Iron

Iron toxicosis usually results when too much iron is injected or less often when too much is given orally. Any of the iron complexes and iron salts may be involved. Baby pigs are most often involved, however, all species are potentially susceptible.

Sources

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<table>
<thead>
<tr>
<th>Major Species</th>
<th>Usual Time of Onset</th>
<th>Usual Duration (if survives)</th>
<th>Full Table for Hepatotoxic Chemicals and Drugs</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dogs, piglets, other species</td>
<td>Minutes to chronic</td>
<td>Hours to permanent damage; acute death most common in piglets</td>
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</tr>
</tbody>
</table>

Iron From

<table>
<thead>
<tr>
<th>Iron From</th>
<th>Percent (%) Elemental Iron</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ferric phosphate</td>
<td>37</td>
</tr>
<tr>
<td>Ferric pyrophosphate</td>
<td>12</td>
</tr>
<tr>
<td>Ferrocholine</td>
<td>12</td>
</tr>
<tr>
<td>Ferrous gluconate</td>
<td>12</td>
</tr>
<tr>
<td>Ferrous fumarate</td>
<td>33</td>
</tr>
<tr>
<td>Ferrous sulfate (hydrate)</td>
<td>20</td>
</tr>
<tr>
<td>Ferrous sulfate (dried)</td>
<td>37</td>
</tr>
<tr>
<td>Ferrous carbonate (anhydrous)</td>
<td>48</td>
</tr>
<tr>
<td>Ferroglycine sulfate</td>
<td>16</td>
</tr>
<tr>
<td>Peptonized iron</td>
<td>17</td>
</tr>
</tbody>
</table>

Toxicity

- Ingestion of 20 to 40 mg elemental iron/kg may result in toxicosis.
- Ingestion of > 60 mg elemental iron/kg is potentially serious.
- Oral doses of iron of > 200 to 300 mg/kg is a roughly estimated lethal dose.

Mechanisms of Action

- Enhances free radical damage by superoxide radical.
- Presumably interferes with sulphydryl groups of enzymes and other proteins.
- Direct (caustic) irritant effect on gastrointestinal tract.
- Enters the mitochondria where it acts as a mitochondrial poison, interfering with cellular respiration and resulting in metabolic
Two main syndromes are involved:

- A peracute syndrome comprised of an anaphylactoid reaction. Sudden death occurs within a few minutes to hours after an iron injection.
- Death accompanied by severe depression and coma after a subacute syndrome.

Predisposing factors include:

- There is no effective mechanism for excretion of iron. Therefore, animals with enough iron on board are more susceptible than those actually needing iron.
- Pigs born to vitamin-E-selenium deficient sows are more susceptible to iron toxicosis.
- Gastrointestinal absorption of iron is controlled; however, massive doses break down the mechanism controlling absorption and toxicosis results.

Absorption, Distribution, Metabolism and Excretion (ADME)

- Approximately 10% of dietary iron is absorbed in the ferrous (Fe⁺²) form. In gastric and intestinal mucosal cells, iron is metabolized to the ferric state and is then transported across the cell membrane into the blood where it is bound to a β-glycoprotein (transferrin) transport protein. Transferrin is normally 25 to 30% saturated in most species.
- In an acute iron overdose, the transferrin can become saturated, allowing total serum iron to exceed iron-binding capacity, increasing free circulatory iron.
- Absorption is enhanced in the presence of ascorbic acid.
- Peak absorption may occur between 1 and 6 hours after ingestion. Sustained release or enteric coated medications tend to have erratic pharmacokinetic behavior.

Chronic Syndrome

Elevated iron in the diet may also cause stunting and rickets. This is a result of precipitation of phosphates in the gut as a complex with iron and has occurred at a dietary Fe concentration of 5,000 ppm.
Signs

- The peracute syndrome mimics an anaphylactic shock reaction and is primarily a vascular collapse followed by rapid death.
- In the subacute form the animal may be drowsy, may exhibit vomiting and diarrhea, both of which may be bloody, and these signs may be followed by a period of apparent improvement. Thereafter cardiovascular collapse and death occur.
- In small animals, early signs from the corrosive effect on the gut with vomiting and diarrhea develop in 0 to 6 hours postingestion. Apparent recovery may occur 6 to 24 hours postingestion followed by shock, CNS depression, GI hemorrhage, acidosis, and liver failure.
- Oliguria, anuria. Secondary to shock-induced acute renal failure.

