RESUMO.- [Fitotoxinas eliminadas através do leite: uma revisão]. O leite é uma mistura complexa de lipídeos suspensos em solução aquosa de proteínas e pode ser veículo de diversos contaminantes, mas, geralmente, não é uma importante via de excreção de tóxicos. O principal problema é a exposição repetida, como ocorre com a ingestão de plantas tóxicas, e seu potencial perigo para os animais que consomem o leite. As fitotoxinas já descritas, que são eliminadas através do leite e podem causar danos à saúde incluem: indolizidine alkaloids, causando o armazenamento de oligossacarídeos; piperidine alkaloids, causando acúmulo de óleos ou malformações; pyrrolizidine alkaloids, que causam lesões hepáticas; quinolizidine alkaloids, como causa de defeitos esqueléticos; glucosinolates, que causam alterações na tireoide; tremetol (ou tremetone), que provoca a doença caracterizada por tremores e em humanos, a doença conhecida como doença do leite; monofluoracetato de sódio, que causa a morte de filhotes após a ingestão de colostro de fêmeas que ingeriram Amorimia septentrionalis durante a gestação; ptaquilosídeo, que induz a carcinogênese em animais que ingerem Pteridium spp. Ipomoea asarifolia, que contém indol diterpenos causando tremores em filhotes lactentes. Chrysocoma ciliata causa alopecia em filhotes, mas seu princípio ativo tóxico ainda é desconhecido. O conhecimento e a divulgação sobre o risco de exposição a essas substâncias via leite e sua disseminação são importantes para a saúde animal e humana.

INDEX TERMS: Toxic plants, fitotoxins, elimination by milk, goats, milk, toxicoses.
substances (fat, lactose, proteins, and minerals) and 7/8 of water (Valsechi 2001).

Milk is a route of excretion of several contaminants, such as microorganisms, toxins, antibiotic residues, antiparasitics, and organochlorine pesticides (Heck et al. 2007). Milk contamination can occur before milking (indirect form), either by a pathogen infecting the animal, drugs used, or substances present in feed (Fink-Gremmels 2008), or during or after milking (direct form), through contamination by the milker’s hands or machinery used in milking until the final industrialization process (Pereira 2011).

Because milk is a complex emulsion of lipids suspended in aqueous protein solution, it is considered a minor route of toxicant excretion. However, depending on the toxin concentration in the blood, the ability of a xenobiotic to diffuse across the cell membrane, its affinity for certain constituents in the milk, the efficiency of major detoxification and excretion routes (liver, urine, feces, etc.) and, specifically, the lipophilicity and basicity of the toxin and the type of plant toxin and its metabolites, toxicants can be irreversibly excreted in milk (Panter et al. 1988).

Milk may contain xenobiotics ranging from polar to lipophilic compounds; however, elimination of a toxin depends on its half-life in body water. The half-lives of most polar substances and the rapidly metabolized lipophilic compounds are usually short in milk, because these toxins are rapidly eliminated by the major routes of excretion. Thus, the percentage of the total amount of such compounds that is eliminated via milk is rather small. The main problem is chronic repetitive exposure, as it occurs from ingestion of poisonous plants and its potential danger to animals consuming the milk (Panter et al. 1988).

Some poisonous principles are readily excreted in milk, including those of high fat solubility that are concentrated in the lipid portion of the milk. These lipophilic xenobiotics have long biological half-lives and are frequently detected in milk at the highest concentrations and for the longest periods of time (Mathews 1980).

Elimination of plant toxins via milk is beneficial to lactating animals that ingest toxins; however, consumption of milk from intoxicated animals may induce intoxication in neonates or suckling animals. Poisoning that may occur in suckling offspring may be more severe than in lactating animals, because of toxin concentration in the milk, and young animals lack the ability to efficiently metabolize or detoxify xenobiotics (Panter & James 1990).

Because of the importance of milk to public health and food safety, the need to determine the disposition of xenobiotics and, in particular, of natural phytotoxins in milk and other dairy products, is important. Therefore, the present study aimed to revise the main phytotoxins eliminated in milk and their potential danger to neonates and suckling animals.

