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Effects of Xenobiotics and Phytotoxins on Reproduction in Food Animals

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KEYWORDS

• Phytotoxins • Plants • Xenobiotics • Reproduction • Animals

The influence of natural toxicants and anthropogenic compounds on reproduction in food animals is significant in its economic impact, and the subject requires more research and further experimental substantiation. Confounding factors such as stress, nutritional status, season of the year, animal species involved, genetic variability, disease conditions, management factors, and so forth exacerbate the difficulty of making an accurate diagnosis and thereby may impede progress to improve reproductive performance on an individual operation. The interaction between the reproductive system and xenobiotics (reproductive toxicology) is a relatively new area of study and a subject of increasing interest, especially in the area of environmental exposures and potential work place toxicants affecting human health and reproduction.[1] Much of the experimental literature about this subject comes from rodent models designed to replicate human exposure; however, the extrapolation to food-producing animals is limited at best. The list of compounds in this article with known effects on reproductive function is extensive and represents most classes of chemicals in the environment; however, this list is not intended to be exhaustive.

Investigation of reproductive dysfunction, especially infertility, abortions, and teratogenesis, should center on a thorough examination of animal condition and health, management practices, and infectious agents while potential toxicants are sought. This method requires a systematic approach including individual animal and herd/flock history, veterinary examination of individual animals, testing of blood, urine, feces, or tissues, gross and pathologic/histologic postmortem examination, and

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toxicologic screening of samples of feed and or tissue. In livestock production systems, these investigations are often limited by economics, and the extent of the battery of tests must be determined in consultation between the animal producer, veterinarian, and diagnostician. Reproductive dysfunction includes all facets of reproduction, and when such dysfunction occurs failure to conceive, abortion, stillbirths, and anomalous fetuses may result.

Although the following discussion focuses on abnormal embryonic and fetal development (teratogenesis), many of the principles and methods outlined in this article may be used to investigate the other causes of reproductive dysfunction.

DEVELOPMENTAL TOXICOLOGY (TERATOGENESIS)

Although the exact molecular mechanism(s) is (are) unknown for many developmental anomalies, the production of an abnormal phenotype may be the result of a single (or multiple) defect(s) in the genotype, environmental insult, or animal-environmental interaction. This process results in tissues either failing to differentiate and develop or in incorrect tissue-tissue interactions. Subsequently, these failures impair normal development. Abnormal development occurs when a threshold of genetic and environmental insults is reached and the fetal compensatory mechanisms are overwhelmed; however, abnormal development is only part of the story of reproductive toxicology.

Six basic principles of teratology were originally described by Wilson[2] in 1959 and further defined in 1977. These principles have withstood the test of time and are applicable for not only developmental toxicology but for other types of reproductive dysfunction.

1. *Genetic susceptibility*. Embryonic/fetal susceptibility to teratogens depends on the interaction of genotype and putative teratogen.
2. *Time of exposure*. Developmental stage of the embryo/fetus at exposure or insult often determines the type of defect. The embryo is often more sensitive than the fetus because this is the stage of organogenesis. However, there are numerous examples whereby the teratogen adversely affects fetal development at various stages of pregnancy, such as lupine-induced "crooked calf disease."[3]
3. *Pathogenesis of defective development.* Teratogenic agents may act on cells or tissues by specific biochemical mechanisms to induce the abnormal development.
4. *Definition of abnormal development.* The final manifestation of abnormal development may include death with subsequent resorption or abortion, morphologic malformations, growth retardation, behavioral anomalies, or organ system dysfunction.
5. *Chemical nature of the teratogen.* The access and adverse influence to embryonic or fetal tissues or organs depend on the biologic, chemical, or physical nature of the teratogen.
6. *Dosage.* The amount of teratogen and size of dam influence the degree of insult from little or no effect to lethality. The effects and/or severity of the toxin or teratogen is dose dependent.

Many genetic, bacterial, and viral factors are responsible for certain malformations, and some of these may mimic defects induced by plant or chemical teratogens, thus confounding a diagnosis.

