the poison®

2024 | Vol. 1 | No. 1: 22-28

ORIGINAL ARTICLE

Accidental ingestion of coumarin rodenticides: A retrospective study of 139 patients in a pediatric hospital

Agostina Popity*, Nuria M. Robla Vilá, Nicolás M. Lufrano Zappitelli, Constanza L. Traverso and Daniel Dozoretz

Toxicology Service, "Superiora Sor María Ludovica" Interzonal Acute Hospital Specialized in Pediatrics, La Plata, Buenos Aires, Argentina.

popityagostina@gmail.com

Submitted: 03/11/2023 - Accepted: 05/12/2023 - Published: 31/01/2024 - DOI: https://doi.org/10.62129/OSHQ7320

Abstract. Coumarin-derived rodenticides are currently the most popular pesticides to control rodents. The accidental ingestion (AI) of these compounds in pediatric patients is frequently a reason for consultations. This is a descriptive retrospective study based on data gathered from the medical records (MRs) of patients seen on-site at the "Superiora Sor María Ludovica" Interzonal Acute Hospital Specialized in Pediatrics in the course of 6 years and 9 months. For this study, 139 MRs of patients between 0 and 14 years of age seen in the Emergency Service and in outpatient care were considered. None of the patients showed at the time of admission signs or symptoms compatible with hemorrhage or irregularities in their coagulation tests, except for two patients. In line with the bibliography consulted, most AI in pediatrics do not have any relevant clinical effect. There is no formal prescription for complementary biochemical studies for patients under 6 years of age with AI of coumarin rodenticides. By means of a thorough anamnesis, the physician will be able to detect those patients that require special care, coagulograms and clinical monitoring with alarm instructions aimed at the appearance of bleedings.

Key words: *Accidental ingestion; Pediatrics; Dicoumarin rodenticides; Superwarfarin; Vitamin K.*

Most consultations in Toxicology are related to the accidental ingestion (AI) of drugs or household products, and have low or no toxicity, either due to the low dosage ingested or to the lack of toxicity of the substance. Among the products available in the household, coumarin rodenticides (both warfarin and superwarfarin-type) are the most common compounds used in rodent control and are rarely related to medically relevant poisoning.[1]

In our field there is no up-to-date epidemiologic data. Therefore, provided below is the detail of the main characteristics of patients seen on-site at the "Superiora Sor María Ludovica" Interzonal Acute Hospital Specialized in Pediatrics (SSMLSP), in the city of La Plata (Buenos Aires, Argentina), regarding AI of coumarin rodenticide in the course of 6 years and 9 months.

MATERIALS AND METHODS

Descriptive retrospective study based on data gathered from the medical records (MRs) of patients seen on-site at the SSMLSP between January 1, 2017 and September 30, 2023. The information was collected from the MRs taken by clinical toxicologists at the Toxicology Service of the aforementioned hospital. 139 MRs of patients presenting AI of coumarin rodenticides between the ages of 0 and 14 who made on-site consultations, whether through the Emergency Service (ES) or outpatient care (OC). A search of available bibliography was performed in virtual databases such as PubMed, TripDataBase, Cochrane, Google Scholar y SciELO, scientific dissemination books, and consensus documents. The keywords used (both in English and Spanish) were: "rodenticides", "anticoagulants", "antithrombotics", "superwarfarin", "warfarin", "poisonings", "accidental inges-

tion", and "pediatrics". The results in both languages were arranged in order of importance and 20 scientific articles were selected including case reports, systematic reviews, consensus and clinical practice guidelines.

RESULTS

The qualitative variables are presented in absolute numbers and in percentages. Out of the 139 patients, 85 (61.1%) were male, 52 (37.4%) were female and 2 patients (1.4%) no data. The age average was 26.7 months, the youngest being 8 months old and the oldest 8 years of age. 124 patients (89%) were seen in the ES and 15 (10.7%) patients in OC. Out of those who visited the ES, 71 patients (58.2%) did it within 2 hours of the ingestion, 8 (6.4%) between 2 and 6 hours, and 6 (4.8%) after 12 hours of the ingestion. There is no data for this variable for 38 patients (30.6%).