Lesions

Lesions include a yellowish-brown discoloration and edema of the tissues, especially near the injection site. The nearby lymph nodes, and the liver and kidneys may all be dark in color. There is often edema at the injection site and subcutaneously in the injected limb. Liver damage may be apparent and histologically is characterized as periportal necrosis. After oral overdose, there may be gastric ulceration and edema.

Diagnosis

- Excessive exposure and signs and lesions are all that may be seen in the field. Iron toxicosis may occasionally occur when animals have received the recommended dose, especially if they have no deficiency to start with.
- Serum iron concentrations that correlate with the development of toxicosis (in man), e.g., human patients with serum iron concentration of > 500 µg/dl (5 ppm) are considered to have serious toxicosis which requires chelation therapy. Note: serum samples drawn before 6 hours may reflect less than peak serum iron concentrations. Samples should be taken at 3, 6, 9, and 12 hours.
- Abdominal radiographs for the presence of metallic foreign bodies. Iron-containing vitamin, tablets may occasionally be apparent on abdominal radiographs.

Treatment

- Anaphylactoid reaction:
  - Antihistamines, epinephrine, oxygen, nursing care.
  - Pigs usually don't live long enough to be treated.
- Subacute:
  - Treatment is hindered by hepatic necrosis, hemorrhage and shock. Steps to enhance excretion of iron as detailed below may be worthwhile.
- Desferal ® (40 mg/kg, IM, q 4 to 8 hours), which is also known as the generic desferrioxamine or more often as deferoxamine is effective as a chelation agent to enhance the excretion of iron. One hundred mg of deferoxamine will bind approximately 9 mg of iron. Its highest affinity for iron in the ferric (+3) state. Ascorbic acid in large oral doses doubles or triples the iron excretion after deferoxamine. However, ascorbic acid should be used only after the gut is thoroughly cleared of iron sources. Deferoxamine must be given slowly in an IV drip (≤ 15 mg/kg/hour). When given rapidly, hypotension and shock may result. The use of deferoxamine has been documented in dogs. It is recommended when the total iron binding capacity of the serum has been exceeded. Thus, the drug is recommended when serum iron values in dogs greater than 350 µg/100 ml are present; or when serum iron cannot be determined in a timely fashion and toxic doses are involved.
  - Deferoxamine challenge doses have been recommended. Deferoxamine will chelate iron, and together this causes a "vin rose" (reddish-brown) appearance to the urine.
  - Chelation therapy (in human patients) is continued until loss of urine color occurs.
- Oral exposure:
  - Early, eggs, water, milk and emetic are indicated. Lavage with a phosphate solution may be sometimes worthwhile. In children, a 1 to 1.5% sodium bicarbonate solution can be used orally to form insoluble ferrous carbonate. Experimental studies in rats suggest that oral complexation is ineffective.
  - An alternative agent to diminish the absorption of iron is milk of magnesia. The milk of magnesia (MgOH) complexes with iron to form FeOH which precipitates and is therefore not as effectively absorbed. MgOH may be of limited value in dogs.
  - Any animal in shock from iron toxicosis should also receive IV fluids and bicarbonate (may not be needed for anaphylaxis) and other appropriate supportive measures.

Prognosis

Iron toxicosis usually carries a poor prognosis.

Ferrous Fumarate Toxicosis in Foals

- In a recent outbreak of unexplained deaths in neonate foals, with deaths occurring at 2 to 5 days of age, the following clinical signs and clinical pathological findings were documented:
  - Severe depression.
- Icterus.
- Increased plasma NH₃.
- Increased aromatic: branched chain amino acid ratio.
- Increased total bilirubin in the serum.
- Increased SGPT.
- Increased alkaline phosphatase.
- Increased PCV.
- Increased partial thromboplastin time.
- Increased prothrombin time.
- Death.

The cause was found to be excessive ferrous fumarate in a *Lactobacillus* preparation in a product named "Primapaste".

**Lesions**

Liver size was reduced to about 1/2 of normal. There was prominent bile duct proliferation which was sufficiently severe, that initially the impression was that the process had to have started *in utero*. Hepatocyte necrosis was accompanied by mild periportal fibrosis. In the brain, the presence of Alzheimer type II cells indicated the presence of hepatic encephalopathy.

