THE MOST COMMON INTENTIONAL POISONING OF DOGS AND CATS ON THE TERRITORY OF THE REPUBLIC OF SERBIA

Jelena Aleksić Radojković[1*], Ivana Davidov[2],
Aleksandra Aleksić Agelidis[1], Jelena Vranešević[3], Saša Ivanović[1]

[1] Faculty of Veterinary Medicine, University of Belgrade, Republic of Serbia
[2] Department of Veterinary Medicine, Faculty of Agriculture,
University of Novi Sad, Republic of Serbia
[3] Scientific Veterinary Institute "Novi Sad", Novi Sad, Republic of Serbia

Abstract

The paper presents the most common toxic substances used in malicious poisoning of dogs and cats in the territory of the Republic of Serbia, mechanisms of their action, symptoms that occur in poisoned animals, antidote therapy and in the case of death, pathomorphological changes. The understanding of the mechanisms of toxic action of the most common substances used and the clinical symptoms in poisoned dogs and cats contribute to a faster diagnosis and the prompt suitable therapy application. The participation of forensic veterinarians in official procedures prior to criminal proceedings is necessary, considering its importance in the recognition and prosecution of acts defined in Article 269 of the Criminal Code (Official Gazette of RS, No. 85/2005, 88/2005 - amended, 107/2005 - amended, 72/2009, 111/2009, 121/2012, 104/2013, 108/2014, 94/2016 and 35/2019).

Key words: animal poisoning, poisons, forensic veterinarian, crime

---

[1*] Corresponding Author: alexjellena@yahoo.com

NAJĆEŠĆA NAMERNA TROVANJA PASA I MAČAKA NA TERITORIJI REPUBLIKE SRBIJE

Jelena Aleksić Radojković[1], Ivana Davidov[2],
Aleksandra Aleksić Agelidis[1], Jelena Vranešević[3], Saša Ivanović[1]

[1] Fakultet veterinarske medicine, Univerzitet u Beogradu, Beograd, Republika Srbija
[2] Departman za veterinarsku medicinu, Poljoprivredni fakultet,
Univerzitet u Novom Sadu, Novi Sad, Republika Srbija
[3] Naučni institut za veterinarstvo „Novi Sad“, Novi Sad, Republika Srbija

Kratak sadržaj

U radu su prikazane toksične supstance koje se najčešće koriste prilikom zlonamernog trovanja pasa i mačaka na teritoriji Republike Srbije, mehanizmi njihovog delovanja, simptomi koji se javljaju kod otrovanih životinja, antidot terapije, a u slučaju uginuća i patomorfološke promene. Poznavanje mehanizama toksičnog dejstva najčešće korišćenih supstanci i karakteristike kliničkih simptoma kod otrovanih pasa i mačaka doprineće bržoj dijagnostici i blagovremenom sprovođenju adekvatne terapije. Učešće veterinara forenzičara u službenim radnjama koje prethode krivičnom postupku je neophodno, uzimajući u obzir njegov značaj u otkrivanju i procesiranju dela definisanih članom 269. Krivičnog zakonika (Službeni glasnik RS, br. 85/2005, 88/2005 - ispr., 107/2005 - ispr., 72/2009, 111/2009, 121/2012, 104/2013, 108/2014, 94/2016 i 35/2019).

Ključne reči: trovanje životinja, otrovi, veterinar forenzičar, krivično delo.

INTRODUCTION

Chemical injuries (*Laesio valetudinis violenta chemica*) or animal poisoning are a global worldwide problem (Wang et al., 2007; Ladislav et al., 2011). They have become an increasingly frequent occurrence on the territory of the Republic of Serbia. Toxins are substances that, depending on the concentration, amount and manner of reaching the body, lead to various toxic effects (Aleksić and Aleksić, 2019). Regarding the intentions of poisoning, they can be unintentional (accidental) and intentional (murderous). Accidental animal poisonings have been documented worldwide (Berny et al., 2010; Guitart et al.,

2010a, Guitart et al., 2010b), they cannot be prevented and their percentage is low compared to intentional poisoning (Giorgi et al., 2007; Berny et al., 2010). Intentional poisoning means the abuse of toxic substances and malicious intent of the perpetrator, but also an act of revenge against a certain animal or its owner or keeper (Merck, 2007).

The Animal Welfare Law, among other things, prohibits the use of poisons and other chemical agents that cause pain, suffering and death of animals, except for the purpose of controlling rodent populations, i.e. rodent control and animal testing for scientific research purposes (Animal Welfare Law, Article 7, Official Gazette No. 41/2009). Along with the criminal offense defined in Article 269 of the Criminal Code (Official Gazette of RS, No. 85/2005, 88/2005 - corrigendum, 107/2005 - corrigendum, 72/2009, 111/2009, 121/2012, 104/2013, 108/2014, 94/2016 and 35/2019), the cases of intentional poisoning of animals often take account of criminal offense against the protection of the general public stated in the Article 278 as well. According to the provisions of the Criminal Code, any person that causes danger to a human life by means of fire, flood, explosion, poison or poisonous gas, radioactive or other ionizing radiation, electricity, motor force or any other dangerous action that has a potential to endanger human life or habitat, will be prosecuted. In addition to a fine, a prison sentence of six months to five years is imposed for this crime. If the crime was committed in a place where a large number of people gather (e.g., in a park, on the street, in a square), and there are signs of a more severe form of poisoning, then a stricter prison sentence is prescribed, from one to eight years, along with a fine.

In most cases, according to the clinical course, intentional poisonings are peracute or acute, so in order to respond in a timely manner and implement appropriate therapy, it is important that veterinarians have information on the most commonly used types of poisons used by perpetrators. According on our case law, perpetrators have most commonly been using anticoagulant rodenticides, organophosphate and carbamate insecticides, creosote and molluscicides (metaldehyde) in the recent years.

The prevalence of poisoning is higher in dogs compared to cat poisoning, which has been established in the countries of the European Union: Belgium, France, Greece, Italy, Spain, Austria (Berny et al., 2010; Wang et al., 2007). Dogs account for about 75% of cases, and cats for about 15% of reported cases of intentional poisoning (Gwaltney-Brant, 2012). The higher incidence of dog poisoning is understandable given their nonselective eating habits compared to cats (Medeiros et al., 2009).

During a six-year period (2006-2012), the Department of Veterinary Forensic Medicine and Legislations of the Faculty of Veterinary Medicine in Belgrade autopsied 48 corpses of dogs with suspected poisoning. Anticoagulant rodenticide poisoning was suspected in 20 cases, creosote poisoning in 17 cases, and organophosphate and carbamate pesticides in 11 cases. According to the data provided by the Public Utility Company "Veterina Belgrade", in 2018, 58 death cases of animals with suspicion of poisoning were reported in Belgrade, while 41 cases were recorded in 2019. There are no official data on the number of intentionally or accidentally poisoned dogs and cats on the territory of the Republic of Serbia (RS), on an annual basis (Aleksić J. et al., 2014).

