CHAPTER 11

Pentachlorophenol and Dinitrophenolic Pesticides

PENTACHLOROPHENOL

Pentachlorophenol (PCP) is presently registered in the United States only as a restricted use pesticide for use as a "heavy duty" wood preservative. It is registered only for use in pressure treatment of utility poles. Heavy duty wood preservatives are defined as those that are applied by pressure treatment rather than by brushing or other surface applications. PCP is a general biocide that has been used as an herbicide, algaecide, defoliant, wood preservative, germicide, fungicide and molluscicide.[1] As a function of the manufacturing process, PCP is contaminated with chlorinated dibenzodioxans (CDDs), chlorinated dibenzofurans (CDFs) and hexachlorobenzene (HCB). These contaminants are toxic and persistent, but their levels in PCP preparations are usually low enough to limit the concern to chronic rather than acute effects. Technical PCP also contains lower chlorinated phenols (4%-12%). Incomplete combustion of PCP-treated wood may lead to further formation of these contaminant compounds.

Pentachlorophenol volatilizes from treated wood. It has a significant phenolic odor, which becomes quite strong when the material is heated. Though not registered for indoor use, heavily treated interior surfaces may be a source of exposure sufficient to cause irritation of eyes, nose and throat.

Toxicology

Pentachlorophenol (PCP) is readily absorbed across the skin, the lungs and the lining of the gastrointestinal tract. USEPA data submitted in support of reregistration of PCP report a dermal LD_{50} >3,980 mg/kg, suggesting very low dermal toxicity. In animals, the dermal LD_{50} has been reported as the same order of magnitude as the oral.[2] With acute exposure it is rapidly excreted, mainly in the urine as unchanged PCP and as PCP glucuronide. In chronic exposures as well as a volunteer study, the elimination half-life has been reported to be very prolonged, up to 20 days. The long half-life was attributed to the low urinary clearance because of high protein binding.[3] It is widely distributed to other tissues in the body, including kidney, liver, heart and adrenal glands.

The primary acute toxicological mechanism appears to be increased cellular oxidative metabolism resulting from the uncoupling of oxidative phosphorylation.[1,4] Heat production is increased and leads to clinical hyperthermia with profuse sweating and electrolyte disturbances. This clinical state may mimic the signs and symptoms of hyperthyroidism. Large doses are toxic to the liver, kidneys and nervous system. Due to depletion of ATP, severe rhabdomyolysis may occur. Numerous additional mechanisms may contribute to chronic toxicity

Based on laboratory experimentation in animals, PCP has been reported to have fetotoxic and embryotoxic properties and to bind to various hormone receptors.[5,6] Epidemiologic evidence suggests exposed women may be at risk for miscarriages, and maternal or paternal exposure can increase risk for reduced birth weight and infant malformations.[7,8]

Pentachlorophenol
HIGHLIGHTS

- Limited use in pressure-treated utility poles
- Volatilizes from treated wood
- Skin, lung, GI absorption
- Low urinary clearance
- Distributes to kidney, liver, heart, adrenals
- Prenatal implications

SIGNS & SYMPTOMS

- Mucosal membrane irritation
- Fatigue, headache, lack of concentration
- Contact dermatitis, chloracne
- Wide variety of non-specific symptoms
- Tachycardia, increased respiratory rate typical in serious poisonings

Pentachlorophenol & Dinotrophenolic Pesticides
TREATMENT

- Control hyperthermia
- Support oxygen, fluids
- Stabilize electrolytes
- Decontaminate skin, eyes
- Consider ICU management

Pentachlorophenol

COMMERCIAL PRODUCTS

chlorophen

PCP

penchlorol

penta

pentacon

penwar

sinituho

The sodium salt is sodium pentachlorophenate

Albuminuria, glycosuria, aminoaciduria and elevated BUN reflect renal injury. Liver enlargement, anemia and leucopenia have been reported in some intensively exposed workers. Elevated serum alkaline phosphatase, AST and LDH enzymes indicate significant insult to the liver, including both cellular damage and some degree of biliary obstruction.