**Phosphorus**

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<td>Dogs, other species</td>
<td>Hours to days</td>
<td>Days to permanent damage, often lethal</td>
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</tbody>
</table>

**Sources**

- White or yellow forms of phosphorus are toxic and red phosphorus is not. The white or yellow types are waxy, whereas the red type is granular, insoluble and not absorbed.
- Phosphorus is occasionally used as a rodenticide and may also be encountered in electrical pastes and in incendiary and smoke bombs, used in bombing practice and warfare. The rodenticide bait is usually comprised of phosphorus mixed with grease which prevents the rapid oxidation of the phosphorus and facilitates its absorption.
- Phosphorus poisoning may result from direct ingestion of the bait or electrical paste, or from ingestion of poisoned rodents. Dermal exposure may result in burns of serious consequence.
- Accidental or malicious.

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

Phosphorus is first absorbed from the gastrointestinal tract into the blood as phosphorus but is then oxidized to phosphate. Some of the phosphorus is eliminated by the lungs which may give the exhaled air an odor of phosphorus (garlic-like) and the exhaled air may glow in the dark. Similarly vomitus or gastrointestinal tract contents may also be luminous and have the same odor.

**Signs**

- The initial signs of phosphorus poisoning are referable to gastrointestinal irritation and the onset may be almost immediate or may be delayed up to several hours. There is severe abdominal pain, profuse vomiting and possibly hematemesis.
- Thereafter there is a period of apparent recovery of a few hours up to 4 days. Then the abdominal pain and vomiting recur, this time accompanied by jaundice. These signs may last several days and then be followed by delirium, convulsions in some animals, then coma and death. Alternatively the animal may make a recovery without any neurologic signs. Horses and poultry may exhibit a paralytic-like weakness without other definitive signs. The latter stages are attributable to profound liver and kidney failure which terminates in shock.
- Oliguria and anuria may occur.

**Clinical Pathology**

Clinical pathologic alterations antemortem may include hypoglycemia, hematuria, and proteinuria.
Lesions

Lesions include inflammation of the gastrointestinal tract, stomach, intestines and skin when dermal exposure has occurred. There is also fatty degeneration of the liver, muscles and endothelium of blood vessels with secondary extravasation of blood into the subcutaneous tissues, skin and muscle. There may also be hematoma formation. Jaundice is common.

Diagnosis

Diagnosis is based on history of exposure, clinical signs, odor and luminescence of the breath, vomitus, and stomach contents and lesions. Phosphorus content in the vomitus or intestinal tract may be determined. In animals surviving the first day, feces may be preferred over stomach contents (seal in a jar and freeze before transport to the laboratory maintaining a frozen state).

Treatment

- Treatment of dermal exposure is initiated by brushing all traces of dry phosphorus from the skin. The white or yellow phosphorus may then be removed from the skin by washing the skin with a copper sulfate solution. The skin is then repeatedly washed with large volumes of water. Oily substances are contraindicated due to the enhancement of absorption.
- For oral exposure, careful gastric lavage is preferred to emesis due to the corrosive action of phosphorus. Lavage with potassium permanganate has been recommended; however, there is no data to confirm the benefit of this treatment. Alternatively, lavage with 0.2% copper sulfate may be performed. As with dermal exposure oils are contraindicated due to facilitation of absorption; however, activated charcoal and saline cathartics are highly recommended.
- For hepatic and renal failure, cystine and a high carbohydrate diet which is low in protein are recommended. In addition, comparatively high doses of B-vitamins and ascorbic acid tend to lessen the severity of the liver failure. Fluids are indicated to increase the urinary output. Naturally, liver and kidney function tests are monitored early on for comparison to subsequent values.
- For hypotension, fluids are administered and if the animal is still unresponsive (with regard to perfusion), then dopamine is administered.
- Hypoprothrombinemia and hemorrhage is treated with vitamin K1 and, where needed, with whole blood or plasma transfusion(s).

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Carbon Tetrachloride

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<td>Hours to days</td>
<td>Days to permanent damage; often lethal but toxicoses are rare</td>
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Source

- Carbon tetrachloride has been used in the treatment of internal parasites especially in the removal of adult liver flukes from sheep.
- It is also an industrial solvent and used to be available for removal of stains from clothing, etc.
- By itself, CC14 is not as toxic to insects in grains as carbon disulfide (CS2) and other effective fumigants. However, until very recently when its use was banned, it was used alone and especially in combination (to reduce the fire hazard associated with fumigation) with either CS2 or ethylene dichloride. When grains are inadequately ventilated after treatment, the likelihood of toxicosis exists. Lower temperature increases the time necessary for adequate ventilation.
- Related anthelmintics may cause similar effects as CC14 but are usually less toxic. Nevertheless, similar precautions should be observed with:
  - N-butyl chloride.
  - Tetrachloroethylene.
  - Tetrachloroethane.
  - Hexachloroethane.

