Mycotoxicoses Introduction

Introduction

The word mycotoxin is derived from myco, meaning mold and toxin, a poison. A great number of mold metabolites have been identified as mycotoxins. Thus mycotoxins are secondary fungal metabolites (i.e., metabolites not essential to the normal growth and reproduction of the fungus) which cause pathologic, physiologic, and/or biochemical lesions in other species (may include animals, plants, other microbes, etc.).

Mycotoxicosis - Poisoning of a biological system by a mycotoxin.

Conditions predisposing to mycotoxin production (not just trichothecenes):

1. **Moisture:**
   - **Field fungi** - Invade developing and mature seed grain while still on the plant. The optimal moisture content for growth is 22% - 25%.
   - **Storage fungi** - Invade seed grain after harvest while in storage. Optimal moisture for growth is 13% - 18%.
   - **Advanced decay fungi** - Generally require moisture of 22% - 25% but rarely develop and grow on seed grain in the field.
2. **Temperature:**
   - Generally molds grow readily between 20 °C and 30 °C. But optimal temperature ranges are from below 0 °C to above 60 °C. Temperature variations affect the growth rate of the mold and also the type and amount of toxins produced.
3. **Aeration:**
   - Molds are aerobic organisms, but a significant difference in oxygen requirements exist between types of molds.
4. **Substrate Availability:**
   - Molds can either be parasitic or saprophytic in nutrient requirements.
5. **Host Stress:**
   - Important for field fungi. Environmental stress, insect damage, and plant disease encourage colonization, growth, and toxin production by fungi.

Many factors contribute to the occurrence of mycotoxicoses in livestock. For example, modern harvesting methods in which corn is handled at higher moisture concentrations combined with damage occurring in harvesting machinery increases the number of kernels in which molds can get started. Also the feeding of ground rations prevents the animals from sorting out and avoiding damaged kernels.
A Partial Listing of the Known Mycotoxins

- Related mycotoxins: Aflatoxins B1, B2, G1, G2, M1, M2, Q1, and aflatoxicol.
  - Sterigmatocysts
  - Versicolorins
  - Asperptoxins
  - Autocystins
  - Sterigmatin
  - Bipolarin
  - Averufarin
  - Curvularin
- Rubratoxins A and B - Hepatotoxic
- Sporodesmin - Hepatotoxic
- Penicillic acid - Hepatotoxic
- Ochratoxin series, especially ochratoxin A - Nephrotoxic, carcinogenic, immunosuppressive
- Citrinin
- Citreoviridin
- Luteoskyrin
- Ergot alkaloids
  - Ergotamine
  - Ergonovine
  - Others
- Tremorgens
  - Penitrem A
  - Roquefortine
  - Paspaline
  - Paspalanine
  - Paspalitrems A and B
  - Verruculogen
  - Fumitremorgen
  - Fumigaclavine
- Slaframine
- Patulin
- Fusarium toxins
  - Trichotheccenes
    - T-2 toxin
    - Diacetoxyscirpenol (DAS)
    - Deoxynivalenol (Vomitoxin) (DON)
    - Verrucarins
    - Roridins
    - Satratoxins
    - (30+ others)
    - Zearalenone and zearalenol
    - Butenolide
    - Moniliformin
    - Fusaric acid
    - Fusarin A-D
    - Unidentified refusal factors
    - Fumonisins

