EPIDEMIOLOGY

HEALTH EFFECTS OF PENTACHLOROPHENOL (PCP) IN HUMANS

The purpose of this chapter is to review the evidence of health effects in humans resulting from exposure to pentachlorophenol (PCP). In particular, the acute and chronic toxicity, teratogenic/ reproductive effects, and carcinogenicity are discussed.

An extensive body of literature exists on the health effects (acute and chronic) of PCP in humans. A number of reviews of literature on PCP and commonly associated substances have been published (Scow and Delpire,1980; EPA, 1984, 1987; NCI, 1985; WHO, 1986; IARC, 1987; 1990). Due to the apparent number and complexity of relationships between PCP exposure and resulting health effects, a simple cause-effect portrait is difficult to conclude. Nevertheless, considerable attention was given to presenting the information collected during the review in as logical a format as possible. Two approaches are used in this section:

- The potential acute health effects of PCP in humans, reported as incident reports from different sources, are summarized.

- A literature search of chronic health effects associated with PCP exposure, including results of epidemiological studies, are summarized.

INCIDENT REPORT DATA ASSOCIATED WITH HEALTH EFFECTS OF PCP EXPOSURE

There are many incident report data associated with health effects after acute PCP exposure. The following data bases have been consulted for the poisoning incident data on the active ingredient Pentachlorophenol (PC Code: 063001):

OPP Incident Data System (IDS) - The Incident Data System of The Office of Pesticide Programs (OPP) of the Environmental Protection Agency (EPA) contains reports of incidents from various sources, including registrants, other federal and state health and environmental agencies, and individual consumers, submitted to OPP since 1992. Reports submitted to the Incident Data System represent anecdotal reports or allegations only, unless otherwise stated. Typically no conclusions can be drawn implicating the pesticide as a cause of any of the reported health effects. Nevertheless, sometimes with enough cases and/or enough documentation risk mitigation measures may be suggested.

Poison Control Centers - as the result of a data purchase by EPA, OPP received Poison Control Center data covering the years 1993 through 1996 for all pesticides. Most of the national Poison Control Centers (PCCs) participate in a national data collection system, the Toxic Exposure Surveillance System which obtains data from about 65-70 centers at

hospitals and universities. PCCs provide telephone consultation for individuals and health care providers on suspected poisonings involving drugs, household products, pesticides, etc.

California Department of Pesticide Regulation - California has collected uniform data on suspected pesticide poisonings since 1982. Physicians are required, by statute, to report to their local health officer all occurrences of illness suspected of being related to exposure to pesticides. The majority of the incidents involve workers. Information on exposure (worker activity), type of illness (systemic, eye, skin, eye/skin and respiratory), likelihood of a causal relationship, and number of days off work and in the hospital are provided.

National Pesticide Telecommunications Network (NPTN) - NPTN is a toll-free information service supported by OPP. A ranking of the top 200 active ingredients for which telephone calls were received during calendar years 1984-1991, inclusive, has been prepared. The total number of calls was tabulated for the categories human incidents, animal incidents, calls for information, and others.

Literature Published Incident Reports - Some incident reports associated with PCP related human health hazard are published in the scientific literature.

OPP's Incident Data System (IDS)

Please note that the following cases from the IDS do not have documentation confirming exposure or health effects.

Incident#285-1

A pesticide incident was reported in 1992, when a woman called the Office of Pesticide Programs to report that workers at a plant using pentachlorophenol were experiencing health effects. She reported chemical burns and dermatitis. No further information on the disposition of the case was reported.

Incident #2796-283

A female neighbor complained of ill health after exposure to fumes from timber treatments of PCP in a nearby building. No further information on the disposition of the case was reported.

Poison Control Center Data - 1993 through 1996

A total of 122 unintentional exposures were reported to the Toxic Exposure Surveillance System from 1993 through 1996. Children under six years of age were involved in 32 of the exposures and half of these were followed to determine outcome. Only five of the children were reported to have developed symptoms, all of which were minor. Six of the children were reported seen in a

health care facility and one was hospitalized. The number of cases reported in children under age six is too small for meaningful comparisons with other pesticides.

There were 90 exposures in adults and older children, 30 of which had a minor outcome, nine with moderate outcome, and one case that was considered life-threatening. Thirty-four cases were seen in a health care facility, two were hospitalized, and one was admitted for critical care. Compared to other pesticides, pentachlorophenol had somewhat higher percents of cases that had a moderate (based on 9 cases) or life-threatening (based on a single case) outcome. However, this finding was due to a relatively small number of cases. A smaller proportion of cases was hospitalized or admitted for critical care (ICU) for PCP than for all pesticides combined. These comparisons are shown in **Table 1** below.

Table 1.
Comparison between PCP and all pesticides for percent cases with symptomatic outcome (SYM), moderate or more severe outcome (MOD), life-threatening or fatal outcome (LIFE-TH), seen in a health care facility (HCF), hospitalized (HOSP), or seen in an intensive care unit (ICU) for adults and children six years and older reported to Poison Control Centers, 1993-1996.

Pesticide	SYM*	MOD*	LIFE-TH*	HCF*	HOSP*	ICU*
PCP	77%	23%	2.56%	38%	5.9%	2.9%
ALL PESTICIDES	72%	12%	0.37%	21%	7.6%	3.3%

* Symptomatic cases based on those cases with a minor, moderate, major, or fatal medical outcome. Denominator for SYM, MOD, and LIFE-TH is the total cases where medical outcome was determined. Denominator for HCF is all exposures. Denominator for HOSP and ICU is all cases seen in a health care facility.

California Data - 1982 through 1996

Detailed descriptions of 71 cases submitted to the California Pesticide Illness Surveillance Program (1982-1996) were reviewed. In 48 of these cases, pentachlorophenol was judged to be responsible for the health effects. Only cases with a definite, probable or possible relationship were reviewed. **Table 2** presents the types of illnesses reported by year. **Table 3** gives the total number of workers that took time off work as a result of their illness and how many were hospitalized and for how long.

Table 2. Cases Due to Pentachlorophenol Exposure in California Reported by Type of Illness and Year, 1982-1996

Year	Illness Type					
	Systemic[a]	Eye	Skin	Respiratory	Combination[b]	Total
1982	15	4	3	-	1	23
1983	1	3	3	-	-	7
1984	-	2	1	-	-	3
1985	1	2	-	-	-	3
1986	2	1	1	-	-	4
1987	-	1	1	-	-	2
1988	1	1	-	-	-	2
1989	-	-	-	-	1	1
1990	-	1	1	-	-	2
1991	-	-	-	-	1	1
1992-96	-	-	-	-	-	-
Total	20	15	10	0	3	48

[a] Category includes cases where skin, eye, or respiratory effects were also reported.
[b] Category includes combined irritative effects to eye, skin, and respiratory system.

Table 3. Number of Persons Disabled (taking time off work) or Hospitalized for Indicated Number of Days After Pentachlorophenol Exposure in California, 1982-1996.

	Number of Persons Disabled	Number of Persons Hospitalized
One day	3	-
Two days	1	-
3-5 days	1	-
6-10 days	-	1
more than 10 days	1	-
Unknown	5	2

Most of the reports of illness in California, 58% of the total, were irritative effects to the eye and skin. The remaining 42% were systemic in nature, including symptoms of headache, nausea, and difficulty breathing. However, only half of the systemic cases were classified as having a probable or definite relationship between the exposure and the health effects. For the time period 1982 through 1994, pentachlorophenol ranked 51st out of 253 active ingredients responsible for systemic poisonings in California. One individual was hospitalized in 1982 for skin grafts due to second and third degree burns after carrying treated lumber for four weeks. The burns were reported to the shoulder, neck, chin, back, and thigh, and characterized as an allergic reaction by one investigator. Nine workers in a county road crew experience drift after the improper application of a wood preservative by an airless sprayer. A variety of worker activities were associated with exposure to pentachlorophenol as illustrated in **Table 4** below.

Handling PCP-treated wood has resulted in skin irritation in some individuals. Applicators are most often affected as a result of getting PCP in their eyes during a spray operation.

Table 4.
Illnesses by Activity Categories for Pentachlorophenol Exposure in California, 1982-1996

Activity Category[a]	Illness Category					
	Systemic[b]	Eye	Skin	Respir-atory	Combi-nation[c]	Total
Applicator	-	9	5	-	-	14
Coincidental	10	2	2	-	-	14
Pack/Proc	1	3	1	-	-	5
Other	9	1	2	-	3	15
Total	20	15	10	-	3	48

[a] Pack/Proc = Packing or processing; Other=other occupational and non-occupational exposures.
[b] Category includes cases where skin, eye, or respiratory effects were also reported
[c] Category includes combined irritative effects to eye, skin, and respiratory system

National Pesticide Telecommunications Network (NPTN)

On the list of the top 200 chemicals for which NPTN received calls from 1984-1991 inclusively, pentachlorophenol was ranked 24th with 145 incidents in humans reported and 1 incident in animals.