Structure

C-Cl4.

Susceptible Species

Carbon tetrachloride is especially toxic to swine. Cattle are somewhat more sensitive than sheep, but individual sheep may be quite
sensitive. Poultry are most tolerant.

**Toxicity**

- LD₃₀ rat (acute oral) is 2,800 mg/kg.
- LC₅₀ in feed (mouse) is 9,528 ppm.
- Poisoning can occur from inhalation, oral or topical exposure.
- Inhalation: a few minutes of exposure to 3,000 ppm is tolerated while levels of 12,000 ppm for 15 minutes cause nonlethal toxicity (see Osweiler et al., 1985).
- Carcinogenic.

**Factors Affecting Toxicity**

- Selenium supplementation may lessen susceptibility.
- Diets high in protein increase the toxicity of carbon tetrachloride and diets low in protein decrease the toxicity.
- Consumption of plants which are hepatotoxic or which contain oxalates tends to increase the effect of CC₁₄ on the liver.
- Experimental exposure to enzyme inducers, such as phenobarbital, DDT, chlordane or dieldrin increase the toxicity of CC₁₄. In man, concurrent ethanol ingestion increases susceptibility to CC₁₄.
- Age is another factor, in that lambs of less than 5 months are predisposed to carbon tetrachloride toxicosis. Ewes which are suckling lambs are also at increased risk. Fat ewes and underweight animals are less tolerant of CC₁₄.

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

- Carbon tetrachloride is slowly absorbed from the intestine in unchanged form. Dividing the dose and administering CC₁₄ in repeated small amounts or administration in conjunction with fat or a high lipid diet increases absorption and increases toxicity.
- CC₁₄ is eliminated via expired air, via the kidneys (primarily after metabolism), and especially via the bile as metabolites.
- Increases in environmental temperature increase panting which enhances removal and decreases toxicity. Similarly, lower environmental temperatures increase toxicity.

**Signs**

- Large doses of carbon tetrachloride are followed by narcosis similar to that associated with chloroform.
- Additional signs include diarrhea, incoordination, and sometimes vascular collapse in 24 to 48 hours. Anorexia, dullness, blood stained feces, constipation then diarrhea, possible hypocalcemia and collapse may precede death.
- The most important toxic effect of CC₁₄ is liver damage. Small doses cause fatty degeneration which, in sheep, may be seen when the animals die 4 days or more after exposure.
- Large amounts cause centrilobular necrosis, which may be observed in sheep dying in 3 days or less. Hepatotoxicity may be associated with swelling and tenderness in the liver antemortem. Lethality due to hepatic damage most often occurs during the 2 weeks following exposure.
- In fatal cases, renal damage may be more severe than liver damage. Casts, proteinuria, hematuria, oliguria and increases in BUN may be present.
- If enough tissue remains functional to allow survival, damaged hepatocytes may undergo resolution and normal function may sometimes be reestablished within about 8 days. Similarly, renal function may be restored within about 3 weeks; however, complete return of liver and kidney function may take up to a year.
- It is recommended that sheep be fed hay a few days before and after treatment with CC₁₄ to kill liver flukes.

**Lesions**

- Gastroenteritis confined especially to the abomasum and upper small intestine.
- Hepatic congestion, fatty degeneration or centrilobular necrosis.
- Renal congestion as well as cloudy swelling and necrosis in renal tubular epithelium.

**Note** - In acute cases may see no liver or kidney lesions.

- With aspiration due to faulty drenching with carbon tetrachloride or due to capsule rupture, inhalation pneumonia is seen.
- Repeated small doses of CC₁₄ may result in hepatic cirrhosis.
Treatment

- Very recent exposure-emetics when not contraindicated.
- Recent exposure-where emesis not indicated-gastric or rumen lavage.
- Activated charcoal and a saline cathartic.
- Artificial respiration if anesthetized.
- IV dextrose in large amounts reportedly delays the hepatotoxic effects.
- Calcium solutions are reportedly beneficial.
- Osmotic diuretics and fluids are used to increase urine output.
- High carbohydrate diet.