The diagnosis of poisoning is based on anamnestic data, clinical, autopsy, histopathological and toxicological findings (Jubb et al., 2007), and in medical-legal cases the chemical-toxicological findings play a crucial role. The aim of this paper is to point out the most commonly used agents for the purpose of intentional poisoning of dogs and cats in the territory of the Republic of Serbia, the characteristics and mechanism of toxic effects of the most commonly used poisons, the clinical picture of poisoned animals, antidote therapy and autopsy findings.

ANTICOAGULANT RODENTICIDE POISONING

Rodenticides are used to control the population of harmful gophers and are the most commonly used type of poison for the purpose of intentional poisoning. The reasons for frequent poisonings by these compounds are their pleasant taste (due to sucrose which is added to make them more attractive to gophers) and lack of odors (Eason et al., 2002; Endepols et al., 2003; Binev et al., 2005; Svendsen et al., 2002). There are different first and second-generation anticoagulants. The first generation includes indandione derivatives (difacion, chlorofacion) and coumarin (warfarin, coumachlor, coumatetralyl). This generation of anticoagulants is characterized by the need for repeated oral administration in order for non-target species to be poisoned. Over time, due to the emergence of rodent resistance to first-generation anticoagulants, second-generation coumarin derivatives have also been developed, which are very toxic to dogs and cats, and therefore poisoning can occur even after single consumption. Difenacoum is the first in a series of second-generation coumarin anticoagulants, and bromadiolone and brodifacoum are also used. Brodifacoum is more recent and has several times higher toxicity than bromadiolone. The oral LD$_{50}$ of brodifacoum for cats is 25 mg/kg and from 0.25 to 3.6 mg/kg of body weight for dogs (Eason and Wickstrom, 2001). In our country, the most used coumarin derivatives are warfarin, bromadiolone and brodifacoum.

Anticoagulant rodenticides act as antagonists of vitamin K and the enzyme vitamin K-epoxide reductase, which participates in the recycling of vitamin K. factors) (Sheafor and Couto, 1999; Merola, 2002). As a result, the synthesis of blood coagulation factors is blocked: II (prothrombin), VII (proconvertin), IX (antihemolytic factor B) and X (Stuart's factor) (Sheafor and Couto, 1999; Merola, 2002). In terms of chemical structure, coumarin is similar to vitamin K_1, and for that reason it competes with vitamin E for its place on the enzyme epoxy reductase (competitive inhibition). There is a reduced regeneration of vitamin K_1, which is essential for the synthesis of coagulation factors. Coumarin is also thought to have a direct toxic effect on capillaries, but the mechanism of action has not yet been sufficiently clarified (Ćupić, 2015).

The latent period depends on the type and amount (dose) of anticoagulant taken, but poisoned individuals usually do not show clinical symptoms in the first 24 to 48 hours after ingestion. Newer anticoagulants have a longer biological half-life and therefore prolonged toxic effects, which requires prolonged treatment. The plasma half-life of warfarin is 15 hours, it is 5 days for diphacinone, and 6 days for bromadiolone. Brodifacoum can be detected in blood serum for up to 24 days. After a drop in a serum concentration, all anticoagulants can be identified in the liver (Khan and Schell, 2014). When a clinical manifestation occurs, the most common signs of poisoning are lethargy, dyspnea, cough and blood in the sputum (Merola, 2002). Clinical signs depend on the site of bleeding, which may be from the oral cavity, nose, vulva, foreskin or rectum. Internal bleeding in the lungs, mediastinum, thymus or trachea can manifest itself in the form of acute dyspnoea, and bleeding in the muscles or subcutaneous tissue in the form of larger hematomas. Bleeding into the joint cavities causes lameness, and in cases of bleeding in the brain or spinal cord, neurological symptoms can develop. Extensive bleeding in the abdomen leads to pallor of the visible mucous membranes, weakness and lethargy of the animal. Bleeding has also been reported in various structures of the eye - subconjunctivally, in the eye cavity, retina, and the presence of blood in the anterior chamber of the eye, between the iris and the cornea has been recorded (Petterino et al., 2004; Cullen et al., 2013, Griggs et al., 2015).

Haematological examination revealed a decrease in hematocrit and blood plasma proteins, as well as a violation of coagulation parameters, namely prothrombin time (PT), activated partial thromboplastin time (aPTT), activated coagulation time (ACT) and protein induced by vitamin K deficiency (PIVKA) (Murphy, 2007).

In the cases of suspected anticoagulant rodenticide poisoning, treatment is based on general, supportive and specific therapy. General therapy includes the use of emetics or gastric lavage, the use of adsorbents and laxatives. In

cases of heavy bleeding or a significant drop in hematocrit, supportive therapy is applied, which is based on the use of fresh plasma or whole blood transfusion every 4 to 8 hours (Chalermchaikit et al., 1993). Specific therapy is the use of vitamin K_1. The recommended doses are 1.5 – 2.5 mg/kg/twice daily, orally, for 3 - 4 weeks. Prolonging the therapy for an additional week will not result in side and harmful effects, and premature cessation of treatment can be a vital threat to poisoned dogs and cats. The most reliable way to determine when therapy should be performed is to check the prothrombin time, 72 hours after the last dosing. If the prothrombin time in that period has a physiological value, vitamin K_1 should be excluded from the therapy, and if the prothrombin time is still extended, the treatment with vitamin K_1 should be given for another week. Vitamin K_1 should be applied with small amounts of foods rich in fats (milk, meat, cheese), because fats improve its absorption. Applying half of the total daily dose every 12 hours ensures a constant level of vitamin K_1. When coagulation factors are not within physiological value levels and the animal shows clinical signs of poisoning, parenteral administration should be avoided due to the risk of bleeding and/or hematoma formation at the injection site, unless vitamin K_1 cannot be administered orally to the animal. Anaphylactic reactions are possible with parental administration of vitamin K_1 (Khan and Schell, 2014).

Anticoagulant rodenticides, especially coumarin, lead to generalized bleeding in various organs (liver, kidneys, intestines, heart and lungs). The autopsy shows bleeding in the meninges, thymus, larynx, kidneys, liver, pericardium, gastrointestinal tract, nasal cavities, joints, muscles and mediastinum, in the chest and abdomen. Petechiae and ecchymoses are often present on the skin, mesentery and mucous membranes of the gastrointestinal tract. The most common postmortem findings are hemoperitoneum, hemothorax, and bleeding in the lung parenchyma (DuVall et al., 1989). Histopathologically, degeneration of the heart muscle, inflammation of the bladder and hepatic dystrophy can be found in dogs (Srebočan and Glomerčić, 1996).

