Chapter Sections
1. Metal that Affect the Skin
   Thallium
   Selenium
   Molybdenum Toxicosis - Copper Deficiency
2. Other Organic Compounds that Affect the Skin
   Polychlorinated Dibenzo(dioxins, Highly Chlorinated Naphthalenes and Related Halogenated Aromatics
   Polychlorinated Biphenyls (PCBs) and Polybrominated Biphenyls (PBBs)
   Turpentine
   Additional Toxicants
3. Other Plants that Affect the Skin (Integument)
   Vicia Villosa - Hairy Vetch
   Winter Vetch (Vicia villosa Roth)
   Hippomane Mancinella - Manchineel Tree

1. Metal that Affect the Skin

   Thallium

<table>
<thead>
<tr>
<th>Major Species</th>
<th>Usual Time of Onset</th>
<th>Usual Duration (if survives)</th>
<th>Full Table for Toxicants that Cause Skin Effects other than Photosensitization</th>
</tr>
</thead>
<tbody>
<tr>
<td>All species; esp. dogs</td>
<td>Hours to weeks</td>
<td>Weeks to months; very often lethal</td>
<td></td>
</tr>
</tbody>
</table>

Please review the chapter in: Osweiler GD. Clinical and Diagnostic Veterinary Toxicology, 3rd ed. Kendall/Hunt Publishing Company, 1984. These notes are intended only to supplement that chapter.

Sources

- Rodenticide or insecticide formulations in the form of syrups, jelly or pastes. Often applied to foods such as cookies, cakes, peanut butter or grain.
- Commercial preparations, such as ant traps, ant baits and rat poisons generally contain 0.5 - 1.0% thallium.
- In 1963, the federal government adopted legislation prohibiting the sale of thallium containing pesticides to the general public.
- In commercial applications, thallium has been largely replaced by other rodenticides such that, at the present time, thallium is infrequently used in the USA but is still commonly used in some countries.

Absorption, Distribution, Metabolism and Excretion (ADME)

- Thallium is absorbed through the skin and from the digestive tract.
- The concentration of thallium in the kidney may be much greater than in other tissues.
- Because of its comparatively slow excretion, thallium may be a cumulative poison if exposure is repeated or continuous.
- The biological half-life is approximately 3 - 8 days.
- During the first day after exposure, the kidney is the main route of excretion and urinary concentrations of thallium are high. Later, the concentrations in feces are approximately twice as high as urinary levels.
Toxicity

- Generally considered a cellular poison.
- LD50 = 10 - 15 mg/kg.
- Lethal dose 20 - 25 mg/kg.
- Will accumulate in body.

Mechanism of Action

Combines with mitochondrial sulfhydryl enzymes, causing an interference with oxidative phosphorylation. Inhibits aerobic metabolism in skin, brain, and kidney. Will exchange for potassium in muscle and nerves.

Diagnosis

- Confirmation of the diagnosis may be possible in some instances by means of laboratory confirmation (atomic absorption spectroscopy) of thallium in urine, feces or kidney.
- Any thallium in body is generally considered significant, although with increasingly sensitive methods of detection, this might change.

Clinical Signs

- Acute (within 1 - 4 days of ingestion) - gastric distress, vomiting, severe hemorrhagic diarrhea, abdominal pain, and anorexia. Lingual ulcers have been reported in cats. Motor paralysis and trembling may occur.
- Subacute - signs appear within 3 - 7 days. Gastric distress and motor disturbances are similar but are more mild. Prominent skin changes occur. Erythema and pustule formation (usually begins on nose and ears, can progress to axillary region and torso). Mucopurulent ocular discharge may occur. Alopecia and encrustation of skin can occur.
- Chronic - may take 7 - 10 days. Alopecia and drying and scaling of skin can occur 1 - 3 weeks postingestion.

Treatment

- Emesis may be indicated for very recent exposures.
- Prussian blue is the preferred agent to enhance the elimination of thallium. Prussian blue is a nonabsorbable lattice of potassium ferric furocyanide. It is not absorbed orally. In theory, the potassium is released and mobilizes intracellular thallium, which is then bound by the lattice structure remaining in the gut. Prussian blue has been shown to lower the thallium concentration in the brain of rats. The use of Prussian blue in human thallium toxicosis has demonstrated favorable clinical improvement correlated with increased fecal excretion of thallium. The soluble form of Prussian blue is most effective in adsorbing thallium. Prussian blue is given orally. In humans, 2 - 500 mg capsules are given orally 3 times a day (TID), depending upon the severity of the case, for 2 - 3 weeks. In severe thallium toxicosis, Prussian blue solution has been recommended at 1,000 mg TID (also in man) via a duodenal tube, because of pyloric spasm and gastric dilatation which may accompany thallotoxicosis. The effectiveness of Prussian blue may be lost in patients not able to evacuate the bowel due to constipation and/or absence of intestinal motility. Therefore, mechanical removal of feces may be necessary before administration of Prussian blue. Prussian blue is available through Aldrich Chemical Co.; 940 West Saint Paul Ave., Milwaukee, WI 53233, USA.
- Forced diuresis should be considered as an adjunct to Prussian blue therapy.
- In vitro absorption studies have shown equal affinity for thallium (Lehmann PA, Favari L. Parameters for the adsorption of thallium ions by activated charcoal and Prussian blue. J Toxicol Clin Toxicol 1984; 22:331-339.). In vivo findings have shown that activated charcoal and Prussian blue are effective antidotes for the treatment of acute thallium intoxication.
Selenium
(See also Clinical and Diagnostic Veterinary Toxicology as well as Astragalus/Oxytropis section of these notes)

Sources

- **Obligate indicator plants** - require Se in large amounts for growth. Therefore their presence indicates high selenium soils are present. These plants concentrate 100 - 10,000 ppm Se.
  - Examples include:
    - *Xylorrhiza* = woody aster.
    - *Oonopsis* = goldenweed.
    - *Stanleya* = prince's plume
    - *Astragalus* = locoweed.
- The selenium is in a water soluble form in seleno amino acid analogs of cysteine and cystathionine.