Incident Reports Associated with Acute Toxic Effects of PCP Published in Scientific Literature.

As summarized by Reigart and Roberts (1999), the following factors apply to acute PCP poisoning:

- Pentachlorophenol volatilizes from treated wood and fabric. It has a significant phenolic odor, which becomes quite strong when the material is heated. Excessively treated interior surfaces may be a source of exposure sufficient to cause irritation to the eyes, nose, and throat.

- At certain concentrations, PCP is irritating to mucous membranes and skin. Contact dermatitis is common among workers having contact with PCP. In a study of employees involved in the manufacture of PCP, chloracne was found in 7% of the workers and the risk was significantly higher among employees with documented skin contact compared to employees without skin contact. Urticaria has also been reported as an uncommon response in exposed persons.

- In addition to the symptoms above, Reigart and Roberts (1999) report fever, muscle spasms, tremor, labored breathing, chest tightness in the more serious cases (Wood et al. 1983, Gray et al. 1985). Some fatalities have been reported from working in hot environments where hyperthermia is poorly tolerated.

The World Health Organization (1987) emphasized extreme weakness, fever, and profuse sweating as signs of poisoning and noted that the minimum lethal human dose was estimated to be 29 mg/kg.

One of the earliest reports recognizing the serious toxic effects of PCP in humans was published by Truhaut et al. in France (1952). The authors described the then current procedures for treatment of lumber to prevent rotting. Workers known as "treaters" soaked freshly sawn lumber in tubs containing a 3% solution of a mixture of 80% pentachlorophenate of sodium and 20% tetrachlorophenate of sodium. After soaking, the lumber was then carried to other workers called "stackers" to be put in stacks. Based on examinations of more than 100 lumber "treaters", symptoms of PCP exposure included skin irritation with blisters, congestion of mucous membranes of eyes and nose, loss of appetite, loss of weight, constriction of throat, respiratory stress, and fainting. Urine levels of PCP in 16 workers who had worked for two months as "treaters" were between 3 and 10 mg/l.

Truhaut et al. (1952) also reported on the deaths of two workers following exposure to PCP. The first worker had worked as a stacker for one month, then for four days as a treater. Prior to his death, he experienced headache, achiness, sweating, and rapid breathing. Autopsy findings included liver poisoning, degenerative lesions in kidney, considerable edema in the lungs, and PCP in liver, kidney, blood, stomach, intestine, heart, lung, and urine. The second fatal case involved a man who worked as a treater for six days. His symptoms included marked lack of appetite, extreme tiredness, profuse sweating, extreme thirst, and an elevated rectal temperature of 43 degrees C. Pathology findings included considerable congestion and edema of the lungs, and albumin in the urine.

At the time of this report (Truhaut et al.1952), acute and short-term effects of exposure to PCP were known and had resulted in implementation of simple protective measures such as wearing gloves and aprons when handling material wetted with PCP. However, the possibility of death from PCP exposure, other than by acute poisoning, was not known. This brief case series provides only limited data upon which to base conclusions, but does suggest death can occur from heavy exposures occurring over a relatively short period of days or weeks.

The study of over 600 factory workers with 7% reporting chloracne, cited by Reigart and Roberts (1999), was based on cumulative incidence (O'Malley et al. 1990). The reported annual incidence in this group was 2%. O'Malley et al. reported that the PCP produced at this plant was contaminated with chlorinated dioxins and dibenzofurans which have been reported to cause chloracne in other human and animal studies. Those workers with records of direct skin

exposure to PCP had a four fold increase in the risk of developing chloracne compared to other workers. The interval between the last report of direct skin contact and the diagnosis of chloracne ranged from 7 weeks to about 14 years among 13 cases. Four of the 13 cases occurred withing 6 months of contact, four occurred between 1 and 2 years after contact, and three occurred more than 10 years after exposure.

Another study of 366 factory workers found a cumulative incidence of 18% with evidence of current or past chloracne (Hryhorczuk et al. 1998). Self-perceptions of health, self-reported hospitalizations, and self-reported doctor/clinic visits did not differ significantly between the exposed and the control group. A general evaluation by an internist did not find any differences between the PCP and unexposed groups. There was no evidence that workers in this study developed porphyria based on medical records or urinary porphyrin levels. However, workers with chloracne had significantly higher excretion of coproporphyrin compared to unexposed workers. Though not clearly stated in this study, it appears that some workers (14) had chloracne that persisted for many years after their last exposure to PCP.

Lambert et al. (1986) reported on 3 cases related to non-occupational PCP exposure. Two cases developed pemphigus vulagaris, an autoimmune disease where the patient develops successive blisters (bullae) which can be potentially fatal if the disease becomes widespread. Both cases had extensive exposure to the sun and only incidental exposure to PCP. In one case the 41 year old male purchased a PCP treated bookcase and in the other case, the 28 year old female had several rafters in the living room treated with PCP. A third case of urticaria occurred in a 35 year old male who worked with PCP-treated wooden framework. The authors noted a "striking parallelism" in all three cases between their disease course and PCP serum levels and stated that these cases suggest "possible new hazardous effects of PCP".

Klemmer et al.(1980) compared clinical findings in a group of 47 workers exposed to PCP and 42 controls. Age standardized prevalence rates for conjunctivitis, chronic sinusitis, and chronic upper respiratory conditions were significantly higher for PCP-exposed workers. It was noted that the conjunctivitis cases only occurred among workers involved in pressure treatment and therefore had mixed exposure to PCP and other chemicals. The authors report that the sinusitis cases typically involved low grade infections that did not require medical intervention. They concluded that workers exposed to PCP during wood treatment under the conditions of their study did not experience serious health effects.

Cole et al. (1986) reported a case involving a 32 year old carpenter who developed chloracne of six months duration. The patient was part owner of a firm that constructed piers for small boat marinas. The lumber used was pre-treated with PCP. Though he was aware of the requirements for protection when working with treated wood, he chose to disregard them and was often lying atop the lumber to measure it accurately. His skin condition developed about 9 months after beginning work. After four and a half months of treatment his skin condition improved considerably and he has remained symptom free for the ensuing two years of observation.

Cooper and Macaulay (1982) reported a case of a 51 year old joiner who applied PCP and zinc naphthanate to new floorboards with a brush and no protective equipment as required on the label. He developed abdominal pain, vomiting and dark urine that were diagnosed as pancreatitis. The authors felt that the evidence of symptoms of PCP poisoning implicated PCP as the cause of the pancreatitis rather than the zinc naphthanate.

Gray et al. (1985) reported the case of a 33 year old man who used a jackhammer to break up large blocks of PCP which were ground into powder. He developed lethargy, rapid respiration, and sweating, which led to his hospitalization. At the hospital he became comatose with high fever and pulmonary edema and died. An OSHA investigation found the employee had not been adequately trained and improper protective equipment had been used.

Wood et al. (1983) reported on five cases of PCP poisoning, two of which were fatal. Typical symptoms included high fever, sweating, rapid heartbeat and breathing, and abdominal pain. These cases occurred at two small wood preservative manufacturing plants. In one of the fatalities the worker had been involved in crushing 2,000 pound blocks of PCP with a jackhammer in a small, poorly ventilated room. The second fatality had been involved in a dry mixing process in an area with poor ventilation. A general air sample taken from this area found PCP levels (4.6 mg/m^3) nine times the OSHA standard.

The U.S. Environmental Protection Agency conducted a survey of PCP-treated log homes and their occupants at the request of the Kentucky Department of Health Services. Environmental and medical data were collected on 21 homes. Serum and urinary levels of PCP were highest in children 4-7 years old and lowest in the over 12 years old age group. For children 4-7 years old, geometric mean levels of PCP were 52 ng/mL in serum (25% greater than levels in those older than 12 years) and 0.036 mg/g creatinine in urine (just over twice as high as those older than 12 years). No significant differences were reported on a health questionnaire between health complaints and serum or urinary levels of PCP. A clinical laboratory examination did not find differences on tests of liver function, microsomal enzyme induction, or renal function with levels of PCP. No significant difference was reported for the neurologic examination or for lymphadenopathy. However, there was a relationship between a finding of skin abnormalities and levels of PCP in the urine or serum. The types of skin abnormalities were not described. The author noted that skin abnormalities might lead to increased absorption of PCP resulting in higher biologic PCP concentrations in blood and urine, rather than PCP being a cause of skin abnormalities.

An earlier review of PCP found that immersion of hands for 10 minutes in a 0.4% solution caused pain and inflammation (Bevenue et al. 1967). Dust and mist concentrations greater than 1.0 mg per cubic meter can result in painful irritation of upper respiratory tract resulting in violent sneezing and coughing in persons not previously exposed to PCP (US EPA 1980). Some nose irritation has been reported at levels as low as 0.3 mg per cubic meter.

