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15. Supplementary Notes

16. Abstract (Limit: 200 words) Information profiles were presented on the following compounds: 2-chlorophenol (95578), 3-chlorophenol (108430), 4-chlorophenol (106489), 2,4-dichlorophenol (120832), 2,5-dichlorophenol (583788), 2,6-dichlorophenol (87650), 2,3,6-trichlorophenol (933755), 2,4,5-trichlorophenol (95954), 2,4,6-trichlorophenol (88062), 2,3,4,6-tetrachlorophenol (58902), and pentachlorophenol (87865). Studies have indicated that, administered in acute lethal doses, the chlorophenols produce excitation and increased respiration followed by motor weakness, hypotonia, convulsions, coma and death. All chlorophenols are well absorbed dermally, and toxic to skin and eyes. Workers exposed to 4-chlorophenol have demonstrated signs of functional disorders of the central and peripheral nervous systems and mucous membrane structure. Tumor development has been promoted in mice exposed to 2,4-dichlorophenol which was nonmutagenic in the Ames assay and produced abnormal fetuses in mice. 2,4,5-Trichlorophenol has caused liver and kidney damage, has promoted the development of papillomas when applied dermally to mice, and is an irritant to the eyes, skin, nose and throat of humans. 2,4,6-Trichlorophenol administered orally has increased the incidence of lymphomas and leukemia in male rats and leukocytosis and monocytosis in rats. Testing in mice has produced increased incidences of hepatocellular carcinomas, adenomas, hepatomas, and reticulum cell sarcomas. Studies of 2,3,4,6-tetrachlorophenol have shown no carcinogenic potentials, mutagenic activity, or teratogenicity of the compound; there were signs of fetotoxicity in rats.

17. Document Analysis a. Descriptors

b. Identifiers/Open-Ended Terms NIOSH-Publication, NIOSH-Contract, Contract-210-79-0030, Chlorinated-hydrocarbons, Preservatives, Laboratory-animals, Carcinogens, Resins, Pigments, Disinfectants, Herbicides, Bactericides, Fungicides

c. COSATI Field/Group

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(See ANSI-Z39.18) *See Instructions on Reverse* OPTIONAL FORM 272(4-77) (Formerly NTIS-35)

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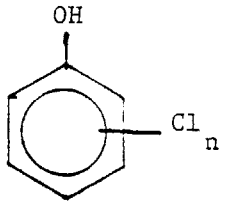
I. SCOPE OF DOCUMENT AND SUMMARY OF MAJOR FINDINGS

A. CLASS IDENTIFICATION

Chlorophenols are identified by the following general chemical structure:



where n, the number of chlorine functions attached to the aromatic ring, can vary from 1 to 5

Although chlorophenols may contain heteroatoms or functions such as bromine, nitro, methyl, or amino groups, the chlorophenols discussed in these profiles are limited to those defined by the general chemical structure shown above. As defined, there are nineteen possible chlorophenol isomers; they are listed in Appendix A.

B. CHEMICALS TO BE ADDRESSED

Individual profiles have been prepared for the following chlorophenols:

2-Chlorophenol
3-Chlorophenol
4-Chlorophenol
2,4-Dichlorophenol
2,5-Dichlorophenol
2,6-Dichlorophenol
2,3,6-Trichlorophenol
2,4,5-Trichlorophenol
2,4,6-Trichlorophenol
2,3,4,6-Tetrachlorophenol
Pentachlorophenol

These chlorophenols were selected for individual profiles because they were identified to have commercial or industrial significance in terms of production or use. The chlorophenols not profiled are primarily produced or used as laboratory or research reagents.

C. SUMMARY OF BIOLOGICAL ACTIVITY

In general, except for information on 2,4-dichlorophenol, 2,4,5-trichlorophenol, and pentachlorophenol, there is a paucity of toxicologic data for the chlorophenols. When administered in acute lethal doses, the chlorophenols produce similar signs of poisoning in animals that include initial excitation and increased respiration followed by motor weakness, hypotonia, convulsions, coma, and death. With the exception of pentachlorophenol, rat oral LD50 values for the chlorophenols are generally in excess of 500 mg/kg. All the chlorophenols appear to be well absorbed dermally, are toxic to the skin and eyes, and are capable of uncoupling oxidative phosphorylation. Other biological effects of these compounds, however, particularly chronic animal and human effects, are not well characterized and are summarized in the following discussion.

Monochlorophenols

Subchronic exposure to 4-chlorophenol has resulted in pathologic changes in the brain, lungs, liver, kidneys, and myocardium of rats, and 2- and 3-chlorophenol promoted tumor development in mice. The carcinogenicity of the monochlorophenols has not been thoroughly investigated, however, and the mutagenic, teratogenic/reproductive, and other chronic effects of the monochlorophenols are not known. Workers exposed to 4-chlorophenol have noted signs of functional disorders of the central and peripheral nervous system and mucous membrane irritation, but other effects of monochlorophenols in humans have not been reported.

Dichlorophenols

Of the dichlorophenols, 2,4-dichlorophenol has been investigated most thoroughly. It promoted tumor development in mice, was nonmutagenic in the Ames assay, and produced abnormal fetuses in mice; however, no information is available on other chronic effects of 2,4-dichlorophenol in animals or on effects

in humans. Except for limited acute toxicity data for 2,6-dichlorophenol in animals, 2,5-dichlorophenol and 2,6-dichlorophenol have only been examined for mutagenicity in the Ames assay (negative results); the mammalian and human toxicities of these dichlorophenols have not been investigated.

Trichlorophenols

The toxicity of 2,4,5-trichlorophenol is fairly well characterized. Subchronic oral administration has resulted in slight liver and kidney damage. When injected subcutaneously into mice, 2,4,5-trichlorophenol did not result in increased incidences of tumors, although it did promote the development of papillomas when painted on the skin of mice. Other chronic effects of administration in animals have not been reported. 2,4,5-Trichlorophenol was non-mutagenic in the Ames assay and non-teratogenic in mice. Technical grade 2,4,5-trichlorophenol can cause irritation and damage to the eyes, skin, nose, and throat of humans, but these health effects may be due to impurities such as 2,3,7,8-tetrachlorodibenzo-p-dioxin (TCDD).

The NCI has reported that chronic oral administration of 2,4,6-trichlorophenol has resulted in an increased incidence of lymphomas and leukemia in male rats and leukocytosis and monocytosis in rats of both sexes. In mice, increased incidences of hepatocellular carcinomas, adenomas, hepatomas, and reticulum-cell sarcomas have variously been reported, although 2,4,6-trichlorophenol did not promote skin tumor development in mice. Current evidence for the mutagenicity of 2,4,6-trichlorophenol is equivocal, but the compound is currently undergoing additional microbial mutagenesis testing by NIEHS. No information on the teratogenic/reproductive or other chronic effects in animals or effects on humans was found in the literature searched.

Other than acute toxicity information, the only data found on 2,3,6-trichlorophenol were the negative results of an Ames Salmonella assay.

2,3,4,6-Tetrachlorophenol

Single studies of 2,3,4,6-tetrachlorophenol have shown no carcinogenic activity in mice, mutagenic activity in S. typhimurium, or teratogenicity in rats, although the compound did produce signs of fetotoxicity in rats. No information on other chronic effects in animals or toxic effects in humans is available.

Pentachlorophenol

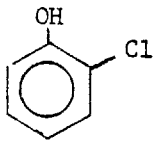
Because of pentachlorophenol's extensive production and widespread use for wood preservation, its toxicity in animals and humans has been thoroughly investigated. Pentachlorophenol is the most acutely toxic of the chlorophenols (rat oral LD50s range from approximately 30-200 ppm) and is readily absorbed via the skin and respiratory tract. Although systemic effects of exposure in both animals and humans are well documented, evidence for pentachlorophenol's carcinogenicity and mutagenicity is equivocal. Increased incidences of abnormal fetuses and resorptions have been reported in rodents. In humans, toxic effects and fatalities resulting from occupational and accidental exposures have been well reviewed, but epidemiological studies are not available. Non-fatal exposures commonly involve irritation of the eyes, skin, and upper respiratory tract; symptoms following fatal exposure are indicative of interference with oxidative phosphorylation and include profuse sweating, thirst, hyperthermia, rapid pulse and respiration, labored breathing, and abdominal pains. A chronic health effect that has been associated with commercial pentachlorophenol is chloracne, but it it apparent that this effect may result from TCDD impurities.

II. INFORMATION PROFILES

A. 2-CHLOROPHENOL

1. Chemical Name: 2-Chlorophenol

2. Chemical Structure:



3. Synonyms: o-Chlorophenol
2-Chloro-1-hydroxybenzene
Phenol, 2-chloro-

4. Chemical Abstracts Service (CAS) Number: 95-57-8

5. Registry of Toxic Effects of Chemical Substances (RTECS) Number:
SK2625000

6. Chemical and Physical Properties:

Description:	colorless to yellow-brown liquid with unpleasant penetrating odor
Molecular Weight:	128.56
Boiling Point:	175-176°C
Melting Point:	9°C
Vapor Pressure:	ca. 2.5 mm Hg (20°C); 1 mm Hg (12.1°C)
Solubility:	<0.1 g/100 g water freely soluble in alcohol, ether, benzene, acetone, and caustic alkali solutions
Specific Gravity:	1.2573^{25}_{4}
Stability:	moderate fire safety hazard Flash point: 225°F

7. Production

Data available from the U.S. EPA (1980) regarding producers of 2-chlorophenol and production volumes are presented in Table 1. These data indicate that between 10 and 100 thousand pounds were produced in 1977 as an end-use product. Although Dow and Rhone-Poulenc reported no production, they dod manufacture 2-chlorophenol as a non-isolated intermediate that is chlorinated to higher chlorophenols.

Table 1. Producers of 2-Chlorophenol and Production Ranges (U.S. EPA, 1980)

Producer and Location	Type of Production	1977 Production Range
Dow Chemical Midland, MI	Manufacturer	none
Monsanto Co. Sauget, IL	Manufacturer	10-100 thousand lb
Rhone-Poulenc Freeport, TX Freeport, TX	Manufacturer Importer	none none
Crescent chemical Hauppauge, NY	Importer	none

Recent importation figures for 2-chlorophenol are as follows (USITC, 1980a, 1979a, 1977a):

Year	Imports (in thousands of pounds)
1979	46.3
1978	18.3
1976	4.4

8. Use

As an end product, 2-chlorophenol is used primarily as an intermediate in the production of dyestuffs; other applications include intermediate use in phenolic resins, pharmaceuticals, and preservatives (Doedens, 1964; Freiter, 1978).

9. Manufacturers and Distributors

2-Chlorophenol is manufactured by (SRI International, 1980; U.S. EPA, 1980):

Dow Chemical	Midland, MI
Monsanto Co.	Sauget, IL
Rhone-Poulenc Inc.	Freeport, TX

In 1977, only Monsanto produced 2-chlorophenol as an end-use product. Dow and Rhone-Poulenc reported no production in 1977 to the U.S. EPA (1980).

In addition to the producers, the distributors of 2-chlorophenol include (Chemical Week: 1981 Buyers' Guide Issue, 1980; Chem Sources--USA, 1980):

Accurate Chem.
Aceto Chem.
Aldrich Chem.
Anachemia Chem.
Atomergic Chemetals
Bio-Clinical Lab
Chemical Dynamics
Chem. Procurement Lab
Chem. Services
Columbia Organics
Eastern Chem.
Eastman Kodak
EM Lab
Fisher Sci.
Gallard-Schelsinger
J.T. Baker Chem.
Lachat Chem.
MCB Reagents
Monomer-Polymer and Dajac Lab
Pfaltz and Bauer
Tridon Chem.

10. Manufacturing Processes

2-Chlorophenol is produced commercially by the chlorination of phenol (Doedens, 1964). Both 2-chloro- and 4-chlorophenol are prepared by the direct chlorination of phenol with molecular chlorine. Gaseous chlorine is passed into molten phenol at temperatures of 50°C to 150°C. 4-Chloro- and 2-chloro-isomers are formed predominately, with small amounts of di- and trichloro-isomers. The chlorophenols can be separated from the unreacted phenol by adding aqueous sodium carbonate to the reaction mixture, thus converting the chlorophenols to the sodium salts. The unreacted phenol is then removed by extraction. After acidification of the chlorophenoxides, washing, and drying, 2-chlorophenol is separated from the 4-chlorophenol by fractional distillation. The 4-chlorophenol is either separated for a final product or used as a feedstock material to make 2,4-dichlorophenol. The 2-chlorophenol can be further purified to a final product, but is more commonly used as a feedstock material for further chlorination to trichloro-, tetrachloro-, or pentachlorophenol. Figure 1 outlines the general process operations.

11. Impurities or Additives

No information was found in the literature searched.

12. Occupational Exposure

The National Occupational Hazard Survey indicates that 495 workers are potentially exposed to 2-chlorophenol.

13. Control Technology and Work Practices

Specific factors that may contribute to or prevent employee exposure to 2-chlorophenol were not found in the literature searched.

14. Biological Effects

a. Animal Studies

(1) Acute Exposures

The acute toxic effects of 2-chlorophenol are summmarized in Table 2. Upon administering 2-chlorophenol intraperitoneally to

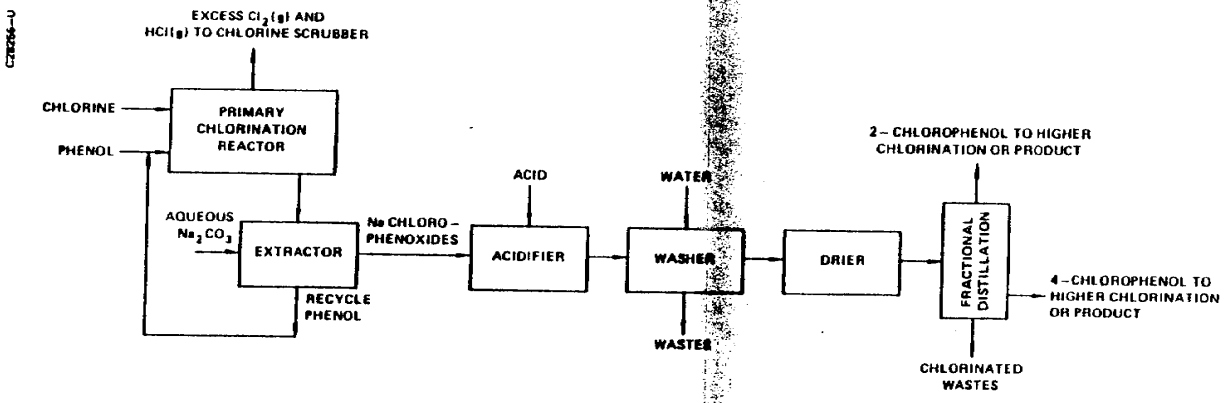


Figure 1. Manufacture of 2-chloro- and 4-chlorophenol (Adapted from Doedens, 1964; Freiter, 1978; Golumbie, 1953)

Table 2. Acute Effects of 2-Chlorophenol

Route[a]	Species	Dose (mg/kg)	Response	Reference
oral	rats	670	LD50	Deichmann, 1943
oral	rats	840	LD50	Deichmann and Mergard, 1948
oral	mice	670	LD50	Bubnov et al., 1969
oral	mice	1000	LD100	Bubnov et al., 1969
i.p.	rats	230	LD50	Farquharson et al., 1958
s.c.	rats	950	LD50	Deichmann, 1943
i.v.	rabbits	120	LDLo	Dittmer, 1959
dermal	mice	4800	TDLo	Boutwell and Bosch, 1959

[a] i.p. = intraperitoneal; s.c. = subcutaneous; i.v. = intravenous.

male rats, Farquharson and coworkers (1958) observed initial excitation and tremors. When poisoning was sufficiently great, convulsions developed along with loss of righting reflex, coma, dyspnea, and death. Body temperature was depressed 2.0°C following the administration of lethal intraperitoneal doses (230 mg/kg), and rigor mortis did not occur within 5 minutes of death as it does with the higher chlorinated phenols. Deichmann (1943) reported that lethal oral and subcutaneous doses of 2-chlorophenol produced similar signs of poisoning in rats: initial restlessness and increased rate of respiration, followed by rapidly developing motor weakness, tremors, clonic convulsions, dyspnea, coma, and death.

Angel and Rogers (1972) determined that the intraperitoneal CD50 (convulsive dose for 50% of a population) of 2-chlorophenol was approximately 100 mg/kg (0.77 mmol/kg) in urethane-anaesthetized mice.

von Oettingen (1949) noted that administration of monochlorophenols to rats produced pathological effects similar to those encountered with phenol toxicosis. Kidney lesions, red blood cell casts in renal tubules, fatty infiltration of the liver, and intestinal hemorrhages were found upon examination of the intoxicated rats. Similar findings of fatty degeneration of the liver, renal granular dystrophy, and necrosis of the stomach and intestinal mucosa were reported in tests on the mouse and blue fox (Bubnov et al., 1969).

(2) Subchronic Exposures

No information was found in the literature searched.

(3) Chronic Exposures

No information was found in the literature searched.

(4) Carcinogenicity

Boutwell and Bosch (1959) reported that commercial grade 2-chlorophenol promoted tumor development when painted repeatedly as 20% solutions on the backs of mice following initiation with single applications of dimethylbenzanthracene (DMBA) (Table 3). It should be noted, however, that small numbers of animals were used in this experiment.

(5) Mutagenicity

No information was found in the literature searched.

(6) Teratogenicity

No information was found in the literature searched.

(7) Reproductive Effects

No information was found in the literature searched.

(8) Other Relevant Information

2-Chlorophenol has been reported to inhibit oxidative phosphorylation in isolated rat liver mitochondria (Parker, 1958; Mitsuda et al., 1963).

Exposure of rabbits to chlorobenzene has resulted in formation of 2-chlorophenol (Lindsay-Smith et al., 1972). The 2-chlorophenol was excreted unchanged and as sulfate and glucuronic acid derivatives in the urine.

b. Human Studies

(1) Pharmacokinetics

Roberts et al. (1977) used human autopsy skin epidermal membranes in an in vitro test system to determine the permeability of the skin to various compounds. 2-Chlorophenol was shown to permeate the skin membrane and to produce damage at a threshold concentration of 0.80% (w/v).

Table 3. Tumor-Promoting Action of 2-Chlorophenol (Boutwell and Bosch, 1959)

Promoter	Number of Mice (survivors/original)	Average Number of Papillomas Per Survivor	Percent Survivors with Papillomas	Percent Survivors with Carcinoma
Experiment 6				
Initiator: 0.3% DMBA in benzene				
Promoter: in benzene				
Data: at 15 weeks				
None (benzene control)	15/20	0.07	7	0
0.5% croton oil	14/20	0.64	29	0
20% 2-chlorophenol	31/35	1.48	61	10
Experiment 9				
Initiator: None				
Promoter: in dioxane				
Data: at 12 weeks				
20% 2-chlorophenol	28/30	0.64	46	0

[a]A single 25 µl application of DMBA was painted on the dorsal skin of 2- to 3-month old female Sutter mice. Single applications of 1 drop (approximately 25 µl) of the chlorophenol solutions (commercial grades; producers and impurities unspecified) were begun 1 week after the application of initiator and were continued twice each week for the duration of the experiment. In experiment 9, where no initiator was used, the duration was measured from the first application of the test substance.

(2) Health Effects

No information was found in the literature searched.

(3) Target Organ Toxicity

No information was found in the literature searched.

(4) Epidemiology

No information was found in the literature searched.

15. Ongoing Studies

Microbial mutagenesis testing of 2-chlorophenol is scheduled to be completed by Stanford Research International in 1980 (NIEHS, 1980). The testing is being supported by the National Institute of Environmental Health Sciences under Contract No. NO1-ES-9-0001.

S. Petrocelli and J. Carroll (1980) of E.G. and G., Inc. (Warehem, MA) are conducting toxicity testing of 2-chlorophenol to develop water quality criteria. One phase of this study is the testing of 2-chlorophenol in the Ames test to determine possible mutagenic activity. The work is funded by the U.S. Environmental Protection Agency (Contract No. EPA 68-01-4646).

16. Exposure Standards

No recommended or promulgated occupational exposure standards for 2-chlorophenol were found.

17. Sources of Additional Relevant Information

No sources of additional relevant information were identified.

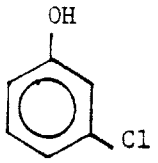
18. Other Pertinent Data

No other information that would aid in the assessment of 2-chlorophenol as an occupational hazard was found in the literature searched.

B. 3-CHLOROPHENOL

1. Chemical Name: 3-Chlorophenol

2. Chemical Structure:



3. Synonyms: m-Chlorophenol
3-Chloro-1-hydroxybenzene
Phenol, 3-chloro-

4. Chemical Abstracts Service (CAS) Number: 108-43-0

5. Registry of Toxic Effects of Chemical Substances (RTECS) Number:

SK2450000

6. Chemical and Physical Properties:

Description:	white crystals with odor similar to that of phenol
Molecular Weight:	128.56
Boiling Point:	213-217°C
Melting Point:	33°C
Vapor Pressure:	1 mm Hg (at 44.2°C)
Solubility:	0.26 g/100 g water soluble in alcohol, ether, benzene, and caustic alkali solutions
Specific Gravity:	1.245_4^{45}
Stability:	moderate fire safety hazard

7. Production

Data available from the U.S. EPA (1980) regarding producers of 3-chlorophenol and production volumes are presented in Table 4.

In 1977, 15.4 thousand pounds were imported; in 1976, 10.2 thousand pounds were imported (USITC, 1978a, 1977a).