Regarding medical treatment, a decontamination procedure with activated charcoal (AC) was performed on 76 patients (61.2%). Tests were performed on 81 patients (58.2%) upon their admission, including a hemogram and coagulogram with prothrombin time (PT) and activated partial thromboplastin clotting time (KPTT). The normality of the PT was tested using the Kolmogorov-Smirnov test. The median was 98 and the interquartile range was between 86-100. The PT median was 91.87 with a standard deviation (SD) of 11.57. Out of this percentage, 50 patients (35.9%) were monitored with a coagulogram after 48 hours of the ingestion, with an average PT of 86.5 and SD of 10.9. 29 patients (20.8%) continued with the examinations after one week, with an average PT of 87 and SD of 7.6. Of these patients, 15 were examined after one month with an average PT of 88.2 and SD of 10.6. Only two patients (1.5%) showed irregularities in their PT upon their admission, successfully treated with the prescription of a dose of vitamin K (VK).

None of the patients showed upon their admission or afterwards any sign or symptoms compatible with hemorrhage. Out of all the patients, 90 (65%) attended the postliminary examinations. These examinations were performed 48 hours, one week and one month after the first consultation. The remaining 49 patients (35%) did not attend the appointments or contact was lost.

DISCUSSION

General aspects

Rodenticides are pesticides made for killing rodents. Three species are considered worldwide plagues: 1) the "brown rat", "sewer rat" or *Rattus norvegicus*, 2) the "black rat" or *Rattus rattus*, and 3) the "house mouse" or *Mus musculu*. They have adapted very well to the urban environment, being related to numerous sanitary issues.[2] A wide variety of rodenticides is used to control them, which pose a potential health risk. Humans can also suffer their effects, being that they are chemicals specifically designed to kill mammals, and both rodents and humans live in the same environment. Rodents have developed a resistance against classic rodenticides, which is why new substances have been created which boast more power, effectiveness and toxicity.[3]

Rodenticides are classified into three groups: gaseous, mineral, and organic. Examples of *gaseous* rodenticides are hydrogen cyanide and methyl bromide. *Mineral* rodenticides include arsenic, phosphorus, thallium, barium and fluorine. Finally, *organic* rodenticides include strychnine and coumarin-based compounds, both warfarin and superwarfarin-type. The latter are VK antagonists, widely used for rodent control worldwide.[4] In Argentina there are 48 formulas available for professional use and 6 sold over-the-counter of warfarin and superwarfarin rodenticides. They are registered in the National Administration of Drugs, Food and Medical Devices (ANMAT, by the Spanish acronym). In professional-grade formulas, 46.2% contain 0.005% brodifacoum, while 40.7% contain bromadiolone at an equal concentration. The rest contain flocoumafen, difetialone, difenacuom or warfarin. Most of those available over-the-counter (66.6%) contain 0.005% Bromadiolone. These rodenticides are sold as paraffin-coated baits, pellets and small seeds.[5] A liquid formula sold in the informal market has been identified, which had hydroxycoumarin as an active ingredient. It was banned by ANMAT in 2018.[6]

The origin of rodenticides can be traced back to 1939 with the identification of bis-hydroxywarfarin or dicoumarol, after hemorrhagic disorders (with a decrease in plasma prothrombin levels) were observed in bovines that had ingested *Melilotus albus* or "sweet clover". This in turn gave way to the later synthesis of warfarin, commercially available from 1955.[7,8] Superwarfarins, a group comprised of 4-hydroxycoumarins and indandiones, were produced as a result of the resistance to the warfarin developed by rodents. The 4-hydroxycoumarins used today are difenacoum, brodifacoum, bromadiolone, and coumatetralyl. Indandiones comprise chlorophacinone, diphenadione, and pindone. All of them have a two-ring structure similar to warfarin.

