

Poisoning of cattle by *Senecio* spp. in Brazil: a review¹

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Poisoning of cattle by plants of the *Senecio* genus represents an important cause of death in cattle and has important economic repercussions in southern Brazil. This review is intended to provide a detailed review of *Senecio* spp. intoxication in cattle and addresses issues regarding the toxic principle and pathogenesis of the disease caused by these plants and the epidemiology, clinical signs, diagnosis, control and prophylaxis of the disease. *Senecio brasiliensis* is the main species associated with natural intoxication of livestock in Brazil, and the number of cases associated with the ingestion of *S. madagascariensis* is increasing. The toxic principle of *Senecio* spp. comprises the hepatotoxic alkaloids of the pyrrolizidine group (pyrrolizidine alkaloids, PAs). The resulting liver lesions are chronic and irreversible and result from the inhibition of hepatocellular mitosis. Deaths of adult cattle may occur both sporadically and in larger outbreaks over an extended period of time. In cattle raising, *Senecio* spp. are consumed mainly during the winter, when there is a dearth of forage; at this time the poisonous *Senecio* species are budding and contain high concentrations of PAs. Spontaneous *Senecio* spp. intoxication in cattle is a chronic condition that frequently involves acute clinical manifestations. Affected cattle may present ascites, emaciation, intermittent dark diarrhea, tenesmus, rectal prolapse, and neurological signs resulting from hepatic encephalopathy. Hepatogenous photosensitization may be observed but is uncommon. Necropsy findings include dependent subcutaneous edema, ascites, and edema of the mesentery, abomasal folds, and gallbladder. The liver is firm, normal or reduced in size with a white, thick capsule. Microscopically, the hallmarks of *Senecio*-associated disease are varying degrees of hepatocellular megalocytosis, bile duct hyperplasia and fibrosis. Sheep are significantly more resistant to *Senecio* intoxication than are cattle and avidly ingest *Senecio* plants; therefore, the use of sheep for grazing infested pasture is recommended for preventing the associated disease in cattle.

INDEX TERMS: Poisonous plants, *Senecio* spp., Brazil, diseases of cattle, intoxications, diseases of the liver, plant poisoning, cattle, sheep, toxicoses.

RESUMO.- [Intoxicação por *Senecio* spp. em bovinos no Brasil: revisão de literatura.] Intoxicação por plantas do gênero *Senecio* representa uma importante causa de morte

em bovinos com grande repercussão econômica na região sul do Brasil. O objetivo dessa revisão é fornecer uma abordagem detalhada da intoxicação por *Senecio* spp. em bovinos, com enfoque nos seguintes aspectos da intoxicação: princípio tóxico e patogenia, epidemiologia, sinais clínicos, diagnóstico e controle e profilaxia. *Senecio brasiliensis* constitui a principal espécie associada a intoxicações espontâneas em animais de produção e há uma crescente incidência de casos relacionados à intoxicação por *S. madagascariensis*. A toxicidade das espécies de *Senecio* deve-se à presença de alcaloides hepatotóxicos pertencentes ao grupo das pirrolizidinas (APs), que produzem lesão hepática crônica e irreversível, caracterizada pela

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inibição da mitose de hepatócitos. As mortes dos bovinos adultos acontecem de forma esporádica ou em surtos durante um período prolongado de tempo, e podem ocorrer durante o ano todo. As espécies do gênero *Senecio* são pouco palatáveis e consumidas pelos bovinos somente em determinadas circunstâncias, principalmente, no inverno, período em que as diferentes espécies estão em brotação, com maior concentração de alcaloides, e a disponibilidade de forragem é escassa. A intoxicação geralmente cursa com um quadro crônico, embora as manifestações clínicas sejam agudas. Os bovinos afetados podem apresentar ascite, emagrecimento, diarreia escura intermitente, tenesmo, prolapso retal e sinais neurológicos (encefalopatia hepática). Ocasionalmente ocorre fotossensibilização hepatógena. Na necropsia, os principais achados incluem edema subcutâneo ventral, ascite, edema de mesentério e das pregas do abomaso, distensão e edema da vesícula biliar e fígado firme, diminuído de tamanho e com a cápsula brancacenta. Microscopicamente, as principais alterações hepáticas consistem de graus variados de hepatomegalocitose, hiperplasia de ductos biliares e fibrose. A profilaxia inclui o uso de ovinos para pastorear os campos infestados pela planta, visto que essa espécie é mais resistente à ação dos APs e apresenta avidez no consumo da brotação da planta.

TERMOS DE INDEXAÇÃO: plantas tóxicas, *Senecio* spp., Brasil, doenças de bovinos, intoxicações, doenças do fígado, intoxicação por plantas, bovinos, ovinos, toxicoses.

INTRODUCTION

Worldwide, over 1,200 *Senecio* (Asteraceae) species have been described, of which approximately 25 have been found to be toxic to domestic animals or human beings (Tokarnia et al. 2012). Depending on the source of information, there are between 90 (Cabrera 1957) and 128 (Motidome & Ferreira 1966) *Senecio* species in Brazil. Among them, nine have been reported as toxic to cattle: *Senecio brasiliensis* (Tokarnia & Döbereiner 1984, Méndez et al. 1990, Driemeier et al. 1991, Barros et al. 2007), *S. cisplatinus*, *S. heterotrichius*, *S. selloi* (Méndez et al. 1990), *S. oxyphyllus* (Barros et al. 1987a, Barros et al. 1992, Driemeier & Barros 1992), *S. madagascariensis* (Cruz et al. 2010, Stigger et al. 2014), *S. tweediei* (Méndez & Riet-Correa 1993) and *S. desiderabilis* (Tokarnia et al. 1990). The toxicity of latter was demonstrated only experimentally.

It is well established that *Senecio* spp. are the most important toxic plants affecting cattle in southern Brazil (Driemeier et al. 1991, Barros et al. 1992). They are responsible for more than 50% of all cattle deaths caused by poisonous plants in the state of Rio Grande do Sul, Southern Brazil (Riet-Correa & Medeiros 2001, Karam et al. 2004, Rissi et al. 2007).

Intoxication with plants of the *Senecio* genus is also important in other countries of South America (Uruguay, Argentina, and Paraguay), North America, Europe, South Africa, Australia, and New Zealand (Kellerman et al. 2005, Molyneux et al. 2011, McKenzie 2012). In South Africa, approximately 250 *Senecio* species have been identified, among which *S. latifolius* and *S. retrorsus* are the most important (Kellerman et al. 2005). Worldwide, other *Senecio* species related to intoxication in livestock include *S. jacobaea*, *S. plattensis* and *S. vulgaris* in North America and *S. bristolensis* and *S. linearifolius* in Australia and New Zealand (Coombs et al. 1991, McEvoy et al. 1991, Kellerman et al. 2005, Molyneux et al. 2011, McKenzie 2012).

The list of identified toxic species is increasing; recently, *S. grisebachii* was found to be toxic to cattle in Uruguay (Preliasco et al. 2017).

In light of the great importance of *Senecio* spp. poisoning in cattle in southern Brazil and the great economic impacts of the disease, this review aims to provide a detailed overview of several aspects of intoxication, namely, the toxic principle, pathogenesis, epidemiology, clinical signs, diagnosis, control, and prophylaxis.