An incident occurred in a nursery for newborn infants in St. Louis in 1967 (Armstrong et al.

1969, Smith et al. 1996). Sodium pentachlorophenate had been used as an antimildew agent by the hospital laundry. Nine cases of illness were seen with fever and profuse sweating. As the disease progressed, respiratory rates increased and breathing became labored. Other common findings included rapid heart rate, enlarged liver, and irritability followed by lethargy. Laboratory tests showed progressive metabolic acidosis, proteinuria, increased levels of blood urea nitrogen, and x-rays suggestive of pneumonia or bronchiolitis. Two of the cases were fatal. The only source of exposure for the infants was skin absorption of the residues of sodium pentachlorophenate on the diapers, undershirts, and bedding. The product label warned against use in laundering diapers and the amount used was 3-4 times the amount recommended for regular laundry. Analysis of freshly laundered diapers showed a quantity of PCP ranging from 1.4 to 5.7 mg per diaper. One infant had 11.8 mg of PCP per 100 ml of serum before a transfusion was performed. A fatal case was found to have 2.1-3.4 mg per 100 grams in various body tissues. The average duration of the hospital stay in the nursery (when contaminated diapers were used) till the appearance of the first symptoms was 9 days.

A study in Germany examined data on 320 subjects with neurologic disorders categorized as probably or possibly due to environmental agents (Lohmann et al. 1996). Of these 320 cases, 136 (79 females and 57 males) showed signs of multiple chemical sensitivity (MCS). Indoor wood preservatives including PCP and/or lindane were implicated as causative agents in 63% of the MCS cases. The authors note that this was a purely descriptive study rather than a controlled epidemiologic study, so that proof of a causal relationship is not intended. Given the relatively large percentage of MCS cases associated with PCP, further study of PCP as a potential cause of MCS is warranted.

An extensive review of human PCP poisoning by Jorens and Schepens (1993) concluded that "use of PCP-based products as indoor wood preservatives poses an unacceptable risk to human health." They recommend that workers in plants and sawmills be required to wear protective clothing that would prevent any skin contact with PCP. They report that four European countries, Sweden, the Federal Republic of Germany, Switzerland, and Denmark, have banned all use of PCP.

EPIDEMIOLOGIC STUDIES ASSOCIATED WITH HEALTH EFFECTS OF PENTACHLOROPHENOL IN HUMANS

To summarize the epidemiologic studies associated with PCP exposure, considerable attention was given to presenting the information collected during the review in as logical a format as possible. Reviewed papers are primarily organized according to the type of epidemiologic method followed, i.e., case series involving chronic effects, cross-sectional, case-control, and cohort studies.

1. Case Series Involving Chronic Effects

In addition to the acute incidence report summarized previously, some chronic health

effects are also reported after exposure to pentachlorphenol and related compounds. The cause-effect relationship is often difficult to establish, particularly because of confounding factors which may occur over a long latency period. These reports are also summarized in this document.

2. **Cross-sectional Study**
   This kind of study usually involves surveying a group of people or a community, perhaps stratified by age, sex, ethnicity, working environment etc., but at one point in time or over a short time interval. Although a snapshot, surveys of prevalence and intensity within different age classes of a community can provide valuable information on the rate at which individuals acquire exposure through time, provided that the exposed population and the source of the risks have remained stable for a period of time. Potential association of the risk factors (exposure) and disease may be suggested by statistical association.

3. **Cohort Study**
   By evaluating individuals selected on the basis of their exposure to the agent under study and monitored for development of disease, prospective studies monitor individuals who initially are disease-free to determine if they develop the disease over time.

4. **Case-Control Study**
   In case-control studies, subjects are selected on the basis of disease status: disease cases and matched-controls of disease-free individuals. The exposure histories of the two groups are compared to determine key risk factors for disease.

Within each category of epidemiologic study, the information in this document includes (1) population investigated, (2) what health effects and other effects were found, and (3) what level of confidence should be assigned to the study results. **Table 5**, attached at the end of this section, summarizes the results of the studies reviewed for this document.

Case Series Involving Chronic Effects Associated with Health Effects of PCP in Humans

Bishop and Jones (1981)

Bishop and Jones (1981) reported the occurrence of two cases of non-Hodgkin's lymphoma (NHL) among 158 workers at a plant that, until 1978, had manufactured PCP and its sodium salt. Several homologues of tetrachlorodibenzodioxin (TCDD), particularly the hexachloro and octachloro dibenzodioxins, were known to exist as contaminants of chemical intermediates (300 ppm) and the plant's final product (5 ppm). During the period of PCP production, a number of cases of chloracne were diagnosed; most were mild, some moderate, and a very few, severe. After cessation of PCP production in 1978, the two cases of NHL were discovered.

The first case was in a 69 year-old male involved in PCP manufacture from 1959 to 1972. In

1976, a tumor in the scalp developed with histology showing infiltration of the dermis and subcutaneous tissue with lymphoid cells suggesting NHL. This patient also had mild chloracne of the face and trunk. The second case occurred in a 53 year-old male who worked as an operator in PCP manufacturing from 1957 to 1978. During his employment, he had severe chloracne of the face, neck, trunk, and genitals. In 1978, this patient developed a tumor in the right occipital region of the scalp with histology showing malignant lymphoma described as NHL. Both NHL patients had worked in processes involving exposure to other chemicals including aromatic hydrocarbons, among them benzene.

No Standard Mortality Ratio (SMR) analysis was reported by the authors, but the expected number of cancers of this type (International Classification of Disease [ICD] 200 and 202) in this population of 158 workers was reported as 0.28. Considering ICD 200 alone, the expected number of cases would be 0.2.

Roberts (1990)

A 25-year compilation of documented case reports of aplastic anemia, pure red cell aplasia, leukemia, lymphoma, and other hematologic disorders following exposure to PCP was reported. The cases occurred between 1963 and 1987 and involved industrial and public exposures to a variety of products containing PCP. Information was derived from clinical experiences of the author, communications with other physicians or investigators, and from EPA records.

Roberts provides a moderate level of detail on 13 cases of aplastic anemia, pure red cell aplasia, and associated disorders. Seven other cases of hematologic disorders attributed to PCP-containing products are presented in tabular form only. Original articles on some of the cases are published elsewhere, some of which are included in this document. Of most interest, and perhaps importance, are the reports of repeated occurrence of disease with subsequent re-exposure and discovery of clusters of cases within very limited exposure environments.

The careful compilation and maintenance of this etiologic history is impressive and should become even more important if additional cases are added as time passes. Certainly, some of the cases and reports are deserving of additional epidemiologic examination. The paper, on its own, lacks enough detail to arrive at any conclusions regarding association between exposure to PCP and development of blood dyscrasias.

Cross-Sectional Studies Associated with Health Effects of PCP in Humans

Gilbert et al. (1990)

Gilbert et al. (1990) conducted a cross-sectional study of 88 wood treaters in Hawaii and 58 controls to assess differences in morbidity and mortality. The exposed group was selected from a total of 182 workers who had worked for long periods and had chronic low-level exposure to wood treating chemicals including PCP. Exposed workers had to be currently employed in a

Hawaiian wood treatment company for at least three months at the time of recruitment for the study or have been previously employed at least 12 months in a Hawaiian wood treatment company since 1960, including at least one 3-month period of continuous employment as a wood treater. Unexposed workers were matched on age, gender, race, level of physical activity, and weight. Of the total of 182 exposed workers recruited for the study, only 88 agreed to participate. Comparisons were made of detailed medical histories, laboratory and physiological tests, physical examinations, actual versus anticipated cancers, and causes of death for the exposed and unexposed.

While the occupationally exposed workers had significantly higher levels of PCP in urine compared to the controls (mean of 174 ppb vs. 35 ppb), no significant differences were seen in medical histories or results of physical exams between the cases and controls. With the exception of elevated hepatic enzymes in both groups, the laboratory data and review of organ systems revealed no clinically significant differences between exposed and unexposed groups. The three incident cases of cancer and the six deaths among the exposed workers were fewer than expected.

Karmaus and Wolf (1995)

Wood preservatives containing PCP and γ-hexachlorocyclohexane (HCH) as biocidal substances, as well as polychlorinated dibenzo-p-dioxins and dibenzofurans (PCDDs, PCDFs) as contaminants, were used extensively in Western Germany, particularly during the 1960s. These products were used not only for exterior wood, but also for treating paneling and other interior wood products.