Toxicokinetics

The oral bioavailability of warfarin is close to 100%, it permeates the blood–brain barrier and it is distributed in the liver, spleen, lungs, and kidneys, with a half-life of 20 to 60 hours. Its duration of action is 2 to 5 days and 99% circulates bound to proteins, with a low volume of distribution. It is metabolized in the liver and excreted in the urine.[10]

Although superwarfarin is mainly absorbed orally, absorption through the skin and via inhalation has also been observed. It is highly fat-soluble (it accumulates in the liver and adipose tissue) and it undergoes enterohepatic circulation. It is excreted in the urine and fecal matter. Superwarfarin is 100 times more potent than warfarin, with a more prolonged action (even after just one dose). The toxic dose of brodifacoum is 0.1 to 0.27 mg/kg, with a half-life of 114 days; for bromadiolone it is 0.17 mg/kg, with a half-life of 28 to 318 days.[7] It has been observed that 1 mg of the active ingredient of brodifacoum could potentially be fatal in adults.[10] As it is not able to act upon already active factors causes the full anticoagulation effects to occur after several hours and even days.[1] Therefore, after being exposed to superwarfarin the onset of coagulopathy (measurable with PT) depends on the half-life of VK-dependent coagulation factors, which range from 6 hours for factor VII to 60 hours for prothrombin.[7] Table 1 shows the half-life (t1/2) of VK1 and VK-dependent coagulation factors.[8]

TABLE 1. Half-life (t1/2) of VK1 and VK-dependent coagulation factors (adapted from Haddad LM et al., 1998).

	Half-life time (t1/2)
VK1	1.7 hrs.
Factor II	50-80 hrs.
Factor VII	6 hrs.
Factor IX	24 hrs.
Factor X	25-60 hrs.

Toxicodynamics

The action mechanism of these pesticides is determined by their disruption of the coagulation cascade. This chain of events begins with the activation of proteases known as *coagulation factors* and ends with the activation of thrombin, which is key for platelet activity and to convert fibrinogen into fibrin. Factors II -or prothrombin-, VII, IX, and X, and proteins C, S, and Z all depend on γ-carboxylase, a VK-dependent liver enzyme.[8,9]

VK is a fat-soluble vitamin which can be synthesized or found in nature. There are currently 3 subtypes of VK, all of them have a two-ring structure with differing carbon side chains.[7,8] Vitamin K1 (VK1), phytomenadione or phytonadione is synthesized by plants and algae; vitamin K2 (VK2), natural or menaquinone is produced by bacteria; and vitamin K3 (VK3) or menadione is synthetic and is converted into active K2 *in vivo*. VK is necessary for γ-carboxylation of glutamate residue in order to activate factors II, VII, IX, and X, and proteins C, S, and Z, all of which have pro-coagulant effect. Through γ-carboxylase, it is responsible for the conversion of glutamate into γ-carboxyglutamate, which is present in active coagulation factors. This compound chelates Ca^{++}, which allows for the bonding of these factors to phospholipid membranes during the activation of the coagulation cascade. A decrease or absence of VK (which has a half-life of 1.7 hours) renders factors II, VII, IX, and X, and proteins C, S y Z inactive, which affects this process and creates an anticoagulable state.[8]

Coumarin rodenticides act by inhibiting the enzyme VK 2,3-epoxide reductase and prevents the organism from recycling VK. Additionally, there is evidence that suggests that these pesticides could also inhibit the enzyme VK quinone reductase.[9] Fig. 1 exhibits the VK cycle and the enzyme inhibition that is produced by superwarfarin rodenticides. The exact mechanism by which these substances inhibit the aforementioned enzymes is still unclear.[7] After the drop in plasma levels of VK, clinically relevant changes can only be witnessed after 24 hours.[7,8]

Medical approach

Anamnesis. It is essential to specify the latency of the ingestion, the amount and the format of the product. Normally, the pesticide is sold in solid rodenticides similar to grains of rice or paraffin-coated baits of various shapes and sizes. The liquid format is less frequent but it can be found, albeit it is more strictly regulated. Fig. 2 pictures different rodenticides we have confiscated in our institution over time.

Decontamination. In cases where the ingested dose is unknown and within one hour of said ingestion, the preferred gastrointestinal decontamination technique is the