**LITERATURE REVIEW**

**Phytotoxins eliminated by milk**

**Indolizidine alkaloids.** The main toxin in this group, called swainsonine, was first identified in *Swainsona canescens* (Colegate et al. 1979) and later in *Oxytropis sereca* and *Astragalus lentiginosus* (Molyneux & James 1982). In Brazil, it is chiefly found in *Ipomoea carnea* subsp. fistulosa (Oliveira et al. 2009), *Ipomoea riedelli*, *Ipomoea sericophyla* (Barbosa et al. 2006), *Ipomoea marcella* (*Ipomoea verbascoides*) (Mendonça et al. 2012), *Turbina cordata* (Dantas et al. 2007), and *Sida carpinifolia* (Driemeier et al. 2000).

Swainsonine inhibits activity of the lysosomal α-mannosidase and Golgi α-mannosidase II enzymes (Dantas et al. 2007), resulting in lysosomal accumulation of incompletely processed oligosaccharides and loss of cellular function followed by cell death (Riet-Correa et al. 2009), causing lysosomal storage diseases (Mendonça et al. 2012).

Regardless of palatability, animals that begin to ingest these plants develop the habit of ingesting them compulsively and, through a social facilitation mechanism, induce other animals of the same species to ingest them. Intoxicated animals show mainly nervous clinical signs, which include ataxia, hypermetria, lateral gait, spastic paresis, intention tremor, and widened base, and may also present somnolence, apathy, anorexia, progressive weight loss, and creepy hair (Dantas et al. 2007, Riet-Correa et al. 2009). The poisoning presents a chronic course, and animals can survive for several months after appearance of the clinical signs. If the animals fail to ingest these plants right after nervous clinical signs are observed or even 15–30 days afterwards, the signs are reversible (Riet-Correa et al. 2009). Histologically, intoxication is characterized by distension and vacuolization in the pericary of neurons, mainly of Purkinje cells of the cerebellum (Oliveira et al. 2009).

In a series of experiments conducted with suckling calves and lambs following a single oral exposure to swainsonine (*Oxytropis sereca*) (0.8 and 2.0mg of swainsonine for kg of body weight, respectively), this locoweed toxin was observed in the milk of both species and confirmed by quantification (Taylor & Strickland 2002). James & Hartley (1977) fed calves, lambs and kittens milk from cows that had ingested *A. lentiginosus* and later found that they showed microscopic lesions characteristic of poisoning caused by this plant, marked by neurovisceral cytoplasmic foamy vacuolization; increased amount of serum aspartate aminotransferase was also observed.

**Piperidine alkaloids.** The most common toxins in this group are found in *Conium maculatum*, causing skeletal defects in calves, piglets, and lambs born to dams that had ingested these toxins at certain stages of pregnancy (Panter et al. 1988). Perhaps the first notable example of poisoning by a member of this group of toxins was the death of Socrates in 399 BC. According to Plato’s famous account in “Phaedo”, the philosopher ingested *C. maculatum*, a plant with high concentrations of conine and γ-coniceine (Reynolds 2005).

In humans, nicotine contained in domestic tobacco (*Nicotiana tabacum*) has been blamed for the occurrence of acute intoxications whose intensities range from mild to severe (Schep et al. 2009). Many other plants of the genera *Nicotiana*, *Lobelia*, *Pinus*, *Dendrobaena*, *Sedum*, *Withania*, *Carica*, *Hydrangea*, *Dichroa*, *Cassia*, *Prosopis*, *Genista*, *Ammodendron*, *Lupinus*, *Liparia*, and *Collidium* also contain piperidine alkaloids (Keeler & Crowe 1985).

Consumption of plants with high contents of piperidine alkaloids can produce acute poisoning (Panter et al. 1999), characterized by frequent urination and defecation, tachycardia, muscle weakness and fasciculation, ataxia, collapse and, eventually, death due to respiratory failure (Panter et al. 1998).