- **Facultative indicator plants** - absorb Se if present in high concentrations, but do not require large amounts for growth. These are, therefore, found in both seleniferous and non-seleniferous soils. If not seleniferous soils, they may concentrate 25 - 100 ppm of Se.
  - Examples include:
    - Other asters.
    - *Atriplex* = saltbrush.
    - *Sideranthus*.
    - *Machaeranthera*.
- **Non-accumulator plants** - such as crop plants when grown on seleniferous soils may also accumulate 1 - 25 ppm Se as part of their protein make-up in integral proteins (i.e., seleno-cystine, selenocysteine, selenomethionine and selenocystathionine) in a water insoluble form. Forages and grains from seleniferous areas may be more palatable than those from other sources.
- High selenium soils and plants are known to exist in western Canada, Arizona, Colorado, the Dakotas, Idaho, Kansas, Nebraska, Nevada, New Mexico and Utah.
- Other sources include errors in feed formulation which are rare.
- Mine wastes, especially from copper, silver and high sulfide ores.
- Iatrogenic administration of excessive doses of selenium intended as therapy or prevention of musculoskeletal disorders.
- Selenium levels are highest in low rainfall areas with alkaline soil.
- Leaching of selenium from the soil as a result of irrigation and transport downstream to evaporation basins has resulted in widespread teratogenesis in water fowl.

Toxicity

- **Requirement**. Most domestic animals require selenium in their diet. For food-producing species, a level of 0.3 ppm in the total diet is often recommended.
- **Acute selenosis**.
  - Ingestion of obligate indicators (400 ppm Se).
  - One to 5 mg Se/kg BW orally is acutely toxic.
  - Parenterally 0.2 mg Se/kg BW is acutely toxic.
  - LD50 in sheep of intramuscularly administered selenium 0.7 mg Se/kg BW.
  - Single minimal lethal doses of oral sodium selenite. Horse 3.3 mg/kg, cattle 10 mg/kg, swine 17 mg/kg.
- **Subacute selenosis of swine**.
  - Sodium selenite at 25 ppm (of selenium) in the diet.
  - Alkali disease (chronic toxicosis) in livestock exposed to Se at 5 - 40 ppm in the diet.

Mechanism of Action

- Possibly due to glutathione depletion and secondary lipid peroxidation.
- Probably not due to sulfhydryl enzyme inhibition.
Signs and Lesions

- **Acute selenosis** - due to ingestion of obligate indicator plants or iatrogenic toxicosis after parenteral administration.
- All species are susceptible-onset of clinical signs within 1 - 2 hours; death 2 hours to 7 days later.
  - Clinical signs include:
    - Lethargy, nonresponsiveness.
    - Dyspnea, cyanosis, nasal discharge.
    - Teeth grinding.
    - Anorexia.
    - Prostration.
    - Mydriasis.
    - Elevated temperature.
    - Incoordination.

- Lesions.
  - Edematous lungs, hydrothorax, pale heart.

- **Subchronic selenosis**.
  - Subchronic selenosis does occur in swine. Sodium selenite in the diet at 20 - 25 ppm selenium will produce focal symmetrical poliomalacia after several weeks.
  - Quadriplegia with flaccid paralysis.
  - Sternal recumbency.
  - Ataxia initially.
  - Some coronary band separation.
  - Some alopecia.
  - Blind staggers in large animals (in the past thought to be due to subchronic selenosis) associated with the ingestion of moderate amounts of obligate or facultative indicator plants over a period of weeks has not been reproduced by feeding selenium salts. Moreover, experimental work with *A. bisulcatus* in cattle produced loco lesions (neurovisceral cytoplasmic vacuolation) and similar clinical signs.

- **Chronic selenosis**.
  - Alkali disease (chronic selenosis) in livestock is due to the ingestion of nonaccumulator plants grown on seleniferous soils (5 - 40 ppm selenium) over a period of weeks or months.
  - Primarily seen in cattle and horses.
  - Signs and lesions.
    - Decreased vitality.
    - Anemia.
    - Joint stiffness.
    - Lameness.
    - Rough hair coat.
    - Hair loss (tail and mane).
    - Horn and hoof deformities (circular break in hoof below coronary band).
    - No anorexia (often graze on knees).
    - Hair loss precedes hoof changes.
  - Lesions: cardiomyopathy and liver cirrhosis.

- **Teratogenesis in waterfowl and poultry**.
  - Underdeveloped feet, legs.
  - Missing or underdeveloped lower or upper beak.
  - Missing or underdeveloped eyes.

**Diagnosis**

- Appropriate clinical signs and lesions.
- Access to a toxic dose of selenium.
- Whole blood selenium.
- Liver selenium
- Appropriate lesions on gross and histologic examination.

**Treatment**

- **Acute selenosis**.
  - Terminate exposure; minimize absorption (if recent oral exposure).
  - Symptomatic therapy (diuretics).
Acetylcysteine: loading dose 140 mg/kg IV followed by 70 mg/kg IV QID

- Chronic selenosis.
  - Dilute diet with feed low in selenium.
  - Increase protein content of ration (SH groups).
  - Increase linseed meal content of ration.
  - Adding organic arsenic to diet to increase biliary excretion has been suggested for poultry, cattle, and pigs; although such an approach has not been recommended for horses.
  - Pretreatment with copper can be protective against selenium toxicity.