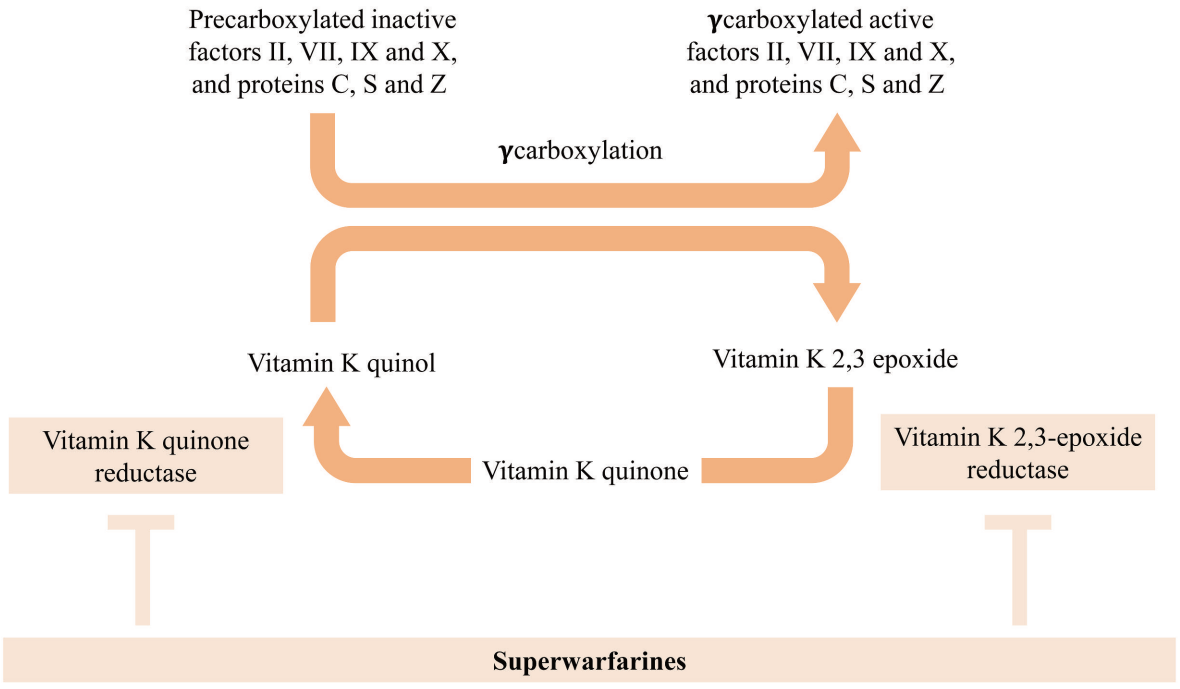

Figure 1. The VK cycle and enzyme inhibition produced by superwarfarin rodenticides (adapted from Nelson L et al., 2019).

administration of AC.[1] Prior nasogastric intubation in order to perform a gastric lavage depends on the rodenticide dose being potentially lethal, which could be possible if the ingestion was deliberate or if the patient suffers from any cognitive disability.

Clinical presentation. In line with our findings and the bibliography that was consulted, most AI in pediatrics do not have clinical effects. None of the patients showed hemorrhage upon admission or in subsequent examinations. Only 2 patients presented irregularities in their PT, which were succesfully treated with a single dose of VK (this could have been caused by a preexisting deficit and not by coumarin rodenticide poisoning). The low risk of poisoning described in the bibliography is linked to the small amounts that are ingested (because of, for example, bittering substances that are added to the rodenticides) and the fact that the dose of active ingredients is usually low in household preparations. In cases where larger amounts are ingested, mainly in adults or children over 6 years of age, these agents begin to have clinical effects 24 to 48 hours after ingestion, due to the half-life of coagulation factors. Signs and symptoms of hemorrhage are the most distinctive clinical characteristics of this poisoning.

The first signs include gingival bleeding, epistaxis, macroscopic hematuria, gastrointestinal bleeding (melena or hematochezia), metrorrhagia, hemoptysis, ecchymosis, and peri-articular hematomas, which in some cases could be severe. Patients can also show signs of anemia or hypovolemia such as tachycardia, arterial hypotension, fatigue and dyspnea on exertion, headache, abdominal or chest pain. In cases of severe poisoning the patient can suffer a hypovolemic shock and subsequent death.[3,7] It has also been observed that VK antagonists could have a procoagulant effect, some cases being reported where patients exposed to superwarfarin suffered from thrombosis as well as bleeding, which is likely to be related with the inhibition of proteins C and S.[12]