**Note** - Epinephrine and norepinephrine are contraindicated as they may induce ventricular fibrillation.

**Note** - Hepatic coma may be treated by efforts to lower the blood NH₃ concentration. Steps include:

- Decreasing protein intake.
- Prevent ammonia absorption from the stool by daily administration of milk of magnesia or sodium sulfate.
- Oral neomycin to lessen intestinal bacteria capacity to break down proteins.
- Peritoneal dialysis.
- Avoid chlorothiazide.

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**Phenolics and Coal Tar**

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<tbody>
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<td>All species</td>
<td>Hours to days</td>
<td>Days to permanent damage; often lethal</td>
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**Sources**

- Phenol itself is used as an agent to produce protein precipitation and has been recommended for the cauterization of corneal and oral ulcerations.
- Flooring materials containing over 6% phenol are toxic to pigs up to 4 kg BW.
- Lignite pitch and bitumen flooring is also toxic because of the high phenol content, while mineral-oil bitumen flooring is not a problem.
- Coal tar is encountered primarily as a result of the consumption of "clay pigeons" which are usually yellow and black, bowl-shaped targets used to practice with shotguns. Coal tar pitch may also be encountered as a result of its use as a coating on wood or even metal surfaces.
- Coal tar itself is a by-product of the destructive distillation of coal. Constituents include benzene, toluene, naphthalene, anthracene, xylene and other aromatic hydrocarbons including phenol, cresol and other phenolics, ammonia, pyridine and other organic bases and thiophene. It is an almost black, thick liquid or semisolid material. In clay pigeons it is mixed with ground limestone.
- Tar paper is another source of coal tar pitch which has proven capable of causing toxicosis.
- Sources of phenols also include creosote, which may also be called wood creosote or beechwood creosote. Creosote from coal tar also exists and the latter is more toxic than the wood derived types. Wood creosotes have been used as antiseptics, expectorants, parasiticides, deodorants, gastric sedatives and gastrointestinal antiseptics although these uses are all largely out-of-date and no longer employed. Creosote from coal tar has been widely used for impregnating wood to protect it from rot and worms, and it is also used as a fungicide, germicide, insecticide and disinfectant.
  - Wood creosote contains creosol (4-hydroxy-3-methoxy-1-methylbenzene) and a mixture of other phenols.
  - Coal tar creosote contains m-cresol (3-methylphenol) and p-cresol (4-methylphenol) and other liquid and solid aromatic hydrocarbons and tar acids and tar bases.
  - Creosote is a restricted-use pesticide (Federal Register, February 1986).
- Other products include more purified cresols (hydroxytoluenes, cresylic acid, tricresols), naphthol, menthol, thymol, guiacol and resorcinol which is synonymous with 1,3 benzenediol. Some Lysol products contain o-phenylphenol.
Phenol

Toxicity

- Oral LD₅₀ of phenol itself is approximately 0.5 g/kg except in the cat which is more sensitive.
- The degree of the toxicity of the phenolics varies widely with phenol itself being one of the most toxic. The cresols have approximately the same toxicity as phenol, but the ortho and para isomers are even more toxic. These compounds are apparently slightly more corrosive than phenol, but are absorbed more slowly and may have a bit milder systemic effect.
- LD₅₀ of clay pigeons in swine: approximately 1 g/kg for several days.

Mechanism of Action

Phenols are protoplasmic poisons causing coagulation necrosis of many tissues. Capillary damage, hepatorenal necrosis and neurotoxicity may occur. Phenol also causes considerable stimulation of the respiratory center which may result in respiratory alkalosis. As the syndrome progresses however, a metabolic acidosis may develop. The clinical course and severity of toxicosis is highly dependent upon the type of phenolic and the degree of exposure as well as the species and age of animal exposed.

Absorption, Distribution, Metabolism and Excretion (ADME)

Phenols are absorbed after oral or dermal exposure and are excreted at least in significant measure as glucuronide conjugates.

Signs

- The clinical course depends upon the amount and type of phenolic.
- Contact with concentrated phenol causes obvious white discoloration of the contacted skin or mucous membranes, however, many of the derivatives do not have this effect.
- Phenol causes considerable stimulation of the respiratory center which may result in a respiratory alkalosis. In humans poisoned with phenol, respiratory alkalosis or metabolic acidosis (possibly later in the syndrome) may be seen.
- Early in phenol poisoning, there is incoordination and mild muscle fasciculations in some animals. The condition often progresses to coma and then respiratory failure.
- Seizures, coma and death are more common in cats.
- Icterus may be present as a result of hepatic damage or sometimes hemolysis.
- Some animals experience renal failure.
- Rapid death may be the primary presenting complaint in swine after exposure to a source of coal tar.
- Some coal tar poisoned swine, however, live for several hours or days after the onset of signs including weakness, recumbency (sternal) and depression. The respiratory rate is increased and there is a tender abdomen which can be detected by digital pressure. A secondary anemia and visible icterus may be seen.
- Methemoglobinemia sometimes occurs in phenol poisoned animals.