MORPHOLOGICAL CHARACTERISTICS OF *Senecio brasiliensis* AND *Senecio madagascariensis*

We present here the characteristics of the most common species of *Senecio* in the country (*S. brasiliensis*) and one of steadily growing importance (*S. madagascariensis*) as representatives of the genus.

S. brasiliensis is the most widely distributed species in Brazil and is responsible for the great majority of cases of spontaneous intoxication in cattle. It is a native weed in South America and widely distributed in the southern region of Brazil. Occasionally, it is observed in high and cold areas of the southeastern region of the country. Elsewhere in South America, *S. brasiliensis* is most frequently found in Uruguay, Argentina and Paraguay (Kissmann & Groth 2000, Lorenzi 2008, Matos et al. 2011). Colloquially, the plant is known mainly as “flor das almas” (Portuguese for “flower for the souls”). The adult plant of *S. brasiliensis* is a perennial, erect bush, propagated by seeds; its height is 0.80-1.60m. The leaves are alternate, oblong-deltoid, pinnatifid, sessile, approximately 12cm in length, and divided into 5-11 complete and linear segments. The flowers are yellow and gathered in dense paniculate corymbose chapters. The fruit is cylindrical, glabrous and dark colored (Kissmann & Groth 2000, Lorenzi 2008) (Fig.1A-C).

In addition to the many cases of *S. brasiliensis*, cases of natural intoxication caused by *S. madagascariensis* have been increasing in southern Brazil (Cruz et al. 2010, Stigger et al. 2014). This plant is native to Madagascar and South Africa. It is an important invasive weed, especially in latitudes similar to those of its origin (Scott et al. 1998). It has been introduced accidentally in several countries, including Australia (McKenzie 2012), the United States (Roux et al. 2006), Argentina (Villalba & Fernández 2005), Uruguay, Japan (Tsumumi 2011) and Brazil (Cruz et al. 2010). It was originally identified in the state of Rio Grande do Sul in 1995 (Matzenbacher & Schneider 2008). This species has great dispersal capacity and exhibits high levels of environmental and climatic adaptation due to its hibernal characteristics (Matzenbacher & Schneider 2008). *S. madagascariensis* is an upright perennial herb 20-60cm in height, hairless or sparsely hairy, occasionally with numerous branching stems. Leaves are alternate in the midregion of the stems; they are mostly simple, 3-10cm in length, and narrow, with 15-25 tiny teeth (denticulations) along the edges. The few divided leaves have one or two narrow-triangular lobes that lie approximately centrally on each side. Groups of two to 20 bright yellow daisy-type flower heads occur at the top of the stem branches. Each flower head has approximately 20 involucre bracts with brown or black tips in an involucre of 4-6mm in length and approximately 3-5mm in diameter. There are 50-70 florets, approximately 13-15 of which are

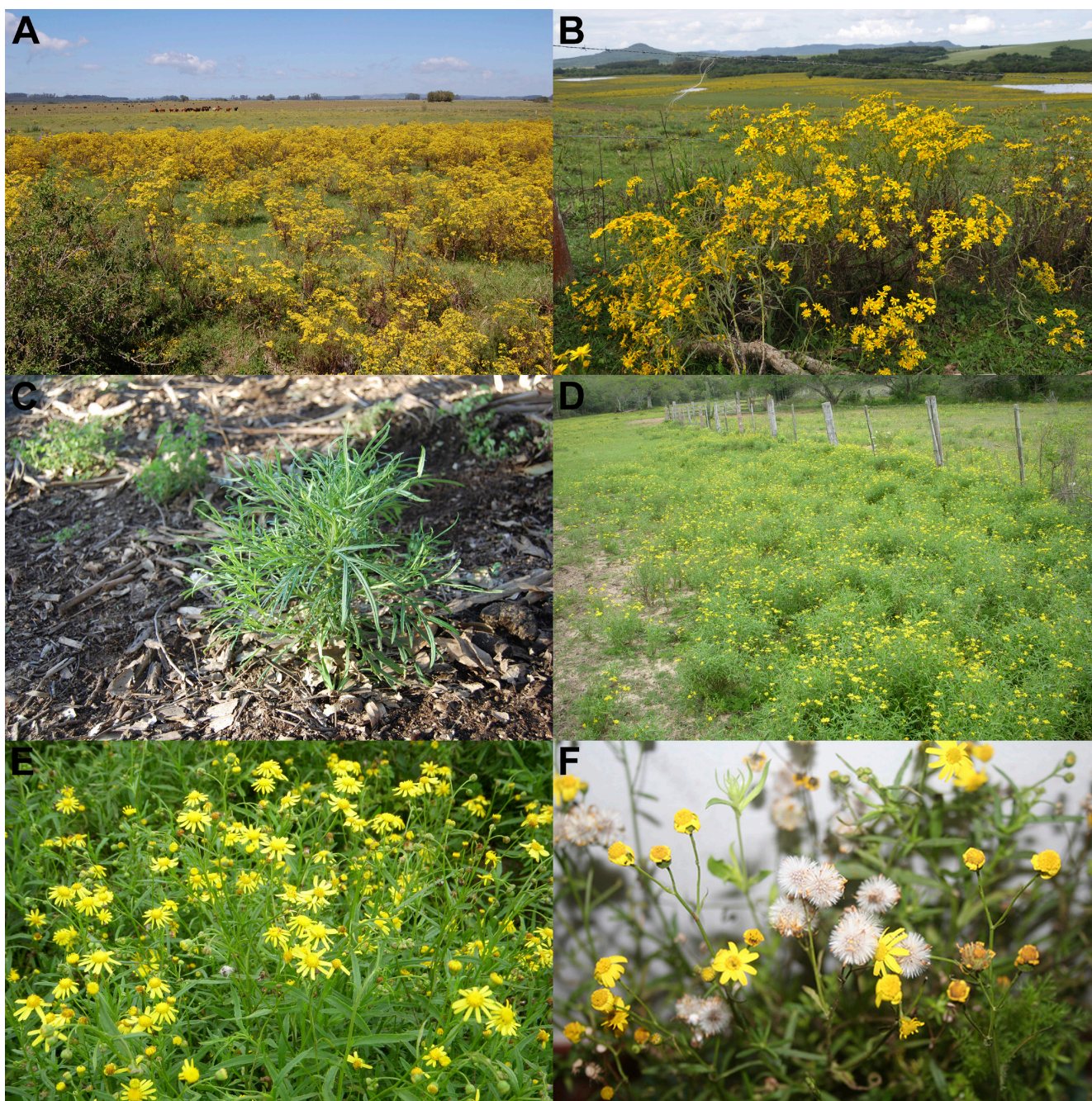


Fig.1. Characteristics of *Senecio brasiliensis* and *S. madagascariensis*. (A) Pasture in the fall intensely invaded by blooming *S. brasiliensis*. (B) Closer view of *S. brasiliensis* specimens; the petals of the flowers are characteristic yellow. (C) A sprouting *S. brasiliensis* specimen during winter can be observed here. At this stage, the weed is more easily ingested by cattle. (D) Pasture in the fall intensely invaded by blooming *S. madagascariensis*; the plant is shorter than *S. brasiliensis*. (E) Closer view of a flowering *S. madagascariensis* specimen. (F) Both flowering and senescence (white heads) phases of *S. madagascariensis* can be observed here.

florets with petals 5-10mm in length. Seeds are mid-to-dark in color; 1.5-2.5mm in length, with pappus bristles 3-6.5mm in length (McKenzie 2012) (Fig.1D-F).