In a cross-sectional study of 398 women employed in day-care centers in Germany, the effect on the women's offspring resulting from exposure of the women to wood preservatives was studied by Karmaus and Wolf (1995). A number of health effects were measured by medical checkups with blood and urine sampling and face-to-face interviews for occupational, lifestyle, and reproductive histories. Official medical documents were used to obtain data on pregnancy outcome, birthweight, and length. Measurements of PCP, HCH, PCDD, and PCDF concentrations had been performed independently by the government as a screening program to control indoor air exposures. For each of the 556 pregnancies from the total study population, exposure to wood preservatives was estimated based on whether the woman had worked in any of 24 facilities known to have PCP concentrations >100 ppm. This assessment resulted in an exposed group of 214 and a control group of 184.

Of the 556 pregnancies, only 49 occurred during periods when the mothers were subject to exposure to wood preservatives. Of these 49 exposed pregnancies, only 32 were associated with first exposures. The number of induced pregnancies, spontaneous abortions, and births by cesarean section were increased in the exposed pregnancy group. Birthweights were reduced by 150 g and birth lengths reduced by 2 cm in the exposed group. Other observations included a higher prevalence of twins and more frequent complications during pregnancy in the exposed

group compared to the unexposed group. Limitations of the study included some inequities between the exposed and unexposed groups and the possibility of bias. The women in the exposed group were older, had a higher average parity, were more often exposed in private homes, and more often had a desire for a child. The proportion of participation was lower in the control group. Birthweight and length data were verified with some knowledge of exposure status, and therefore could be somewhat biased.

The study provides reasonable evidence that exposure of mothers during pregnancy to wood preservatives may decrease birthweights and lengths of offspring. However, considerable differences between the exposed and unexposed groups, and the possibility of some data collection bias, somewhat diminishes the importance of findings. Because exposures were to multiple substances, any negative detrimental effect cannot be attributed to a specific substance.

Walls et al. (1998)

A cross-sectional study was performed by Walls et al. (1998) on a group of 127 timber sawmill workers who were self-identified as having health concerns related to PCP exposure. A questionnaire-based survey was used to collect data on occupational and lifestyle histories, exposure to PCP, past health status, and current symptoms. An exposure metric incorporating length of PCP exposure and a cumulative score for types of PCP work, type of vehicle, use of personal protection, and intensity of exposure, was calculated for each participant. Based on this exposure metric, participants were categorized into three exposure groups.

Within the limits imposed by the data used in this study, a dose-response relationship was identified between PCP exposure and reported symptoms associated in the literature with PCP exposure (sweating, weight loss, fatigue), and with a screening measure for neuropsychological dysfunction. The study was not designed to show association between PCP exposure and chronic or fatal diseases, such as cancer. While the results of the study agree with those in a number of other similar studies, major limitations lie in the fact that the study participants self-identified and many also had exposures to other chemicals typically used in the timber industry and to organopesticides.

Case Control Studies Associated with Health Effects of PCP in Humans

Pearce et al. (1985)

Pearce et al. (1985) conducted a case-control study of 734 male malignant lymphoma and multiple myeloma patients to investigate possible associations of these diseases with particular occupations, especially farming. The cases consisted of all male patients registered with the New Zealand Cancer Registry between 1977 and 1981 who were classified under ICD codes 200-203 and who were at least age 20 at the time of registration. Four controls for each case (n=2936) also were selected from the registry and matched on age (within two years), year of registration, and who were not registered as cases of NHL, Hodgkins's disease, multiple myeloma, or Soft

Tissue Sarcoma (STS).

The risk factor investigated in this study, occupation, was determined from cancer and death registrations, both of which included a brief description of each individual's current or most recent occupation at time of registration. This occupational information, codified through the New Zealand Standard Classification of Occupations was used to compare occupational distributions of cases and controls. Social class distributions also were compared for the cases and controls. A significant excess of professional and technical workers and workers in agriculture, forestry, and fishing were observed in the case group. A significant excess also was seen in occupations of the upper social classes. The authors suggested that the excess of professional and technical persons in the case group may have resulted from social class confounding.

The precision of the exposure variable (occupation) used in this study was very crude, and the excesses observed for agricultural occupations were not large. With regards to evaluating possible associations of PCP exposure with NHL, malignant lymphoma, or multiple myeloma, the significance of the findings in this study are limited.

Eriksson et al. (1990)

Eriksson et al. (1990) assessed the influence of previous jobs and exposures to a number of agents, including pesticides, in a study of 237 males with STS and 237 controls matched on age, gender, and county of residence in Sweden. Cases were identified as all male patients, aged 25 to 80 years, who were reported to a cancer registry in Sweden with a diagnosis of STS. Exposure was assessed from responses to a questionnaire mailed to living participants or to next-of-kin of deceased participants. Included were questions about participants' complete work history, details on 16 specific occupations including farming, forestry, carpentry, painting, and mining, questions about various exposures, and questions about smoking. Incomplete information on exposures of particular interest was completed through telephone interviews. Completed questionnaires were collected for 218 cases and 212 controls. Exposure to chlorophenols and organic solvents for one week or more continuously or at least one month totally was classified as high grade; less exposure was classified as low grade.

Exposure to phenoxyacetic acids and high grade exposure to chlorophenols yielded a Relative Risk (RR) of 1.83 (95% Confidence Interval [CI] = 1.10-3.04) in the matched analysis, while exposure to phenoxyacetic acids only yielded a nonsignificantly increased RR of 1.34 (CI = 0.70-2.56). More interesting for the purpose of this review, high grade exposure to chlorophenols, excluding phenoxyacetic acid produced a RR of 5.25 (CI = 1.69-16.34). The same type exposure to PCP yielded a RR of 3.85 (CI = 1.15-12.88). The median latency for development of STS in persons with high grade exposure was 31 years, and exposure to PCP was a factor in almost all cases. No significant differences in relative risk of disease for cases and controls were observed for exposure to any other chemicals.

Smith and Christophers (1992)

A case-control study of 30 males with STS and 52 males with malignant lymphoma was conducted to determine if there was an association between these diseases and past exposure to chlorinated phenoxy acid herbicides or chlorophenols (Smith and Christophers, 1992). The study was conducted in Australia, and cases were selected from all male cancer patients 30 years or older at the time of registration in the Victorian Cancer Registry over the period of 1982-1988. One population control and one cancer control for each case were matched on age, place of residence, and gender.

Exposure to pesticides and wood preservatives was assessed through interviews administered by an occupational hygienist with experience in pesticide exposures. The interview included questions about occupational history, education, leisure activities, and alcohol and tobacco use. If the interviewee reported exposure to the substances of interest for the study, details of the nature and duration of the exposure(s) were sought. Interview results showed that 16 cases, 18 population controls, and nine cancer controls were definitely or probably exposed to chlorinated phenoxy compounds or chlorophenols for at least one day prior to five years before the year of disease diagnosis. An additional seven cases, six population controls, and four cancer controls were possibly exposed.

Very little evidence was produced in this study to show an association between development of STS or malignant lymphoma and exposure to chlorinated phenoxy herbicides or chlorophenols. None of the relative risks for cases versus cancer controls or for cases versus population controls were significantly elevated. This is particularly notable since PCP is the main chlorophenol wood preservative used in Victoria, Australia.

Hardell et al. (1994)

Hardell et al. (1994) investigated possible associations between NHL and selected occupations or exposures to chlorophenoxyacetic acid, chlorophenols, or organic solvents. The 105 cases consisted of all men, 25-85 years old, who were admitted to an oncology center in Umea, Sweden between 1974 and 1978 with verified NHL. The 335 controls were matched to cases on gender, age, place of residence, vital status, and deceased controls also were matched on year of death.

Exposure assessment was based on responses to mailed questionnaires, supplemented with information collected via telephone. Occupations were classified by an established system and exposure to the substances of interest was classified as low-grade (less than one week continuously or less than one month in total) or high-grade if more than that. The questionnaire also provided for designation of the specific type of pesticide or preservative exposure. PCP was the chlorophenol most prominently used in Sweden.

No increased risk for NHL was found for any occupations identified from the exposure assessment questionnaire. The odds ratio for exposure to phenoxyacetic acids or chlorophenols

was 4.6 (CI = 2.7-7.8) and for exposure to all types of phenoxyacetic acids was 5.5 (CI = 2.7-11). Exposure to organic solvents yielded odds ratio of 2.9 (CI = 1.6-5.6) for high-grade and 1.8 (CI = 0.8-3.8) for low-grade. Exposure to DDT also was positively associated with NHL (odds ratio = 2.4, CI = 1.2-4.9); smoking, use of snuff, or exposure to asbestos was not associated with NHL.

Of greater interest for this review, odds ratio for high-grade exposure to chlorophenols was 9.4 (CI = 3.6-25) and for low-grade exposure to chlorophenols was 3.3 (CI = 1.6-6.8). The odds ratio for high-grade exposure to PCP specifically was 8.8 (CI = 3.4-24). The risk for NHL was shown to be increased with increasing exposure to chlorophenols as measured in number of days.