Horizontal hoof-wall cracks characteristic of chronic selenium poisoning (alkali disease).

Approximate geographic distribution of seleniferous soils in North America (shaded areas) based on plant selenium levels in excess of 0.1 ppm. Marginal seleniferous soils are indicated by light shading.
Molybdenum Toxicosis - Copper Deficiency
(Supplements Clinical and Diagnostic Veterinary Toxicology; see also Copper Toxicosis section of these notes)

Sources
- Molybdenum toxicosis is most often seen in ruminant animals.
- Usually a concomitant copper deficiency is also present.
- The molybdenum concentration of forage can be unusually high when:
  - There is a naturally high content of Mo in the soil (e.g., Florida, Oregon, Nevada and California).
  - Molybdenum is added to fertilizers to increase nitrogen fixation in legumes.
  - Industrial contamination of pastures occurs in the vicinity of mining or metal alloy production plants.

Toxicity
- Cattle are more susceptible than sheep and young animals are more susceptible than old.
- Problem in cattle when the dietary Cu:Mo ratio is less than 2:1.
- Problem in sheep when the dietary Cu:Mo ratio is less than 1.1 - 4.1:1.
- High dietary sulfate concentrations exacerbate the condition.

Mechanism of Action
- Debatable or controversial: Mo forms an \textit{in vivo} complex with dependent copper.
- May actually just be a depletion of copper enzymes such as:
  - Ceruloplasmin (Fe absorption, mobilization and utilization).
  - Lysyl oxidase - amine oxidase (elastin of vessels and polypeptide chains in bone collagen).
  - Tyrosinase (melanin production).
  - Cytochrome C oxidase (energy for phospholipid synthesis in myelin).
  - Dopamine-ß-hydroxylase.

Signs and Lesions
- Typical bovine syndrome.
  - Morbidity may approach 80%.
  - Onset 8 - 10 days after being put on a pasture high in molybdenum.
  - Clinical signs.
    - Diarrhea with gas bubbles.
    - Emaciation.
    - Decreased milk production.
    - Decreased fertility and libido.
    - Lameness.
    - Anemia (microcytic, hypochromic).
    - Achromotrichia.
  - Chronically - Bone fractures.

Lesions
- Osteoporosis, bone fractures.
- Sheep syndrome.
  - Enzootic ataxia (reported in Australia).
  - Ewes - Stringy depigmented dark wool with loss of crimp, anemia.
  - Lambs - Ataxia, blindness.

Treatment
Copper supplementation either as Cu SO₄ in feed or as copper glycinate injections. Be especially careful when supplementing copper intake in sheep (see section on copper toxicosis).
2. Other Organic Compounds that Affect the Skin

**Polychlorinated Dibenzodioxins, Highly Chlorinated Naphthalenes and Related Halogenated Aromatics**

<table>
<thead>
<tr>
<th>Specific Agents</th>
<th>Major Species</th>
<th>Usual Time of Onset</th>
<th>Usual Duration (if survives)</th>
<th>Full Table for Toxicants that Cause Skin Effects other than Photosensitization</th>
</tr>
</thead>
<tbody>
<tr>
<td>Highly Chlorinated Naphthalenes</td>
<td>All species</td>
<td>Chronic</td>
<td>Chronic, potentially lethal, toxicoses rare in domestic species</td>
<td></td>
</tr>
<tr>
<td>Related Halogenated Aromatics</td>
<td>All species</td>
<td>Chronic</td>
<td>Chronic, often lethal, toxicoses rare in domestic species</td>
<td></td>
</tr>
</tbody>
</table>

**Dioxins** - The term dioxin is commonly used to denote compounds that are actually polychlorinated dibenzodioxins and, much less often, other polyhalogenated dibenzodioxins).

**Dibenzofurans** - The term dibenzofuran is used to denote polychlorinated dibenzofurans and other polyhalogenated dibenzofurans).

**Azoxybenzenes.**

**Azobenzenes.**

**Highly Chlorinated Naphthalenes.**

**Sources**

- Dioxin and dibenzofuran contaminants are often in waste oils from chlorophenol plants, for example, from the manufacture of:
  - Trichlorophenol.
  - Pentachlorophenol.
  - Hexachlorophene.
- **Note** - In 1974, 200 x 10^6 lb of chlorophenols were produced by the chemical industry.
  - Contaminants in a deliberately produced chlorophenol generally include other chlorophenols, chlorobenzenes, and chloronitrobenzenes. For example, contaminants of pentachlorophenol include hexachlorobenzene, octachlorodibenzo-dioxin, and hexachlorodibenzodioxin.
  - Contaminants may also be present in chlorophenol-derived products and related compounds; such as 2,3,7,8-tetrachlorodibenzo-dioxin (TCDD) in the herbicide, 2,4,5-T (part of Agent Orange). Potential dioxin contaminants may also occur in the organophosphorus insecticide ronnel and the benzoic acid herbicide dicamba.
  - Environmental pollutants may be released as a result of accidents at chlorophenol plants. For example, a spontaneous exothermic reaction producing dioxins can be initiated when system pressure and heat are excessive.
  - Combustion - Low level contamination.
  - Leather processing wastes and leather meal used in swine and other feeds may contain toxic amounts of hexachlorodibenzo-dioxins from pentachlorophenol.
- Highly chlorinated naphthalenes.
  - Lubricating oils, greases, insulating materials, wood preservatives (old products - no longer added to oils and greases).
- These and other environmental contaminants are potentially present in hazardous waste dumps, and have been spread about by disreputable waste haulers.