ORGANOPHOSPHATE INSECTICIDE POISONING

Organophosphates are phosphoric acid esters by chemical composition. They include some of the most important compounds for the development of life processes such as nucleic acids (DNA and RNA) and essential cofactors, and some compounds from this group are used in human medicine in the treatment of glaucoma (echothiophate, isoflurophate), Alzheimer's disease, *myasthenia gravis* and dysfunction urinary tract. In veterinary medicine,

they are used as anti ectoparasitics (diazinon) and anthelmintics (trichlorfon). They are often used as pesticides for plant protection in agriculture and forestry (malathion, parathion, diazinon, fenthion, dichlorphos, chlorpyrifos). Throughout history, they have also been used as nerve agents (sarin, soman, tabun, VX) (Gupta and Milatović, 2012).

They can be taken orally, through the skin and by inhalation. After absorption, they are distributed in the body, and the highest concentration due to lipophilicity is in adipose tissue and the brain (Gupta, 2012). The order of the most frequently used organosphosphate pesticides from extremely toxic to less toxic is the following: disulfoton, terbufos, forate, parathion, chlorpyrifos, fenthion, diazinon, malathion, tetrachlorvinphos. Chlorpyrifos is particularly toxic to cats, with an oral LD_{50} of 10 to 40 mg/kg (Fikes, 1992). Organophosphates act by inhibiting acetylcholine esterase (AChE), an enzyme that breaks down the neurotransmitter acetylcholine (ACh) within the synapses of the autonomic nervous system, neuromuscular synapses, and cholinergic synapses of the CNS. Inhibition of AChE results in accumulation of ACh and overstimulation of postsynaptic neurons or muscle cells (Ivanović et al, 2016). Organophosphate compounds have the property of "aging complex" with AChE molecules, which results in irreversible inhibition of this enzyme, which is why the effects of organophosphate are much longer-lasting and more pronounced compared to the toxic effects of carbamates (Merck, 2007).

Clinical signs of organophosphate poisoning are the result of excessive stimulation of nicotine and muscarinic receptors. Signs of excessive stimulation of nicotinic receptors are tremor of the muscles, tetanic spasms, stiffness accompanied by general weakness of the animal, paresis and paralysis. Peripheral muscarinic signs are salivation, lacrimation, frequent urination and defecation, miosis, increased bronchial secretion, dyspnoea, bradycardia, and abdominal pain. Central cholinergic signs are anxiety, restlessness, generalized convulsions, and in the later course of CNS depression and in the terminal phase coma. In some cases, not all symptoms are present, and their intensity varies depending on the dose administered, the mode of exposure, the type of animal, and the type of organophosphate compound (Merck, 2007). In dogs and cats, CNS stimulation usually progresses to convulsions. In dogs, disorders of the gastrointestinal tract often occur with diarrhea, vomiting and abdominal pain, and in cats, muscarinic effects dominate. The onset of clinical symptoms after exposure to organophosphates usually occurs within a few minutes to several hours. In some cases, delayed onset of symptoms may follow after a few days. Death is a result of respiratory disorders (bronchoconstriction, bronchosecretion, laryngospasm) or paralysis of respiratory muscles (diaphragm, intercostal muscles).

An unavoidable procedure in the diagnosis of organophosphate poisoning is the determination of AChE activity in erythrocytes, which is structurally similar to AChE in nerve tissue and as a surrogate marker reflects its activity in synapses. However, inhibition of AChE in erythrocytes is not always closely correlated with the intensity of the clinical picture. Signs of poisoning are manifested when erythrocyte AChE activity is inhibited >70%. In order to reliably diagnose poisoning, the activity of AChE erythrocytes is determined immediately before and a few minutes after the application of oximes used in the therapy of poisoning with these compounds. If after the application of oxime there is a noticeable increase in AChE activity, poisoning with these compounds is confirmed. This method also confirms those poisonings in which the initial values of AChE were within physiological limits (Izraeli et al., 1986).

Proving the presence of organophosphates in biological materials is uncertain, because these compounds are degradable and do not remain in their original form in tissues for long. In order to identify and quantify the organophosphate compound, a sample of gastric contents is delivered to the laboratory and analyzed by gas-mass chromatography (GC-MS) or with more advanced instrumental techniques (e.g. LC/MS/MS). Blood/serum and urine residues can also be analyzed for organophosphate residues or their metabolites. More than 70% of organophosphates produce one or more dialkyl phosphates (dimethyl phosphate, diethyl phosphate, dimethyl thiophosphate, diethyl thiophosphate, dimethyl dithiophosphate and diethyl dithiophosphate).

Three groups of drugs are used in the treatment of organophosphate poisoning: (1) emetics and adsorbents in order to reduce further absorption; (2) muscarinic receptor antagonists; (3) AChE reactivators. Atropine sulfate blocks the central and peripheral muscarinic effects of organophosphate. In dogs and cats, it is administered in a dose of 0.2 to 2 mg/kg (lower limit of the dose range for cats), every 3 to 6 hours or as often as the severity of the clinical picture requires. Atropinization is adequate when mydriasis occurs, salivation stops, and the animal appears more conscious (awake). Animals initially respond well to atropine sulfate, but after repeated treatments, the intensity of the response decreases, so excessive use of atropine should be avoided. However, since atropine does not reduce the nicotinic cholinergic effects (fasciculations and paralysis of the intercostal muscles and diaphragm), lethal outcome is still possible due to respiratory insufficiency. Experimental studies in primates have shown that the inclusion of diazepam in therapy reduces the frequency of muscle convulsions and increases survival rates. The efficacy of the treatment is increased by combining atropine with oximes (2-PAM, pralidoxime chloride) that reactivate inhibited AChE. The dose of 2-PAM is 20 - 50 mg/kg and is applied as a 5% solution i.m. or slow i.v. (for 5 to 10 minutes),

with a repeated half dose as needed. The i.v. administration of 2-PAM must be carried out slowly to avoid skeletal muscle paralysis and respiratory arrest. As the possibility of AChE reactivation weakens with time after exposure, oxime application must be started as soon as possible, no later than 24 to 48 hours. The rate at which the enzyme-organophosphate complex reacts to reactivators varies depending on the type of organophosphate compound (Gupta and Milatović, 2012; Gupta, 2014a).

There are no specific pathoanatomical changes at autopsy. The hair coat or stomach contents may smell of kerosene, sulfur or garlic. There may be pale mucous membranes, bleeding in the digestive tract, congestion of the stomach, especially the fundus. The liver is pale with multifocal fields of necrosis, and congestion and hemorrhage are present in the lungs. Splenomegaly, mild meningeal congestion, and multifocal necrosis fields in the kidney have been observed (Ola-Davies et al., 2018). Pathohistologically, pulmonary edema and pancreatitis can be established (Merck, 2007; Srebočan and Glomerčić, 1996).