8. Use

3-Chlorophenol is used as an intermediate in specialty syntheses such as formation of various phenol resins (Doedens, 1964) and in dyestuff syntheses.

Table 4. Producers of 3-Chlorophenol and Production Ranges (U.S. EPA, 1980)

Producer and Location	Type of Production	1977 Production Range
Plant Site Not Listed	---	10 to 100 thousand lb
Diaz Chemical Corp. Holley, NY	Manufacturer	confidential
Eastman Kodak Rochester, NY	Manufacturer	none
Gallard-Schelsinger Chem. Carle Place, NY Carle Place, NY	Importer Small Manufacturer	confidential confidential

9. Manufacturers and Distributors

3-Chlorophenol is manufactured by (SRI International, 1980; U.S. EPA, 1980):

Aldrich Chemical	Milwaukee, WI
Diaz Chemical Corp.	Holley, NY
Eastman Kodak	Rochester, NY
Gallard-Schlesinger Chem.	Carle Place, NY
R.S.A. Corp.	Ardsley, NY
Specialty Organics	Irwindale, CA

Distributors include (Chemical Week: 1981 Buyers' Guide Issue, 1980; Chem Sources--USA, 1980):

Accurate Chem.	J.T. Baker Chem.
Anachemia Chem.	Kennedy and Klim
Atomergic Chemetals	Koch Chemical
Bio-Clinical Lab	Lachat Chem.
Chem. Procurement Lab.	Marstan Chem.
Chem. Services	MCB Reagents
Columbia Organics	Mobay Chem.
Eastern Chem.	Montedison USA
Eastern Guardian Chemical	Pfaltz and Bauer
EM Lab.	Research Organics/Inorganics
Fairfield Chem.	Shawnee Chem.
Fisher Sci.	Sigma Chem.
ICN/K and K	Tridom Chem.

10. Manufacturing Processes

3-Chlorophenol can be prepared by vapor-phase hydrolysis of 1,2,4-trichlorobenzene or by hydrolysis of 1,3-dichlorobenzene with KOH or NaOH (Freiter, 1978). Other synthesis routes include diazotization of m-chloroaniline or its sulfate; after diazotization, the products are treated with boiling water and sulfuric acid. During the latter step, steam is introduced into the reaction mixture, and the chlorophenol is steam distilled out as soon as it is formed (Doedens, 1964).

11. Impurities or Additives

No information was found in the literature searched.

12. Occupational Exposure

The National Occupational Hazard Survey does not provide an estimated of the number of workers who are potentially exposed to 3-chlorophenol.

13. Control Technology and Work Practices

Specific factors that may contribute to or prevent employee exposure to 3-chlorophenol were not found in the literature searched.

14. Biological Effects

a. Animal Studies

(1) Acute Exposures

The acute toxic effects of 3-chlorophenol are summarized in Table 5. Upon administration of 3-chlorophenol to rats, Farquharson and coworkers (1958) observed initial excitation and tremors. When poisoning was sufficiently great, convulsions developed along with loss of righting reflex, coma, dyspnea, and death. Body temperature was depressed 2.5°C following the administration of lethal intraperitoneal doses (355 mg/kg), and rigor mortis did not occur within 5 minutes of death as it does with the higher chlorinated phenols. Deichmann (1943) reported that lethal oral and subcutaneous doses of 3-chlorophenol produced similar signs of poisoning in rats: initial restlessness and increased rate of respiration, followed by rapidly developing motor weakness, tremors, clonic convulsions, dyspnea, coma, and death.

Angel and Rogers (1972) determined that the intraperitoneal CD50 (convulsive dose for 50% of a population) of 3-chlorophenol was approximately 110 mg/kg (0.86 mmol/kg) in urethane-anaesthetized mice.

von Oettingen (1949) noted that administration of monochlorophenols to rats produced pathological effects similar to those encountered with phenol toxicosis. Kidney lesions, red blood cell casts in renal tubules, fatty infiltration of the liver, and intestinal hemorrhages were found upon examination of the intoxicated rats.

Table 5. Acute Effects of 3-Chlorophenol

Route[a]	Species	Dose (mg/kg)	Response	Reference
oral	rats	570	LD50	Deichmann, 1943
i.p.	rats	355	LD50	Farquharson et al., 1958
s.c.	rats	1390	LD50	Deichmann, 1943
dermal	mice	6000	TDLo	Boutwell and Bosch, 1959

[a] i.p. = intraperitoneal; s.c. = subcutaneous.

(2) Subchronic Exposures

No information was found in the literature searched.

(3) Chronic Exposures

No information was found in the literature searched.

(4) Carcinogenicity

Boutwell and Bosch (1959) reported that commercial grade 3-chlorophenol promoted papilloma (but not carcinoma) development when painted repeatedly as 20% solutions on the backs of mice following initiation with single applications of dimethylbenzanthracene (DMBA) (Table 6). It should be noted, however, that small numbers of animals were used in this experiment.

(5) Mutagenicity

No information was found in the literature searched.

(6) Teratogenicity

No information was found in the literature searched.

(7) Reproductive Effects

No information was found in the literature searched.

(8) Other Relevant Information

3-Chlorophenol has been reported to inhibit oxidative phosphorylation in isolated rat liver mitochondria (Mitsuda et al., 1963; Weinbach and Garbus, 1965).

Exposure of rabbits to chlorobenzene has resulted in formation of 3-chlorophenol (Lindsay-Smith et al., 1972). The 3-chlorophenol is excreted unchanged and as sulfate derivatives in the urine.

b. Human Studies

(1) Pharmacokinetics

No information was found in the literature searched.

Table 6. Tumor-Promoting Action of 3-Chlorophenol (Boutwell and Bosch, 1959)[a]

Promoter	Number of Mice (survivors/original)	Average Number of Papillomas Per Survivor	Percent Survivors with Papillomas	Percent Survivors with Carcinoma
Initiator: 0.3% DMBA in benzene Promoter: in benzene Data: at 15 weeks				
None (benzene control)	15/20	0.07	7	0
0.5% croton oil	14/20	0.64	29	0
20% 3-chlorophenol	21/33	1.38	67	0

[a]A single 25 µl application of DMBA was painted on the dorsal skin of 2- 3-month old Sutter mice. Single applications of 1 drop (approximately 25 µl) of 3-chlorophenol (commercial grade; producer and impurities unspecified) were begun 1 week after the application of initiator and were continued twice each week for the duration of the experiment.

(2) Health Effects

No information was found in the literature searched.

(3) Target Organ Toxicity

No information was found in the literature searched.

(4) Epidemiology

No information was found in the literature searched.

15. Ongoing Studies

Microbial mutagenesis testing of 3-chlorophenol is scheduled to be completed by Stanford Research International in 1980 (NIEHS, 1980). The testing is being supported by the National Institute of Environmental Health Sciences under Contract No. NO1-ES-9-001.

16. Exposure Standards

No recommended or promulgated occupational standards for 3-chlorophenol were found.

17. Sources of Additional Relevant Information

No sources of additional relevant information were identified.

18. Other Pertinent Data

No other information that would aid in the assessment of 3-chlorophenol as an occupational hazard was found in the literature searched.

C. 4-CHLOROPHENOL

1. Chemical Name: 4-Chlorophenol

2. Chemical Structure:

3. Synonyms: p-Chlorophenol
4-Chloro-1-hydroxybenzene
Phenol, 4-chloro-

4. Chemical Abstracts Service (CAS) Number: 106-48-9

5. Registry of Toxic Effects of Chemical Substances (RTECS) Number:

SK2800000

6. Chemical and Physical Properties:

Description:	white to yellow-pink crystals with unpleasant penetrating odor
Molecular Weight:	128.56
Boiling Point:	217-220°C
Melting Point:	42-43°C
Vapor Pressure:	1 mm Hg (at 49.8°C); 0.1 mm Hg (20°C)
Solubility:	2.71 g/100 g water (20°C) very soluble in alcohol, ether, benzene
Specific Gravity:	1.306
Stability:	moderate fire safety hazard Flash point: 250°F

7. Production

In 1977, domestic manufacture of 4-chlorophenol as an end-use product is estimated to have been roughly 1-2 million pounds (SRC estimate). It is also produced as an intermediate that is chlorinated to higher chlorophenols, but is not isolated for end-uses.

Data available from the U.S. EPA (1980) regarding producers of 4-chlorophenol and production volumes are presented in Table 7.

Table 7. Producers of 4-Chlorophenol and Production Ranges (U.S. EPA, 1980)

Producer and Location	Type of Production	1977 Production Range
Dow Chemical Midland, MI	Manufacturer	none
Monsanto Co. Sauget, IL	Manufacturer	0.1-1.0 million lb
Rhone-Poulenc Freeport, TX Freeport, TX	Manufacturer Importer	0.1-1.0 million lb 0.1-1.0 million lb
Aceto Chem. Flushing, NY	Importer	none

Recent importation figures for 4-chlorophenol are as follows (USITC, 1980a, 1979a, 1978a):

Year	Imports (in thousands of pounds)
1979	46.3
1978	149.1
1977	493.9

8. Use

The majority of 4-chlorophenol produced is used as a starting material for the manufacture of other products. Large quantities of 4-chlorophenol manufactured at plant site were used on-site to make higher chlorophenols such as 2,4-dichlorophenol. As a final product for sale or use, 4-chlorophenol has a number of commercial uses. The most important commercial uses are as an intermediate in the production of dyes and pigments and in the production of quinizarin (antioxidant for lubricants). In 1977, about 0.75 million pounds of 4-chlorophenol were used to make quinizarin; a similar amount may have been used in dye syntheses (SRC estimate). Other intermediate uses of 4-chlorophenol include those in medicinals such as phenacetin, miticides, and the disinfectant chlorophene (2-benzyl-4-chlorophenol) made by Monsanto. In addition to being used as an intermediate, 4-chlorophenol is employed as a selective solvent in refining mineral oils and as a denaturant for ethanol. Salts of 4-chlorophenol are used as antigumming agents for gasoline, wash liquids for fuel gas purification, and germicides (Doedens, 1964; Freiter, 1978).

The following tabulation presents the approximately percentage of the total amount of 4-chlorophenol produced that is used in each of the applications listed (SRC estimate):

	Percentage of Total
Synthesis of Dyes and Pigments	35-45
Synthesis of Quinizarin	35-45
Miscellaneous	10-30

9. Manufacturers and Distributors

4-Chlorophenol is manufactured by (SRI International, 1980; U.S. EPA, 1980; USITC, 1980b):

Dow Chemical	Midland, MI
Monsanto Co.	Sauget, IL
Rhone-Poulenc	Freeport, TX

Although Dow Chemical reported no production to the U.S. EPA (1980), they do produce 4-chlorophenol as a non-isolated intermediate in the manufacture of higher chlorophenols.

In addition to the manufacturers, the distributors include (1980-81 OPD Chemical Buyers Directory, 1980; Chemical Week: 1981 Buyers' Guide Issue, 1980; Chem Sources--USA, 1980):

Accurate Chem.
Aceto Chem.
Aldrich Chem.
Alfa Products
Anachemia Chem.
Atomergic Chemetals
Bio-Clinical Lab.
Chemical Dynamics
Chem. Procurement Lab.
Chem. Services
Eastern Chem.
Eastman Kodak
EM Lab.
Fisher Sci.
Gallard-Schelsinger
ICN/K and K
J.T. Baker Chem.
Lachat Chem.
LaPine Sci.
Mallinckrodt
Marshallton Res. Lab.
MCB Reagents
Mobay Chem.
Pfaltz and Bauer
Rambach Co.
Reichhold Chem.
Sigma Chem.
T.R. America Chem.
Tridom Chem.

10. Manufacturing Processes

4-Chlorophenol and 2-chlorophenol are produced by the direct chlorination of phenol with molecular chlorine (Doedens, 1964). Gaseous chlorine is passed into molten phenol at temperatures of 50°C to 150°C. 4-Chloro- and 2-

chloro-isomers are predominately formed, with small amounts of di- and trichloro-isomers. The chlorophenols can be separated from the unreacted phenol by adding aqueous sodium carbonate to the reaction mixture, thus converting the chlorophenols to the sodium salts. The unreacted phenol is then removed by extraction. After acidification of the chlorophenoxides, washing, and drying, 2-chlorophenol is separated from the 4-chlorophenol by fractional distillation. The 2-chlorophenol can be further purified to a final product, but is more commonly used as a feedstock material for further chlorination to trichloro-, tetrachloro-, or pentachlorophenol. The 4-chlorophenol is either separated for a final product or used as a feedstock material to make 2,4-dichlorophenol. Figure 2 outlines the general manufacturing operations.

11. Impurities or Additives

No information was found in the literature searched.

12. Occupational Exposure

The National Occupational Hazard Survey indicates that 4,847 workers are potentially exposed to 4-chlorophenol.

13. Control Technology and Work Practices

Specific factors that may contribute to or prevent employee exposure to 4-chlorophenol were not found in the literature searched.

14. Biological Effects

a. Animal Studies

(1) Acute Exposures

The acute toxic effects of 4-chlorophenol are summarized in Table 8. Upon administering 4-chlorophenol intraperitoneally to male rats, Farquharson and coworkers (1958) observed initial excitation and tremors. When poisoning was sufficiently great, convulsions developed along with loss of righting reflex, coma, dyspnea, and death. Body temperature was depressed 2.5°C

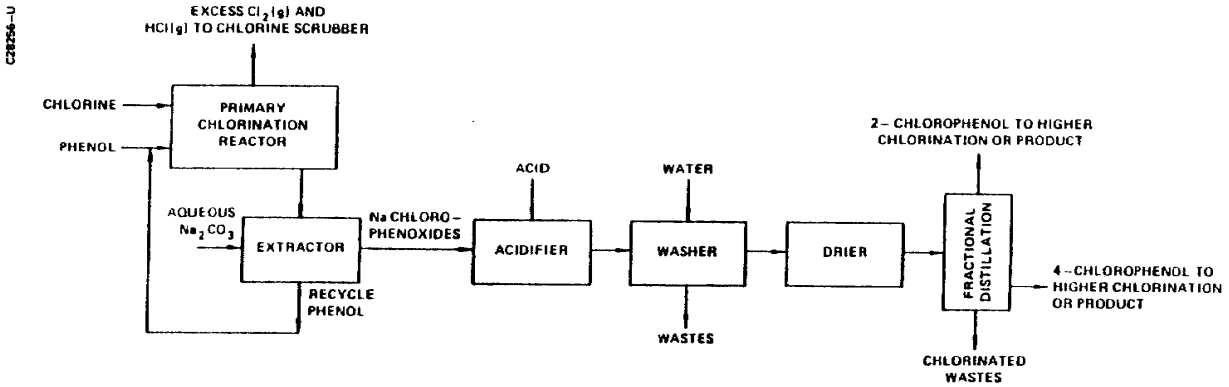


Figure 2. Manufacture of 2-chloro- and 4-chlorophenol (Adapted from Doedens, 1964; Freiter, 1978; Golumbie, 1953)

Table 8. Acute Effects of 4-Chlorophenol

Route[a]	Species	Dose (mg/kg)	Response	Reference
oral	rats	660	LD50	Deichmann and Mergard, 1948
oral	rats	500	LD50	Gurova, 1964
oral	mice	860	LD50	Schrotter et al., 1977
i.p.	rats	281	LD50	Farquharson et al., 1958
s.c.	rats	1030	LD50	Deichmann, 1943
inhalation	mice	11 mg/m^3	LD50	Gurova, 1964
dermal	rats	1500	LD50	Gurova, 1964

[a] i.p. = intraperitoneal; s.c. = subcutaneous.

following the administration of lethal intraperitoneal doses (281 mg/kg), and rigor mortis did not occur within 5 minutes of death as it does with the higher chlorinated phenols. Deichmann (1943) reported that lethal oral and subcutaneous doses of 4-chlorophenol produced similar signs of poisoning in rats: initial restlessness and increased rate of respiration, followed by rapidly developing motor weakness, tremors, clonic convulsions, dyspnea, coma, and death.

Angel and Rogers (1972) determined that the intraperitoneal CD50 (convulsive dose for 50% of a population) of 4-chlorophenol was approximately 115 mg/kg (0.90 mmol/kg) in urethane-anaesthesized mice.

von Oettingen (1949) noted that administration of monochlorophenols to rats produced pathological effects similar to those encountered with phenol toxicosis. Kidney lesions, red blood cell casts in renal tubules, fatty infiltration of the liver, and intestinal hemorrhages were found upon examination of the intoxicated rats.

Rats that inhaled 13 mg/m^3 of 4-chlorophenol for 2 hours displayed increased oxygen consumption and increased neuromuscular excitability in response to electrical stimulation of peripheral nerves (Gurova, 1964). Increased oxygen consumption also resulted when mice were exposed to only 2 mg/m^3 of 4-chlorophenol.

Gurova (1964) also reported that dermal application of 4-chlorophenol (dose not indicated) caused skin irritation and necrosis in rabbits, rats, and guinea pigs, and sometimes resulted in convulsive seizures and death.

Harrison and Madonia (1971) conducted dermal and ocular toxicity tests in rabbits with 1 or 2% aqueous solutions of 4-chlorophenol and 35% camphorated 4-chlorophenol. (4-Chlorophenol is currently used as an

antimicrobial agent for endodontic therapy in dentistry at a concentration of 35% in camphor.) When 0.1 ml of each solution was injected intradermally in white rabbits, the 1 and 2% aqueous solutions produced mild inflammation after 24 and 72 hours. The 35% camphorated 4-chlorophenol caused a severe inflammatory response including necrosis. When 0.15 ml of the 1% aqueous solution was placed on the cornea of rabbits, slight hyperemia was observed; 0.15 ml of the 2% aqueous solution produced a more severe response characterized by moderate to severe hyperemia, mild to moderate edema, cloudy cornea, and exudation. The 35% camphorated 4-chlorophenol produced a severe response. The changes induced by the 1% and the 2% aqueous solutions became evident after 5 minutes, were most intense after 5 hours, and subsided by 96 hours after administration.

(2) Subchronic Exposures

Gurova (1964) exposed rats for 6 hours/day for 4 months to 2 mg/m^3 of 4-chlorophenol by inhalation. Effects included a loss of weight in the first 30 days, followed by an increased weight gain. Myoneural excitability was increased, but body temperature, hemoglobin, red and white blood cells, and sedimentation rates were unchanged.

Lesions were described in rats and mice exposed to 4-chlorophenol by inhalation (concentration not specified) for 4 hours per day for 28 days (Gurova, 1964). Autopsy revealed congestion and focal hemorrhages in the brain, lungs, liver, kidneys, and myocardium. Thickened alveolar septa, atelectasis, and emphysema occurred in the lungs, and degenerative changes were found in the brain cortical and glia cells and in the liver and myocardium.

(3) Chronic Exposures

No information was found in the literature searched.

(4) Carcinogenicity

No information was found in the literature searched.

(5) Mutagenicity

Amer and Ali (1968, 1969) reported some effects of 4-chlorophenol on mitosis and meiosis in flower buds and root cells of vetch (Vicia faba). When flower buds were treated directly with or sprayed with 0.1 M 4-chlorophenol, meiotic alterations included chromosome stickiness, lagging chromosomes, anaphase bridges, and fragmentation. When root cells were exposed to 62.5 ml/liter 4-chlorophenol, a decrease in the mitotic index was observed. Induced types of anomalies in the mitotic stages included disturbed meta-telophase and ana-telophase, lagging chromosomes, disintegration, bridging, and cytomixis. It should be noted that the relationship of these changes to alterations in mammalian cells has not been established.

(6) Teratogenicity

No information was found in the literature searched.

(7) Reproductive Effects

No information was found in the literature searched.

(8) Other Relevant Information

4-Chlorophenol has been reported to inhibit oxidative phosphorylation in isolated rat liver mitochondria (Parker, 1958; Mitsuda et al., 1963; Weinbach and Garbus, 1965).

Exposure of rabbits to chlorobenzene has resulted in formation of 4-chlorophenol (Lindsay-Smith et al., 1972). The 4-chlorophenol was excreted unchanged and as sulfate and glucuronide derivatives in the urine.

b. Human Studies

(1) Pharmacokinetics

Roberts et al. (1977) used human autopsy skin epidermal membranes in an in vitro test system to determine the permeability of the skin to

various compounds. 4-Chlorophenol was shown to permeate the skin and to produce damage at a threshold concentration of 0.75% (w/v).

Gurova (1964) reported that the phenol content in 24-hour urine samples of workers exposed to 4-chlorophenol dermally during the manufacture of aniline and of laboratory technicians working with 4-chlorophenol was 100 to 300 mg more than in those of persons not in contact with the chemical.

(2) Health Effects

Gurova (1964) reported 2 cases of accidental acute 4-chlorophenol poisoning among workers in an aniline dye manufacturing plant. Symptoms included signs of nervous system involvement: headache and dizziness, respiratory disorder, vomiting, loss of coordination, tremors, and, in one case, liver enlargement.

(3) Target Organ Toxicity

Workers exposed to 4-chlorophenol in an aniline dye plant have noted symptoms and signs of functional disorders of the central and peripheral nervous systems, as well as signs of irritation of the mucous membranes, and sometimes a functional disorder of the bladder (Gurova, 1964).

