Intoxication with carbamate insecticides and toxicological risk to animals

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Citation: Petrichev, M. (2022). Intoxication with carbamate insecticides and toxicological risk to animals. . *Zhivotnovadni Nauki*, *59*(1), 67-74 (Bg).

Abstract

Carbamate biocidal compounds (carbamic acid derivatives – aryl and alkyl esters) were discovered in the early 1950s. Shortly afterwards, along with organophosphorus insecticides (ORPs), they began to be widely used in the form of carbamate insecticides (CIs) with contact and gastric action, less often systemic. They have a similar mechanism of toxic action to ORPs. A little later, esters of thiocarbamic acid (thiocarbamates), which are mainly herbicides, were synthesized to the carbamine derivatives. Dithiocarbamates, which are mainly fungicides, were then synthesized (Melnikov, 1987). Carbamate insecticides are esters of methylcarbamic acid. Aryl esters of N-methylcarbamic acid have the strongest insecticidal action.

Key words: Intoxications, carbamate insecticides, toxicological risk, animals, ecotoxicity

Etiology and toxicological data:

Carbamate insecticides are solids, slightly soluble in water and better in organic solvents. Different pharmaceutical forms are used: suspensions, powders and others. Poisonings are mainly acute in nature, as carbamate insecticides accumulate very slowly and their toxic effects are quickly depleted.

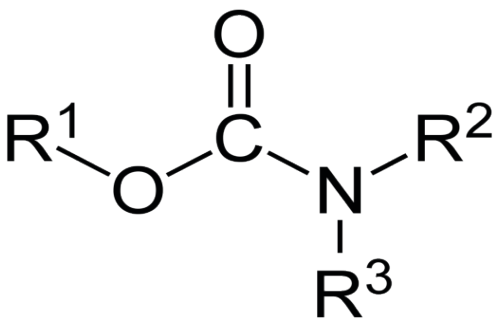

Fig. 1. General structural formula of carbamate insecticides

They are not stable in the external environment – in high heat, direct sunlight and in an alkaline environment, they are hydrolyzed to α-naphthol. In terms of toxicokinetics, they are easily and rapidly absorbed by internal administration and skin treatment (in higher concentrations). They are distributed throughout the body without binding to blood proteins. They are metabolized in the liver to α-naphthol and as α-naphtholglucuronide are excreted mainly in the urine up to 1–2 days after oral administration and up to 4–5 days after dermal administration. They are also excreted in the milk and eggs of productive animals.

Carbamate insecticides are highly toxic compounds known as poisons, identical or almost equivalent in toxicological risk to Organophosphorus insecticides, some of which may be possible war poisons. Their toxicity varies widely (Table 1), and is very different for different species of animals.

For example, the most common and widely used product – Sevin (carbaryl), has an LD_{50} for

Table 1. Representatives of carbamic acid (carbamates)

Pesticide	Commercial product	LD_{50} mg / body weight	Quarantine period, days
Aldicarb	Temik	0.93	Systemic action in seeds for sowing
Dioxacarb	Elokron	60–80	5–21
Diflubenzurol	Dimilin	4640	30
Etiofencarb	Croneton	415	4–7
Carbaryl	Sevin	307–800	7
Carbosulfan	Marshall-25	182	21
Carbofuran	Furadan	5–11	90
Kartal	Padan	325	14
Mercaptodimetur	Mesurol	60–130	15
Pirimicarb	Pirimor	100	7–21

internal use for rats 310–850 mg/body weight, as females are 1.7 times more sensitive; for calves LD_{50} is 100–150 mg/body weight, for cats – 153 mg/body weight, for sheep – 280 mg/body weight, for pigs – 508 mg/body weight, for rabbits – 700 mg/body weight, for pigs – 800–1000 mg/body weight, for hens – 2083 mg/body weight, for ducks – 3054 mg/body weight. For skin treatment LD_{50} for rats is 4000 mg/body weight , for rabbits – 5000 mg/body weight, and for horses – 50 mg/body weight. From the above data we can conclude that Sevin is more suitable for use in ducks, chickens, pigs and rabbits. Great care should be taken when using it in sheep and pigs, due to the higher risk of intoxication. In horses, calves and cats its use should be avoided (Dilov et al., 2021).