TOXIC PRINCIPLE AND PATHOGENESIS

The toxic principle of plants of the genus *Senecio* comprises pyrrolizidine alkaloids (PAs). PAs are naturally occurring phytochemicals in approximately 6,000 plant species of

different genera and families (Lucena et al. 2010). In addition to occurring in the genus *Senecio*, PAs are present in other plants, mainly of the genera *Echium*, *Crotalaria* and *Heliotropium* (Kellerman et al. 2005). Toxicity is of great importance in livestock, and although rare, there are reports of intoxication in humans, primarily in underdeveloped countries and related to eating habits (McLean 1970, Molyneux et al. 2011). PAs cause irreversible damage to the liver and have a potential

carcinogenic effect (McLean 1970). The PAs contained in the plants are not chemically reactive, and most of them are excreted unchanged. However, they become toxic when they biotransform in the liver into a highly reactive pyrrole, known as 1,2-dehydropyrrolizidine, which is the primary toxic metabolite. Secondary toxic metabolites, termed alcoholic pyrroles, are also formed (McLean 1970, Prakash et al. 1999).

The biosynthesis of PAs begins at the roots of the plant, where N-oxides are produced. PAs are then transported to higher plant structures, namely, the leaves and flowers. There they undergo molecular changes, resulting in different PAs. However, they only become toxic when they are metabolized by the liver into a highly reactive pyrrole (Silva et al. 2006), as previously described. A number of PAs have been extracted from *S. brasiliensis*, including integerrimine, senecionine, retrorsin, and usuramine (McLean 1970, Hirschmann et al. 1987, Silva et al. 2006, Matos et al. 2011, Molyneux et al. 2011, Pavarini et al. 2012). Alkaloids identified in other species of *Senecio* include the following: neosenkirkina, integerrimina and florosena in *S. leptolobus*; retrorsin, senecionin, 18-hydroxy-jaconin and senecivernin in *S. selloi*; retrorsin and senecionine in *S. cisplatinus*; retrorsin and integerrimine in *S. heterotrichius*; and retrorsin and ligularizine in *S. oxyphyllus* (Méndez et al. 1990, Liddell et al. 1992, Krebs et al. 1996, Pavarini et al. 2012, Tokarnia et al. 2012). The accumulation of pyrrolizidine alkaloids might be related to the seasonality and phenology of *Senecio* species (Karam et al. 2002).

Chemically, PAs are heterocyclic molecules that contain a nitrogen atom attached to the main ring and are generally alkaline substances. The basic nucleus of an aminoalcohol is termed a necine (pyrrolizidine nucleus), consisting of two rings of five atoms joined by a single nitrogen atom; the acidic portion is termed a necic acid (aliphatic acid) and is composed of one or two branches of a carboxylic ester (McLean 1970, Molyneux et al. 2011, Pavarini et al. 2012).

The basic structure responsible for the hepatotoxicity of PAs is determined by at least four structural characteristics (Prakash et al. 1999): (1) one 3-pyrroline ring, (2) one or two hydroxyl groups attached to the pyrroline ring, (3) one or two esterified groups, and (4) a branched chain on the acid residue. However, the essential characteristic underlying hepatic toxicity, both acute and chronic, is the unsaturated necine between carbons 1 and 2 (Sandini et al. 2013).

After absorption, PAs reach the liver via portal circulation and are biotransformed by the hepatic microsomal enzymes of the cytochrome P450 complex, yielding highly toxic pyrroles. The major routes of hepatic metabolism of PAs are ester hydrolysis, N-oxidation, and dehydrogenation. The first two reactions are involved in the detoxification mechanism, whereas dehydrogenation is related to pyrrole formation. Pyrroles, responsible for toxicity (Santos et al. 2008), are electrophilic and react with nucleophilic tissue components, such as nucleic acids and proteins (Sperl et al. 1995). As the liver is the site of production of these toxic pyrroles, it is a major target organ, followed by the lungs (Sandini et al. 2013). Pyrroles injure hepatocytes, irreversibly binding to DNA (the alkylating effect) and inhibiting hepatocyte mitosis. As DNA continues to be synthesized in the nucleus, the nuclear and cytoplasmic volumes of the non-dividing cell continue to increase. This increase in the whole cell volume (not only the nucleus volume) is termed hepatomegalocytosis

(Bull 1955). Despite their volume, megalocytes are not higher functioning cells; their metabolism diminishes considerably (Seawright et al. 1991), and those attempting mitosis die (McLean 1970) and are replaced by connective fibrous tissue; these changes are referred to as hepatocyte loss and fibrosis, respectively. A portion of the pyrroles may escape into the general circulation (spillover effect), causing damage to other tissues, such as those of the kidney and lungs, as cytochrome P450 enzymes are also present in these organs (McLean 1970, Molyneux et al. 2011).

All parts of *S. brasiliensis* are toxic, as fresh or dried material (Tokarnia et al. 2012). However, some studies have shown variations in toxicity related to the time of year (seasonal variation), development stage (budding, flowering), and plant part (stems, roots, or seeds) (Johnson et al. 1985, Karam et al. 2002, Tokarnia et al. 2012, Sandini et al. 2013). The content of PAs in *S. madagascariensis* is highest in the aerial parts, especially the flowers during spring. The variety of PAs present and the variation in the content of each directly influence the toxic effect of the plant and consequently, the manifestation of disease (Karam et al. 2011).

The toxic dose can be highly variable depending on the plant species considered, the stage of growth, the content of alkaloids present, the period (duration) of ingestion, and idiosyncratic factors related to the animal itself (Karam et al. 2004). Acute intoxication with *S. brasiliensis* was reproduced with single doses corresponding to 17.5 and 35g/kg/body weight (bw) of green plant. The chronic manifestation of disease was observed with single doses of 5-10g/kg/bw of fresh green plant or with repeated daily doses of 0.625-5g/kg/bw totaling 75-150g/kg/bw. Chronic intoxication was also reproduced with weekly doses equivalent to the accumulation of seven daily doses of 2.18-8.75g/kg/bw, totaling 61.25-78.75g/kg for 1-8 months (Tokarnia & Döbereiner 1984). Experiments with other *Senecio* species in cattle were lethal at total doses of 22.5g/kg/bw (*S. cisplatinus*), 180g/kg/bw (*S. heterotrichius*) and 45-180g/kg (*S. selloi*) of dried plant (Méndez et al. 1990).