Causes of many human congenital malformations remain obscure, with estimates of 20% to 25% of developmental defects being attributable to genetic anomalies, 5% to identifiable toxicants, and the vast majority (40%–60%) to unknown causes

associated with gene-toxicant interactions.[4,5] While Wilson's principles defining abnormal development have been validated consistently over time, the mechanisms responsible for xenobiotic-induced congenital defects remain elusive, and few studies have identified the pathways of the abnormalities. However, this area of research is rapidly progressing by using molecular tools superimposed on toxins with known effects.[6,7] **Table 1** outlines teratogenic plants and **Table 2** documents other xenobiotics with teratogenic effects.

ABORTION-INDUCING TOXICANTS

Certain natural toxins from plants, fungi, and man-made toxicants have been implicated or associated with abortion, embryonic death, or neonatal loss. In **Tables 3–6** the toxicants of significance to animals are listed, accompanied by the chemical name of the toxicant (if known), the clinical effects, and species affected. **Table 4** specifically lists pines, junipers, and other tree and shrub species that contain the abortifacient toxin isocupressic acid (ICA) or ICA derivatives associated with the so-called pine-needle abortion syndrome in cattle.[10,11] ICA was identified as the primary abortifacient in cattle from Ponderosa pine,[10] and since its discovery numerous tree and shrub species have been screened and found to contain ICA or related compounds (see **Table 4**). As toxin-induced abortions are relatively rare, more frequent causes should be excluded first. The differential diagnosis should also include bacterial or viral agents such as salmonellosis, brucellosis, leptospirosis, mycotic placentitis, bovine viral diarrhea (BVD), infectious bovine rhinotracheitis (IBR), and so forth, and nutritional factors such as deficiencies in β-carotene, selenium, copper, iron, iodine, and so forth.[12–15] Other factors may also be considered such as removal of corpus luteum by palpation or pharmacologically, insemination of the pregnant uterus, multiple fetuses, maternal anemia, uterine or umbilical torsion, rupture of amniotic vesicle, and so forth.

Unfortunately, identifying the exact diagnosis of abortion has a relatively low success rate (<40%). Of course, with improved clinical history, physical examination of affected animals and premises, blood tests, and postmortem evaluation, successful identification of the abortifacient is much better. There obviously is a need to advance methods and techniques to improve the exact diagnosis and to thoroughly identify causes of abortion. Readers are referred to Miller[12] for details of the diagnosis of abortion in livestock.

TOXICANTS AFFECTING FERTILITY

Toxicants causing infertility may result in a temporary reduction in reproductive function or may result in permanent dysfunction. Temporary infertility usually returns to normal when the source is removed and a period of time passes. Subtle changes in herd fertility are difficult to diagnose. Until production records are carefully evaluated and compared with past records, reductions in conception rates of 10% or less may go unrecognized. Even with good records, it is difficult to retrospectively implicate a toxicant when many other factors such as nutrition, stress, genetics, disease, and management may all contribute to such a reduction.

Toxins affecting reproduction may cause dysfunction through one or more mechanisms of action. Toxins may act directly by destroying oocytes or spermatocytes as do some alkylating agents; xenobiotics may act as hormone agonists or antagonists; or toxins may be metabolized to toxic intermediates or to putative compounds with

Table 1
Teratogenic plants

Plant	Toxicant	Effects	Specie and Stage (days) of Development
Veratrum californicum (skunk cabbage, false hellebore)	Steroidal alkaloids cyclopamine, jervine, cycloposine	Cyclopia, cleft palate, limb defects, tracheal stenosis, embryonic death	Cattle, goats, sheep: day 14 cyclopia; day 28–31 limb reductions; day 31–33 tracheal stenosis (sheep)
Veratrum eschscholtizi	Unknown, possibly as above	Cyclopia	Horses
Veratrum album	As above	Cyclopia	Llamas and alpacas
Oxytropis/Astragalus (locoweeds)	Swainsonine, swainsonine *N*-oxide	Bowed limbs, embryo/fetal death	Sheep, cattle, horses; most stages of pregnancy
Lupinus spp *L caudatus* *L sericeus* *L nootkatensis* *L sulphureus*	Anagyrine	Cleft palate, contracture-type skeletal defects	Cattle, 40–100 d
L formosus *L arbustus* *L argenteus*	Ammodendrine	Cleft palate, contracture-type skeletal defects	Cattle, 40–100 d; goats, 30–60 d
Nicotiana tabacum *N glauca*	Anabasine	Cleft palate, contracture-type skeletal defects	Pigs, 30–60 d; cattle, 40–100 d; sheep/goats, 30–60 (35–41 d cleft palate only)
Conium maculatum (poison-hemlock)	Coniine and γ-coniceine	Cleft palate, contracture-type skeletal defects	Pigs, 30–60 d; sheep/goats, 30–60 d; cattle, 40–100 d

