kidneys. The free acid appears to be more toxic than the esters, and equal in toxicity to the sodium salt (HALTS, 1980).

2,4-D increased the frequency of tumors in rats (Hansen et al, 1971; but most other studies have not shown a carcinogenic effect in animals. 2,4-D is fetotoxic in high doses and may be a weak teratogen. Duffard et al (1981) demonstrated reduced hatchability and an increased frequency of malformations in chick eggs painted with 2,4-D. In a second study, painting eggs with 2,4-D resulted in postnatal alterations in the chemical composition of chick brain (Duffard et al, 1982)

The LD_{50} of 2,4-D in man is estimated at 80-800 mg/kg. Autopsy findings from two fatal human ingestions showed acute demyelination in the brain (patient with senile dementia), peripheral neuropathy, degenerative changes in the ganglion cells, hepatic necrosis, and congestion of most organs (Nielsen et al, 1965; Dudley and Thapar, 1972). Seven cases of peripheral neuropathy following dermal exposure to 2,4-D have been reported in the literature (Goldstein et al, 1959; Todd, 1962; Berkeley and Magee, 1963; Wallis et al, 1970; Halts, 1980). Signs and symptoms of a symmetric, "dying back," sensorimotor neuropathy began within 1-2 weeks after exposure. While nerve conduction times were at or slightly below the lower limit of normal, electromyography revealed denervation phenomena in the most severely affected patients. Recovery was slow with some residual deficits.

Epidemiologic studies of occupational exposure to the phenoxy herbicides are discussed under the section on PCDDs and PCDFs.

3.7 2,4,5-Trichlophenoxyacetic Acid

2,4,5-Trichlorophenoxyacetic Acid (2,4,5-T) was widely used as a post-emergent herbicide for controlling woody plant growth until 1979, when many of its uses were curtailed by the US EPA. 2,4,5-T is a light tan solid produced by reacting 2,4,5-Trichlorophenol with chloroacetic acid under alkaline conditions. The esters are produced by reacting 2,4,5-T with the appropriate alcohol. 2,4,5-T may be contaminated with 2,3,7,8-TCDD, HCDD, and perhaps some PCDFs. Most commercial preparations contain the ester or amine salt. The amine salts are soluble in water while the esters are emulsifiable in water and soluble in most oils.

2,4,5-T is rapidly absorbed from the gastrointestinal tract in healthy male volunteers (Matsumura, 1970; Gehring et al, 1973; Kohli et al, 1974). Rates of skin absorption vary from 0.22-1.13 mg/sq ft/hr for spray concentrations of 2-32 lb 2,4,5-T/100 gal (GRB, 1981). Elimination is first order with a plasma half life of 19-23 hours. Metabolites have been detected in animals but not in humans. 2,4,5-T propylene glycol butyl ether ester is rapidly hydrolyzed to the free acid in rats (Young et al, 1981).

The LD_{50} of 2,4,5-T and its derivatives ranges from 100 to 940 mg/kg in various species (JRB, 1981). The free acid appears to be more toxic than the salts or esters. Acute toxic effects in animals include anorexia, vomiting, diarrhea, locomotive disturbances, and depression. Histopathologic changes are nonspecific. The mechanism of toxic action of 2,4,5-T is unknown.

2,4,5-T with less than 1 ppm TCDD produced cleft palate and growth

retardation in mice (Roll, 1971; Hood et al, 1979). 2,4,5-T increased the incidence of tumors in C3Hf mice (Muranyi-Kovacs et al, 1976). Tumor incidence was not increased, however, in other strains of mice or in other animal species.

The health effects observed in humans after chronic exposure to 2,4,5-T are usually ascribed to the 2,3,7,8-TCDD contaminant. There are no reported cases of acute poisoning with pure 2,4,5-T in humans.

3.8 Polychlorinated Dibenzo-p-Dioxins (PCDDs) and Polychlorinated Dibenzofurans (PCDFs)

PCDDs and PCDFs are two series of tricyclic aromatic compounds which are inadvertantly formed during the synthesis of chlorinated phenols and their derivatives. The dibenzo-p-dioxin and dibenzofuran nuclei can hold from one to eight chlorine atoms. The numbers of possible positional PCDD and PCDF isomers are given in Table 3. Each of the 75 PCDD and 135 PCDF isomers may have different chemical, physical, and toxicological properties. As a general trend in both series, solubility in most solvents and volatility decrease with an increasing number of chlorine atoms.

Levels of PCDDs and PCDFs reported in mono-, di-, and pentachlorophenols are shown in Table 4. PCDDs do not appear to be common contaminants of mono- and di-chlorophenols. The levels of PCDFs in these compounds are unknown. Hexa, hepta, and octa-dibenzo-p-dioxins and dibenzofurans have been repeatedly detected in PCP. The tetra- and penta-dibenzofuran congeners have been detected in numerous samples of 2,4,5-T. 2,4-D is frequently contaminated with DCDD, tri-CDD, and 1,3,6,8-TCDD. (Table 5).

The various PCDD and PCDF isomers vary considerably in toxic potential. The LD_{50}s range from 0.6-2.0 mcg/kg for 2,3,7,8-TCDD in guinea pigs to over

TABLE 3. POSSIBLE NUMBER OF POSITIONAL ISOMERS OF PCDDs AND PCDFs.

Chlorine Substitution	Number of Isomers PCDDs	PCDFs
mono-	2	4
di-	10	16
tri-	14	28
tetra-	22	38
penta-	14	28
hexa-	10	16
hepta-	2	4
octa-	1	1
	75	135

TABLE 4. PCDDs and PCDFs Reported in o-chlorophenol, 2,4-Dichlorophenol and Pentachlorophenol

Chlorophenol	PCDDs, ppm[a] mono-CDD	DCDD	tri-CDD	TCDD	penta-CDD	hexa-CDD	hepta-CDD	OCDD	Data Source
Monochlorophenol									
o-chlorophenol	ND	ND	ND	ND	ND	ND	ND	ND	Firestone et al, 1972
o-chlorophenol	--	--	--	0.037 (2,3,7,8)[b]	--	--	--	--	Esposito et al, 1972
Dichlorophenol									
2,4-dichlorophenol	ND	ND	ND	ND	ND	ND	ND	ND	Firestone et al, 1972
Pentachlorophenol									
PCP (Dowcide 7)	--	--	--	--	--	9	235	250	Buser, 1975
PCP	--	--	--	ND (0.5)	--	10-100	100-1000	100-1000	Woolson et al, 1972
Na-PCP (1967)	ND	ND	ND	ND	ND	14	14.5	3.8	Firestone et al, 1972
Na-PCP (1969)	ND	ND	ND	ND	ND	20	11.3	3.3	"
PCP (1970)	ND	ND	ND	ND	ND	39	49	15	"
PCP (1970)	ND	ND	ND	ND	ND	35	23	ND	"
PCP (1967)	ND	ND	ND	ND	ND	0.17	ND	ND	"
PCP (1969)	ND	ND	ND	ND	ND	13	47	ND	"
PCP (1970)	ND	ND	ND	ND	ND	0.19	2.1	5.3	"
PCP (1970)	ND	ND	ND	ND	ND	15	23	15	"
PCP (1978)	--	--	--	ND(0.1)	--	19	140	432	USEPA, 1978
Pentachlorphenate	--	--	--	--	--	--	+	+	Jensen and Renberg,1972
PCP formulation	--	--	--	--	--	--	870	50-3300	"
PCP (technical grade)	--	--	--	ND	--	33-42	19-24	7-11	Villanueva et al,
PCP (reagent grade)	--	--	--	ND	--	0.02-0.03	0.04-0.09	0.02-0.03	"
PCP (many samples	--	--	--	ND	--	9-27	90-135	575-2510	"
PCP's (17)	--	--	--	--	--	0-23	--	0-3600	"

(continue

Table 4 (cont.)

	PCDDs, ppm[a]								
	mono CDF	DCDF	tri-CDF	TCDFs	penta-CDFs	Hexs-CDFs	Hepta-CDFs	Octa-CDFs	Data Source
PCP or PCP-Na (7)	--	--	--	--	--	0.03-10	0.06-180	5.5-370	Buser and Bosshardt,1976
PCP (Dowcide 7 1970)	--	--	--	--	--	4	125	2500	USEPA, 1978
PCP (Dowcide 7 1970) (distilled)	--	--	--	--	--	1.0	6.5	15	"
PCP	--	--	--	--	--	9-27	--	575-2510	Johnson, 1973
Na-PCP(Dowcide G 1978)	--	--	--	--	--	ND-2	1-12	4-173	"
	PPDFs, ppm								
Pentachlorophenol									
PCP (USA)	--	--	--	0.9	4	32	120	130	Rappe, 1978
PCP (USA)	--	--	--	--	--	30	80	80	USEPA, 1978
PCP (USA)	--	--	--	$\leq$0.4	40	90	400	260	Goldstein, 1977
PCP (Germany)	--	--	--	--	--	0.03	0.8	1.3	Rappe, 1981
PCP	--	--	--	0.20	0.20	13	70	55	Buser and Bosshardt, 1976

[a]Key to abbreviations and symbols: ND = Not detected (minimum detection level, ppm). Other numbers in parentheses indicate year chlorophenol sample was obtained, or specific dioxin detected.
-- = Not analyzed or not reported.

[b]Presence of 2,3,7,8-TCDD confirmed but not quantitatively reported.

TABLE 5. PCDDs IN 2,4,5-T AND 2,4-D

Pesticide Sample	PCDDs ppm Mono-CDD	DCDD	Tri-CDD	TCDD	Penta-CDD	Hexa-CDD	Hepta-CDD	OCDD	Data Source
2,4,5-T (1973)	--[a]	--	--	10.0	--	10.0	--	--	Fishbein, 1973
2,4,5-T Acid (1952)	--	--	--	1.10[b]	--	--	--	--	Rappe and Buser, 1980
2,4,5-T Ester	--	--	--	0.50	--	--	--	--	"
2,4,5-T Ester	--	--	--	0.05	--	--	--	--	"
2,4,5-T Ester (1960)	--	--	--	0.40	--	--	--	--	"
2,4,5-T Ester (1962)	--	--	--	0.95	--	--	--	--	"
2,4,5-T Ester (1966)	--	--	--	0.10	--	--	--	--	"
2,4,5-T Ester (1967)	--	--	--	0.05	--	--	--	--	"
2,4,5-T Ester (1967)	--	--	--	0.22	--	--	--	--	"
2,4,5-T Ester (1967)	--	--	--	0.18	--	--	--	--	"
2,4,5-T Acid (1964)	--	--	--	4.8	--	--	--	--	"
2,4,5-T Acid (1969)	--	--	--	6.0	--	--	--	--	"
Herbicide Orange	--	--	--	0.12	--	--	--	--	"
Herbicide Orange	--	--	--	1.1	--	--	--	--	"
Herbicide Orange	--	--	--	5.1	--	--	--	--	"
2,4-D Ester (1980)	--	--	0.35	0.23[c]	--	--	--	--	Cochrane et al, 1982
2,4,-D Ester (1980)	--	2.72	2.08	0.72	--	--	--	--	"
2,4-D Ester (1980)	--	4.20	1.63	1.75	--	--	--	--	"
2,4-D Ester (1980)	--	0.10	0.64	0.32	--	--	--	--	"
2,4-D Ester (1980)	--	1.24	1.82	0.85	--	--	--	--	"
2,4-D Ester (1980)	--	0.11	0.93	0.49	--	--	--	--	"
2,4-D Ester (1980)	--	0.10	0.68	0.32	--	--	--	--	"
2,4-D Ester (1980)	--	--	--	--	--	--	--	--	"

TABLE 5 (cont.) PCDDs in 2,4,5-T and 2,4-D

Pesticide Sample	PCDDs ppm Mono-CDD	DCDD	Tri-CDD	TCDD	Penta-CDD	Hexa-CDD	Hepta-CDD	OCDD	Data Source
2,4,-D Ester (1980)	--	0.20	0.16	0.21	--	--	--	--	Cochrane et al, 1982
2,4-D Salt (1980)	--	--	0.038	0.054	--	--	--	--	"
2,4-D Salt (1980)	--	--	0.58	0.28	--	--	--	--	"
2,4-D Salt (1980)	--	0.005	0.054	0.02	--	--	--	--	"
2,4-D Salt (1980)	--	--	--	--	--	--	--	--	"
2,4-D Salt (1980)	--	0.033	0.53	0.21	--	--	--	--	"
2,4-D Salt (1980)	--	--	--	--	--	--	--	--	"
2,4-D Salt (1980)	--	--	--	--	--	--	--	--	"
2,4-D (1972)	--	--	--	--	--	0.5-10	--	--	Woolson et al, 1972

[a]Not detected, not tested, or not reported.

[b]Levels of TCDD in this and subsequent 2,4,5-T formulations are of the 2,3,7,8 isomer.

[c]Levels of TCDD in this and subsequent 2,4-D formulations are of the 1,3,6,8 isomer.

4.0×10^6 mcg/kg for OCDD in mice. (Esposito et al, 1980). The LD_{50} for 2,3,7,8-TCDF in guinea pigs is 2 to 4-fold higher than that reported for 2,3,7,8-TCDD (More et al, 1979). Chemical structural requirements for toxicity in both series appear to be chlorine substitutions at positions 2,3, and 7 with at least one hydrogen remaining on the nucleus.

The mechanism of toxic action of PCDDs and PCDFs is still unknown. A cytosol receptor has been identified in mouse and rat liver which binds certain PCDDs and corresponds to their potency to induce aryl hydrocarbon hydroxylase activity (Huff et al, 1980). The ability of these compounds to induce aryl hydrocarbon hydroxylase correlates with their toxicity in animal studies. Iron deficiency protects mice from some of the toxic effects of 2,3,7,8-TCDD, but the mechanism of this interaction is unclear (Jones and Sweeney, 1982).

The toxicokinetics of 2,3,7,8-TCDD have been studied in several species including rats, guinea pigs, and monkeys (Piper at al, 1973; Rose et al, 1976; Nolan et al, 1979; Gasiewicz and Neal, 1978; Van Miller, et al, 1976). 2,3,7,8-TCDD is moderately well absorbed from the gastrointestinal tract in most species. There are significant differences in the tissue distribution of this compound among various animal species. Following a single administration of 14 C-2,3,7,8-TCDD, the largest percentage of the dose appears in the liver in rats and in the adipose tissue in guinea pigs and monkeys. Materials other than 2,3,7,8-TCDD constitute a significant fraction of the 14 C activity in the feces, but no metabolites have yet been identified. After repeated oral dosing in the rat, a fraction of the 14 C acivity may also appear in the urine. The excretion of a single oral dose of 14 C-2,3,7,8-TCDD in rats follows a one-compartment, open model with a half life of 31 days.

The toxicokinetics of other PCDDs can differ considerably from those of 2,3,7,8-TCDD. Norback (1975) studied the toxicokinetics of OCDD in the rat following chronic oral dosing: OCDD concentrated in rat liver and was excreted mainly by the urinary system with a half-life of about 3 weeks. Tulp and Hutzinger (1978) studied the rat metabolism of a series of PCDDs. They demonstrated that some PCDDs can be metabolized by hydroxylation at the lateral (2,3,7 and/or 8) positions in the molecule. When these positions are blocked by chlorine atoms, metabolism via epoxide formation is much less likely to occur.

Decad et al (1982) studied the toxicokinetics of 2,3,7,8-TCDF in guinea pigs, rats, and monkeys. Gastrointestinal absorption of 2,3,7,8-TCDF was nearly complete in rats and guinea pigs. The liver was the major initial depot for 2,3,7,8-TCDF in all three species with lesser amounts in adipose tissue, skin, and muscle. Rats, and to a lesser extent, monkeys were able to metabolize 2,3,7,8-TCDF whereas guinea pigs could not. The whole body half-life of TCDF in guinea pigs, monkeys, and rats was 20, 8, and 2 days respectively.

The metabolism of PCDF isomers in man may depend on the positions of the chlorine atoms on the dibenzofuran nucleus. Rappe analyzed liver samples for PCDFs from two patients with Yusho disease and compared the distribution of the isomers to that found in the ingested rice oil (Rappe et al, 1981). He found that the PCDF isomers which had apparently been excreted had two vicinal hydrogenated carbon atoms in at least one of the two rings; these unblocked positions are presumably involved in the metabolism by forming epoxides.

The toxic effects produced by PCDDs and PCDFs vary quantitatively and qualitatively among different species. Within a given species, the effects produced by the toxic PCDD and PCDF isomers are similar to those of 2,3,7,8-TCDD, differing mainly in the intensity of toxic effect. In all laboratory animals the lethal effect is slow and ensues days or weeks after a single dose. The spectrum of acute toxic effects of 2,3,7,8-TCDD in mice, guinea pigs, and monkeys is presented in Table 6. The most striking finding in most species is substantial loss of body fat. Involution of the thymus and testicular alterations have been observed in all species studied. Biochemical effects of 2,3,7,8-TCDD include induction and/or suppression of various enzyme systems, changes in porphyrin metabolism, and alteration of lipid profiles. 2,3,7,8-TCDD and HCDD have produced chloracne in animals. Rats fed TCDD were found to have decreased thyroxine, free thyroxine index, glucose, and insulin levels in the serum (Potter et al, 1983). Doses of 2,3,7,8-TCDD which do not produce overt clinical or pathological changes may still be capable of causing immunosuppression. (Thigpen et al, 1975).

Moore et al (1979) studied the toxicity of TCDF in mice, guinea pigs, and monkeys. The toxic effects in guinea pigs and monkeys were similar to those produced by 2,3,7,8-TCDD but required 2-20 fold higher doses of TCDF. Mice did not demonstrate clinical signs of toxicity at a dose of TCDF which was 23 fold higher than the TCDD $LD_{50/30}$. The interspecies variation in acute toxicity may be due to differences in detoxification metabolism (Decad et al, 1982).