**Toxicity**

- By far, the most toxic of these compounds is 2,3,7,8-tetrachlorodibenzo-dioxin (2,3,7,8-TCDD). This compound has never been produced on purpose but has accidentally been produced as a true contaminant in the manufacture of trichlorophenol and the herbicide, 2,4,5-T. This herbicidal compound was half of the formulation used in Agent Orange which was applied in Southeast Asia during the Vietnam War.
The single oral dose LD$_{50}$s for 2,3,7,8-TCDD are:
- Guinea pigs - 0.6 µg/kg.
- Monkeys - 50 - 70 µg/kg.
- Mice - 284 µg/kg.

Because of the extreme sensitivity of mammals and birds to this compound, samples must be analyzed by methods with a sensitivity for TCDD in the area of 0.01 ppb. The 2,3,7,8-TCDD isomer is 3 - 100 times as toxic as other TCDDs. Other dioxins vary widely in toxicity, therefore specific identification of particular dioxins is essential. Unfortunately this process is extremely expensive, and few laboratories have the necessary equipment and/or expertise to perform these procedures.

TCDDs can cause immunosuppression with exposure at levels too low to produce clinical or pathological changes. The principle effects are on T-cells. B-cells and, therefore, humoral immunity are not greatly affected.

**Mechanism of Action**

- It is believed that the compounds bind to a cytosolic enzyme, which is transferred into the nucleus and thereafter triggers gene expression, causing induction of mixed function oxidase enzymes and "other toxic effects." The affinity for the binding of the cytosol proteins and the tendency to induce mixed function oxidase enzymes tends to parallel the acute toxicity of the different compounds.
- Interference with heme metabolism and build-up of porphyrins have been associated with some of the dermal lesions observed.
- See the following handout on PCBs and PBBs (Mechanism of Action section).

**Signs and Lesions**

- Laboratory animals.
  - Chronic weight loss.
  - Skin lesions (often hyperkeratosis).
  - Liver damage.
  - Mutagenesis.
  - Carcinogenesis (primarily liver and oral tumors).
  - Teratogenesis.
    - Cystic kidneys and cleft palate in mice.
    - Absence of eyelids in hamsters
  - Fetotoxicity.
    - Gastrointestinal hemorrhage in rats.
    - Overgrowth of renal papillae.
    - Thymic atrophy.
    - Fatty liver.
    - Generalized edema.
    - Low birth weight.
    - Fetal resorption.
    - Embryolethality.
    - Death.
  - Mice - Behavioral effects.
    - Hyperirritability, aggressiveness, restlessness.
- Cats and dogs.
  - Chronic weight loss.
  - Chronic respiratory infections.
  - Oral and nasal lesions.
  - Hair loss.
  - Centrilobular hepatic degeneration.
  - Renal tubular degeneration.
- Cattle.
  - Weight loss and emaciation.
  - Splenic atrophy.
  - May eat normally but feed conversion extremely poor.
  - Drop in milk production.
  - Hydropic degeneration in kidney.
  - Hypertrophy of all squamous epithelia, including the skin.
- Horses (in contact with heavily contaminated soil).
  - Chronic anorexia.
  - Listlessness.
  - Rapid loss of weight, emaciation with serous atrophy of fat.
- Weakness and unsteady gait.
- Subcutaneous edema.
- Hair loss, especially of the mane and tail; hair may fall out in clumps.
- Skin and oral ulcerations and fissures, resulting in alligator-like skin.
- Lymphoid atrophy.
- Conjunctivitis.
- Polydipsia.
- Colic.
- Severe laminitis, with inflammation of the sole and frog.
- Liver enlargement up to 3 times normal size.
- Hepatic portal cirrhosis, biliary proliferation, fibrosis around central vein.
- Hypogammaglobulinemia.
- Ascites.
- Icterus.
- Diarrhea, tarry feces.
- Hematuria.
- Some mares develop thick "stallion-like" necks.
- Failure to conceive.
- Abortion, usually with the fetus presented dead.
- Death in foals.
- Gastric ulcers.
- Pulmonary hemorrhage, edema and bronchopneumonia.
- Death in adults.
- Chickens and turkeys.
  - Hydropericardium.
  - Edema.
  - Ascites.
  - Endothelial proliferation.
- Monkeys.
  - Severe weight loss.
  - Blepharitis, periorbital edema.
  - Loss of fingernails and eyelashes.
  - Facial alopecia.
  - Acneform eruptions.
  - Mild anemia.
  - Thrombocytopenia.
  - Lymphopenia, lymphoid atrophy, especially thymic atrophy.
  - Increased relative weights of liver, kidney and adrenal.
  - Ascites.
  - Gangrenous necrosis of the phalanges.
  - Irregular estrous cycles, decreased fertility.
  - Embryotoxicity.
  - Abortion and stillbirth.
- Humans (accidentally exposed workers).
  - Chloracne.
  - Liver damage.
  - Polyneuropathy especially affecting the legs; decreased conduction velocity confirmed on EMG; but with no lesion.
  - Weakness and pain in legs.
  - Somnolence or insomnia.
  - Psychiatric disorders.
  - Sexual dysfunction.
Polychlorinated Biphenyls (PCBs) and Polybrominated Biphenyls (PBBs)

