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**Toxicants that Cause Fevers** *(9-Aug-1999)*

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**Pentachlorophenol**

**Sources**

- Also referred to as penta and "PCP" although the latter term should be avoided due to its street use as a term denoting phencyclidine, which is also known as Sernylan®, or "angel dust".
- Pentachlorophenol was, until recently, the most commonly employed chemical in wood preservation. It was principally applied in hydrocarbon solvents as pentachlorophenol itself, although some sodium pentachlorophenate, which is water solubilized has also been used. Pressure-treated often meant "penta-treated", but at the present time, pressure-treated usually means treated with CCA (copper chromated arsenic).
- Pentachlorophenol is still sometimes used in light oils for brush-on application to wood, often used on natural, outdoor wood surfaces. Should never be applied indoors.
- "Penta"-treated feed and water troughs, fencing, and barn boards have been sources of contamination of livestock.
- Pentachlorophenol pressure-treated wood would sometimes "bleed" when it was relatively new. Its application under pressure would heavily soak the wood. Generally 11 g of penta was applied per board foot.
- Light solvent-based products may sometimes crystalize on wood surfaces and become airborne or sublime into sufficiently warm, enclosed surroundings.
- Miscellaneous other applications involve the herbicidal, fungicidal, insecticidal, bacteriocidal and molluscacidal (biocidal) properties of pentachlorophenol.
- Has been used in treatment of leather and in paper (to control mildew), in rug shampoos and for mothproofing of fabrics.
- Most wood is at least surface treated with a wood preservative to prevent mildew during shipping.
- Many other commonly used wood preservatives are also highly toxic. They may contain creosote (a phenolic), and the previously mentioned copper chromated arsenic (which causes effects most like arsenic toxicosis), among other possibilities. Such toxicants have a different spectrum of effects than those of pentachlorophenol.
- Homes constructed from pressure-treated (penta) wood had to be abandoned due to apparent toxicosis in their human occupants.
- Pentachlorophenol residues may also occur in animals as the result of the breakdown of hexachlorobenzene (HCB) or pentachlorobenzene. Up to 38% of an ingested HCB dose can be excreted as PCP.
Toxicity

- In all species evaluated, including domestic animals, the acute oral or dermal LD₅₀ is 10 - 200 mg/kg.
- The multiple exposure lethal dose is 50 - 70 mg/kg. Minimal toxic daily doses of 20 - 35 mg/kg in calves.
- Young swine have died following exposure to oily, freshly treated wood used in farrowing crates or farrowing houses.
- Toxic to fish at 30 - 300 ppb and fish kills have resulted from spills into lakes and streams, primarily after a rain has flushed pentachlorophenol from an area used in wood treatment into the body of water.
- LC₅₀ in the feed of birds is 3400 - 5200 ppm.
- Rats tolerate feed containing 1000 ppm (approx. 50 mg/kg) for 90 days but develop moderate hepatocellular necrosis and interstitial fibrosis. The no-effect feed concentration in rats was 25 - 50 ppm in the diet (1.5 - 3.0 mg/kg).

- Contaminants:
  - Many studies evaluating the toxicity of pentachlorophenol must be evaluated with the knowledge that chlorinated dibenzodioxin or chlorinated dibenzofuran contaminants (although often present in varying amounts) were neither quantitated nor considered in the interpretation of the data. These dioxins and dibenzofurans tend to be far more toxic than the pentachlorophenol itself in most cases. Sub acute or chronic toxicity is often dependent upon the nature and extent of contamination of the particular batch of pentachlorophenol in question.
  - When calves were fed pentachlorophenol at 15 - 20 mg/kg/day with varying degrees of contaminants present, depression in body weight gains were proportional to the concentrations of contaminants contained. Signs first developed after 8 weeks.
  - At high doses contaminants are embryotoxic or fetotoxic, but purified pentachlorophenol itself is reportedly not teratogenic.
  - Pentachlorophenol contaminants include various isomers of hexa-, hepta-, and octachlorodibenzodioxin, various dibenzofurans, hexachlorobenzene, and other compounds such as tetrachlorophenols. Of these, the hexachlorodibenzodioxins are of greatest concern and this group of compounds is now believed to have caused chick-edema disease from feeding the birds a ration containing waste oils originating at a leather processing plant.
  - The super-toxic, 2,3,7,8-tetrachloro-dibenzodioxin, which is the principle dioxin of concern in some of 2,4,5-T used to formulate Agent Orange and of concern in such areas as Times Beach, MO, and Love Canal, NY, has never been detected in any significant concentration in pentachlorophenol preparations.
  - Apparently, Dow Chemical Co. developed a process to make a much cleaner (far less dioxin-containing) pentachlorophenol and offered the technology to all producers of the pesticide. They were supported neither by their colleagues in industry, nor by the EPA, in spite of the fact that the increased cost would have been only pennies per gallon. Dow went ahead and manufactured their product with the new technology, but because their product was slightly more expensive Dow is no longer in the pentachlorophenol business.
  - Air concentrations of 1 mg/m³ cause respiratory tract inflammation.