CARBAMATE INSECTICIDE POISONING

Carbamates are esters of carbamic acid and have a less complex chemical structure compared to organophosphates. Regarding the total consumption in the world, they are ahead of organophosphates, because they are considered safer to use. In veterinary medicine, they are available as anti ecto parasitics in various pharmaceutical formulations (powders, concentrated emulsions, sprays, shampoos, flea and tick collars). They are used in agriculture for plant protection, and due to improper or malicious use, they are often the cause of acute poisoning of domestic animals, birds, fish and wild animals (Gupta, 2012). In terms of toxicity, this group of insecticides includes substances with a wide range of LD_{50} values. In rats, carbaryl has an oral LD_{50}>300 mg/kg, and aldicarb, which is a highly toxic LD_{50}, is 0.9 mg/kg. Highly toxic carbamates include methomyl (oral LD_{50} for rats 17 mg/kg) and carbofuran (oral LD_{50} for rats 8 mg/kg, for dogs 19 mg/kg), and propoxur has several times lower toxicity than the previous two compounds (oral LD_{50} for rats 95 mg/kg). Animals usually ingest carbamates by ingestion, but percutaneous and inhalation routes of poisoning are also possible. After absorption, this group of compounds is distributed in most tissues, it passes through the placental barrier and leads to inhibition of fetal AChE. In young animals, they are metabolized more slowly, which is why they are more toxic to them compared to older categories of animals. About 80% of the resorbed compound is excreted in the urine in the first 24 hours after ingestion (Gupta, 2014b).

In our country, in order to intentionally poison animals from the carbamate group, the preparation "Furadan 35 ST" (FMC Corporation) whose active substance is carbofuran is most commonly used. Its trade and use has been legally prohibited in our country since December 31st 2013, but the perpetrators are still used for the purpose of deliberate poisoning of dogs and cats.

In some parts of the world, intentional poisoning of dogs with the carbamate pesticide aldicarb is becoming more common (Frazier et al., 1999; Motas-Guzman et al., 2003; Verster et al., 2004). On the world market, one of the most famous preparations containing aldicarb is "Temik" (Bayer CropScience). It is used in agriculture against harmful insects and plant parasitic nematodes. It contains 15% aldicarb and is most often in the form of small black granules. The cases of intentional poisoning by this compound are still present, although aldicarb-based preparations are prohibited in phyto-pharmaceutical formulations. EU Directive 2003/199/EC of 2003 prohibits aldicarb and it cannot be used in plant protection products in the European Union. The derogation period referred to France (for vines and sugar beet) with a ban on sales after the May 30th, 2007 and a ban on use after December 31st, 2007 (EU Directive 2003/199/EC). Poisoning in the course is often peracute, since it is an extremely toxic carbamate compound that leads to lethal outcome within a few minutes after ingestion, due to respiratory failure (Goswamy et al., 1994; Jokanović, 2009; Ragoucy-Sengler et al., 2000).

In the cases when clinical symptoms develop in dogs, muscle tremor, hypersalivation accompanied by vomiting, miosis, bradycardia, convulsions, and difficulty breathing are observed (Verster et al., 2004). Frequent urination, paresis and paralysis may also occur. Death is a result of respiratory failure due to bronchospasm, paralysis of the diaphragm and intercostal muscles, and depression of the respiratory center (Fikes, 1990; Goswamy et al., 1994; Jokanović, 2009). In the acute course of poisoning, the appearance of acute necrotic-hemorrhagic pancreatitis is possible. Excessive cholinergic stimulation results in spasm of the Odi's sphincter and the consequent enzyme pathway in the pancreatic ducts, which increases intraductal pressure and creates the potential for enzyme transfer to the interstitium (Aslan et al., 2010; Makridges et al., 2005). In peracute cases of poisoning, this pathohistological finding is most often absent.

Carbamates act by the same mechanism as organophosphates - by inhibiting AChE at neuro-neuronal and neuro-muscular synapses. In the case of poisoning with carbamate compounds, the inhibition of AChE is reversible, because the formed bonds of carbamate with the enzyme are much weaker, and thus shorter, which is why the inhibition of AChE in the blood (erythro-

cytes) during laboratory analysis is often not evident. Clinical signs of poisoning last shorter compared to organophosphate poisoning. They include hypersalivation, gastrointestinal hypermotility, abdominal cramps, vomiting, diarrhea, sweating, dyspnoea, cyanosis, miosis, muscle fasciculations (in extreme cases, tetany accompanied by weakness and paralysis) and convulsions. The most pronounced clinical manifestations of carbamate and organophosphate poisoning are salivation, lacrimation, urination, diarrhea (SLUD). Death is a result of hypoxia due to respiratory insufficiency caused by paralysis of the respiratory muscles, bronchoconstriction and tracheobronchial hypersecretion (Gupta, 2014b).

The diagnosis of poisoning is based on the anamnesis and a positive response to atropine therapy. However, when the history is unknown, and cholinergic signs and a clear positive response to atropine suggest carbamate or organophosphate poisoning, it is necessary to determine AChE activity in erythrocytes, whole blood (for live animals) or in the cerebral cortex (for dead animals). Enzyme activity that is significantly inhibited (>50%) confirms the suspicion of poisoning by these compounds. Clinical signs of hypercholinergic activity are observed when AChE inhibition is >70%. Identification and quantification of a particular carbamate and differential diagnosis of organophosphate insecticide poisoning is possible by examining the contents of the gastrointestinal tract using GC-MS (Gupta, 2014a).

The recommended dose range of atropine for dogs and cats is from 0.2 to 2 mg/kg, parenterally, with one-quarter of the dose administered i.v. and the remainder s.c. (lower dose range is recommended for cats). Dosing is repeated as needed. The use of oxime (2-PAM) alone is contraindicated in carbamate poisoning, because it is not effective, and it can also increase the toxic effect of carbamates. In combination with atropine, 2-PAM may also worsen the clinical picture, depending on the dose administered, and in the best outcome the combination with atropine gives only a slightly better therapeutic effect compared to atropine alone. Because of all this, the use of 2-PAM is useful only if the poisoning is caused by a mixture of organophosphates and carbamates or when there are symptoms of excessive cholinergic activity, which is the case with organophosphate poisoning. 2-PAM can be fatal if applied too quickly, so its careful and slow application is necessary, i.e. in 5% saline for 10 minutes, as described in the section on organophosphate poisoning therapy. It is important that the 2-PAM solution is fresh during application, because solutions that have been unused for a long time can lead to the formation of cyanide (Gupta and Milatović, 2012; Gupta, 2014a). As part of symptomatic therapy, fluid, electrolyte replacement and vitamins B, C and E are used, because the

mechanism of toxic action of organophosphates and carbamates partly takes place through oxidative stress. The use of morphine or barbiturates in carbamate poisoning is contraindicated.