### Sources

- **PCBs.**
  - Transformers, other electrical insulators (especially fluids), building materials, old lubricants.
- **PBBs.**
  - Fire retardant was accidentally mixed in feeds in Michigan.
- Polychlorinated biphenyls (PCBs) are organic compounds which are widely distributed in the environment. Polybrominated biphenyls (PBBs) are similar compounds which are less widespread, but still constitute a chemical hazard.
- Commercially, PCBs and PBBs consist of mixtures of several major and many minor components, the major ones being biphenyl compounds with varying degrees of chlorination or bromination, in some 210 possible halogenation patterns.
- The minor components are contaminants such as brominated naphthalenes and halogenated dibenzofurans or dibenzodioxins.
- In the past, massive quantities of PCBs and PBBs were widely used in industry without much concern over their potential toxic effects.
- These organic compounds are highly stable, nonflammable, lowly volatile, resistant to acids and bases, insoluble in water, and have a high dielectric constant. These characteristics make them useful in heat exchangers and dielectric fluids, hydraulic and lubricating fluids, plasticizers, printing inks, paints, adhesives, duplicating paper, flame retardants, and extenders for pesticides.
- Over 500,000 tons of PCBs were produced in the USA since 1929 and marketed under the trade name Aroclor. Foreign trade names include Clophen, Phenoclor, and Kaneclor.
- Although, the production of PCBs and PBBs was halted prior to 1979, after the potential toxicity of polyhalogenated biphenyls was realized, many PCB and PBB containing products are still in use.
- It is estimated that over 400,000 tons of PCBs have been lost to the environment since 1932.
- Most of these compounds are highly lipophilic, largely resistant to microbial breakdown and biotransformation, and only slightly photodegradable; characteristics which have resulted in intensive bioaccumulation. Persistence depends on the degree and pattern of halogenation. They persist in food chains, aquatic sediments, landfills, and other biological and physical reservoirs. Fish and fish-eating wildlife are the primary biological magnifiers.
- Contaminated feedstuffs are responsible for most exposures of domestic animals. This contamination is often a result of: utilizing fishmeal or recycled animal or paper products in the feed; leakage of lubricants from processing machinery; dissolution of compounds from paints and sealants on silos, water and feed troughs, or storage tanks; availability of insulation or flaking paint in degenerated animal housing; and occasionally from an accidental mixing of PCBs or PBBs in feed or other products offered to livestock. In 1973, the accidental mixing of PBBs instead of magnesium oxide into Michigan livestock feeds resulted in the contamination and destruction of nearly 30,000 cattle, 5,920 hogs, 1,470 sheep, 1.5 million chickens, and massive quantities of animal feed, eggs, and dairy products.

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

- Cattle have been shown to excrete up to 76 ppb PCBs in their milk when fed PCB containing paper products as 30% of their diet.
- Several studies have reported transmission *in utero* or through the milk to feti or nursing offspring of contaminated dams. The fetal fat of cows fed PCBs at 200 mg/day contained 130.6 ppm PCBs as opposed to 0.65 ppm in that of control cows.
- In addition, PCBs were still detected in high amounts 6 months after cessation of the test feed.
- Dermal application of PCBs also results in extremely rapid absorption.
Species differences exist with regard to relative susceptibility to PCBs and PBBs.

Among domestic animals, the ranch mink appears to be the most susceptible with a dietary level of only 1 ppm PCB causing decreased litter size and viability of offspring.

Swine appear to be somewhat tolerant clinically, but high doses elicit effects.

All species of animals, whether clinically affected or not, can accumulate PCBs and PBBs in their tissues.

**Mechanism of Action**

- The mechanism of action of even the most studied components of PCB and PBB mixtures are not completely understood.
- In mammals, birds, and fish, most halogenated biphenyls are inducers of hepatic mixed-function oxidases, but the potencies and specificities vary widely. Generally, PBBs appear more potent than comparable PCBs in inducing these enzymes. In contrast, some congeners depress P450 activity.
- Toxicity of PCBs and dioxins depends on the chlorination pattern.
- PCBs with chlorines to the outside (flat = coplanar molecules which are therefore similar to 2,3,7,8,-TCDD) bind to the arylhydrocarbon hydroxylase receptor and are translocated into the nucleus where they initiate transcription of a number of proteins - including some P450 enzymes (e.g., "arylhydrocarbon hydroxylase" = Ah) → liver enlarges. Generally, these are also result in chronic weight loss, skin damage (chloracne in people, scaly, scabby lesions in animals), birth defects (crossed bills in birds), and anti-estrogenicity (altered sexuality, sexual function; low milk production).
- PCBs and dioxins with chlorines to the inside (large chlorines interfere with one another causing the molecule to twist the two rings are no longer flat via the same plane, therefore = noncoplanar) tend to be associated with antithyroid, antidopaminergic, and/or estrogenic effects. Their acute toxicity is generally lower than with the coplanar molecules. However, their chronic effects may be significant (some think that they may contribute to decrements in intelligence in children via effects on thyroid during development - partial cretinism - and inhibition of dopamine synthesis/concentrations in the brain).
- Higher doses of the lower halogenated compounds may induce hepatic dysfunction with subsequent abnormalities in heme synthesis that result in accumulation of large quantities of dermatitis-inducing porphyrin.
- Some of these compounds are also known to be acnegenic, and capable of producing hyperkeratosis and hyperpigmentation of the skin in various species.
- Some studies have shown the metabolism of endogenous substances such as steroids and estradiols to be enhanced in liver and skin, but inhibited in the adrenals. A variety of reproductive effects have been seen in numerous species.
- Effects on the immune system are unclear. PCBs have been shown to potentiate duck hepatitis virus in ducklings, induce septicemia in sows, increase disease susceptibility in fish, and reduce the response of guinea pigs to tetanus toxoid. Gestating sows fed PBBs at 200 ppm of the diet showed a decreased lymphocytic response to mitogen stimulation, however, bacteriocidal activity was not consistently altered. In one study, however, lactating cows exhibited normal immune competence until tissue concentrations exceeded 1000 mg/kg at which time they became moribund.