EPIDEMIOLOGY

Several studies have demonstrated the sensitivity of cattle to *Senecio* intoxication and the high frequency of cases in cattle (Méndez et al. 1987, Driemeier et al. 1991, Barros et al. 1992, Basile et al. 2005, Barros et al. 2007, Pedroso et al. 2007, Rissi et al. 2007, Grecco et al. 2010, Lucena et al. 2010, Giaretta et al. 2014a, Panziera et al. 2017). Typically, spontaneous disease is observed in 2-year-old or older grazing cattle (Barros et al. 2007, Barros 2016). Occurrence in calves is uncommon (Basile et al. 2005, Barros et al. 2007, Panziera et al. 2017). However, it has been shown experimentally that young cattle are more susceptible to intoxication than are older cattle (Torres & Coelho 2008). Occasionally, intoxication is associated with the consumption of hay that has been contaminated with the plant (Barros et al. 1987b, Basile et al. 2005, Barros et al. 2007, Barros 2016).

Most cases of poisoning occur in cattle that have undergone a period of forage deprivation during the year or the previous year. The risk of ingestion of *Senecio* spp. through direct grazing is higher in times of lack of forage dearth, as *Senecio* spp. are not palatable and are consumed by cattle only under certain conditions. It is estimated that *Senecio* spp. are ingested in greater amounts during the winter, from May to August.

During this time, plant sprouting occurs, and there is a higher concentration of alkaloids in the weed. Furthermore, during this period, the availability of fodder is scarce in the native fields of Southern Brazil (Barros et al. 1987a, Driemeier et al. 1991, Barros et al. 1992, Riet-Correa & Méndez 2007, Tokarnia et al. 2012). Cattle deaths may occur months or years after the last intake of the plant or after the plant has wilted and is no longer evident in the pasture (Barros 2016).

The overcrowding of cattle during the winter and the large number of sprouting weeds will predispose their ingestion, especially if the sprouts are in close association with forage grass (Driemeier et al. 1991, Barros et al. 1992). Although the intake frequency of *Senecio* spp. by cattle is higher from May to August (winter), ingestion and intoxication can occur outside this period. Under favorable environmental conditions for plant growth (precipitation, soil moisture, light, temperature, and pasture management in each property), sprouting may occur at any time of the year. Depending on the damage suffered, such as excessive trampling and cutting, *Senecio* spp. can behave as annual, bi-annual, or perennial species. If injury is intense or frequent, many *Senecio* spp. will exhibit a bi-annual cycle, with most plants needing two or more years to bloom. However, if conditions are consistently favorable for growth, some plants may flower during the first year, behaving as annuals (Karam et al. 2004, 2011). In Rio Grande do Sul, it has been observed that *Senecio* spp. in a vegetative stage are consistently present, indicating the constant exposure of livestock to the weed. Thus, cattle deaths can occur throughout the year (Karam et al. 2002, 2004, Riet-Correa & Méndez 2007).

CLINICAL SIGNS

The clinical manifestations of *Senecio* spp. poisoning in cattle are secondary to chronic hepatic lesions (Barros 2016). Acute cases of the disease are rare in nature and are mostly restricted to experimental trials (Tokarnia et al. 2012). Repeated ingestion of small amounts of the sprouting plant over a prolonged period causes progressive hepatic injury over weeks or months until the disorder becomes sufficiently severe and signs of liver failure ensue. In such cases, cattle ingest quantities insufficient to induce the acute form. However, small portions are capable of producing negligible lesions that, over extended periods of time, can merge into large chronic injuries that result in clinical signs of liver failure (Tokarnia & Döbereiner 1984, Lucena et al. 2010). Morbidity in outbreaks of *Senecio* spp. has varied from 4.92–58.6% (mean of 17%), and lethality is near 100% (Barros 2016).

Two clinical courses are observed as follows: 1) a chronic course in which death is preceded by weight loss and intermittent diarrhea over several weeks or months (e.g., winter ingestion followed by death in the following winter) and 2) a clinical course that is acute (24–96 hours) and may occur in apparently healthy cattle that suddenly develop neurological signs such as aimless walking, circling, head pressing, incoordination, and blindness. Affected cattle can become oblivious to the environment or attack people or objects in their path. Nervous signs are secondary to hepatic encephalopathy and are generally premonitory of impending death (Barros 2016).

The performance of several studies of *Senecio* spp. poisoning in cattle in Rio Grande do Sul allows us to classify

the clinical signs according to their relative frequencies. Common clinical manifestations (observed in more than 60% of cases) include a rough hair coat, anorexia, isolation from the herd, and rectal tenesmus. Moderately frequent signs (20–60% of cases) are weight loss, diarrhea (Fig.2A), rectal prolapse (Fig.2B), neurological disorders (Fig.2C), and ascites. Uncommon manifestations (less than 20% of cases) consist of jaundice, photosensitization (Fig.2D), polydipsia, and subcutaneous dependent edema (Driemeier et al. 1991, Barros et al. 1992).

Neurological signs result from the accumulation of substances such as ammonia, short chain fatty acids, and mercaptans in the bloodstream, cerebrospinal fluid, and brain as well as changes in neurotransmitter concentrations. Typically, toxic substances are eliminated while passing through the liver. This clearance does not occur under severe and diffuse liver damage, culminating in liver failure. Consequently, these substances can reach the brain and, as false neurotransmitters, cause neurological clinical signs. Ammonia is considered the main factor involved in the pathogenesis of hepatic encephalopathy (Summers et al. 1995).

In cases of photosensitization, a more extended clinical course of intoxication (between 30–60 days) is observed (Tokarnia et al. 2012). In such cases, photosensitization is secondary (hepatogenous) and associated with tissue accumulation of phylloerythrin, a photodynamic pigment. When non-pigmented areas where phylloerythrin has been deposited are exposed to ultraviolet light, necrotizing dermatitis develops. The lesions are frequently observed in the nasal plane (Fig.2D), ears, udder and teats, periocular and vulvar skin, the skin of the dorsum, and ventral aspects of the tongue. Initially, the signs are characterized by photophobia, lacrimation, nasal secretion, and erythematous and exudative cutaneous lesions that evolve to severe crust lesions (Motta et al. 2000, Tokarnia et al. 2012, Giaretta et al. 2014a, Panziera et al. 2017). The lesion on the tongue is observed in the ventral portion (ventral diphtheric glossitis). Due to the nasal serous secretion, the affected bovine compulsively licks the secretion at the nostrils, which results in continuous exposure of the ventral aspect of the tongue to sunlight (Giaretta et al. 2014a, Panziera et al. 2017). It is important to note that other plants are also associated with hepatogenous photosensitization in livestock in Brazil, sometimes more frequently; such plants include *Brachiaria decumbens* and *B. brizantha* (Riet-Correa et al. 2011, Assumaidae & Mustapha 2012), *Lantana* spp. (Brito et al. 2004), *Panicum dichotomiphlorum* (Riet-Correa et al. 2009), *Myoporum laetum* (Raposo et al. 1998) and *Enterolobium* spp. (Leal et al. 2017). Thus, the epidemiological evaluation and the anatomopathological findings are important for accurate diagnosis.