The autopsy report is not specific. Congestion of parenchymal organs and pulmonary edema may be observed. The contents of the stomach or suspect substance may have the smell of oil, sulfur or garlic. For the purpose of pathohistological analysis, the tissue of the lungs, heart, liver, kidneys, pancreas and lumbar part of the spinal cord is sampled. The contents of the stomach, intestines, bladder and feces are sampled for chemical and toxicological analysis. Pathohistological changes are diverse and include lung congestion, hyperemia and degenerative changes of myocardial cells, renal hyperemia and renal tubular degeneration, hyperemia and necrotic fields in the liver parenchyma. Examination of pancreatic tissue samples shows acute pancreatitis with wider fields of necrosis involving the parenchyma and interlobular connective tissue. In the ventral horns of the lumbar part of the spinal cord, lysis of the nuclei of motor neurons, loss of the tigroid substance and pericellular edema are noted. Sensitive neurons in the dorsal horns of the spinal cord are usually morphologically preserved (Aleksić et al., 2011).

CREOSAN POISONING

Creosan (4-6 dinitro-ortho-cresol - DNOC) is a derivative of cresol and belongs to the chemical group of dinitrophenol, which includes dinoseb and dinotherb. It is used in agriculture as an insecticide, herbicide and fungicide, and due to its characteristic yellow color, it is known as "yellow powder", which can be seen in the dog shown in Figure 1, which was submitted to the Department of Forensic Veterinary Medicine and Legislation, Faculty of Veterinary Medicine, University of Belgrade. It was withdrawn from use in the countries of the European Union in 2000 (EU Directive 1999/164/EC), and in our country it was banned in 2003. The oral LD_{50} for cats is 50 mg/kg TM (World Health Organization, Geneva, 2000).

Figure 1. Canine coat colored intensely yellow in the area of the lower jaw and front right paw

It enters the body orally, percutaneously and by inhalation. In terms of physical and chemical properties, it is less hydrosoluble, i.e., it has a more pronounced liposolubility, which is why it is characterized by rapid resorption (Agency for Toxic Substances and Disease Registry, 2018). The effect is achieved by separating the process of oxidation and phosphorylation in the respiratory chain in mitochondria. Oxidation cannot take place in the respiratory chain and the accompanying phosphorylation of ADP and the creation of the energy-rich adenosine triphosphate compound ATP are absent. As a result, there is a sharp increase in oxygen consumption and the release of a large amount of energy that is converted into heat (hyperthermia). In the organism of poisoned individuals, catabolic processes (glycolysis, glycogenolysis and metabolism of fatty acids) increase sharply. Due to the lack of ATP in vital organs (heart, respiratory muscles), their function may cease. The dominant symptom is high fever (malignant hyperthermia), which reaches a value of up to 42 °C. Dyspnoea, convulsions, coma, and lethal outcome with rapid development of corpse stiffness are also present. Death is most often a result of cardiac arrest or paralysis of the respiratory center (Decision Guidance Document, 2005; Ćupić, 2015).

There is no specific antidote and nonspecific therapy is used. If the poisoning occurred by ingestion, and the animal is conscious and actively manifests signs of anxiety, vomiting should be induced. If the animal has CNS depression, gastric lavage should be performed and activated charcoal should

be used. In order to control hyperthermia, the procedure of physical cooling (cold baths, cold compresses) is recommended, without the use of antipyretics. Diazepam (not barbiturates) should be used to sedate the animal. Phenothiazines are contraindicated. Infusions of saline and/or dextrose solution in combination with diuretics contribute to the alleviation of dehydration and faster elimination of creosone from the body, since it is excreted in the urine. The success of therapy is significantly contributed by i.v. sodium bicarbonate administration, parenteral vitamin A administration, and oxygen administration (Gupta, 2020).

Pathoanatomical changes are not specific. The contact of the animal with this compound is indicated by the discoloration of the dog's coat, skin and mucous membranes with an intense yellow color that is present for several weeks. Urine has a characteristic fluorescent yellow color. After death, corpse stiffness develops rapidly. The dominant macroscopic findings are round-shaped particles in gastric contents, intensely yellow in color. The gastric mucosa is hyperemic and wrinkled (Đurđević et al., 2018). The presence of this compound in the stomach contents is confirmed by GC-MS.

MOLLUSCICIDES POISONING (METALDEHYDE)

Metaldehyde is a tetramer of acetaldehyde and belongs to the group of pesticides intended for the control of snail populations in the areas with wet soil. Although most poisonings with this neurotoxic substance have been reported in dogs, poisoning is also possible in other species of domestic and wild animals, and is associated with careless or malicious placement of baits. In commercial molluscicides, metaldehyde may be present in combination with other pesticides such as carbamates to make them more effective. Also, molluscicides can contain bran or molasses in order to be more attractive to snails, but in that way, they become more attractive for dogs and other types of animals. Metaldehyde is not considered a stable substance, but it may remain effective for 10 days. The preparations are usually in the form of blue-green granules or pellets with a mild odor of aldehyde and contain 1.5 to 5% of metaldehyde. During an autopsy of a dead dog, blue-green granules were found at the Department of Forensic Veterinary Medicine and Legal Regulations, Faculty of Veterinary Medicine, University of Belgrade, which indicates poisoning with molluscicidal preparations of metaldehyde (Figure 2). In terms of toxicity, the oral LD_{50} of metaldehyde is 100 mg/kg for dogs and about 200 mg/kg for cats (Dolder, 2003).

Metaldehyde after ingestion, under the action of gastric acid, undergoes partial hydrolysis to form acetaldehyde, and then both compounds are rapidly

resorbed from the gastrointestinal tract. The properties of the stomach contents and the speed of its emptying significantly affect the speed of absorption, and thus the beginning of the clinical manifestation of poisoning. After absorption, metaldehyde is rapidly metabolized. Enterohepatic circulation can prolong the retention of metaldehyde in the body, but eventually both metaldehyde and acetaldehyde are excreted in the urine (Blakley, 2013). Clinical manifestations are primarily attributed to metaldehyde, because studies in mice have shown that metaldehyde crosses the blood-brain barrier and that its presence is detected in the brain (Puschner, 2001). Signs of toxicity may be due to a decrease in the concentration of γ-amino-butyric acid (GABA) in the brain as a major inhibitory amino acid, resulting in CNS excitation. As the concentration of GABA in the brain decreases, the mortality rate increases (Osweiler, 1996). Another factor that contributes to morbidity and mortality is hyperthermia. It most often appears secondary to neurological manifestations. Muscle tremor also occurs. When the body temperature exceeds 41.6 °C in all organ systems, cell necrosis begins in a few minutes. Metaldehyde also affects electrolyte balance and acid-base status by causing metabolic acidosis, which is often associated with central nervous system depression and hyperpnea (Puschner, 2001). In dogs, the signs of this toxicosis can occur from a few minutes to three hours after ingestion. Neurological symptoms are predominant, and muscle tremors, anxiety, hyperesthesia, ataxia, tachycardia, and hyperthermia may occur. Metabolic acidosis is present and as it is more pronounced, depression and hyperpnea can be further intensified. Typical signs of advanced toxicosis are opisthotonus and continuous tonic convulsions that do not respond to external stimuli (unlike in cases of strychnine poisoning). Symptoms often include vomiting, diarrhea, hypersalivation, colic, cyanosis, mydriasis, and feline nystagmus. Deaths due to respiratory failure can occur within hours of ingestion (Blakley, 2013; Beasley, 1999; Booze and Oehme, 1985).