**Clinical Signs**

- The toxic response to PCBs differs depending on species, age, sex, and dose with young animals and, oftentimes, females being more susceptible.
- Relatively high concentrations of PCBs or PBBs can accumulate in animal tissues without expression of acute effects or lesions. Nevertheless, chronic biochemical and physiologic changes occur with dietary exposure to feedstuffs containing less than 1 ppm.
- With low level feeding, the usual signs are depressed weight gain and anorexia. Intermittent exposure appears to be more detrimental than constant and/or gradually increasing exposure. In addition, a dose of PCBs administered over time produces more severe effects than the same dose administered acutely.
- Growing swine fed 20 ppm PCBs for 13 weeks showed a slight decrease in weight gain and feed efficiency as compared to controls. In a similar study, a smaller total dose administered within a shorter time (100 ppm for 1 week) resulted in similar but more intense effects during the following 16 weeks. Another feeder pig diet containing PBBs at 200 ppm caused decreases in average daily gain and feed intake to about one-half of control values.
- Depression, septicemia, mummification of feti, and an increase in stillbirths may also occur in swine. Sows fed 20 ppm PCB during gestation and nursing, farrowed and weaned about half as many pigs as control sows.
- In cattle, acute signs of toxicosis do not appear until dietary concentrations approach 5,000 ppm.
- Clinical signs include decreased milk production, anorexia, lacrimation, salivation, dehydration, diarrhea, alopecia, hyperkeratosis, weight loss and terminal recumbency.
- Many of these, especially hyperkeratosis, are also observed in animals suffering from "X disease" which affects cattle, sheep, and swine. This is now known to be caused by highly chlorinated naphthalenes which are frequent contaminants of PCBs.
- Heifers fed 25 g of PBBs per day were anorexic within 4 days and moribund within 33-66 days. With low level exposure, sub-clinical effects may be interpreted as "poor-doers", poor management, and/or nutritional imbalances. However, in some instances of suspected PCB or PBB exposure, gross management or nutritional problems have been ignored. This often presents a diagnostic dilemma for the clinician.
Lesions

- Necropsy findings in swine and primates characteristically include gastric irritation and hyperemia. With higher exposures, mucosal hyperplasia and ulceration of the stomach may be present.
- Reproductive effects in cattle include abortions, embryonal resorption, and decreased fertility. Prepartum exposure to PBBs significantly increases fetal birth weight and the subsequent incidence of dystocia. Cows fed 250 mg per day for 180 or 202 days had a 100% incidence of dystocia. In addition, offspring exposed to PBBs in utero had significant conception difficulties at puberty.
- Necropsy findings in cattle may include dehydration, marked emaciation, fetal death with cotyledonary necrosis and hemorrhage, greatly enlarged pale kidneys, and dermal hyperkeratosis.
- Occasional findings include mucosal edema and ulcerations of the gastrointestinal tract, especially the abomasum, a thickened gall bladder wall, and thymic atrophy.
- Gross lesions are rarely present at dietary concentrations below 5000 ppm, so that necropsy may fail to indicate actual PCB or PBB poisoning. However, varying amounts of liver hypertrophy occur with either low level chronic exposure or high level acute exposure. The enlargement is not usually severe and is characterized histologically by scattered areas of glycogen depletion, dilatation of sinusoids, fatty degeneration, and very rarely, at higher exposures, centrilobular necrosis.

Effects in Birds

- In birds, PCBs and PBBs initiate clinical signs and lesions somewhat different than those of mammals. "Chick Edema" is now known to be caused by PCBs and their chlorinated naphthalene and dibenzodioxin contaminants. Primary signs and lesions include decreased body weight, anorexia, ascites, subcutaneous edema, dermatitis, hydropericardium, enlarged kidneys, centrilobular hepatic necrosis, splenic atrophy, and occasional enteritis with intestinal hemorrhage. A toxic plant (Crotalaria) may cause similar lesions.
- A diet containing 10 - 20 ppm PCBs or PBBs may cause adverse reproductive effects including decreased comb weight in cockerels, decreased fertility and egg production in hens, teratogenesis, reduced hatchability of eggs, and reduced chick viability.
- PCBs have been associated with abnormal sea gull wing development.

Diagnosis

Diagnosis is aimed at detecting PCBs or PBBs in milk fat, body fat, fresh liver samples, feed or other suspected sources. Specimens of milk should be collected in clean (acetone rinsed) glass jars with caps lined with aluminum foil. Tissues may be shipped frozen in (acetone rinsed) aluminum foil. Analysis is usually by gas chromatography with electron capture detection.

Treatment and Control

- There is no specific treatment for PCB or PBB toxicosis. Various agents such as activated charcoal, phenobarbital, vitamin A, vitamin D, and vitamin E, and thyroprotein have been administered without significantly affecting the rate of elimination from the body fat.
- In guinea pigs, ascorbic acid had some therapeutic potential based on its inducement of mixed function oxidases.
- The major goal in control is to discover and eliminate the source of contamination.
- The residue level must be determined in order to calculate the estimated clearance time, and thereby decide whether to decontaminate or destroy the animal.
- In lactating animals, the major route of excretion of these compounds is in the milk fat with a minor fecal component. Three factors affect the resultant half life: 1) total body fat, 2) rate and direction of change in the amount of body fat, and 3) milk fat production.
- Weight loss, parturition, lactation, or other metabolic changes mobilize fat stores and therefore increase the rate of metabolism and excretion of PBBs or PCBs.
- When these compounds are fed, residues tend to reach a steady state within 60 days. Once exposure ceases, there is an initial rapid drop in body fat residues, then a much slower decline.
- The estimated half-lives for PCBs and PBBs for the initial phase are 5.7 and 10.5 days. For the slow phase, the PCB and PBB half-lives are 68 and 60 days (range 33 - 110 days), respectively. After consumption is terminated, there is a nearly constant ratio between milk fat and body fat residues of approximately 0.42:1. The estimated half-life of transmission in eggs is 17 - 28 days.
- These relationships are not valid if exposure is still occurring or during rapid changes in body composition. Furthermore, animals massively exposed and now on a "clean" feed may be continually exposed to a lesser degree from a contaminated environment.
- The long-term residue problems and potential for permanent effects often makes treatment in livestock uneconomical.