Sevin is used for treatment of walls and floor against ticks in 0.1–0.5% aqueous suspension, 100–200 ml/m2, for treatment of non-productive animals against ixodic ticks – 1% aqueous suspension. For dogs, carbaryl is teratogenic (Georgiev et al., 2010).

Of the carbamate insecticides used in Bulgaria with the highest toxicity and toxicologically the most risk is carbofuran (Furadan, Diafuran, Carbodan) LD_{50} orally for rats is from 5 to 11 mg/body weight, for dogs – 19 mg/body weight. The toxic dose for adult cattle is 5 grams, and for calves up to 1 year – 0.25–1 mg/body weight. In sheep, the toxic dose after oral administration is 2.5 mg/body weight (Dilov, P., et al., 2005). The toxic dose of carbofuran for sheep is 2.0 mg/body weight and the lethal dose is 3.0 mg/body weight (Petrichev, unpublished data).

Toxicological risks for productive animals and wild mammals and birds.

Although carbofuran has a well-defined nematicidal and acaricidal action, due to its high toxicity it is used only for wet treatment of seeds for sowing (corn, sunflower, wheat); not applicable to animals. The seeds are indicated (colored), most often in orange, red or blue to know that they are not intended for feed. When carbofuran-treated seeds are not well buried in the soil after sowing, they can cause intoxication in many animal species, including wild mammals and birds. Especially birds (2–3 grains of treated corn are enough to poison a pheasant).

Many cases have been observed in Bulgaria in which farmers, in excess, discard the indicated seeds near the field. This poses a potential toxicological risk to all animals, especially small and large ruminants.

Pirimicarb (Pirimor) has a higher toxicity than carbaryl and a lower toxicity than carbofuran. LD_{50} orally for mice is 68 mg/body weight, for rats – 100 mg/body weight, for dogs – 100–200 mg/body weight. For absorption through the skin LD_{50} for rabbits is 500–600 mg/body weight. This product is used mainly as an insecticide for plant protection – 0.1% solution (100 grams of substance per 1 dka). Animals can be poisoned after eating treated feed or dead insects. Mass

poisoning of pheasants has been observed after spraying forest against caterpillars (Petrichev, unpublished data).

Carbamate insecticides have been shown to have embryotoxic and teratogenic properties, although weaker, mutagenic and carcinogenic (in the presence of nitrates in a weakly acidic environment, they form the carcinogen N-nitrosocarbaryl). All this requires carbamate insecticides not to be used in breeding herds, especially in pregnant and lactating animals, in laying hens and before the forthcoming slaughter of animals.

Toxicogenesis. The mechanism of toxicity of carbamate insecticides is similar to that of organophosphorus insecticides. They also inhibit the enzyme cholinesterase, carbamylating the active site. This inhibition occurs only with the whole molecule of monomethylcarbamates – directly before they are metabolized. Blockade of cholinesterase is not as permanent as that of organophosphorus insecticides, with spontaneous reactivation and release of the enzyme usually occurring soon after. In carbamate insecticide intoxication, therefore, the so-called "aging" of the enzyme cholinesterase is not observed because its carbamylation is not permanent. Paralysis of the legs (chickens), muscle degeneration and brain edema (pigs) caused by high doses of carbaryl are not associated with inhibition of cholinesterase.