2,3,7,8-TCDD increases the incidence of neoplasms in rats and mice. (Van Miller et al, 1977; Kociba et al, 1978; Toth et al, 1979). The data implicating 2,3,7,8-TCDD as a mutagen are conflicting, and it is unclear whether 2,3,7,8-TCDD acts as an initiator or a promotor. Carcinogenecity studies of other

Table 6. Summary of Acute Toxicity Effects of 2,3,7,8-TCDD[a]

	Mice	Guinea pigs	Monkeys (female)
Thymus involution	+++	+++	+++
Spleen reduction (white pulp)	+	+	+
Bone-marrow hypoplasia	±	++	+
Liver, megalocytosis/degeneration	+++	-	-
Bile-duct hyperplasia	±	±	+++
Testicular degeneration	++	+++	N/A
Renal-pelvis hyperplasia	-	++	+
Urinary-bladder hyperplasia	-	++	-
Adrenal-cortical atrophy (Zona Glomerulus)	-	++	-
Hemmorhage: Intestinal	+	+	-
Adrenal	-	++	-
Acites	++	-	+
Cutaneous lesions	-	-	+++

[a]Source: Esposito, Tiernan, and Dryden, 1980

Key as follows:
- - no effect
- + mildly affected
- ++ moderately affected
- +++ severely affected

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PCDDs are in progress. The carcinogenic potentials of PCDFs have not been studied.

2,3,7,8-TCDD is teratogenic in mice and hamsters. The threshold teratogenic dose in mice was estimated to be 0.1 mcg per day (Smith et al, 1976). 2,3,7,8-TCDD has been shown to be fetotoxic in a wide variety of species, including primates. HCDD was teratogenic in rats at a dose of 100 mcg/kg per day (IARC, 1977) There is as yet no data on the fetotoxic potentials of PCDFs in animals.

The toxic effects of 2,3,7,8-TCDD in man are summarized in Table 7. The toxic effects most consistently observed in occupational studies are chloracne, liver dysfunction, neuropsychiatric disturbances, and abnormalities in porphyrin metabolism. Table 8 summarizes the findings of the morbidity studies of workers exposed to 2,3,7,8-TCDD to date. The few follow-up studies which have been done show resolution of gross liver dysfunction and porphyrin abnormalities following removal from exposure. (Pazderova-Vijlupkova et al, 1981; Suskind, 1984).

Several of the occupational exposures occurred as the result of uncontrolled exothermic reactions during the production of trichlorophenol. A similar process accident at Seveso, Italy in 1976 resulted in widespread community exposure to 2,3,7,8-TCDD. Health effects included chloracne, primarily in children, and peripheral neuropathy in a small percent of those exposed (Pocchiari et al, 1979).

The epidemiologic studies on the carcinogenecity of TCDD are summarized in Table 9. While individual occupational mortality studies reveal no excess of cancer, the pooled data suggest an excess of soft tissue sarcoma (Honchar and Halperin, 1981).

Table 7. Toxic Effects of 2,3,7,8-Tetrachlorodibenzo-*p*-dioxin in Man.[a]

Effects
DERMATOLOGICAL
Chloracne
Porphyria cutanea tarda
Hyperpigmentation and hirsutism
INTERNAL
Liver damage[b]
Elevated serum hepatic enzyme levels
Disorders of fat metabolism
Disorders of carbohydrate metabolism
Cardiovascular disorders
Urinary tract disorders
Respiratory disorders
Pancreatic disorders
NEUROLOGICAL
Polyneuropathies (perpheral neuritis)
Lower extremity weakness
Sensory impairments (sight, hearing, smell, taste)
PSYCHIATRIC
Neurasthenic or depressive syndromes

[a]Source: Huff, Moore, Saracci, and Tomatis, 1980

[b]Mild fibrosis, fatty changes, hemofuscin deposition and parenchymal-cell degeneration were observed in a few cases.

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TABLE 8. REPORTED OCCUPATIONAL EXPOSURES IN CHLORINATED PHENOLS RESULTING IN HUMAN ILLNESS[a]

Year, Place, and chemical(s)	Type of exposure and no. of cases	Effects on the skin	Neurological effects	Effects on the liver and serum lipids	Other effects	References
1936 Michigan Tetrachlorophenol 2-(2-chlorophenyl) phenol	Production 21	Chloracne, hyperkeratosis			Fatigue, weight loss	Butler, 1937
1936 Mississippi Tetrachlorophenol	Wood treatment 300-400	Chloracne, facial erythema, vesiculation, ulceration, hyperkeratosis, hyperpigmentation			Fatigue, colored urine, urinary problems, venous thrombosis	Anonymous, 1936: Stingily, 1940
1949 West Virginia Trichlorophenol 2,4,5-T	Explosion 117 Production 111	Chloracne, facial erythema, hyperpigmentation, melanosis	Nervousness, irritability, insomnia, personality change, depression, headache, vertigo, pain and weakness lower extremeties, paresis, peripheral neuropathy, abnormal nerve biopsy (loss of myelin)	Hepatomegaly, abnormal liver function, toxic hepatitis, elevated triglycerides and cholesterol	Fatigue, weight loss, weakness, decreased libido, impotence, intolerance to cold, increased susceptibility to infection (especially respiratory)	Ashe and Suskind, 1949, 1950; Suskind, 1953; Suskind, 1977
1949 Germany Trichlorophenol Tetrachlorophenol Pentachlorophenol	Production, Industrial Laboratory 17	Chloracne, hyperpigmentation, scarring	Lower extremity pain and weakness, paresis without atrophy, paresthesia, polyneuritis	Abnormal liver function, cirrhosis	Fatigue, severe bronchitis, decreased libido, impotence, bursitis, myocardial damage	Baader and Bauer, 1951

1952 Germany Trichlorophenol	Production 31	Chloracne, hyperpigmentation	Lower extremity pain and weakness, paresthesia, memory and concentration deficits, sleep disturbances, hypersomnolence, abnormal psychological tests (apathy, dulled emotional response)	Toxic hepatitis, abnormal liver biopsy	Fatigue, chronic bronchitis, persistent blepharoconjunctivitis, myocardial damage, intolerance to alcohol	Suskind, 1977
1953 Germany Trichlorophenol	Explosion 55	Chloracne	Sensory impairment of smell, taste, hearing; tendency to orthostatic collapse, limited paresis, peripheral neuropathy, reading difficulties	Toxic hepatitis	Fatigue, drowsiness, bronchitis, laryngitis, blepharoconjunctivitis, hemorrhagic pleuritis, myocardial damage, increased susceptibility to infection	Goldman, 1973
1956 France Trichlorophenol 1966 France Trichlorophenol	Production 17 Explosion 21	Chloracne	Peripheral neuropathy	Toxic hepatitis, elevated tryglycerides and cholesterol		Dugois et al, 1956; Dugois et al, 1968
1956 New Jersey Trichlorophenol	Production 29	Chloracne, hyperpigmentation, hypertrichosis, acquired porphyria cutanea tarda	Clinical examination normal	Abnormal liver function, abnormal liver biopsies (parenchymal cell degeneration, fluorescence)	Right upper quadrant pain	Bleiberg et al, 1964
1963 Holland Trichlorophenol 2,4,5-T	Explosion 106	Chloracne, facial erythema	No information	Liver function normal	Fatigue	Vos et al, 1977

1964 USSR Trichlorophenol 2,4,5-T	Production 128	Chloracne	Headache, loss of memory, somnolence, sleeplessness, increased sweating		Fatigue, joint pain, stomach pain	Telegina and Bikbulatova, 1970
1968 England Trichlorophenol	Explosion 79	Cloracne, facial erythema		Abnormal liver function	Transient glycosuria, mild conjunctivitis	May, 1973; Jensen and Walker, 1965; Jensen et al, 1972
1965-1968 Czechoslovakia Trichlorophenol Pentachlorophenol 2,4,5,-T	Production 80	Chloracne, hyperpigmentation, hypertrichosis, scarring, acquired porphyria cutanea tarda	Lower extremity weakness and pain,somnolence, headache, insomnia, emotional and psychiatric disorders, peripheral neuropathy (confirmed by abnormal EMG)	Hepatomegaly, abnormal liver function, abnormal liver biopsies (mild steatosis, periportal fibrosis, fluorescence). Elevated triglycerides, phospholipids, and cholesterol	Fatigue, weight loss, abnormal blucose tolerance, no evidence of myocardial or renal damage or of increased eye inflammation or respiratory infection	Jiraskek et al, 1964; Pazderova-Vejlupkova et al, 1980; Pazderova-Vejlupkova et al, 1981
1969 New Jersey Trichlorophenol 2,4,5-T 2,4-D	Production 73 Followup of plant studied by Bleiberg (above)	Chloracne in 48, hypertrichosis in 16, hyperpigmentation in 30, no overt porphyria cutanea tarda	Lower extremity weakness, correlation between chloracne and hypomania scale on MMPI	No significant abnormalities	Eye irritation, mild uroporphyrinuria in one worker	Poland et al, 1971 (see Bleiberg et al, 1964)
1978 England Trichlorophenol no longer in production	Followup of 41 workers in 1968 explosion (above) 41	Chloracne		Elevated GGT, elevated triglycerides, elevated urinary D-glucaric acid		May, 1982

1949 West Virginia Trichlorophenol 2,3,5-T	226 Followup of plant studied by Ashe and Suskind (above)	Chloracne 70-residual 47-by history	Abnormal sensory findings in those with chloracne	Elevated GGT in those with chloracne	Decreased libido, sexual dysfunction	Moses et al, 1984
1949 West Virginia Trichlorophenol 2,4,5-T	204 Followup of plant studied by Ashe and Suskind and Moses et al (above)	Chloracne in 107 Actinic Elastosis			History of GI ulcer Lower pulmonary function in exposed smokers	Suskind and Hertzberg, 1984
1976 Seveso Trichlorophenol	No. not given ICMESA workers follow-up five years after explosion			Elevated Alk. Phos.	Elevated urinary porphyrins	Ghezzi et al, 1984

[a]
Source: Moses et al, 1984

Table 9 Epidemiologic Studies on the Carcinogenicity of TCDD.[a]

Type and Place of Exposure	Number of Cases	TCDD Level of Exposure	Time Elapsed Since Exposure	Frequency of Cancer Death	Reference
Accidental, Monsanto, USA	228	Unknown	30 years	No Excess	Zack, 1980
Accidental, Boehringer, RFG	24	Unknown	28 years	No Excess	Krause, 1978
Accidental, Basf, RFG	55	Unknown	27 years	Excess of Stomach Cancer	Theiss, 1982
Accidental, Philips, Netherland	50	10,000 ppb	17 years	No Excess	Vos, 1978
Accidental, Dow Chemical, USA	60	Unknown	16 years	No Excess	Cook, 1980
Accidental, Spolana, Czechoslovakia	78	24,200 ppb	15 years	No Excess	Jirasek, 1978
Accidental, Coalite, UK	79	400 ppb	12 years	No Excess	May, 1980
Accidental, Chemie Werke, Linz, Austria	50	140 ppb	7 years	----	----
Herbicide Spraying, Sweden, Backsprayers	348	0.00315 ppt	Over 10 years	Excess of Stomach Cancer	Axelson, 1979
Herbicide Spraying, Finland, Backsprayers	1960	0.00315 ppt	Over 10 years	No Excess No Lymphomas	Rihmaiki, 1980
Herbicide Contamination, Sweden	72	0.0001 ppb 0.1 ppt	Over 10 years	Excess of Lymphomas	Hardell, 1979
Agent Orange Spraying USAF, VietNam	1242	1.9 ppm	Over 13 years	No Excess	Lathrop, 1983

[a] Source: Reggiani, 1980

A review of these cases revealed that several were not true soft tissue sarcomas; moreover, exposure in a few of the cases was minimal (Fingerhut et al, 1984). Swedish case-control studies of soft tissue sarcoma found an association with previous exposure to phenoxy acids or chlorophenols (Hardell et al, 1979; Eriksson et al, 1979)

The Yusho cases provide our only data on the human toxicity of PCDFs. Yusho disease was caused by ingestion of rice oil accidentally contaminated with PCDFs, PCBs, and polychlorinated quarterphenyls; as such it is difficult to separate the effects of the various toxic principles. The clinical symptomatology of the Yusho cases is presented in Table 10. The Yusho oil was clearly fetotoxic. There is as yet no data on the carcinogenic potential of PCDFs in man.

Table 10. Clinical Symptomology of Yusho Cases, 1969-1972.[a]

Effects	Percent
Skin Acneform eruptions, distinctive hair follicles, red plaques on limbs, dark brown pigmentation of nail, skin and mucous membranes, itching, sweating of palms.	82-87%
Ocular manifestation Increased eye discharge, swelling of the upper eyelids, hyperemia of conjunctives, transient visual disturbance.	83-88
Jaunidce No abnormalities of liver functions in the majority of cases.	10
Numbness of the limbs, feeling of weakness, spasm of the muscles	32-39
Reduced sensory and motor nerve conduction velocity in few cases	9
Hearing difficulties	18
Headaches, vomiting, diarrhea	17-39
Chronic Bronchitis Lower serum Ig A and Ig M. PCB in the sputum	40
Irregular menstrual cycles	60
Dark brown skin pigmentation of newborn, which gradually faded away, retarded growth and abnormal teeth number and shape.	

[a]Source: Reggiani, 1980

4. DESIGN

4.1 Study Design

The design of this study combines elements of both cohort and cross-sectional designs. Two historical cohorts, exposed and non-exposed, will be identified and followed to ascertain their current vital and employment status. The health status of surviving members of both cohorts will be assessed by an in-depth medical survey to determine prevalence of clinical and sub-clinical disease states. Previous incidence of disease will be ascertained by subjects' self-reporting and verified by medical record review. Differences in health outcomes between the two cohorts will be compared statistically, after adjusting for the effects of confounding variables.

4.2 Ascertainment of Exposure

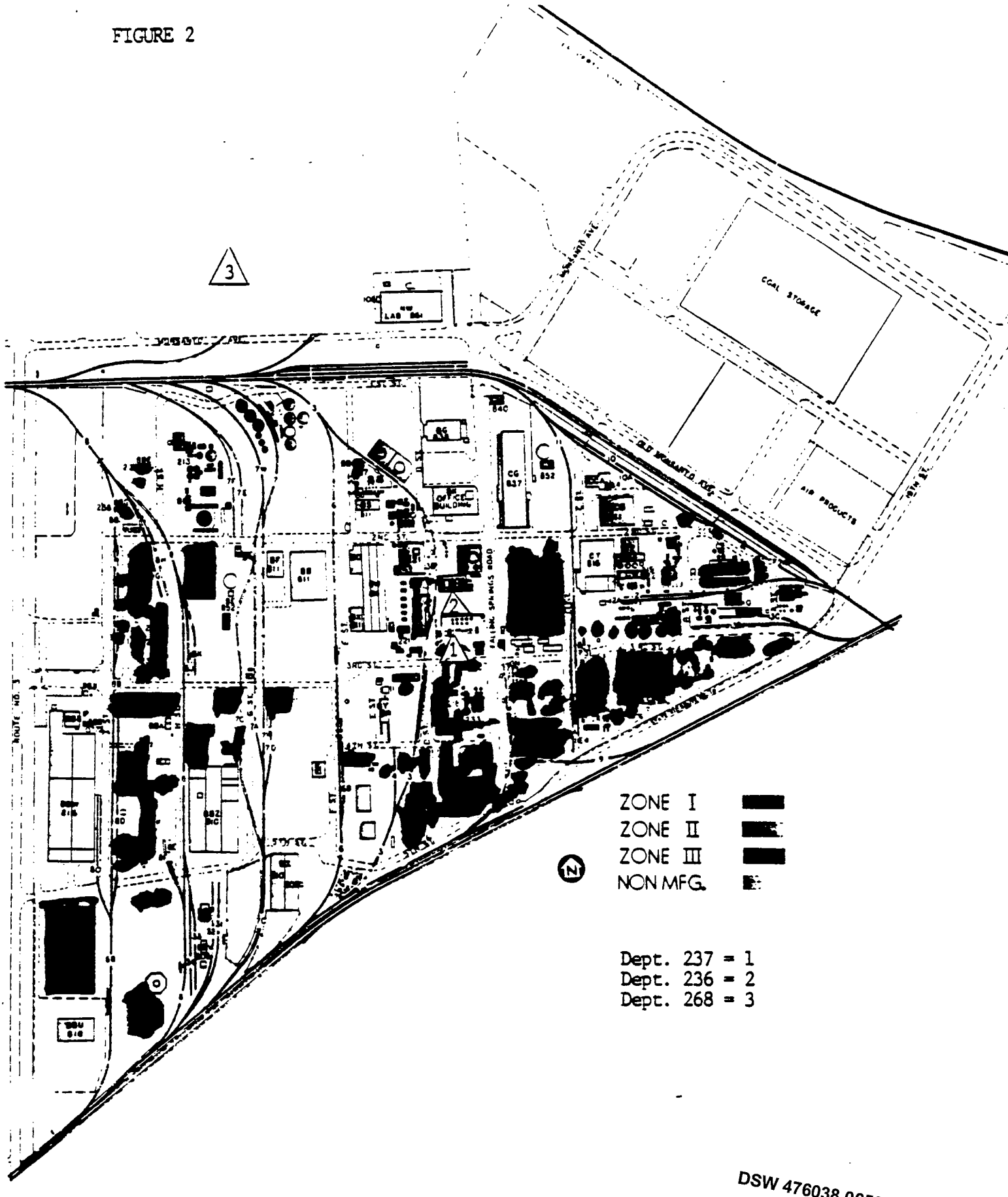
The departments where employees were most likely to be exposed to PCDDs include Departments 226 (Santobrite), 236 (Penta), 237 (chlorophenols) and Department 268 (agricultural esters). The locations of these departments within the plant are shown in Figure 2.

4.2.1 Processes

Departments 236 (Penta) and 226 (Santobrite)

The production of Pentachlorophenol (PCP) began at the Krummrich Plant in 1938. PCP was marketed in the flake form from 1939 to the late 1950's or early 1960's. At that time Penta (PCP)and Penta 60 (so called because it contained 60% PCP and 35% tetrachlorophenol) were offered in prilled form. From 1970, PCP was also offered in the 2000 lb. block form. The sodium salt of PCP (first called Santophen 20S and later Santobrite) was produced in powder, briquette, and 30% aqueous solution forms throughout its history.