(4) Epidemiology

Gurova (1964) conducted a health survey comparing 43-60 workers exposed to 4-chlorophenol with 23-70 other nonexposed workers in the same aniline dye manufacturing plant in the USSR. Air levels of 4-chlorophenol ranged from 0.3 to 21 mg/m^3 (Table 9). The exposed workers were reported to have a significantly higher incidence of neurologic disorders, with symptoms that included neurasthenia, insomnia, irritability, frequent mood changes, and rapid fatigability. Physiologic testing showed a reduction of thresholds characterizing nerve tissue lability, and stimulation of peripheral nerves revealed an increase in myoneural excitability among exposed workers. In two-point touch

Table 9. Concentration of 4-Chlorophenol in the Air of an Aniline Dye Manufacturing Plant (Gurova, 1964)

Work Place	Industrial Operation	Number of Samples	Average Concentration (in mg/m^3)
At the chlorinator	Loading	2	2.3
At the chlorinator	Chlorination	11	2.1
At the still	Collection of the mass	2	17.0
At the still	Purification of the tar	12	1.5
At the still	Purification of the tar	2	21.0
At the collectors	Collection of the fractions	13	1.2
At the collectors	Sampling	7	2.5
At the 4-chlorophenol airlift	Extrusion into the measuring tank	3	7.5
At the measuring tank	Discharge into the condenser	3	3.5
At the measuring tank	Sampling	2	1.7
At the measuring tank	Level measuring	2	15.0
At the condenser	Condensation	6	0.3
Other		15	

discrimination tests, the minimum detection distance between points was increased among workers exposed to 4-chlorophenol. Unspecified changes in the capillaries of fingernail folds were also reported.

15. Ongoing Studies

Microbial mutagenesis testing of 4-chlorophenol is scheduled to be completed by Stanford Research International in 1980 (NIEHS, 1980). The testing is being supported by the National Institute of Environmental Health Sciences under Contract No. NO1-ES9-0001.

S. Petrocelli and J. Carroll (1980) of E.G. and G., Inc. (Warehem, MA) are conducting toxicity testing of 4-chlorophenol to develop water quality criteria. One phase of this study includes the testing of 4-chlorophenol for mutagenic activity in the Ames test. The work is funded by the U.S. Environmental Protection Agency (Contract No. EPA 68-01-4646).

A. Teass (1980) of the National Institute for Occupational Safety and Health (NIOSH), Division of Physical Science and Engineering (Cincinnati, OH), is the principal investigator of a project designed to develop personal air sampling and analytical methods to be used for monitoring worker exposure to organic carcinogens of industrial or regulatory importance. Methods are to be developed for 4-chlorophenol. The study is funded by the U.S. Dept. of Health, Education, and Welfare, NIOSH, under Contract No. VQU-C23-472.

16. Exposure Standards

Gurova (1964) recommended an average permissible air concentration of 3 mg/m^3 for industrial workers exposed to 4-chlorophenol. No other recommended or promulgated occupational exposure standards for 4-chlorophenol were found.

17. Sources of Additional Relevant Information

No sources of additional relevant information were identified.

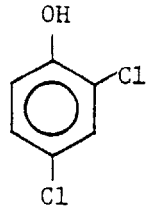
18. Other Pertinent Data

No other information that would aid in the assessment of 4-chlorophenol as an occupational hazard was found in the literature searched.

D. 2,4-DICHLOROPHENOL

1. Chemical Name: 2,4-Dichlorophenol

2. Chemical Structure:



3. Synonyms: DCP
2,4-Dichloro-1-hydroxybenzene
Phenol, 2,4-dichloro-

4. Chemical Abstracts Service (CAS) Number: 120-83-2

5. Registry of Toxic Effects of Chemical Substances (RTECS) Number:

SK8575000

6. Chemical and Physical Properties:

Description:	white solid with unpleasant persistent odor
Molecular Weight:	163.01
Boiling Point:	210-211°C
Melting Point:	45°C
Vapor Pressure:	1 mm Hg (at 53°C)
Solubility:	0.46 g/100 g water (20°C) very soluble in alcohol and ether soluble in benzene and chloroform
Specific Gravity:	1.383^{60}_{25}
Stability:	slight fire hazard when exposed to heat or flame; can react vigorously with oxidizing materials Flash point: 237°F

7. Production

Data available from the U.S. EPA (1980) regarding producers of 2,4-dichlorophenol and production volumes are presented in Table 10.

Based upon use estimates and sales data, domestic production of 2,4-dichlorophenol in 1977 was on the order of 50 million pounds (SRC estimate).

Table 10. Producers of 2,4-Dichlorophenol and Production Ranges (U.S. EPA, 1980)

Producer and Location	Type of Production	1977 Production Range
Dow Chemical USA Midland, MI	Manufacturer	10-50 million pounds
Monsanto Sauget, IL	Manufacturer	1-10 million pounds
Chem South Childersburg, AL	Manufacturer	1-10 million pounds
Transvaal (Vertac) Jacksonville, AR	Manufacturer/ Produced Site Limited	confidential
Rhone-Poulenc Freeport, TX	Manufacturer	10-50 million pounds

8. Use

The most important use of 2,4-dichlorophenol is in production of the herbicide 2,4-D (dichlorophenoxyacetic acid and salts). In 1974, approximately 60 million pounds of 2,4-D were manufactured (Blackford, 1975); in 1977, production was about the same (Chemical and Engineering News, 1978). This would have required roughly 40 to 45 million pounds of 2,4-dichlorophenol.

Alkali metal salts of 2,4-dichlorophenol have found utility as germicides and antiseptics. 2,4-Dichlorophenol is also used commercially in the synthesis of various disinfectants, germicides, and antiseptics and in the synthesis of various pesticides such as Butyrac, Modown, dichlorprop, and Genite-EM-923 (Doedens, 1964; Ayers et al., 1976).

Use of 2,4-dichlorophenol for applications other than 2,4-D production amounts to at least several millions of pounds annually. In 1979, 9 million pounds of 2,4-dichlorophenol were sold on the open market by the producers (USITC, 1980b).

The following tabulation presents the approximate percentage of the total amount of 2,4-dichlorophenol produced that is used in each of the applications listed:

	Percentage of Total
2,4-D herbicide production	80-90
Other herbicide production	5-10
Miscellaneous (germicides, antiseptics, organic syntheses)	5-10

9. Manufacturers and Distributors

Data available from the U.S. EPA (1980) regarding producers of 2,4-dichlorophenol and production volumes are presented in Table 10.

Dow, Transvaal, and Rhone-Poulenc all produce 2,4-D herbicide; Rhone-Poulenc also makes other herbicides from 2,4-dichlorophenol. Therefore, the

bulk of 2,4-dichlorophenol production is captively consumed by the manufacturers.

Other distributors of 2,4-dichlorophenol include (Chem Sources-USA, 1980):

Aceto Chem.	Chem. Procurement Lab.	ICN/K and K
Aldrich Chem.	Chem. Services	Lachat Chem.
Anachemia Chem.	Eastman Kodak	MCB Reagents
Atomergic Chemetals	EM Lab.	Pfaltz and Bauer
Biochemical Lab.	Fisher Sci.	Polysciences
Chemical Dynamics	Gallard-Schelsinger	Spectrum Chem.
		Tridom Chem.

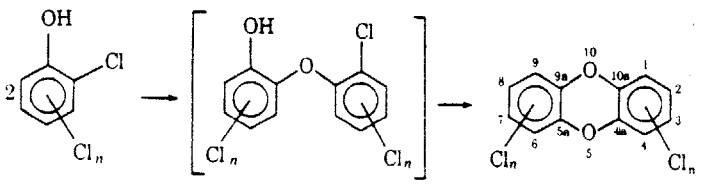
10. Manufacturing Processes

2,4-Dichlorophenol may be prepared by the direct chlorination of phenol with two moles of chlorine; chlorine is passed into molten phenol at 80°C to 100°C until a product with a melting point of 34°C to 36°C is obtained (Doedens, 1964). The phenol can also be dissolved in liquid SO_2 and treated with cold gaseous chlorine to yield 2,4-dichlorophenol (Freiter, 1978).

2,4-Dichlorophenol can also be made by chlorination of 4-chlorophenol; 2-chlorophenol is not normally utilized because of excess formation of 2,6-dichlorophenol. The trichlorophenol by-products and dichlorophenols are separated and purified by distillation and crystallization (Golumbic, 1953). Figure 3 outlines a general manufacturing scheme.

11. Impurities or Additives

Chlorinated dibenzo-p-dioxins are formed, by the reaction illustrated below, during the manufacturing processes used to produce polychlorinated phenols.



chlorinated dibenzo-*p*-dioxin

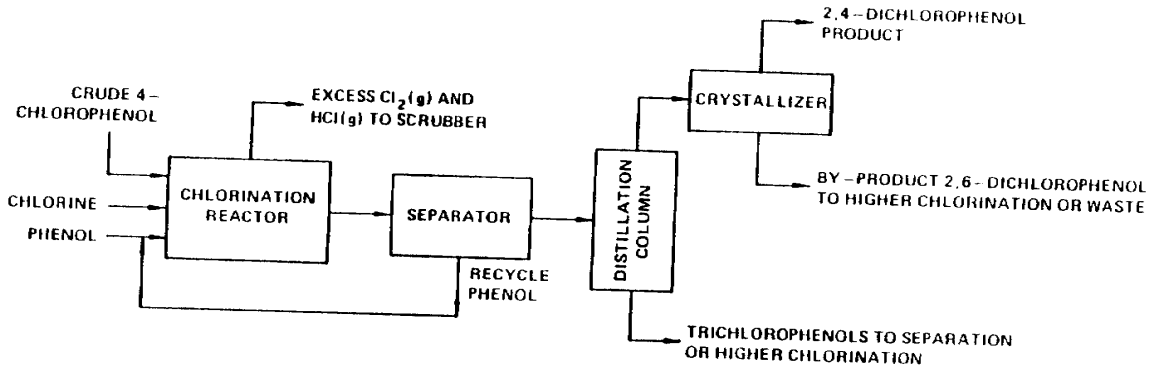


Figure 3. Manufacture of 2,4-Dichloro- and 2,6-Dichlorophenol (Adapted from Doedens, 1964; Columbic, 1953)

12. Occupational Exposure

The National Occupational Hazard Survey does not provide an estimate of the number of workers who are potentially exposed to 2,4-dichlorophenol.

13. Control Technology and Work Practices

Specific factors that may contribute to or prevent employee exposure to 2,4-dichlorophenol were not found in the literature searched.

14. Biological Effects

a. Animal Studies

(1) Acute Exposures

The acute toxicity of 2,4-dichlorophenol is summarized in Table 11. Intraperitoneal injection of 2,4-dichlorophenol into male albino rats produced symptoms including hypotonia that began in the hind legs and spread to the forelegs and neck, lack of response to muscle stimulation, and weakened eye reflexes (Farquharson et al., 1958). Polypnea occurred initially and was followed by bradypnea. Body temperature was depressed 0.5°C following the administration of lethal intraperitoneal doses (430 mg/kg), and rigor mortis did not occur within 5 minutes of death as it does with the higher chlorinated phenols. Deichmann (1943) reported that lethal oral and subcutaneous doses of 2,4-dichlorophenol produced similar signs of poisoning in rats: initial restlessness and increased rate of respiration, followed by rapidly developing motor weakness, tremors, clonic convulsions, dyspnea, coma, and death.

(2) Subchronic Exposures

Kobayashi et al. (1972) evaluated average body weights, food consumption, organ weights, serum glutamic oxalacetic transaminase (SGOT) and serum glutamic pyruvic transaminase levels (SGPT), erythrocyte and leukocyte counts, and histopathological changes in male mice fed 2,4-dichlorophenol in the diet for 6 months. The estimated daily dose levels were 45 mg/kg, 100 mg/kg, and

Table 11. Acute Effects of 2,4-Dichlorophenol

Route[a]	Species	Dose (mg/kg)	Response	Reference
oral	rats	580[b]	LD50	Deichmann, 1943
oral	rats (male)	3600	LD50	Kobayashi et al., 1972
oral	rats (female)	4500	LD50	Kobayashi et al., 1972
oral	mice	1600	LD50	Kobayashi et al., 1972
i.p.	rats	430	LD50	Farquharson et al., 1958
s.c.	rats	1730	LD50	Deichmann, 1943
dermal	mice	312	TDLo (after 39 weeks of intermittent exposure)	Boutwell and Bosch, 1959

[a] i.p. = intraperitoneal; s.c. = subcutaneous.

[b] In fuel oil.

230 mg/kg. No adverse effects were found except for some nonspecific microscopic liver changes in the group receiving the maximum dose. The changes included infiltration of the round cells and swelling of hepatocytes with some differences in cell size. It was concluded that 100 mg/kg/day is a maximum no-effect level in mice.

(3) Chronic Exposures

No information was found in the literature searched.

(4) Carcinogenicity

Boutwell and Bosch (1959) reported that commercial grade 2,4-dichlorophenol promoted tumor development when painted repeatedly on the backs of mice following initiation with single applications of dimethylbenzanthracene (DMBA) (Table 12). It should be noted that small numbers of animals were used in the experiments.

(5) Mutagenicity

2,4-Dichlorophenol was reported to be non-mutagenic in the Ames Salmonella/microsome assay in tester strains TA98, TA100, TA1535, TA1537, and TA1538, both in the presence and absence of liver activation systems (Rasanen et al., 1977; Simmon et al., 1977).

Amer and Ali (1968, 1969) reported some effects of 2,4-dichlorophenol on mitosis and meiosis in flower buds and root cells of vetch (Vicia faba). When flower buds were treated directly with or sprayed with 0.1 M 2,4-dichlorophenol for 5 successive days, meiotic alterations included chromosome stickiness, lagging chromosomes, and anaphase bridges. When root cells were exposed to 62.5 mg/l of 2,4-dichlorophenol, a decrease in the mitotic index was observed; induced mitotic anomalies included disturbed meta-telophase and ana-telophase, lagging chromosomes, chromosome stickiness, anaphase bridging, and occasional cytomyxis. Later studies (Amer and Ali, 1974) confirmed the effect of

Table 12. Tumor-Promoting Action of 2,4-Dichlorophenol (Boutwell and Bosch, 1959)[a]

Promotor	Number of Mice (survivors/original)	Average Number of Papillomas per Survivor	Percent Survivors with Papillomas	Percent Survivors with Carcinomas
Experiment 6				
Initiator: 0.3% DMBA in benzene				
Promoter: in benzene				
Data: at 15 weeks				
None (benzene control)	15/20	0.07	7	0
0.5% croton oil	14/20	0.64	29	0
20% 2,4-dichlorophenol	27/33	1.07	48	11
Experiment 8				
Initiator: None				
Promoter: in benzene				
Data: at 24 weeks				
None (benzene control)	27/32	0.15	11	0
20% 2,4-dichlorophenol	16/23	1.62	75	6 (62% at 39 wks)

[a]A single 25 µl application of DMBA was painted on the dorsal skin of 2- to 3-month old female Sutter mice. Single applications of 1 drop (approximately 25 µl) of the chlorophenol solution (commercial grade; producers and impurities unspecified) were begun 1 week after the application of initiator and were continued twice each week for the duration of the experiment. In experiment 8, where no initiation was used, the duration was measured from the first application of the test substance.

chromosome stickiness, lagging chromsomes, and fragmentation in developing 15- and 35-day old Vicia faba. It should be noted that the relationship of these changes to alterations in mammalian cells has not been established.

(6) Teratogenicity

2,4-Dichlorophenol was administered daily by subcutaneous injection in dimethylsulfoxide (DMSO) at a dosage level of 74 mg/kg in BL6 and AKR mice on days 6 through 14 and 6 through 15 of gestation, respectively (BRL, 1968). The mice were sacrificed on day 18 (BL6) and day 19 (AKR) of gestation. Results showed that there was a significant increase in the number of abnormal fetuses in the AKR mice; the more frequent anomalies were extended legs and short limbs. Fetal mortality was unchanged, but the fetal weights were significantly less than those of the controls.

(7) Reproductive Effects

No information was found in the literature searched.

(8) Other Relevant Information

2,4-Dichlorophenol inhibits oxidative phosphorylation in isolated rat liver mitochondria (Mitsuda et al., 1963).

b. Human Studies

(1) Pharmacokinetics

Roberts et al. (1977) used human autopsy skin epidermal membranes in an in vitro test system to determine the permeability of the skin to various compounds. 2,4-Dichlorophenol permeated the skin membrane, but did not cause damage when tested at aqueous concentrations up to saturation.

(2) Health Effects

No information was found in the literature searched.

(3) Target Organ Toxicity

No information was found in the literature searched.

(4) Epidemiology

No information was found in the literature searched.

15. Ongoing Studies

2,4-Dichlorophenol is currently undergoing carcinogenesis testing in the National Toxicology Program (NTP, 1980a). Rats and mice are receiving the compound in feed as part of the pre-chronic testing phase of the carcinogenesis bioassay.

S. Petrocelli and J. Carroll (1980) of E.G. and G., Inc. (Warehem, MA) are conducting toxicity testing of 2,4-dichlorophenol to develop water quality criteria. One phase of this study includes the testing of 2,4-dichlorophenol for mutagenic activity in the Ames test. The work is funded by the U.S. Environmental Protection Agency (Contract No. EPA 68-01-4646).

2,4-Dichlorophenol is also scheduled for microbial mutagenesis testing in 1980 under the sponsorship of the National Institute of Environmental Health Sciences (NTP, 1980b). The work will be performed at Case Western Reserve (Contract No. NO1-ES-9-2136) and Stanford Research International (Contract No. NO1-ES-9-0001).

16. Exposure Standards

No recommended or promulgated occupational exposure standards for 2,4-dichlorophenol were found.

17. Sources of Additional Relevant Information

No sources of additional relevant information were identified.

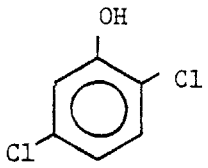
18. Other Pertinent Data

No other information that would aid in the assessment of 2,4-dichlorophenol as an occupational hazard was found in the literature searched.

E. 2,5-DICHLOROPHENOL

1. Chemical Name: 2,5-Dichlorophenol

2. Chemical Structure:



3. Synonyms: 2,5-Dichloro-1-hydroxybenzene
Phenol, 2,5-dichloro-

4. Chemical Abstracts Service (CAS) Number: 583-78-8

5. Registry of Toxic Effects of Chemical Substances (RTECS) Number:

Not listed

6. Chemical and Physical Properties

Description:	solid with a strong persistent odor
Molecular Weight:	163.01
Boiling Point:	212-213°C
Melting Point:	58°C
Vapor Pressure:	---
Solubility:	sparingly soluble in water very soluble in alcohol and ether soluble in benzene and hot petroleum ether
Specific Gravity:	---
Stability:	slight fire hazard

7. Production

2,5-Dichlorophenol is manufactured as an intermediate in the production of the herbicide Banvel. In 1975, about 2.8 million of Banvel were consumed domestically (Ayers et al., 1976), requiring roughly 2 million pounds of 2,5-dichlorophenol for synthesis.

8. Use

2,5-Dichlorophenol is used commercially to produce the herbicide Banvel (Ayers et al., 1976).

9. Manufacturers and Distributors

2,5-Dichlorophenol is made by Velsicol Chemical Corp., Beaumont, TX (SRI International, 1980); it is used captively to make the herbicide Banvel.

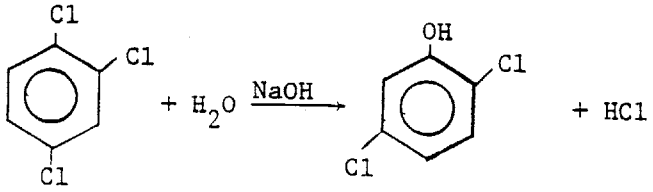
According to the U.S. EPA (1980), Kodak (Rochester, NY) is a manufacturer that had no production in 1977.

Distributors of 2,5-dichlorophenol include (1980-81 OPD Chemical Buyers Directory, 1980; Chem Sources-USA, 1980):

Aceto Chem.
Aldrich Chem.
American Hoechst
Atomergic Chemetals
Chem. Procurement Lab.
Columbia Organics
EM Lab.
Fisher Sci.
ICN/K and K
Koch Chem.
Lachat Chem.
MCB Reagents
PCR Research Chem.
Pfaltz and Bauer
Tridom Chem.

10. Manufacturing Processes

2,5-Dichlorophenol is not made commercially via chlorination of phenol because it is not readily produced by direct chlorination; rather, it is made by hydrolysis of chlorinated benzene (Doedens, 1964; Freiter, 1978). The general chemical reaction is the following:

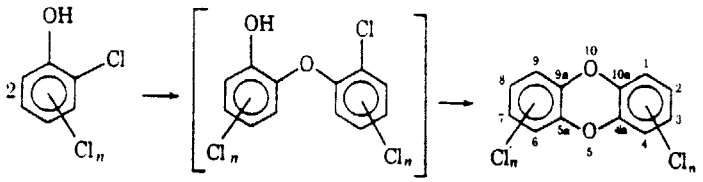


Generally, the hydrolysis is carried out in aqueous alkaline solutions at high temperatures and under pressure. Very often solvents such as ethanol or methanol are added to the reaction media to increase solubility and, thus, reaction rate; however, some methyl or ethyl ether of the chlorinated phenol is then obtained through side reactions. Reaction temperatures vary from 160°C to 300°C, reaction times are from 15 to 90 minutes, pressures vary from atmospheric to 500 psi, and conversions of 80% to 98% can be obtained (Doedens, 1964).

Figure 4 illustrates a general manufacturing operation. After hydrolysis, the reaction mass is extracted with an organic solvent to remove the bulk of the organic by-products, acidified, and distilled to recover the 2,5-dichlorophenol.

11. Impurities or Additives

Chlorinated dibenzo-p-dioxins are formed, by the reaction illustrated below, during the manufacturing processes used to produce polychlorinated phenols.



chlorinated dibenzo-*p*-dioxin

12. Occupational Exposure

The National Occupational Hazard Survey does not provide an estimate of the number of workers who are potentially exposed to 2,5-dichlorophenol.