Figure 2. Molluscicide preparation of metaldehyde in gastric contents

The diagnosis is based on anamnestic data and clinical symptoms. Gastric contents, gastric lavage fluid, and expired air may have an acetaldehyde odor that is similar to formaldehyde or acetylene but less intense. To confirm the diagnosis of poisoning, it is important to analyze the contents of the stomach for metaldehyde and acetaldehyde.

Although there is no specific antidote, timely and intensive symptomatic therapy during the first 24 hours allows most poisoned animals to recover within the next 2 to 3 days. The goals of symptomatic therapy are prevention of metaldehyde absorption, control of clinical symptoms, monitoring and correction of metabolic acidosis and dehydration. If no more than 30 minutes have elapsed since ingestion and if there are no contraindications in dogs and cats, vomiting with hydrogen peroxide (1 to 5 mL/kg, maximum 45 mL) or apomorphine hydrochloride should be induced. Otherwise, gastric lavage with animal anesthesia and endotracheal intubation should be undertaken to prevent aspiration (Plumb, 1999; Dorman, 1995). In dogs and cats, the use of activated charcoal in a dose of 1 to 4 g/kg TM is recommended, and repeated application of half of the original dose every 6 to 8 hours contributes to a better therapeutic effect. Enema with warm water is also used to eliminate metaldehyde from the gastrointestinal tract. To control convulsions, i.v. diazepam at a dose of 1 to 5 mg/kg TM. If necessary, other anticonvulsants can be used, such

as inhalation anesthesia (for severe and persistent convulsions) or barbiturates, which must be used with caution because during biotransformation in the liver as a substrate may compete with enzymes involved in acetaldehyde metabolism (Plumb, 1999 Carson and Osweiler, 1997). Hyperthermia resulting from muscle tremors and seizures is usually corrected when tremor and seizures are kept under control. Therefore, aggressive physical cooling measures such as ice baths should not be used, as they can cause hypothermia. Of essential importance for the correction of metabolic acidosis and electrolyte imbalance is i.v. application of sodium lactate or sodium bicarbonate, and i.v. administration of dextrose or calcium borogluconate may reduce liver damage. Prolonged excessive muscle activity (tremor, convulsive seizures) can cause myoglobinuria and secondary renal dysfunction. In such cases, the use of diuretics is recommended to prevent kidney damage (Dolder, 2003; Blakley, 2013).

In poisoned dogs, the autopsy finding is nonspecific. Hyperemia of the liver, lungs, and kidneys, inflammation of the gastric mucosa, and subendocardial and subepicardial hemorrhages may be found (Beasley, 1999).

CONCLUSION

In order to reduce the frequency of malicious poisoning of dogs and cats on the territory of our country, it would be important to conduct strict control of the sale of agricultural preparations whose active substances have high toxicity for both humans and animals. In order to monitor the frequency of this phenomenon in our society, which is sanctioned by Article 269 of the "Criminal Code" ("Official Gazette of RS", No. 85/2005, 88/2005 - amended, 107/2005 - amended, 72/2009, 111/2009, 121/2012, 104/2013, 108/2014, 94/2016 and 35/2019), it is important to introduce a central register of confirmed cases of poisoning of owner dogs and stray dogs.

The processing of cases of intentional poisoning of animals should be based on reliable findings of forensic veterinarians and toxicological confirmation of poisoning. Judicial practice indicates that such cases are difficult to process due to the lack of evidence linking the perpetrator to the abuse of toxic substances and in this sense better cooperation and coordination of state administration bodies (police, public prosecutor's office, and veterinary inspectors), veterinarians and accredited laboratories performing chemical-toxicological analyses is required.

Author's Contribution:

JAR and SI made contributions to the idea of the publication, organisation of work and writing the manuscript; JV, ALL and ID were involved in the writing of the manuscript, JV reviewed the manuscript; JAR and SI gave the final approval of the manuscript to be published.

Competing interest

The authors declare that they have no competing interests.

REFERENCES

1. Agency for Toxic Substances and Disease Registry (ATSDR), 2018. Toxicological Profile for Dinitrocresols, U.S. Department of health and human services.
2. Aleksić J., Batrićević A., Jovašević D., Aleksić Z., 2014. Trovanje životinja-veterinarsko medicinski i krivično pravni aspekti, Veterinarski glasnik. 68, 3-4, 251-263. doi: 10.2298/VETGL1404251A.
3. Aleksić J., Merćep D., Aleksić Z., Jovanović M. 2011. Trovanje psa Furadanom 35-ST (karbamatni insekticid), Veterinarski glasnik. 65, 3-4, 277-285. doi: 10.2298/VETGL1104277A.
4. Aleksić Z. and Aleksić J. 2019. Sudska veterinarska medicina: opšti deo. Fakultet veterinarske medicine, Beograd, drugo izdanje. ISBN: 978-86-80446-23-3.
5. Animal Welfare Law, Official Gazette of RS, No. 41/2009.
6. Aslan S., Cakir Z., Emet M., Serinken M., Karcioglu O., Kandis H., Uzkeser M. 2010. Acute abdomen associated with organophosphate poisoning. Journal of Emergency Medicine, 41, 5, 507-512. doi:10.1016/j.jemermed.2010.05.072.
7. Beasley V.R. 1999. Toxicants associated with CNS stimulation or seizures. In: *A Systems Affected Approach to Veterinary Toxicology*. University of Illinois, College of Veterinary Medicine, Urbana, USA, 94-97.
8. Berny P., Caloni F., Croubels S., Sachana M., Vandenbroucke V., Davanzo F., Guitart R. 2010. Animal poisoning in Europe. Part 2: Companion animals. The Veterinary Journal 183, 3, 255-259.doi: 10.1016/j.tvjl.2009.03.034.
9. Binev R., Petkov P., Rusenov A. 2005. Intoxication with anticoagulant rodenticide bromadiolone in a dog - a case report. Veterinarski Arhiv, 75, 3, 273-282

10. Blakley B.R. 2013. Overview of Metaldehyde Poisoning. The Merck Veterinary Manual. Available at: https://www.msdvetmanual.com/toxicology/metaldehyde poisoning/metaldehyde-poisoning-in-animals. Accessed: August 10th 2021.

11. Booze T.F., Oehme F.W. 1985. Metaldehyde toxicity: A review. Veterinary and Human Toxicology. 27, 1, 11-19.

12. Carson T.L., Osweiler G.D. 1997. Insecticides and molluscacides. In: *Handbook of Small Animal Practice*. Ed. Morgan R.V. 3rd edition, W.B. Saunders, Philadelphia, USA, 1256-1258. ISBN: 978-0787657598.

13. Chalermchaikit T., Felice L.J., Murphy M.J. 1993. Simultaneous determination of eight anticoagulant rodenticides in blood serum and liver. Journal of Analytical Toxicology, 17, 1, 56-61.doi: 10.1093/jat/17.1.56.

