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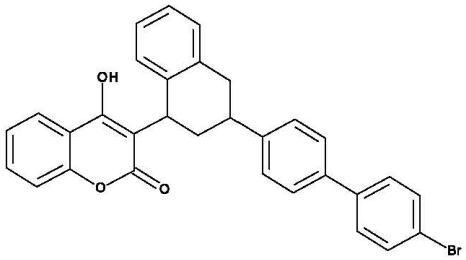
Brodifacoum in Synthetic Cannabinoids

Toxic Adulterant Alert

Substance use treatment providers, clinicians, outreach workers, and public health clinics should be aware of the following information. The commercially available rodenticide, brodifacoum, is becoming more frequently identified in synthetic cannabinoid products, commonly known as K2 and Spice. Brodifacoum, derived from warfarin, is classified as a "superwarfarin" due to its high potency, long duration of its anticoagulant effect, and danger when ingested in even a single dose. The only clinically consequential effect is bleeding, which can be delayed, prolonged, and severe, and itself can lead to life-threatening clinical effects. Brodifacoum is not a controlled substance in the United States and is available commercially at low concentrations in rodenticide products.

Background: Brodifacoum is a second generation, highly toxic pesticide commonly used for the elimination of rodents. It was registered by the U.S. Department of Agriculture (USDA) in 1979 after Congress passed the Federal Insecticide, Fungicide, and Rodenticide Act (FIFRA) in 1947. The U.S. Environmental Protection Agency (EPA) determined that certain toxic substances (including brodifacoum) needed to be reregistered and reevaluated post its initial registration in 1979. The reregistration eligibility decision for the rodenticide cluster was approved, and the risk mitigation decision in 2008 stated the second-generation anticoagulants were able to be reregistered for use in commercial pest control and not in consumer products. The EPA pesticide product label for brodifacoum from May 5, 2021, states that this pesticide can be fatal if swallowed, inhaled, or absorbed through the skin. It acts as an inhibitor for the vitamin K1 epoxide reductase enzyme in the liver, thus inhibiting the production and recycling of activated vitamin K1, which is used to make functional blood clotting factors. Brodifacoum is classified as an anticoagulant because blood clotting is inhibited.

Brodifacoum



Recommendations for Clinicians

- Be aware that illicit drugs (especially synthetic cannabinoids) may contain **brodifacoum**, which can alter the clinical presentation or obscure the diagnosis.
- Be familiar with the signs and symptoms associated with **brodifacoum** poisoning.
- Be aware that the anticoagulant and hemorrhagic effects of **brodifacoum** can be delayed following exposure.

Frequent Indicators of Toxicity

- Gum bleeding
- Epistaxis
- Ecchymosis
- Hematoma
- Hematemesis
- Hematuria
- Blood in feces
- Vaginal bleeding
- Abdominal pain
- Shortness of breath (anemia)
- Extreme fatigue (anemia)

Recommendations for MEs & Coroners

- Conduct testing for **brodifacoum** in postmortem cases involving unexplained bleeding and suspected synthetic cannabinoid use.

Recommendations for Forensic and Clinical Laboratories

- Test for anticoagulants, like **brodifacoum**, in case with a history of synthetic cannabinoid use.
- Perform additional testing in cases that appear to be related to anticoagulants, e.g., where excessive bleeding is noted upon admission to an emergency department.
- Consider laboratory analysis of seized drug samples taken from suspected drug overdose investigations where excessive bleeding was present.
- Share data on adulterants in drug seizures in your jurisdiction with local health departments, medical examiners, and coroners.