Diagnosis. The gold standard is the determination of superwarfarin in serum by a high-performance liquid chromatography (HPLC)[7], which in our context is performed in few laboratories and with limited access. The PT and the international normalized ratio (INR) are widely available biomarkers which can be used to identify the coagulopathy caused by coumarin rodenticides.[7] Alterations in these parameters are normally seen 24 to 48 hours post ingestion, after VK-dependent coagulation factors decay. The PT reference range varies from 10 to 14 seconds and activity over 70%. Results may vary significantly depending on the technique used, which is why INR was developed in an attempt to standardize said result.[12,13]

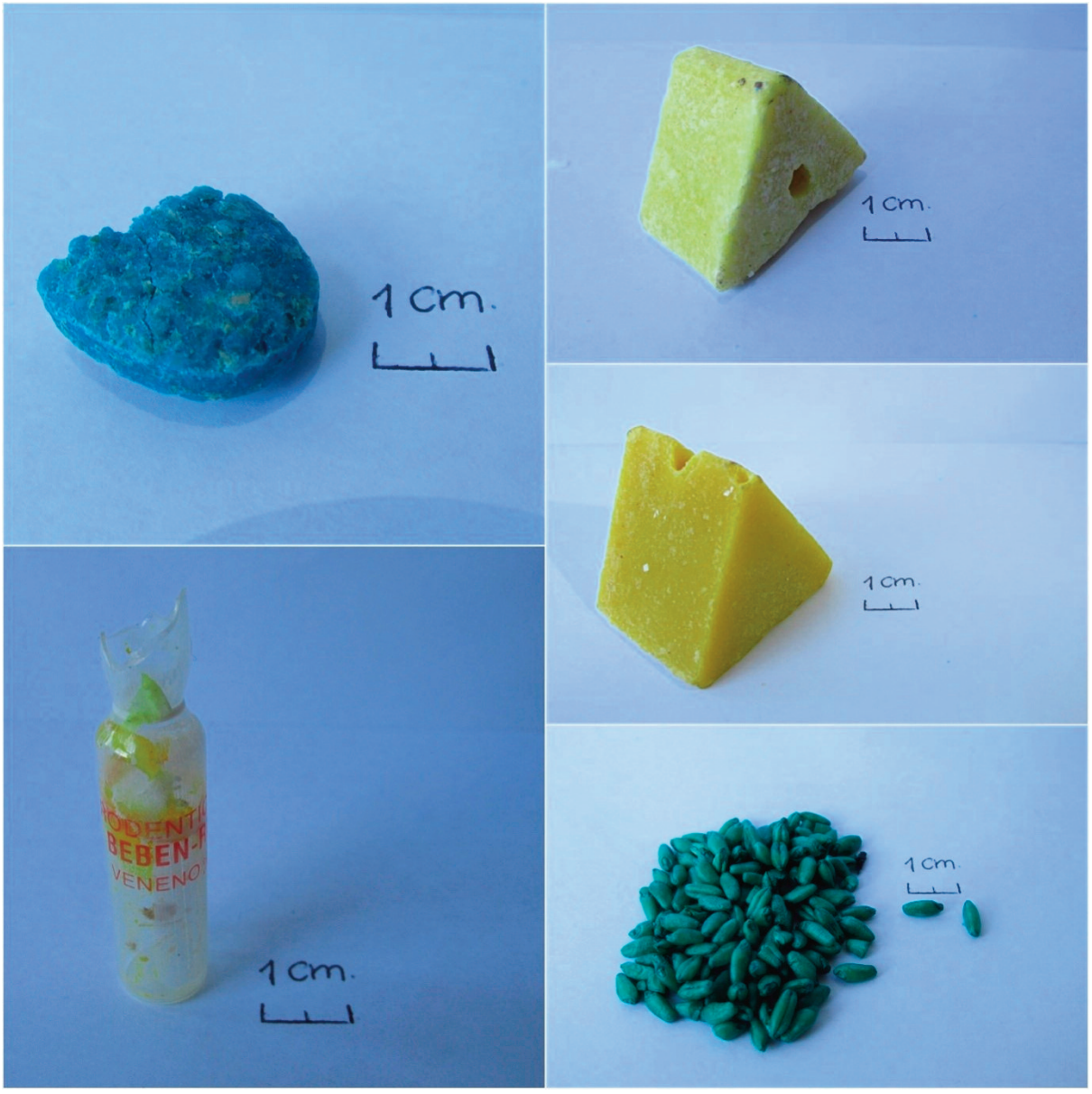

Figure 2. Photographs of rodenticides brought by patients seen in our hospital. The different formats of this product should be noted: paraffin-coated baits, ampoules (liquid content), and "grains of rice".