Prunus serotina (wild black cherry)	Cyanogenic compounds suspected	Cleft palate, contracture-type skeletal defects	Pigs
Datura stramonium (jimsonweed)	Unknown; possibly alkaloids	Cleft palate, contracture-type skeletal defects	Pigs
Sorghum vulgare *S sudanese*	Cyanogen compounds suspected	Contracture-type skeletal defects	Horses
Lathyrus spp *L cicera* *L odoratus*	Lathyrogens	Skeletal defects	Cattle and sheep
Ipomoea carnea	Calystegines and or Swainsonine	Fetal growth reduced	Rats, goats, rabbits: organogenesis
Luffa acutangula	Proteins; luffin b and lufaculin	Fetal growth reduced; cleft palate	Rats; postimplantation
Mimosa tenuiflora	Unknown	Skeletal defects, brachygnathia, cranial deformities	Sheep, goats, cattle
Caulophyllum thalictroides (Blue cohosh)	Unknown	Cardiovascular and craniofacial cartilage defects	Japanese Medaka embryos
Aspidosperma pyrifolium	Unknown	Delayed fetal development	Rats, goats
Senna occidentalis	Anthraquinones	Delayed behavioral development	Goats

Data from Refs.[3,8,19–36]

Table 2
Teratogenic xenobiotics[a]

Toxicants	Source	Effect	Species
Parbendazole	Anthelmintic	Vertebral column and other skeletal defects	Sheep, goats, cattle, pigs
Methallibure	Pituitary inhibitor	Contracture-type defects	Pigs, 30–50 d gestation
Riboflavin deficiency	Vitamin	Cleft palate, limb reductions	Mammals, birds
Sulfonamides	Sulfur bacteriostatic agents	Beak and feet defects	Chickens
Tetrahydrophthalimide	Captan fungicides	Skull, limb, and visceral defects	Chickens
Tryptophane	Amino acid	Limb and visceral defects	Chickens
Trichlorfon	Organophosphoric insecticide	Cerebral hypoplasia	Pigs
Aminoacetonitrile	Synthetic osteolathyrogen	Skeletal defects	Cattle, sheep
Vitamin A deficiency	Vitamin	Ocular, facial, and central nervous system (CNS) defects	Pigs, cattle, rabbits
Copper deficiency	Trace element	Skeletal and brain defects	Sheep, pigs, horses
Manganese	Trace element	Limbs and vertebrae defects	Rabbits, calves
Molybdenum excess	Trace element	Demyelination resulting in CNS defects	Sheep
Selenium toxicity	Trace element	Fetal hoof defects	Cattle, horses
Aflatoxins	*Aspergillus* spp	Skeletal defects	Rats, goats
Cyanide (cyanogenic glycosides)	Plants	Skeletal contracture defects	Goats

[a] Many other teratogens with reference to rodent models are found in Shepard and Lemire[8] and Szabo.[9]
Data from Refs.[8,9,20,34,35,37–39]

structural similarities to endogenous compounds. These biologic imposters may compete at active sites or alter clearance of natural hormones.

Over the last 30 years, most of the reproductive toxicology research has focused on human reproductive vulnerability to disruption by drugs or workplace and environmental xenobiotics.[1] This research and the risk assessments in humans are generally determined using rodent models, primarily mice or rats. Although research using a rodent model clearly demonstrates potential problems, the direct extrapolation of results from these models to predict toxin-induced reproductive dysfunction or sex-dependent differences in xenobiotic toxicity in livestock species or humans can be inadequate or misleading.