FIGURE 2



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Santophen 20 P.A. (a PCP/pine oil/alcohol mixture) was only offered for a few years. The production of Na PCP was discontinued in 1972. The production of PCP and Penta 60 was discontinued in 1978. Over the years, the chemistry for the production of Penta and Santobrite remained essentially the same. The flow sheets for the process are shown in Figures 3 and 4. Department 236 was contained in a building which has since been dismantled.

Phenol, or chlorophenol fractions from the production of o-, p-, or 2,4-dichlorophenol were progressively chlorinated with subsequent increases in reaction temperature until the appropriate crystallization point was reached (for Penta, 174-182° C; for Penta 60, 145° C). Iron powder was first used as the catalyst; later, it was replaced by aluminum. Santobrite was simply the neutralization of Penta with sodium hydroxide.

Flaked Penta was produced by feeding molten Penta into a container from which it was picked up on the surface of a cold rotating drum. The material was flaked off the surface as the drum rotated against a stationary blade. The material was then mechanically conveyed to a packing area where it was bagged into cylindrical fiber backs or loaded into steel drums.

Prilled Penta was produced by dispersing molten Penta into fine streams using a shower head type prill plate. The molten streams would solidify by cooling with ambient air. The cooling chamber was an 8' diameter x 40' high prill tower. The prilled material would be further cooled in a Roto-Louvre cooler and would then be conveyed in a bucket elevator to a storage hopper to await packaging. The prills were packed into fiber packs or drums using a pneumatic packer. The air used for cooling passed through a Venturi scrubber where it was scrubbed with a dilute caustic solution.

FIGURE 3.

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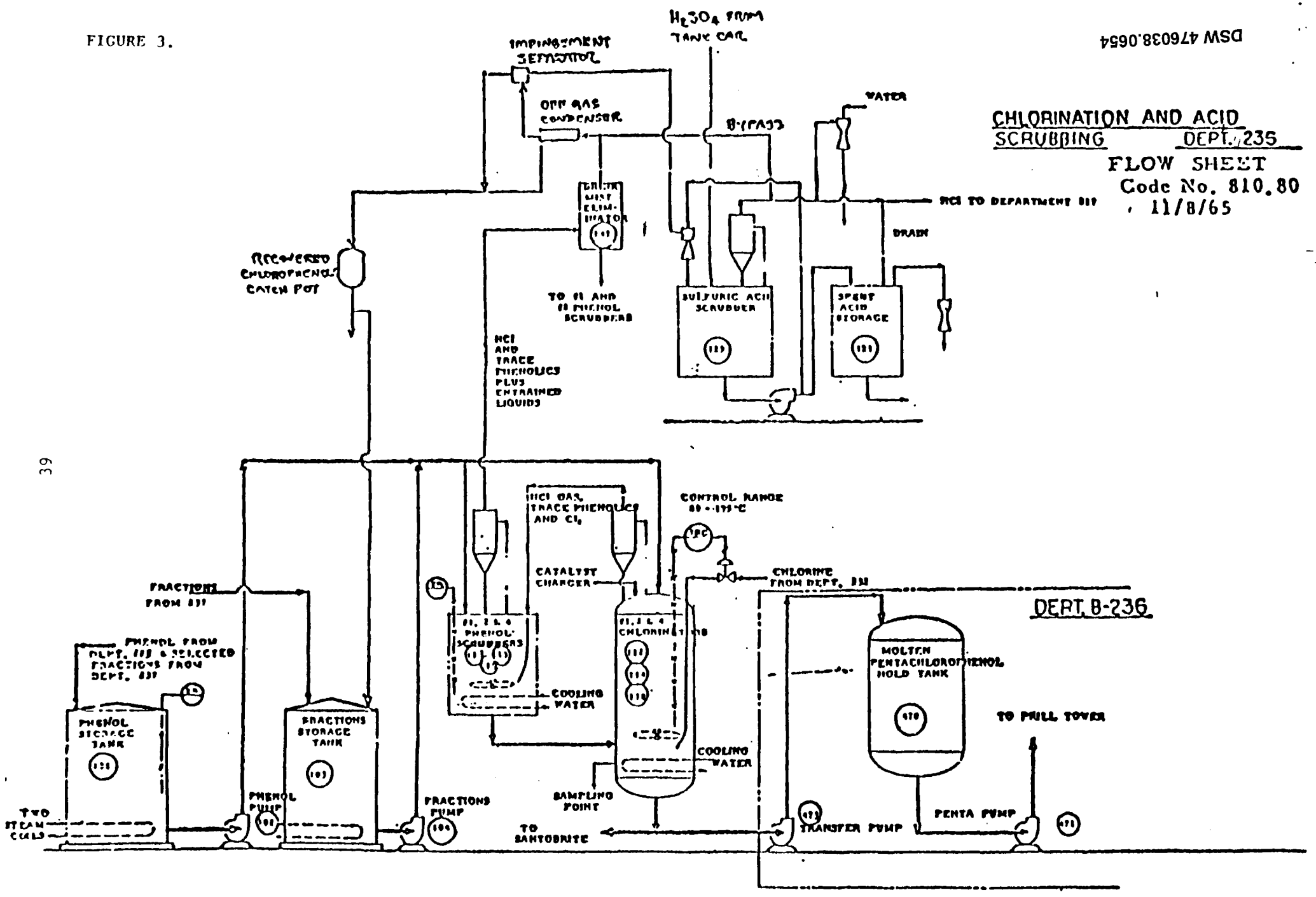
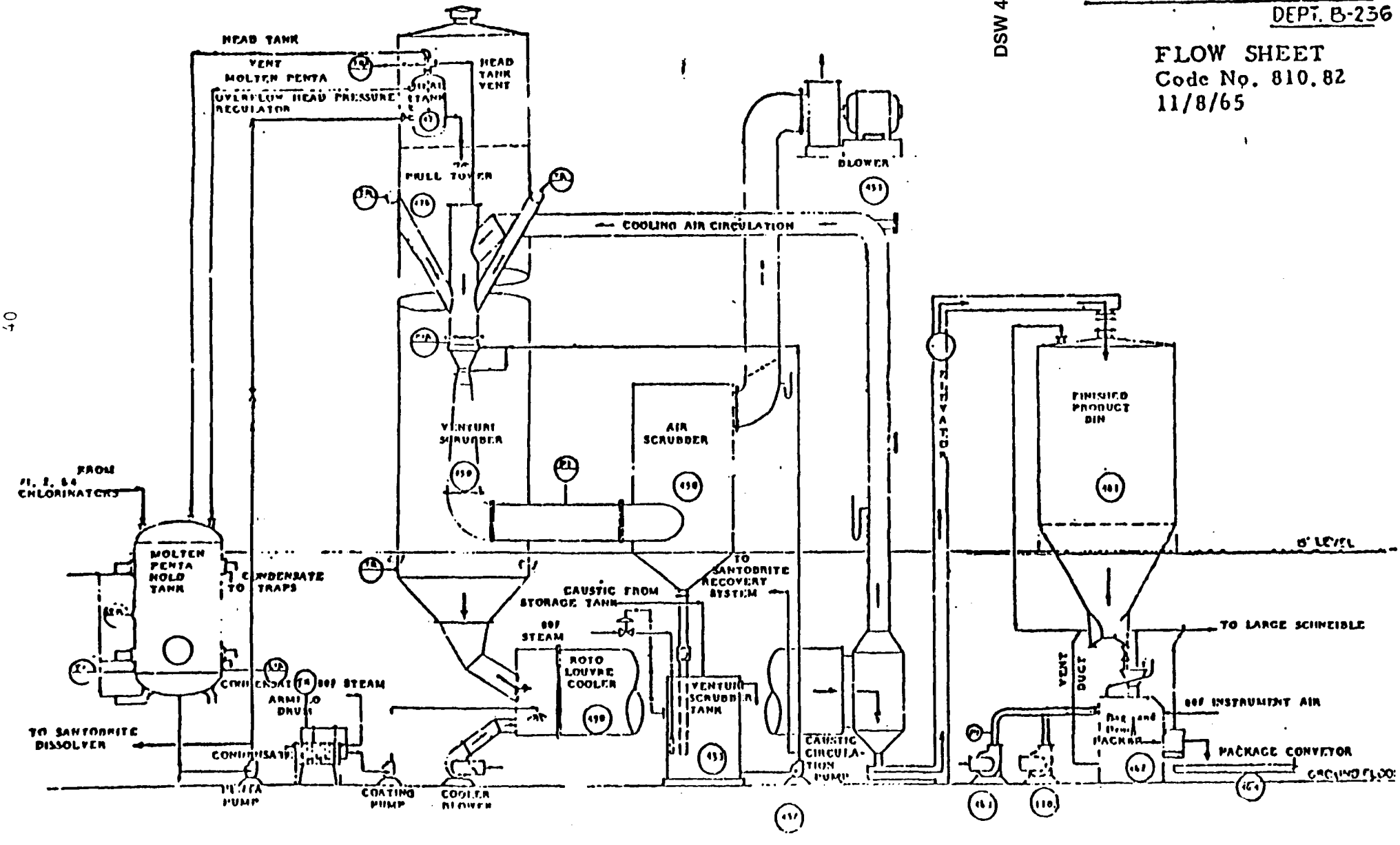


FIGURE 4.


PRILLING AND PACKAGING
DEPT. B-236
FLOW SHEET
Code No. 810.82
11/8/65
DSW 476038.0655
STLCOPCB4042819
HEAD TANK
VENT
MOLTEN PENTA
OVERFLOW HEAD PRESSURE REGULATOR
HEAD TANK VENT
PRILL TOWER
BLOWER
COOLING AIR CIRCULATION
VENTURI SCRUBBER
AIR SCRUBBER
FINISHED PRODUCT BIN
FROM #1, 2, &4 CHLORINATORS
MOLTEN PENTA HOLD TANK
CONDENSATE TO TRAPS
TO SANTOBRITE RECOVERY SYSTEM
CAUSTIC FROM STORAGE TANK
80# STEAM
ROTO LOUVRE COOLER
TO LARGE SCRUBBER
VENT DUCT
80# INSTRUMENT AIR
PACKAGE CONVEYOR
TO SANTOBRITE DISSOLVER
CONDENSATE
COATING PUMP
COOLER BLOWER
CAUSTIC CIRCULATION PUMP

Penta blocks were produced by pouring molten Penta into large tapered molds and allowing it to set. The material was removed from the mold by heating it with a welding torch.

Penta 60 was produced in the same way as molten Penta, except that the chlorination was terminated earlier (batch temperature 153-157° C; 145° crystalization point). It was prilled in the same manner as molten Penta.

A list of the job titles in Department 236 is given in Table 11.

Department 237 (Chlorophenols)

The production of chlorophenols began at the Krummrich plant in 1938 and continued through 1983. The principal products of this Department were o-chlorophenol, p-chlorophenol, and 2,4-dichlorophenol. P-chlorophenol was transferred to Department 239 where it was reacted with benzyl chloride to produce Santophen 1 (orthobenzyl p-chlorophenol). 2,4-dichlorophenol was transferred to Department 262 where it was reacted with chloroacetic acid to produce 2,4-dichlorophenoxyacetic acid. Chlorophenol fractions from Department 237 were also used as feedstock for production of pentachlorophenol in Department 236.

The flowsheets for the production of mono- and di-chlorophenols are shown in Figure 5. The overhead layout of the work area is shown in Figure 6. Department 237 was an open area located adjacent to Department 236.

The chemistry for the production of the chlorophenols appears to have remained unchanged over the years. Crude monochlorophenol was prepared by the batchwise chlorination of phenol at a temperature of 70-90° under a pressure of 2-5 psig in a Monel chlorinator. Crude mono contained 45%

TABLE 11. JOB DESCRIPTIONS LISTED IN THE MONSANTO COMPANY/ CHEMICAL WORKERS UNION WORKING AGREEMENTS

DSW 4760380657

DEPT	JOB DESCRIPTION	YEARS 37/38	38/39	39/40	40/41	41/42	42/43	43/44	44/45	45/46	46/47	47/48	48/49	49/51	51/52	52/53	53/54	54/55	55/56	56/58	58/59	59/61	61/63	63/65	65/68	68/71	71/74	74/77	77/80
226	Relief Foreman				X			X	X		X	X	X	X	X	X	X												
	Chief Operator	X			X		X	X	X		X	X	X	X	X	X	X												
	Operator	X			X			X	X		X	X	X	X	X	X	X												
	Helper Day	X			X			X	X		X	X	X	X	X	X	X												
	Repairman								X		X	X	X	X	X	X	X												
236	Relief Foreman				X			X	X		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
	Chief Operator						X	X	X		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
	Repairman								X		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
	Operator Building BD												X	X	X	X	X	X	X	X		X	X						
	Operator Building BO													X	X	X	X	X	X	X									
	Intermediate Op. Bldg. BD																X	X	X	X									
	B Operator - Oiler																X	X											
	Pelletizer Operator																X	X	X	X	X	X	X						
	Helper				X		X	X		X	X	X	X	X		X	X	X	X	X										
	Porter																X	X		X	X	X							
	A Operator Bldg. BD																			X	X	X		X	X				
	B Operator Bldg. BD											X	X	X	X	X				X	X	X	X	X	X				
	Briquette Operator Bldg. BD																			X	X	X	X	X	X				
	Premium Operator Bldg. BD																				X	X	X	X	X				
	Helper Porter																						X	X	X	X			
	Santobrite Operator																							X	X	X			
	Packer Helper																							X				X	X
	Operator				X			X	X		X	X	X																
	Premium Operator																									X			X

JOB DESCRIPTIONS LISTED IN THE MONSANTO COMPANY/ CHEMICAL WORKERS UNION WORKING AGREEMENTS

DEPT	JOB DESCRIPTION	YEARS																								
		37/38	38/39	39/40	40/41	41/42	42/43	43/44	44/45	45/46	46/47	47/48	48/49	49/51	51/52	52/53	53/54	54/55	55/56	56/58	58/59	59/61	61/63	63/65	65/68	68/71	71/74	74/77	77/80
236 (Cont'd)	A Operator																									X	X	X	X
	B Operator																									X	X	X	X
	Briquette Operator																									X	X	X	
	237 Operator																										X	X	X
237	Relief Foreman				X			X	X		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X			
	Operator	X			X			X													X	X	X	X	X	X			
	Helper Shift				X																								
	Operator New Dept.								X		X	X	X	X	X	X	X	X	X										
	Operator Old Dept.								X		X	X	X	X	X	X													
	Repairman										X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X			
	Helper Day										X	X	X	X	X	X	X	X	X	X	X	X	X						
	Chief Operator												X	X	X	X	X	X	X	X	X	X	X	X	X	X			
208	Premium Operator																						X	X	X	X			
	Intermediate Operator																						X	X	X	X			
	Utility Helper																								X				