Kogevinas et al. (1995)

Case-control studies of STS and NHL in members of the large IARC registry of workers involved in production or spraying of phenoxy herbicides and chlorophenols were conducted by Kogevinas et al. (1995). Cases were identified from death certificates and through cancer registration records. Five controls for each of the eleven cases of STS and 32 cases of NHL were matched on age, gender, and country of residence (two NHL controls were excluded for lack of information).

Few actual exposure measurements were available. Estimates of exposures to 21 chemicals or mixtures were made by three industrial hygienists based on individual job records, company reports, and detailed company questionnaires. Cumulative exposure scores were calculated for each subject from estimated levels of exposures for difference jobs and duration of employment.

Significant excess risks of STS were associated with exposure to several phenoxyacetic acids, polychlorinated dibenzodioxin, and furan (odds ratios = 4.3 - 11.3). No excess risk was observed for exposure to chlorophenols and other chemicals examined.

In general, the associations between NHL and exposures were weaker than those for STS. Nonsignificant excess risks were observed for trichlorophenoxyacetic acid or furan, and tetrachlorodibenzo-p-dioxin (TCDD). For the medium or high exposure groups, three to fourfold excesses were found for TCDD and pentachlorophenol, although neither excess was significant.

These case-control studies were nested in a quite large and well structured data base. Little evidence was produced to support an association between exposure to PCP and development of STS or NHL.

Hardell et al. (1995)

Hardell et al. (1995) aggregated data from four previous case-control studies for a meta-analysis of association between exposure to pesticides and development of STS. With few exceptions, methods for the four supporting studies were similar. Cases were selected from cancer registries and controls from population registries. Deceased controls from a national registry on causes of

death were used for deceased cases. A total of 434 male cases and 948 male controls were selected.

Exposure was assessed via an extensive self-administered questionnaire that queried for work history including specific job categories and exposures, smoking habits, and leisure time exposures. When necessary, telephone interviews were used to clarify or supplement the written questionnaire. For classification as exposed to phenoxyacetic acids or chlorophenols, a minimum of one day was required. Chlorophenol exposure was classified as high-grade (one week or more continuously or at least one month total) or low-grade if exposure was less. Occupations were classified according to the Nordic Working Classification.

No significant odds ratios were observed for any occupations with potential exposure to phenoxyacetic acids, chlorophenols, or dioxins. Risk of STS was significantly increased for workers exposed to chlorophenols. Most interesting for the purpose of this review was the odds ratio of 2.8 (CI = 1.5-5.4) for exposure to PCP. Contrary to other reports, tobacco use did not increase the risk for STS.

Dimich-Ward et al. (1996)

Dimich-Ward et al. (1996) conducted a case-control study on the 19,675 offspring of 9,512 sawmill production and maintenance workers to determine any association between paternal exposure to dioxin-contaminated chlorophenols and adverse reproductive outcomes in offspring. Cases were selected as children born to fathers who worked for at least one year between 1950 and 1985 in sawmills with potential for exposure to chlorophenates. For each case, five controls were chosen from the total set of offspring at risk when the case event occurred. For cases and controls, only offspring born after their father began employment at the study sawmills were used in the analyses.

Since chlorophenate measurements were not available, exposure assessments for each job title were made by experienced workers for each time period characterized as having relatively constant exposure. Each worker's exposure estimate was calculated by multiplying this exposure constant by duration of employment in each job for each time period.

Relative risk estimates for five major reproductive health indicators, including prematurity, size for gestational age, birthweight, stillbirth, and neonatal death, were calculated for each 100 hours of fathers' exposures to chlorophenates, estimated by four different methods based on hours of exposure relative to time of conception. None of the five major reproductive health indicators were positively associated with any of the exposure variables. When further analyses were performed to look for associations between fathers' exposures and a broad range of birth defects in offspring (3-digit ICD categories), statistically significant increases in risk for anomalies of the eye and genital organs, and for anencephaly or spina bifida, were associated with at least one of the exposure variables. Because of the large number of comparisons made in the analyses, the strength of the associations observed between fathers' exposures and anomalies of the genital

organs and for anencephaly or spina bifida in offspring were weak. However, the association between fathers' exposures and anomalies of the eye in offspring were highly statistically significant ($p < 0.005$). When congenital anomalies, positively associated with fathers' exposures and with at least ten cases, were analyzed using four-digit ICD codes, fathers with higher cumulative exposure to chlorophenates during the three-month period before conception showed a 5.7-fold increased risk of having children with congenital cataracts (CI = 1.4-22.6). None of the other associations between congenital anomalies and fathers' exposures, observed in the previous analyses, were very different when analyzed using the more specific ICD sub-categories.

This study has increased credibility because of the large size of the sawmill cohort and the specificity of the measured outcomes. The study is limited by the imprecise exposure estimates common to the majority of studies of health effects of exposure to chlorophenols and common contaminants. Also, because of the large number of comparisons made to identify associations between parental exposures and birth defects in offspring, the probability of observing chance positive associations was increased.

Seidler et al. (1996)

In a case-control study conducted in Germany, Seidler et al. (1996) investigated possible associations between Parkinson's disease (PD) and a broad range of environmental factors and exposures, including exposure to wood preservatives. Cases (380) were recruited for the study from neurological patients with clinical diagnoses of PD in 1987 or later at nine clinics and who were 66 years old or less. Two controls per case were identified; one from the case's immediate neighborhood and the second from the case's urban or rural region.

Experienced interviewers collected data on environmental, residential, and occupational exposures, including specific data on usage of pesticides, insecticides, solvents, and wood preservatives. The interviewees were informed of the health study, but were unaware of the specific hypotheses being tested. In addition, experts were used to assess occupational exposures to materials specific for common industries.

Risk of association of PD with exposure to wood preservatives was assessed in three ways. The number of PD patients reporting wood paneling in their homes was significantly greater than the number of controls, and a dose gradient was seen with increasing years of exposure. PD patients also reported exposure to wood preservatives at work and at home significantly more often than controls. However, the analysis based on the job exposure matrix developed by industrial experts showed no difference between exposures for patients and controls.

Results of this study provide reasonable evidence of an association between exposure to wood preservatives and development of PD. This evidence is weakened by the imprecision of exposure assessments and by possible bias.

Gerhard et al. (1999)

Gerhard et al. (1999) conducted a study of 171 women who were referred to a gynecological clinic in Germany because of infertility or other gynecological and/or endocrinological conditions to investigate possible effects of PCP exposure on the endocrine system. PCP serum levels greater than 20 µg/liter were measured in 65 of the women. The other 106 women who served as controls had PCP levels less than 20 µg/liter and were matched on age, underlying condition, and geographical region.

The median PCP level in the PCP group was 35.9 µg/liter compared to 9.5 µg/liter for the controls. Concentrations of FSH and triiodothyronine (T3) were significantly lower in the PCP group while stimulated cortisol concentrations were significantly higher. Euthyroid goiters were found more frequently in the PCP group than the controls (50% versus 30%).

This study showed that relatively high serum PCP levels in women are associated with a number of gynecological hormonal effects. While significant differences were observed between the PCP exposed and the controls, most measured parameters were within normal ranges. Interpretation and significance of the findings for the purpose of this review are limited, because of the quite unique characteristics of the study population. Adequate matching of controls increased the significance of the results.

Cohort Studies Associated with Health Effects of PCP in Humans

Klemmer et al. (1980)

A group comparison study was conducted to determine if differences in biochemical or hematological parameters, or in illness conditions existed between workers with or without exposure to PCP (Klemmer et al. 1980). Within a total cohort of 422 workers in Hawaii, 42 had no history of occupational exposure, 333 had histories of mixed exposures to various pesticides while working as farmers or pest control operators, and 47 worked at firms involved with treatment of wood products with PCP. Twenty-six workers in the PCP-exposed group were also exposed to other wood preservatives.

Results of clinical laboratory analyses showed that PCP exposure was highly associated with increased numbers of immature leucocytes (band cells), increased blood plasma cholinesterase levels, and increased alkaline phosphatase levels. Other analyses showed PCP exposure associated with increased gamma globulin, basophils, uric acid, and reduced serum calcium.

Analysis of illness prevalence rates showed that rates for conjunctivitis, chronic sinusitis, and chronic upper respiratory conditions were significantly higher among workers exposed to PCP than among the controls. Prevalence rates of infections of the skin and subcutaneous tissue, and gout were also higher in the PCP-exposed individuals, but not significantly.

The significant differences in clinical laboratory measurements between PCP-exposed and unexposed workers in this study do not appear to be associated with serious illness, with the possible exception of the increased uric acid levels and gout. Otherwise, the only detrimental health effects seen were increased prevalence of low-grade infections and inflammatory tissue reactions.