Absorption, Distribution, Metabolism and Excretion (ADME)

- Rapid absorption from the skin, digestive tract and lung. Peak blood concentrations are reached within a few hours of ingestion.
- With a constant level of intake, blood concentrations generally plateau in five days.
- Most pentachlorophenol is in the plasma, with only small amounts in red blood cells.
- The highest tissue concentrations are in liver and kidney.
- Eliminated in the urine of all species tested and has a half-life of 1.5 - 2 days.
- Metabolites include tetrachlorohydroquinone and glucuronide conjugates; although some free pentachlorophenol is eliminated in the urine.

Mechanism of Action

- The acute toxicity of pentachlorophenol-containing products is primarily a result of the pentachlorophenol itself, which uncouples oxidative phosphorylation. Uncoupling of oxidative phosphorylation by pentachlorophenol appears to be due to the chlorophenate ion. By "uncoupling" the transfer of electrons down the cytochromes from the actual mitochondrial production of ATP, there is rapid utilization of the body's energy stores.
- It has also been suggested that there are inhibitory effects on enzymes, such as cellular kinases, dehydrogenases and reductases.
- The effects of the halogenated dioxin and dibenzofuran contaminants will be discussed in a subsequent section.
Normal Function: Sources of Electrons and Components of the Electron Transport Chain
Mechanism of Pentachlorophenol

Probable Sites of Energy Conservation in the Respiratory Chain: This process actually depends upon H⁺ (proton) pumping. As electrons pass down the cytochrome chain, hydrogen ions are pumped from inside the inner mitochondrial membrane to between the inner and outer membranes. This proton gradient drives ATPase. The gradient is destroyed by ferrying of protons by pentachlorophenol which alternates from dimer to monomer as it carries protons.

Signs

- When cows received technical grade penta, they became unthrifty after 8 weeks and, at 160 days, had dry scaly skin, diarrhea, urethritis, cystitis and a normocytic, normochromic anemia.
- With respiratory exposure, pain in the respiratory tract is accompanied by sneezing and coughing. Acclimated humans will tolerate up to 2.4 mg/m³.
- Mild toxicoses:
  - Weakness.
  - Anorexia.
  - Lethargy.
- Moderate toxicoses:
  - Rapid respiratory rate.
  - Hyperpyrexia (106 - 108 °F) and possible hyperglycemia, and glycosuria.
  - Diaphoresis (sweating) in capable species.
- Lethal toxicoses:
  - The above listed signs.
  - Cardiac and skeletal muscular collapse and death.
  - Rapid onset of rigor mortis.
  - Renal damage may result in proteinuria and increased blood urea nitrogen.
- Chronic toxicoses:
  - Anemia.
  - Dependent upon contaminants and may include weight loss, poor growth, dry scaly skin, diarrhea, and urethritis/cystitis.
Lesions

- Local irritation of areas contacted by the pentachlorophenol.
- Pulmonary edema and congestion.
- Hepatic enlargement, centrilobular degeneration and fatty change.
- Renal tubular hydropic and fatty change.
- Cattle: (nonlethal dose of 15 - 20 mg/kg, technical pentachlorophenol)
  - Reduction in splenic white pulp (nonspecific change reflecting stress, similar to lesions of acute viral infection).
  - Bile duct hyperplasia, and no other hepatic changes noted.
  - Villous hyperplasia of the mucosa of the urinary bladder (severe).
  - Hyperkeratosis of the skin (probably largely dependent upon contaminant concentrations).

Diagnosis

- A background blood pentachlorophenol determination in control animals revealed levels of 130 ppb.
- Clinical signs of pentachlorophenol toxicosis generally occur when blood concentrations are from 40 - 80 ppm. Acute lethal toxicoses occur with blood concentrations of 100 ppm and tissue of 200 ppm.
- Blood concentrations of 2 ppm or less are not associated with clinical signs. Also concentrations of 10 - 300 ppb in the blood are common in animals in barns built in part with penta treated wood but are not associated with clinical signs.
- Blood concentrations of 33 - 87 ppm in cattle fed 15 - 20 mg/kg/day of technical pentachlorophenol were associated with mild to moderate toxicoses at 160 days of dosing.
- In cattle fed technical penta at 15 - 20 mg/kg/day, liver chlorodioxin concentrations after 160 days were 29, 1057, and 3456 ppb for the hexa, hepta, and octa isomers, respectively.
- Immunologic effects may include a reduction in immunoglobulins.