FIGURE 5. PROGRESS FLOWSHEET FOR CHLOROPHENOLS

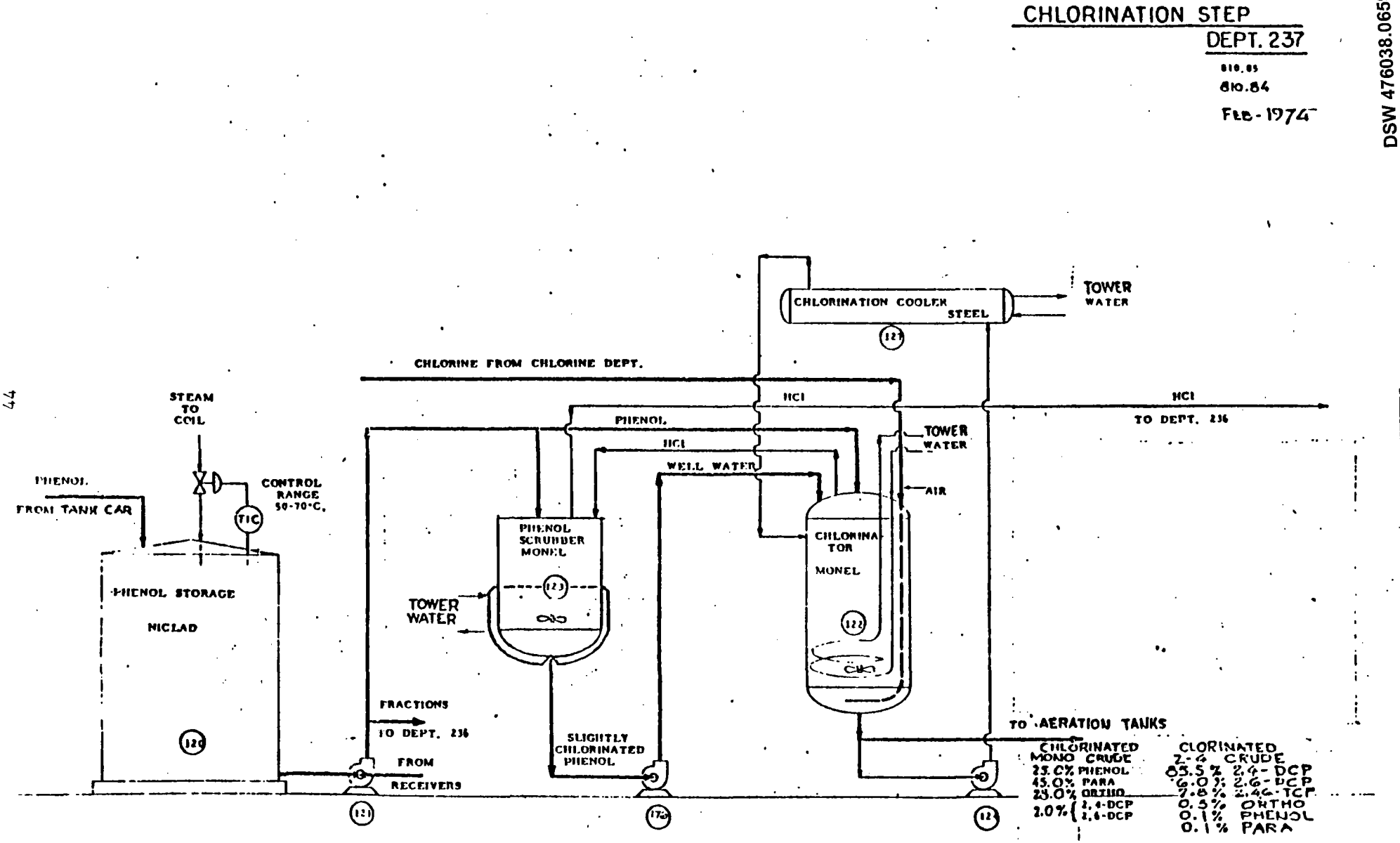
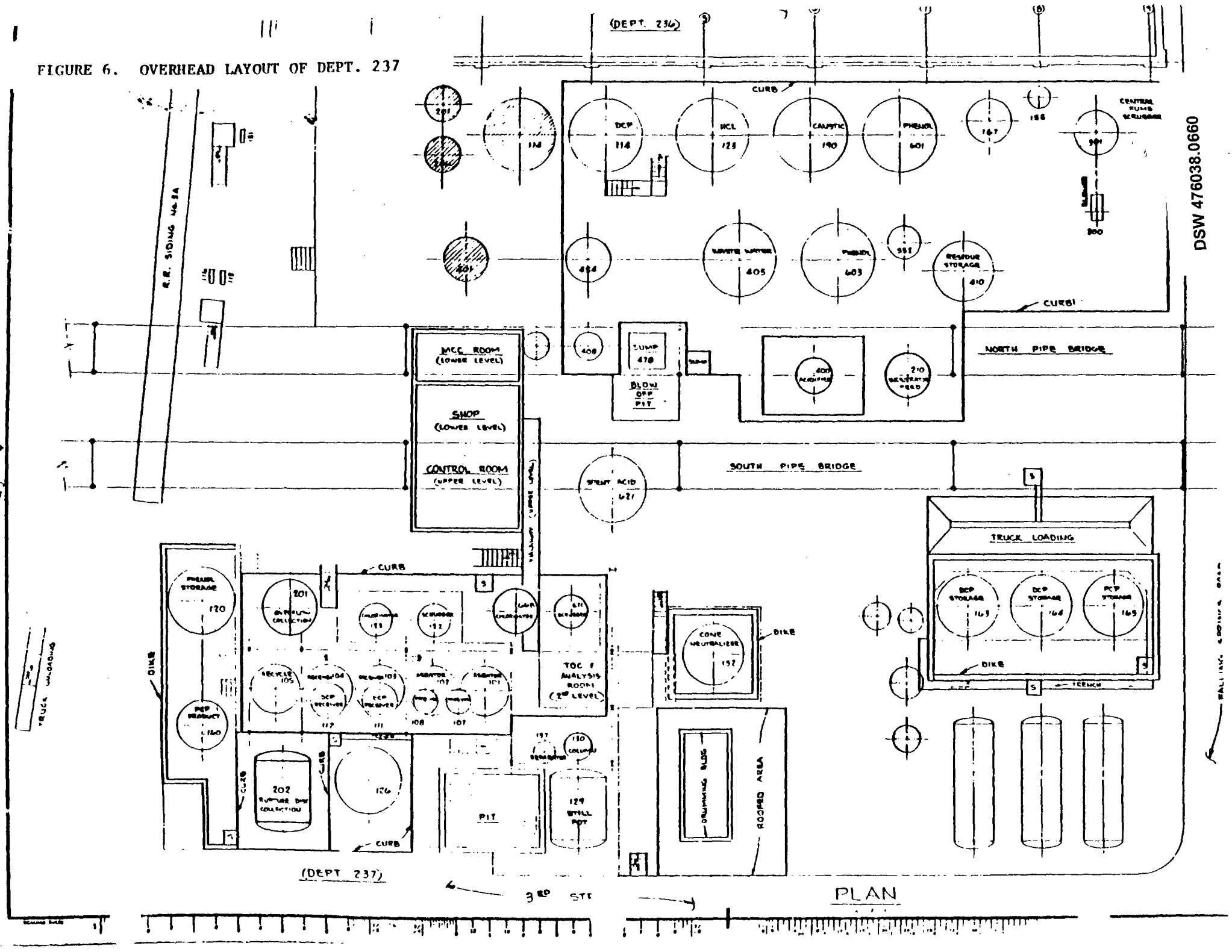


FIGURE 6. OVERHEAD LAYOUT OF DEPT. 237



parachlorophenol (P-CP), 28% orthochlorophenol (O-CP), and 2% dichlorophenol (DCP). The crude material was blown with air to remove dissolved HCl gas. The byproduct HCl gas was piped to Department 236's clean-up system.

The crude mono was neutralized with 50% caustic and distilled in a Linde tray fractionating column. Normal cuts from this batch distillation were water, wet fractions, O-CP, dry fractions, and P-CP. The dry fractions were transferred to Department 236 for use as raw materials in the production of molten pentachlorophenol.

Crude dichlorophenol was prepared by the batchwise chlorination of phenol at 80-90° C and at atmospheric pressure. The crude material contained 85.5% 2,4-DCP, 6.0% 2,6-DCP, 0.5% O-CP, 7.8% 2,4,6 trichlorophenol, 0.1% P-CP, and 0.1% phenol. The chlorinated crude material was blown with air to remove the bulk of dissolved HCl; the remaining HCl was neutralized with caustic.

The 2,4 isomer in the crude DCP was recovered by vacuum batch distillation in a Monel fractionating column. The remaining chlorophenol fractions stripped from the crude were transferred to Department 236 for use in pentachlorophenol production. The byproduct HCl was sent to Department 236's clean-up system.

A list of the job titles in Department 237 is given in Table 11.

Department 268 (Agricultural Esters)

The production of the butyl, isobutyl, and isooctyl esters of 2,4,5-trichlorophenoxyacetic acid (2,4,5-T) and 2,4-dichlorophenoxyacetic acid (2,4-D) began at the Krummrich plant in 1960 and continued through about 1970. The 2,4,5-T was shipped in from Monsanto's plant in Nitro, West Virginia. The 2,4-D was transferred to Department 268 from Department 262. The flow sheets for the pre-mix, reaction, and neutralization/filtration stages of the process are shown in Figures 7, 8, and 9, respectively.

FIGURE 7.

A. PRE-MIX (SLURRY)

DEPT. 268

BUTYL 2,4,5-T	894.12
ISO BUTYL 2,4,5-T	894.28

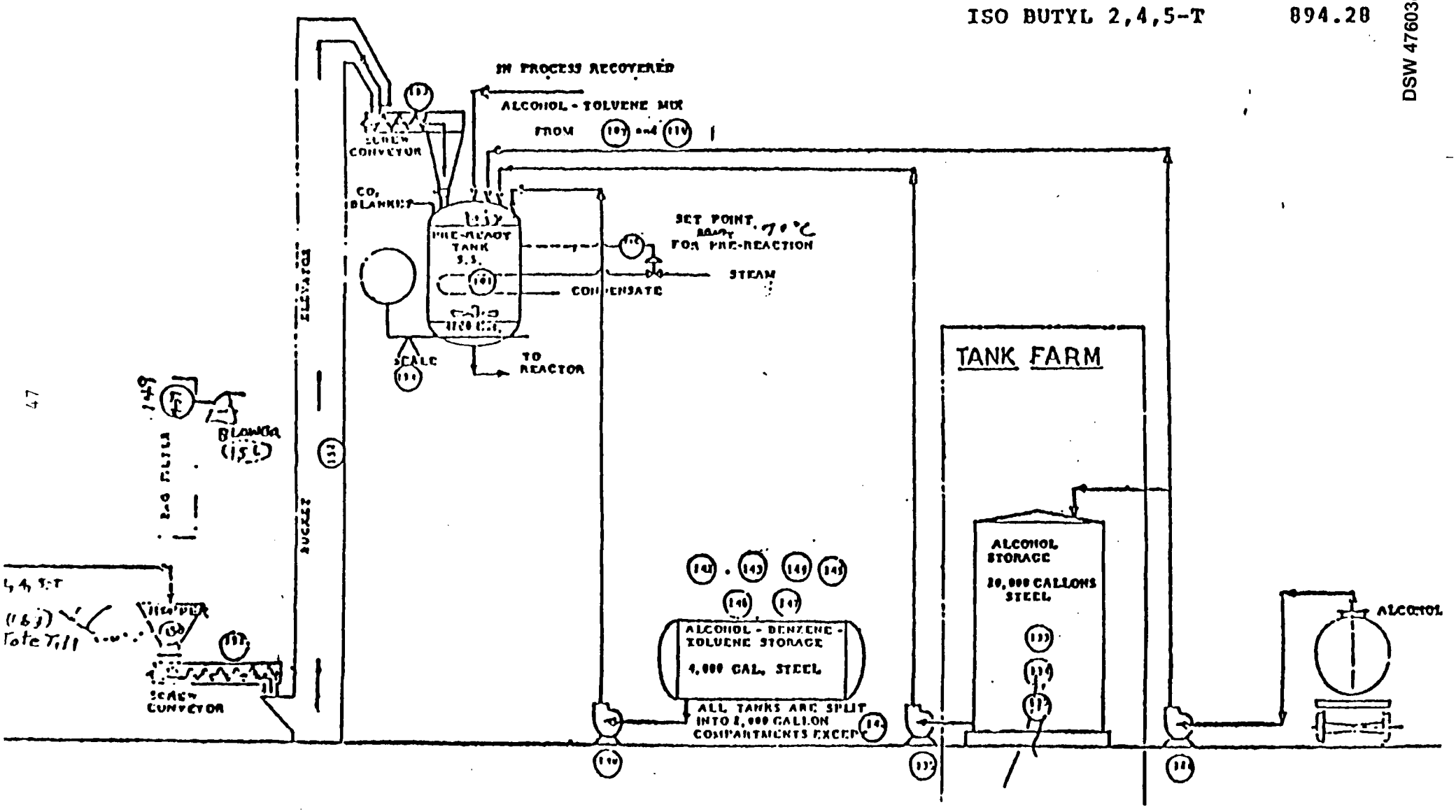


FIGURE 8.

B. REACTION

DEPT. 268

BUTYL 2,4,5-T 894.12

ISO BUTYL 2,4,5-T 894.28

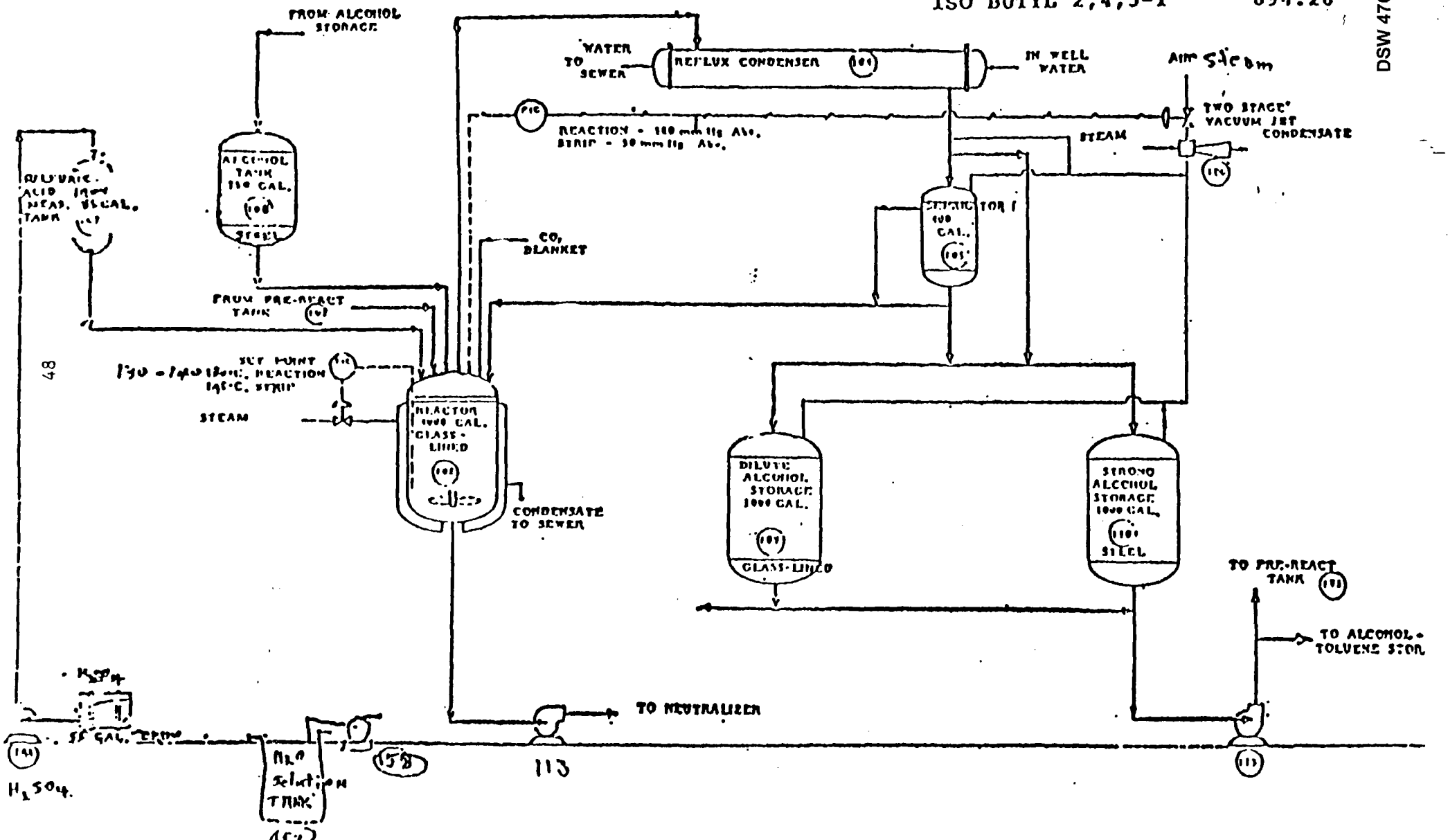
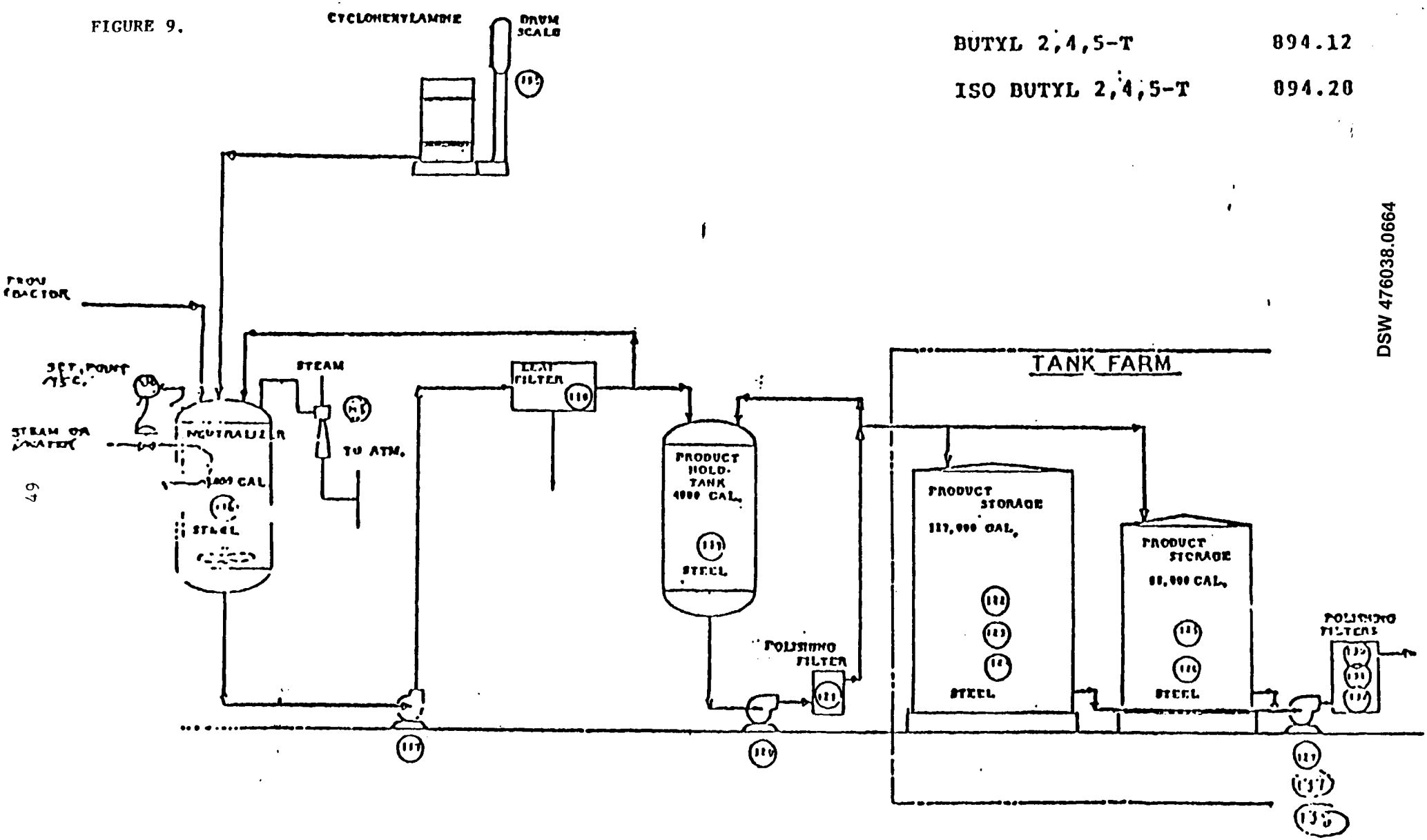


FIGURE 9.

BUTYL 2,4,5-T	894.12
ISO BUTYL 2,4,5-T	894.20



The esters were produced by reacting the chlorphenoxy acids with the appropriate alcohol using a small amount of sulfuric acid as a catalyst. The materials were pre-mixed in a slurry tank, then dropped into the reactor where the sulfuric acid was added. The reactor was then set at the appropriate temperature and pressure (butyl and isobutyl esters of 2,4,5-T; 130-140° C, 580 mm Hg; isooctyl ester of 2,4,5-T; 135-140° C, 200 mm Hg.) The reaction was originally driven to completion by removing the binary alcohol/water azeotrope and, on cooling and separating, recycling the alcohol. The 1969 processes for the butyl and isobutyl esters used toluene as a solvent for increased efficiency in driving the reaction to completion and in the water/alcohol separation.