Lesions

- In coal tar poisoning of swine, the liver is usually very enlarged with a variegated mottling and engorgement. It is often quite friable and the lobular pattern is exaggerated. Some lobules are dark red; other lobules are yellowish. The mottling is especially apparent on the cut surface. The lymph nodes of the abdominal cavity become enlarged and hemorrhagic. Often the kidneys are enlarged and pale. Generalized icterus is common.
- The corrosive effects of phenols or cresols may be seen in the oral and upper gastrointestinal tracts of orally exposed animals. These tissues may initially be whitish, having a cooked egg appearance or may be edematous and hemorrhagic. At death there is often severe centrilobular hyperemia, fatty degeneration and necrosis of the liver. Renal damage is also common. Renal tubular degeneration and necrosis may be seen microscopically.
**Diagnosis**

- The clinical signs, lesions and the history of exposure may suggest the etiology. There may be an aromatic lamp oil odor to the breath.
- A positive rapid presumptive test may be performed to confirm the diagnosis: 10 ml of urine is mixed with 1 ml of 20% ferric chloride. A purple color indicates the presence of phenol.
- Serum, urine or kidney may be analyzed for the presence of phenol at selected toxicology laboratories.

**Treatment**

- Only after assessing the severity of mucosal damage may emetics and/or gastric lavage be considered. If severe damage is present, these techniques should not be used.
- Activated charcoal and a saline cathartic may be worthwhile and are recommended.
- In the past, poorly absorbed oils such as olive oil were recommended, although mineral oil was avoided since it would not dissolve phenol.
- For dermal exposure, the preferred agent for dilution and removal is polyethylene glycol or, as an alternative, glycerol (= glycerine) prior to washing. Whether or not one of these agents can be used first, the animal is bathed with generous amounts of a liquid dish detergent (not the automatic dishwasher type) and thoroughly rinsed with water. This may be followed by castor oil used as an additional cleansing agent and then additional bathing and finally by 0.5% sodium bicarbonate soaked dressings. It is wise to avoid oily dermatologic preparations other than castor oil, early in the course of phenol toxicosis in small animals as these may enhance the absorption of phenol.
- Additional therapy may involve respiratory support and control of shock and metabolic acidoses although such severely affected animals may warrant a poor prognoses in many cases.
- Fluid therapy is indicated since phenolic metabolites are eliminated in the urine.
- For oral exposure, demulcents such as milk and egg are indicated after the use of activated charcoal to help protect injured mucous membranes from further damage.
- Acetylcysteine has been recommended for animals with methemoglobinemia at a loading dose of 140 mg/kg, followed by 70 mg/kg QID per os for 3 days.
- Steps should be taken to prevent further exposure. Clay pigeons in fields for up to 35 years have resulted in serious outbreaks of toxicosis in swine.

### Nitrosamines

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<td>Sheep, human</td>
<td>Hours to chronic</td>
<td>Weeks to permanent damage, potentially lethal; toxicoses are rare</td>
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</table>

**Sources**

- The nitrosamines have been known for a long time, but the extreme toxicity of members of this group of chemicals has only recently been recognized. Generally, they serve no useful purpose.
- Nitrosamines are readily formed when nitrite-preserved meats are cooked at exceedingly high temperatures.
- The nitrosamines also can be readily synthesized in the laboratory and apparently under biological conditions. The 2 basic chemicals required for the production of nitrosamines, secondary amine and nitrite, can form nitrosamines spontaneously in the warm acid conditions of mammalian stomachs.
- Few reports of nitrosamine poisoning have been documented in domestic animals. In one instance, a large number of sheep were poisoned following consumption of nitrate treated fish meal in which nitrosamines had formed.
- A similar outbreak of nitrosamine toxicosis occurred in mink fed fish meal.
- In humans, there is also concern, since nitrosamines may form from nitrates and secondary amines in the stomach. This may occur after ingestion of antacid drinks which keep the stomach pH temporarily above 4, or after ingestion of nitrite and overheated protein foods.
- The processes of formation of nitrosamines in vivo are shown below.
The signs of nitrosamine toxicosis are compatible with acute, subacute or chronic hepatotoxicity.