Acute intoxications caused by piperidine alkaloids are assigned to their ability to desensitize the nicotinic
acetylcholine receptors (Green et al. 2010) and inhibition of cation conduction (Na+, Ca2+, and K+). Through their action at the neuromuscular junction, for instance, alkaloids cause transient fasciculation in the skeletal muscles, which are quickly followed by paralysis, progressing to respiratory failure (Arias 2000).

Many plants of these genera are consumed directly or indirectly by humans and animals, and some of them are used in human medicine. Piperidine alkaloids can be eliminated in milk, placing nursing infants at risk of toxicity and pregnant women at risk of teratogenicity. Few cases of transfer of piperidine alkaloids via milk have been reported, but maybe this is due to lack of research (Panter & James 1990).

In 1980, there was an incident in which dairy cows were fed green chopped hay containing approximately 60% C. maculatum. It was reported that 160 lactating cows and 66 heifers were intoxicated. Subsequently, 10 cows and 14 heifers died, and an additional 14 cows and 12 heifers were slaughtered (Kubik et al. 1980). Piperidine alkaloids were detected using thin layer chromatography, and odor typical C. maculatum was detected in the milk and urine of the cows. To avoid hazard to humans, the milk obtained for a period of several days was discarded (Panter & James 1990).

**Pyrrolizidine alkaloids.** Pyrrolizidine alkaloids are naturally occurring phytochemicals in approximately 6,000 plant species of different genera and families (Smith & Bababumi 1980).

They are hepatotoxins that cause irreversible damage to the liver, and many of them may present carcinogenic action. Most plants containing pyrrolizidine alkaloids occur in three families, namely, Boraginaceae, Compositae, and Leguminosae. *Senecio brasiliensis* (Compositae) and *Crotalaria* spp. (Leguminosae) are the main plants associated with pyrrolizidine alkaloid intoxication in Brazil (Cheeke 1998).

In domestic animals, poisoning by plants containing pyrrolizidine alkaloids is mainly due to ingestion when there is shortage of pasture or through prolonged consumption of hay or grain contaminated with these plants, because these compounds present cumulative action (McLean 1970) and can cause a variety of symptoms, including hepatotoxicity, carcinogenicity, genotoxicity and pneumotoxicity (Boppré 2011).

In isolation, these alkaloids are nontoxic, but they become toxic when bio-transformed by the hepatic monooxygenase enzyme into a highly reactive form known as pyrrole (Prakash et al. 1999). The toxicity of pyrroles is associated with their high reactivity, acting as alkylating agents and easily binding to DNA molecules. In addition, pyrroles act by inhibiting mitosis in hepatocytes, leading to megalocytosis, necrosis and, consequently, reduction in the number of hepatocytes, which are replaced with fibrous connective tissue, giving rise to clinical signs and death owing to hepatic dysfunction (Santos et al. 2008). Part of the pyrroles escape into the general circulation, causing lesions in other tissues such as the kidneys and lungs (Radostits et al. 2002).

Natural poisoning can occur acutely or chronically, and is primarily characterized by apathy, anorexia, ascites, jaundice, photosensitization, incoordination, aggression, and head pressure against objects (Lucena et al. 2010).

Aiming to determine the transfer of pyrrolizidine alkaloids by milk, Medeiros et al. (1999) fed a goat with *Crotalaria spectabilis* seeds, which contain the pyrrolizidine alkaloid monocrotaline, and incorporated its milk into the diet of young rats for 60 days; at the end of the experiment, the pups showed lower weight gain and pulmonary and hepatic lesions compared with those in the control group. Goeger et al. (1982) fed lactating goats *Senecio jacobaea*, used their milk in the diet of rats for a prolonged period, and observed mild hepatic pathologies at the end of the experiment.

**Quinolizidine alkaloids.** Quinolizidine alkaloids are widely distributed among the legumes, which use them as a defense against predators because high concentrations of these toxins produce a bitter taste, limiting their consumption. The genus *Lupinus* is the richest of this type of alkaloid. In general, lupines have been used as fodder, green manure, and feed; in folk medicine, they are used as antitumor, anti-diabetic, antioxidant and antifungal agents (Galasso et al. 2006).