- Our present knowledge of many of these and numerous other known mycotoxins is extremely limited. In many instances, no surveys of the frequencies of occurrence have been done. In other instances, the compounds have been investigated in some detail but surveys have not revealed sufficiently frequent occurrence in the United States for these toxins to be of major concern to veterinarians. For example, T-2 toxin and diacetoxyscirpenol have been studied in some detail but are only rarely encountered in the United States. T-2 toxin, however, was apparently responsible for severe outbreaks of mycotoxicosis in humans and animals in the Soviet Union and has caused occasional outbreaks of toxicosis in the midwestern USA and Canada. Similarly the nephrotoxic mycotoxin, ochratoxin A, although not often a major problem in the USA, has caused severe problems in poultry in the US, occasional problems in swine in the US, and widespread outbreaks of toxicosis in swine in Denmark.
- For the present, 4 mycotoxins account for at least 95% of the confirmed diagnoses of mycotoxicoses in the midwestern USA. These toxins include the fumonisins, deoxynivalenol (vomitoxin), zearalenone, and aflatoxins.
- When extremely high concentrations of these mycotoxins are present, interpretation of the significance of residues in feeds is straightforward.
However, when low concentrations are present in feeds, the interpretation of the toxicologic significance of mycotoxin residues can be more difficult. This is because experimental mycotoxicoses cannot always be extrapolated directly to the field situation.

### Reasons why Experimental and Field Cases of Mycotoxin Poisoning are not Identical

- **Experimental mycotoxin administration.**
  - Only 1 purified toxin is usually administered.
  - The diet is usually balanced and contains undamaged grains.
  - The toxin is evenly mixed in the diet.
  - The toxin concentration is known.
  - The sample is presented to the laboratory without additional mold growth or toxin production occurring.
  - A controlled environment is provided for experimental animals.

- **Naturally occurring mycotoxin poisoning.**
  - The identified toxin is consumed along with related mold metabolites and possibly other unidentified mycotoxins.
  - Mold damaged, stressed grains may be of lower nutrient value and altered palatability.
  - The toxin(s) is (are) unevenly distributed in the diet.
  - The concentration(s) is (are) generally so variable that multiple samples are required to estimate concentration(s) present.
  - If sufficient moisture and appropriate temperatures occur during transit, additional mold growth and toxin production may occur.
  - Stresses such as infectious agents, reproduction, lactation, crowding, temperature variation, etc., overlap and interact with effects of mycotoxins.

### Mycotoxicoses

Mycotoxicoses can occur in 3 categories: **1) acute, 2) subacute or chronic and 3) subclinical with predisposition to nutritional and/or infectious disorders.** Most mycotoxins cause syndromes of all 3 types. Zearalenone toxicoses, however, tend to fall into only the second category.

### Zearalenone and Zearalenol

<table>
<thead>
<tr>
<th>Major Species</th>
<th>Usual Time of Onset</th>
<th>Usual Duration (if survives)</th>
<th>Full Table for Estrogenic and Anti-androgenic Toxicants</th>
</tr>
</thead>
<tbody>
<tr>
<td>Swine, cattle, sheep</td>
<td>Days to weeks</td>
<td>Days to weeks, permanent reproductive damage rare</td>
<td></td>
</tr>
</tbody>
</table>

### Introduction

- **Zearalenone**

  This estrogen-like toxin and its relatives such as zearalenol cause subacute poisoning, as a rule, but do not cause death losses, and probably do not greatly predispose to either nutritional or infectious disorders. Zearalenone and its derivatives are the only known mycotoxins whose effects are primarily estrogenic in nature and swine are among the most sensitive domestic animals to this toxin. A 3-dimensional model of the zearalenone molecule can be used to demonstrate the similar configuration of this toxin to estradiol. As a result, zearalenone can occupy and stimulate estrogenic receptors.
Zearalenol

α-Zearalenol is associated with natural zearalenone occurrence and may have 3 times the estrogenic activity of zearalenone. It is not, however, routinely included in mycotoxin screens by analytical laboratories. Although zearalenone and α-zearalenol may occur as products of other species of *Fusarium* and may coexist with T-2 toxin and other mycotoxins, they are produced primarily by *F. roseum* and coexist (as far as we know at present) primarily with deoxynivalenol (vomitoxin). In the field, estrogenic effects may occur in swine fed rations in which only a few parts per million of zearalenone are present. In these instances the diagnosis is usually confirmed when normal reproductive function occurs after withdrawal of the contaminated feed. Of course efforts to rule out infectious agents, in the case of infertility and/or abortion should not await the results of mycotoxin assays. In swine, estrogens are luteotropic and would be expected to maintain pregnancy.