Jaundice, which has been observed in a few cases, can occur due to the failure of the liver to excrete and secrete pigments, bile acids, and bile salts, with consequent tissue deposition of such substances in the tissues. Subcutaneous edema arises from hypoproteinemia and is attributed to the failure of the liver to synthesize albumin and other plasma proteins. Additionally, there are increases in portal pressure and the activation of the angiotensin aldosterone system due to the low renal perfusion resultant from ascites. The resultant increase in sodium uptake elevates blood volume and,

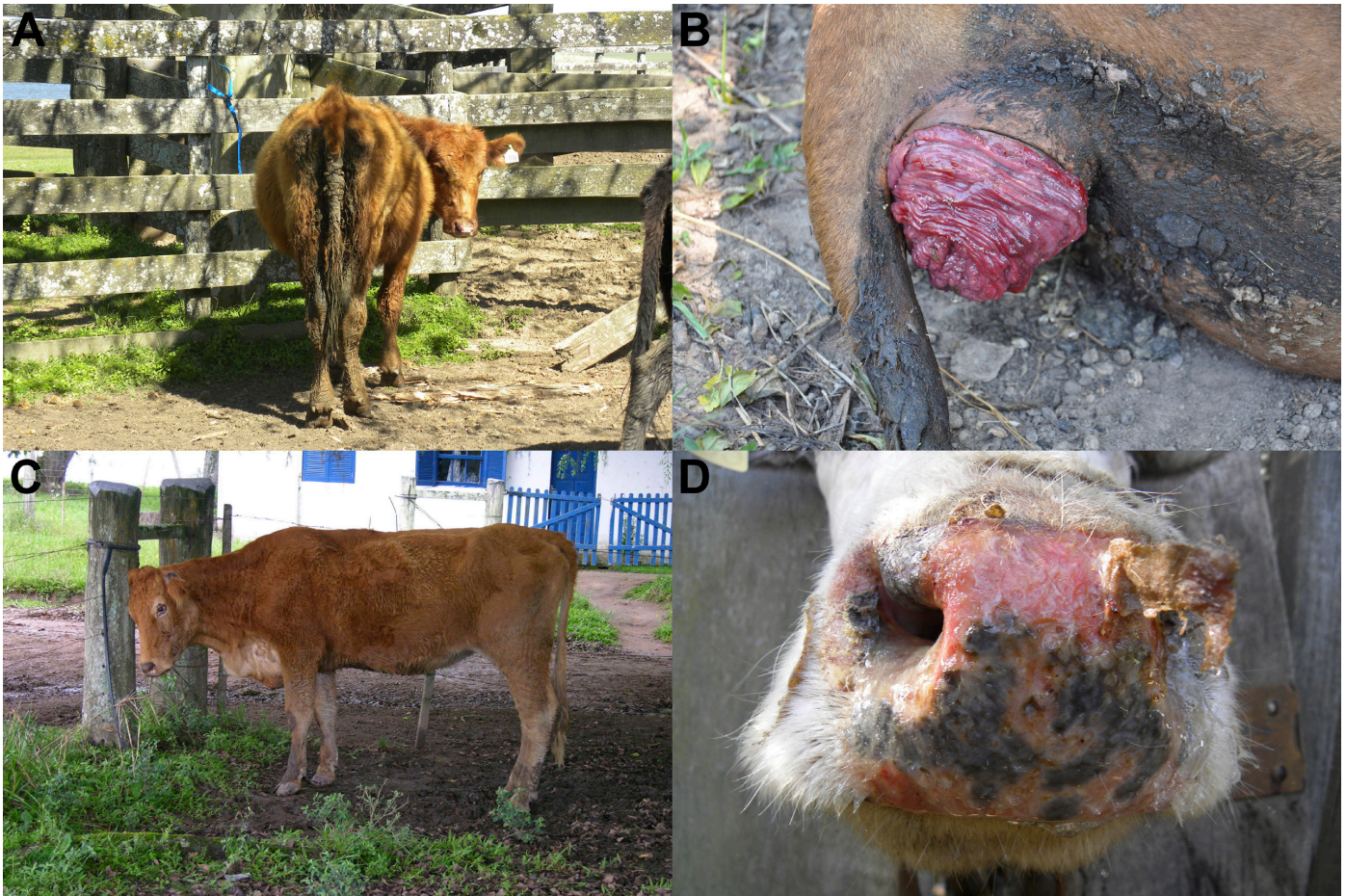


Fig.2. Clinical signs of *Senecio* spp. poisoning in cattle. (A) Affected steer with markedly distended abdomen (ascites), rough hair coat and dry feces adhered to the tail and perineum (evidence of diarrhea). (B) Affected steer with marked prolapse of rectum secondary to tenesmus. Dried stools adhered to the tail and perineum indicate diarrhea. (C) Heifer with head pressing. This neurological sign is secondary to liver failure (hepatic encephalopathy). (D) Cow with photodermatitis of the muzzle, secondary (hepatogenous) to liver compromise.

consequently, hydrostatic pressure (Santos et al. 2008), thus compounding the edema.

PATHOLOGY AND DIAGNOSIS

The diagnosis of intoxication by *Senecio* spp. in cattle is made based on epidemiological, clinical and pathological findings associated with evidence of plant consumption by animals. It is important to consider that cattle deaths may occur several months after the last ingestion of the plant. The morphological changes, predominantly hepatic changes or changes secondary to hepatic failure, are important for a definitive diagnosis (Driemeier et al. 1991, Barros et al. 1992).

Necropsy findings are those of a chronic toxic hepatopathy and are widely described (Driemeier et al. 1991, Barros et al. 1992). A significant and almost invariably gross lesion is a firm consistency of the liver. Liver size is often standard or slightly decreased. In most cases, the hepatic capsular surface is smooth and gray due to thickening of the Glisson's capsule by fibrosis (Fig.3A). Occasionally, small nodules appear on both the capsular and cut surfaces. The hepatic cut surface is crisscrossed by a fine fibrous tissue web that divides the hepatic parenchyma into irregular nodules (Fig.3B). These nodules, which are interpreted as regenerative, may be well

developed or absent. Some nodules might be yellow due to fatty degeneration. In most cases, the color of the cut surface of the liver is lighter (due to fibrosis) or dark brown (Fig.3C). In some cases, red spots (necrosis and hemorrhage) are observed in the hepatic parenchyma. The gallbladder is markedly distended, often with an edematous wall and a lumen filled with inspissated bile. Edematous polyps occur in approximately 30% of cases in the mucosa of the gallbladder (Fig.3D). In almost all cases of cattle intoxication with *Senecio* spp., edema of the mesentery (Fig.4A) and abomasal folds (Fig.4B) is observed. The edema has a translucent and gelatinous appearance and is typically marked. A large amount (5-30 liters) of a citrine or serous fluid can be found within the abdominal cavity (ascites) (Fig.4C), primarily in adult cattle. Subcutaneous edema, mainly in the ventral portions of the mandible, neck, and brisket (dependent edema); hydrothorax (Fig.4D); hydropericardium; and portosystemic shunts are also observed, along with hemorrhages in the serosa of the abdominal viscera (Barros 2016).