Cytisine is a quinolizidine alkaloid found in an ornamental tree commonly known as the Golden Chain or Golden Rain (*Laburnum anagyroides*) and in plants of the genus *Cytisus* (Cheeke & Shull 1985), and their seeds have caused intoxications in humans and horses characterized by excitation, incoordination, seizures, coma, and death by asphyxia (Kingsbury 1964).

Lupines contain the quinolizidine alkaloid anagyrine, which is known to cause skeletal defects and cleft palate in calves when their dams ingested *Lupinus* sp. during days 40 to 70 of gestation, shown to be a teratogenic alkaloid (Keeler 1978). A case study of skeletal abnormalities in a child from California, USA, revealed that the primary source of milk consumed by the mother during pregnancy was from goats that had grazed lush pastures of lupine (*Ortega & Lazerson 1987*). Among the herd, several goats spontaneously aborted and the fetuses showed skeletal defects similar to those of the calf disease reported by Keeler (1978). The mother recalled being clinically ill on many occasions after ingestion of the goats’ milk. Further evidence implicating the milk from goats that ingested *Lupinus* was suggested after several puppies born to a bitch fed the same goats’ milk during gestation showed similar malformations (*Ortega & Lazerson 1987*).

**Glucosinolates.** Glucosinolates are glycosides of β-D-thioglucose that yield isothiocyanate, nitrite, thiocyanate or similar chemicals upon hydrolysis. They occur in the Cruciferae family, whose most of the glucosinolate-containing crucifers that are important in human or animal nutrition are in the genus *Brassica*, which includes cabbage, broccoli, kale, mustard, and turnips, among others. These compounds are responsible for the desirable taste in condiments such as mustard and horseradish sauces (Panter & James 1990).

Goitrin, a hydrolyzed glucosinolate present in some plant species, inhibits thyroid function and causes thyroid hyperplasia and hypertrrophy, inhibiting the incorporation of iodine into thyroxine precursors, interfering with the secretion of this thyroid hormone, and its anti-thyroid effect cannot be corrected by adding iodine to the diet. (Panter & James 1990). Nitrites formed from glucosinolates are toxic, causing poor growth, liver and kidney lesions, bile duct hyperplasia, and liver necrosis (Paik et al. 1980).

Glucosinolates and their derivatives can be transferred to the milk of lactating animals, causing thyroid enlargement in young animals or in humans ingesting the milk; placental transfer of these compounds may also occur. Throckmorton et al. (1981) observed goiter and altered serum thyroid hormones in newborn
Sodium monofluoraceta. Sodium monofluoraceta is a potent naturally occurring toxin in more than 50 plant species in Africa, Australia, and South America (Lee et al. 2014). In Brazil, 12 species are known, belonging to the families Rubiaceae, Bignoniaceae, and Malpighiaceae, causing sudden death syndrome associated with exercise (Carvalho et al. 2009), and sodium monofluoraceta was identified as the toxic agent that causes this syndrome. Owing to their severe toxicity, the Palicourea margravi, Palicourea aeneofusca and Amorimia septentrionalis species are among the most important toxic plants for ruminants in the Country (Tokarnia et al. 2012).

There are reports of intoxication outbreaks by these plants in sheep and goats in the state of Paraiba, Brazil (Vasconcelos et al. 2008). The following clinical signs were observed in experimentally intoxicated goats: dyspnea, tachycardia, and sternal decubitus evolving to lateral decubitus with pedaling movements, followed by death. Some less affected animals recover (Paraguassu 1983). In addition, ingestion of A. septentrionalis during pregnancy causes embryonic mortality and abortion in goats (Silva et al. 2017).