13. Control Technology and Work Practices

Specific factors that may contribute to or prevent employee exposure to 2,5-dichlorophenol were not found in the literature searched.

14. Biological Effects

No information was found in the literature searched regarding the biological effects of 2,5-dichlorophenol except one mutagenicity study. 2,5-Dichlorophenol was reported to be non-mutagenic in the Ames Salmonella/microsome assay in tester strains TA98, TA100, TA1535, and TA1537, both in the presence and absence of S-9 fraction of rat liver homogenate (Rasanen et al., 1977).

15. Ongoing Studies

Microbial mutagenesis testing of 2,5-dichlorophenol is scheduled to be completed by EG and G Mason (Rockville, MD) in 1980 (NIEHS, 1980). The testing

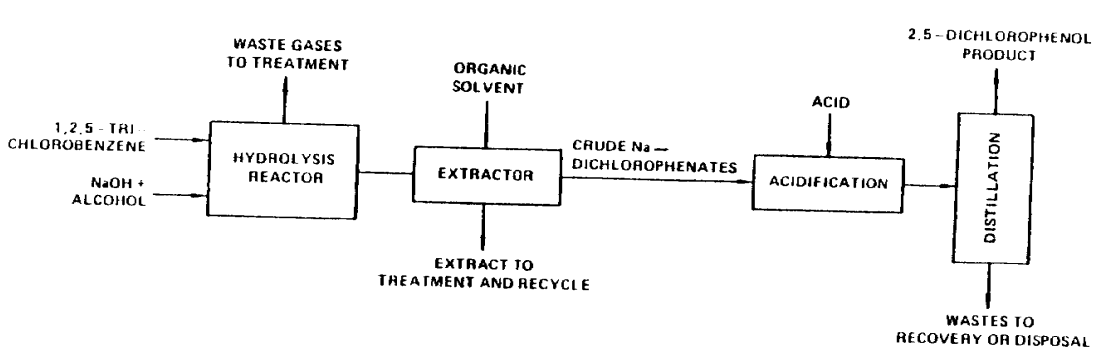


Figure 4. Manufacture of 2,5-Dichlorophenol (Adapted from Doedens, 1964)

is being supported by the National Institute of Environmental Health Sciences under Contract No. NO1-ES-9-2137.

16. Exposure Standards

No recommended or promulgated occupational exposure standards for 2,5-dichlorophenol were found.

17. Sources of Additional Relevant Information

No sources of additional relevant information were identified.

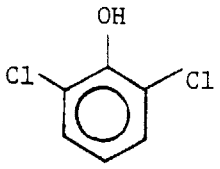
18. Other Pertinent Data

No other information that would aid in the assessment of 2,5-dichlorophenol as an occupational hazard was found in the literature searched.

F. 2,6-DICHLOROPHENOL

1. Chemical Name: 2,6-Dichlorophenol

2. Chemical Structure:



3. Synonyms: 2,6-Dichlorofenol
2,6-Dichloro-1-hydroxybenzene
Phenol, 2,6-dichloro-

4. Chemical Abstracts Service (CAS) Number: 87-65-0

5. Registry of Toxic Effects of Chemical Substances (RTECS) Number:

SK8750000

6. Chemical and Physical Properties:

Description:	solid with a penetrating odor resembling that of 2-chlorophenol
Molecular Weight:	163.01
Melting Point:	67°C
Boiling Point:	219-220°C (740 mm Hg)
Vapor Pressure:	1 mm Hg (at 59.5°C)
Solubility:	very soluble in alcohol and ether soluble in benzene and hot petroleum ether
Specific Gravity:	---
Stability:	slight fire hazard

7. Production

No production data for 2,6-dichlorophenol are available, but the compound is produced only as a by-product.

8. Use

The 2,6-dichlorophenol produced commercially is formed as a by-product during 2,4-dichlorophenol production and is used as a feedstock for making higher chlorophenols (Doedens, 1964). Relatively small amounts may be used for specialized organic syntheses.

9. Manufacturers and Distributors

2,6-Dichlorophenol is manufactured by (SRI International, 1980):

Aldrich Chemical Co.	Milwaukee, WI
Specialty Organics	Irwindale, CA

Both of the above companies make primarily reagent grade chemicals. Rhone-Poulenc is also listed as a manufacturer, but having no production in 1977 (U.S. EPA, 1980).

2,6-Dichlorophenol is formed as a side-product during 2,4-dichlorophenol production. Producers of 2,4-dichlorophenol include Dow, Monsanto, Chem. South, Vertac (Transvaal), and Rhone-Poulenc (U.S. EPA, 1980).

Distributors include (1980-81 OPD Chemical Buyers Directory, 1980; Chem Sources-USA, 1980):

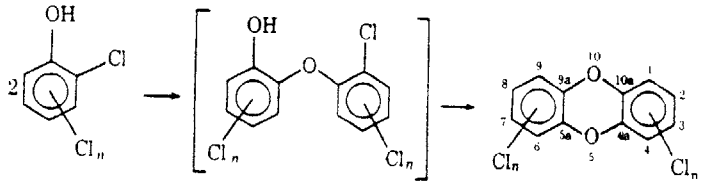
Accurate Chem.
Atomergic Chemetals
Biochemical Lab.
Bio-Clinical Lab.
Bodman Chemicals
Chemical Dynamics
Chem. Procurement Lab.
Chem. Services
Columbia Organics
Eastern Chem.
EM Lab.
Fairfield Chem.
ICN/K and K
Koch Chemicals
Lachat Chem.
Marshallton Lab.
MCB Reagents
Pfaltz and Bauer
Spectrum Chem.
Tridom Chem.

10. Manufacturing Processes

2,6-Chlorophenol is formed as a by-product of 2,4-dichlorophenol manufacture. Figure 5 outlines the general operations.

11. Impurities or Additives

Chlorinated dibenzo-p-dioxins are formed, by the reaction illustrated below, during the manufacturing processes used to produce polychlorinated phenols.



chlorinated dibenzo-*p*-dioxin

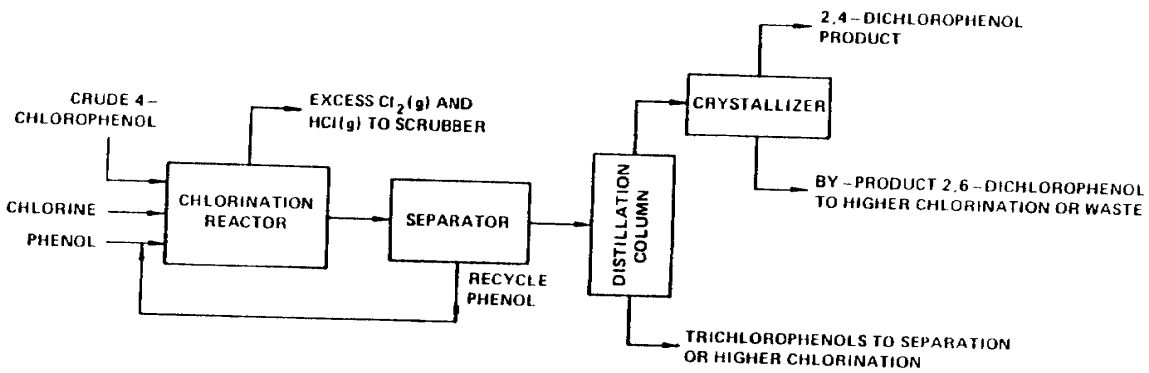


Figure 5. Manufacture of 2,4-Dichloro- and 2,6-Dichlorophenol (Adapted from Doedens, 1964; Golumbic, 1953)

12. Occupational Exposure

The National Occupational Hazard Survey does not provide an estimate of the number of workers who are potentially exposed to 2,6-dichlorophenol.

13. Control Technology

Specific factors that may contribute to or prevent employee exposure to 2,6-dichlorophenol were not found in the literature searched.

14. Biological Effects

a. Animal Studies

(1) Acute Exposures

Farquharson et al. (1958) reported an LD50 of 390 mg/kg for rats following intraperitoneal injection of 2,6-dichlorophenol. When 2,6-dichlorophenol was administered intraperitoneally, initial excitation and tremors were observed. When poisoning was sufficiently great, convulsions developed along with loss of righting reflex, hypotonia, coma, dyspnea, and death. Body temperature was depressed 0.7°C following the administration of lethal intraperitoneal doses (230 mg/kg), and rigor mortis did not occur within 5 minutes of death as it does with the higher chlorinated phenols.

(2) Subchronic Exposures

No information was found in the literature searched.

(3) Chronic Exposures

No information was found in the literature searched.

(4) Carcinogenicity

No information was found in the literature searched.

(5) Mutagenicity

2,6-Dichlorophenol was reported to be non-mutagenic in the Ames Salmonella/microsome assay in tester strains TA98, TA100, TA1535, and TA1537, both in the presence and absence of S-9 fraction of rat liver homogenate (Rasanen et al., 1977).

(6) Teratogenicity

No information was found in the literature searched.

(7) Reproductive Effects

No information was found in the literature searched.

(8) Other Relevant Information

No information was found in the literature searched.

b. Human Studies

(1) Pharmacokinetics

No information was found in the literature searched.

(2) Health Effects

No information was found in the literature searched.

(3) Target Organ Toxicity

No information was found in the literature searched.

(4) Epidemiology

No information was found in the literature searched.

15. Ongoing Studies

Microbial mutagenesis testing of 2,6-dichlorophenol is scheduled to be completed by EG and G Mason (Rockville, MD) in 1980 (NIEHS, 1980). The testing is supported by the National Institute of Environmental Health Sciences under Contract No. NO1-ES-9-2137.

16. Exposure Standards

No recommended or promulgated occupational exposure standards for 2,6-dichlorophenol were found.

17. Sources of Additional Relevant Information

No sources of additional relevant information were identified.

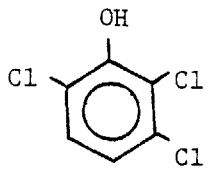
18. Other Pertinent Data

No other information that would aid in the assessment of 2,6-dichlorophenol as an occupational hazard was found in the literature searched.

G. 2,3,6-TRICHLOROPHENOL

1. Chemical Name: 2,3,6-Trichlorophenol

2. Chemical Structure:



3. Synonyms: Phenol, 2,3,6-trichloro-

4. Chemical Abstracts Service (CAS) Number: 933-75-5

5. Registry of Toxic Effects of Chemical Substances (RTECS) Number:

SN1300000

6. Chemical and Physical Properties:

Description:	solid crystals
Molecular Weight:	197.46
Boiling Point:	272°C
Melting Point:	55-58°C
Vapor Pressure:	---
Solubility:	slightly soluble in hot water very soluble in alcohol, ether, and benzene soluble in acetic acid and ligroin
Specific Gravity:	---
Stability:	nonflammable

7. Production

According to the U.S. EPA (1980), Dow Chemical in Midland, MI, produced between 1 to 10 million pounds of 2,3,6-trichlorophenol in 1977. No other literature sources, however, indicate that 2,3,6-trichlorophenol is made in such large quantities.

8. Uses

According to various patent literature, 2,3,6-trichlorophenol is used in fungicidal compounds and plant growth regulators and in the synthesis of fungicidal compounds, bactericides, and miticides.

9. Manufacturers and Distributors

2,3,6-Trichlorophenol is manufactured by Dow Chemical in Midland, MI (U.S. EPA, 1980).

Distributors include (1980-81 OPD Chemical Buyers Directory, 1980; Chem Sources—USA, 1980):

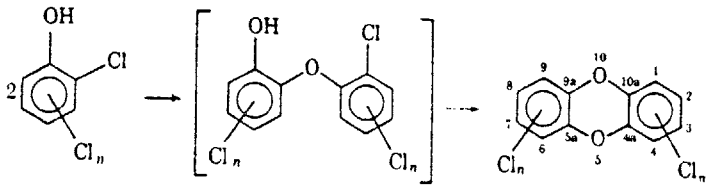
Aldrich Chem.
Atomergic Chemetals
Chem. Procurement Lab.
Chem. Services
EM Lab.
International Enzymes
Koch Chem.
Lachat Chem.
MCB Reagents
Pfaltz and Bauer
Tridom Chem.

10. Manufacturing Processes

2,3,6-Trichlorophenol can be produced by two methods. First, it is formed as a side-product during the hydrolysis of 1,2,4,5-tetrachlorobenzene to produce 2,4,5-trichlorophenol (Jenney and Nicolaisen, 1956). Second, it can be made by the vapor-phase reduction of 2,3,4,6-tetrachlorophenol (Brainerd and Poffenberger, 1961). This vapor-phase reduction uses a moving bed catalyst of activated alumina containing 2% to 25% CuCl. The tetrachlorophenol is reacted with two moles of hydrogen at elevated temperature over the catalyst. The reaction mixture is condensed and fractionally distilled to yield the 2,3,6-trichlorophenol.

11. Impurities or Additives

Chlorinated dibenzo-p-dioxins are formed, by the reaction illustrated below, during the manufacturing processes used to produce polychlorinated phenols.



chlorinated dibenzo-*p*-dioxin

12. Occupational Exposure

The National Occupational Hazard Survey does not provide an estimate of the number of workers who are potentially exposed to 2,3,6-trichlorophenol.

13. Control Technology and Work Practices

Specific factors that may contribute to or prevent employee exposure to 2,3,6-trichlorophenol were not found in the literature searched.

14. Biological Effects

a. Animal Studies

(1) Acute Exposures

Farquharson et al. (1958) reported a LD50 of 308 mg/kg for rats following intraperitoneal injection of 2,3,6-trichlorophenol. When 2,4,6-trichlorophenol was administered intraperitoneally, initial excitation and tremors were observed. When poisoning was sufficiently great, the rats often convulsed violently when handled, but otherwise lay prostrate with hypotonia. Coma, dyspnea, and death ensued. Following injection of the drug, hypotonia was observed in the hind-limbs of the rats within 2 to 3 minutes; this gradually progressed to involve the forelimbs and neck so that the animals were completely prostrate. Respiration was at first accelerated, but became slower and dyspneic as coma developed. The intraperitoneal administration of the 2,3,6-trichlorophenol also elevated body temperature 0.5°C, and onset of rigor mortis occurred within 5 minutes of death as compared to 50 minutes for control rats.

(2) Subchronic Exposures

No information was found in the literature searched.

(3) Chronic Exposures

No information was found in the literature searched.

(4) Carcinogenicity

No information was found in the literature searched.

(5) Mutagenicity

2,3,6-trichlorophenol showed no mutagenic activity in the Ames assay using Salmonella typhimurium tester strains TA98, TA100, TA1535, and TA1537, both in the presence and absence of rat liver homogenate fraction (Rasanen et al., 1977).

(6) Teratogenicity

No information was found in the literature searched.

(7) Reproductive Effects

No information was found in the literature searched.

(8) Other Relevant Information

No information was found in the literature searched.

b. Human Studies

(1) Pharmacokinetics

No information was found in the literature searched.

(2) Health Effects

No information was found in the literature searched.

(3) Target Organ Toxicity

No information was found in the literature searched.

(4) Epidemiology

No information was found in the literature searched.

15. Ongoing Studies

No current toxicological or environmental studies of 2,3,6-trichlorophenol were found.

16. Exposure Standards

No recommended or promulgated occupational exposure standards for 2,3,6-trichlorophenol were found.

17. Sources of Additional Relevant Information

No sources of additional relevant informational were identified.

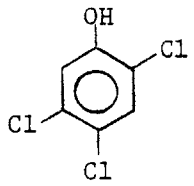
18. Other Pertinent Data

No other information that would aid in the assessment of 2,3,6-trichlorophenol as an occupational hazard was found in the literature searched.

H. 2,4,5-TRICHLOROPHENOL

1. Chemical Name: 2,4,5-Trichlorophenol

2. Chemical Structure:



3. Synonyms: Phenol, 2,4,5-trichloro-
Collunsol
Dowicide 2
Preventol 1
Nurelle

4. Chemical Astracts Service (CAS) Number: 95-95-4

5. Registry of Toxic Effects of Chemical Substances (RTECS) Number:

SN1400000

6. Chemical and Physical Properties:

Description:	gray flakes to sublimed mass with strong phenolic odor
Molecular Weight:	197.46
Boiling Point:	252°C (sublimes)
Melting Point:	68°-70°C
Vapor Pressure:	1 mm Hg (at 72°C)
Solubility:	0.12 g/100 g water (20°C) soluble in alcohol, organic salts, and ligroin
Specific Gravity:	1.678^{25}_{4}
Stability:	nonflammable

7. Production

Data available from the U.S. EPA (1980) regarding producers of 2,4,5-trichlorophenol and production volumes are presented in Table 13.

The most recent production figure for 2,4,5-trichlorophenol is 28 million pounds in 1968 (USTC, 1970). Current production is judged to be less because the major use of 2,4,5-trichlorophenol in making the herbicide 2,4,5-T

Table 13. Producers of 2,4,5-Trichlorophenol and Production Ranges (U.S. EPA, 1980)

Producer and Location	Type of Production	1977 Production Range
Dow Chemical Midland, MI	Manufacturer	10-50 million lb
Chem South Corp. Childersburg, AL	Manufacturer	0.1-1.0 million lb
Drake Chemical Lock Haven, PA	Manufacturer	confidential
Gallard-Schelsinger Chem. Carle Place, NY	Importer	none
Givaudan Corp. Clifton, NJ	Importer	less than 1000 lb

has declined since 1968. Current annual production probably falls in the range of 10 to 20 million pounds (SRC estimate).

Importation of 2,4,5-trichlorophenol in recent years is as follows (USTIC, 1980a, 1979a, 1977a):

Year	Imports (in thousands of pounds)
1979	451.0
1978	158.6
1976	192.0

8. Use

2,4,5-Trichlorophenol is used as an intermediate in the manufacture of the herbicides 2,4,5-trichlorophenoxyacetic acid (2,4,5-T) and 2-(2,4,5-trichlorophenoxy)propionic acid (silvex), the germicide hexachlorophene, and the insecticides trichloronate and Fenchlorophos (Freiter, 1978). In 1975, roughly 10 to 12 million pounds of 2,4,5-T were produced, with 6.7 million pounds consumed domestically (Ayers et al., 1976) and the rest exported; 2 million pounds of silvex were domestically consumed (Ayers et al., 1976). This would have required roughly 10 million pounds of 2,4,5-triphenol for production.

2,4,5-Trichlorophenol itself is used as an antifungal agent in adhesives, as a preservative in polyvinylacetate emulsions, in the automotive industry to preserve rubber gaskets, and in textiles to preserve emulsions used in the rayon industry (Freiter, 1978).

The sodium salt of 2,4,5-trichlorophenol is also used as a fungicide and bactericide (Freiter, 1978). Uses include adhesives, in cooling water as an inhibitor of microbial growth in recirculating water, in foundry core wash to prevent breakdown of oils and scum formation, in leather dressing and finishes to prevent the decomposition of nitrogenous compounds, in metal working fluids to prevent oil breakdown, and in emulsifying agents and other components. An aqueous solution of the sodium salt is normally used in these applications.

9. Manufacturers and Distributors

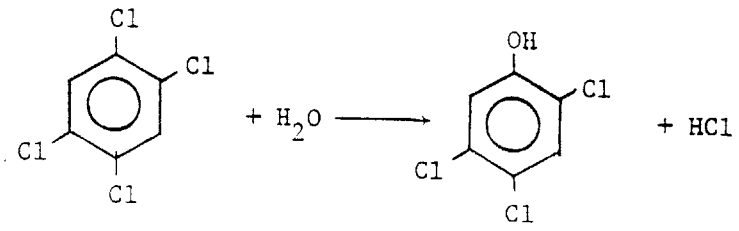
The manufacturers of 2,4,5-trichlorophenol are listed in Table 13 (U.S. EPA, 1980).

Other distributors include (Chemical Week: 1981 Buyers Guide Issue, 1980; Chem Sources - USA, 1980):

Aldrich Chem.
American Hoechst
Amer. Research Prod.
Anachemia Chem.
Atomergic Chemetals
Biochemical Lab.
Chemical Dynamics
Chem. Procurement Lab.
Chem. Services
Continental Trading Co.
EM Lab.
J.T. Baker Chem.
Lachat Chem.
MCB Reagents
McKesson Chem.
Pfaltz and Bauer
Polysciences
Tridom Chem.
Vertac Chem.

10. Manufacturing Processes

2,4,5-Trichlorophenol is not manufactured commercially via phenol chlorination because it is not readily produced by direct chlorination; rather, it is made by hydrolysis of chlorinated benzenes (Doedens, 1964; Freiter, 1978). The general chemical reaction is the following:

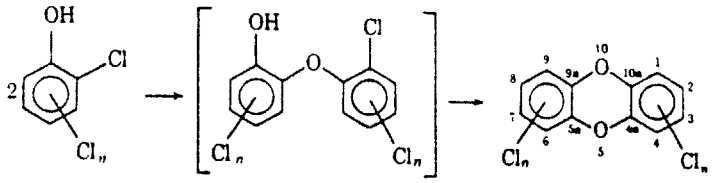


For the commercial production of 2,4,5-trichlorophenol specifically, the hydrolysis is carried out continuously in a coil reactor at 160°C in the presence of methanol and sodium hydroxide. Contact time is approximately 7 hours, and yields of 80% to 85% of the theoretical yield are achieved. The chief impurity is 2,4,5-trichloroanisole, which results from the reaction of 2,4,5-trichlorophenol with some of the methanol. After the hydrolysis is complete, the reaction mass is extracted with an organic solvent to remove the bulk of the

anisole derivative, acidified with hydrochloric acid, and distilled to recover the trichlorophenol (Doedens, 1964). The basic operations are shown in Figure 6.