Lesions

- Nitrosamines are, for the most part, strongly hepatotoxic and many synthetic nitrosamines are known to be carcinogenic, especially affecting the liver.
- In the sheep mentioned above, severe liver damage occurred.

Prevention

In meats preserved with nitrites, sodium erythrobate and/or ascorbic acid are added to limit formation of nitrosamines.
Thiacetarsamide Sodium (Caparsolate ®)

Source

Thiacetarsamide is an arsenical used to kill adult heartworms in dogs.

\[
\text{As} \quad \text{SCH}_2\text{COONa} \\
\text{SCH}_2\text{COONa} \\
\text{CONH}_2
\]

Signs

- Adverse reactions to thiacetarsamide apart from pulmonary thromboemboli occurring from 5 to 30 days posttreatment are comprised primarily of hepatotoxicosis and, to a lesser extent, of nephrotoxicosis.
- Clinical signs include extremely persistent vomiting, icterus and orange urine. Affected animals may become persistently anorectic and hepatic encephalopathy is possible.
- The earliest sign of hepatotoxicity is bilirubinuria. It has been suggested that bilirubinuria (regardless of severity) is not an indication to stop a treatment regimen if only one dose remains and if there are no other signs of illness. However, bilirubinuria which occurs after only the first or second dose indicates the need to terminate treatment.
- Icterus, on the other hand, is always a sign signalling the need to terminate the use of thiacetarsamide. Generally, animals for whom treatment is terminated may receive a full regimen of thiacetarsamide after a 4-week rest and these individuals usually tolerate the regimen very well.

Clinical Pathology

- About 20% of all dogs with normal serum glutamine pyruvic transaminase (SGPT) and serum alkaline phosphatase (SAP) values prior to thiacetarsamide treatment develop elevations above the normal range after treatment. Generally the elevation occurs on the first day or 2 after treatment but the SGPT values decline within 7 days.
- Preexistent elevations of SGPT, SAP or BSP are not indications to delay adulticidal treatment, and microfilaricide treatment before adulticide treatment is not indicated.
- Thiacetarsamide induced renal failure is more likely in dogs with previously compromised renal function. Therefore, the BUN and urinalysis results should be evaluated before treatment.

Treatment

- Supportive care includes rest and a high carbohydrate diet such as K/D. Tigan rectal suppositories, dosage adjusted according to weight, are useful in controlling vomiting. B-vitamins and liver sparing agents, although not of proven benefit, may be given.
- Although the benefit of British Anti-Lewisite BAL (Dimercaprol) or other arsenic chelators would seem likely, its use is not widely documented (if at all) in the management of thiacetarsamide.
Mebendazole - (Telmin ®, Telmintic ®, Vermox ®)

**Toxicity**

Generally, the anthelmintic mebendazole is of low toxicity and has a wide margin of safety in animals. Nevertheless, there have been reports of mebendazole toxicosis in a group of Doberman Pinschers and Dachshunds and in a Labrador which were dosed at the recommended therapeutic level for 5 days.

**Mebendazole**

**Signs**
- Develop at approximately 2 weeks after treatment.
- Anorexia, depression, vomiting, icterus, hemorrhagic diarrhea and sometimes dehydration.

**Clinical Pathology**

Elevations occur in SGPT, alkaline phosphatase, and bilirubin (especially direct bilirubin). Apart from the effects of dehydration, blood counts were unaffected.