Signs and Symptoms of Poisoning

The most common effects of airborne PCP include mucosal membrane irritation of the eyes, nose and throat, producing conjunctivitis, rhinitis and pharyngitis.[9,11] Additional common features include fatigue, lack of concentration and headache.[10,11,12] In adequate concentration, PCP is irritating to skin. Effects include irritation, contact dermatitis or, more rarely, diffuse urticaria or chloracne.[11,13,14] Contact dermatitis is common among workers having contact with PCP. In a study of employees involved in the manufacture of PCP, chloracne was found in 7% of the workers, and the risk was significantly higher among employees with documented skin contact compared to employees without skin contact.[14] Urticaria has also been reported as an uncommon response in exposed persons. Individual cases of exfoliative dermatitis of the hands and diffuse urticaria and angioedema of the hands have been reported in intensively exposed workers. Several infant deaths occurred in a nursery where a PCP-containing diaper rinse had been used.[15] Severe poisoning and death have occurred as a result of intensive PCP exposure.[10,16,17]

Acute poisoning occurs with systemic absorption that can occur by any route of sufficient dosage, although most occupational poisonings occur through dermal contact.[16,17] Most of the signs and symptoms of PCP are non-specific and, therefore, the diagnosis can be difficult. Symptoms include abdominal pain, anorexia, intense thirst, dizziness, restlessness and altered mental status. Workers exposed over long periods may experience weight loss. Serious poisoning may be manifested by hyperthermia, muscle spasm, tremor, respiratory distress, chest tightness and altered mental status, including lethargy and coma.[1,10,16,17] Tachycardia and increased respiratory rate are usually apparent. Most adult fatalities have occurred in persons working in hot environments where hyperthermia is poorly tolerated. In severe poisonings that have resulted in death, severe hyperthermia with temperatures up to 108°F has been reported.[16] Multiorgan system failure (seizures and coma, hepatic necrosis, renal failure, cardiovascular collapse and rhabdomyolysis) are often contributing factors in fatal outcomes.[15,16]

PCP has been classified as B2 (probable human carcinogen). Cases of aplastic anemia and leukemia have been reported that were associated temporally with PCP exposure. Causal relationships in these cases were not established.[18] For more information, see the cancer section in **Chapter 21, *Chronic Effects***.

Peripheral neuropathies have also been reported in some cases of long-term occupational exposure; however, a causal relationship has not been supported by longitudinal studies.[19] Studies of health effects in a community where a wood treatment plant is located have suggested an association with long-term adverse health effects. Residents in the community had a higher prevalence of cancer, respiratory disease and neurological disorders than those in the control group. It is unclear from the study, however, whether PCP or creosote, another wood preservative (see **Chapter 19, *Miscellaneous Pesticides, Solvents and Adjuvants***), was the primary pesticide of concern.[20]

Confirmation of Poisoning

> **CAUTION:** ***If poisoning is suspected on the basis of exposure, symptoms and signs, do not postpone treatment until diagnosis is confirmed.***

PCP can be measured in plasma, urine and adipose tissue by gas-liquid chromatography. **Plasma levels can be much higher than urine levels (ratio of blood to urine is 1.0 to 2.5), so care must be taken to interpret results**.[19,21] There is no clear-cut determination of what constitutes an abnormally high level of PCP, and there is great variability among different references. Most information on the extent of serum levels in relation to toxicity is based on individual cases or small series of patients. Reports exist of asymptomatic infants with serum levels as high as 26 parts per million (ppm);[15,21] however, most other reports of non-occupational exposure in the general public have levels in the parts per billion range.[1,22,23,24] Food is probably the main source of this nanogram-level dosage.[1] Serum levels among occupationally exposed persons often exceed 1 ppm.[1] A report of a lethal case describes a plasma level of 16 ppm,[17] but most cases generally involve serum levels in the range of 100 ppm or higher.[16] It is reasonable to assume that levels greater than 1 ppm are consistent with an unusual exposure and that levels approaching 100 ppm are cause for great concern.

DINOTROPHENOLIC PESTICIDES

Dinitrophenolic pesticides have many uses in agriculture worldwide: herbicides (weed killing and defoliation), acaricides, nematocides, ovicides and fungicides. Relatively insoluble in water, most technical products are dissolved in organic solvents and are formulated for spray application as emulsions. There are some wettable powder formulations. Only dinocap is currently registered in the United States.