14. COMMISSION DECISION (EC) No. 164/1999 of 17 February 1999 concerning the non-inclusion of DNOC of active substance in Annex I to Council Directive 91/414/EEC and the withdrawal of authorisations for plant protection products containing this active substance (notified under document number C(1999) 332) (Text with EEA relevance).

15. COMMISSION DECISION (EC) No. 199/2003 of 18 March 2003 concerning the non-inclusion of aldicarb in Annex I to Council Directive 91/414/EEC and the withdrawal of authorisations for plant protection products containing this active substance.

16. Cullen M.W., Kim S., Piccini J.S., Ansell J.E., Fonarow G.C., Hylek E.M., Singer D.E., Mahaffey K.W., Kowey P.R., Thomas L., Go A.S., Lopes R.D., Chang P. Peterson E.D., Gersh B.J., ORBIT-AF Investigators. 2013. Risks and benefits of anticoagulation in atrial fibrillation: insights from the Outcomes Registry for Better Informed Treatment of Atrial Fibrillation (ORBIT-AF) registry. Circulation: Cardiovascular Quality and Outcomes; 6, 4, 461-69, doi: 10.1161/CIRCOUTCOMES.113.000127.

17. Ćupić V. 2015. Najčešća trovanja u veterinarskoj medicini, Naučna KMD, Beograd, Srbija, ISBN: 978-86-910653-2-4.

18. Decision Guidance Document, 2005. DNOC (Dinitro-ortho-cresol), Rotterdam Convention - Operation of the Prior Informed Consent (PIC) procedure for banned or severely restricted chemicals.

19. Directive EU 1999/164/EC: Commission Decision of 17 February 1999 concerning the non-inclusion of DNOC of active substance in Annex I to Council Directive 91/414/EEC and the withdrawal of authorisations for plant protection products containing this active substance.

20. Directive EU 2003/199/EC: Council Decision of 18 March 2003 concerning the non-inclusion of aldicarb in Annex I to Council Directive 91/414/

EEC and the withdrawal of authorisations for plant protection products containing this active substance.

21. Dolder L.K. 2003. Metaldehyde toxicosis. Veterinary Medicine, 98, 213-215.

22. Dorman D.C. 1995. Emergency treatment of toxicosis. In: *Kirk's Current Veterinary Therapy XII Small Animal Practice*. Ed. Bonagura J.D., W.B. Saunders, Philadelphia, USA, 211-217. ISBN: 978-0721651880.

23. Đurđević B., Samojlović M., Kartalović B., Ratajac R. 2018. Poisoning of domestic carnivores by banned pesticides in South Bačka district, Archives of Veterinary Medicine, 11, 1, 53 - 65. doi: 10.46784/e-avm.v11i1.17.

24. DuVall M.D., Murphy M.J., Ray A.C. et al. 1989. Case studies on second-generation anticoagulant rodenticide toxicities in nontarget species. Journal of Veterinary Diagnostic Investigation, 1, 1, 66-68. doi: 10.1177/104063878900100118.

25. Eason C.T., Murphy E.C., Wright G.R., Spurr E.B. 2002. Assessment of risks of brodifacoum to non-target birds and mammals in New Zealand. Ecotoxicology, 11, 1, 35-48. doi: 10.1023/a:1013793029831.

26. Eason C.T., Wickstrom M. 2001. Vertebrate pesticide toxicology manual (poisons). Department of Conservation, Wellington, New Zeland, ISBN: 0-478-22035-9.

27. Endepols S., Klemann N., Pelz H.J., Ziebell K.L. 2003. A scheme for the placement of rodenticide baits for rat eradication on confinement livestock farms. Preventive Veterinary Medicine, 58, 3-4, 115- 123. doi: 10.1016/s0167-5877(03)00024-2.

28. Fikes F.D. 1990. Organophosphorous and carbamate insecticides. Veterinary Clinics of North America: Small Animal Practice 20, 2, 353-367. doi: 10.1016/S0195-5616(90)50029-7.

29. Fikes J.D. 1992. Feline chlorpyrifos toxicosis. In: *Current Veterinary Therapy XI*. Eds. Kirk R.W., Bonagura J.D., Saunders Company, Philadelphia, USA, 188-191

30. Frazier K., Hullinger G., Hines M., Liggett A., Sangster L. 1999. 162 cases of aldicarb intoxication in Georgia domestic animals from 1988–1998. Veterinary and Human Toxicology 41,4, 233-235.

31. Giorgi M., Meucci V., Intorre L., Soldani G., Mengozzi G. 2007. Use of pesticide products in poisonous baits in the past seven years in tuscany. In: *Environmental Fate and Ecological Effects of Pesticide.* Eds. Del Re A.A.M., Capri E., Fragoulis Trevisan M.G., La Goliardica Pavese s.r.l., Pavia, Italy. 750–753.

32. Goswamy R., Chaudhuri A., Mahashur A.A. 1994. Study of respiratory failure in organophosphate and carbamate poisoning. Heart and Lung 23, 6, 466–472.

33. Griggs A.N., Allbaugh R.A., Tofflemire K.L., Ben-Shlomo G., Whitley D., Paulsen M.E. 2015. Anticoagulant rodenticide toxicity in six dogs pre-

senting for ocular disease. Veterinary Ophthalmology, 19, 1, 73-80. doi: 10.1111/vop.12267.

34. Guitart R., Croubels S., Caloni F., Sachana M., Davanzo F., Vandenbro-ucke V., Berny P. 2010a. Animal poisoning in Europe. Part 1: farm live-stock and poultry. The Veterinary Journal 183, 3, 249-254. doi: 10.1016/j.tvjl.2009.03.002.

35. Guitart R., Sachana M., Caloni F., Croubels S., Vandenbroucke V., Berny P. 2010b. Animal poisoning in Europe. Part 3: Wildlife. The Veterinary Journal 183, 3, 260-265. doi: 10.1016/j.tvjl.2009.03.033.

36. Gupta C.R. 2014a. Organophosphates (Toxicity), Merck Veterinary Manual. Available at: https://www.msdvetmanual.com/toxicology/insectici-de-and-acaricide-organic-toxicity/organophosphates-toxicity. Accessed: August 11th 2021.

37. Gupta C.R. 2014b. Carbamate insecticides (Toxicity), Merck Veterinary Manual. Available at: https://www.merckvetmanual.com/toxicology/in-secticide-and-acaricide-organic-toxicity/carbamate-insecticides-toxicity. Accessed: August 11th 2021.

38. Gupta P.K. 2020. Organic Herbicides Toxic to Animals (Dinitrophenol Compounds Toxic to Animals), Merck Veterinary Manual. Available at: https://www.msdvetmanual.com/toxicology/herbicide-poisoning/orga-nic-herbicides-toxic-to-animals. Accessed: August 14th 2021.