Sources

- Zearalenone is produced by species of *Fusarium*, primarily *F. roseum*.
  - Corn, wheat, other grains, and occasionally forages may be contaminated by zearalenone.
  - Very high concentrations up to approximately 20 ppm have been found in 1996 wheat.

Susceptible Species

Swine, cattle, sheep; whereas chickens appear to be largely resistant.

Effects of Zearalenone

- Swine (most susceptible).
  - In prepubertal gilts.
    - Swelling and edema of vulva.
    - Vaginal and rectal prolapse.
    - Uterine enlargement, edema.
    - Atrophy of ovaries.
    - Enlargement of mammary glands.
    - Thin catarrhal exudate from vulva.
    - Differential diagnosis-normal estrus, injury to external genitalia.
  - In young boars.
    - Atrophy of testes.
    - Zearalenone in prepubertal boars may reduce libido and plasma testosterone.
  - In castrated or prepubertal males.
    - Enlargement of mammary glands.
    - May see preputial enlargement.
  - In sows.
    - Anestrus or nymphomania dependent on stage of animal's estrous cycle when first exposed.
    - Reduced litter size due to fetal resorption (mummification) and/or implantation failure when dietary zearalenone is present at 7 - 10 days postmating.
    - Weak or stillborn pigs. Piglets occasionally exhibit swollen vulvas at or shortly after birth (juvenile hyperestrogenism) whether this is from exposure *in utero* and/or through the dam's milk is currently under investigation.
    - Pseudopregnancy.
    - Field observations of zearalenone-caused abortions are now thought to be largely erroneous since estrogens are luteotropic in swine. Instead, it is suspected that implantation failure followed by pseudopregnancy leads to a diagnosis of abortion. Other etiologies (different mycotoxins, viruses, etc.) should be considered to more likely to account for most late-term abortions.
  - Differential diagnoses.
    - Pseudorabies.
    - Leptospirosis.
    - Enterovirus.
    - Parvovirus.
    - Encephalomyocarditis (EMC) virus.
    - Other mycotoxins.

- Cattle.
  - In cattle, ruminal metabolism may alter toxicity; may be associated with precocious udder development in heifers and reduced fertility in breeding animals.
Most animals exposed to zearalenone for brief periods of time will probably recover normal reproductive function. However, at least in females, severe toxicosis may be characterized by ovarian fibrosis and changes in the oviduct and uterus which could conceivably have more prolonged effects on reproduction. Further study of this area is needed.

- Sheep.
  - Decrease in ovulation rate and lambing percentage.
  - *Fusarium* spp. growing on pasture is a recognized cause of exposure to estrogenic mycotoxins in New Zealand.

**Diagnosis**

- Zearalenone and zearalenol can be quantified by high performance liquid chromatography in feedstuffs at most veterinary diagnostic laboratories. Also request zearalenone glycoside.
- Second choice screening tests include Neogen's Veratox, Agriscreen®.
  - ELISA test (used to screen feeds) for zearalenone.

**Management**

- Recent research has suggested that permanent reproductive damage rarely occurs. Once animals are on clean feed and have excreted the zearalenone, normal reproductive function should occur.
- Recovery should occur in 7 - 10 days, although more time may be required for sows to start cycling. However, culling sows may be more economical than waiting for a return to a normal reproductive cycle.
- Recent studies indicate that zearalenone is extensively recycled through the enterohepatic system. Therefore, intestinal binding agents (activated charcoal, bentonite clays) or agents that decrease GI transit time (e.g., alfalfa fiber) may enhance elimination and decrease the time needed for animals to regain normal function.
- Other mycotoxins have been associated with reproductive abnormalities (experimental evidence). Also, interactions of mycotoxins must be considered in field conditions.