More than 50 years ago sex-linked differences were identified in xenobiotic metabolism. This difference was first observed in rats, where the female was found to be more sensitive to the effects of barbiturates than the male.[5] Subsequent studies

Table 3
Abortifacient plants

Plant	Toxicant	Effect	Species
Pinus, Juniperus, and other woody spp needles and bark: see **Table 4** for specific information on multiple species	Isocupressic acid (ICA) and other ICA derivatives or labdane resin acids	Induced premature parturition	Cattle and bison; anecdotal information suggests llamas also susceptible
Gutierrezia sarothrae or *microcephala*	Unknown	Abortion when grown on sandy soil	Cattle, sheep, goats
Oxytropis and *Astragalus* (locoweeds)	Swainsonine (indolizidine alkaloid)	Abortion, embryonic death	All livestock
Swainsona spp (Australia)	Swainsonine	Similar to locoweeds	Cattle, sheep
Vicia villosa (hairy vetch)	Unknown	Abortion	Cattle
Leucaena leucocephala	Mimosine	Infertility, abortion	Pigs
Aspidosperma pyrifolium	Unknown	Abortion, resorptions	Small ruminants, rats
Tetrapterys spp	Unknown	Abortion	Goats
Artemisia monosperma	Ethanol extracts	Abortion, resorptions	Rats
Bambusa vulgaris	Aqueous extracts	Abortion, resorptions	Rabbits
Ateleia glazioviana	Green or dried leaves	Abortion, stillbirth	Sheep

Other suspected abortifacient plants: *Veratrum californicum* (false hellebore), *Cupressus macrocarpa* (Monterey cypress), *Indigofera spicata* (creeping indigo), *Raphanus raphanistrum* (wild radish), *Lantana camara*, *Iva augustifolia* (narrow-leaf sumpweed), hybrid Sudan (*Sorghum* spp).
Data from Refs.[10,20,23,27,32,37,40–46]

Table 4
Concentration of isocupressic acid or other related metabolic compounds from selected species and locations

Species	Common Name	Location	Isocupressic Acid Conc. (% Dry Weight)[a]
Abies concolor	White fir	Arizona	n.d.[b]
		California	n.d.
		Colorado	0.04
		Utah	n.d.
Abies grandis	Grand fir	Idaho	n.d.
		Oregon	n.d.
Abies lasiocarpa	Subalpine fir	Oregon	n.d.
		Colorado	n.d.
		Idaho	0.04
		Utah	n.d.
Abies magnifica	Red fir	California	0.05
Cupressus macrocarpa	Monterey cypress	California	n.d.–0.06
		New Zealand	0.89–1.24
Cupressus ovensii	—	New Zealand	0.81
Juniperus californica	California juniper	California	0.93 needles
		—	0.05 bark
Juniperus communis	Mountain common juniper	Colorado	2.05–2.88
		Utah	1.50–5.0
Juniperus monosperma	One-seed juniper	Arizona	0.14
		New Mexico	n.d.
Juniperus occidentalis	Western juniper	Oregon	0.10
		—	Imbricatoloic acid = 1.0
Juniperus osteosperma	Utah juniper	Utah	n.d.
		Nevada	0.07
		Arizona	n.d.
		Colorado	n.d.
		Utah	Agathic acid = 1.50
Juniperus scopulorum	Rocky Mountain juniper	Utah	0.84
		New Mexico	0.33
		Arizona	0.42
Juniperus virginiana	Eastern red cedar	Nebraska	needles, low bark, <0.10–high
Larix occidentalis	Western larch	Oregon	n.d.
Libocedrus decurrens	Incense cedar	Oregon	0.07
Picea engelmannii	Engelmann spruce	California	0.27
		Colorado	n.d
		Idaho	0.04
		Montana	0.31
		Oregon	n.d.
		Utah	n.d.
Picea pungens	Colorado blue spruce	Utah	0.17
		Colorado	n.d.
Pinus aristata	Bristle cone pine	Colorado	0.01–0.05
Pinus arizonica	Arizona pine	California	n.d.
		Arizona	n.d.