39. Gupta C.R. 2012. Non-anticoagulant rodenticides. In: *Veterinary toxico-logy: basic and clinical principles*. Ed. Gupta C.R., 2nd edition, Academic Press, London, UK, 698-711. ISBN: 978-0-12-385926-6.

40. Gupta C.R., Milatović D. 2012. Toxicity of organophosphates and carba-mates. In: *Mammalian Toxicology of Insecticides*. Ed. Marrs T.C., Royal Society of Chemistry, Cambridge, UK, 104-136.ISBN:978-1-84973-191-1.

41. Gwaltney-Brant S.M. 2012. Epidemiology of animal poisonings in the United States. In: *Veterinary Toxicology: Basic and Clinical Principles*. Ed, Gupta R.C., 2nd edition, Academic Press, San Diego, CA, 80-87.

42. Ivanović S.R., Dimitrijević B., Ćupić V., Jezdimirović M., Borozan S., Savić M., Savić D. 2016. Downregulation of nicotinic and muscarinic receptor function in rats after subchronic exposure to diazinon. Toxicology reports, 3, 523-530. doi: 10.1016/j.toxrep.2016.06.002.

43. Izraeli S., Glikson M., Ziv I. 1986. Diagnosis of organophosphate poiso-ning. Western Journal of Medicine, 145, 5, 698.

44. Jokanović M. 2009. Medical treatment of acute poisoning with organo-phosphorus and carbamate pesticides. Toxicology Letters 190, 2, 107–115. doi: 10.1016/j.toxlet.2009.07.025.

45. Jubb K.V.F., Kennedy P.C., Palmer N. 2007. Pathology of domestic animals. Academic Press, New York, USA, 5th edition, ISBN: 978-0-7020-2823-6. doi: 10.1016/B978-0-7020-2823-6.X5001-5.

46. Khan A.S., Schell M.M. 2014. Anticoagulant Rodenticides (Warfarin and Congeners), Merck Veterinary Manual. Available at: https://www.merckvetmanual.com/toxicology/rodenticide-poisoning/overview-of-rodenticide-poisoning-in-animals. Accessed: August, 11th 2021.

47. Criminal Code (Official Gazette of RS, No. 85/2005, 88/2005 - amended, 107/2005 - amended, 72/2009, 111/2009, 121/2012, 104/2013, 108/2014, 94/2016 and 35/2019).

48. Ladislav N, Jan M., Alena H., Petr O., Kamil K., Oldřich V., Václav R., Petr C. 2011. Incidental poisoning of animals by carbamates in the Czech Republic. Journal of Applied Biomedicine. 9, 157–161.doi:10.2478/v10136-009-0035-3.

49. Makridges C., Koukouvas M., Achillews G., Tsikkos S., Vounou E., Symeonides M. 2005. Methomyl-induced severe acute pancreatitis: possible etiological association. Journal of the Pancreas 6, 2, 166-171.

50. Medeiros R.J., Monteiro F.O., Silva G.C., Nascimento Junior A. 2009. Casos de intoxicações exógenas em cães e gatos atendidos na Faculdade de Veterinária da Universidade Federal Fluminense durante o período de 2002 a 2008. Ciência Rural 39, 7, 2105-2110. doi: 10.1590/S0103-84782009005000151.

51. Merck D. M. 2007. Veterinary Forensics: Animal Cruelty Investigations, Blackwell Publishing, Ames, Iowa, USA, 1st edition, ISBN: 978-0813815015.

52. Merola M.V. 2002. Anticoagulante rodenticides: Deadly for pets, dangerous for pets, Veterinary Medicine, 97, 10, 716-722.

53. Motas-Guzman M., Maria-Mojica P., Romero D., Martinez-Lopez E., Garcia-Fernandez A.J. 2003. Intentional poisoning of animals in southeastern Spain. A review of veterinary toxicology service from Murcia, Spain. Veterinary and Human Toxicology 45, 1, 47-50.

54. Murphy J.M. 2007. Anticoagulant rodenticides. In: *Veterinary Toxicology - Basic and Clinical Principles*, Ed: Gupta C.R. 2nd edition, Academic Press, 525-547. ISBN: 978-0-12-370467-2. doi: 10.1016/B978-0-12-370467-2.X5095-0.

55. Ola-Davies O.E., Azeez O.I., Oyagbemi A.A., Abatan M.O. 2018. Acute coumaphos organophosphate exposure in the domestic dogs: Its implication on haematology and liver functions, International Journal of Veterinary Science and Medicine, 6, 1, 103-112, DOI: 10.1016/j.ijvsm.2018.04.004.

56. Osweiler G.D. 1996. Insecticides and molluscacides. In: *Toxicology*. Williams & Wilkins, Philadelphia, USA, 250-251. ISBN: 9780683066647.

57. Petterino C., Bianciardi P., Tristo G. 2004. Clinical and Pathological Features of Anticoagulant Rodenticide Intoxications in Dogs, Veterinary and Human Toxicology, 46, 2, 70-5.

58. Plumb D.C. 1999. Veterinary Drug Handbook, 3rd edition, Wiley-Blackwell, 412-413. ISBN: 978-0813823539.

59. Puschner B. 2001. Metaldehyde. In: *Small Animal Toxicology.* Eds. Peterson M.E.,Talcott P.A., W.B. Saunders, Philadelphia, USA, 553-562.

60. Ragoucy-Sengler C., Tracqui A., Chavonnet A., Daijardin J.B., Simonetti M., Kintz P, Pileire B. 2000. Aldicarb poisoning. Human and Experimental Toxicology, 19, 12, 657-662. doi: 10.1191/096032700672133218.

61. Sheafor S.E., Couto C.G. 1999. Anticoagulant rodenticide toxicity in 21 dogs. ournal of the American Animal Hospital Association, 35, 1, 38-46, doi: 10.5326/15473317-35-1-38.

62. Srebočan V., Glomerčić H. 1996. Veterinarski priručnik, peto izmijenjeno izdanje, Medicinska naklada, Zagreb, Hrvatska. ISBN: 953-176-041-1.

63. Svendsen S.W., Kolstad H.A., Steesby E. 2002. Bleeding problems associated with occupational exposure to anticoagulant rodenticides. International Archives of Occupational and Environmental Health, 75, 7, 515- 517. doi: 10.1007/s00420-002-0339-z.

64. Verster R.S., Botha C.J., Naidoo V., Van Schalkwyk O.L. 2004. Aldicarb poisoning of dogs and cats in Gauteng during 2003. Journal of the South African Veterinary Association 75, 4, 177-181.doi: 10.4102/jsava.v75i4.479.

65. Wang Y., Kruzik P., Helsberg A., Helsberg I., Rausch W.D. 2007. Pesticide poisoning in domestic animals and livestock in Austria: a 6 years retrospective study, Forensic Science International. 169, 157-160. doi:10.1016/j.forsciint.2006.08.008.

66. World Health Organization, Geneva, 2000. Dinitro-ortho-cresol, Environmental health criteria 220.