Treatment

- Terminate exposure: May include the use of bedding materials to remove animals from surfaces bleeding penta and resulting in dermal exposure; avoidance of contact of feed with penta-treated surfaces; control of interior temperature to reduce volatilization from warm areas; consider increased ventilation or removal of animals if extremely high concentrations or toxic effects are already present.
- Bathe off any exposed surfaces with a dish detergent.
- For early ingestions, the use of an emetic, activated charcoal and a cathartic are likely to be of value. For higher doses, lavage, including enterogastric or rumen lavage, may be appropriate depending upon the species and time factors involved.
- Correct acidoses if present with bicarbonate in fluids.
- Correct dehydration and promote excretion of pentachlorophenol and conjugates by the administration of fluids.
- Maintain positive energy balance to combat energy losses due to the biochemical effects of pentachlorophenol and to allow hepatic conjugation of the pesticide.
- Minimize stress and control any environmental conditions which may result in physiological increases in body temperature, stressors these have previously been shown to increase the likelihood of acute toxicoses with other uncouplers of oxidative phosphorylation.
Disophenol

Sources

- Disophenol (DNP®, or 2,6-diiodo-4-nitrophenol) is administered to dogs and cats as an anthelmintic to eliminate hookworms. The product is a yellow, injectable solution.
- DNP® is supplied commercially as a 4.5% solution (45 mg disophenol/ml) in a water/polyethylene glycol vehicle for administration by subcutaneous injection.
- A routine therapeutic dose of disophenol for dogs is 10 mg/kg.
- Similar anthelmintic formulations include Ancylol® and Syngamix®.
- Disophenol is used to remove gapeworms (*Syngamus trachea*) from turkey poults. The gapeworm formulation is given in the feed or in capsules.
- The dose for turkey poults given in the feed is 3.5 mg/lb body weight.

![Disophenol](image)

Disophenol

Toxicity

- Disophenol has approximately a 3-fold margin of safety in the dog and cat, when administered subcutaneously. Generally animals may respond to an apparent stinging sensation immediately after injection.
- It is reported that puppies as young as 2 days of age may be given the drug without adverse effects, except that occasional opacity of the lens is seen at less than 4 months of age.
- Reportedly, there are no side effects in pregnant animals, regardless of the stage of gestation.
- Disophenol has been recommended for severely parasitized animals.
- LD₅₀ values in male rats:
  - Oral 170 mg/kg.
  - IV 105 mg/kg.
  - IP 105 mg/kg.
  - SC 122 mg/kg.
- LD₅₀ values in male mice:
  - Oral 212 mg/kg.
  - IV 88 mg/kg.
  - IP 107 mg/kg.
  - SC 110 mg/kg.
- In acute toxicity studies the minimum lethal oral dose was between 100 and 200 mg/kg. Single injectable doses of 30 mg/kg were safe, but doses above 36 mg/kg were lethal (Wood et al., 1961).
- There is evidence to suggest that elevation of body temperature may increase susceptibility of an animal to acute toxicosis. Exposure to high environmental temperatures or vigorous exercise is therefore contraindicated after disophenol administration. Large breeds with heavy coats may be predisposed to toxicosis in the summer, due to inherent thermoregulatory difficulty.

Mechanism of Action

Uncouples oxidative phosphorylation in a manner probably like that associated with pentachlorophenol. The energy-releasing processes of the cytochrome chain are disconnected (uncoupled) from the energy-requiring endergonic processes that form ATP and apparently much of the free energy is dissipated as heat.
Absorption, Distribution, Metabolism and Excretion (ADME)

- The half-life of DNP is reported as 9 - 15 days.
- Because of the comparatively long half-life, retreatment is not recommended within 21 days.
- In chronically dosed dogs, a dose 1.6 times the recommended dose (i.e., 16.5 mg/kg SC) once a week for 8 weeks was not toxic to healthy dogs; while a lower than recommended dose (7.5 mg/kg), if repeated daily was lethal in 6 days. Lower doses (5.0 mg/kg) repeated daily in dogs did not cause overt toxic effects when administered for 60 days.

- Signs are associated with an increased metabolic rate with cellular energy depletion and include tachycardia, polyneva, hyperthermia, and early rigor mortis in fatal cases.
- Lenticular opacity of varying severity is likely to occur in adults (as well as in young dogs) given higher than recommended doses of disophenol.
- At least in young puppies given the recommended dose, the lenticular opacity is not severe and regresses within 7 days.
- Vomiting is another sign of acute toxicosis, dehydration is slight to moderate.
- In acute toxicosis, death is believed to result from direct circulatory depression, hyperpyrexia, acidosis and anoxemia. Hyperventilation is common, in addition to the polypnea mentioned above. Pyrexia may commence from 1 - 6 hours after dosing, and, in survivors, it may cease after 40 hours.