Triebig et al. (1987)

Triebig et al. (1987) conducted a longitudinal study of nerve conduction velocity (NCV) on 10 individuals who had worked with PCP or PCP-containing substances including tetrachlorophenol (TCP), γ hexachlorocyclohexane (lindane), and aldrin for an average of 16 years (range = 4-24 years). NCV measurements were available for comparison for years 1980 and 1984 for the 10 subjects. In addition, serum and urine concentrations of PCP and were measured.

Limited industrial hygiene data showed PCP concentrations in the air during the subjects' employment of less than the allowable limit (500 $\mu g/m^3$). Results of biological monitoring showed serum concentrations between 38-1270 $\mu g/m^3$ (upper normal limit = 150 $\mu g/m^3$) and urine concentrations between 8-1224 $\mu g/m^3$ (upper normal limit = 60 $\mu g/m^3$) showing definite internal exposure. No significant changes in NCV during the period 1980-1984 were demonstrated in any of the subjects, leading to the conclusion that occupational exposure to PCP over several years at the levels reported likely does not result in adverse effects on the peripheral nervous system.

Robinson et al. (1987)

Robinson et al. (1987) conducted a cohort mortality study of 2,283 plywood mill workers who were potentially exposed to PCP as well as wood dust, wood volatiles, formaldehyde, and carbon disulfide. The workers were employed at four softwood plywood mills in Washington and Oregon between 1945 and 1955 and followed through 1977. Protein glues were used to join the veneer plies, and PCP was often added to the glues as a mold preventative. PCP was also added to oils used as mold release agents during finishing of the plywood panels. Based on plant employment records, a subcohort of workers who were known to have exposure to PCP and formaldehyde were identified.

No statistically significant excess mortality was found in this study, although nonsignificant excesses were seen for lymphatic and hematopoietic cancer excluding leukemia (SMR=156, CI = 90-252). The excess risk increased with duration of employment which is consistent with other studies of wood processing industry workers. Based on two cases an SMR of 333 was observed for Hodgkin's disease within the subcohort identified specifically as having exposure to PCP and formaldehyde.

Jäppinen et al. (1989)

Jäppinen et al. (1989) studied cancer incidence in 1,223 men and women who worked in a Finnish sawmill. The cohort consisted of all workers employed for at least one year between 1945 and 1961 as determined by company records. The study participants were followed until death or the end of 1981, and cancer incidence was determined from records at the Finnish Cancer Registry from 1953 through 1980. The registry data was believed to be virtually complete, including histological typing. The total number of years of follow-up was 28,646.

No monitoring data were used for assessment of individual exposures. All participants were assumed to be exposed to materials common to sawmills, including wood dust, sawing vapors, and fungal spores. A commercial chlorophenol product containing the sodium salt of PCP had been used as an antistain agent since 1945, and separate analyses were performed for those participants who were first employed after January 1, 1945.

A number of excess cancers were observed in the study population, although most of the excesses were not statistically significant. Among the male sawmill workers, excesses were found for all primary cancers, skin cancer (Standard Incidence Ratio [SIR] = 313, CI = 115-680), cancer of the lip, mouth, and pharynx, colon cancer, lymphomas (especially Hodgkin's disease), and leukemia. For all of the excesses, the numbers of observed and expected cases were low. Among women participants, excesses were observed in all primary cancers, rectal cancer, and leukemia. The numbers of observed and expected cases for excess cancers in women were also low.

Most of the findings in this study reflect findings in studies of similar populations. The significant excess in skin cancer in male workers was not anticipated and certainly is notable. That four of the six men with skin cancer were employed for the first time after 1945 when chlorophenol was first used in the plant suggests an association with chlorophenol. However, two of the total eight participants with skin cancer had no exposure to chlorophenol. As is true for many similar studies, the mixed exposures available to the study population and the lack of individual exposure assessments limits the significance of the findings.

Saracci et al. (1991) and Kogevinas et al. (1992)

A number of cohort analyses have been conducted using the International Registry of Workers Exposed to Phenoxy Herbicides and Contaminants. The registry is maintained by IARC in association with US National Institute of Environmental Health Sciences and includes workers with potential for exposure during production or use (typically spraying) of chlorophenoxy herbicides or chlorophenols such as PCP. Polychlorinated dioxins such as tetrachlorodibenzo-*p*-dioxin (TCDD) and furans are often found as contaminants during production of both groups of compounds and therefore also are potential exposures for production workers and users. Saracci et al. (1991) and Kogevinas et al. (1992) reported a historical mortality study of 18,910 production workers or sprayers (male and female) from ten

countries whose records were found in the registry. Follow-up was based on computerized national record systems or on active follow-up procedures. Exposure assessment for the study cohort was based on questionnaires completed by industrial hygienists, workers, or other factory personnel. Production records and job histories were also used when available. Workers were categorized according to type of work (production or spraying), type of chemical (chlorophenoxy herbicide, chlorophenol, or TCDD), year since first exposed, years of exposure, and type of department (main production, maintenance and cleaning, other, and unclassifiable). Exposure classifications were as follows: exposed (n=13,482), probably exposed (n=416), unknown (n=541), and non-exposed (n=3951). Exposed workers (13,482) were defined as those known to have sprayed chlorophenoxy herbicides and those who worked at factories that produced chlorophenoxy herbicides or chlorophenols in departments such as synthesis, formulation, maintenance, laboratory, transportation, cleaning, and others likely to provide opportunity for exposure to these substances.

For the total cohort, mortality from all causes was lower than expected, although workers in the unknown exposure group showed high all-cause mortality (SMR=319, CI = 182-518). Workers in the exposed group had SMRs greater than 200 for cancers of unspecified digestive organs, nose and nasal cavity, breast (males), testis, other endocrine glands, thyroid, and for Soft Tissue Sarcoma (STS). Four deaths from STS occurred among males who had worked as sprayers. All deaths occurred 10-19 years after first exposure which produced a six-fold excess risk for STS within the entire cohort. For this category of duration of exposure, the excess risk for exposed sprayers was even greater (SMR=882, CI = 182-2579). Mortality from Hodgkin's disease was less than expected. Mortality from NHL was slightly increased among production workers with most of the 11 deaths occurring more than 10 years after the workers were first exposed. Increased risks for cancers of the thyroid and other endocrine glands were also found, but these were based on very few deaths.

While the major emphasis of this study was exposure to chlorophenoxy herbicides, many workers in the study population also had exposure to chlorophenols, including PCP. In addition, many of the production workers had potential for exposure to dioxin and furan contaminants which is usually the case for any workers exposed to PCP or other chlorophenols. The excess risk found for death from STS following long-term exposure is consistent with a number of other studies of similar populations.

Cheng et al. (1993)

Cheng et al. (1993) investigated the prevalence of chloracne, urinary porphyins, and nerve conduction velocities in a cohort of 109 workers who had worked in the PCP department at a large production plant in China during the years 1968 to 1985. In this plant, four separate buildings are involved in the pentachlorophenol manufacturing process: the T.B. building (trichlorobenzene), the HCB building (hexachlorobenzene), the PCPNa building (pentachlorophenate sodium), and the PCP building (pentachlorophenol). The cohort included four subgroups who worked in these four separate buildings. The workers did not typically

rotate among different jobs, but work clothes were laundered in the same machine. Workers from all four buildings were defined as the exposed group. A control group, matched on age and gender, was selected from workers in a NaCl plant with no known hazardous exposures. Data collection consisted of examination by a dermatologist, retrieval of work history, and analysis of a spot urine sample for delta-amino levulinic acid (δ ALA) and porphyrins. Median and peroneal motor nerve conduction was also measured for workers and controls.

The prevalence rate of chloracne in the cohort was 60-95% with the highest prevalence seen in workers in the T.B. building(20/21, 95%) and among the maintenance workers (13/15, 87%). Chloracne developed an average of one year after first exposure and progressed from disfiguring facial blemishes, through cysts, to scarring. Areas most affected were the scrotum, around the eye, and behind the ear.

Levels of urinary δ ALA and porphyrins were higher among workers in the PCP plant than in controls. There was no significant difference in levels of δ ALA or porphyrins among the four subgroups.

Workers in the T.B. and PCP buildings had slower motor nerve conduction (both median and peroneal) when compared with matched controls. However, differences were statistically different only for median nerve conduction in the workers in the T.B. building.

Therefore, this study demonstrated that workers in the pentachlorophenol plant tended to have higher incidences of chloracne, increase level of urinary porphyrins and/or δ ALA, and slower motor motor neve conduction.

Ramlow et al. (1996)

A cohort of 770 workers at a large US chemical manufacturing plant with potential for exposure to PCP was evaluated for mortality from 1940 through 1989 (Ramlow et al., 1996). This cohort was a subset of a larger cohort of people who worked in departments with potential for exposure to technical-grade PCP products found to contain polychlorinated dibenzodioxins (PCDDs) and dibenzofurans as process byproducts. Potential for exposure to PCP was assessed by evaluating available industrial hygiene data, including some quantitative environmental PCP measurements, and process data. Potential exposure for each job held by cohort members were assigned an estimated exposure intensity score on a scale of 1 (low) to 3 (high). An estimated cumulative exposure index was calculated for each subject by multiplying duration for each job by the estimated exposure intensity for the job and summing.