Toxicology

Nitroaromatic compounds are highly toxic to humans and animals with LD_{50}s in the range of 25 to 50 mg/kg.[25] Most **dinitrophenols** are well absorbed from the gastrointestinal tract, across the skin and by the lung when fine droplets are inhaled.[26]

Dinitrophenols undergo some biotransformation in humans, chiefly reduction (one nitro group to an amino group) and conjugation at the phenolic site. Although dinitrophenols and metabolites appear consistently in the urine of poisoned individuals, hepatic excretion is probably the main route of disposition. Elimination is slow, with a documented half-life in humans between 5-14 days.[25] Blood and tissue concentrations tend to increase progressively if an individual is substantially exposed on successive days.

The basic mechanism of toxicity is stimulation of oxidative metabolism in cell mitochondria, by the uncoupling of oxidative phosphorylation. This leads to hyperthermia, tachycardia, headache, malaise and dehydration and, in time, depletes carbohydrate and fat stores. The major systems prone to toxicity are the hepatic, renal and nervous systems. The dinitrophenols are more active as uncouplers than chlorophenols such as pentachlorophenol. Hyperthermia and direct toxicity to the central nervous system cause restlessness and headache and, in severe cases, seizures, coma and cerebral edema. The higher the ambient temperature, such as in an agriculture environment, the more difficult it is to dissipate the heat.[25,26] Liver parenchyma and renal tubules show degenerative changes. Albuminuria, pyuria, hematuria and azotemia are signs of renal injury.

Dinotrophenolic Pesticides

HIGHLIGHTS

Only dinocap currently registered in U.S.

Absorbed from GI, skin, lung

Hepatic excretion with 5 to 14-day half-life

SIGNS & SYMPTOMS

Non-specific and may include

Sweating

Thirst

Fever

Headache

Confusion

Malaise

Restlessness

Serious poisoning

Hyperthermia

Tachycardia

Tachypnea

Renal failure

Bright yellow staining of skin, hair

TREATMENT

Same as Pentachlorophenol

CONTRAINDICATED

Antipyretic therapy with salicylates

Atropine

Dinotrophenolic Pesticides
COMMERCIAL PRODUCTS

While there are many dinitrophenolic pesticides, dinocap is the only one that is still actively registered in the United States.

Other products (no longer registered in the United States) included:

3Dinitrophenol (Chemox PE)

dinitrocresol (DNOC, DNC, Chemsect DNOC, Elgetol 30, Nitrador, Selinon, Sinox, Trifocide)

dinobuton (Acrex, Dessin, Dinofen, Drawinol, Talan)

dinopenton

dinoprop (Crotothane, Karathane)

dinosam (DNAP, Chemox General),

dinoseb (DNBP, dinitro, Basanite, Caldon, Chemox General, Chemox PE, Chemsect DNBP, Dinitro, Dinitro-3, Dinitro General Dynamyte, Elgetol 318, Gebutox, Hel-Fire, Kiloseb, Nitropone C, Premerge, Snox General, Subitex, Unicrop DNBP, Vertac, Dinitro Weed Killer 5, Vertac General Weed Killer, Vertac Selective Weed Killer)

dinoseb acetate (Aretit)

continued next page

Cataracts occur in laboratory animals given dinitrophenols and have occurred in humans, both as a result of ill-advised medicinal use and as a consequence of chronic occupational exposure.[27] Cataract formation is sometimes accompanied by glaucoma.

Signs and Symptoms of Poisoning

Most patients present within a few hours of exposure with generalized non-specific signs and symptoms including profuse sweating, thirst, fever, headache, confusion, malaise and restlessness. The skin may appear warm and flushed as hyperthermia develops, along with tachycardia and tachypnea, all of which indicate a serious degree of poisoning. Apprehension, anxiety, manic behavior, seizures and coma reflect cerebral injury, with the latter two signifying an immediately life-threatening intoxication. Respiratory distress and cyanosis are consequences of the stimulated metabolism and tissue anoxia. Renal failure may occur early in cases of severe exposure. Liver damage is first manifested by jaundice, and cell death can occur within 48 hours and is dose dependent.[28] Death may occur within 24 to 48 hours after exposure in cases of severe poisoning.[26] In cases of survival of severe poisoning, complete resolution of symptoms may be slow due to the toxicant's long half-life.[26,29]