Clinical Pathology

- High packed cell volume, neutrophilia and lymphopenia occurred in a clinical case of disophenol toxicosis.
- Congestion and hydropic degeneration of the lungs and liver, and fatty degeneration of the myocardium were reported in dogs with acute disophenol toxicosis.
- Only one report of a disophenol-poisoned dog involved evaluation of blood pH and consistent changes were not apparent in that animal.

Treatment

- Fluids, such as lactated Ringer's with bicarbonate may be indicated.
- Ice packs.
- Very limited investigation of the antipyretic, dipyrone, indicated that the drug may be of benefit. However, the results were not statistically significant and, in view of the peripheral mechanism of heat generation in pentachlorophenol toxicosis, a logical basis and confidence in success with the use of dipyrone is lacking.
- Animals should not be stressed in order to avoid increasing the body temperature.
- An attempt should be made to maintain a positive energy balance in the affected animal (provide dextrose, food, etc.).
- In instances of accidental overdose, in which it is recognized immediately after injection that a large overdose (in the neighborhood of 3-fold or greater) has been given, actual excision of the subcutaneous tissue underlying the injection may be indicated to save the animal's life. There is no data on the rate of absorption of disophenol from the subcutaneous injection site and therefore the benefit of this approach remains to be substantiated.
- Halothane anesthesia should be avoided due to its tendency to cause malignant hyperthermia.
Dinitrophenol and Other Uncouplers of Oxidative Phosphorylation

**Sources**

- Various dinitro derivatives of cresol and phenol are used as insecticides, acaricides, fungicides, and herbicides (nonselective biocides). They are applied in sufficient amounts to wet the target organism for contact action. Included in these compounds are: dinitrophenol (2,4-dinitrophenol, an insecticide, acaricide, fungicide which is phytotoxic to green plants); dinoseb (DNBP, Dinitro®, Basanite®, Dow General Weed Killer®, and several other products used as a herbicide, dessicant or dormant fruit spray); DNOC (dinitrocresol); DNAP (Dinosam®, a rarely encountered herbicide); and 5 DN-111, a discontinued product.
- Animals may be seriously exposed from entering treated fields, or by contact with concentrated forms of these pesticides.

![Dinitrophenol](image)

**Toxicity**

- The LD₅₀ of dinitrophenol in the rat is 0.027 - 0.10 mg/kg.
- The acute oral LD₅₀ of dinoseb in the rat is 40 - 60 mg/kg.
- The acute oral LD₅₀ of DNOC in the rat is 20 - 50 mg/kg.

**Absorption, Distribution, Metabolism and Excretion (ADME)**

Dinitrophenol is about twice as toxic as disophenol on a single dose basis, but is less toxic on a repeated basis, indicating that it is not as cumulative as disophenol.

**Mechanism of Action**

Uncouples oxidative phosphorylation, presumably by the same mechanism as that of pentachlorophenol.

**Treatment**

See Pentachlorophenol and Disophenol handouts.
Other Uncouplers of Oxidative Phosphorylation

- Other agents, some previously mentioned which may uncouple oxidative phosphorylation to a clinically significant degree in some instances of toxicosis include:
  - Pentachlorophenol
  - Disophenol
  - Other chlorophenols
  - Aspirin
  - Hexachlorophene*
  - Bromethalin*

*Hexachlorophene is known to cause fevers in animals exposed to high doses and both hexachlorophene and bromethalin seem to cause primary effects on myelin of the central nervous system (see other sections for details).

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Additional Toxicants

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<th>Usual Time of Onset</th>
<th>Usual Duration (if survives)</th>
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<tr>
<td>Aspirin</td>
<td>Most species</td>
<td>Hours</td>
<td>Days for most compounds; often lethal</td>
</tr>
<tr>
<td>Bromethalin</td>
<td>Most species</td>
<td>Hours</td>
<td>Days for most compounds; often lethal</td>
</tr>
<tr>
<td>Hexachlorophene</td>
<td>Most species</td>
<td>Hours</td>
<td>Days for most compounds; often lethal</td>
</tr>
</tbody>
</table>

Halothane

- Swine, dogs (esp. greyhounds)
- Minutes to hours
- Hours; often lethal

Garbage toxicity

(See Bacterial Toxins that Affect the GI Tract)

Any Syndrome with seizures or exertion

(See Toxicants Associated with Stimulation or Seizures)

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References

Pentachlorophenol


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