The study cohort provided 20,107 person-years of observation, during which 229 deaths were observed. No excess in deaths for all causes, nor for all cancers were seen. There were also no excess deaths in the cancer categories of particular interest for this type of population including cancers of the liver (primary) and thyroid gland, leukemia, and other lymphohematopoietic

cancers. Noncancer mortality statistics were also unremarkable. Unexpectedly, there were small excesses in deaths from cancers of the stomach, larynx, and kidney, none of which were statistically significant.

When cumulative PCP exposure was logged for 5 and 15 years, possible trends for excess deaths were observed for cancer of the kidney, other and unspecified lymphohematopoietic cancer, gastric and duodenal ulcer, cirrhosis of the liver, and for all accidents.

Hertzman et al. (1997)

Hertzman et al. (1997) conducted a cohort study of more than 26,000 sawmill workers in Canada to further investigate the suspected association of exposure to chlorophenate wood preservatives with increased risk of NHL and STS. Secondary illnesses of interest included Hodgkin's disease, lung cancer, and nasal cancer. The study cohort was selected from 11 chlorophenate using mills (23,829 workers) and three control mills that did not use chlorophenates (2658 workers). Plant records were available to determine work histories for study cohort members, including duration of work within different job titles. Representative exposures were determined for three or four time periods for each mill. A cumulative exposure score was calculated for each worker by multiplying the job title specific exposure score for each job held by the worker by the length of employment and summing.

The study cohort provided 583,190 person-years of observation in the chlorophenate mills and 41,280 person-years of observation for the nonchlorophenate mills. SMRs and SIRs were calculated by counting person-years by two methods, (1) until the year last known alive and (2) until the end of the follow-up period (1990 for SMRs, 1989 for SIRs). Within the total cohort, there were 4710 deaths between 1950 and 1990, and 1547 incident cases of cancer between 1969 and 1989.

The all-cause SMRs for workers at chlorophenate mills were 0.96 and 0.81 for these two methods. Few positive associations between chlorophenate exposure and mortality were observed. When mortality was plotted against level of exposure to chlorophenates, no statistically significant exposure response gradient was seen for any causes of death of interest, although there was hint of a trend for lymphosarcoma.

SIRs for several cancers appeared to be in excess when person-years were counted to the last known year alive, but were not in excess when person-years were counted to 1989. Nonsignificant excesses for both NHL and SRS were observed in analyses using both methods for calculating person-years. The authors opined that the increased risk for NHL, even though slight, was meaningful since (1) the case fatality rate was lower than expected and (2) a trend of increasing risk with increased exposure was observed when person-years lost to follow-up were included. SIRs greater than 1.5 were also observed for cancers of the tongue, gum, eye, and endocrine gland, and for nasal cancer, but these also were nonsignificant.

Kogevinas et al. (1997) and Vena et al. (1998)

Mortality experience was studied in a cohort of 21,863 male and female workers in the IARC administered data base of workers involved in production or spraying of phenoxy herbicides (Kogevinas et al. 1997, Vena et al. 1998). Study members were followed from 1939 to 1992, producing a total of 488,482 person-years of follow-up.

Exposure assessment was based on individual job records, exposure questionnaires, and limited industrial hygiene data for some subjects and focused on potential exposure to one of the most hazardous of the common contaminants of phenoxy herbicides, tetrachlorodibenzo-p-dioxin (TCDD). Each of the 21,863 workers exposed to phenoxy herbicides or to chlorophenols was categorized as (1) exposed to TCDD or higher chlorinated dioxins (n=13,831), (2) not exposed to TCDD or higher chlorinated dioxins (n=7,553), or (3) unknown exposure to TCDD or higher chlorinated dioxins (n=479). Workers were first categorized by the longest-held exposed job, then aggregated into five groups of jobs judged to have similar activities and exposures.

In the entire cohort, 4,159 deaths (4,026 males and 133 females) and 1,127 cancers (1,083 in males and 44 in females) were observed. The SMR for all causes of death in workers exposed to phenoxy herbicides or chlorophenols was lower than expected for both men and women. The SMR for mortality from all cancers was slightly increased for men (1.07) and was statistically significant, but was not increased for women (0.93). Mortality from NHL and STS, the two diseases of highest interest, and lung cancer were also slightly increased, but not significantly. Mortality risks for all cancers, sarcomas, and lymphomas were found to increase with time from first exposure to dioxin-contaminated herbicides.

The risks of mortality from all circulatory disease and from ischemic heart disease were significantly related to levels of exposure to TCDD and HCD. The risks of mortality from cerebrovascular diseases (RR=1.54, CI = 0.83-2.88) and diabetes (RR=2.25, CI = 0.53-9.50) were also increased in exposed workers, but neither increase was significant.

These studies involve a large cohort and incorporate considerable data. However, exposure assessments were not specific for PCP which diminishes the usefulness of the studies for evaluation of health effects of PCP.

UNCERTAINTIES IN EVALUATING THE HEALTH EFFECTS OF PENTACHLOROPHENOL IN HUMANS

A thorough review of the literature for the purpose of evaluating health effects from exposure to pentachlorophenol readily identifies a number of important uncertainties. The first uncertainty, or shortcoming, pertains to the quality of the body of literature available for review. For a substance that has been widely used for many years by a large number of people in many geographical areas and for many different purposes, it is reasonable to expect that much information would be written about the substance, and indeed, this is the case. The literature is

quite rich with documents reporting production and usage data, physical and chemical properties, and toxicological effects. In addition, many documents have been written describing occurrences of both routine and accidental exposures to pentachlorophenol. However, relatively few structured epidemiologic studies with credible exposure assessments and appropriate controls have been performed. This is especially true prior to the current decade, during which more critical studies have been done.

A second, major uncertainty hindering the critical evaluation of health effects of PCP, pertains to the methods of exposure assessment used in literature. The majority of papers in the earlier literature are case reports of selected effects in populations in which exposures were based on either personal recall or on general employment records. Even in the more recent literature, measurements of personal exposures are very limited or absent.

A third uncertainty also pertains to exposure assessment and specifically, to what the members of the reported population are exposed. In most instances, exposures are not to pure PCP alone. More typically, exposures may be categorized as follows:

1. Exposure to technical grade PCP (85-90% PCP)
2. Exposure to chemical solutions or mixtures containing technical grade PCP and one or more, known or possibly unknown, contaminants
3. Exposure to technical grade PCP simultaneously with exposure to other industrial substances
4. Exposure to technical grade PCP with exposure to other industrial substances during a different period of time

In some papers, the identity of other simultaneous, previous or subsequent exposures, are known and reported; in other papers, this information is not known.

A fourth uncertainty limiting the assessment of health effects of PCP is the size of the study populations. Fortunately, this is not the case in all studies where multiple cohorts are combined to form extremely large study populations. Unfortunately, many of these studies still suffer from the previously described limitations in exposure assessment.

Finally, due to the nature of PCP and the circumstances that provide potential exposure, the route of exposure may be difficult to ascertain. In many, if not most situations, persons with known dermal exposure will also have inhalation exposure to a known or unknown degree.

Acknowledgment of these uncertainties or limitations should not discourage the reader from weighing the available evidence and generating conclusions. Uncertainties and limitations are presented to provide as complete a picture of the available information as possible. As time goes by, and additional studies are performed with more complete and precise exposure assessment data, the quality and magnitude of the health effects of PCP should be determined.

SUMMARY AND CONCLUSIONS OF THE HEALTH EFFECTS OF PENTACHLOROPHENOL IN HUMANS

The body of information addressing possible associations between exposure to PCP and subsequent development of disease is quite large. Because of anecdotal evidence and general interest, many studies of populations with known or suspected exposures to PCP have been conducted over the past half century. Still, firm and precise conclusions regarding the relationship between exposure and disease have been difficult to establish.

Many of the PCP studies are well structured and appear in the literature to be well executed. Populations are well defined, controls are generally selected appropriately, and analyses are appropriate and adequate. However, as explained in the previous section, major weaknesses in exposure assessment methods often limit the validity of reported findings, either positive or negative. Of the 24 original articles reviewed for this document, a large majority used questionnaire or interview data, provided either by the study participants or by surrogates, as exposure variables. Often, even this information was necessarily for mixed exposures including known or unknown contaminants rather than for PCP alone. Very rarely was actual industrial hygiene monitoring data available for assessment of individual exposures. In some instances, industrial hygiene expertise was used to judge exposures, but this assessment is also relatively crude.