Acetylcholinesterase (AchE) is a key enzyme in cholinergic impulse transmission in the nervous system and is widespread in vertebrates and invertebrates (Bocquene et al., 1997). AChE functions at cholinergic synapses through a chemical impulse of the neurotransmitter acetylcholine (Ach). AChE is a very effective enzyme that hydrolyzes ACh to acetate and choline (Roex et al., 2003). The toxicity of organophosphate (OP) and carbamate (CB) insecticides is caused by the progressive inhibition of AChE in nerve tissue, leading to the accumulation of ACh in the synaptic cleft. Subsequently, overstimulation of ACh receptors leads to neurotoxic symptoms. The mechanism by which esterases hydrolyze their own substrates were studied using both biochemical and structural tools from a number of research groups (Wheelock et al, 2005).

Clinical signs. They are almost identical to those in intoxications with organophosphorus insecticides. They usually appear earlier, may be slightly milder and last for a shorter time, depending on the amounts of carbamate insecticides used and often on the type of product itself in the range of its toxicity. Carbamates reversibly inhibit acetylcholinesterase and plasma pseudocholinesterase. They cause increased activity of acetylcholine at nicotinic and muscarinic receptors. Often used carbofuran, propuxur Aldicarb, and other carbamates – benomyl, carbaryl, carbendazim. Central nervous system symptoms are not particularly noticeable in carbamate poisoning due to the poor permeability of these compounds across the blood-brain barrier (Ashish and Praveen, 2007).

The clinical picture of carbamate insecticide intoxication begins with mild agitation, bristling of the hair and feathers – first around the head, with mild hypermotility. Shortly after this first stage, the more characteristic signs of the second stage begin with a muscarinic (M-cholinomimetic) character – profuse salivation, tearing of the eyes, miosis, vomiting (in carnivores and pigs), bronchorrhea, bronchospasm, cough, frequent defecation and urination.

In the third stage, the symptoms are nicotinomimetic in nature – hypermotility with generalized tremor of dual origin - central and peripheral. Tremor usually begins with contractions of the muscles of the head and successively descends back to the muscles of the body. Later, clonic-tonic seizures also develop in birds with torticollis and opisthotonus.

The fourth stage can be considered the phase in which the aggravation of poisoning prevails, with manifestations of paresis and paralysis of the skeletal muscles, including the respiratory (intercostal muscles and diaphragm).

The last fifth stage is associated with prostration – complete immobility and slackness and severe respiratory depression (stage of asphyxia).

In experimentally reproduced intoxication in pigs (Zhelev, 2005) treated with carbofuran at a dose of 3.0 mg/body weight, showed the fol-

lowing clinical signs: loss of appetite, moderate salivation, lethargy, anxiety, wandering gaze, urges to vomiting, barely noticeable clonic-tonic spasms (starting from the hind limbs and reaching the neck muscles). Based on the data shown, the same author assumes that the dose around and below 3.0 mg/body weight, is the minimum toxic dose of carbofuran for fattening pigs.

In animals receiving a single dose of 8.0 mg/body weight carbofuran, clinical signs of intoxication were observed as early as 15 minutes and were expressed as depression, salivation with thick saliva, chewing movements, miosis and bradycardia. Diarrhea, tracheobronchial secretion and difficulty breathing were also observed at 20 minutes (Zhelev, 2005). Pigs in the group treated with carbofuran at a dose of 12.0 mg/body weight, showed similar signs of intoxication, with the difference that at 1 hour one of the treated animals was fatal and all other animals recovered within 3 hours of treatment. Based on these data, the author assumes that the minimum lethal dose of carbofuran for fattening pigs at 3 months of age is about and below 12.0 mg/body weight (Zhelev, 2005).

All animals treated with 18.0 mg/body weight orally showed signs of intoxication and were fatal. Based on these results, the author determined an initial maximum lethal dose LD_{95-98} of carbofuran for fattening pigs, around and below 18.0 mg/body weight. The same author also examined the mean lethal dose (LD_{50}) of carbofuran in fattening pigs by the method on Prozorovsky et al. (1978) – LD_{50} 14.1 mg/body weight (13.0–16.0 mg/body weight).