Histologically, the hepatic lesions due to *Senecio* spp. poisoning in cattle are morphologically compatible with cirrhosis and consist of (1) hepatocyte loss, (2) hepatomegalocytosis, (3) proliferation of bile ducts, and (4) varying degrees of

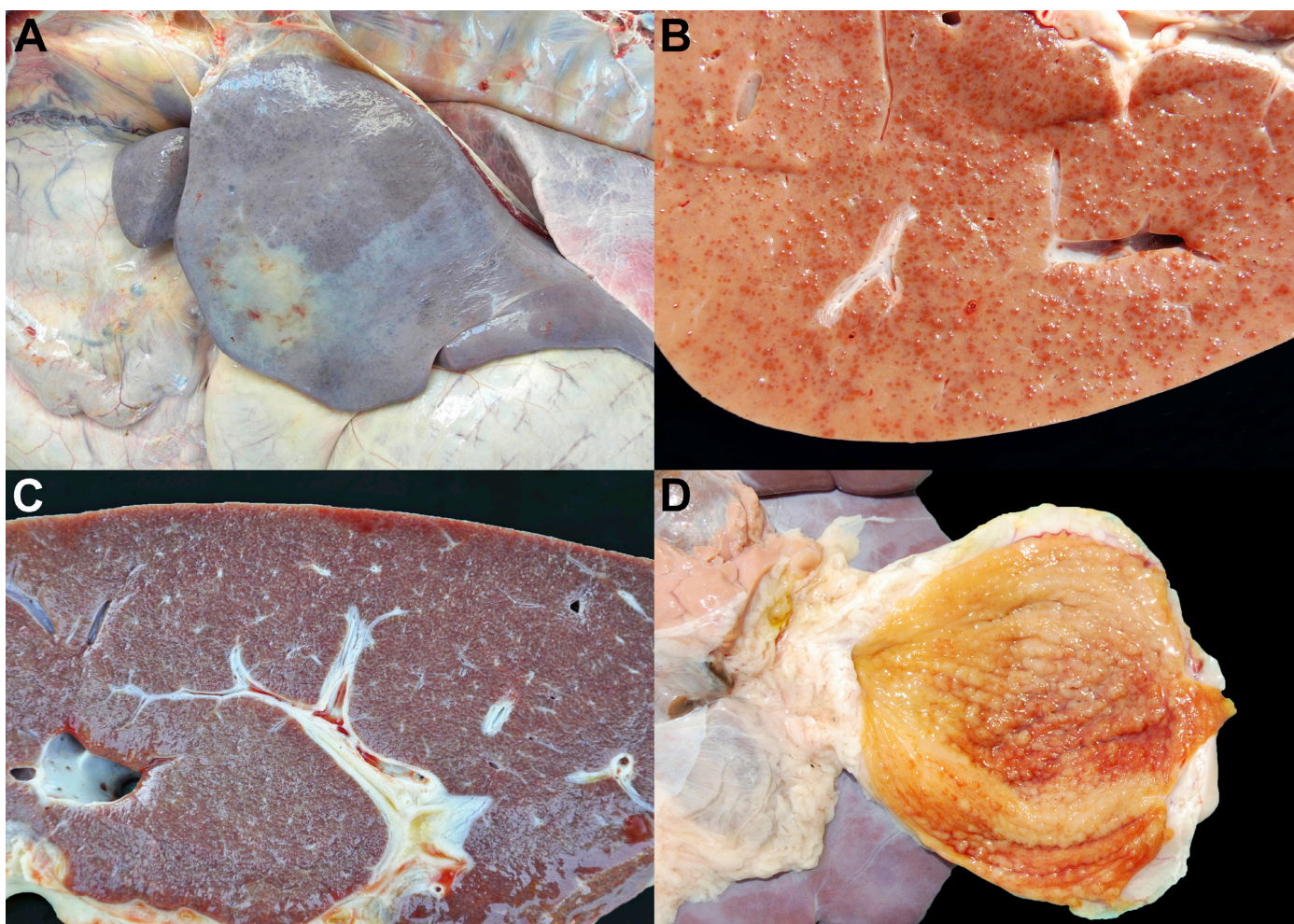


Fig.3. Necropsy findings of poisoning by *Senecio* spp. in cattle. (A) The hepatic capsule is thick, white slightly irregular. (B) Hepatic cut surface showing numerous small brown nodules of regeneration amidst a white background (fibrosis). (C) Hepatic cut surface showing another macroscopic pattern of liver injury caused by *Senecio* spp. In this case, there is a predominant brown parenchyma crisscrossed by a network of fine white strands (fibrosis). (D) Gallbladder; multiple edematous polyps are observed in the mucosa.

fibrosis (Fig.5A) (Driemeier et al. 1991, Barros et al. 1992). Hepatic fibrosis is typically of the dissecting type and causes disorganization in the normal architecture of the hepatic lobe. Frequently are observed groups of hepatocytes (regenerative nodules) often displaying vacuolar degeneration, and surrounded by a thin layer of connective tissue (Fig.5B). A disorganized proliferation of reticular fibers (reticulin) fibers dissects the parenchyma disrupting its normal collagen scaffold (Fig.5C). Occasionally, proliferated fibrous tissue obliterates centrilobular veins (veno-occlusive lesion) (Barros 2016). Veno-occlusive injury has been reported in cattle affected by aflatoxicosis (Pierezan et al. 2010, Pierezan et al. 2012) and in cases of *Senecio* spp. poisoning in humans (McLean 1970, Stalker & Hayes 2007). In some cases, hepatocellular necrosis and hemorrhage are apparent.

The encephalic alterations secondary to hepatic failure (hepatic encephalopathy) are characterized by varying degrees of vacuolization (*status spongiosus*), mainly at the junction between the gray matter and the subcortical white matter of the frontal, parietal and occipital telencephalon and the white matter of the cerebellar peduncles (Barros 2016) (Fig.5D).

In more severe cases, vacuolization can also be observed in the thalamus, brain stem and spinal cord (Panziera et al. 2017).

Although the morphological lesions previously described are classical for *Senecio* spp. intoxication in cattle, in some cases, the pattern of hepatic lesions vary depending on the course of the disease. Such variation is related to the amount and distribution of fibrosis and the extents of megalocytes and biliary proliferation (Grecco et al. 2010, Panziera et al. 2017).

Spontaneous subacute cases of intoxication are uncommon; when they occur, they are characterized by the predominance of degenerative and necrotic lesions associated with a milder proliferation of ductal epithelium and fibrous connective tissue (Tokarnia & Döbereiner 1984, Panziera et al. 2017). It is extremely important to recognize the different patterns caused by the ingestion of PAs, as the occurrence of uncommonly observed gross lesions might hinder the initial diagnosis of intoxication (Panziera et al. 2017).