A characteristic bright yellow staining of skin and hair is often present with topical exposure and can be an important diagnostic clue to the clinician.[25,26,29] Yellow staining of the sclerae and urine indicate absorption of potentially toxic amounts. Weight loss occurs in persons continually exposed to relatively low doses of dinitrophenols.[25,27]

Confirmation of Poisoning

If poisoning is probable, do not await confirmation before commencing treatment, but save urine and blood specimens on ice at a temperature below 20°C in the event confirmation is necessary later. Unmetabolized dinitrophenols can be identified spectrophotometrically, or by gas-liquid chromatography, in the serum at concentrations well below those that have been associated with acute poisonings. The data on exposure and systemic levels of compounds in this group are limited and most reports specify the compound dinitro-ortho-cresol. In general, blood levels of 10 µg/dL or greater are usually seen when systemic toxicity is evident.[25,30] One fatal case occurred with a level of 75 µg/dL.[30] Blood analysis is useful in confirming the cause of poisoning. Monitor levels routinely during acute intoxication to better establish a decay curve and determine when therapy can be safely discontinued.

Treatment of Poisoning

Treatment of pentacholorophenol and dinitrophenol and its derivatives is the same, though there are some differences in toxicity as noted above.

1. Provide support treatment, including oxygen, fluid replacement and, most important, control of hyperthermia. There is no specific antidote for PCP or dinitrophenol toxicity.

2. Since these patients require aggressive control of hyperthermia, administer sponge baths and use fans to increase evaporation.[31] Cooling blankets and ice packs to body surfaces may also be used. In fully conscious patients, administer cold, sugar-containing liquids by mouth as tolerated. Antipyretic therapy with salicylates is **strongly contraindicated**, as salicylates also uncouple oxidative phosphorylation. Other antipyretics are thought to be of no use because of the

peripherally mediated mechanism of hyperthermia in poisoning of this nature. Note that profuse sweating is common in this poisoning, indicating that central acting antipyretics would have no effect. Neither the safety nor the effectiveness of the other antipyretics has been tested.

3. Administer oxygen continuously by mask to minimize tissue anoxia. Unless there are manifestations of cerebral or pulmonary edema or of inadequate renal function, administer intravenous fluids to restore hydration and support physiologic mechanisms for heat loss and toxicant disposition. Monitor serum electrolytes, adjusting IV infusions to stabilize electrolyte concentrations. Follow urine contents of albumin and cells, and keep an accurate hourly record of intake/output to forestall fluid overload if renal function declines.

   CAUTION: ***In the presence of cerebral edema and/or impaired renal function, intravenous fluids must be administered very cautiously to avoid increased intracranial pressure and pulmonary edema. Central monitoring of venous and pulmonary wedge pressures may be indicated. This is particularly important when cardiac dysfunction or heart failure is observed. Such critically ill patients should be treated in an intensive care unit.***

4. Decontaminate the skin with soap and water, as outlined in **Chapter 3, *General Principles*.**

5. Treat eye contamination by irrigating the exposed eyes with copious amounts of clean water or saline for at least 15 minutes. Remove contact lenses, if present, prior to irrigation. Send patient for further medical attention if irritation or other injury persists.

6. Treat severe systemic poisoning in an intensive care unit setting with appropriate supportive care including respiratory support, intravenous fluids, cardiac monitoring and renal function support as necessary. The toxicant itself and severe electrolyte disturbances may predispose the patient to arrhythmias and myocardial weakness. Atropine is a medication that is absolutely contraindicated, and it is essential not to confuse the clinical signs for dinitrophenol with manifestations for cholinesterase inhibition poisoning.[26]

7. To reduce production of heat in the body, control agitation and involuntary motor activity with sedation. Lorazepam or other benzodiazepines should be effective, although use of these drugs in these poisonings has not been studied. Control seizures as outlined in **Chapter 3**.

8. Although most occupational poisoning is from inhalation, if ingested, consider gastrointestinal decontamination as outlined in **Chapter 3**.

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Dinotrophenolic Commercial Products, cont.

dinoseb methacrylate (binapacryl, Morocide, Acricid, Ambox, Dapacryl, Endosan, FMC 9044, Hoe 002784, Morrocid, NIA 9044)

dinosulfon

dinoterb acetate

dinoterb salts

dinoterbon

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