In experimentally reproduced intoxication in broiler chickens (Zhelev, 2005) treated with carbofuran at a dose of 4.0 mg/body weight, showed the following clinical signs: loss of appetite, feathering, adynamia (lasted about 2 hours), dilation of the pupils, a slight deepening of respiratory movements, some of the birds have shown and leakage of clear secretions from the beak. The same author based on his research assumes that the dose around and below 4.0 mg/body weight, for the minimum toxic dose of carbofuran for broiler chickens. All birds in the group treated with carbofuran at a dose of 12.0 mg/body weight, showed similar signs of intoxication, including watery diarrhea, with the difference that at 1 hour one of the treated animals was fatal and all other animals recovered by 3 hours of treatment.

Based on these studies, the author assumes that the minimum lethal dose of carbofuran for this species is around and below 12.0 mg/body weight (Zhelev, 2005). The same author also studied the mean lethal dose (LD_{50}) of carbofuran in broiler chickens by the method of Prozorovsky et al. (1978) – LD_{50} – 15.95 mg/body weight (13.10–19.17 mg/body weight).

Pathomorphology. The pathomorphological picture is similar to poisoning with organophosphorus insecticides, but in acute intoxication inflammation in the digestive tract is more often found after internal administration of carbamate insecticides. Edema and foamy exudate, often pink in color, are observed in the lungs. In hens, bleeding and necrotic areas in the ovaries and fallopian tubes are common. The pathological morphological finding after acute poisoning of productive animals with carbofuran is uncharacteristic: hemorrhages in the parenchymal organs (brain, liver and kidneys) and pulmonary outflow (Petrichev, unpublished data).

Diagnosis:

From clinical signs – agitation, not infrequently depression, salivation, bronchospasm, bronchorrhea and muscle tremor, less seizures (mostly in severe cases). The response to treatment with atropine administered intravenously at a dose of 0.02–0.04 mg/body weight is important.

Laboratory diagnosis. It is more difficult than that of organophosphorus insecticides because carbamate insecticides inhibit cholinesterase (their main laboratory marker) permanently (reversibly) and incompletely. The inhibitory effect on cholinesterase, especially in the first hours, is significant, but its possible absence, especially later, does not preclude poisoning with carbamate insecticides. Therefore, the diagnosis must be substantiated comprehensively and in the dynamics of the development of poisoning.

The greatest paraclinical significance for the lifelong diagnosis of carbofuran poisoning is the

establishment of high-grade (over 40–50%) inhibition of AchE in whole blood and plasma, as well as hyperglycemia, and postmortem – the inhibition of AchE in the cerebral cortex (Petrichev, unpublished data).

Differential diagnosis. It is difficult due to the similarity of poisoning with organophosphorus insecticides, but this is not a problem, as the mechanism of action of both types of poisons is identical, and the measures of therapy are the same.

Prognosis:

Often depends on the type and amount of product that the animals have taken orally. It also depends on the species, age and sex of the animals and other factors. Animals in which, after more severe clinical manifestations, milder manifestations of poisoning gradually begin to be observed, usually recover quickly (24–48 hours after the onset of poisoning). Consideration should be given to aggravating the prognostic outcome in pregnant animals and egg-laying birds due to the risk of harm to their offspring. Prolonged anorexia may occur in cats.

Therapy. In carbamate insecticide poisoning, in most cases, a single application of atropine sulphate in high doses is sufficient to remove the poisoned animals from lethal risk. After anorexia in animals it is necessary to apply a special diet.

Ecotoxicity. Organophosphorus and carbamate pesticides are used in domestic and natural conditions and environments to control a wide variety of insect pests and disease vectors. Some carbamate pesticides are used as repellents for birds and others as herbicides in various parts of the world. These two pesticide groups, numbering about 250, are formulated in thousands of products that are available on the world market for a variety of applications to wetlands, pastures, cultivated crops, forests, rural and urban areas. However, due to deviation, run-off or applicator error, pesticides degrade inevitably and are found in water, soil and vegetation outside the treated area – sometimes in toxic concentrations and for a duration far beyond the expected residual life of the product. The most widely used organophosphorus and carbamate pesticides are highly toxic, but are relatively short-lived (eg 2 to 4 weeks) and are easily metabolized and excreted by homoiothermal animals.