Zoonotic Risk

- There is definite evidence of toxicosis in humans chronically exposed to PCBs and PBBs. Some reports have revealed some evidence of carcinogenicity in lab animals. It appears that PCBs are only weak initiators of carcinogenesis but are potent promoters of hepatic carcinomas. Effects in vivo often differ from those in vitro, with the latter suggesting a greater risk. Epidemiologic studies have not revealed clear evidence for carcinogenicity of PCBs in field exposure situations. Because of this, the USDA has developed tolerances for PCBs and actionable levels for PBBs in animal products and feeds (see Table).
To prevent residues in livestock or their products it is estimated the total dietary concentration of PCBs or PBBs should be less than 10% of any regulatory guidelines.

---

**Turpentine**

**Synonyms** - Gum spirits, spirits of turpentine, oil of turpentine

**Uses**

- Used as a treatment for bloat.
- It is a constituent of stimulating ointments.
- Industrially:
  - Insecticide.
  - Solvent for waxes, production of synthetic camphor.
  - In shoe, stove and furniture polish.
  - As a diluent for oil paints and to clean brushes.

**Toxicity**

- Adult (Human) - 140 ml orally may be fatal.
- Pediatrics (Human) - 15 ml turpentine-benzene mixture orally was fatal, but 2 - 3 ounces of turpentine have been ingested with survival.
- Turpentine is readily absorbed through the skin, gastrointestinal tract, and lungs.

**Signs and Lesions**

- General.
  - Depression.
  - Lethargy.
  - Nausea.
- Topical.
  - Can produce a severe rubefacient effect.
  - Warmth, redness of the skin.
  - Vocalization consistent with intense pain.
  - Vesicular eruption.
  - Urticaria.
- Ingested.
  - Burning abdominal pain.
  - Excitement, delirium, ataxia.
  - Convulsions, coma.
  - May cause nephritis.
- Inhaled (high concentration).

---

<table>
<thead>
<tr>
<th>Tolerance/Action Levels</th>
<th>PCB Tolerance Levels</th>
<th>PBB Actionable Levels</th>
</tr>
</thead>
<tbody>
<tr>
<td>Animal feeds</td>
<td>0.2 ppm</td>
<td>0.05 ppm</td>
</tr>
<tr>
<td>Milk (fat)</td>
<td>1.5 ppm</td>
<td>0.30 ppm</td>
</tr>
<tr>
<td>Red meat (fat)</td>
<td>3.0 ppm</td>
<td>0.30 ppm</td>
</tr>
<tr>
<td>Eggs</td>
<td>0.3 ppm</td>
<td>0.05 ppm</td>
</tr>
</tbody>
</table>
o Hyperpnea.
o Tachycardia.
o Convulsions.
o May cause nephritis.

**Treatment**

- Emesis is probably contraindicated.
- Activated charcoal and saline cathartic.
- Control seizures with diazepam (in appropriate species), or if it fails, give phenobarbital IV, if seizures still cannot be controlled induce anesthesia with pentobarbital.
- Dermal.
  - Rinse skin with copious amounts of water and wash with a mild liquid dish detergent.
  - If necessary, medicate skin to control drying, cracking, secondary self trauma, and infection.

**Additional Toxicants**

<table>
<thead>
<tr>
<th>Specific Agents</th>
<th>Major Species</th>
<th>Usual Time of Onset</th>
<th>Usual Duration (if survives)</th>
</tr>
</thead>
<tbody>
<tr>
<td>DIESEL FUEL</td>
<td>All species</td>
<td>Minutes to hours</td>
<td>Hours to days, rarely lethal</td>
</tr>
<tr>
<td>(Petroleum hydrocarbons)</td>
<td>(Petroleum hydrocarbons)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>KEROSENE</td>
<td>All species</td>
<td>Minutes to hours</td>
<td>Hours to days, rarely lethal</td>
</tr>
<tr>
<td>(Petroleum hydrocarbons)</td>
<td>(Petroleum hydrocarbons)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>OTHER SOLVENTS</td>
<td>All species</td>
<td>Minutes to hours</td>
<td>Hours to days, rarely lethal</td>
</tr>
<tr>
<td>FORMALDEHYDE AND FORMALIN</td>
<td>All species</td>
<td>Minutes to hours</td>
<td>Hours to days, rarely lethal with skin only exposure, toxicoses rare</td>
</tr>
<tr>
<td>PHENOLIC</td>
<td>All species</td>
<td>Minutes to hours</td>
<td></td>
</tr>
<tr>
<td>EFFUXED</td>
<td>All species</td>
<td>Minutes to hours</td>
<td></td>
</tr>
<tr>
<td>5-FLUOROURACIL (Effudex®)</td>
<td>All species</td>
<td>Minutes to hours</td>
<td></td>
</tr>
<tr>
<td>(See Toxicants that Affect the Liver)</td>
<td>(See Toxicants that Affect the Liver)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