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**Trifolium (Clovers) and Medicago (Alfalfa and Medics)**

- *Trifolium hybridum* - Alsike clover
- *T. incarnatum* - Crimson clover
- *T. pratense* - Red clover
- *T. repens* - White clover
- *T. subterraneum* - Subclover, subterranean clover
- *Medicago sativa* - Alfalfa
- *Medicago spp.* - Barrel Medic
- *M. denticulata (M. hispida)* - Bur clover

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</thead>
<tbody>
<tr>
<td>Sheep and possible cattle</td>
<td>Chronic</td>
<td>With prolonged exposure, can have permanent infertility</td>
<td></td>
</tr>
</tbody>
</table>

**Family** - Leguminosae (pulse or bean family)

**Images**

- Crimson clover, *Trifolium incarnatum* - Google Image Search. - To view this image in full size go to the IVIS website at www.ivis.org.


Habitat

- Strains of clover and alfalfa are cultivated in pastures or for hay, in sandy and more fertile soils.
- *T. hybridum* - United States and Canada.
- *T. incarnatum* - Central Eastern States.
- *T. repens* - Europe, New Zealand.
- *T. subterraneum* - Pacific Northwest; Australia.
- *M. sativa* - United States and Canada.
- *M. denticulata* - Greatest abundance in California and Cotton Belt.

Description/General

- Plant - Tufted or diffuse herb.
- Leaves - Palmate (sometimes pinnate), 3 foliate; leaflets, toothed; stipules united with the petiole.
- Flowers - In heads or spikes; calyx-5 cleft, corolla mostly withering or persistent.
- Fruit - Small membranous pods often included in calyx; 1 - 6 seeded, indehiscent.

Toxic Principles; Absorption, Distribution, Metabolism and Excretion (ADME)

- *T. hybridum*
  - Unknown agent causing primary and/or secondary (hepatogenous) photosensitization.
- *T. incarnatum*.
  - Stiff wiry hairs; mechanical injury (impaction), may cause photosensitization.
- *T. pratense*.
  - May contain isoflavone estrogens including formononetin especially in spring. Estrogenicity declines after flowering.
  - May cause photosensitization.
  - When attacked by *Rhizoctonia leguminicola*, the muscarinic toxin, slaframine (causes most problems due to red clover ingestion) may be present (in the fungal elements), swainsonine also may be produced.
- *T. repens*.
  - Moderate amounts of cyanogenic glycosides.
  - When affected by foliar diseases, may produce estrogenic coumestans including coumestrol, trifoliol, and repensol.
- *T. subterraneum*.
  - Genistein, formononetin, and biochanin A are isoflavone estrogens causes most if not all the problems associated with subterranean clover. Formononetin is low in estrogenic activity and is converted to the estrogenic metabolite, equol. The fresh plant and rapidly dried hay retain the isoflavone estrogens. The scenescent plant loses estrogenicity.
- *M. sativa*.
  - Coumestan estrogens including coumestrol, 4-methoxycoumestrol and sativol.
  - Estrogenic compounds are potentially produced in larger concentrations in response to damage by aphids or fungi.
  - Strains of alfalfa, fertilizer, humidity, and age of the plant may also influence estrogenicity.
  - Saponins (cause bloat).
- *Medicago* spp. (annual medics).
  - Coumestrol and 4-methoxycoumestrol.

Susceptible Species

- *T. hybridum* (Alsike clover).
  - Horses seem most sensitive.
- *T. incarnatum* (Crimson clover).
  - Horses are primarily affected (impaction with phytobezoars).
- *T. pratense* (Red clover).
Cattle, horses, sheep are all susceptible to slaframine.

- T. repens (White clover).
  - May contain cyanogenic glycosides but cyanide toxicosis is quite unlikely.
  - Ergot-like effects reported in other countries as were paresis in newborn pigs from spinal cord demyelination.

- T. subterraneum (Subterranean clover).
  - Sheep are mainly affected. Cattle are less sensitive and may excrete phytoestrogens faster than sheep.