The determination of the serum activity of gamma-glutamyltransferase (GGT) represents the best biochemical diagnostic parameter to identify the poisoning of cattle with *Senecio* spp. (Lopes et al. 1994). GGT is an enzyme

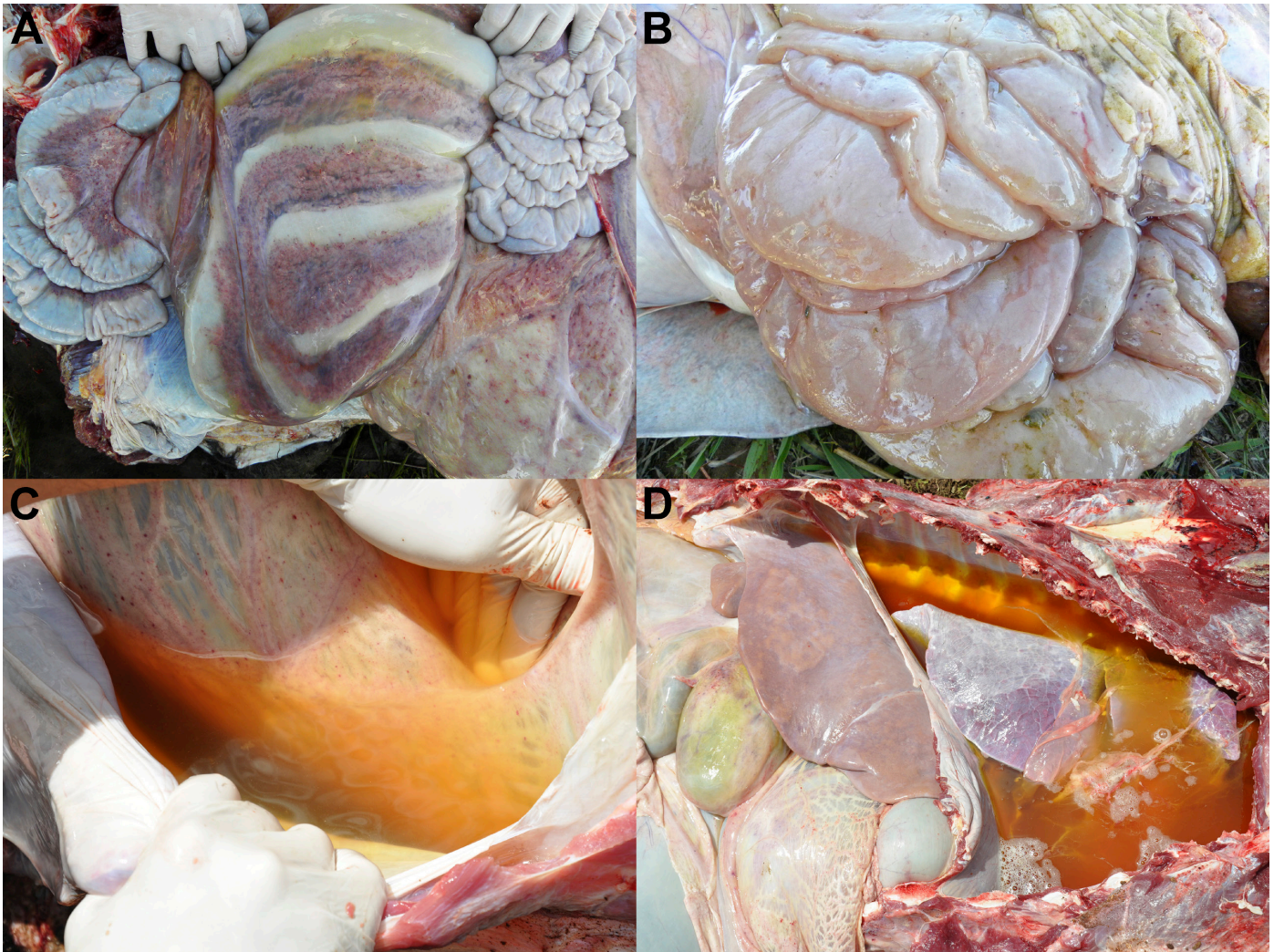


Fig.4. Necropsy findings of poisoning by *Senecio* spp. in cattle. (A) Marked edema of the mesentery. (B) Translucent edema markedly distends the abomasal folds. (C) Accumulation of citrine fluid in the abdominal cavity (ascites). (D) Marked accumulation of citrine fluid in the thoracic cavity (hydrothorax). The white material floating in the liquid are fibrin flakes. Furthermore, the gallbladder in this image is markedly distended.

originating from the membranes of the canaliculi and bile ducts. An increase in its serum activity is exclusively related to intra- and extra-hepatic cholestasis and the proliferation of bile ducts. This enzyme is typically restricted to the smooth endoplasmic reticulum, where the mixed oxidase system is active. This system activates the pyrrolizidine alkaloids, causing hepatocyte damage and serum GGT release (Santos et al. 2008). However, hepatic function tests are unreliable in detecting subclinical and even clinical cases of intoxication (Panziera et al. 2017) since hepatic function can be normal during this stage (Barros et al. 2007). Thus, in an outbreak of intoxication by *Senecio* spp. in cattle, a liver biopsy is indicated for identifying cattle with hepatic lesions, with or without clinical signs, since hepatic lesions in this intoxication are diffuse and biopsy guidance is not required. The point of choice for the introduction of the biopsy needle is the 11th right intercostal space, approximately 20cm below the dorsal line, at the intersection of an imaginary line between the external tuberosity of the ileum and the scapula and another line perpendicular to the 11th intercostal space.

This site corresponds to the topographic position of the right lobe of the liver. Liver biopsy is a valuable, highly specific tool, and its application can either replace liver function tests or be applied concomitantly. Liver biopsy has almost no adverse effects and can be used to obtain epidemiological data since it allows for the estimation of the true extent of an outbreak of intoxication with *Senecio* spp. (Barros et al. 2007).

CONTROL AND PROPHYLAXIS

Senecio spp. poisoning in cattle can cause irreversible chronic hepatotoxic disease; there is no specific or symptomatic treatment available that can allow the recovery of affected cattle (Riet-Correa & Méndez 2007). Thus, control and prevention methods are critical to avoid cattle intoxication with *Senecio* spp., and adequate management practices for areas invaded by the plant have been recommended. In Brazil, as in other parts of the world, biological and chemical methods are used to eliminate or reduce the development of the weed. Biological methods include the use of sheep