(*continued on next page*)

Table 4
(*continued*)

Species	Common Name	Location	Isocupressic Acid Conc. (% Dry Weight)[a]
Pinus contorta	Lodgepole pine	Oregon	0.28
		Idaho	0.11
		Colorado	0.29–0.47
		Utah	0.66
		Canada (BC)	0.45
Pinus densiflora	Japanese redpine	Korea	n.d.
Pinus echinata	Short-leaf pine	Arkansas	n.d.
Pinus edulis	Pinyon pine	Arizona	n.d.
		Colorado	0.12
		New Mexico	0.10
		Utah	0.45
Pinus elliottii	Slash pine	Arkansas	n.d.
Pinus flexilis	Limber pine	Colorado	n.d.-0.06
		Utah	n.d.
Pinus halepensis	Aleppo pine	California	n.d.
Pinus jeffreyi	Jeffrey pine	California	0.04–0.54
Pinus koraiensis	Korean pine	Utah	Positive
		Korea	0.02
Pinus monophylla	Single-leaf pinyon	Nevada	0.32
Pinus montezumae	Montezuma pine	California	n.d.
Pinus palustris	Long-leaf pine	Arkansas	n.d.
Pinus patula	Patula pine	South Africa	<0.10
Pinus ponderosa	Ponderosa pine	Oregon	0.74–1.30
		Arizona	0.49
		California	0.08–1.35
		Utah	0.51
		Colorado	0.49–0.58
		South Dakota	0.10–1.30
		Wyoming	0.58–1.11
		Germany	0.62
Pinus radiata	Radiata pine	New Zealand	n.d.–0.26
Pinus taeda	Loblolly pine	Arizona	n.d.
		Arkansas	n.d.
Pseudotsuga menziesii	Douglas fir	Utah	0.04
		Colorado	0.05
		California	n.d.
		Idaho	n.d.
		Arizona	n.d.
		Oregon	n.d
Thuja plicata	Western red cedar	Arizona	0.42
		New Mexico	0.33
		Utah	0.84
		Germany	n.d.
Tsuga mertensiana	Mountain hemlock	Oregon	n.d.

[a] Values are for measured concentrations of isocupressic acid, or where otherwise noted, may include the measurement of a similar related diterpene in samples where the indicated compound was identified and was also the major labdane acid present in the sample.
[b] n.d., not detected (<0.01%).

Data from Gardner DR, Molyneux RJ, James LF, et al. Ponderosa pine needle-induced abortion in beef cattle: identification of isocupressic acid as the principal active compound. J Agric Food Chem 1994;42:756; and Yakubu MT, Bukoye BB, Oladiji AT, et al. Toxicological implication of aqueous extract of *Bambusa vulgaris* leaves in pregnant Dutch rabbits. Hum Exp Toxicol 2009;28:591.

Table 5
Mycotoxins associated with abortions

Fungi	Toxicant	Effect	Species
Claviceps spp (infected grains and grasses)	Ergot alkaloids	Vasoconstriction, abortion	Pigs, cattle, horse, sheep
Acremonium coenophialum (endophyte-infected fescue)	Perloline, peramine, formylloline	Stillbirths, abortion	Cattle, horses, sheep, pigs, rabbits
Balansia spp (infected grasses)	Ergot alkaloids	Similar to *Claviceps* spp	Cattle
Fusarium spp (trichothecenes)	Diacetoxyscirpenol (DAS)	Feed refusal, nausea, abortion	Cattle, pigs
Aspergillus spp and *Penicillium* spp	Ochratoxins (isocoumarins and phenylalanine derivatives)	Nephropathy, enteritis in swine; abortion in cattle	Pigs, cattle

Other mycotoxins suspected to cause abortion include: *Penicillium roqueforti* contaminated grains and corn silage reported in cattle; *Stachybotrys alterrans* contaminated hay or straw reported to cause anorexia, necrotic dermatitis, ulcerative lesions in horses, cattle, sheep and swine, and abortions in swine and cattle in terminal stages; and phomopsins from infected sweet lupines.
Data from Refs.[15,20,37,47,48]

demonstrated that in general, male rats have higher rates of xenobiotic metabolism than do females. This finding was further supported when experiments determined that female rats have 10% to 30% less total cytochrome P450 enzymes than male rats.[13] These sex-dependent differences are further demonstrated in the expression of cytochrome P450 isoforms that catalyze the hydroxylation of steroids.[16] While most literature on sex-dependent differences uses the rat model, there is some limited research suggesting similar sex-dependent differences in metabolism in mice, rabbits, dogs, monkeys, and humans.[1] In livestock there is very little if any research demonstrating similar differences.