When the reaction was complete, the alcohol and toluene were stripped off maintaining the reactor at 50 mm Hg and 140-150° C for two hours. The batch was then neutralized with cyclohexylamine. After filtration, the product was pumped to storage, tank cars, tank trucks, or 55 gallon drums.

A list of the job titles in Department 268 is given in Table 11.

4.2.2 Industrial Hygiene

Departments 226 and 236

Chemical exposures in Departments 226 and 236 included pentachlorophenol, tetrachlorophenol, phenol, chlorophenol fractions, chlorine, hydrochloric acid, sodium hydroxide, iron, aluminum and PCDDs/PCDFs. Repeated overexposure to phenol may result in chronic phenol poisoning. Symptoms include vomiting, difficulty in swallowing, diarrhea, lack of appetite, headache, fainting, dizziness, dark urine, mental disturbances, and possibly skin rash. Liver and kidney damage and discoloration of the skin may also occur. Chlorine, hydrogen chloride, and sodium hydroxide are irritating to the skin, eyes, and mucous membranes. Overexposure to chlorine and hydrogen chloride gas may result in tracheobronchitis and pulmonary edema (NIOSH, 1977). Exposures to the iron and aluminum powder catalysts are not likely to result in serious health effects. The toxicities of the chlorophenols have been reviewed in Section 3.

The earliest information regarding the industrial hygiene conditions in Department 236 comes from a report of an inspection conducted in 1947 by the State Department of Labor's Division of Factory Inspection. The report listed several conditions which needed improving: 1) the drum flakers on the first floor of Building BD (Dept. 236) emitted considerable fumes and dust under ordinary operating conditions; 2) maintenance personnel who handled the Draco Dust Collector System were exposed to the product when the Draco bags occasionally broke; 3) employees involved in the drumming and bagging operation which was connected to the Draco Dust Collection System bagged much of the material by hand; 4) the hopper which fed the Santobrite pelletizing system was frequently blocked and was dug out by hand; and 5) the ventilation system on the Penta briquette operation was poor. A 1954 company memo acknow-

ledges a chloracne problem in Department 236 which had existed for several years. In 1963 a Schneible Dust Collector System was installed in both the Penta and Santobrite operations.

On October 24, 1965 a fire broke out in one of the chlorinators. The batch in the chlorinator was in the trichlor-tetra stage. The cause of the fire was unknown. No material was lost from the chlorinator. The operators who were on duty did not appear to suffer any acute health effects.

In 1967 a central fume scrubber was installed for sample hoods, tank vents, and loading areas.

Monsanto began reviewing the literature on dioxins in 1970. That same year the Medical Department established a registry of employees at the Krummrich Plant who had developed chloracne or who worked in Departments where chloracne was prevalent. In 1972 Monsanto began monitoring the dioxin levels in PCP. The levels of PCDDs in PCP, PCP-cuts, and PCP residue from 1972 to 1979 are given in Table 12.

The production of Santobrite stopped in 1972. The same year special hygiene practices (showers, clothes changes, washing, cleansing housing with Seba-Nil Solution) were begun for employees who continued to produce PCP in Department 236.

Environmental monitoring for PCP began in 1977. Levels of PCP in air and wipe samples are given in Table 13. All of the air samples collected between April and October of 1977 were below the TLV of .5 mg/m^3.

In May of 1977, MIC staff personnel conducted an environmental audit of Department 236. The audit concluded that: 1) overchlorination of PCP could potentially cause major process accidents; 2) since 1975, 40% of the

TABLE 12 LEVELS OF PCDD IN PCP, PCP-CUTS, AND PCP RESIDUE (ppm)

DATE	SAMPLE	C_1	C_2	C_3	C_4	C_5	C_6	C_7	C_8
1972	PCP	"3000 ppm Total Dioxin"							
6/75	PCP	-	-	-	(<.01)	(<.07)	11	220-538	460
8/75	PCP	-	-		(<.01)	(<.07)	-	"	490
4/16/79	Blown Crude	(BDL)	(BDL)	(BDL)	(BDL)	(BDL)	(BDL)	(BDL)	(BDL)
	Dry Fraction	"	"	"	"	"	"	"	"
	Phenol Cut	"	"	"	"	"	"	"	"
	Para-Rich Cut	"	"	"	"	"	"	"	"
	PCP-Cut	"	"	"	"	"	"	"	"
2/28/79	PCP Residue with Caustic	63	59	15	3.1	6.7	1.3	2.2	.44
3/1/79	"	240	190	64	6.2	.1	.44	.08	.14
3/2/79		250	200	35	5.9	1.9	5.2	1.3	.16
3/11/79		240	1,400	1,600	410	4.7	.62	.81	.17
5/11/79	PCP Residue without Caustic	(<1)	(<1)	(<1)	(<1)	(<1)	(<1)	(<1)	(<1)
4/6 to 6/9/79	PCP with Caustic	2 -22	1 -5.4	.18 -1.4	(<.01)	(<.05)	(<.05)	(<.02)	(<.025)
4/25 to 6/9/79	PCP Without Caustic	(<.01) -.52	(<.01) -.47	(<.01) -.11	(<.01) -.016	(<.05)	(<.05)	(<.02)	(<.06)

TABLE 13.

PCP AIR (mg/m^3) AND WIPE ($mcg/100\ cm^2$) SAMPLES FROM DEPARTMENT 236

DATE	SAMPLE	PCP AIR	PCP WIPE
4/26/77	Personal, 8-Hour	.14	
	Operator	(<.001)	
	"		
	Area, 2nd Level		
	Outside Control Room	.026	
8/10/77	Personal, 8-Hour	.066	
	Operator	.034	
	"	.026	
10/7/77	"	.025	
3/77	(All Penta Control Room)		
	Sink Area		15.5
	Table		30.7
	Ice Box		24.5
	Cabinet		24.2
	Desk		13.0
	Table		216
	Bookshelf		39
8/77	Sink Area		6.14
	Table		11.10
	Ice Box		1.39
	Cabinet		15.1
	Desk		8.89
	Table		1.89
	Bookshelf		4.64

personnel in Department 236 had developed chloracne; 3) the TLV and STEL for PCP were at times exceeded during the block pouring, sawing of the 1000 pound molds, and chlorinator sampling operations; and 4) serious sources of direct operator contact with the dusty product included prilling, prill bagging, bulk loading, and routine cleaning.

In 1977 Monsanto instituted more stringent industrial hygiene practices (disposable dishes, midshift shower for dirty jobs). Wipe sampling (Table 13) showed a reduction in the levels of surface contamination in the Penta Control Room between March and August of 1977. Monsanto decided to shut down the Penta operation and to explore ways to further reduce the levels of product and workplace contamination.

In 1978 the Penta operation was shut down. In 1979 Monsanto developed the capability to measure PCDDs with greater analytical precision. Wipe sampling of the Department (Table 14) revealed surface contamination with trace amounts of higher chlorinator PCDDs. That same year, Monsanto discovered that the levels of PCDDs in PCP could be greatly reduced by removing sodium hydroxide from the process (Table 12). Department 236 was not re-opened, however, and the building was subsequently dismantled.

Department 237

Chemical exposures in Department 237 included phenol, o-chlorophenol, p-chlorophenol, 2,4-dichlorophenol, 2,6-dichlorophenol, 2,4,6-trichlorophenol, PCP (possibly from adjacent Dept. 236), chlorine, hydrochloric acid, and the lower-chlorinated PCDDs.

The earliest record of any problem in Department 237 dates back to April 25, 1952 when an explosion destroyed a 2,4-DCP transfer pump. The

TABLE 14.

LEVELS OF PCDDs IN WIPE SAMPLES FROM DEPARTMENT 236

DATE	SAMPLE	C_1	C_2	C_3	C_4	C_5	C_6	C_7	C_8
6/6/79	Blower (mcg/m^2)	(BDL)	(BDL)	(BDL)	(BDL)	(BDL)	400	8,000	58,000
	Office Wall (")	"	"	"	4.5	"	(BDL)	50	9,000
	Handrail (")	"	"	"	(BDL)	"	"	14	1,800
	Beam (")	"	"	"	10	"	60	140	47,000
	Wall (")	"	"	"	1	"	(BDL)	2	700
5/81	Penta Purification Column								
	3rd Level (ng/100 cm^2)	-	-	-	1	44	112	34	36
	Top of Column (")	-	-	-	7	61	46	16	38
	Open Top Wall (")	-	-	-	19	74	46	10	36

pump overheated after it ran dry. The two operators who were in the vicinity did not appear to suffer any serious health effects.

Chloracne does not appear to have been prevalent in Department 237. Early company memos dealing with the chloracne problem do not identify Department 237 as a problem area. Only one of six employees who had worked exclusively in this Department was found to have questionable chloracne by Dr. Suskind in 1979.

Environmental monitoring for phenol and chlorophenols began in 1977. Air levels of these chemicals in Department 237 between 1977 and 1982 are given in Table 15. None of the air levels for phenol exceeds the TLV of 19 mg/m^3. TLVs for o-chlorophenol, p-chlorophenol, and 2,4-dichlorophenol have not been established. Air levels of PCP exceeded the TLV on several occasions.

Air samples for chlorine and hydrochloric acid were collected between September of 1979 and January of 1980. Air levels of HCl ranged from .06 - .32 mg/m^3, well below the 7 mg/m^3 ceiling value. Air levels of chlorine ranged from .02-.10 mg/m^3. One air sample collected near the chlorinator showed an unusually high chlorine level of 5.4 mg/m^3, which is above the 3 mg/m^3 TLV.

In 1979 Monsanto analyzed batches of o-chlorophenol and 2,4-dichlorophenol for PCDDs. (Table 16) O-chlorophenol was contaminated with ppb levels of mono-, di-, and tri-CDDs. 2,4-dichlorophenol was contaminated with mono-, di-, tri-, and tetra CCDs. Removal of the caustic addition resulted in a marked reduction in PCDD contamination. An OSHA inspection in 1979 found 300 ppb of PCDDs (>50% 2,3,7,8-TCDD) in an ortho-crude spill, but Monsanto questioned the validity of this analysis.

TABLE 15. AIR LEVELS OF CHLORINATED PHENOLS AND PHENOL IN DEPARTMENT 237 (mg/m^3)

DATE		PHENOL	O-CP	P-CP	D-CP	T-CP	PCP
3/15/77	Personal, 8-Hour	.15	.30	-	-	-	.05
	"	.12	.25	-	-	-	.55
3/16/77	"	.075	.19	-	-	-	.05
	"	.39	.93	-	.09	-	.50
	"	.13	.10	-	.04	-	.05
	"	.21	.57	-	.06	-	.32
	"	.53	.44	-	4.13	-	.48
3/31/77	"	.14	.34	-	.06	-	.04
	"	.06	.27	-	.06	-	.05
	"	-	-	-	-	-	.14
4/14/77	"	.16	.76	-	.12	-	.18
	"	.38	.20	-	.05	-	.14
	"	.28	.44	-	.23	-	.05
	"	.37	.40	-	.06	-	.15
	"	.03	.02	-	-	-	-
3/10/78	" (Operator)	.53	1.88	-	-	-	.57
	" "	1.70	12.66	-	-	-	.93
1980	" (Control Room)	.20	.18	.18	.09	-	-
	Personal, 8-Hour Samples	.21 -.66	.20 - .70	.12 -.18	.10 -.11	-	-
7/80	Personal, 8-Hour	.73	-	-	.15	-	2.35
	"	.75	-	-	.79	-	1.53
	Area, Analytical Shed	.90	-	-	.67	-	1.15
8/80	Personal, 8-Hour	.62	-	-	.37	-	4.88[a]
	"	.67	-	-	.19	-	5.17[a]
7/28/81	"	.18 -.31	.1C -.14	.07 -.14	.02 -.03	-	-
5/82	"	.40 -.53	.01 -1.5	.19 -1.2	.03 -.29	(<.01)	-
8/21/82	Area, Shift, Control Room	.59	.02	.24	.24	(<.01)	-
	GLC Room	.10	.05	.06	.50	(<.01)	-

TABLE 16.

LEVELS OF PCDDs IN O-CP AND D-CP (ppm)

DATE	SAMPLE	C_1	C_2	C_3	C_4	C_5	C_6	C_7	C_8
2/28 to 4/16/79	O-CP With Caustic	(<.05) -.89	(<.02) -.18	(<.03) -.45	(<.01)	(<.05)	(<.05)	(<.02)	(<.05)
4/25/79	O-CP Without Caustic	(<.01)	(<.02)	(<.01)	(<.01)	(<.05)	(<.05)	(<.07)	(<.08)
3/3 to 4/18/79	D-CP With Caustic	(<.02) -9.5	(<.01) -29	(<.02) -13	(<.02) -.19	(<.02)	(<.05)	(<.10)	(<.10)
5/15 to 5/31/79	D-CP Without Caustic	(<.01)	(<.01) -.04	(<.01) -.25	(<.01) -.04	(<.05)	(<.05)	(<.01)	-

Trace amounts of OCDD were found in surface wipes of the chief operators desk and the desk in the Department 237 Control Room. It is not known whether these samples were analyzed for other PCDDs.

PCDFs were not routinely measured in the samples collected for PCDD analysis.

Department 268

Chemical exposures in Department 268 included 2,4,5-T, n-butyl alcohol, isobutyl alcohol, isooctyl alcohol, toluene, sulfuric acid, and cyclohexylamine. Exposures to high concentrations of the alcohol vapors may cause headache, dizziness, and drowziness. Keratitis characterized by corneal vacuoles has been reported following exposure to the vapors of n-butyl and isobutyl alcohols. Toluene is a central nervous system depressant. Prolonged, heavy over-exposure may result in permanent encephalopathy. Cyclohexylamine and sulfuric acid are skin and eye irritants. Repeated inhalation of sulfuric acid mist may lead to chronic bronchitis.

The only information regarding industrial hygiene conditions in Department 268 comes from an internal industrial hygiene survey (undated) conducted in the 1960s. The report states that some dust was generated when 2,4-D was loaded into the fill hopper through the front end pay loader. 2,4,5-T was received from the Nitro plant in Lever packs; this was changed over to tote bins to reduce the amount of dust exposure during charging. The Drumming Station was not vented. The filter press was cleaned every three days. The operators who were not manually handling the material operated the equipment from an air-conditioned control room. The 2,4-D and 2,4,5-T esters were apparently not analyzed for PCDDs. The levels of PCDDs in these products were probably not much different from those reported in the literature (Table 5).

4.2.3 Chloracne Registry

In 1970 the Medical Department at the Krummrich Plant instituted a registry of current employees who had developed chloracne or who had worked in departments where chloracne was prevalent. Employees were examined for chloracne if they 1) worked in Department 236 or 237; 2) worked in Maintenance and had worked for more than 200 hours in the area containing Departments 236 and 237; or 3) were self-referred because of concern over chloracne.

One hundred forty-five employees appear on the Chloracne Registry. Fifty-five of these were noted to have chloracne on at least one visit. Thirty-three of the employees were working in Maintenance at the time of examination. Twenty of these were noted to have chloracne.

4.2.4. Maintenance Employees

In addition to the production workers in Departments 226, 236, 237, and 268, an unknown number of maintenance workers were exposed to chlorophenols, chlorphenoxy acids and dioxins in these work areas. One thousand nine hundred and forty employees held maintenance jobs between 1940 and 1980 and are presently alive according to company records. The demographic characteristics of these workers are shown in Table 17.

A review of personnel and payroll records and interviews with maintenance supervisors have revealed that there are no existing records of Department assignments for maintenance workers prior to 1976. Self-reporting was considered as a means for ascertaining maintenance worker exposure. Moses et al (1984) attempted this approach and found it unfeasible in their study of the Nitro plant. Fingerhut and her co-workers at NIOSH are not including Krummrich maintenance workers in the Dioxin Registry due to the difficulties in assigning exposure.

TABLE 17

DEMOGRAPHIC CHARACTERISTICS OF MAINTENANCE WORKERS EMPLOYED BETWEEN 1940 AND 1980.

CHARACTERISTIC	N (Total = 1940)	Percent
Employment Status		
Active/Temp. Inac.	741	38
Terminated	572	29
Retired	627	32
Payroll		
Hourly	1,629	84
Salaried	311	16
Sex		
Male	1,871	96
Female	68	4
Unknown	1	<1
Race		
White	1,602	83
Black	317	16
Unknown	21	1
Age		
<20	2	<1
20-24	2	<1
25-29	37	2
30-34	55	3
35-39	72	4
40-44	130	7
45-49	146	8
50-54	118	6
55-59	272	14
60-64	311	16
65-69	312	16
70+	483	25

We have decided to adopt the approach of Moses et al (1984) and use chloracne as a marker of exposure for maintenance workers. These workers will be identified through a review of plant medical records. In addition we will consider any maintenance worker who appears on the Chloracne Registry as exposed. This approach is expected to identify approximately 48 maintenance workers with the highest dioxin exposures.

4.2.5 Definition of Exposed Cohort

The exposed cohort in this study will consist of all past and present Krummrich employees who are alive and who meet one or more of the following criteria:

1) Hourly and salaried employees who had worked in Departments 226, 236, 237, or 268 for one or more days between January 1, 1938 and December 31, 1983.
2) Maintenance employees who appear on the Chloracne Registry.
3) Employees who were noted to have chloracne on plant medical records (with the exception of employees who were exclusively engaged in the production of PCBs or tetrachlorobenzene).

The first entry criterion encompasses most of the members of the exposed cohort. One thousand seven employees worked in Departments 226, 236, 237, and 268 between 1/1/46 and 1/1/75. The identification of employees who were hired and left before 1946 or between 1976 and 1980 has not yet been completed. Two hundred twenty-one of the 1007 employees are deceased, leaving 786 survivors. The distribution of 720 of these employees by length of employment in one or more of these departments and by employment status is given in Table 18.