11. Impurities or Additives

Chlorinated dibenzo-p-dioxins are formed, by the reaction illustrated below, during the manufacturing processes used to produce polychlorinated phenols.



chlorinated dibenzo-*p*-dioxin

In the case of 2,4,5-trichlorophenol, the corresponding dioxin formed is the very toxic 2,3,7,8-tetrachlorodibenzo-p-dioxin (TCDD). This dioxin appears in the caustic insolubles in commercial 2,4,5-trichlorophenol (Crummett and Stehl, 1973).

12. Occupational Exposure

The National Occupational Survey indicates that 11,578 workers are potentially exposed to 2,4,5-trichlorophenol.

13. Control Technology and Work Practices

Specific factors that may contribute to or prevent employee exposure to 2,4,5-trichlorophenol were not found in the literature searched.

14. Biological Effects

a. Animal Studies

(1) Acute Exposures

The acute toxic effects of 2,4,5-trichlorophenol are summarized in Table 14. The clinical signs of poisoning following lethal oral and subcutaneous doses of 2,4,5-trichlorophenol include decreased activity and motor weakness (Deichmann, 1943). Tremors, clonic convulsions, dyspnea, and coma ensued until death, but the convulsive seizures were not as severe as with the

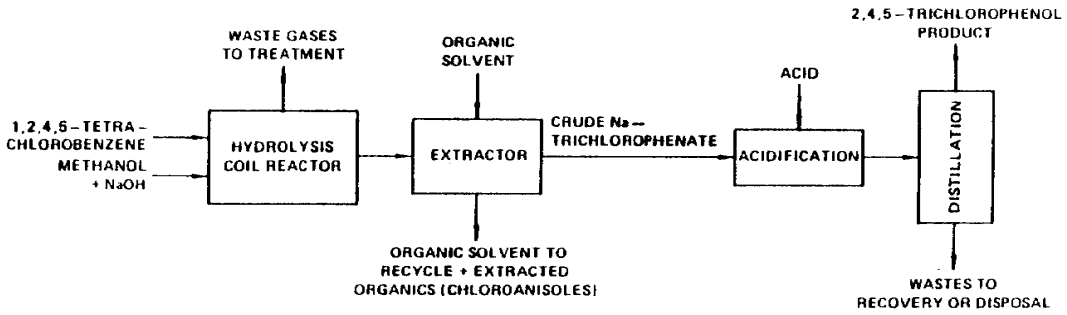


Figure 6. Manufacture of 2,4,5-Trichlorophenol
(Adapted from Doedens, 1964)

Table 14. Acute Effects of 2,4,5-Trichlorophenol and its Sodium Salt

Compound	Route[a]	Species	Dose (mg/kg)	Response	Reference
2,4,5-Trichlorophenol	oral	rats	820	LD50	Deichmann, 1943
	oral[b]	rats (male)	2830	LD50	Dow Chemical Co., 1969a
	oral	rats (male)	2960	LD50	McCollister et al., 1961
	oral[b]	rats (female)	2460	LD50	Dow Chemical Co., 1969a
	oral	guinea pigs	1000-3000	LD50	Meister, 1972
	i.p.	rats	355	LD50	Farquharson et al., 1958
	s.c.	rats	2260	LD50	Deichmann, 1943
	dermal	mice	6700	TDLo	Boutwell and Bosch, 1959
2,4,5-Trichlorophenol, Sodium Salt	oral	rats (male)	1870	LD50	Dow Chemical Co., 1969b
	oral	rats (female)	1620	LD50	Dow Chemical Co., 1969b
	dermal	rabbits	2000-4000 (crystalline)	LD50	Dow Chemical Co., 1969b
			>4000 (10% aqueous solution)	LD50	Dow Chemical Co., 1969b

[a] i.p. = intraperitoneal; s.c. = subcutaneous.
[b] Technical grade 2,4,5-Trichlorophenol.

monochlorophenols. When Farquharson et al. (1958) injected 2,4,5-trichlorophenol intraperitoneally into male albino rats, hypotonia was observed in the hind limbs within 2 to 3 minutes; this gradually progressed to involve the forelimbs and neck so that the rat was completely prostrate. Respiration was at first accelerated, but became slower and dyspnoeic as coma developed. The intraperitoneal administration of the 2,4,5-trichlorophenol also elevated body temperature 0.5°C, and onset of rigor mortis occurred within 5 minutes of death as compared to 50 minutes for controls.

Brief exposure to 2,4,5-trichlorophenol or its sodium salt caused a slight reddening and burning of rabbit skin, and 24-hour exposure resulted in mild to moderate chemical burns (Dow Chemical Co., 1969a). The dermal irritation effects are summarized in Table 15.

When applied to the eyes of rabbits, both technical grade 2,4,5-trichlorophenol and its sodium salt caused severe conjunctival redness and moderate or severe swelling (Dow Chemical Company, 1969a, 1969b). Technical grade 2,4,5-trichlorophenol further resulted in slight to moderate corneal injury, and its sodium salt caused slight iritis and moderate to severe corneal injury.

(2) Subchronic Exposures

One rabbit given 20 oral doses by intubation of 100 mg/kg of 2,4,5-trichlorophenol in 5% gum acacia solution for 28 days developed very slight kidney changes, and another that received 500 mg/kg had very slight liver and kidney changes (McCollister et al., 1961). The pathologic changes were not detailed in either case. No effects were found when 5 rabbits were given doses of 1 or 10 mg/kg.

In a related experiment, McCollister and coworkers (1961) administered 18 doses of 30, 100, 300, or 1000 mg/kg 2,4,5-trichlorophenol in

Table 15. Skin Irritation Effects of 2,4,5-Trichlorophenol and its Sodium Salt in Rabbits

Compound	Exposure	Response	Reference
2,4,5-Trichlorophenol, technical grade	Single short exposure	Slight erythema after a few minutes, slight edema, and a slight to moderate burn after 1 to 1-1/2 hours.	Dow Chemical Co., 1969a
	20 applications of a 10% chloroform solution to the ears	No chloracnegenic activity.	Dow Chemical Co., 1969a
2,4,5-Trichlorophenol, sodium salt	5-hour exposure	Slight chemical burn; abraded skin responded with a slight burn in 1 to 2 hours.	Dow Chemical Co., 1969b
	24-hour exposure	Moderate to severe swelling and severe chemical burn of intact and abraded skin.	Dow Chemical Co., 1969b
	Prolonged exposure to 10% aqueous solution	Very slight to slight redness, and very slight swelling.	Dow Chemical Co., 1969b
	20 applications of a 10% chloroform solution to the ears.	No chloracnegenic activity.	Dow Chemical Co., 1969b

olive oil to groups of 5 male rats over 24 days. The rats that received 1000 mg/kg lost a small amount of body weight during the first 10 days (average 10 g loss from 270 g total body weight), but the loss was quickly recovered, and the animals were gaining normally by the 14th day. At autopsy, the kidneys of these rats showed a slight weight increase in comparison to those of control animals. No other differences were found between experimental and control animals after examination of blood, organs, and growth and mortality records.

McCollister et al. (1961) also maintained groups of male and female rats (10 of each sex per group) at dietary levels of 100, 300, 1000, 3000, or 10,000 mg of 2,4,5-trichlorophenol per kg of feed for 98 days. No adverse effects were detected at the lower dosage levels, but mild diuresis and slight degenerative changes in the liver and kidney of both sexes were noted at the 0.3 and 1.0% levels. The kidneys showed moderate changes in the epithelium lining of the convoluted tubules and early proliferation of the interstitial tissue. The liver showed mild centrilobular degenerative changes characterized by cloudy swelling and an occasional area of focal necrosis. Slight proliferation of the bile ducts and early portal cirrhosis were also observed. It should be noted that these changes were considered to be mild, reversible, and probably minor.

(3) Chronic Toxicity Data

No information was found in the literature searched.

(4) Carcinogenicity

Bionetics Research Laboratories (BRL, 1968a) subcutaneously injected 1000 mg/kg of commercial grade 2,4,5-trichlorophenol (Collunosol; Dowicide 2; impurities unspecified) in corn oil into groups of 18 male and 18 female (C57BL/6 x x C3H/Anf)F_1 mice and 18 male and 18 female (C57BL/6 x AKR)F_1 mice on the 28th day of age. All animals were observed until 78 weeks of age, at which time 16, 11, 18, and 18 mice were alive from the four groups, respectively.

Results showed that the total incidence of mice with tumors was 4/17, 0/18, 2/18, and 3/18 among the experimental groups; these incidences were not increased ($P > 0.05$) relative to negative control groups consisting of mice that were either untreated or received gelatin, corn oil, or dimethylsulfoxide (DMSO).

Boutwell and Bosch (1959) reported that commercial grade 2,4,5-trichlorophenol promoted tumor development when painted repeatedly on the backs of mice following initiation with single applications of dimethylbenzanthracene (DMBA) (Table 16). It should be noted, however, that a small number of animals were used in the experiment and that no mice were treated with 2,4,5-trichlorophenol alone.

(5) Mutagenicity

2,4,5-Trichlorophenol was reported to be non-mutagenic in the Ames Salmonella/microsome assay using tester strains TA98, TA100, TA1535, and TA1537, both in the presence and absence of S-9 rat liver homogenate fraction (Rasanen et al., 1977).

Repeated spraying of flower buds of vetch (Vicia faba) with an aqueous solution of 2,4,5-trichlorophenol increased the frequency of abnormalities in pollen mother cells, including stickiness and lagging of chromosomes during cell division and chromosome fragments (Amer and Ali, 1974).

(6) Teratogenicity

2,4,5-Trichlorophenol was administered daily by subcutaneous injection in dimethylsulfoxide (DMSO) at a dose level of 85 mg/kg in BL6 and AKR mice on days 6 through 14 and 6 through 15 of gestation, respectively (BRL, 1968b). The mice were sacrificed on day 18 (BL6) and day 19 (AKR) of gestation. Results showed that the incidence of abnormal fetuses was within the normal range and that the administration of the compound had no fetotoxic effects.

Table 16. Tumor-Promoting Action of 2,4,5-Trichlorophenol (Boutwell and Bosch, 1959)[a]

Promoter	Number of Mice (survivors/original)	Average Number of Papillomas per Survivor	Percent Survivors with Papillomas	Percent Survivors with Carcinomas
Experiment 11				
Initiator: 0.3% DMBA in acetone				
Promoter: in acetone				
Date: at 16 weeks				
None (acetone control)	18/20	0	0	0
21% 2,4,5-trichlorophenol	19/20	0.95	42	0 (5% at 30 weeks)

[a]A single 25 µl application of DMBA was painted on the dorsal skin of 20 2- to 3-month old female Sutter mice. Single applications of 1 drop (approximately 25 µl) of the chlorophenol solution (commercial grade dissolved in 21% reagent grade acetone, producers and impurities unspecified) were begun 1 week after the application of initiator and were continued twice each week for the duration of the experiment.

(7) Reproductive Effects

No information was found in the literature searched.

(8) Other Relevant Information

Feeding of 2,4,5-T (2,4,5-trichlorophenoxyacetic acid) and silvex (2-(2,4,5-trichlorophenoxy)propionic acid) to sheep and cattle produced high levels of 2,4,5-trichlorophenol in liver and kidney and low levels in muscle and fat (Clark et al., 1976).

2,4,5-Trichlorophenol inhibits oxidative phosphorylation in isolated rat liver mitochondria (Mitsuda et al., 1963; Weinback and Garbus, 1965).

b. Human Studies

(1) Pharmacokinetics

No information was found in the literature searched.

(2) Health Effects

Technical grade 2,4,5-trichlorophenol can cause irritation to the eyes, skin, nose, and throat. Depending on the degree of exposure, ocular damage may include the conjunctiva, iris, or cornea, with the damage varying from slight irritation to chemical burns (Dow Chemical Company, 1969a). Skin contact may result in mild to moderate chemical burns or chloracne. Technical grade 2,4,5-trichlorophenol contains a number of impurities, however, including 2,3,7,8-tetrachlorodibenzo-p-dioxin (TCDD); TCDD may well be the causative agent of chloracne (IARC, 1977, 1978; Holmstedt, 1980). Other adverse health effects have been seen in workers exposed to 2,4,5-trichlorophenol contaminated with TCDD; these effects, probably due to TCDD, include liver dysfunction, neuromuscular weakness, porphyria, and psychological changes (see Other Pertinent Data).

McCollister et al. (1961) reported the results of skin irritation and sensitization testing on 200 human subjects. When a 5% solution of 2,4,5-trichlorophenol in sesame oil was used, a mild irritating action was observed in a few individuals upon prolonged contact, but there was no evidence of sensitization.

Compared to the trichlorophenol, sodium 2,4,5-trichlorophenate has toxic properties similar in kind but somewhat more intense in degree (Dow Chemical Company, 1969b).

(3) Target Organ Toxicity

No information was found in the literature searched.

(4) Epidemiology

No information was found in the literature searched.

15. Ongoing Studies

The distribution and fate of 2,4,5-trichlorophenol will be determined in laboratory rats in connection with long-term growth-feed efficiency and thyroid physiology evaluations (Street, 1980). This work is to be conducted by J.C. Street of the Department of Animal Science at the Utah State University Agricultural Experiment Station (Logan, UT) under contract with the U.S. Department of Agriculture (Grant No. 0006756; UTA00603).

16. Exposure Standards

No recommended or promulgated occupational exposure standards for 2,4,5-trichlorophenol were found.

17. Sources of Additional Relevant Information

No sources of additonal relevant information were identified.

18. Other Pertinent Data

Out-of-control chemical reactions during the industrial preparation of 2,4,5-trichlorophenol have proceeded to the explosive stage, thereby exposing

workers to toxic levels of 2,3,7,8-tetrachlorodibenzo-p-dioxin (TCDD) (Holmstedt, 1980; IARC, 1977, 1978); a list of both accidents and involuntary contamination is presented in Table 17. Although an assessment of the toxicity of TCDD is beyond the scope of this profile, it should be noted that its extreme toxicity is not disputed. In humans, chloracne is one of the most constant and prominent features of TCDD exposure. Other findings may include neuromuscular symptoms, porphyria cutanea tardia, hepatic dysfunctions, hyperlipidemia, cutaneous hyperpigmentation and hirsutism, chronic eye irritation, emotional disorders, and neuropsychiatric syndromes. A number of cases of cancer have been reported in workers exposed to TCDD, but no adequate epidemiological studies are available (IARC, 1977, 1978). In animals, TCDD is teratogenic and carcinogenic.

Table 17. Industrial Incidents Associated with the Manufacture of Chlorinated Phenols (Adapted from Young et al. (1978) by Homstedt (1980)

Year	Country	Manufacturer/Location[a]	Production/ Product[b]	Primary Source of Exposure	Number of of Cases	Years from Incident to Last Observation[c]	Reference
1949	United States	Monsanto/Nitro, WV	TCP	Explosion	228	30	IARC, 1977, 1978; Suskind, 1976; Zack and Suskind, 1980
1949	Federal Republic of Germany	NA/Nordrhein-Westfalen	PCP, TCP	Occupational	17	1	Baader & Bauer, 1951
1952	Federal Republic of Germany	NA/NA	TCP	Occupational	60	---	Bauer et al., 1961
1952-1953	Federal Republic of Germany	Boehringer/NA	TCP	Occupational	37	---	Hay, 1977
1953	Federal Republic of Germany	BSAF/Ludwigshafen	TCP	Explosion	75	24	Goldman, 1972, 1973; IARC, 1978; Theiss & Goldman, 1976; Theiss & Frentzel-Beyme, 1977
1953-1971	France	Rhone Poulenc/Grenoble	TCP	Occupational and explosion	17	2	Dugois et al., 1958
1954	Federal Republic of Germany	Boehringer, Ingelheim/Hamburg	TCP 2,4,5-TCP	Occupational	31	9	Kimmig & Schulz, 1957a,b; von Krause and Brassow, 1978
1956	United States	Diamond Alkalai/ Newark, NJ	2,4-DCP, 2,4,5-TCP	Occupational	29	13	Bleiburg et al., 1964; Poland et al., 1971
1956	United States	Hooker/NA	TCP	Occupational	Many	---	Hay, 1977
1959	Italy	Industrie Chimiche Melegnanesi Saronio/NA	TCP	Occupational	5	20	Hofman & Meneghini, 1962
1960	United States	Diamond Shamrock/NA	TCP	Occupational	Many, 1 fatal	---	Hay, 1977
1963	Netherlands	Philips-Duphar/ Amsterdam	TCP	Explosion	100	14	Berlin et al., 1976; Dalderup, 1974a,b; IARC, 1978
1964	USSR	NA/NA	2,4,5-TCP	Occupational	128	---	IARC, 1977; Teleginar & Bikbulatova, 1970
1964	United States	Dow Chemical/ Midland, MI	2,4,5-TCP	Occupational	30	6	Firestone, 1980; Vahrenholt, 1977

Table 17. Industrial Incidents Associated with the Manufacturing of Chlorinated Phenols (Adapted from Young et al. (1978) by Holmsted (1980)

Year	Country	Manufacturer/Location[a]	Production/ Product[b]	Primary Source of Exposure	Number of Cases	Years from Incident to Last Observation[c]	Reference
1964-1969	Czechoslovakia	Spolana/NA	TCP	Occupational	80, 2 fatal	6	Jirasek et al., 1973, 1974, 1976; Pazderova et al., 1974
1968	United Kingdom	Coalite and Chemicals Products/ Bolsover, Derbyshire	TCP	Explosion	90	9	IARC, 1978; May, 1973
1970	Japan	NA/NA	PCP 2,4,5-TCP	Occupational	25	3	Miyra et al., 1974
1972	USSR	NA/NA	TCP	Occupational	1	1	Zelikov & Danilov, 1974
1972-1973	Austria	Linz Nitrogen Works/NA	2,4,5-TCP	Occupational	50	---	Forth, 1977; May, 1977
1974	Federal Republic of Germany	Bayer/Uerdingen	2,4,5-TCP	Occupational	5	---	Forth, 1977; May, 1977
1975	United Sates	Thompson-Hayward/ Kansas City, KS	TCP	Occupational	---	---	May, 1977
1976	Italy	ICMESA/Meda	TCP	Explosion	134	3	Kamedo, 1977; Reggiani, 1977a,b,c; 1978a,b

[a]The name of the factory or company and its location was cited whenever it was available because considerable confusion exists in the published literature as to what incident is addressed. NA indicates that the information was not available.

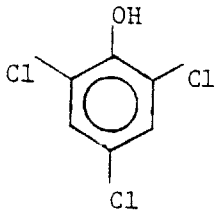
[b]TCP = trichlorophenol; PCP = pentachlorophenol; 2,4,5-TCP = 2,4,5-trichlorophenol; 2,4-DCP = 2,4-dichlorophenol.

[c]Frequently individuals involved in an incident who were examined initially may have also been examined at a later date. The years that lapsed from the exposure until the most recent examination are cited in this column. The absence of a number indicates that only an initial examination was reported in the referenced literature.

I. 2,4,6-TRICHLOROPHENOL

1. Chemical Name: 2,4,6-Trichlorophenol

2. Chemical Structure:



3. Synonyms: Phenol, 2,4,6-trichloro-
Dowicide 2S
Omal
2,4,6-T
Phenaclor
NCI-C02904

4. Chemical Abstracts Service (CAS) Number: 88-06-2

5. Registry of Toxic Effects of Chemical Substances (RTECS) Number:

SN1575000

6. Chemical and Physical Properties:

Description:	yellow flakes with a strong phenolic odor
Molecular Weight:	197.46
Boiling Point:	246-249°C
Melting Point:	68°C
Vapor Pressure:	1 mm Hg (at 76.5°C)
Solubility:	0.09 g/100 g water (20°C) soluble in acetone, alcohol, ether, toluene, hot acetic acid
Specific Gravity:	1.675^{25}_{4}
Stability:	nonflammable

7. Production

Data available from the U.S. EPA (1980) regarding producers of 2,4,6-trichlorophenol and production volumes are presented in Table 18.

8. Use

The principal use of 2,4,6-trichlorophenol is in the manufacture of slime-control agents for cooling towers and paper mills (Golumbic, 1953). In addition, the compound has been cited as an effective germicide, wood

Table 18. Producers of 2,4,6-Trichlorophenol and Production Ranges (U.S. EPA, 1980)

Producer	Type of Production	1977 Production Range
Dow Chemical Midland, MI	Manufacturer	none
Fike Chemical Nitro, WV	Manufacturer	none
Rhone-Roulenc Freeport, TX Freeport, TX	Manufacturer Importer	10-100 thousand lb 10-100 thousand lb
Eastman Kodak Rochester, NY	Importer	under 1000 lb

preservative, glue preservative, insecticide ingredient, bactericide, and anti-mildew treatment for textiles (Doedens, 1964). 2,4,6-Trichlorophenol is used as a raw material for making chloranil, a widely used seed protectant for crops. Various soap germicides are also made with 2,4,6-trichlorophenol (Doedens, 1964).

9. Manufacturers and Distributors

The manufacturers of 2,4,6-trichlorophenol are listed in Table 18 (U.S. EPA, 1980).

Distributors include (1980-81 OPD Chemical Buyers Directory, 1980; Chemical Week: 1981 Buyers Guide Issue, 1980; Chem Sources-USA, 1980):

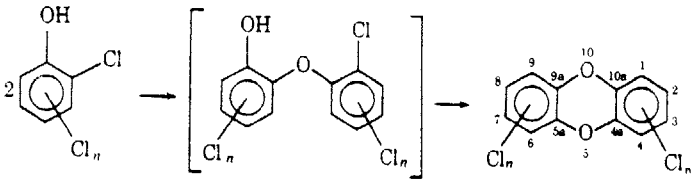
Aceto Chem.
Aldrich Chem.
American Research Prod.
Anachemia Chem.
Atomergic Chemetals
Chem. Procurement Lab.
Chem. Services
Eastman Kodak
Fisher Sci.
International Enzymes Inc.
Lachat Chem.
McKesson Chem.
Pfaltz and Bauer
Polysciences
Tridom Chem.