The ecological hazard of organophosphorus and carbamate pesticides to wildlife is primarily due to acute anticholinesterase toxicity, but also includes the association of species habitats and feeding preferences. The toxicological risk may be directly from the application of pesticides, contact with or ingestion of contaminated water, soil or vegetation or ingestion of contaminated prey (secondary toxicity) or impregnated seeds or granules with pesticides. Other factors also affect wildlife tolerance to contaminated environments with organophosphorus and carbamate pesticides. For example, the base of the prey can be changed and affect the success of the search for feed; sublethal exposure can affect critical behaviors such as reproduction and migration; and to upset the balance between soil organisms and water systems.

Fish and other aquatic organisms also vary considerably in exposure tolerance to organophosphorus and carbamate pesticides depending on the inherent sensitivity and factors of water quality, chemistry and temperature. Less than a quarter of the carbamates registered on the world market are insecticides with significant anticholinesterase activity; others are fungicides and herbicides with low toxicological risk to birds and mammals. Of the approximately 50 carbamate pesticides registered worldwide, only about eight (aldicarb, carbaryl, carbofuran, formetanate, methiocarb, methomyl, oxamyl, and propoxur) are used to control insects in crops, forests, and pastures; methiocarb and methomyl are also used as repellents for birds.

Carbamate insecticides exhibit their toxicity by acute inhibition of ChE, and all of the above except carbaryl are classified as highly toxic to birds and mammals. The LD_{50} is usually around and below 20 mg/body weight, as for most wild animals, LD_{50} 0.8 mg/body weight for aldicarb in male rats and 0.5 mg/body weight for carbofuran in male ducks (Hoffman et al., 2003).

Carbamate insecticides usually have a short life (1 to 4 weeks) and require several applica-

tions during the growing season; when applied to the soil, significant residues can occur that last from 2 to 16 months. There is little information on the biological risk in many applications, such as aldicarb and carbofuran. Both compounds are highly toxic to terrestrial animals (Smith, 1987; U.S. Environmental Protection Agency, 1991).

Aldicarb is toxic to fish; carbofuran is not as toxic as aldicarb in 96-hour LC_{50} tests with freshwater fish (Edwards and Fisher, 1991). Toxic residues of aldicarb and its degraded (mainly aldicarb-sulfoxide and sulfone compounds) were detected in groundwater and agricultural production up to one year after application. Due to its extreme toxicity to mammals and danger to agricultural workers, aldicarb is a pesticide with limited use in the United States. Carbofuran is also a pesticide with limited use, but it is still widely used on regulatory concerns about environmental hazards (Hall and Rumack, 1992).

Carbofuran in Bulgaria is mainly used for wet treatment of seeds before sowing, for control of soil and leaf insects and nematodes. Its use poses a serious toxicological risk to wildlife, mainly waterfowl. Granular forms are preferred, but similar mortality continues. These incidents usually occur within the first 2 to 3 days after the application of pesticides to field crops. Additional mortality was observed in both terrestrial and aquatic wildlife after heavy rainfall for more than 6 months after treatment (Hill, 1999). Carbofuran is the embodiment of an acutely toxic poison for the environment. That is, trivial exposure (eg 0.1–5 mg/body weight) can be fatal in less than 5 minutes, especially for some waterfowl. Environmental factors such as wind, rain and UV radiation rapidly reduce the risk of toxicity within 2 to 3 days, although systemic insecticidal activity may last for more than a month.