Even considering the above limitations, a reasonably strong argument can be made that exposure to PCP is associated with increased risks of a number of diseases, namely chloracne, STS, and NHL. Increased risks of developing STS were reported in six studies, although statistical significance was reached in only three. Of five studies reporting increased risk for NHL, only one was statistically significant. Increased risks were also reported for lymphatic cancer, hematopoietic cancer, and PD, but the associations were generally not significant. While it is known that nerve conduction velocity is slowed by exposure to chlorophenols, as well as many other chemicals, studies with this dysfunction as an endpoint showed ambivalent results. Two studies showed associations between exposure of parents to chlorophenols and negative effects in subsequently-born offspring, but results in these studies were not statistically significant.

Considering the number of studies, the consistency among a number of outcomes, as well as the general absence of statistical significance, there appears to be reasonable evidence that exposure to chlorophenols may often be associated with chloracne, STS, NHL, and possibly abnormal births. Whether these deleterious health effects result from exposure to PCP specifically, or to one or more other chemicals typically found as contaminants, is not at all clear. Based on the evidence collected to date, careful control of exposures to chlorophenols, including PCP, is certainly warranted. However, until studies can be conducted wherein exposures are known with considerably more precision, conclusions regarding cause-effect relationships must be deferred.

Table 5. Health studies in workers and non-workers exposed to pentachlorophenol.									
				Population			Exposure Pure/ Mixed	Effects	
Date	Journal	Author(s)	Study type	Location	Category	N		Health	Other
1981	The Lancet	Bishop, CM and Jones, AH	Case report	Britain	Occup	2	Mixed	NHL, chloracne	
1990	Journal of the Florida Medical Association	Roberts, HJ	Case report	Multiple	Occup and public	Unk	Mixed	Aplastic anemia, pure red cell aplasia, , leukemia, other blood disorders reportedly associated with exposure to products containing PCP	
1990	Arch. Environ. Contam. Toxicol.	Gilbert, F.I. et al.	Cross-sectional	Hawaii	Occup	88/58	Mixed	Lower frequency of reporting stiffness or swelling of joints. No increase in deaths or cases of cancer	Significantly increased urinary PCP residue. Normal but higher systolic blood pressure and heart rate. Elevated serum protein level.
1995	Environ Hlth Perspectives	Karmaus, W and Wolf, N	Cross-sectional	Germany	Occup	214/184	Mixed	Significantly reduced birth weight and length	
1998	New Zealand Medical Journal	Walls, CB et al.	Cross-sectional	New Zealand	Occup	127	Pure	(All self-reported) “Dermatitis” reddened eyes, sore throat, “acne-like” skin condition, fever, sweating, weight loss, ongoing fatigue	Positive response to screening measure of neuropsychological dysfunction
1985	American J of Epidemiology	Pearce, NE et al.	CC	New Zealand	Public	734/4X	Mixed	Increased odd ratios for NHL and MM associated with agricultural occupations.	
1990	J Natl Cancer Inst	Eriksson, M et al.	CC	Sweden	Public	237/237	Pure	RR for STS = 3.85 (95% CI=1.15-12.88)	
1992	Brit J of Cancer	Smith, J G, and Christophers, A J	CC	Great Britain	Patient	82/82	Mixed	No significant association between exposure and development of STS and lymphoma	

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Date	Journal	Author(s)	Study type	Location	Category	N		Health	Other
1994	Cancer Research	Hardell, L et al.	CC	Sweden	Occup	105/335	Mixed and pure	OR for NHL = 3.3-9.4 for low and high exposure to chlorophenols. OR = 8.8 for high exposure to pentachlorophenol	
1995	Epidemiology	Kogevinas, M et al.	CC (STS) CC (NHL)	International	Occup	11/55 32/158	Pure or mixed	Odds ratios of 3-4 for NHL	
1995	Internat J of Oncology	Hardell, L et al.	Meta-analysis	Sweden	Occup	434/948	Mixed and pure	OR for STS = 3.3 for high exposure to chlorophenols. OR = 2.8 for high exposure to pentachlorophenol	
1996	Scand J Work Environ Health	Dimich-Ward, H et al.	Case-referent	British Columbia	Occup (offspring)	9512 (19,675 offspring)	Pure and mixed	Exposure of workers to chlorophenates associated with congenital anomalies of eye and genital organs, and to anencephaly and spina bifida in offspring.	
1996	American Academy of Neurology	Seidler	CC	Germany	Patient (Parkinson's disease)	380/379	Mixed		Patients reported higher frequencies of herbicide and pesticide usage, wood paneling in homes, exposure to wood preservatives, organochlorine usage.

Table 5. Health studies in workers and non-workers exposed to pentachlorophenol.									
				Population			Exposure Pure/ Mixed	Effects	
Date	Journal	Author(s)	Study type	Location	Category	N		Health	Other
1999	Environ Research Section A	Gerhard, I et al.	CC	Germany	Public	65/106	Pure		FSH concentrations, triiodothyronine (T3) concentrations, stimulated 21-deoxycortisol levels 120 min following iv ACTH, basal testosterone, DHEA, DHEAS, 17-OH-progesterone, and 17-OH-pregnenolone levels less than controls (ss). Number of euthyroid goiter greater than controls. Stimulated cortisol concentrations greater than controls (ss).
1980	Arch Environm Contam Toxicol	Klemmer, H W et al.	Cohort (Group compare)	Hawaii	Occup	400	Pure and mixed	NA	Increased mean serum levels, Higher age-standardized prevalence rates for low grade infections or inflammations of skin and other tissues, Increased bands and basophils, cholinesterase, alkaline phosphatase, gamma globulin, and uric acid, and decreased serum calcium
1987	Brit J Ind Med	Triebig et al.	Longitudinal	Unk	Occup	15	Mixed	None	
1987	NIOSH - 00197140	Robinson, C F et al.	Cohort mortality	Washington and Oregon	Occup	2,283	Mixed	Non-significant excess mortality for lymphatic and hematopoietic cancer (excluding leukemia). Elevated risk for Hodgkin's disease.	

Table 5. Health studies in workers and non-workers exposed to pentachlorophenol.

Date	Journal	Author(s)	Study type	Population			Exposure Pure/ Mixed	Effects	
				Location	Category	N		Health	Other
1989	Scand J Work Environ Health	Jäppinen, P et al.	Cohort	Finland	Occup	1,223	Mixed	Non-significant excesses of all cancers, cancer of lip, mouth, and pharynx, colon cancer, lymphomas, and leukemia in men. Non-significant excesses of all cancers, rectal cancer, and leukemia in women. Significant excess of skin cancer in men (SIR=313, CI = 115-680)	
1991	The Lancet	Saracci, R et al.	Historical cohort	International	Occup	17,372 males + 1537 females + 1 Unk	Mixed	Excess risk for STS (not significant). Small non-significant increase in mortality from NHL.	
1992	Chemosphere	Kogevinas, M et al.	Cohort	International	Occup	16,863 males + 1,527 females	Miixed	Six-fold excess risk for SRS occurring 10-19 years from first exposure	
1993	Amer J Ind Med	Cheng, W N et al.	Prevalence, Cohort mortality	China	Occup	109 + controls	Pure	Chloracne (73.4%)	Elevated urine δ-ALA and porphyins. Decreased median and peroneal nerve conduction velocities
1996	American J of Industrial Medicine	Ramlow, JM et al.	Cohort mortality	Michigan	Occup	770	Pure	Excess deaths due to cancer of kidney, gastric and duodenal ulcer, cirrhosis of liver, and all accidents.	
1997	American J of Public Health	Hertzman, C et al.	Cohort	British Columbia	Occup	23,829/ 2,658	Mixed	Increased risk for NHL	

Table 5. Health studies in workers and non-workers exposed to pentachlorophenol.

Date	Journal	Author(s)	Study type	Population			Exposure Pure/ Mixed	Effects	
				Location	Category	N		Health	Other
1997	American J of Epidemiology	Kogevinas, M et al.w	Cohort mortality	Multiple	Occup	13,831	Mixed Mixed (no TCDD)	Excess deaths from all cancers (ss), STS (ns), NHL (ns), lung cancer (ns), all respiratory cancers (ss), kidney cancer (ss), breast cancer (ns), endometrial cancer (ns), and cancer of "other endocrine organs" (ns). Excess deaths from all cancers (ns) and lung cancer (ns).	
1998	Environ Health Perspectives	Vena, J. et al.	Cohort mortality (36 cohorts)	12 countries	Occup	21,863	Mixed	Excess mortality from all cancers, ischemic heart disease, diabetes, suicide	

Unk = unknown, NA = non applicable, CC = case control, n/n = number of cases or subjects/number of controls, ss = statistically significant, ns = not statistically, significant, STS = soft tissue sarcoma, NHL = non-Hodgkin's lymphoma, MM = multiple myeloma, FSH = follicle-stimulating hormoone.

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