Certain reproductive disorders in male children have been increasing in the last decade.[17] Reproductive tract abnormalities such as cryptorchidism, hypospadias, and testicular cancer are increasing in certain human populations. Declining sperm counts have also been reported in certain areas of the world. Similar reproductive disorders have been reported in wildlife species, and have been suggested to be caused by highly contaminated ecosystems. Although few of these types of reproductive disorders in livestock species have been associated with environmental toxicants, more and more anecdotal links are sure to come forth in this regard.

Where xenobiotic-induced reproductive dysfunction is suspected in livestock species, if at all possible the suspected toxicant should be evaluated in the target species. More research is needed to identify toxicants that have adverse impacts on livestock reproduction. Toxicants known to affect male and female fertility are listed in **Tables 7** and **8**, and those affecting fowl are listed in **Table 9**.

Table 6
Other xenobiotics associated with abortion

Toxicant	Source	Effect	Species
Nitrates/nitrites	Plants, water, fertilizers	Poor growth, infertility, abortion, death	Ruminants most susceptible
High protein diets, excess urea	Immature high protein pastures, high urea added to diet	Abortion, embryonic death	Cattle
Carbon monoxide	Incomplete combustion, poor ventilation	Inhibited respiratory function, abortion, stillbirths	Pigs; all species potentially affected
Estrogens/phytoestrogens	Plants, silage, pharmaceuticals	Abortion, infertility, anestrus	Sheep sensitive; other species affected
Glucocorticoids	Pharmaceuticals	Abortion, retained placenta	All species
Halogenated dioxins and related compounds	Wood preservatives, lubricants, solvents	Hypovitaminosis, abortion	Cattle
Lead	Discarded materials, paint, greases, batteries	Ataxia, head pressing, encephalopathy, abortion suspected	All species
Phenothiazine	Anthelmintic	Primary photosensitization, abortion suspected	Cattle, sheep, horses, pigs
Prostaglandins	Pharmaceuticals	Abortions, retained placenta	All species
Oxytocin	Pharmaceuticals	Induced parturition	Horses
DDT, dieldrin, heptachlor	Pesticides	Residues detected in aborted fetuses	Cattle
Warfarin (coumarin)	Rodent bait	Abortion	Cattle

Data from Refs.[14,15,20,37]

Table 7
Toxicants causing infertility

Toxicant	Source	Effect	Species
Phytoestrogens Coumestrol Daidzein Biochanin A Formononetin	*Trifolium subterraneum* (subterranean clover), *Medicago sativa*, *Medicago truncata* (alfalfa)	Infertility, decreased conception, irregular estrous cycles	Sheep, cattle, horses
Zearalenone	*Fusarium* molds	Vulvovaginitis	Pigs most susceptible; other species affected
Zearalenol A and B	*Fusarium roseum*	Anestrus, uterine hypertrophy, anovulatory estrus	Pigs
Steroidal estrogens	Rayless goldenrod	Lactation in unbred ewes and wethers; dystocia, infertility	Sheep
Diethylstilbestrol (DES)	Pharmaceutical (discontinued)	Transplacental carcinogen, abnormal development in fetal reproductive tract	All species
Wheat germ	Wheat grains	Estrogenic effects	Unknown
o,p′-DDT	DDT metabolite	Estrogen effects (egg shell thinning)	Avian species
Ergot	*Ergot sclerotia* (seed grains)	Infertility, abortion, agalactia, decreased prolactin	Cows, sheep, goats, pigs, horses
Swainsonine	Locoweeds, *Swainsona* spp	Early embryonic loss, decreased estrus behavior, reduced ovulation rate, abortion	All species
Mimosine	*Leucaena leucocephala*	Infertility, abortion	Pigs
Selenium	Grasses and forbs on seleniferous soils	Inhibits estrous cycle in excess and may increase spontaneous abortion if deficient	Pigs, cattle
β-Carotene	Excess vitamin A	Reduced conception rates	Dairy cattle
Glucosinolates	*Brassica* spp	Infertility	All species
Ethanol extract	*Abrus precatorius* L.	Infertility/DNA damage to spermatozoa	Mice
Alcohol extract	Neem flower	Blocks ovulation	Rats