10. Manufacturing Processes

Manufacture of 2,4,6-trichlorophenol is readily accomplished by the direct chlorination of phenol. Mono- and dichlorophenols, obtained as co-products, are easily removed by distillation. The mono- and dichlorinated compounds are subsequently converted to the desired product by recycling and further chlorination. In industry, manufacturers of 4-chlorophenol and 2,4-dichlorophenol dispose of by-product 2-chlorophenol and 2,6-dichlorophenol by chlorinating them to 2,4,6-trichlorophenol (Doedens, 1964).

11. Impurities or Additives

Chlorinated dibenzo-p-dioxins are formed, by the reaction illustrated below, during the manufacturing processes used to produce polychlorinated phenols.



chlorinated dibenzo-*p*-dioxin

Commercial grade 2,4,6-trichlorophenol has the following composition (Rhone-Poulenc, 1979):

2,4,6-Trichlorophenol	97%
2,4-Dichlorophenol	1.5%
2,3,4,6-Tetrachlorophenol	1.5%

12. Occupational Exposure

The National Occupational Hazard Survey indicates that 112 workers are potentially exposed to 2,4,6-trichlorophenol.

13. Control Technology and Work Practices

Specific factors that may contribute to or prevent employee exposure to 2,4,6-trichlorophenol were not found in the literature searched.

14. Biological Effects

a. Animal Studies

(1) Acute Exposures

The acute toxic effects of 2,4,6-trichlorophenol are summarized in Table 19. Upon administering 2,4,6-trichlorophenol intraperitoneally to male rats, Farquharson and coworkers (1958) observed initial excitation and tremors. When poisoning was sufficiently great, convulsions developed along with loss of righting reflex, coma, dyspnea, and death. Body temperature increased 0.5°C following the administration of lethal intraperitoneal doses (276 mg/kg), and rigor mortis occurred within 5 minutes of death as compared to 50 minutes for control rats.

(2) Subchronic Exposures

The National Cancer Institute (NCI, 1979) has published subchronic toxicity data that are the result of preliminary experiments conducted to determine maximum tolerated doses of 2,4,6-trichlorophenol to be used in a long-term bioassay for possible carcinogenicity. In this range-finding study, groups of 5 male and 5 female F344 (Fischer) rats and B6C3F1 mice were fed

Table 19. Acute Effects of 2,4,6-Trichlorophenol

Route	Species	Dose (mg/kg)	Response	Reference
oral	rats	820	LD50	AAPCO, 1966
i.p.[a]	rats	276	LD50	Farquharson et al., 1958

[a] i.p. = intraperitoneal.

diets ad libitum that contained 10,000 to 46,000 ppm 2,4,6-trichlorophenol for rats and 6800 to 31,500 for mice for a period of 7 weeks, followed by 1 week of additional observation.

Mean body weights of the dosed rats and mice of each sex were found to be lower than those of corresponding controls and were dose related (NCI, 1979). The lowest dose at which histopathologic findings were observed in the rats was 46,000 ppm; at this dose, moderate to marked increase in splenic hematopoiesis was seen in male and female rats, and midzonal vacuolation of hepatocytes was seen in 2 male rats. In male and female mice dosed at 21,500 ppm, all tissues were reported to be essentially normal.

(3) Chronic Exposures

No information was found in the literature searched.

(4) Carcinogenicity

The National Cancer Institute has completed a carcinogenesis bioassay of 2,4,6-trichlorophenol in which groups of 50 male and 50 female F344 rats were administered 5000 or 10,000 ppm of the compound (96-97% pure) in the feed for 106 or 107 weeks (NCI, 1979). Twenty untreated rats of each sex were used as controls. In the male rats, lymphomas or leukemias occurred at incidences that were statistically significant in the low-dose (25/50) and high-dose (29/50) groups compared to controls (4/20) (Table 20). In the female rats, monocytic leukemia did not occur at incidences that were significant. An increased incidence of hyperplasia of the bone marrow and increased leukocytosis and monocytosis of the peripheral blood was found among dosed rats of both sexes.

In the same study, groups of 50 male B6C3F1 mice were administered 5000 and 10,000 mg/kg 2,4,6-trichlorophenol in the diet for 105 weeks; groups of 50 female mice were given 10,000 and 20,000 mg/kg diet for 38 weeks, then 2500 and 5000 mg/kg in the diet for 67 weeks (NCI, 1979). Twenty

Table 20. Effects of Chronic Exposure to 2,4,6-Trichlorophenol in Rats and Mice (NCI, 1979)

Species	Tumor Type	Males			Females		
		Control	Low Dose	High Dose	Control	Low Dose	High Dose
Rats	Number of animals necropsied	20	50	50	20	50	50
	Malignant lymphoma	1(5%)	2(4%)	0(0%)	0(0%)	0(0%)	2(4%)
	Leukemia	3(15%)	23(46%)	29(58%)	3(15%)	11(22%)	11(22%)
	Bone marrow hyperplasia	0(0%)	26(52%)	15(30%)	0(0%)	6(12%)	3(6%)
	Leukocytosis	0(0%)	13(26%)	11(22%)	0(0%)	6(12%)	3(6%)
Mice	Number of animals with tissues examined microscopically	20	49	47	20	50	48
	Hepatocellular adenoma	3(0%)	22(45%)	32(68%)	1(5%)	12(24%)	17(35%)
	Hepatocellular carcinoma	1(5%)	10(20%)	7(15%)	0(0%)	0(0%)	7(14%)
	Hyperplasia	2(10%)	12(24%)	6(13%)	1(5%)	1(2%)	6(13%)

untreated mice of each sex were used as controls. In both male and female mice, hepatocellular carcinomas or adenomas occurred at incidences that were dose related (Table 20); their incidence was statistically higher in the low-dose males (32/49) and high-dose males (39/47) compared to controls (4/20) and in high-dose females (24/48) (low-dose, 12/50; controls, 1/20).

Bionetics Research Laboratories (BRL, 1968) administered commercial grade 2,4,6-trichlorophenol (Omal; Dowicide 25; impurities unspecified) to groups of 18 male and 18 female (C57BL/6 x C3H/Anf)F_1 mice and 18 male and 18 female (C57BL/6 x AKR)F_1 mice according to the following schedule: 100 mg/kg in 0.5% gelatin at 7 days of age by stomach tube and the same amount (not adjusted for increasing body weight) daily up to 4 weeks of age; subsequently, the mice were fed 260 mg/kg in the diet until they reached 78 weeks of age. The dose was the maximum tolerated dose for infant and young mice. At the end of the experiment, 10, 16, 16, and 17 mice were still alive in the four groups, respectively. The total numbers of tumor-bearing animals were 9/18, 7/18, 3/17, and 2/17 in treated males and females of the two strains, compared with 22/79, 8/87, 16/90, and 7/82 in pooled controls. According to IARC (1979b), statistically significant increases ($P < 0.05$) in the incidences of hepatomas (5/36) and reticulum-cell sarcomas (6/36) were observed in the (C57BL/6 x C3H/AnF)F_1 mice when the numbers of tumors in males and females were combined. It was noted, however, that the statistical significance of the results disappears when the incidences in males and females are considered separately or when matched controls are considered (IARC, 1979).

In the same study, groups of 18 (C57BL/6 x C3H/AnF)F_1 mice and 18 (C57BL/6 x AKR)F_1 mice of both sexes were given single subcutaneous injections of the commercial grade 2,4,6-trichlorophenol (464 mg/kg) in corn oil at 28 days of age (BRL, 1968). All animals were observed until approximately 78

weeks of age. At this time, all treated mice were still alive and tumor incidences were not increased.

Boutwell and Bosch (1959) reported that commercial grade 2,4,6-trichlorophenol did not promote tumor development (papillomas or carcinomas) in mice when applied repeatedly to the skin following initiation with dimethylbenzanthracene (DMBA). A single application of 75 µg DMBA (25 µl of a 0.3% solution in benzene) was painted on the backs of 29 Sutter mice; single drops (approximately 25 µl) of 20% chlorophenol solutions (in benzene) were begun 1 week after the application of initiator and were continued twice a week for 14 weeks.

(5) Mutagenicity

2,4,6-Trichlorophenol was found to be non-mutagenic in the Ames test, with and without microsomal activation, using Salmonella typhimurium strains TA98, TA100, TA1535, and TA1537 (Rasanen et al., 1977).

2,4,6-Trichlorophenol increased the mutation rate, but not the rate of intragenic recombination, in Saccharomyces cerevisiae MP-1 (Fahrig et al., 1978).

Fahrig et al. (1978) reported that 2 of 340 offspring from 74 female mice that had been injected intraperitoneally with 50 mg/kg of 2,4,6-trichlorophenol on day 10 of gestation had changes in hair coat color (spots) of genetic significance. At 100 mg/kg, there was 1 spot out of 175 offspring from 42 females.

(6) Teratogenicity

No information was found in the literature searched.

(7) Reproductive Effects

No information was found in the literature searched.

(8) Other Relevant Information

2,4,6-Trichlorophenol interferes with mitochondrial oxidative phosphorylation and inhibits cytochrome P-450-dependent mixed-function oxidases *in vitro* (Mitsuda *et al.*, 1963; Arrhenius *et al.*, 1977).

b. Human Studies

(1) Pharmacokinetics

Roberts *et al.* (1977) used human autopsy skin epidermal membranes in an *in vitro* test system to determine the permeability of the skin to different compounds. 2,4,6-Trichlorophenol permeated the skin membrane, but did not cause damage when tested at aqueous concentrations up to saturation.

(2) Health Effects

No information was found in the literature searched.

(3) Target Organ Toxicity

No information was found in the literature searched.

(4) Epidemiology

No informaion was found in the literature searched.

15. Ongoing Studies

Microbial mutagenesis testing of 2,4,6-trichlorophenol is to be conducted in 1980 by Stanford Research International (NIEHS, 1980). The testing is supported by the National Institute of Environmental Health Sciences under Contract No. NO1-ES-9-0001.

16. Exposure Standards

No recommended or promulgated occupational exposure standards for 2,4,6-trichlorophenol were found.

17. Sources of Additional Relevant Information

No sources of additional relevant information were identified.

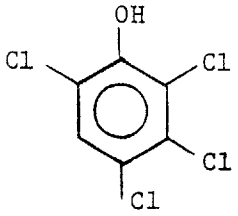
18. Other Pertinent Data

No other information that would aid in the assessment of 2,4,6-trichlorophenol as an occupational hazard was found in the literature searched.

J. 2,3,4,6-TETRACHLOROPHENOL

1. Chemical Name: 2,3,4,6-Tetrachlorophenol

2. Chemical Structure:



3. Synonyms: Phenol, 2,3,4,6-tetrachloro-
2,4,5,6-Tetrachlorophenol
Dowicide 6
TCP

4. Chemical Abstracts Service (CAS) Number: 58-90-2

5. Registry of Toxic Effects of Chemical Substances (RTECS) Number:

SM9275000

6. Chemical and Physical Properties:

Description:	brown flakes to sublimed mass with characteristic odor
Molecular Weight:	231.91
Boiling Point:	164°C (at 23 mm Hg)
Melting Point:	69°C to 70°C
Vapor Pressure:	1 mm Hg (at 100°C)
Solubility:	0.10 g/100 g water (20°C) soluble in alcohol, benzene, chloroform, petroleum ether, ether, sodium hydroxide, acetone, hot acetic acid
Specific Gravity:	1.839^{25}_{4}
Stability:	nonflammable

7. Production

The only production figure available for 2,3,4,6-tetrachlorophenol is 9 million pounds in 1960 (Doedens, 1964). There are no data regarding production volumes or manufacturers available from the U.S. EPA (1980).

8. Uses

Like the trichloro- compounds, tetrachlorophenol is a general disinfectant and fungicide and is used extensively as a preservative for

cellulosic products such as wood, insulation board, and paper. Other uses include latex preservation, insecticides, and leather preservatives (Golumbic, 1953; Doedens, 1964; Freiter, 1978).

9. Manufacturers and Distributors

2,3,4,6-Tetrachlorophenol is made by Dow Chemical in Midland, MI (SRI International, 1980). Dow sales personnel have indicated, however, that Dow has not produced 2,3,4,6-tetrachlorophenol (Dowicide 6) as a final product since 1974.

Distributors include (Chemical Week: 1981 Buyers' Guide Issue, 1980; Chem Sources--USA, 1980):

Aldrich Chem.	McKesson Chem.
Chem. Procurement Lab.	Pfaltz and Bauer
Dynamit Nobel Akt.	Robeco Chem.
ICN/K and K	Tridom Chem.
Lachat Chem.	

10. Manufacturing Processes

In industry, the starting material for the production 2,3,4,6-tetrachlorophenol can be a mixture containing 2-chlorophenol, 2,6-dichlorophenol, and 2,4,6-trichlorophenol (Doedens, 1964). The mixture can be charged into a chlorinator and chlorinated with gaseous chlorine. The reaction products can be separated via distillation with reuseables recycled to the chlorinator. Tetrachlorophenol can also be separated as a co-product in the production of pentachlorophenol.

Commercial 2,3,4,6-tetrachlorophenol (Dowicide 6) contains roughly 70% tetrachlorophenol and 20% other cholorophenols.

11. Impurities or Additives

The analytical descriptions of commercial grade and purified samples of 2,3,4,6-tetrachlorophenol are given in Table 21 (Schwetz et al., 1974). As

Table 21. Analytical Descriptions of 2,3,4,6-Tetrachlorophenol Samples (Schwetz et al., 1974)[a]

	Commercial Grade 2,3,4,6-Tetrachlorophenol	Purified 2,3,4,6-Tetrachlorophenol
Identification	MM-05040-1481-G	Ref. No. 27-87-3
Phenolics(%)[b]		
Pentachlorophenol	27	0.1
Tetrachlorophenol	73	99.6
Trichlorophenol	--	<0.05
Nonphenolics (ppm)[c]		
Dibenzo-p-dioxins		
2,3,7,8-Tetrachlorodibenzo-p-dioxin	<0.05	<0.05
Hexachlorodibenzo-p-dioxin	28	<0.5
Heptachlorodibenzo-p-dioxin	80	<0.5
Octachlorodibenzo-p-dioxin	30	<0.5
Dibenzofurans		
Hexachlorodibenzofuran	55	<0.5
Heptachlorodibenzofuran	100	<0.5
Octachlorodibenzofuran	25	<0.5

[a]The test samples were supplied by the Dow Chemical Co., Midland, Michigan 48640.

[b]Determined by gas-liquid chromatography.

[c]Determined by use of an LKB 9000 gas chromatograph-mass spectrometer.

noted, hexa-, hepta-, and octachlorodibenzo-p-dioxins and dibenzofurans have been identified in commercial preparations.

12. Occupational Exposure

The National Occupational Hazard Survey does not provide an estimate of the number of workers who are potentially exposed to 2,3,4,6-tetrachlorophenol.

13. Control Technology and Work Practices

Specific factors that may contribute to or prevent employee exposure to 2,3,4,6-tetrachlorophenol were not found in the literature searched.

14. Biological Effects

a. Animal Studies

(1) Acute Exposures

The acute toxic effects of 2,3,4,6-tetrachlorophenol are summarized in Table 22. Deichmann (1943) reported that lethal oral and subcutaneous doses resulted in restlessness and increased rate of respiration and, subsequently, motor weakness, dyspnea, coma, and death. Tremors and convulsions were absent until the terminal stage of poisoning. When 2,3,4,6-tetrachlorophenol was injected intraperitoneally into rats at lethal doses, hypotonia was observed in the hindlimbs within 2 to 3 minutes (Farquharson et al., 1958). This gradually progressed to involve the forelimbs and neck so that the rats were completely prostrate. Respiration was at first accelerated, but became slower and dyspneic as coma developed. The intraperitoneal injection of the 2,3,4,6-tetrachlorophenol also elevated body temperature 4.0°C, and onset of rigor mortis occurred within 5 minutes of death as compared to 50 minutes for control rats.

(2) Subchronic Exposures

In a preliminary tolerance study to a teratogenicity evaluation using nonpregnant rats, groups of 5 rats each were administered 3, 10, 30,

Table 22. Acute Effects of 2,3,4,6-Tetrachlorophenol

Route[a]	Species	Dose (mg/kg)	Response	Reference
oral[b]	rats	140	LD50	Deichmann, 1943
oral (in 40% ethanol)	mice (female)	131	LD50	Ahlborg and Larsson, 1978
oral (in 40% ethanol)	mice (male)	163	LD50	Ahlborg and Larsson, 1978
oral (in propylene glycol)	mice (female)	735	LD50	Ahlborg and Larsson, 1978
oral (in propylene glycol)	gerbils (female)	698	LD50	Ahlborg and Larsson, 1978
oral	guinea pigs	250	LD50	Meister, 1972
i.p.	rats	130	LD50	Farquharson et al., 1958
i.p. (in 40% ethanol)	mice (female)	82	LD50	Ahlborg and Larsson, 1978
i.p. (in propylene glycol)	mice (female)	121	LD50	Ahlborg and Larsson, 1978
s.c.[b]	rats	210	LD50	Deichmann, 1943
s.c.	mice	100	TDLo	BRL, 1968
dermal	rabbits	250	LD50	Dittmer, 1959

[a] i.p. = intraperitoneal; s.c. = subcutaneous.

[b] Tetrachlorophenol, isomer not specified.

100, or 300 mg/kg/day of commercial grade tetrachlorophenol for 10 consecutive days by gavage (Schwetz et al., 1974). The maximum tolerated dose was found to be 30 mg/kg/day; signs of toxicity and death were observed at 100 and 300 mg/kg/day.

(3) Chronic Exposures

No information was found in the literature searched.

(4) Carcinogenicity

Bionetics Research Laboratories (BRL, 1968) subcutaneously injected 100 mg/kg of commercial grade 2,3,4,6-tetrachlorophenol in dimethylsulfoxide (DMSO) into groups of 18 male and 18 female (C57BL/6 x C3H/Anf)F_1 mice and 18 male and 18 female (C57BL/6 x AKR)F_1 mice on the 28th day of age. All animals were observed until 78 weeks of age, at which time 14, 18, 18, and 17 mice were alive from the four groups, respectively. Results showed that the total incidence of tumors in mice was 5/17, 1/18, 2/18, and 3/18 among the groups; these incidences were not increased relative to negative control groups which consisted of mice that were either untreated or received gelatin, corn oil, or DMSO.

(5) Mutagenicity

2,3,4,6-Tetrachlorophenol showed no mutagenic activity in the Ames assay using Salmonella typhimurium tester strains TA98, TA100, TA1535, and TA1537, both in the presence and absence of rat liver homogenate fraction (Rasanen et al., 1977).

(6) Teratogenicity

Schwetz et al. (1974) conducted a study in which commercial and technical grades of 2,3,4,6-tetrachlorophenol were administered by gavage to pregnant rats. Groups of 20-40 rats received 10 or 30 mg/kg/day of the compound by gavage on days 615 (inclusive) of gestation. Maternal weight gain during

gestation was not affected by the administration of the compound, and no signs of maternal toxicity were observed among the dams either during gestation or at the time of cesarean section and autopsy on day 21 of gestation. Results showed that neither grade of tetrachlorophenol was teratogenic or embryolethal. Both forms were, however, fetotoxic; subcutaneous edema was observed among fetuses at the 10 mg/kg dose level (but not at 30 mg/kg), and delayed ossification of fetal skull bones was seen at 30 mg/kg.

(7) Reproductive Effects

No information was found in the literature searched.

(8) Other Relevant Information

2,3,4,6-Tetrachlorophenol has been reported to inhibit oxidative phosphorylation in isolated rat liver mitochondria (Mitsuda et al., 1963; Weinbach and Garbus, 1965).

Ninety-four percent of an intraperitoneally administered dose of 2,3,4,6-tetrachlorophenol was excreted unchanged in 24 hours in the urine by rats (Ahlborg and Larsson, 1978). After 48 hours, no measurable concentrations of the parent compound could be detected. Trichloro-p-hydroquinone was identified as a minor metabolite of 2,3,4,6-tetrachlorophenol.

b. Human Studies

(1) Pharmacokinetics

No information was found in the literature searched.

(2) Health Effects

No information was found in the literature searched.

(3) Target Organ Toxicity

No information was found in the literature searched.

(4) Epidemiology

No information was found in the literature searched.

15. Ongoing Studies

No current toxicological or environmental studies of 2,3,4,6-tetrachlorophenol were found.

16. Exposure Standards

No recommended or promulgated occupational exposure standards for 2,3,4,6-tetrachlorophenol were found.

17. Sources of Additional Relevant Information

No sources of additional relevant information were identified.

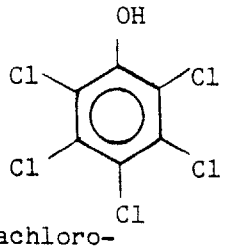
18. Other Pertinent Data

No other information that would aid in the assessment of 2,3,4,6-tetrachlorophenol as an occupational hazard was found in the literature searched.