* Diesel fuel (See Organic Compounds that Affect the Lungs)
* Kerosene (See Organic Compounds that Affect the Lungs)
* Other Solvents (See Organic Compounds that Affect the Lungs)
* Phenolics (See Toxicants that Affect the Liver)
* Formaldehyde and Formalin
3. Other Plants that Affect the Skin (Integument)

**Vicia villosa - Hairy Vetch**

<table>
<thead>
<tr>
<th>Major Species</th>
<th>Usual Time of Onset</th>
<th>Usual Duration (if survives)</th>
<th>Full Table for Toxicants that Cause Skin Effects other than Photosensitization</th>
</tr>
</thead>
<tbody>
<tr>
<td>Herbivores</td>
<td>Chronic</td>
<td>Months; often lethal</td>
<td></td>
</tr>
</tbody>
</table>

**Images**


**Habitat**

Hairy vetch (Roth Vetch, Winter Vetch), *Vicia villosa*, is a pasture plant that is high in protein and deliberately sowed in some areas. Has been reported to be a problem in Oklahoma, grows in Midwest also.

**Toxic Principles**

- In some types of vetch seed, cyanide is a potential problem.
- Hepatotoxins occur in others.
- The agent causing dermal lesions has not yet been characterized.

**Signs**

- Two primary syndromes occur in the bovine animal.
  - Delirium and rapid death syndrome.
  - Dermal, gastrointestinal syndrome.
    - Dermatitis.
    - Conjunctivitis.
    - Anorexia.
    - Weight loss.
    - Increased temperature.
    - Diarrhea, often bloody.
- The dermatitis associated with hairy vetch is associated with pruritus. Lesions begin with alopecia of the udder, tailhead, neck and later affect the face, trunk and the limbs. It is notable that black animals are most affected and especially those over 3 years of age.
- The onset is after 2 - 3 weeks of grazing and a low morbidity of approximately 6 - 8% is seen. In animals affected, however, the mortality may be high, up to 50% in some cases. Death occurs 10 - 14 days after the onset in most cases.
- The syndrome occurs especially in the late spring when the plant is growing maximally, and less often late in the season, although toxicosis may also occur from consumption of vetch in hay.
- The dermal, gastrointestinal (granulomatous) syndrome has also been recognized in horses.

**Lesions**

- In addition to dermatitis in the skin, lesions seen histologically may include macrophage, lymphocyte and plasma cell as well as giant cell and eosinophil infiltration into the heart, adrenal gland, kidney, thyroid, brain, and lungs.
- Grossly these areas of infiltration may be identifiable as gray or gray-yellow foci or streaks in the above mentioned tissues. Lymph nodes may be normal in size to markedly enlarged.
Winter Vetch (*Vicia villosa Roth*)

**Family** - Pea (Leguminosae)

**Growth Form** - Annual herbs.

**Stems** - Stems spreading to ascending, hairy, up to 2 feet long.

**Leaves** - Alternate, divided into 16 - 24 leaflets, the leaflets usually narrowly oblong, pointed at the tip, tapering or rounded at the base, without teeth, smooth, up to 3/4 inch long.

**Flower Arrangement** - Flowers several, in 1-sided axillary racemes, the racemes up to 4 inches long.

**Flowers** - Violet and white, up to 1/2 inch long, borne on very short stalks.

**Sepals** - 5, green, hairy, united below.

**Petals** - 5, violet and white, arranged to form a pea-shaped flower.

**Stamens** - 10.

**Pistils** - Ovary superior.

**Fruits** - Pod oblong, up to 1 1/4 inches long, smooth or nearly so.

**Habitat** - Fields and along roads.

**Range** - Throughout the state.

**Time of Flowering** - June to August.

**Associated Plants** - Hairy chess (*Bromus tectorum*), horseweed (*Erigeron canadensis*), white sweet clover (*Melilotus alba*), and common evening primrose (*Oenothera biennis*).

**Images**

*Vicia* spp. Source: Cornell University, Poisonous Plants Informational Database (www.ansci.cornell.edu/plants/index.html). - To view this image in full size go to the IVIS website at www.ivis.org . -

Winter vetch, *Vicia villosa Roth* - Google Image Search. - To view this image in full size go to the IVIS website at www.ivis.org . -

**Hippomane Mancinella - Manchineel Tree**

<table>
<thead>
<tr>
<th>Major Species</th>
<th>Usual Time of Onset</th>
<th>Usual Duration (if survives)</th>
<th>Full Table for Toxicants that Cause Skin Effects other than Photosensitization</th>
</tr>
</thead>
<tbody>
<tr>
<td>Most species</td>
<td>Minutes to hours</td>
<td>Days, rarely lethal</td>
<td></td>
</tr>
</tbody>
</table>

**Images**

Manchineel Tree, *Hippomane mancinella* - Google Image Search. - To view this image in full size go to the IVIS website at www.ivis.org . -

**Description**

The manchineel tree (*Hippomane mancinella*) is 10 - 20 feet tall with a small trunk up to 6 inches in diameter.

**Habitat**

In the USA, the tree is restricted to Florida, south of Palm Beach and Fort Meyers. The tree is now primarily found in the Everglades.

**Toxic Principle**

- One reason for the restricted range of this tree is that the early settlers destroyed the tree wherever they found it, because of its extremely caustic resin.
- The fruit, which is not bad tasting, is also toxic.
Signs

- Plant (resin) contact effects:
  - Severe skin or eye irritation.
- Fruit ingestion, effects:
  - Vomition.
  - Abdominal pain.
  - Bloody feces.
  - Occasional deaths.

Manchineel tree (*Hippomane mancinella*)

References

**Thallium**


**Vicia Villosa - Hairy Vetch**


All rights reserved. This document is available on-line at www.ivis.org. Document No. A2632.0899.