Common factors influencing the risk of carbofuran to wildlife include formulation and application, its solubility in water and potential for transport outside the treated area, and the likelihood of it entering wetlands. Carbofuran is soluble in water up to about 700 mg/L and substantially stable in an acidic medium. The fate of carbofuran in water is influenced by pH, photolysis, temperature and traces of impurities. The half-lives of carbofuran in distilled water at 25 °C and pH 5.5, 7, 8 and 9 are about 16 years, 1 month, 6 days and 6 hours, respectively (Stinson, E. R. and Bromley, P. T., 1991). The rate of hydrolysis positively correlates with ambient temperature. Carbofuran in the soil is influenced by the composition of the pesticides, the rate and method of application, soil type, pH, precipitation and irrigation, temperature, moisture content and microbial populations. Carbofuran decomposes rapidly in alkaline soil and is stable at pH 5.5; the hydrolytic half-life in soil at pH 7 is about 35 days (Briggs, 1992).

The half-life of terrestrial scattering of carbofuran in irrigated soils is 4 to 11 days in sandy clays, 1 month in clay soils, and less than 5 months in muddy soils. Carbofuran is mobile and is found in streams, surface waters and runoff from treated watersheds. This suggests that carbofuran may be quite stable in relation to acid rain. It has also been suggested that carbofuran may remain in the soil at a characteristic acidic pH, such as aldicarb (Ecobichon, 1996).

Carbofuran is rapidly metabolized in live animals and is rapidly excreted. However, secondary toxicity of carbofuran occurs in predatory vertebrates that feed on dead and fighting insects, earthworms, and small birds and mammals. This type of poisoning is most likely from unabsorbed carbofuran in the gut of the main subject (Mineau, 1999).

Insecticide poisoning is an important cause of bird poisoning in France. In this country, it accounts for 33% of all aldicarb, mevinphos and especially carbofuran poisonings found in baits (Berny and Gaillet, 2008). Cholinesterase inhibitors account for 42.5% of all causes of death in birds (Lamarque et al., 1999). High mortality was observed in pigeons after the use of furathiocarb, carbamate, as a coating of pea seeds (Lelièvre et al., 2001).

In the Dadia forest (northeastern Greece), seven vultures and an eagle were found dead, along with 11 red foxes (*Vulpes vulpes*) poisoned with carbofuran, suggesting secondary poisoning of birds of prey by fox consumption (Antoniou et al., 1996). Data collected by various Spanish Laboratories between 1990 and 2005 show that

58 wild birds were studied, including 10 cinera vultures and one Spanish Imperial Eagle, which were poisoned by various types of pesticides (Martínez-Haro et al., 2008).

A retrospective analysis of the intoxications registered in our country in wild birds and mammals was performed in the period 2009–2012, and the reasons for their occurrence were analyzed. A total of 36 samples (liver and gastrointestinal contents) from wild birds, mammals and baits were examined and a laboratory differential diagnosis was performed to prove the cause of the poisoning. During the period of this study, 2 major incidents in wild mammals and birds were recorded. The data from the conducted researches have shown that the poisonings in the wild birds and mammals (critically endangered, endangered and vulnerable species), included in the "Red Book" of the Republic of Bulgaria are 7 species, as in 5 species of wild animals the death occurred due to intoxication with anticholinesterase pesticides (most often in birds of prey), (Petrichev et al., 2013).

In Bulgaria in the period from 2018 to 2020, 3 major incidents of poisoning were registered, with carbamate insecticides in ruminants and wild birds and mammals (Petrichev, unpublished data).

Conclusion

Poisoning is widespread and is of great importance and research problem for toxicological laboratories and forensic examinations. Accidental toxic disasters are difficult to prevent and control, but of greater concern are cases of illegal and deliberate use of poisons, including human activities (baiting, hunting), all of which have significant consequences for endangered species.

Knowledge of the clinical signs of animal poisoning is essential to any effort to reduce morbidity and mortality, and therefore coordinated and integrated efforts between countries to facilitate the flow and sharing of information to minimize the risks of accidental and fatalities are essential intentional poisoning.

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