K. PENTACHLOROPHENOL

1. Chemical Name: Pentachlorophenol

2. Chemical Structure:



3. Synonyms:

Phenol, pentachloro-	NCI-C54933
Penta	Durotox
Santophen 20	Thompson's Wood Fix
PCP	Term-1-Trol
Dowicide 7	Permite
Chlorophen	Penta-Kil
Penchloro	Pentanol
Sinituho	Pentasol
Weedone	Penwar
Santobrite	Perotox
EP30	Permacide
Liroprem	Permagard
Lauxtol	Permatox
Fungifen	Chem-tol

4. Chemical Abstracts Service (CAS) Number: 87-86-5

5. Registry of Toxic Effects of Chemical Substances (RTECS) Number:

SM6300000

6. Chemical and Physical Properties:

Description:	white to light-yellow beads, powder, or crystals with a strong odor when hot
Molecular Weight:	266.35
Boiling Point:	309-310°C
Melting Point:	190°C
Vapor Pressure:	0.00011 mm Hg (20°C); 0.12 mm Hg (100°C)
Solubility:	0.008 g/100 g water (20°C) very soluble in ethanol and ether soluble in hot benzene limited solubility in carbon tetrachlordie slightly soluble in petroleum ether
Specific Gravity:	1.978^{22}_{4}
Stability:	nonflammable

7. Production

Recent production quantities of pentachlorophenol are as follows (USITC, 1980b; 1979b; 1978b; 1977b).

Year	Production in Millions of Pounds
1979	51.41
1978	39.99
1977	44.86
1976	43.87

Data available from the U.S. EPA (1980) regarding producers of pentachlorophenol and production volumes are presented in Table 23. Note that this U.S. EPA listing is incomplete as compared to the CMR (1980) list of manufacturers appearing below. The U.S. EPA (1980) listing includes only non-confidential data as claimed by the producers; if a manufacturer does not wish to be identified, they are not identified in this source.

CMR (1980) estimates that the demand for pentachlorophenol will increase at a rate of 0.7% per year through 1984.

8. Use

The following tabulation presents the percentage of the total amount of pentachlorophenol produced that is used in each of the applications listed (CMR, 1980):

	Percentage of Total
Wood preservative for utility poles, crossarms, and fenceposts, etc.	80
Sodium pentachlorophenate	10
Miscellaneous including mill uses, consumer wood preservation formulations, and herbicide intermediate	10

The sodium salt (sodium pentachlorophenate) is also used as a general antifungal and antibacterial agent (Freiter, 1978).

9. Manufacturers and Distributors

Manufacturers, and their respective plant capacities, are as follows (CMR, 1980):

Table 23. Producers of Pentachlorophenol and Production Ranges (U.S. EPA, 1980)

Producer	Type of Production	1977 Production Range
Carroll Products Wood River Junction, RI	Not distributed	none
Plant Site Not on File	---	10 to 100 thousand lb

Producer	Location	Annual Capacity in Millions of Pounds
Dow Chemical	Midland, MI	30
Reichhold Chemical	Tacoma, WA	18
Vulcan Chemical	Wichita, KS	20

Distributors of pentachlorophenol include (1980-81 OPD Chemical Buyers Directory, 1980; Chemical Week: 1981 Buyers' Guide Issue, 1980; Chem Sources—USA, 1980):

Advent Chem.
Aldrich Chem.
Atomergic Chemetals
Bio-Clinical Lab.
Chapman Chemical
Chemical Dynamics
Chemical Specialties
Chem. Procurement Lab.
Chem Services
Continental Trading Co.
Cromptom and Knowles
Dynamit Nobel Akt.
Eastern Chem.
EM Lab.
George Uhe and Co.
ICN/K and K
ICN Nutritional
J.T. Baker Chem.
Koppers Co.
Lachat Chem.
LaPine Sci.
MCB Reagents
McKesson Chem.
Michlin Chem.
Orlex Chem.
Pfaltz and Bauer
Pierce Chem.
Research Organics
Sigma Chem.
Sonford International
Stewart Sanitary Supply
TransWorld Chem.
Tridom Chem.
U.S. Biochemical
USS Chemicals
Vega Biochemicals

10. Manufacturing Processes

Pentachlorophenol is made by the direct chlorination of phenol. The chemical reaction is the following:

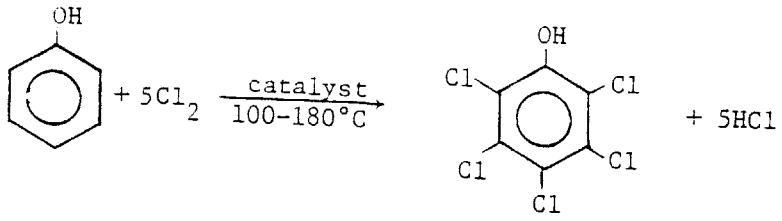


Figure 7 outlines a general manufacturing scheme.

The following passage from the Kirk-Othmer Encyclopedia of Chemical Technology (Freiter, 1978) describes the manufacturing process:

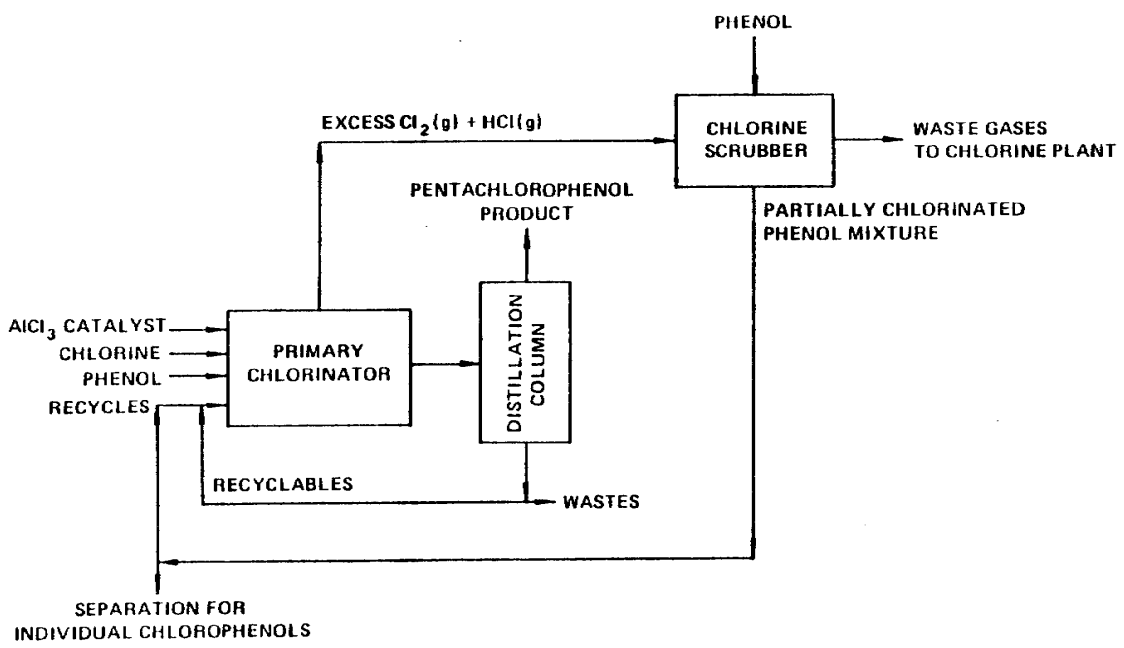


Figure 7. Manufacture of Pentachlorophenol
(Adapted from Freiter, 1978)

The chlorination is done neat with a starting temperature between 65-130°C (preferably 105°C). After three to four atoms of chlorine have been substituted onto phenol, the temperature of the reaction mixture is increased to maintain a temperature approximately 10°C over the melting point of the chlorinated mixture. The reaction is complete in 5-15 h. Catalyst concentration is critical and is about 0.0075 mol/mol of phenol. The HCl and chlorine gases from the primary reactor are treated further with phenol to form pure HCl gas and a mixture of chlorinated phenols. The HCl gas can be oxidized back to chlorine gas and recycled. The partially chlorinated phenols can be separated or recycled to the primary reactor. Crude pentachlorophenol has been purified by distillation under reduced pressure in the presence of 0.05 to 2 wt % amine or alkanolamine (Freiter, 1978).

The composition of commercial pentachlorophenol has been reported as follows (Johnson et al., 1973; Schwetz et al., 1974, 1978; Goldstein et al., 1977):

	Content Percent
Pentachlorophenol	85 to 90
Tetrachlorophenol	3 to 8
Trichlolophenol	<0.1
Higher chlorophenols	2 to 6
Caustic insolubles	1

Commercial pentachlorophenol also typically contains two classes of non-phenolic components: polychlorinated dibenzo-p-dioxins and polychlorinated dibenzofurans. The following tabulation presents the concentrations in which those impurities are typically present:

	Concentration in ppm
Dibenzo-p-dioxins	
2,3,7,8-Tetrachloro	<0.05
Tetrachloro-	<0.1
Pentachloro-	<0.1
Hexachloro-	1-27
Heptachloro-	6.5-520
Octachloro-	15-2500
Dibenzofurans	
Tetrachloro-	≤4
Pentachloro-	40
Hexachloro-	3.4-90
Heptachloro-	1.8-400
Octachloro-	<1-260

Hexachlorobenzene has also been found at levels of 400 ppm in commercial pentachlorophenol (Schwetz et al., 1978).

11. Impurities or Additives

As detailed in the previous section (Manufacturing Processes), commercial pentachlorophenol typically contains non-phenolic components that fall into two classes of chemicals: polychlorinated dibenzo-p-dioxins and polychlorinated dibenzofurans.

12. Occupational Exposure

The National Occupational Hazard Survey indicates that 177,934 workers are potentially exposed to pentachlorophenol.

13. Control Technology and Work Practices

Specific factors that may contribute to or prevent employee exposure to pentachlorophenol were not found in the literature searched.

14. Biological Effects

a. Animal Studies

(1) Acute Exposures

The acute toxic effects of pentachlorophenol and sodium pentachlorophenate are summarized in Table 24. The reactions observed in laboratory animals following intraperitoneal, percutaneous, or oral administration appear to be similar (McGavack et al., 1941; Deichmann et al., 1942; Farquharson et al., 1958). There is always a rise in body temperature and an initial acceleration in respiration, which becomes slower and dyspneic as coma develops. Dying animals have shown cardiac and muscular collapse and terminal asphyxial convulsive movements. Increased blood pressure, hyperglycemia and glycosuria, hyperperistalsis, and decreased urinary output have also been noted. Following death, the onset of rigor mortis is immediate and pronounced.

Table 24. Acute Toxicity of Pentachlorophenol and Sodium Pentachlorophenate

Compound	Route[a]	Species	Dose (mg/kg)	Response	Reference
Pentachlorophenol	oral	rats	27-78	LD50	Deichmann et al., 1942
	oral	rats	30	LD50	Deichmann, 1943
	oral	rats (male)	205	LD50	Dow Chemical Co., 1969a
	oral	rats (female)	135	LD50	Dow Chemical Co., 1969a
	oral	rats	50-140	LD50	Meister, 1972
	oral	mice	74	LD50	Ahlborg and Larsson, 1978
	oral	hamsters	168	LD50	Cabral et al., 1979
	oral	rabbits	70	LDLo	Deichmann et al., 1942
	i.p.	rats	56	LD50	Farquharson et al., 1958
	i.p.	rabbits	135	LDLo	Dittmer, 1959
	s.c.	rats	100	LD50	Deichmann, 1943
	s.c.	mice	46	TDLo	BRL, 1968a
	s.c.	rabbits	70	LDLo	Deichmann et al., 1942
	s.c.	dogs	135	LDLo	Dittmer, 1959
	dermal	rats	105	LD50	Noakes and Sanderson, 1969
	dermal	rabbits	40	LDLo	Deichmann et al., 1942

Table 24. Acute Toxicity of Pentachlorophenol and Sodium Pentachlorophenate (Cont'd)

Compound	Route[a]	Species	Dose (mg/kg)	Response	Reference
Sodium Pentachlorophenate	oral	rats	210.6	LD50	Deichmann et al., 1942
	oral	rats	210	LD50	Dow Chemical Co., 1969b
	oral	rabbits	275	LD50	Dow Chemical Company, 1969b
	oral	rabbits	250-300	LDLo	Deichmann et al., 1942
	oral	rabbits	550	LDLo	McGavack et al., 1941
	oral	guinea pigs	80-160	LD50	Dow Chemical Co., 1969b
	i.p.	rats	30	LD50	Hoben et al., 1976
	i.p.	rabbits	135	LDLo	McGavack et al., 1941
	s.c.	rats	80	LD50	Deichmann et al., 1942
	s.c.	mice	56	LDLo	Dittmer, 1959
	s.c.	rabbits	100	LDLo	Deichmann et al., 1942
	s.c.	rabbits	275	LDLo	McGavack et al., 1941
	s.c.	dogs	135	LDLo	Dittmer, 1959

Table 24. Acute Toxicity of Pentachlorophenol and Sodium Pentachlorophenate (Cont'd)

Compound	Route[a]	Species	Dose (mg/kg)	Response	Reference
Sodium Pentachlorophenate	i.v.	rabbits	22	LDLo	Deichmann et al., 1942
	inhalation	rats	11.7	LD50	Hoben et al., 1976
	dermal	rabbits	250	LDLo	Deichmann et al., 1942
	dermal	rabbits	100-300 (20% solution)	LD50	Dow Chemical Co., 1969b
	dermal	rabbits	512	LDLO	McGavack et al., 1941
	dermal	guinea pigs	266	LDLo	Dittmer, 1959

[a] i.p. = intraperitoneal; s.c. = subcutaneous; i.v. = intravenous.

[b] h = hour.

Autopsies revealed extensive vascular damage and heart failure in rats, rabbits, guinea pigs, and dogs following oral administration of pentachlorophenol (Deichmann et al., 1942). In rabbits acutely intoxicated with sodium pentachlorophenate, the brains and spinal cords showed a slight capillary congestion and some degenerative changes in the motor neurons (McGavack et al., 1941).

When applied to the skin of rabbits in relatively low concentrations, both pentachlorophenol and sodium pentachlorophenate cause pronounced edema and inflammation and subsequent wrinkling, cracking, desquammation, and loss of hair (McGavack et al., 1941; Deichmann, et al., 1942). Single dermal applications of 10% sodium pentachlorophenate solution (60-600 mg/kg) to the skin of rabbits invariably produced microscopic changes that included irregular thickening (hyperkeratinization and hypertrophy of the hair follicles), thinning and disappearance of the upper skin layers, and widespread foci of atrophy and necrosis. The subcutaneous layer became either thin and flattened or thick and edematous and gradually underwent fibrillar thickening with hyaline degeneration.

(2) Subchronic Exposures

Deichmann et al. (1942) fed pentachlorophenol to 2 groups of 10 rats each; 1 group ingested approximately 5 mg of the compound in 8.5 g of food per day for 26 weeks, and the other consumed daily about 3.9 mg of pentachlorophenol in 13 g of food for 28 weeks. The administration of the compound at these levels reportedly caused no gross tissue damage and only insignificant (unspecified) histological abnormalities. Diminished weight gain was attributed to an inadequate consumption of food, presumably due to an unpleasant taste imparted to the diet by the compound. Dow Chemical Co. (1969a) reported that mild liver and kidney damage (unspecified) was noted in rats that had received a

solution containing 100 mg/kg of sodium pentachlorophenate by intubation for 20 days (Dow Chemical Co., 1969a).

When 23 rabbits were given 90 oral doses (on successive days except Sundays) of the sodium pentachlorophenate in a 0.1% solution (each dose equivalent to 3 mg pentachlorophenol/kg), no signs of acute poisoning were observed (Deichmann et al., 1942). Sodium pentachlorophenate was also reported to produce no adverse effects in rabbits when fed as a 5% solution (100 mg/kg/day) for 20 days (Dow Chemical Co., 1969a). When 4 cats were administered dietary pentachlorophenol or its sodium salt in doses equivalent to 1.25 and 2.5 mg/kg for 10 weeks, some loss of appetite and loss of weight was observed, but none of the cats displayed signs of pentachlorophenol poisoning (Deichmann et al., 1942).

McGavack et al. (1941) subcutaneously administered sodium pentachlorophenate daily to 3 groups of 6 rabbits each at 1/20, 1/10, and 1/4 the minimum lethal dose (13.7, 27.5, and 70.0 mg/kg, respectively). The dosing was continued until death (27.5 mg/kg, 15 days; 70.0 mg/kg, 8 days) except in the group receiving 13.7 mg/kg; the rabbits in this group were sacrificed at the end of 60 days. The compound was also administered intraperitoneally in daily doses of 15 mg/kg; this concentration proved fatal in each of 3 rabbits after an average of 11 days' administration. The systemic reactions to the subchronic sodium pentachlorophenate exposures were reportedly similar to those seen in acute intoxications; listlessness, frequent defecation, increasing activity to inactivity, and slight motor weakness were invariably encountered for some time prior to death. Death always occurred in convulsive seizures, but the convulsions were not as vigorous as in acutely poisoned rabbits. When blood analyses were performed on the rabbits, secondary anemia, leucopenia with relative

lymphocytosis, polycythemia, and increased blood sugar levels were variously observed.

Post-mortem findings included heart dilation, hemorrhages and congestion in the lungs and kidneys, hypertrophy of the pulmonary artery, cloudy swelling of the liver, and degenerative changes in the kidney tubules (McGavack et al., 1941). In the brain and spinal cord, capillary congestion, slight chromatolysis of nerve cells, diffuse focal areas of perivascular lymphocytic and mononuclear infiltration, and circumscribed subpial collections of small, round cells were commonly present.

When 40 mg/kg of a 1% solution of sodium pentachlorophenate was applied daily (except Sundays) for 100 consecutive days to the skin of 6 rabbits, mild irritation but no wrinkling, cracking, or loss of hair was observed (Deichmann et al., 1942). In other studies, rabbits exposed to shorter dermal applications of 1% pentachlorophenol in mineral oil (21 successive daily treatments of 40 mg/kg) and 2% aqueous sodium pentachlorophenate (32 successive daily treatments to 63 mg/kg) showed no illness, weight loss, or injury to the skin.

A complicating factor in the study of pentachlorophenol toxicity is that chlorinated dibenzo-p-dioxin and chlorinated dibenzofuran contaminants may be the actual causes of toxic effects. Several subchronic studies have been done comparing the effects of pure and technical grade pentachlorophenol in rats (Table 25); results show that technical grade pentachlorophenol has produced hematological changes, increased liver and kidney weights, and hepatic alterations that cannot be attributed to pentachlorophenol itself. Goldstein et al. (1977) concluded that a number of the liver changes observed are consistent with the effects of biologically-active chlorinated dibenzo-p-dioxins and dibenzofurans.

Table 25. Subchronic Effects of Technical and Pure Pentachlorophenol in Rats

Pentachlorophenol	Impurities	Dose[a]	Effects	Reference
Technical grade	1980 ppm octachlorodibenzo-p-dioxin 19 ppm hexachlorodibenzo-p-dioxin	3, 10, and 30 mg/kg/d in the feed for 90 d	Elevated serum alkaline phosphatase. Decreased serum albumin, hemoglobin, and packed cell volume. Increased liver and kidney weights, with minimal focal hepatocellular degeneration and necrosis.	Johnson et al., 1973
Pure grade	No detectable chlorinated dioxins	3, 10, 30 mg/kg/d x 90 d	Increased liver and kidney weights, but no gross or microscopic tissue changes.	Johnson et al., 1973
Improved technical	30 ppm octachlorodibenzo-p-dioxin 1.0 ppm hexachlorodibenzo-p-dioxin	3, 10, 30 mg/kg/d x 90 d	Results similar to those obtained with pure pentachlorophenol.	Johnson et al., 1973
Technical Grade	1380 ppm octachlorodibenzo-p-dioxin 520 ppm heptachlorodibenzo-p-dioxin 8 ppm hexachlorodibenzo-p-dioxin 260 ppm octachlorodibenzofuran 400 ppm heptachlorodibenzofuran 90 ppm hexachlorordibenzofuran 40 ppm pentachlorodibenzofuran 4 ppm tetrachlorodibenzofuran	20, 100, and 500 ppm in the diet x 8 mo	Hepatic porphyria and increased hepatic aryl hydrocarbon hydroxylase and glucuronyl transferase activities, liver weight, cytochrome P-450, and microsomal heme. Decreased body weight at 500 ppm.	Goldstein et al., 1977
Pure grade	< 0.1 ppm of all the above contaminants	20, 100, and 500 ppm in the diet x 8 mo	No significant effect on the above parameters except glucuronyl transferase, which was increased at 500 ppm. Decreased body weight gain at 500 ppm which was comparable to that observed for the technical grade pentachlorophenol.	Goldstein et al., 1977

[a] d = day; mo = month.

Knudsen et al. (1974) fed technical grade pentachlorophenol (containing 200 ppm octachlorodibenzo-p-dioxin and 82 ppm pre-octachlorodibenzo-p-dioxin) to rats at dietary levels of 0, 25, 50, and 200 ppm for 12 weeks. Male and female rats fed 25 ppm did not show any toxicologic effects. In female rats, weight gain was decreased in the groups fed 25 ppm and 200 ppm. Liver weight in the female rats in the 50 and 200 ppm groups increased and was accompanied by increased liver aniline hydoxylase activity at 200 ppm in both sexes. Levels of 50 ppm and 200 ppm resulted in decreased hemoglobin and hematocrit values in male but not female rats.

(3) Chronic Exposures

Rats fed 5 mg pentachlorophenol/day for 6 months failed to grow, and others given 3.9 mg/day for 28 weeks had retarded growth (Deichmann et al., 1942).