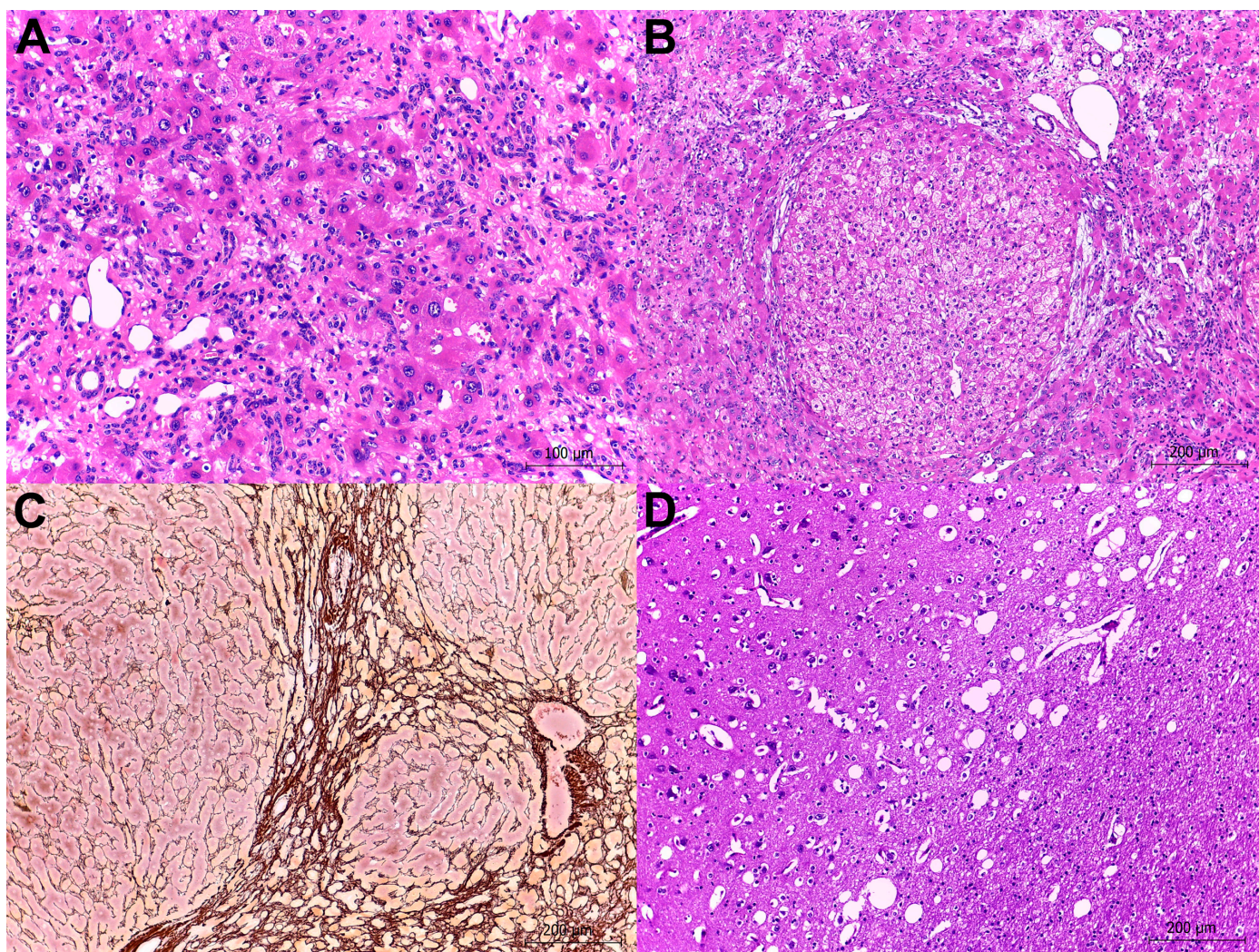


Fig.5. Histopathology of the liver and brain in *Senecio* spp. poisoning of cattle. (A) Most of the liver parenchyma is replaced (hepatocellular loss) by fibrosis and marked bile duct hyperplasia. The remaining hepatocytes have large nuclei and abundant eosinophilic cytoplasm (megalocytosis). HE, obj.20x. (B) Liver, groups of hepatocytes (regenerative nodules) with vacuolar degeneration are surrounded by a thin layer of connective tissue. HE, obj.10x. (C) Liver, a disorganized proliferation of reticular fibers dissects the parenchyma disrupting its normal scaffold. Gordon and Sweet's silver stain, obj.10x. (D) Telencephalon; vacuolation of the white matter is observed at the junction with the cortical grey matter. HE, obj.10x.

and (less commonly) insects, and chemical methods consist of the application of various herbicides (Coombs et al. 1991, McEvoy et al. 1991, Olson & Lacey 1994, Jacobs & Sing 2009, Bandarra et al. 2012). In addition, it is recommended that an adequate supply of good quality pasture proportional to animal stocking be maintained, especially during critical periods, such as the winter and the period in which *Senecio* spp. have higher PA contents (Karam et al. 2004, Riet-Correa & Méndez 2007, Tokarnia et al. 2012).

Sheep grazing represents the most efficient method of biological control of *Senecio* spp. (Barros et al. 1987a, Driemeier et al. 1991, Barros et al. 1992, Olson & Lacey 1994, Soares et al. 2000, Jacobs & Sing 2009, Bandarra et al. 2012), as sheep will avidly consume *Senecio* spp. and thus prevent cattle intoxication. *Senecio* intoxication typically occurs in pastures where there are no sheep. Rates of 0.43 ovine/hectare (Soares et al. 2000) or 3.0 sheep/hectare (Bandarra et al. 2012) have been found effective for *Senecio* spp. control. It is

estimated that cattle are 30-40 times more susceptible than are sheep and goats to the effects of PAs. The difference appears to be related to the ability of the smaller ruminants to detoxify PAs in the liver, likely a result of the diet consumed prior to domestication. In addition, sheep and goats are less selective in food intake and have thus developed greater resistance to toxins (Radostits et al. 2007, Santos et al. 2008). The resistance of sheep can also be attributed to the greater number of microorganisms in the rumen of sheep relative to cattle, allowing the more efficient inactivation of PAs by sheep (Karam et al. 2011). However, the use of sheep on pastures severely invaded by *Senecio* spp. for prolonged periods of time might lead to intoxication (Ilha et al. 2001, Grecco et al. 2011, Giaretta et al. 2014b).

The use of insects represents an alternative method for *Senecio* control (Coombs et al. 1991, McEvoy et al. 1991, Jacobs & Sing 2009, Karam et al. 2011). The effectiveness of this method was demonstrated in a control study of

S. jacobaea in the United States after the introduction of three insect species: *Tyria jacobaeae* (Lepidoptera: Arctiidae), *Longitarsus jacobaeae* (Coleoptera: Chrysomelidae), and *Hylemya seneciella* (Diptera: Anthomiidae) (McEvoy et al. 1991). In Brazil, *Phaedon confinis* is potentially useful for the biological control of *S. brasiliensis* (Mendes et al. 2005).

To control the *Senecio* population, practices that cause the soil to become devoid of other vegetation should be avoided (Karam & Jarenkow 2011). Mowing can be performed before flowering, e.g., before the production and dispersal of seeds (Jacobs & Sing 2009, Karam et al. 2011). This practice should be repeated when the sprouts reach 10-15 cm in height to deplete the plant's nutritional reserves and cause its disappearance. Areas with sprouts can be grazed with sheep. This method has been successfully adopted by some farmers who reported clearing the field during the transition of *Senecio* spp. from the vegetative to the reproductive stage, shortly before flowering, and that this practice reduced plant size by approximately 90% (Karam et al. 2011)

Chemical control has been used for species that have vegetative propagation capacity; however, with *Senecio* spp., chemical control should be performed only as an auxiliary method within integrated management (Jacobs & Sing 2009). For *S. madagascariensis*, localized applications of low-residual post-emergent herbicides are recommended at the stage when the plants exhibit five leaves; at this stage, the minimum dose is effective, and application costs can be minimized. The herbicide does not act on the seeds. Both mechanical and chemical control should be completed during the winter if climatic conditions do not anticipate flowering. *S. madagascariensis* goes through several blooming periods within one year, and mechanical control has proven inefficient (Karam et al. 2011). Formulations of amine, low volatile ester forms of 2,4-D or 2,4-D emulsions are effective when applied in a proportion equivalent of one kilogram of acid per 0.4 hectares (Jacobs & Sing 2009, Bandarra et al. 2012).

The practice of making hay or silage from areas invaded by *Senecio* spp. should be discouraged. The desiccation of the plant makes it more difficult for cattle to avoid it and can increase the plant's palatability (Karam et al. 2011).

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