It is recommended to perform a coagulogram upon admission and 48 to 72 hours after in the following cases: 1) ingestion of unknown or large doses; 2) children over 6 years of age in which the ingested dose, even a single AI, may be toxic; 3) patients with symptoms; 4) intentional ingestion; 5) chronic or repeated ingestions; 6) ingestion in patients using other anticoagulants; and 7) suspected Munchausen syndrome, negligence, child abuse and neurodevelpment disorders.[1,15] In the first two, the initial coagulogram can be omitted, assuming that it should report normal values. As stated in the bibliography, several authors[7,10,20] have dismissed performing coagulograms in cases of AI of non-toxic doses -under 1 mg of active ingredient- in patients under 6 years of age.[7,14] Those patients can be subject to outpatient care with attention to warning signs and clinical follow-ups, given that there were no clinical symptoms in patients in this age group who presented AI.[1,16,20]

Treatment. The specific treatment is VK1 supplementation. It is recommended in patients with signs of hemorrhage

www.thepoisonjournal.com | Cite as: Poison 2024; 1(1):22-28 | DOI: 10.62129/OSHQ7320

or biochemical alterations and not prophylactically.[10,15] Presently, there is no established dose. According to some studies, a dosage of 30 mg/day of VK1 in doses divided by day is accepted, ideally PO. It will depend on the patient's PT and/or INR and ranges from 25 to 50 mg per day[19]. Intramuscular (IM) route is not advised due to the risk of creating hematomas. 1 mg/kg intravenous (IV) VK is mainly used in hemodynamically unstable patients or who have active bleeding.[18,19] Serum brodifacoum and chlorophacinone were found useful to observe exposure and to determine when the VK treatment can be stopped.[15] In cases where the patient presents active bleeding, in addition to the specific treatment an additional treatment is recommended, which consists of prothrombin complex concentrates (with factors II, VII, IX, and X) or activated recombinant factor VII or fresh frozen plasma if the concentrates are not available[17].

Monitoring. AIs in children under 6 years of age have a low clinical toxicity index. No cases of hemorrhage or other clinical symptoms were observed in this age group with accidental exposure.[15,20] Therefore, only clinical monitoring and blood tests should be performed on the groups described in the *Diagnosis* section.

CONCLUSIONS

Coumarin rodenticides are compounds that can be easily accessed by children. Consistent with the findings in our hospital and in line with the bibliography, we can conclude that AI of rodenticides in pediatric patients under 6 years of age does not warrant additional routine biochemical tests. A detailed anamnesis will allow the physician to detect those patients that require special care, coagulograms and clinical monitoring with warning instructions aimed at the appearance of bleedings.

Conflicts of interest

The authors declare no conflicts of interest.

REFERENCES

1 Beriain Rodríguez M, Gómez Cortés B, Benito Fernández J, Mintegui Raso S. Ingesta accidental de superwarfarinas. An Pediatr. 2008 May;68(5):503-6. Available from: https://doi.org/10.1157/13120051

2 Moreno Marí J, López Ferrer J, Jiménez Peydró R. El control de los roedores: revisión de los rodenticidas registrados en el ámbito de la sanidad ambiental en España. Rev Esp Salud Pública. 2004;78(1):05-16. Available from: https://scielo.isciii.es/scielo.php?script=sci_arttext&pid=S1135-57272004000100002&lng=es&tlng=es.

3 EPA en español | US EPA [Internet]. Raticidas; [cited 2023 Nov 10]. Available from: https://espanol.epa.gov/sites/default/files/2015-09/documents/spch17.pdf

4 Nogué Xarau S, Garriga S. Intoxicación aguda por raticidas. In: Morán Chorro I, Baldirà Martínez de Irujo J, Marruecos - Sant L, Nogué Xarau S, editors. Toxicología Clínica. 8th ed. Madrid: Grupo difusión; 2011. p. 431-5.