**Lesions**
- Severe, generalized, centrilobular hepatic necrosis with loss of hepatocytes, sinusoidal collapse and replacement by hemorrhage.
- Hepatocytes near portal triads and bile duct epithelia were vacuolated and had swollen nuclei.
- Occasional inflammatory cell infiltrates were present.
- Overall the hepatic lesion was classified as a cytotoxic form of massive, hemorrhagic, necrotic hepatitis.
- In contrast to these clinical effects, experimental attempts to reproduce these findings were unrewarding. The effect of repeated and exaggerated mebendazole administration was evaluated in dogs with and without experimentally induced altered liver function. Irish Setters and Toy Poodles were dosed at 1, 3, and 5 times the therapeutic dose (22 mg/kg) of mebendazole for 17 days, without any effect on the liver. Mixed breed dogs that received increasing doses of mebendazole at 11 to 110 times the therapeutic dose for 2 months did not show adverse effects and remained in good health throughout the experiment. There was no substantial evidence that carbon tetrachloride-induced liver changes were exacerbated by subsequent repeated treatments with mebendazole at 15 times the therapeutic dose.
- Additionally, in dogs in which liver function was compromised experimentally by glutathione depletion or microsomal enzyme induction, administration of mebendazole at this same dosage for 30 days did not result in any hepatotoxic effect. When mebendazole was given at 15 times the therapeutic dose prior to a hypoxic episode in dogs pretreated with a barbiturate and high protein diet, there was no evidence of any adverse effect on liver function.
- These metabolic manipulations, in conjunction with mebendazole administration, failed to reveal any mechanism of hepatic dysfunction associated with mebendazole treatment. Unrecognized factors appear to be involved with the rare cases of hepatic dysfunction that have been reported after mebendazole administration. Only careful documentation of field cases and further laboratory research can identify these factors.
- For these reasons mebendazole toxicosis of dogs is considered an idiosynratic drug reaction.

### Major Species | Usual Time of Onset | Usual Duration (if survives)
--- | --- | ---
Dogs | Around 2 weeks | Days to weeks; often lethal

<table>
<thead>
<tr>
<th>Major Species</th>
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<th>Usual Duration (if survives)</th>
<th>Full Table for Hepatotoxic Chemicals and Drugs</th>
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<tbody>
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Tannic Acid

Sources

- Tannic acid has been recommended for forming insoluble salts with some heavy metals, for alkaloid and glycoside inactivation, for the treatment of burns and diarrhea, and has been combined with barium for use in barium enemas. These uses are losing favor with many toxicologists.
- It may also be encountered in children's chemistry sets and is used for "tanning" hides in leather processing.
- Tannic acid is also used as an astringent. Astringents are agents which precipitate proteins, but have little penetrating ability, so that their primary effects result from altered cell surface characteristics. Consequently, the cell itself remains viable, but its permeability is greatly reduced.

Absorption, Distribution, Metabolism and Excretion (ADME)

- Tannic acid N.F. is formed from a number of glycosides (or tannins) comprised of glucose and tannic acid. The rate of hydrolysis of the glycosides and release of tannic acid varies with different plant sources. The most common tannic acid, which is a powder, soluble in water, glycerine, or alcohol, is derived from nutgalls of oak trees. A tannic acid glycerite, which is 20% tannic acid and 1% sodium citrate in glycerine is also available. Protected or slow release tannic acid formulations are more hazardous, since more of the tannic acid tends to be absorbed.
- In the gastrointestinal tract, tannic acid is converted to gallic acid, which is nonastringent, and glucose, and is then absorbed. Gallic acid is then degraded in the body and a small amount is excreted in the urine. Toxicosis results when sufficient intact tannic acid is absorbed.
- Although widely effective in precipitating some metals, and inactivation of some alkaloids, there are several members of these classes of toxicants which are not precipitated as tannates. These include cocaine, nicotine, physostigmine, atropine, morphine, arsenic, antimony and mercury. In addition, tannic acid interferes with the adsorbent action of activated charcoal.

Signs

- Ingestion of large doses of tannic acid can produce severe gastroenteritis and abdominal pain.
- Although widely used in barium enemas, 5 deaths in children and 3 deaths in adults, apparently as a result of tannic acid-induced hepatic necrosis have been reported.
- Toxicosis has also resulted from absorption of intact tannic acid from the intestine after large doses are consumed and after cutaneous
absorption of tannic acid from treated burned areas.

**Treatment**

- Treatment of tannic acid ingestion is comprised of administration of milk to dilute the tannic acid followed by an emetic, unless contraindicated. When emetics are contraindicated or ineffective, lavage should be employed.
- Gelatin or egg white may be instilled in the initial fluid to form insoluble tannates, which are then removed by the lavage.
- Emesis or lavage is followed by activated charcoal and a saline cathartic.
- Supportive therapy for liver failure is indicated since hepatic necrosis is the usual lethal mechanism in tannic acid toxicosis regardless of the route of administration.
  - At the present time there are few indications for tannic acid for which safer and more effective treatments are not available.

**Note** - Gallotannins (and possibly other constituents) which are encountered by livestock consuming oak buds or acorns are associated with effects largely on the gastrointestinal tract and the kidneys.

**References**

**Iron**


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