Schwetz et al. (1978) fed groups of 27 Sprague-Dawley rats of each sex 0, 1, 3, 10, or 30 mg low non-phenolic content pentachlorophenol/kg body weight/day for 22-24 months. Autopsy disclosed dark and discolored livers and kidneys among female rats receiving 10 or 30 mg/kg/day of pentachlorophenol. Microscopic examination of the organs revealed an unknown brown granular pigment within the renal tubular epithelial cells and the hepatocytes and reticuloendothelial cells surrounding the central veins of the liver.

By the end of the study, the serum glutamic pyruvic transaminase (SGPT) activity had increased significantly among both sexes of rats maintained at the high dose level. In addition, the mean body weight of females fed 30 mg/kg pentachlorophenol (378 g) was significantly less than that of female control rats (428 g). Experimental and control animals were also compared for the following features: brain, heart, liver, kidney, and testes weights; blood parameters including hemoglobin levels, packed cell volume, total

erythrocyte counts, and total and differential leukocyte counts; and demeanor, food consumption, and survival. No differences were seen between the two groups.

Deichmann and coworkers (1942) applied doses of 10-50 mg/kg pentachlorophenol as a 4% solution in fuel oil to the dorsal skin of rabbits once or twice a week for 6-61 weeks. The compound was not washed off and the local effects produced were the same as those induced by a single large dose: irritation of the skin and local damage (edema followed by wrinkling, cracking, and loss of hair), followed by recovery. Elevations (2-3°F) in rectal temperatures were observed 8 hours after treatment, but no changes in body weight or in hematological parameters were observed. It should be noted, however, that only a limited number (1-4) of rabbits were tested in this experiment at various dose levels, and although no specific signs of poisoning were reported, 8 of 20 rabbits died during the study. Among the surviving rabbits, unspecified gross and histopathological tissue changes were directly related to the size of the dose and length of treatment.

(4) Carcinogenicity

BRL (1968a) administered commercial grade pentachlorophenol (Dowicide-7; impurities not specified) to groups of 18 male and and 18 female (C57BL/6 x C3H/Anf)F_1 mice and 18 male and 18 female (C57BL/6 x AKR)F_1 mice. From the age of 7 days to 28 days, 46.4 mg pentachlorophenol/kg/day in 0.5% gelatin was administered by stomach tube, and from age 4 weeks until the termination of the experiment at age 78 weeks, 130 ppm pentachlorophenol was fed to the mice in their diet. Sixteen, 18, 17, and 16 mice survived from the four groups, respectively. The incidence of tumors was 3/18, 4/18, 3/17, and 2/18 among the groups, but these values did not differ significantly from those of 79-90 necropsied mice of each sex and strain which either had been untreated or had received only gelatin.

In the same study, four other identical groups of mice were given single subcutaneous injections of 46.4 mg/kg of the commercial grade pentachlorophenol in corn oil at 28 days of age (BRL, 1968a). They were observed until 78 weeks of age, at which time 14, 18, 18, and 16 mice were alive from the four respective groups. The 613 control animals and received either no treatment or an injection of gelatin, corn oil, or dimethylsulfoxide (DMSO). Results showed that male mice of the first strain had an increased number of hepatomas (4/17) relative to those in controls (9/141); IARC (1979a) noted that this incidence was statistically significant ($P < 0.05$).

Schwetz et al. (1978) investigated the possible carcinogenic effects of chronic administration of pentachlorophenol low in non-phenolic impurities to male and female Sprague-Dawley rats. Groups of 27 rats of each sex were fed 0, 1, 3, 10, or 30 mg pentachlorophenol/kg/day for 22-24 months. Although these dose levels were sufficiently high to cause signs of mild toxicity, histopathologic examination gave no indication of carcinogenicity; the total and individual tumor incidences by sites, the times of appearance of tumors, and the average numbers of tumors per animal (predominantly benign neoplasms) were not significantly different from those observed in control rats.

Boutwell and Bosch (1959) reported that commercial grade pentachlorophenol (producers and impurities not specified) did not promote tumor development (papillomas or carcinomas) in Sutter mice when applied repeatedly to the skin following initiation with dimethylbenzanthracene (DMBA). A single application of 75 µg DMBA (25 µl of a 0.3% solution in benzene) was painted on the backs of 35 2- to 3-month old mice; single drops (approximately 25 µg) of 20% pentachlorophenol solutions (in benzene) were begun once a week after the application of initiator and were continued twice a week for 14 weeks.

(5) Mutagenicity

Pentachlorophenol was negative in the Ames assay with 8 nspecified Salmonella typhimurium tester strains (Anderson et al., 1972) and or Salmonella typhimurium strains TA98, TA100, TA1535, TA1537, and TA1538 Simmon et al., 1977) in both metabolically-activated and non-activated systems. odium pentachlorophenate was non-mutagenic for Salmonella typhimurium LT-2 in a on-activated Ames system (Lemma and Ames, 1975).

Pentachlorophenol was also reported to be ineffective in nducing foward mutations in Escherichia coli, back mutations in Sarratia arcescens, recessive lethal mutations in Drosophila melanogaster, or chromosome berrations in human lymphocytes in vitro (Fahrig, 1974). Vogel and Chandler 1974) found that pentachlorophenol failed to induce sex-linked recessive ethals in meiotic and postmeiotic stages of male germ cells in Drosophila.

In lymphocyte cultures of 6 workers exposed to pentachloro- henol at a factory, the incidence of chromosome aberrations (breaks and gaps) as not significantly different from that in 4 "control" workers (Wyllie et al., 975).

It has been found that pentachlorophenol was effective in nducing mitotic gene conversion in Saccharomyces cerevisiae (Fahrig, 1974; ahrig et al., 1978), and that it displayed weak activity in the host-mediated ssay in mice using Salmonella typhimurium G46 and Sarratia marcescens Hy a 21 Fahrig, 1974). Buselmaier et al. (1973) reported, however, that entachlorophenol was not mutagenic in the mouse host-mediated assay with the ame indicator microorganisms. Pentachlorophenol was weakly positive in the ec-assay with Bacillus subtilus (Shirasu, 1976).

When Fahrig et al. (1978) injected female mice with intra- eritoneal doses of either 50 or 100 mg/kg of recrystallized pentachlorophenol

on the 10th day of gestation, 4 out of 473 offspring were reported to have changes in hair coat color (spots) of genetic significance.

Amer and Ali (1968, 1969) reported some effects of pentachlorophenol on mitosis and meiosis in flower buds and root cells of vetch (Vicia faba). When flower buds were treated directly with or sprayed with saturated aqueous pentachlorophenol, meiotic alteration included chromosome stickiness, lagging chromosomes, and anaphase bridges. When root cells were exposed to 43.5-174 mg/l of pentachlorophenol, a decrease in mitotic index was observed; induced mitotic anomalies included disturbed meta-telophase and ana-telophase, lagging chromosomes, anaphase bridging, fragmentation, and cytomyxis.

(6) Teratogenicity

Larsen and coworkers (1975) administered single oral doses of 60 mg/kg pure pentachlorophenol to groups of 6 Charles River CD strain rats on days 8, 9, 10, 11, 12, or 13 of gestation; fetuses were examined for malformation on day 20. A significant ($P < 0.05$) reduction in fetal weight gain was noted among rats dosed on day 9 or 10 of gestation (the average reduction in weight was about 20 and 13%, respectively), but no effects were seen with administration on day 11, 12, or 13. Four abnormalities were found among a total of 97 fetuses; 1 of 46 fetuses from day-8 exposure was a dwarf, and among 51 fetuses from day-9 exposure, 3 had different abnormalities consisting of exencephaly, macrophthalmia, and taillessness. The authors concluded that the number of fetal malformations was minimal and could have been due to maternal toxic effects. The incidence of resorptions in the treated animals was not significantly greater than that in controls.

Hinkle (1973) gave daily oral doses of 1.25 to 20.0 mg/kg of pentachlorophenol (purity not specified) to pregnant Golden Syrian Hamsters from

days 5-10 of gestation. Fetal deaths and/or resorptions were observed in 3 of 6 test groups (groups sizes not reported).

Schwetz et al. (1974) conducted a similar study in which rats were given 550 mg/kg of commercial or technical grade pentachlorophenol orally on a daily basis during days 6-15 of gestation. No effect on the incidence of fetal resorption was noted with doses of 5.8 mg/kg commercial pentachlorophenol or 15 mg/kg of the purified compound. Significant increases in the incidence of fetal resorptions occurred with administrtion of 15, 34.7, or 50 mg/kg of commercial grade pentachlorophenol and with 30 and 50 mg/kg of purified pentachlorophenol. Resorption was 100% at the 50 mg/kg dose level of the purified substance. It was also noted that the sex ratio of surviving offspring was significantly altered among dams that received 50 mg/kg commercial grade or 30 mg/kg purified pentachlorophenol, with the majority of survivors being males.

A number of fetal effects including reductions in body weight, subcutaneous edema, dilated ureters, and skeletal anomalies were seen in offspring of dams given 15 mg/kg/day or more of either compound. Skeletal abnormalities included lumbar spurs, supernumerary or fused ribs, and supernumerary, mis-shapen, missing, or unfused centers of ossification of the vertebrae or sternebrae. Ossification of the skull was delayed in offspring of the 5 mg/kg purified pentachlorophenol group.

In another reproductive study (Schwetz et al., 1978), groups of 10 male and 20 female rats were fed 3 or 30 mg/kg of a pentachlorophenol low in non-phenol impurities each day for 62 days prior to mating, during 15 days of mating, and afterward throughout gestation and lactation. No adverse effects were seen with administration of 3 mg/kg of the compound. At the 30 mg/kg levels, however, the mean neonatal body weight was reduced, and there were

significant decreases in the percentage of live births and in the survival of pups to days 7, 14, and 21 of lactation. An increase in the number of lumbar spurs and vertebrae with unfused centra was thought by the authors to reflect perinatal toxicity rather than an effect on the neonate alone. Adult female rats fed 30 mg/kg pentachlorophenol had a significantly lowered mean body weight (378 g) compared to that of female control rats (428 g).

Commercial pentachlorophenol (Dowicide-7, impurities unspecified) was administered daily by subcutaneous injection in DMSO at a dosage level of 25 mg/kg in BL6 mice on days 6-14 of gestation (BRL, 1968b). When the mice were sacrificed on day 18 of gestation, results showed that the incidence of abnormal fetuses was within the normal range as was fetal mortality.

Johnson et al. (1973) reported that a commercial grade of pentachlorophenol produced a positive response in the chick edema bioassay. A chemically pure pentachlorophenol, having no detectable concentrations of any chlorinated dioxins, produced a negative reponse in this test.

(7) Reproductive Effects

No information was found in the literature searched.

(8) Other Relevant Information

Pentachlorophenol uncouples oxidative phosphorylation in rat liver mitochondria (Mitsuda et al., 1963; Weinbach and Garbus, 1965). It has also been shown to disturb electron transport from flavins to cytochromes in microsomes, suggesting microsomal detoxification malfunction (Arrhenius et al., 1977).

Deichmann and coworkers (1942) indicated that a tolerance developed in rabbits when sublethal oral doses of pentachlorophenol were administered repeatedly. Each of 5 rabbits was given a daily oral dose of 35 mg/kg pentachlorophenol (about 1/8 of the lethal dose) as a 0.5% solution of

the sodium salt for 15 days. During the following 19 days, a 5% solution was used and the dose was raised gradually to 600 mg/kg (about twice the lethal dose). One animal died after having ingested a total of 1.9 g of pentachlorophenol per kilogram; 2 died after the ingestion of 2.9 g/kg, and 2 others after 3.9 g/kg. Evidence of tolerance to the compound was indicated by the finding of blood concentrations ranging from 14-39 mg % of pentachlorophenol in the animals that died; after single lethal doses of pentachlorophenol, the blood concentration in rabbits did not exceed 8 mg %.

b. Human Studies

(1) Pharmacokinetics

Both pentachlorophenol and sodium pentachlorophenol can be readily absorbed through the skin, but the sodium salt is appreciably more active (Dow Chemical, 1969a, 1969b). A 10-minute accidental exposure of hands to 0.4% pentachlorophenol has been shown to result in urine concentrations of 236 ppb (Bevenue, 1967). Fatalities have been reported among users of spray applicators with concentrations of 1-14% sodium pentachlorophenate (Gordon, 1956) and from manual submission of wood into 1.5-2.0% solution of sodium pentachlorophenate over a 3 to 30-day period (Menon, 1958). More recently, 9 of 20 infants were poisoned, 2 fatally, by sodium pentachlorophenate residues on hospital diapers and linens (Armstrong et al., 1969; Robson et al., 1969).

The respiratory tract may be a significant route of worker exposure to pentachlorophenol. Air and urine samples taken at 25 factories using pentachlorophenol as a wood preservative showed that the average worker's exposure in air was 0.013 mg/m^3, with a maximum range of 0.004-1.000 mg/m^3, and the level in urine ranged from 0.12-9.68 mg/l (Arsenault, 1976). When worker exposure to pentachlorophenol at a wood treatment plant was measured over a 5-month period, serum and urine levels of pentachlorophenol were 348.4-3963 µg/l

and 41.3-760 µg/l, respectively (Wyllie et al., 1975); pentachlorophenol residues in the workplace air were in the range of 5-15,275 ng/m^3. Average serum and urine levels of pentachlorophenol were about 30% and 50% higher in 6 exposed workers than in 4 control workers.

The half-life for absorption in humans after oral ingestion of pentachlorophenol is 1.3 ± 0.4 hours. A peak plasma concentration of 0.248 mg/l was observed 4 hours after ingestion of a 0.1 mg/kg dose (Braun et al., 1978).

Autopsy results of fatal cases of intoxication resulting from dermal and inhalation exposure indicate that the highest levels of pentachlorophenol are found in the liver, kidney, lungs, blood, and fat (Gordon, 1956; Armstrong et al., 1969). In non-fatal cases of poisoning, there is evidence suggesting that pentachlorophenol may be bound to plasma protein, but not to blood cells (Casarett et al., 1969).

In 4 male volunteers who ingested 0.1 mg pentachlorophenol/kg, approximately 74% of the dose was eliminated in the urine as pentachlorophenol and 12% as its glucuronide; 4% was eliminated in feces as pentachlorophenol and its glucuronide (Braun et al., 1978). Edgerton et al. (1979) detected pentachlorophenol and measurable quantities of the metabolites tetrachlorohydroquinone and tetrachloropyrocatechol in urine samples from the human general population and in the urine from a worker occupationally exposed to pentachlorophenol.

In humans, the primary mode of excretion for pentachlorophenol is in the urine (Braun et al., 1978). The half-lives for elimination of pentachlorophenol and pentachlorophenol glucuronide from urine following ingestion of 0.1 mg/kg pentachlorophenol by 4 volunteers were 33.1 ± 4.5 and 12.7 ± 5.4 hours. Approximately 74% and 12% of the doses were eliminated as

pentachlorophenol and its glucuronide, respectively, in the urine within 168 hours after ingestion. Four percent of the dose was eliminated as pentachlorophenol and pentachlorophenol glucuronide in the feces. Begley et al. (1977) reported that the mean blood and urine concentration of 18 wood-treatment industry employees decreased by approximately 56% at the end of a 20-day vacation period over concentrations found prior to the nonexposure period.

(2) Health Effects

Dermal absorption is the major route of occupational exposure (Chapman and Robson, 1965; Bevenue et al., 1967), although inhalation can also be pathogenic (Casarett et al., 1969). Cases of pentachlorophenol poisoning have been repeated in herbicide sprayers in Australia (Gordon, 1956) and in sawmill and wood-processing plant workers in Asia and Canada where pentachlorophenol or its sodium salt was used as a preservative (Menon, 1958; Bergner et al., 1965). Symptoms following fatal exposure are indicative of interference with oxidative phosphorylation and include profuse sweating, thirst, elevated body temperature, rapid pulse and respiration, labored breathing, abdominal pain, and death within 24 hours of the onset of symptoms (Bergner et al., 1965; Gordon, 1956; Menon, 1958). As of 1969, 30 fatal cases of pentachlorophenol poisoning had been reported (Robson et al., 1969).

Non-fatal exposures commonly involve sneezing and coughing and irritation of the eyes, skin, and upper respiratory tract. In addition, less severe systemic disorders of the kind described in fatal cases have also been noted (Bergner et al., 1965). Repeated exposure of the skin to sodium pentachlorophenate may produce dermatitis, systemic intoxication, and, in a limited number of people, an allergenic response. Contact with the eyes can produce corneal damage resulting in permanent impairment of vision (Dow Chemical Company, 1969a).

Adverse health effects have been minimal in workers chronically exposed to pentachlorophenol (Klemmer, 1972; Takahashi et al., 1976). Increased levels of the enzymes serum glutamic oxalacetic transaminase (SGOT), serum glutamic pyruvic transaminase (SGPT), and lactate dehydrogenase (LDH) and elevated levels of total bilirubin and creatine phosphokinase were noted, but all levels remained within normal limits. A significantly higher prevalence of gamma mobility C-reactive protein (CRP) was also detected in the sera of chronically exposed workers (Takahashi et al., 1976); CRP levels are often elevated in acute states of various inflammatory disorders or tissue damage. Begley et al. (1977) found that prior to a 20-day vacation, wood treatment plant workers exhibited depressed creatine clearance and phosphorus reabsorption values. By the end of the vacation, both of these values had improved significantly, suggesting that pentachlorophenol exposure reduced both glomerular filtration rate and tubular function.

A chronic health effect that has been associated with human exposure to certain types of commercial pentachlorophenol is chloracne (Baader and Bauer, 1951). It should be noted, however, that the chloracne could have resulted from chlorodioxin impurities in the pentachlorophenol (IARC, 1978).

(3) Target Organ Toxicity

Exposure to pentachlorophenol has resulted in lesions that include inflammed gastric mucosa, fatty metamorphosis of the liver, degeneration of renal tubules and myocardium, enlargement of the spleen, and lung effects including congestion, hemorrhage, and edema (Gordon, 1956; Menon, 1958; Bergner et al., 1965; Robson et al., 1969).

(4) Epidemiology

No information was found in the literature searched.

15. Ongoing Studies

Carcinogenesis testing, under the auspices of the National Toxicology Program, has begun on (1) technical grade pentachlorophenol, (2) purified pentachlorophenol, and (3) the commercial pentachlorophenol product identified as Dowicide EC-7 (NTP, 1980a). In all three bioassays, the compound is being added to the feed of mice.

A study of the chronic toxicity of pentachlorophenol is scheduled to be completed in 1980 by the Environmental Biology Branch of the National Institute of Environmental Health Sciences (Project No. ZO1-ES-30095) (NIEHS, 1980).

NIEHS (1980) is also supporting the microbial mutagenesis testing of pentachlorophenol. This testing is being conducted by EG and G Mason (Rockville, MD) under Contract No. NO1-ES-9-2137 and is scheduled to be completed in 1980.

The Food and Drug Administration's Division of Toxicology is currently conducting subchronic toxicity testing (Project No. 11165), teratology tests (Project No. 09687), and biochemical testing (Project No. 00248) on pentachlorophenol (FDA, 1980).

16. Exposure Standards

A Threshold Limit Value-Time Weighted Average (TLV-TWA) of 0.5 mg/m^3 has been recommended by the ACGIH (1980) and adopted by OSHA (1976). The ACGIH (1980) has also recommended a Threshold Limit Value-Short Term Exposure Limit (TLV-STEL) of 1.5 mg/m^3. It was noted by the ACGIH (1980) and OSHA (1976) that there may be a significant potential contribution to overall exposure by the cutaneous route.

17. Sources of Additional Relevant Information

Health hazard evaluation/toxicity determinations have been conducted at Koppers Company, Inc., North Little Rock, AR (Markel et al., 1977), and Wayhaeuser Treating Plant, DeQueen, AR (Markel and Lucas, 1975). Both plants are engaged in the treatment of wood with pentachlorophenol.

18. Other Pertinent Data

Workers may be exposed to chlorinated dibenzo-p-dioxins, particularly 2,3,7,8-tetrachlodibenzo-p-dioxin (TCCD), that are formed during the production of pentachlorophenol (see Impurities or Additives). Although an assessment of the toxicity of TCDD is beyond the scope of this profile, it should be noted that its extreme toxicity is not disputed (IARC, 1978). In humans, chloracne is one of the most constant and prominant features of TCDD exposure. Other findings may include neuromuscular symptoms, porphyria cutanea tardia, hepatic dysfunction, hyperlipidemia, cutaneous hyperpigmentation and hirsutism, chronic eye irritation, emotional disorders, and neuropsychiatric syndromes. A number of cases of cancer have been reported in workers exposed to TCDD, but no adequate epidemiological studies are available (IARC, 1978). In animals, TCDD is teratogenic and carcinogenic.

APPENDIX

The following list of chemicals comprises all chlorophenols considered for inclusion in this information profile, regardless of their commercial importance or biological activity.

	CAS Number
2-Chlorophenol	95-57-8
3-Chlorophenol	108-43-0
4-Chlorophenol	106-48-9
2,3-Dichlorophenol	576-24-9
2,4-Dichlorophenol	120-83-2
2,5-Dichlorophenol	583-78-8
2,6-Dichlorophenol	87-65-0
3,4-Dichlorophenol	95-77-2
3,5-Dichlorophenol	591-35-5
2,3,4-Trichlorophenol	15950-66-0
2,3,5-Trichlorophenol	933-78-8
2,3,6-Trichlorophenol	933-75-5
2,4,5-Trichlorophenol	95-95-4
2,4,6-Trichlorophenol	88-06-2
3,4,5-Trichlorophenol	609-19-8
2,3,4,5-Tetrachlorophenol	4901-51-3
2,3,4,6-Tetrachlorophenol	58-90-2
2,3,5,6-Tetrachlorophenol	935-95-5
Pentachlorophenol	87-86-5

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