- Medicago spp. (Alfalfa, medics, bur clover).
  - Excellent forage plant but may cause bloat in ruminants; estrogenic effects are less frequently encountered and occur primarily in ruminants.

**Mechanisms of Action, Signs and Lesions**

- T. hybridum (Alsike clover).
  - Syndrome I (especially horse).
    - Nervous and digestive disorders.
    - Photosensitization: "Trifoliosis" is characterized by reddening of the skin as a response to sunlight, superficial or deep dry necrosis of the skin or edematous swelling and serous discharge from the affected area. Sometimes called "Dew poisoning": moist areas of the body are most susceptible.
    - Painful irritation and shallow ulceration of oral mucous membranes and the tongue.
    - Colic, diarrhea, depressed or excited.
    - If stomatitis is severe, horses will not eat and develop dermatitis.
  - Syndrome II.
    - Recurring attacks of severe icterus.
    - Severe emaciation, sluggishness, anorexia, unsteadiness, depression, eventual stupor, manic walking, urine dark colored.
    - "Big Liver Disease" - Liver pale and rubbery.

- T. incarnatum (Crimson clover).
  - Colic and/or death due to impaction with phytobezoars.

- T. pratense (Red clover).
  - The effects of slaframine are discussed in a previous handout.
  - May cause bloat.
  - May be estrogenic.
  - Haylage has caused infertility in female cattle.
  - Rarely may contain toxic amounts of cyanogenic glycosides or goitrogens. Also, rarely may cause hepatic necrosis and photosensitization.

- T. repens (White clover).
  - Refer to other handouts on cyanide and cyanogenic plants or on ergot alkaloids, depending upon the syndrome observed.

- T. subterraneum (Subterranean clover).
  - Formononetin causes cystic glandular hyperplasia of the cervix. The cervical mucosa may resemble that of the uterus. Ewes are most prone to this effect.
    - Increases in amount and fluidity of cervical mucus causing poor sperm penetration to the oviduct.
    - Increased loss of fertilized embryos.
    - Hydrops uteri, uterine infections and reduced milk production.
    - Infertility may persist after animals are removed from pasture and has been called permanent.

- Males
  - Coumestrins and formononetin.
    - Rams - Fertility unaffected.
    - Wethers - Develop enlarged teats, with occasional lactation (clear or milky). Increased mortality with animals on these pastures, associated with urinary obstruction.

- Medicago sativa (Alfalfa).
  - Coumestrin - Induced infertility is generally regarded as temporary.
  - Coumesterol of alfalfa causes decreased fertility by decreasing the rate of transport of ova in the oviduct (thought to be reversible upon cessation of exposure). Most phytoestrogens are a problem in green plants except coumesterol (in Medicago spp).
  - Saponins may cause bloat.

**Diagnosis**

- Identification of Trifolium or Medicago, evidence of sufficient consumption and appropriate clinical signs.
- Note - Infertility often may arise without outward signs of estrogenicity. However, histologic lesions of the cervix are an important
diagnostic criterion, especially in ewes.

Treatment

- Remove from source of plant.
- For photosensitization, keep indoors for 5 - 7 days or until sensitivity passes.
Alsike Clover (*Trifolium hybridum* L.)

**Family** - Pea (Leguminosae).

**Growth Form** - Perennial herb.

**Stems** - Upright, smooth or nearly so, branched, up to 2 feet tall.

**Leaves** - Alternate, divided into 3 leaflets, the leaflets obovate, rounded at the tip, tapering to the base, toothed, smooth, up to 1 inch long.

**Flower Arrangement** - Many flowers, crowded together into spherical heads, each head borne on a long stalk.

**Flowers** - Pink or pinkish white, about 1/3 inch long, borne on very short stalks.

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

**Petals** - 5, pink or pinkish white, arranged to form a typical pea-shaped flower.

**Stamens** - 10.

**Pistils** - Overy superior.

**Fruits** - Pods elongated, with 2 - 4 seeds.

**Habitat** - Open, disturbed soils.

**Range** - Throughout the state.

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

**Note** - The scientific name of *hybridum* comes from the fact that this species appears to be an intermediate between white clover and red clover.
Black Medic (*Medicago lupulina* L.)