5 Inicio | Argentina.gob.ar [Internet]. Listado de insecticidas y raticidas; 2021 Sep 20 [cited 2023 Nov 10]. Available from: https://www.argentina.gob.ar/sites/default/files/anmat_listado_de_insecticidas_y_raticidas_actualizado_al_20-9-21.pdf

6 ANMAT | Argentina.gob.ar [Internet]. A.N.M.A.T.; [cited 2023 Nov 10]. Available from: http://www.anmat.gob.ar/alertas_domisanitarios.asp

7 Chong YK, Mai TW. Superwarfarin (Long-Acting Anticoagulant Rodenticides) Poisoning: from Pathophysiology to Laboratory-Guided Clinical Management. ClinBiochem Rev. 2019;40(4):175-85. Available from: https://doi.org/10.33176/aacb-19-00029

8 Lai M, Burns Ewald M. Anticoagulants. In: Haddad L, Shannon M, Winchester J, editors. Clinical management of poisoning and drug overdose. 4th ed. Philadelphia: Saunders; 1998. p. 1051-64.

9 Chen B, Su M. Antithrombotics. In: Nelson L, Howland M, Lewin N, Smith S, Goldfrank L, Hoffman R, Flommenbaum N, editors. Goldfrank's toxicologic emergencies. 11th ed. New York: McGraw-Hill Education; 2019. p. 883-907.

10 Gallardo Ferrada A, Lizana Gajardo F, Gutiérrez Torres W. Superwarfarin rodenticide poisoning. Acta Toxicol Argent. 2015;23(1):lil-757035. Available from: http://www.scielo.org.ar/pdf/ata/v23n1/v23n1a05.pdf

11 Card DJ, Francis S, Deuchande K, Harrington DJ. Superwarfarin poisoning and its management. Case Rep. 2014 Oct 13;2014(oct13 1). Available from: https://doi.org/10.1136/bcr-2014-206360

12 Jourdi G, Calmette L, de Maistre E, Hurtaud MF, Siguret V, Gouin-Thibault I. Tiempo de Quick (tasa de protrombina), INR. EMC Tratado Medicina. 2017 Dec;21(4):1-7. Available from: https://doi.org/10.1016/s1636-5410(17)86938-5

13 López-Santiago N. Pruebas de coagulación. Acta Pediatr Mex. 2016 Jun 29;37(4):241-5. Available from: https://doi.org/10.18233/apm37no4pp241-245

14 Ingels M, Lai C, Tai W, Manning BH, Rangan C, Williams SR, Manoguerra AS, Albertson T, Clark RF. A prospective study of acute, unintentional, pediatric superwarfarin ingestions managed without decontamination. Ann Emerg Med. 2002 Jul;40(1):73-8. Available from: https://doi.org/10.1067/mem.2002.125449

15 Caravati EM, Erdman AR, Scharman EJ, Woolf AD, Chyka PA, Cobaugh DJ, Wax PM, Manoguerra AS, Christianson G, Nelson LS, Olson KR, Booze LL, Troutman WG. Long-acting anticoagulant rodenticide poisoning: An evidence-based consensus guideline for out-of-hospital management. ClinToxicol. 2007 Jan; 45(1):1-22. Available from: https://doi.org/10.1080/15563650600795487

16 Micromedex® Helthcare series. Truven Health Analytics Inc. [CD-ROM] Vol 172, 2017.

17 Watt BE, Proudfoot AT, Bradberry SM, Vale JA. Anticoagulant Rodenticides. Toxicol Rev. 2005; 24(4):259-69. Available from: https://doi.org/10.2165/00139709-200524040-00005

18 Ng WY, Ching CK, Chong YK, Ng SW, Cheung WL, Mak TW. Retrospective Study of the Characteristics of Anticoagulant-Type Rodenticide Poisoning in Hong Kong. J Med Toxicol. 2018 Apr 23;14(3):218-28. Available from: https://doi.org/10.1007/s13181-018-0660-x

19 Greco V, Spera M. Vitamina K1-Fitomenadiona. In: Díaz M, Greco V, editors. Guía de antídotos y tratamiento en intoxicaciones. 2nd ed. El Palomar: Hospital Nacional Profesor Alejandro Posadas; 2021. p. 153-5.

20 Mullins ME, Brands CL, Daya MR. Unintentional Pediatric Superwarfarin Exposures: Do We Really Need a Prothrombin Time? Pediatrics. 2000 Feb 1;105(2):402-4. Available from: https://doi.org/10.1542/peds.105.2.402