Treatment generally involves removal of source and recovery is usually spontaneous.
Data from Refs.[17,20,37,48–50]

Table 8
Toxicants affecting male reproduction

Toxicant	Source	Effect	Species
Swainsonine	Locoweed	Decreased libido, reduced sperm production, increased abnormal sperm	All species
Gossypol	Cotton seed meal	Blocks spermatogenesis, reduces sperm motility, male infertility, testicular degeneration	All species
Phytoestrogens	Clover and alfalfa (see **Table 6**)	Mammary development in wethers, reduced libido in rams	Sheep most susceptible; cattle affected
Boric acid	Commercial applications (roach control, therapeutic and industrial products)	Altered spermatogenesis, decreased sperm motility, increased abnormal sperm	Laboratory species
Anabolic steroids and androgenic hormones	Pharmaceuticals	Prolonged use results in masculinization, testicular degeneration	Horses; most species
Halogenated dioxins	Solvents, lubricants	Masculinization	Horses
Chlorinated naphthalene	Solvents, wood preservatives, lubricants	Testicular degeneration	All species
Acute cadmium toxicosis	Industrial contaminant, anthelmintic	Testicular degeneration	All species

Treatment: Observed changes in spermatogenesis are usually delayed 30 to 60 days, whereas changes in libido may be immediate; treatment usually involves removal of the source and recovery will occur spontaneously. With anabolic steroids, halogenated dioxins, chlorinated naphthalenes, and cadmium toxicosis, the effects may be permanent.

Data from Refs.[8,20,32,37]

Table 9
Toxicants affecting fowl reproduction

Toxicant	Source	Effect	Species
Gossypol	Cotton seed meal	Green yolks, pink albumin, decreased hatchability of eggs	Poultry
Aflatoxin, citrinin, patulin	*Aspergillus* spp	Thickened egg shells	Chickens (residues)
DAS (diacetoxyscirpenol) and others in *Fusarium*; DON (deoxynivalenol) and zearalenone	*Fusarium roseum*	Decreased hatchability, reduced egg production and egg shell weight	Chickens
Ammonia	Pit gases	Decreased egg production	Chickens
Lindane	Organochlorine pesticide	Smaller clutch size, reduced yolk protein	Ducks
DDT (DDE)	Organochlorine pesticide (illegal); residue still in environment	Reduced egg shell thickness, poor hatch, lighter eggs, delayed ovulation, reduced clutch size	All fowl
Lead	Lead-containing products	Reduced egg production	Chickens, quail
Thiocarbamates (thiram, ziram, ferbam, maneb, zineb)	Fungicides	Retarded testicular growth, abnormal seminiferous tubules, infertility	Chickens and other fowl
Selenium	Runoff from Se soils and additives to feeds	Decreased hatchability	All fowl
Glucosinolates	*Brassica* spp, crambe meal rapeseed, etc	Decreased egg production, off-flavored eggs, embryo thyroid enlargement	Chickens, turkeys
Linatine, linamarin	Raw soybean meal	Decreased growth	Chickens
Phytoestrogens	Red clover, subterranean clover (phytoestrogens during dry conditions)	Decreased reproduction rate	California quail
Mimosine	*Leucaena leucocephala*	Infertility at >10% *Leucaena* in diet	Chickens

Data from Refs.[18,20,51–56]

SUMMARY

With the technological advances made in molecular biology, biochemistry, chemical detection, and toxicology, reproductive toxicology has made significant progress in the identification of toxins and mechanisms of action. However, much of the reproductive toxicology research has been done in rodent models and may or may not be totally applicable to food-producing animals or humans. Novel molecular and biochemical probes will enable investigators to move to higher levels of sophistication in their search for mechanisms of action.[18] The charge to protect human health, animal health, and the environment from reproductive toxicants is a challenging one. An effective response will require the talents of multidisciplinary teams of scientists applying novel ideas and techniques. In this article the authors attempt to provide brief information in tabular form for rapid reference with regard to food-producing species. Although this list is undoubtedly incomplete, it demonstrates the extent and complexity of diagnosing the causes of reproductive dysfunction.

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