**Family** - Pea (Leguminosae).

**Growth Form** - Annual herb from fibrous roots.

**Stems** - Spreading, branched, hairy, up to 18 inches long.

**Leaves** - Alternate, divided into 3 leaflets, the leaflets oval to obovate, rounded at the tip, tapering or rounded at the base, toothed, hairy, about 1/2 inch long.

**Flower Arrangement** - Several flowers crowded together into dense heads 1/2 to 3/4 inch long, the head borne on a stalk.

**Flowers** - Yellow, about 1/12 inch long.

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

**Petals** - 5, yellow, arranged to form a typical pea-shaped flower.

**Stamens** - 10.

**Pistils** - Ovary superior.

**Fruits** - Pods spirally curved, smooth, black, 1-seeded.

**Habitat** - Open ground, in fields and along roads.

**Range** - Throughout the state.

**Time of Flowering** - May-July.
**Diethylstilbestrol (DES)**

- Used in dogs - Urinary incontinence, mismating.
- Mechanism of action of estrogens (as abortifacients), change oviduct or uterine environment, alleviation of transit time through uterine tubes, or inhibition of implantation.
- Carcinogenic.
  - Related to higher incidence of breast cancer in women (chronic exposure).
  - Adenocarcinoma of the vagina in female offspring of women treated with DES early in pregnancy (transplacental carcinogenesis).
  - Methods are available to detect DES residues in meat (DES use as a growth promotant in cattle was banned years ago).
  - Possible cause of bone marrow suppression (rare).

**Estradiol Cypionate (ECP)**

- ECP is the oil-soluble 17β-cyclopropylpropionate ester of alpha estradiol.
- Used for mismating treatment in dogs.
- ECP, estrone, estradiol benzoate may cause bone marrow depression and aplastic anemic. Estrogens may also cause cystic ovaries and uterine abnormalities.
- Administration of ECP during diestrus has been associated with increased incidence of endometrial hyperplasia and pyometra.

**Wheat Germ**

Estrogenic, but relationship to clinical estrogenic effects not established.

**Soybeans, Tofu, Other Soy-Based Foods**

Genistein, glycitin, and daidzen in soybeans are comparatively weak isoflavone estrogens that, by competing for natural estrogens, are associated epidemiologically with a decrease in the incidence of breast cancer in women. Also, in elderly women, the estrogens seem to decrease osteoporosis.
DDT and Metabolites: Reproductive Effects and Effects on the Adrenal Gland

<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><strong>Estrogenic Compounds</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>DDT and DDE</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Some PCBs</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td><strong>Anti-androgenic Toxicants</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>p,p'-DDT, and especially p,p'-DDE</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Some PCBs</td>
<td>-</td>
<td>-</td>
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</tr>
</tbody>
</table>

**Adrenal Effects**

Another contaminant of DDT and a lesser metabolite in DDT metabolism, o,p'DDD causes damage to the adrenal cortex of dogs. A resulting decrease in response to ACTH occurs. As a result of this property, o,p'DDD is used in primary hyperadrenocorticism of dogs in a pharmaceutical preparation, (generic also called mitotane) and the brand name Lysodren. Excessive or prolonged therapy with this drug may result in excessive damage to the adrenal cortex and Addisonian crisis.

**Reproductive Effects**

o,p'DDT, a contaminant of technical grade DDT is more estrogenic than p,p'DDT which makes up the bulk of the formulation. The feminizing effects of DDT are now thought to be due primarily to the anti-androgenic effects of p,p'DDE. Feminization is related to effects of DDT derivatives at hormone receptors rather than to an ovarian response.