TABLE 18. DISTRIBUTION OF EXPOSED COHORT BY LENGTH OF EXPOSURE AND EMPLOYMENT STATUS AS OF 1/1/84[a]

Employment Status	Length of Exposure (months)					Total
	<1	1-≤3	>3-≤6	>6-≤12	>12	
Active	55	42	48	39	82	266
Retired	33	24	22	33	65	177
Transferred within Monsanto	2	0	2	0	2	6
Leaves of Absence	4	7	5	5	8	29
Military Leave	9	10	11	14	9	53
Other Terminations	35	47	34	43	30	189
Total	138	130	122	134	196	720[b]

[a]Cohort limited to employees who had worked in Departments 226, 236,237, and 268 between 1/1/46 and 1/1/75.

[b]Sixty six additional employees have as yet not been classified by length of exposure

Thirty-three Maintenance personnel are included on the Chloracne Register indicating that they had either developed chloracne or had worked in Departments 226, 236, 237, or 268 for more than 200 hours after 1970. Company documents dated before 1970 contain lists of names of employees who had developed chloracne. An additional 15 names are expected to result from this entry criterion.

The current estimate of the total number of individuals in the exposed cohort is approximately 834.

4.2.6. Demographic Characteristics of the Exposed Cohort

At this time demographic information is available on the employees who had worked in Departments 226, 236, 237, and 268 between 1/1/46 and 1/1/76. These individuals comprise about 90% of the total exposed cohort. Eighty-five percent of these workers are white, 14% are black, and in 1% the race is unknown. Ninety-seven percent of these workers are male. The age distribution of these workers is given in Table 19. Fifty percent are 60 years of age or older. Ninety-three percent of the workers were hourly employees and 7% were salaried.

4.2.7. Follow-Up, Accessibility, and Participation of the Exposed Cohort

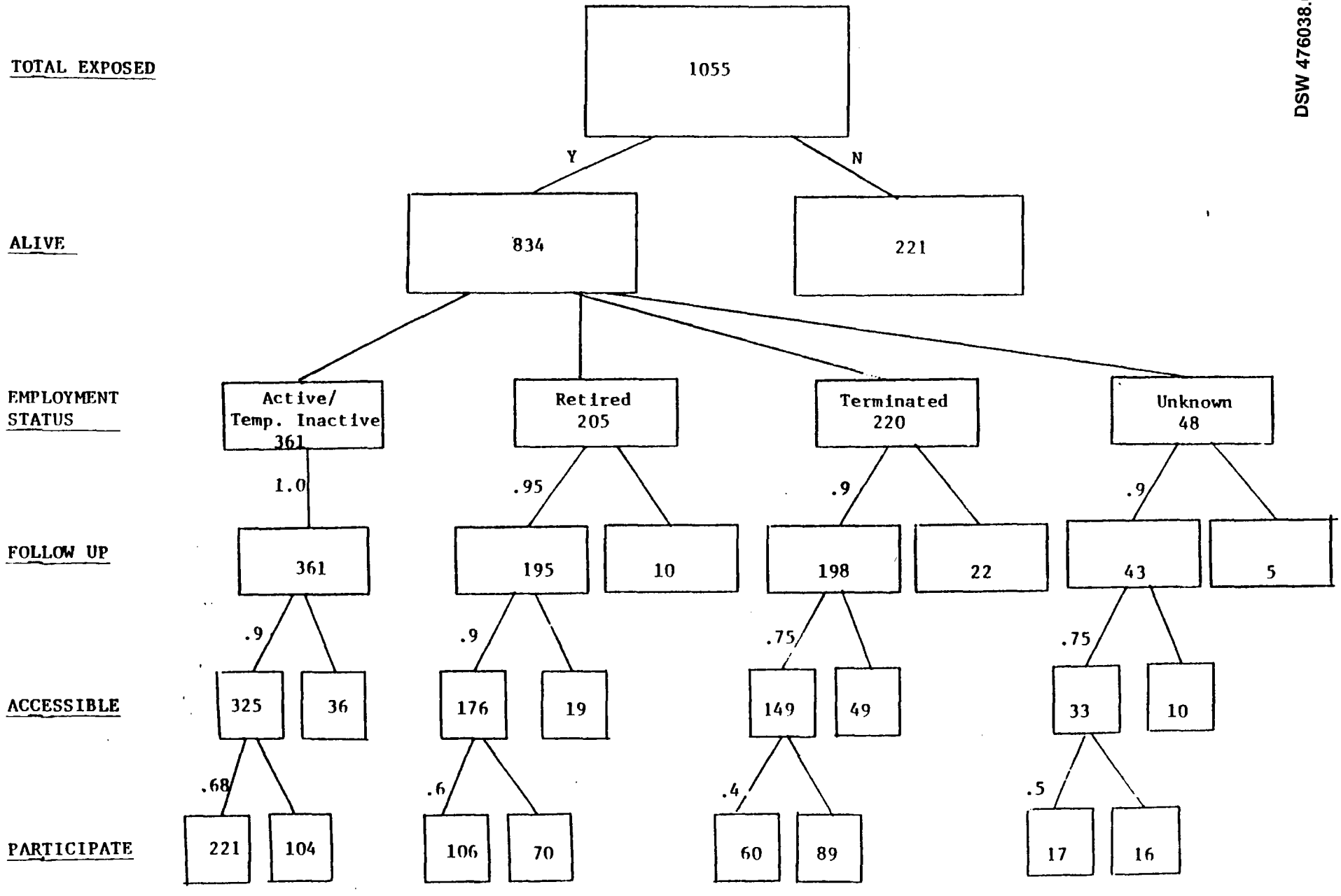
The size of the exposed population which will undergo medical examination will depend on the rates of follow-up, accessibility for examination, and participation. These rates are expected to vary by employment status. The effects of these rates in determining the size of the examined cohort are shown in Figure 10.

Follow-up is expected to be complete for active and temporarily inactive workers. An estimated 90% of these workers will be accessible for

TABLE 19. AGE DISTRIBUTION OF THE EXPOSED COHORT AS OF 1984

AGE	N	PERCENT
25-29	13	2%
30-34	9	1
35-39	14	2
40-44	60	8
45-49	74	9
50-54	64	8
55-59	160	20
60-64	145	18
65-69	115	15
70 +	132	17
TOTAL	786	100%

FIGURE 10. ESTIMATED FOLLOW-UP, ACCESSIBILITY, AND PARTICIPATION OF THE EXPOSED COHORT



tal Number Participating = 404

medical examination. In Suskind's 1979 survey of this same population, 68% of the active employees chose to participate. A similar participation rate in the present study would result in 221 active and temporarily inactive workers.

The follow-up rate for retirees is estimated at 95%, since these workers are traceable through pension records. Over ninety percent are known to be living within 300 miles of St. Louis and accessible for examination. A participation rate of 60% would result in 106 retirees.

The follow-up rate for terminated workers is projected at 90%. The locating of terminated workers will be performed by Equifax. An estimated 75% are still living within 300 miles of St. Louis. Approximately 30 employees who had worked in Department 268 terminated employment at the Krummrich Plant when their area of the plant was sold to the Edwin Cooper Company. This group of employees will be especially targeted for participation in the study. A participation rate of 40% would result in 60 terminated workers. Retired and terminated workers will receive a reasonable reimbursement for their time and travel.

The follow-up rate for employees whose employment status is as yet unknown is estimated at 90%. The accessibility and participation rates for these employees are estimated at 75% and 50% respectively, resulting in an additional 17 workers.

A total of 404 exposed employees are expected to participate in the medical examinations. Present and past employees who choose not to participate in the study will be surveyed as to their reasons for non-participation and general health status. This information will be useful in detecting and measuring non-responder bias.

4.2.8 Internal Control Group

The internal control group will consist of all present and past employees at the Krummrich Plant who are alive and meet all of the following entry criteria:

1) Never worked in Departments 226, 236, 237, or 268.
2) Did not appear on the Chloracne Registry.
3) Were not listed on company documents as having chloracne.
4) Never worked in Maintenance.
5) Never worked in Department 239 (Santophen).
6) Never worked in Department 224 (chlorinated benzenes).
7) Never worked in Department 262 (2,4-D).
8) Never worked in Department 218 (muriatic acid - chlorinated benzene).
9) Never worked in Department 246 (PCBs).
10) Never worked in Department 233 (chlorinated benzene).
11) Never worked in Department 861 (laboratory).

One thousand seventy-seven employees meet the entry criteria for the internal control group. Thirty-three percent are active workers, 59% are terminated, and 9% are retired. Ninety-five percent are hourly employees and 5% are salaried. Ninety-six percent are male. Seventy-eight percent are white, 11% are black, and in 11% the race is unknown.

The demographic characteristics of the exposed cohort and the internal controls, are compared in Table 20. The exposed and non-exposed groups are similar with respect to age, sex, race, and payroll. A larger percentage of the internal controls are terminated employees. A larger percentage of the exposed cohort are retired, regardless of whether the terminated employees

TABLE 20.

COMPARISON OF THE PERCENT DISTRIBTUIONS OF DEMOGRAPHIC CHARACTERISTICS BETWEEN THE EXPOSED COHORT AND THE INTERNAL CONTROLS

CHARACTERISTIC	Exposed (n=786)	Control (n=1077)
Employment Status		
Active/Temp. Inactive)	46	33
Terminated	28	59
Retired	26	9
Payroll		
Hourly	91	95
Salaried	9	5
Sex		
Male	97	96
Female	3	4
Unknown	<1	<1
Race		
White	85	78
Black	14	11
Unknown	1	11
Age		
<20	0	1
20-24	0	0
25-29	2	1
30-34	1	2
35-39	2	6
40-44	8	7
45-49	9	6
50-54	8	9
55-59	20	20
60-64	18	20
65-69	15	11
70+	17	17

are included or excluded. Overall, the two groups are acceptably comparable with respect to the major demographic variables.

If we assume similar rates of follow-up, accessibility, and participation,[1] an estimated 218 active, 50 retired, and 141 terminated workers are expected to comprise the internal controls. The 409 internal controls and 404 exposed result in a control:exposed allocation ratio of 1.01:1.

[1]Thirty-three percent of non-exposed terminated workers are expected to participate in the study as opposed to 40% of the exposed terminated workers.

4.3 Ascertainment of Health Status

The comprehensive medical examination will ascertain the subjects' present and past health status. The incidence of past health events will be determined through the medical questionnaire and validated through medical record review. The examiners will be blinded as to the exposure status of the exposed cohort and the internal controls. The components of the medical examination are summarized in Table 21.

4.3.1. Medical History Questionnaire

A trained medical interviewer will administer a standard medical history questionnaire which will be a modification of the questionnaire previously used by the U.S.A.F. School of Aerospace Medicine in their Ranch Handy Study (Lathrop et al, 1983). The questionnaire will contain the following elements:

1. Current health status including any chief complaints or medical problems.
2. Past medical history, including hospitalizations for medical illness, surgical procedures, or transfusions. Specific questions will be asked about the presence of hypertension, cardiovascular, cerebrovascular, pulmonary, hepatic, intestinal, urogenital, reproductive, neurologic, mental, and psychiatric diseases.
3. Family history including health status of all first degree relatives, causes of death, hospitalizations, etc.
4. Social history including marital status (current and previous spouses), habits of alcohol and tobacco use.

5. Review of systems including:
   a. Constitutional symptoms of weight change, energy level, etc.
   b. Headaches
   c. Eye (vision, pain, discomfort)
   d. Ear (hearing, pain, discharge)
   e. Nasal (congestion, discharge, sense of smell)
   f. Mouth (lesions, dental, dysphagia)
   g. Respiratory (sputum, cough, dyspnea, etc.)
   h. Cardiac (chest pain, palpitations, PND)
   i. Abdomen (pain, diarrhea, constipation, nausea, vomiting, etc.)
   j. Urogenital (dysuria, urgency, frequency, infection, nephrolithiasis, sexual dysfunction)
   k. Joints (pain, swelling, deformity)
   l. Neurologic (weakness, paresthesia, memory change, etc.)
   m. Psychologic (sleep disturbance, anxiety, depression)
   n. Dermatologic (rashes, blisters, sunburn, excess hair)
   o. Gynecologic (regularity of menses, character of flow, etc.)
6. Medication history which will include current as well as past use of prescription and over-the-counter preparations.

4.3.2 Reproductive History

At the time of the medical history, permission will be sought to conduct a phone interview with current and previous spouses concerning reproductive outcomes. The Ranch Hand spouse's questionnaire will be administered by trained, medical telephone interviewers and will include questions on the number of pregnancies, their outcomes, and any congenital

malformations in offspring of the subjects. Permission will be sought to verify reported congenital malformations in offspring through medical record review.

4.3.3 Dietary History

Participants will be asked to complete a three-day dietary history. They will be instructed in the completion of this diary by a trained nutritionist.

4.3.4. Physical Activity Assessment

Participants will be administered a seven-day activity recall questionnaire (Taylor et al, 1984) to determine their level of physical activity.

4.3.5. Occupational and Environmental History

A trained interviewer (other than those administering the other components of the medical examination) will administer a questionnaire designed to determine each of the following items as best remembered by the subject:

1. Job classification, duration, and duties for each position held at the Krummrich plant.
2. Job classification, duration, and duties for all employment other than at the Krummrich plant.
3. Description of any hobbies or other pursuits involving exposure to chemicals which might be confounding.
4. Military history (if any) with particular attention to service in Vietnam, especially Operation Ranch Hand.

4.3.6. Medical Records Review

Permission will be sought for review and release of medical records from treating physicians and hospitals for purposes of confirming the

previously obtained medical histories. The medical records will be reviewed by registered medical record technicians. Diagnoses and procedures will be classified into ICD-9.

4.3.7 Internist's Physical Examination

The general physical examination will be performed by an internist blinded to the exposure history of the worker.

The examination will consist of the following:

1. General appearance and vital signs: supine and sitting blood pressure and pulse, respiratory rate, height and weight.
2. Head: shape, evidence of trauma.
3. Eyes: pupillary response, presence of conjunctivitis, icterus.
4. Ears: hearing, appearance of tympanic membranes.
5. Nose: appearance of mucosa, purulent secretions, polyps.
6. Mouth: appearance of teeth, tonsils, mucous.
7. Neck: adenopathy, size and consistency of thyroid, range of motion.
8. Lungs: percussion, auscultation.
9. Heart: size and description of PMI, abnormalities of heart sounds, extra sounds and murmurs.
10. Abdomen: tenderness, masses, bowel sounds, liver and spleen size.
11. Genital (males): testicular size and consistency, hernias.
12. Rectal: mucosal surfaces, prostate size and consistency (males), stool hemocult.

13. Joints: range of motion, effusion, deformity.

14. Back: range of motion, tenderness.

15. Breasts (females): masses, discharge.

16. Pelvic (females): cervix, adnexal tenderness or masses.

17. Peripheral pulses.

4.3.8 Dermatologic Examination

The dermatologists will be trained in the diagnosis of chloracne by an internationally recognized expert in the field. The dermatologic examination will be performed and recorded in a standardized manner to permit quantitative assessment of the findings. Particular attention will be devoted to the detection and scoring of chloracne, porphyria cutanea tarda, and basal cell carcinoma.

4.3.9. Neurologic Examination

A neurologist will perform a mental status examination and examine the cranial nerves, motor, and sensory systems. Reflexes and cerebellar function will be tested.

4.3.10. Electrocardiogram

A trained technician will do a 12-lead, resting electrocardiogram.

4.3.11. Pulmonary Function Tests

A trained technicial will measure the subject's forced vital capacity and forced expiratory volume at one second.

4.3.12. Chest X-ray

A trained technician will take a standard PA and lateral film.

4.3.13. Quantitative Sensory Examination

A trained technician will quantitate the subject's perception of temperature and vibration.

4.3.14. Nerve Conduction Velocities

A trained technician, under the supervision of the neurologist, will measure the nerve conduction velocities of the median and sural nerves (one side only) using standardized methods.

4.3.15. Neurobehavioral Testing

A trained technician will administer an automated neurobehavioral test battery (Baker et al, 1984) using computer terminals, which will include the following tests:

1. Paired associate learning
2. Mood scales
3. Continuous performance
4. Vocabulary
5. Symbol-digest substitution
6. Hand-eye coordination
7. Visual retention
8. Digit span
9. Paired associate recall

4.3.16. Blood Tests

Venous blood will be drawn after a 12-hour fast and distributed in the following manner:

1. 5cc of EDTA anticoagulated blood for complete blood count, differential white cell count, and platelet count.
2. 5cc of EDTA anticoagulated plasma for total cholesterol, HDL and LDL cholesterol and triglycerides.

3. 5cc of serum for SMA 20 (albumin, alkaline phosphatase, bilirubin, calcium, chloride, bicarbonate, creatine, GGT, glucose, phosphorus, potassium, LDH, protein, GOT, GPT, sodium, BUN, acid.).
4. 5cc of serum for LH, FSH, testosterone.
5. 2cc of serum for T4, T3 resin uptake and free thyroid index, TSH.
6. 3cc of serum for IgA, IgG, IgM.
7. 1cc of frozen serum for CPK.
8. 4.5cc of blood drawn into blue-top tube and delivered on ice for prothrombin time.
9. 5cc of EDTA plasma for apoproteins AI, AII, B, and E (Dr. Schoenfeld's laboratory).
10. 20cc of heparinized blood for lymphocyte stimulation studies (concanavalin A, phytohemaglutin, and Poke week mitogen).
11. 20cc of heparinized whole blood, 3cc of EDTA anticoagulated blood and 2 slides will be drawn for T and B cell determinations, T helper and suppressor cell ratio.
12. 10cc of serum will be frozen and banked to permit future analyses.

4.3.17. Urine Tests

The subjects will be asked to provide a clean catch, mid-stream urine

specimen for urinalysis after which a 24-hour urine collection will be begun using a light-proof container. The 24-hour urine collection will be kept refrigerated and appropriate preservatives will be used.