After goat and sheep producers mentioned that kids and lambs, born to dams that grazed in areas with plants of the genus Amorimia during gestation, died suddenly after colostrum ingestion, suggesting that sodium monofluoraceta can be excreted by milk, Vasconcelos et al. (2008) fed two pregnant goats with A. septentrionalis (2g of fresh plant per kg of body weight) and reported that one kid from one of the goats died 5 min after sucking colostrum. Similarly, Lopes et al. (2018) fed eight pregnant goats (1g of fresh plant per kg of body weight) and reported that four kids, born of two goats, received colostrum and presented with apathy, wheezing, lateral decubitus, bleating, and death after 15 min; and two other kids from two goats that delivered during the night were found dead in the morning and, at necropsy, colostrum was found in the abomasum of both kids, indicating that they died after ingesting it.

Ptaquiloside. Described as the most toxic principle found in Pteridium arachnoideum (P. aquilinum), a plant popularly known as field fern or simply fern, ptaquiloside can act as a carcinogenic agent (Alvarenga 2015).

Fern is an invading plant with successful adaptation. Its only limitation regards distribution in extremely low temperatures (Rasmussen 2003). In Brazil, pastures invaded by fern have been reported in all states (Tokarnia et al. 2012).

Ptaquiloside is identified as a nor-sesquisterepine glycoside, amorphous, colorless compound, of formula C_{20}H_{20}O_{8}, found in all structures of the plant, with the shoot apex as the aerial part of the plant with the largest content of that compound (Niwa et al. 1983). Ptaquiloside crosses the cell membranes and, in the nucleus, is able to associate with the proteins with exposed amino terminals, such as DNA (Alonso-Amelot & Avendaño 2002), provoking permanent changes in genes that encode the activation of others, or that present regulatory function such as apoptosis regulation and tumor suppression (Santos et al. 1992).

The toxic and/or carcinogenic effect of fern varies according to the amount ingested, ingestion time, and the animal species involved (Tokarnia et al. 2012), and may cause hemorrhagic diathesis, bovine enzootic hematuria, and upper digestive tract carcinomas; occasionally, occurrence of thiamine deficiency.
intestinal tumors, and progressive retinal degeneration are observed (Cruz & Bracarense 2004).

Alonso-Amelot et al. (1998) fed six lactating cows fern (6kg/animal/day); 38 hours after the animals began to ingest the plant, 8.6±1.16% of the amount of ptaquiloside contained in the plant was identified in the milk. Alvarenga (2015) used 30% of the cheese produced from the milk of cows that had ingested 6g/kg/day of fern in the production of feed provided to rats for 176 days. At the end of the experiment, histopathology revealed that the animals that received feed containing cheese from the cows that ingested fern developed pre-neoplastic lesions (hyperplasia/dysplasia) in the stomach, intestines, and bladder, suggesting that the indirect consumption of ptaquiloside via the milk may induce carcinogenesis.

Studies have demonstrated that, even after pasteurization, part of the amount of ptaquiloside remains in the milk, and that there is positive correlation between the higher prevalence of gastric cancer in humans and permanence in areas invaded by fern (Alonso-Amelot & Avendaño 2002).

**Indole diterpene.** *Ipomoea asarifolia* R. et Schult. is a prostrate or climbing herbaceous plant belonging to the family Convolvulaceae (Tokarnia et al. 2012), native of South and Central America. In Brazil, it is very commonly found in the Amazon and Northeast regions, as well as along the coast, from the Northeast to the Southeast regions (Kissmann & Groth 1992).

*Ipomoea asarifolia* provokes intoxication in cattle, sheep, goats, and buffaloes, especially during the dry season, when there is shortage of forage. The main clinical sign in the different species is muscular tremor that, beginning at the head, is characterized by continuous lateral movements (intention tremors). When animals are restless or scared, the tremors increase and become widespread in the body, with possible loss of balance and falls (Riet-Correa et al. 2003).