**Note** - p,p'DDE associated feminization is believed to account for an epidemic of feminization in alligators in parts of Florida. p,p'DDE is the principal environmental degradation product of DDT.

DDT is also known to cause induction of thin eggshells in raptors. Because of the lipophilicity of DDT and its metabolites, the agents accumulate in the lipids of living organisms, especially in aquatic systems. As a result, aquatic predators such as bald eagles were among the most severely affected. There may also be another problem, which has been hypothesized to be due to enzyme induction and resultant enhanced metabolism of estrogens. Delayed estrus; fewer eggs laid; and some young born too late to be ready to leave for the fall migration may result.

**Other Organochlorines**

Dieldrin, endosulfan and some PCB have estrogenic properties. Dieldrin, endosulfan, and presumably others may exhibit marked synergism with regard to estrogenic effects.
Estrogen-induced Pancytopenia in the Ferret

Source

The female European ferret (*Mustela outorius*) is an induced ovulator. Female ferrets usually reach sexual maturity at 8 months of age. The onset of estrus is indicated by pronounced vulvar swelling. Unbred females may remain in heat for long periods of time (up to 1 year). The prolonged presence of elevated blood estrogen levels results in bone marrow suppression and pancytopenia.

Clinical Signs

Often present as lethargic, with a history of having been in heat for an extended period of time (months). Affected females are from 8 months to 7 years of age. Physical exam reveals pale mucous membranes, and ecchymotic or petechial hemorrhage of the oral mucosa and subcutis. A systolic murmur, weak rapid femoral pulse, dyspnea, hypothermia, and dark mucoid stool may be noticed. Weight loss is a constant finding (normal average adult female weight 680 grams, rectal temperature 102.0, heart rate 216 - 242/minute). Partial or complete alopecia may be present.

Clinical Pathology

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Normal</th>
<th>Pancytopenia</th>
</tr>
</thead>
<tbody>
<tr>
<td>PCV (%)</td>
<td>35.0 - 51.0</td>
<td>4.0 - 17.0</td>
</tr>
<tr>
<td>TP (gm/dl)</td>
<td>5.8 - 7.4</td>
<td>5.5 - 12.0</td>
</tr>
<tr>
<td>Platelets (/µl)</td>
<td>68,000 - 500,000</td>
<td>33,000 - 420,000</td>
</tr>
<tr>
<td>WBC (/µ)</td>
<td>9,000 - 13,000</td>
<td>2,000 - 6,900</td>
</tr>
<tr>
<td>RBC X 10^6 /µl</td>
<td>9.98</td>
<td>1.2 - 3.0</td>
</tr>
</tbody>
</table>

Treatment

- Supportive treatment for hypothermia and dehydration is often required for a successful outcome. IV fluid therapy should be started (tranquilization or anesthesia may be required; ketamine hydrochloride 10 - 30 mg/kg IM or SQ may be given). IV administration of corticosteroids may be required for shock. Transfusion therapy if PCV is below 10% is ideal (jugular is preferred site for collection from donor ferret).
- Therapy of choice for estrus termination is via administration of human chorionic gonadotropin or ovariohysterectomy after stabilization of clotting parameters and restoration of a near normal blood profile. Postoperative hypothermia may occur and should be avoided. A high calorie, vitamin-mineral enriched diet may be required in the immediate postoperative period.
Additional Toxicants

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<tbody>
<tr>
<td><strong>Nonylphenol</strong></td>
<td></td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Plasticizer and component of some detergents and a surfactant used in pesticides; pollution may feminize aquatic animals, possibly terrestrial animals as well</td>
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</tr>
</tbody>
</table>

### References

**Zearalenone and Zearalenol**


**Trifolium (Clovers) and Medicago (Alfalfa and Medics)**


**Other Estrogenic Toxicants**


**DDT and Metabolites: Reproductive Effects and Effects on the Adrenal Gland**


**Estrogen-Induced Pancytopenia in the Ferret**


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