Aliquots will be sent for:

1. Creatine (creatinine clearance)
2. Protein (24-hour protein excretion)
3. Quantitative porphyrins

TABLE 21. SUMMARY OF COMPREHENSIVE MEDICAL EXAMINATION

1. Medical History Questionnaire (trained interviewer)
    - Current medical problems
    - Past medical history
    - Family history
    - Social history
    - Review of systems
    - Medication
2. Reproductive History (telephone interview by trained interviewer)
3. Dietary History (nutritionist-instructed 3-day diary)
4. Physical Activity Assessment
5. Occupational and Environmental History (trained interviewer)
6. Medical Record Review (internist)
7. General Physical Examination (internist)
8. Dermatologic Examination (dermatologist)
9. Neurologic Examination (neurologist)
10. 12-lead EKG (EKG technician)
11. Pulmonary Function Tests (PFT technician)
12. Chest x-ray, PA and lateral (technician)
13. Quantitative Sensory Examination (technician)
14. Nerve Conduction Velocities (NCV technician)
15. Neurobehavioral Testing
    - Paired associate learning
    - Mood scales
    - Continuous performance
    - Vocabulary

TABLE 21 (continued)

Symbol-digest substitution

Hand-eye coordination

Visual retention

Digit span

Paired associate recall

16. Blood Tests

Complete blood count

Platelet count

Cholesterol

HDL and LDL cholesterol

Triglycerides

Apoproteins AI, AII, B, and E

Glucose

BUN

Creatinine

Electrolytes

Uric Acid

Protein

Albumin

Bilirubin

Alkaline phosphatase

LDH, GOT, GPT

GGT

LH, FSH, testosterone

CPK

TABLE 21. (continued)

T4, T3 resin uptake, free thyroid index, TSH

IgA, IgG, IgM

Prothrombin time

Lymphocyte stimulation studies

T and B cell populations, T helper and suppressor ratio

Banked serum.

17. Urine Tests

Urinalysis

Creatinine clearance

24-hour protein excretion

Quantitative porphyrins

5. DATA ANALYSIS

5.1. Data Entry, Processing, and Storage

Data management and analysis will be performed at the Northwestern University Medical School. The data management system will include quality control measures at each step of the process to ensure completeness and accuracy of data entry.

Data entry and quality control will be facilitated through the use of standardized data entry forms. Whenever possible, original data will be recorded on the data entry forms to minimize transcription errors. A list of the original data, initial records, and data entry forms is given in Table 22.

The data from each employee's health examination will be visually inspected on site for completeness, legibility, and obvious inaccuracies. Errors in data collection or recording will be corrected on site. The data will be transported by courier to the Northwestern University Medical School for processing and storage. Results of laboratory analyses will be mailed to the School and inserted in each employee's data file.

Recording of data will be performed by data entry clerks following specific procedures under the supervision of the Data Manager. Data contained in the data entry forms will be entered into intelligent terminals using an Intelligent Data Entry program. A screen image of the data entry form will appear on the CRT. Spaces will be included for entering values as they are reported on the data entry form. The Intelligent Data Entry program will have checks on range values and numeric types to trap transcription errors.

Transactions from a forms entry session will be transmitted from the mini computer to the main frame over a phone line. The entry will be checked against

TABLE 22. FORMS FOR COLLECTION, RECORDING, AND CODING OF DATA

Components of Health Survey	Original Data	Initial Record	Data Entry Form
Information for Follow-up	Personnel Record	Computer Printout	Recoded
Employment Record	Personnel Record	Computer Printout	Recoded
Medical History	Face to Face Interview	Questionnaire	Same
Occupational History	Face to Face Interview	Questionnaire	Same
Reproductive History	Phone Interview	Questionnaire	Same
Internist's Exam	Physical Exam	Exam Form	Same
Dermatologist's Exam	Physical Exam	Exam Form	Same
Neurologist's Exam	Physical Exam	Exam Form	Same
PFT's	Flow-Volume Loop Volume-Time Graph	Computer Printout	Recoded
CXR	Film	Radiologist's Report	Recoded
Quantitative Sensory	Sensory Exam	Exam Form	Same
EKG	EKG	Cardiologist's Report	Recoded
EMG/NCV	Tracing	EMG/NCV Form	Same
Automated Neuro-behavioral Test	Neurobehavioral Exam	Computer Printout	Same
Blood Tests	Blood Specimen	Lab Report	Recoded
Urine Tests	Urine Specimen	Lab Report	Recoded
Non-Participant Survey	Phone Interview	Questionnaire	Same

the full data base on certain data items to prevent duplicate and other invalid entry. The original data will be stored and archived in the Northwestern University Medical School. Entered data will be stored on disks with archive copies to prevent inadvertant loss of the data base.

5.2. Quality Control

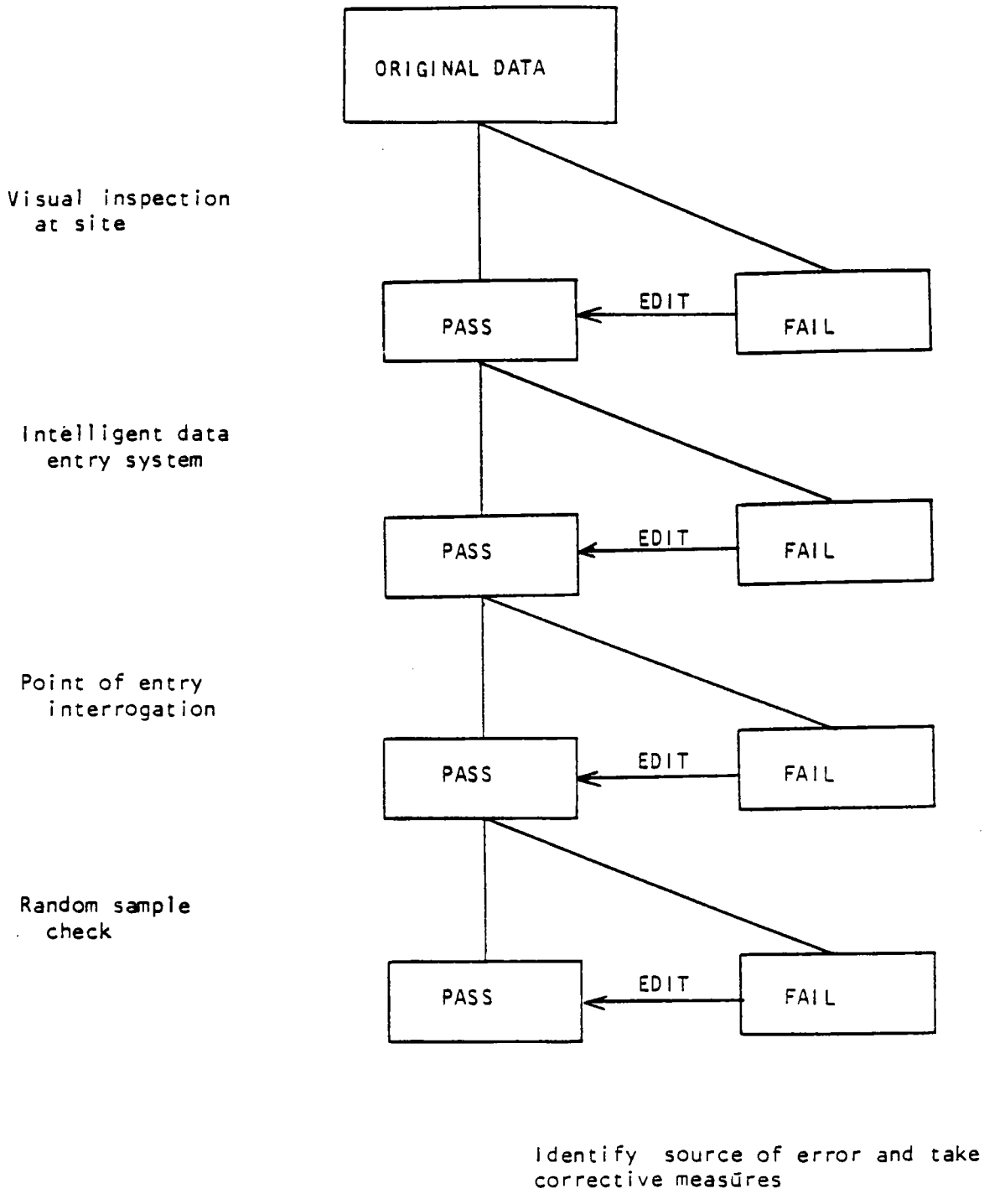
Personnel data on employment history which is supplied by Monsanto will be checked for accuracy by comparing a 10% random sample of this data to the original personnel records. The employee's occupational history will serve as a further check on the accuracy of the personnel data.

The most important step in the quality control of data management is the complete and accurate recording of data. Each employee's medical examination data will be visually inspected on site for completeness, legibility, and obvious inaccuracies.

Transcription errors during data entry will be minimized through the use of the previously described intelligent data entry system. Duplicate and other invalid entry will be prevented by comparing each entry against the full data base.

The final step in quality control will be an ongoing comparison of a 10% random sample of entries against the original data. Errors will be traced to their source and control measures taken to prevent their recurrence. Inaccurate or incomplete data will be corrected and re-entered. These quality control measures are summarized in Figure 11. Error tolerance will be set at .1%.

FIGURE 11. QUALITY CONTROL OF DATA ENTRY



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5.3 Analysis

5.3.1 Classification of Exposure

Each individual's exposure will be classified 1) dichotomously, 2) by length of exposure, and 3) by exposure score. All three exposure variables will be treated as categorical variables. The exposed cohort will be analyzed as a whole and, where sample size permits, by individual department.

In the dichotomous classification of exposure, individuals who meet one or more of the exposure criteria will be classified as exposed, and those who do not will be classified as non-exposed.

As an employee's length of employment in a department increases, his exposure to the chemicals in that department is expected to increase. The length of employment will be divided into the following four intervals: 1) 0 months, 2) >0-$\leq$3 months, 3) >3-$\leq$12 months, and 4) >12 months. Classification by length of exposure will permit analyses for dose-resonse.

NIOSH is currently developing a dioxin exposure score for the Dioxin Registry. The exposure score will be a numerical scale based on the department, job titles, length of exposure, and industrial hygiene data. The exposure score will be directly applicable to Krummrich employees, since employees from this plant are included in the Dioxin Registry. The exposure score is expected to be ready by March, 1985, and will be assigned to each employee without knowledge of the results of the medical examination. While the exposure score may be a continuous variable, we will treat it more conservatively as an ordinal varible with four exposure categories.

Our review of the industrial hygiene and process information leads us to conclude that analyses by individual departments are warranted. While

all four departments share the possibility of PCDD exposure, the mix of PCDDs was different for each department. Employees in Department 237 were exposed to the lower chlorinated dioxins, while employees in Departments 226 and 236 were exposed to the higher chlorinated dioxins. While no PCDD analyses were performed on the products from Department 268, historical information indicates that these employees were exposed to 2,3,7,8-TCDD. The departments will be categorized as 226/236, 237, 268, and Maintenance/Other.

5.3.2. Classification of Disease

The comprehensive health status evaluation, which includes a medical history, reproductive history, medical record review, physical examination, and laboratory tests, will generate a large number of categorical and continuous health outcome variables. The details of the medical survey are given in Section 4. The problem of repeated measures is discussed in Section 7.8.

5.3.3. Confounders and Effect Modifiers

5.3.3.1. Demographic Characteristics

The potential demographic confounders in this study include age, sex, race, socio-economic status, employment status, and urban/rural residence. The internal controls are similar to the exposed cohort with respect to age, sex, race, and payroll class. The effects of confounding will be controlled through stratified and multivariate analysis.

5.3.3.2. Lifestyle Characteristics

The potential lifestyle confounders in the study include smoking, alcohol consumption, physical activity, and diet. These variables will be ascertained through the medical history and controlled for in the statistical analysis.

5.3.3.3. Chemical Exposures

Employees at the Krummrich Plant are potentially exposed to chemicals other than the chlorophenols, phenoxy acid esters, and their contaminants. The major chemical products and intermediates are discussed in Section 2.2. The average Krummrich employee rotates from between 10 to 20 departments prior to retirement. The Krummrich Plant contains approximately 110 active and discontinued departments. Each employee will be dichotomously classified as having worked or not worked in each department. An employee will be considered as having worked in a department if he had worked in that department for a total of more than 3 months during his term of employment. A list of the chemical exposures in each department is available through Monsanto's MEHI computer system.

Each significant health finding in the comparison with the internal controls will be reviewed to determine if it could be associated with chemical exposures in a department where the employee had previously or subsequently worked (e.g. tremor on neurologic exam and exposure to mercury in the Denora Cell House). If the potential for confounding exists, the extent of confounding will be determined by cross-tabulating the confounding exposure with the abnormal health finding. If confounding is present, we will re-examine the original association after adjusting for confounding using Mantel-Haenszel methods. Major abnormal findings may warrant nested case-control study.

The Krummrich employees may have had exposure to chlorophenols, chlorphenoxy herbicides, and dioxins outside of their employment. These outside exposures will be ascertained through the administered questionnaire (e.g. history of farm use of chlorphenoxy herbicides). Confounding by

outside exposures will be controlled through the use of the aforementioned methods.

5.3.3.4. Effect Modifiers

A factor which will influence the prevalence of residual health effects is the time since last exposure. The few longitudial morbidity studies of dioxin-exposed occupational cohorts have shown that several acute health effects improve with time. The time since last exposure will be considered in the multivariate analysis.

Another factor which may influence our measurement of exposure is the calendar time of exposure. The industrial hygiene information suggests that the chemical exposures in Departments 226 and 236 were higher before 1970 than after 1970. There is no information to suggest a similar variation in exposure in Departments 237 or 268. The temporal variation in exposure will probably be factored into the NIOSH Exposure Score. If not, we will include it as a variable for study in the analysis of the data from Departments 226 and 236.

5.3.4. Statistical Tests

The strategy for statistical analysis of parametric data will consist of 1) examination of crude associations; 2) stratified analysis; 3) tests for dose-response; and 4) multivariate analysis using SAS statistical packages.

Crude associations between dichotomous variables will be examined by cross-tabulation, calculation of prevalence odds ratios, and testing for significance using Fisher's Exact or Chi Square Tests. Differences in means between continuous variables will be tested using the Student T Test.

In the next step of the analysis, we will stratify on major confounding variables and calculate factor-adjusted odds ratios using

Mantel-Haenszel methods. Differences in means between continuous variables will be adjusted for confounding and tested for significance using analysis of covariance.

Dose-response relationships between the ordinal exposure variables and dichotomous dependent variables will be examined using the test for trend. Confounding variables will be controlled using the Mantel extension. Multivariate analysis of dichotomous dependent variables will be performed using multiple logistic regression. Multivariate analysis of continuous dependent variables will be performed using multiple linear regression. Multivariate analysis of categorical dependent variables will be performed using log linear analysis.

6. IMPLEMENTATION

6.1 Identification and Recruitment of the Study Populations

The exposed and non-exposed employees at the Krummrich Plant will be identified through 1) Monsanto's MEHI computer system; 2) the chloracne register; and 3) a review of company memoranda dealing with chloracne at the Krummrich Plant prior to 1970. The addresses of active employees are available through current personnel records. The present addresses of retirees are available through the company's pension plan. Terminated workers will be located through Equifax.

Northwestern University will work together with Monsanto's Public Relations Department, and the international Chemical Worker's Union, and in recruiting Monsanto employees for the study. Active workers will be approached through the individual plants. Northwestern researchers will meet with the workers at the plants to discuss the purpose, scope, and implementation of the study. Retirees will be contacted by mail and also through existing retiree associations. Terminated workers will be contacted by mail.

6.2 Development of Survey Instruments

The medical history, occupational and environmental history, and non-participant questionnaires will be developed in conjunction with the Survey Research Laboratory. The Survey Research Laboratory will also provide trained medical interviewers to administer these instruments.

6.3 Medical Examinations

Northwestern University will place a team of health professionals at the plant sites to conduct the medical examinations. An examination is expected to take 8 hours of an employee's time, including breakfast and lunch. The examination will be completed during a single 8-hour shift with

the exception of the 24-hour urine collection, 3-day dietary history, and spouse's reproductive history. The team will be able to examine 18 employees per day by using a rotating-station examination system. Blood and urine samples will be processed and sent to the appropriate laboratories in daily batches.

Consent for medical record review will be sought at the time of examination. The medical records will be mailed to the Department of Medicine for review by medical record technicians after the examinations have been completed. The female spouses of the study participants will be asked to consent to a telephone interview to obtain pertinent reproductive history. The telephone interviews will be conducted by trained interviewers from the Survey Research Laboratory.

6.4 Data Analysis

Data analysis is discussed in detail in Section 5.

6.5 Report

6.5.1. Reports to Individual Participants

Each participant will be debriefed as to available medical findings on site upon completion of the medical examination. In addition, each participant will receive a report summarizing the results of his medical examination. The report will be prepared by the internist who examined the participant. The report will contain recommendations for further medical follow-up by the participant's personal physician when appropriate. If the participant so desires, the results of individual tests will be forwarded to the participant's physician.

6.5.2. Final Report

Northwestern University will submit a final report to Monsanto upon completion of the study. A draft of the final report will be reviewed by the

Peer Review Committee prior to submittal to Monsanto. The report will contain an introduction, presentation of methods, results of analyses, discussion, and conclusions.