In sheep, poisoning was observed in suckling lambs that remained confined, without ingesting the plant, while their dams ingested the plant in the field, but without showing signs of intoxication, suggesting that the plant active principle was eliminated in the milk (Araújo et al. 2008). Initially, this hypothesis was confirmed in mice; when newly-born females began consuming feed containing 20% *I. asarifolia* and, after two days, the suckling pups presented with tremors characterized mainly by lateral movements of the head, intensified when they were restless. The pups recovered 4 to 7 days after weaning (Lopes et al. 2014). Lucena et al. (2014) also demonstrated, but in sheep, that the toxic principle of *I. asarifolia* is excreted via milk of lactating females, when they observed that 50% of the lambs, although kept under confinement, showed tremors after ingesting the milk from ewes grazing in areas where the plant was present, or receiving 20% dry leaves of *I. asarifolia* in their feed. The clinical signs disappeared 1-4 weeks after the end of plant consumption by the dams of the sucking lambs.

Recently, it has been demonstrated that *Ipomoea asarifolia* contains indole diterpenes (terpendol C; terpendol K; 6,7-dehyro-11-hydroxy-12,13-epoxy-terpendol A; paxilline) that cause tremors in mice (Gardner et al. 2018).

**Other phytotoxins.** Several other phytotoxins or their metabolites are excreted via milk, namely, myosin (*Leucaena leucocephala*) (Ghosh et al. 2007), selenium compounds (Kenneth & McConnell 1948), colchicine (Hale 1999), indole, and 3-methylindole (Eisele 1986), but they pose little risk because the amount eliminated is insufficient to cause intoxication.

**Phytotoxins not yet identified**

*Chrysocoma ciliata* L. (Asteraceae). Described as a dense, perennial shrub, approximately 500mm in height, *C. ciliata* presents a rounded shape and numerous small leaves that are slightly sticky and bitter; it has been referred to as "bitter bush". *C. ciliata* is native of southern Africa, and is considered an invasive plant; dense concentrations of this plant indicate occurrence of overgrazing and pasture degradation. A herd will graze large amounts of bitter shrub only if more palatable species are not available (Vahrmeijer 1981).

This plant is associated with alopecia in lambs whose dams ingested the plant during gestation. The exact amount of plant that has to be ingested by sheep for their offspring present with alopecia is still unknown (Steyn 1931).

Steyn (1931) reported that a lamb, whose dam was fed 12.5kg dry *C. ciliata* for 35 days developed alopecia and fatal diarrhea.

The unidentified toxin is transmitted via milk to the young, and this explains why the affected lambs or kids have normal hair at birth: because twins, which consume less milk, are less susceptible to alopecia than the individual offspring, and because the risk of alopecia can be reduced by partial emptying of the udders. Lambs or kids develop alopecia approximately three to 14 days after birth, rarely later. The first signs are pruritus and scratches or bites on the affected areas, often accompanied by swallowing of the hair. The hair becomes creepy and the fleece tufts can be easily pulled. Hair loss begins on the shoulders and sides of the body until eventually only remain at the ends (tail, lower limbs, ears) and at the top of the head. As a result of sun exposure, the hairless areas become reddish and tender, followed by cutaneous exudation and crust formation. In lambs, another common complication is bronchopneumonia, caused by exposure to cold winds. No primary gross lesions were found on the skin of the hairless areas. The non-pigmented skin is notably more easily affected than the pigmented parts. Morbidity in affected farms can range from 1% in dry years to 100% in extremely rainy years. Unless lambs are properly treated, more than 50% mortality can be expected (Steyn 1931).

The most appropriate treatment for affected animals is protection against sun rays and wind, with the use of emollient solution on the hairless areas to avoid hardening of the skin; and as a preventive measure, overgrazing in areas where the plant is present should be avoided (Steyn 1931).

**CONCLUSIONS**

Elimination of phytotoxins via milk, in addition to being a problem for production animals, is a public health concern, because it can directly or indirectly affect the health of humans.

Knowledge about the risk of exposure to these substances via milk and its dissemination are important for veterinary and human health.

**Conflict of interest statement.**- The authors have no competing interests.
REFERENCES


the ingestion of milk from ewes that ingest the plant. Toxicon 92:129-132. <http://dx.doi.org/10.1016/j.toxicon.2014.10.019> | PMID:25448307