6.6 Timetable

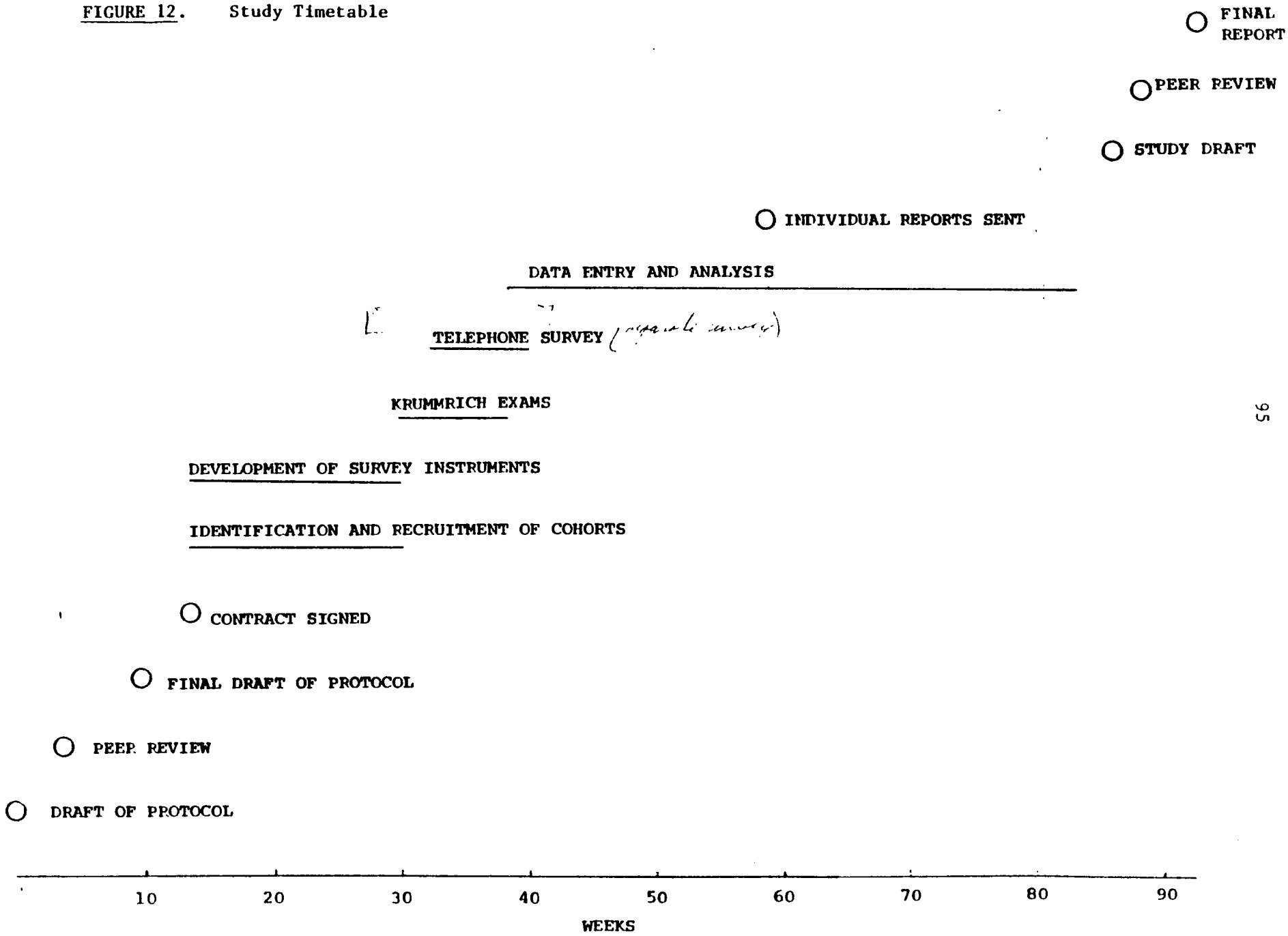
The study is expected to take 78 weeks to complete. The duration and timing of specific tasks are presented in Figure 13.

6.7 Human Subjects Review

The study is contingent upon approval by Northwestern University's Human Subjects Review Board. The major risks to participants are the discomfort of the medical examination and breach of confidentiality. The medical examination is by design non-invasive, with the exception of venopuncture. Venopuncture will be performed by a certified technician under the supervision of the examining physician.

Each participant's examination results will be confidential and will not be released to other parties without the participant's signed consent. Each participant will receive a study code number which will serve as his identifier. No personal identifiers will be entered into the computer or included in the group data file. A participant may elect to have his test results sent to his personal physician. A Monsanto employee may also elect to have his test results sent to the Monsanto Medical Department in lieu of his annual medical surveillance examination.

FIGURE 12. Study Timetable



7. Study Limitations and Corrective Measures

7.1 Loss to Study

Losses to the study may occur through 1) incomplete follow-up, 2) inaccessibility for examination, and 3) non-participation. If the losses are not random, then the study sample may not be representative of the entire exposed cohort. Losses will be especially damaging to the validity of the study if they are due to exposure and disease. For example, if exposure leads to illness, and illness results in termination, then losses due to terminations will bias the study in the negative direction.

Less than 10% of the exposed cohort are expected to be lost due to incomplete follow-up. These losses should not result in serious bias. Losses due to inaccessibility for examination are expected to be low, since 90% of the retirees and 75% of the terminated employees are estimated to be living within 300 miles of St. Louis. Non-participation is expected to result in substantial losses despite intensive recruitment efforts. We will compare the study sample with the entire exposed cohort on the basis of age, sex, race, payroll, work area, length of employment, and hospitalization rates while employed (available through the health insurance carrier) to determine if the sample is representative of the target population. We will also survey non-participants as to their reasons for non-participation and general health status.

7.2 Survival

If exposure results in the death of the most susceptible individuals, then a morbidity survey of survivors will underestimate the strength of the association between the exposure and disease. The mortality study conducted by Zack (1980) suggests that exposures at the Krummrich Plant are not resulting in excessive mortality.

7.3 Incidence-Prevalance Bias

Medical surveys are designed to measure the prevalence of disease at the time of the survey; they are much less sensitive at detecting incident events that may have occurred many years before. The present study is aimed at measuring long-term health effects; as such, prevalence is an appropriate measure of disease frequency.

The incidence of past events remains of interest, however, and will be measured by 1) asking incidence-type questions on the medical history (e.g. "Have you ever been hospitalized for an ulcer"), and by 2) medical record review.

7.4 Recall Bias

The exposed employees will know the purpose of the study and may be more likely to recall information on the medical history than non-exposed employees. This source of bias will be controlled by 1) medical record confirmation of major health events and 2) correlating physical and laboratory findings with medical history findings.

7.5 Interviewer/Examiner Bias

The medical interviewers and examiners may be biased in their measurement of health status if they know the subject's exposure history. This source of bias will be eliminated through 1) blinding the interviewers and examiners with respect to the subject's exposure status; 2) training of interviewers and examiners; and 3) use of standardized questionnaires and physical examination protocols.

7.6 Misclassification of Exposure

Employees at the Krummrich Plant may be misclassified with respect to their degree of exposure due to 1) temporal changes in exposure; 2) personal

differences in work practices; and 3) non-documented exposures. Misclassification of exposure will bias the study in the negative direction. Our chief concern is the frequent and undocumented assignment of employees to the Utility work force which may briefly place them in an exposed work area. These exposures will be ascertained through the occupational and environmental history questionnaire.

7.7 Confounding Chemical Exposures

Differences in health status between the exposed cohort and the internal controls may be due to the confounding effect of chemical exposures incurred in other departments. We will code the employment histories of Krummrich employees to allow for statistical search for confounding. Exposures incurred outside the Krummrich Plant will be analyzed in a similar manner. If confounding appears to be present for major health outcomes, a nested case-control approach may be warranted.

7.8 Repeated Measures

The comprehensive medical survey will provide data on a large number of health outcomes. If we set out alpha error at .05, one out of twenty will be significant by chance alone. A reduction of the alpha error would result in an unacceptably high beta error for low frequency events. The judgement of causality will not rely on statistical significance alone

Associations will be judged for causality on the following criteria:

1. Statistical significance
2. Temporal Sequence: The exposure must have preceded the disease.
3. Consistency: The association should be consistent with findings from previous studies.

4. Strength of Association: The larger the value of the prevalence odds ratio or the greater the difference in means, the less likely the association is to be spurious.
5. Dose-Response: The frequency and severity of disease should increase as the exposure increases.
6. Specificity: Alternative causes, such as confounding by demographic, lifestyle, or outside exposure variables, have been ruled out.
7. Biological Plausibility: The association is plausible in light of existing toxicological and epidemiological data.

7.9 Statistical Power Limitations

The study is limited in its statistical power to detect some associations by the size of the exposed cohort. Power analyses for dichotomous variables by size of the prevalence odds ratio are given in Table 25. Power analyses for continuous variables by the difference in means is given in Table 26. As is clear from these Tables, the sample size is adequate to detect mean differences of 10% for most of the continuous variables and prevalence odds ratios of 2 for many of the important dichotomous variables.

These estimates are conservative in that they are based on a total sample size of only 600 participants. A sample size of 800 would provide an additional 10-30% increase in power for many of the study variables.

TABLE 23

POWER ANALYSIS FOR DICHOTOMOUS VARIABLES BY SIZE OF THE ODDS RATIOS
(EXPOSED = 328; CONTROLS = 283; α =.05)

Variable	Control	Prevalence(%)	Power by ψ							
			1.1	1.25	1.5	1.75	2	3	4	5
History										
Acne	RH[a]	35.2	.14	.37	.78	.96	.99	.99	.99	.99
"	S[b]	29.5	.13	.35	.76	.95	.99	.99	.99	.99
Chloracne	S	0.0								
Skin Cancer	S	2.5	.07	.11	.20	.32	.54	.87	.99	.99
Other Cancer	S	1.2	.06	.09	.14	.20	.27	.59	.85	.97
Any Cancer	RH	40	.08	.14	.27	.44	.61	.97	.99	.99
Hepatitis	RH	4.1	.08	.14	.28	.45	.62	.97	.99	.99
Jaundice	RH	4.5	.08	.14	.29	.48	.66	.98	.99	.99
Cirrhosis	RH	.4	.06	.07	.09	.11	.13	.25	.39	.55
UGI Ulcer	S	5.5	.08	.16	.33	.54	.72	.99	.99	.99
Heart Disease	RH	17.6	.12	.28	.64	.89	.98	.99	.99	.99
" " Verified	RH	14.1	.11	.25	.58	.84	.95	.99	.99	.99
Myocardial Infarction	RH	.5	.06	.07	.10	.12	.15	.30	.48	.66
" " Verified	RH	.4	.06	.07	.09	.11	.13	.25	.39	.55
Coronary Artery Disease	S	6.1	.09	.16	.36	.58	.77	.99	.99	.99
Angina	S	6.1	.09	.16	.36	.58	.77	.99	.99	.99
Hypertension	S	24.5	.13	.33	.73	.94	.99	.99	.99	.99
Psychosis	RH	.5	.06	.07	.10	.12	.15	.30	.48	.66
Anxiety	RH	.5	.06	.07	.10	.12	.15	.30	.48	.66
Other Neuroses	RH	.8	.06	.08	.12	.16	.20	.44	.69	.87

TABLE 23 (continued)

Variable	Control	Prevalence(%)	Power by Ψ 1.1	1.25	1.5	1.75	2	3	4	5
Alcohol Dependence	RH	.3	.06	.07	.08	.10	.11	.19	.30	.42
Nervousness/Anxiety/ Depression	S	11.7	.10	.23	.53	.79	.93	.99	.99	.99
Decreased Libido	S	15.3	.11	.26	.60	.86	.97	,99	.99	.99
Impotence	S	11.7	.10	.23	.53	.79	.93	.99	.99	.99
Chronic Sinusitis and Upper Resp. Disease	RH	55.7	.14	.38	.79	.96	.99	.99	.99	.99
Kidney Disease	RH	3.5	.08	.13	.25	.40	.57	.95	.99	.99
Miscarriage	RH	13.6	.17	.49	.92	.99	.99	.99	.99	.99
"	S	11.8	.16	.46	.89	.99	.99	.99	.99	.99
Stillbirth	RH	.8	.07	.11	.19	.30	.43	.85	.98	.99
"	S	1.3	.08	.13	.26	.57	.60	.97	.99	.99
Birth Defects	RH	6.5	.12	.32	.72	.94	.99	.99	.99	.99
"	S	2.9	.09	.20	.45	.71	.88	.99	.99	.99
Physical Exam										
Appears Ill	RH	.1	.05	.06	.06	.07	.07	.09	.11	.14
Chloracne	S	0.0								
Acne Vulgaris	S	11.7	.10	.23	.53	.79	.93	.99	.99	.99
Hirsutism	S	1.8	.07	.10	.17	.26	.36	.76	.96	.99
Comedones	RH	20.7	.12	.31	.69	.92	.99	.99	.99	.99
Acneiform Lesions	RH	17.5	.12	.28	.64	.89	.98	.99	.99	.99
Acneiform Scars	RH	10.4	.10	.22	.49	.76	.91	.99	.99	.99
Cysts	RH	10.5	.10	.22	.50	.76	.91	.99	.99	.99
Hyperpigmentation	RH	7.1	.09	.18	.39	.63	.81	.99	.99	.99

TABLE 23 (continued)

Variable	Control	Prevalence (%)	Power by Ψ 1.1	1.25	1.5	1.75	2	3	4	5
Hepatomegaly	RH	.8	.06	.08	.12	.16	.20	.44	.69	.87
Pinprick	RH	9.6	.10	.21	.47	.73	.89	.99	.99	.99
Light Touch	RH	7.5	.09	.18	.41	.65	.83	.99	.99	.99
Muscle Status	RH	3.6	.08	.13	.25	.41	.57	.95	.99	.99
Vibration	RH	8.8	.09	.20	.45	.70	.87	.99	.99	.99
Patellar	RH	.6	.06	.07	.12	.16	.17	.34	.56	.75
Achilles	RH	3.4	.08	.13	.25	.40	.56	.95	.99	.99
Biceps	RH	.5	.06	.07	.10	.12	.15	.30	.48	.66
Babinski	RH	.3	.06	.07	.08	.10	.11	.19	.30	.42
Tremor	RH	4.0	.08	.14	.27	.44	.61	.97	.99	.99
Coordination	RH	3.9	.08	.14	.27	.43	.60	.97	.99	.99
Romberg	RH	19.1	.12	.30	.67	.90	.98	.99	.99	.99
Gait	RH	1.8	.07	.10	.17	.26	.36	.76	.96	.99
Lab										
Sed Rate										
≤40 y.o.	RH	4.2	.07	.10	.18	.28	.39	.80	.97	.99
>40 y.o.	RH	5.4	.07	.11	.21	.33	.46	.87	.99	.99
RBCs on U/A	RH	1.3	.06	.09	.14	.21	.28	.63	.88	.98
Protein on U/A	RH	2.6	.07	.11	.21	.33	.46	.87	.99	.99
ECG										
<40 y.o.	RH	23.1	.10	.21	.46	.71	.87	.99	.99	.99
≥40 y.o.	RH	28.4	.10	.22	.50	.75	.90	.99	.99	.99

TABLE 24

POWER ANALYSIS FOR CONTINUOUS VARIABLES BY DELTA %

(Exposed=300: Controls=300)

VARIABLE	Power by Delta %								
	5	10	15	20	30	40	50	75	100
Alk. Phosphatase	.59	.99	1	1	1	1	1	1	1
GGT Males	.17	.53	.86	.98	1	1	1	1	1
LDH Males	.99	1	1	1	1	1	1	1	1
SGOT (AST)	.38	.91	1	1	1	1	1	1	1
SGPT (ALT) Males	.25	.73	.97	1	1	1	1	1	1
Triglycerides	.44	.95	1	1	1	1	1	1	1
Glucose	1	1	1	1	1	1	1	1	1
Urea Nitrogen	.74	1	1	1	1	1	1	1	1
Creatinine Males	.98	1	1	1	1	1	1	1	1
Total Protein	1	1	1	1	1	1	1	1	1
Total Bilirubin	.31	.84	.99	1	1	1	1	1	1
LDL	.92	1	1	1	1	1	1	1	1
HDL	.7	1	1	1	1	1	1	1	1
LH Males	.43	.73	.94	1	1	1	1	1	1
FSH Males	.26	.74	.98	1	1	1	1	1	1
Testosterone Males	.54	.98	1	1	1	1	1	1	1
T-4 by RIA	.84	1	1	1	1	1	1	1	1
T-3 Uptake Ratio	1	1	1	1	1	1	1	1	1
Free Thyroxine Index	1	1	1	1	1	1	1	1	1

Table 24 (continued)

	Power by Delta %								
	5	10	15	20	30	40	50	75	100
WBC	.85	1	1	1	1	1	1	1	1
Hemoglobin	1	1	1	1	1	1	1	1	1
HCT	1	1	1	1	1	1	1	1	1
Platelet Count	.66	1	1	1	1	1	1	1	1
Ferritin	.09	.22	.43	.67	.95	1	1	1	1
Creatinine Clearance	.98	1	1	1	1	1	1	1	1
Delta Ammino Levulinic Acid	.13	.37	.69	.91	1	1	1	1	1
Porphobilinogen	.4	.93	1	1	1	1	1	1	1
Copropophyrin	.2	.6	.91	.99	1	1	1	1	1
IgG	.86	1	1	1	1	1	1	1	1
IgA	.28	.8	.99	1	1	1	1	1	1
IgM	.4	.93	1	1	1	1	1	1	1
Total Protein-Urine	.86	1	1	1	1	1	1	1	1
T-Pan	.67	1	1	1	1	1	1	1	1
T-Helper	.38	.91	1	1	1	1	1	1	1
T-Suppressor	.36	.97	1	1	1	1	1	1	1
T-Helper/T-Suppressor	.56	.99	1	1	1	1	1	1	1

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9. PEER REVIEW COMMITTEE

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Morgantown, West Virginia

PRELIMINARY BUDGET ESTIMATES FOR KRUMMRICH PROJECT

1) Data Gathering - 18 subjects per day by a team of 6 physicians (3 internists, 2 neurologists, 1 dermatologist) working 5 days per week and communting from chicago on a weekly basis. (All figures assume 813 subject examination.)

Physician Fees	585,360
Physician Expenses	65,800
Blood & Urine Test	654,000
Paramedical Salaries	78,750
Equipment Lease/Purchase	46,300
Survey Research Lab	170,000
Neuro Behavioral Exam	12,810
Subject Reimbursement	54,000
	1,667,020

2) Data analysis - assumes 18 month required for data analysis and generation of individual reports.

Salary of Investigators	156,000
Salary for Support Personel	356,134
Office Equipment, Supplies	45,465
Equifax Cohort Search	45,150
Data Coding Service	31,150
Consultation Fees & Expenses	13,632
Peer Review	10,000
	657,531

Totals:	
I	1,667,020
II	657,531
University Overhead	53,250
	2,377,801

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