Epidemiological Reports: Following the first documented case on March 8, 2018 in Illinois, 160 people from Florida, Indiana, Illinois, Kentucky, Maryland, Missouri, Pennsylvania, Virginia, and Wisconsin used synthetic cannabinoids presented to healthcare facilities with unexplained bleeding. Brodifacoum exposure was confirmed in 60 of these cases, and 7 synthetic cannabinoid samples related to these cases tested positive for brodifacoum. AB-FUBINACA and brodifacoum were both confirmed in one of the synthetic cannabinoid samples. In a series of patients, in Peoria, Illinois between March 28 and April 21, 2018, who used synthetic cannabinoids and developed unexplained coagulopathy. Confirmatory testing on biological specimens identified brodifacoum in 15 of 34 samples tested. In June 2018, the U.S. Food & Drug Administration (FDA) released an alert after receiving reports regarding brodifacoum that was detected in the plasma of donors who had used synthetic cannabinoids. In July 2018, the FDA issued a warning related to the dangers associated with using synthetic cannabinoids due to the risk of contamination with brodifacoum. The Center for Disease Control and Prevention (CDC) in 2022 reported on 52 cases of suspected brodifacoum poisoning linked to synthetic cannabinoid use in Florida, four of which resulted in death. Outside of the United States, instances of brodifacoum-adulterated synthetic cannabinoids have been reported in Israel (95 hospitalizations and 3 deaths) and Jordan.

Case Reports: A case report described a 15-year-old girl who intentionally ingested brodifacoum that resulted in a massive pulmonary hemorrhage and death. Reported concentrations were 3,919 ng/mL in femoral blood and 4,276 ng/mL in bile. A 29-year-old woman presented to the emergency department with vaginal and rectal bleeding along with vomiting blood after using synthetic cannabinoids. Blood collected from the individual resulted in a concentration of 127 (units not provided but presumed to be ng/mL). Treatment included blood transfusions and intravenous vitamin K1. Following discharge, the patient remained on vitamin K1 three times per day for 3 to 6 months until her international normalized ratio (INR) stabilized, at which point the vitamin K1 was weaned.

Initial management of coagulopathy in patients with brodifacoum poisoning consists of rapid reversal with clotting factors, such as fresh frozen plasma or four factor prothrombin complex concentrate (PCC). Intravenous vitamin K1 is generally administered, though it requires several hours to be effective. Replacement of blood volume and identification and control of any bleeding sites should be done as required. Long-term oral vitamin K1, generally for several months, is necessary to prevent recurrence of coagulopathy as the long-acting anticoagulant is slowly eliminated from the body. Prescribed oral vitamin K1 is currently expensive. There are no established interventions to increase the clearance of long-acting anticoagulants.

References and Related Articles:

- Tole, M.; LaBedz, S.; Feinstein, D. L.; Rubinstein, I. Adherence to Long-Term Follow-Up of Patients with Life-Threatening, Inhaled Synthetic Cannabinoids-Associated Coagulopathy in Chicago. *Lung* 2019, *197* (3), 349–352. https://doi.org/10.1007/s00408-019-00227-2.
- Kelkar, A. H.; Smith, N. A.; Martial, A.; Moole, H.; Tarantino, M. D.; Roberts, J. C. An Outbreak of Synthetic Cannabinoid–Associated Coagulopathy in Illinois. *N Engl J Med* 2018, *379* (13), 1216–1223. https://doi.org/10.1056/NEJMoa1807652.
- Watt, B. E.; Proudfoot, A. T.; Bradberry, S. M.; Vale, J. A. Anticoagulant Rodenticides. *Toxicol Rev* 2005, *24* (4), 259–269. https://doi.org/10.2165/00139709-200524040-00005.
- PubChem. *Brodifacoum*. https://pubchem.ncbi.nlm.nih.gov/compound/54680676 (accessed 2023-03-28).
- Nosal, D. G.; van Breemen, R. B.; Haffner, J. W.; Rubinstein, I.; Feinstein, D. L. Brodifacoum Pharmacokinetics in Acute Human Poisoning: Implications for Estimating Duration of Vitamin K Therapy. *Toxicol Commun* 2021, *5* (1), 69–72. https://doi.org/10.1080/24734306.2021.1887637.
- COCA Clinical Action: Outbreak Alert Update: Potential Life-Threatening Vitamin K-Dependent Antagonist Coagulopathy Associated With Synthetic Cannabinoids Use. https://emergency.cdc.gov/newsletters/coca/042318.html
- Palmer, R. B.; Alakija, P.; de Baca, J. E.; Nolte, K. B. Fatal Brodifacoum Rodenticide Poisoning: Autopsy and Toxicologic Findings. *J Forensic Sci* 1999, *44* (4), 851–855.
- Research, C. for B. E. and. Important Information for Blood Establishments Regarding Brodifacoum Contamination of Synthetic Cannabinoids. *FDA* 2022.
- *Labels for BRODIFACOUM TECHNICAL (100-987) | US EPA*. https://ordspub.epa.gov/ords/pesticides/f?p=PPLS:102:::::P102_REG_NUM:100-987 (accessed 2023-03-28).
- Caravati, E. M.; Erdman, A. R.; Scharman, E. J.; Woolf, A. D.; Chyka, P. A.; Cobaugh, D. J.; Wax, P. M.; Manoguerra, A. S.; Christianson, G.; Nelson, L. S.; Olson, K. R.; Booze, L. L.; Troutman, W. G. Long-Acting Anticoagulant Rodenticide Poisoning: An Evidence-Based Consensus Guideline for out-of-Hospital Management. *Clinical Toxicology* 2007, *45* (1), 1–22. https://doi.org/10.1080/15563650600795487.
- Coble, N. Notes from the Field: Coagulopathy Associated with Brodifacoum Poisoning — Florida, December 2021. *MMWR Morb Mortal Wkly Rep* 2022, *71*. https://doi.org/10.15585/mmwr.mm7140a5.
- Moritz, E.; Austin, C.; Wahl, M.; DesLauriers, C.; Navon, L.; Walblay, K.; Hendrickson, M.; Phillips, A.; Kerins, J.; Pennington, A. F.; Lavery, A. M.; Zahran, E.; Kauerauf, J.; Yip, L.; Thomas, J.; Layden, J. Outbreak of Severe Illness Linked to the Vitamin K Antagonist Brodifacoum and Use of Synthetic Cannabinoids — Illinois, March–April 2018. *US Department of Health and Human Services/Centers for Disease Control and Prevention* 2018, *67* (21), 607–608.
- Pharm.D, M. S.; Pharm.D, C. U.; DABAT, A. F., PharmD; FACMT, J. A., DO, MPH, FACEP; FAACT, D. S., Pharm D. ,. DABAT. *Poison Control: 2021 Brodifacoum-Contaminated Synthetic Cannabinoid Outbreak: Overview of Identification and Management of the Exposed Patient | FCEP*. https://fcep.org/poison-control-2021-brodifacoum-contaminated-synthetic-cannabinoid-outbreak/ (accessed 2023-03-28).
- US EPA, O. *Restrictions on Rodenticide Products*. https://www.epa.gov/rodenticides/restrictions-rodenticide-products (accessed 2023-03-28).
- US EPA, O. *Rodent Control Pesticide Safety Review*. https://www.epa.gov/rodenticides/rodent-control-pesticide-safety-review (accessed 2023-03-28).
- OPP/ SRRD/ Loquetus. Rodenticide Cluster: Reregistration Eligibility Decision (RED): Fact Sheet | US EPA ARCHIVE DOCUMENT, 1998. https://archive.epa.gov/pesticides/reregistration/web/pdf/2100fact.pdf.
- *Rodenticides*. http://npic.orst.edu/factsheets/rodenticides.html#references (accessed 2023-03-28).
- Commissioner, O. of the. *Statement from FDA warning about significant health risks of contaminated illegal synthetic cannabinoid products that are being encountered by FDA*. FDA. https://www.fda.gov/news-events/press-announcements/statement-fda-warning-about-significant-health-risks-contaminated-illegal-synthetic-cannabinoid (accessed 2023-03-28).
- Chong, Y.-K.; Mai, T. W.-L. Superwarfarin (Long-Acting Anti-Coagulant Rodenticides) Poisoning: From Pathophysiology to Laboratory-Guided Clinical Management. *CBR* 2019, *40* (4), 175–185. https://doi.org/10.33176/AACB-19-00029.
- Chua, J. D.; Friedenberg, W. R. Superwarfarin Poisoning. *Archives of Internal Medicine* 1998, *158* (17), 1929–1932. https://doi.org/10.1001/archinte.158.17.1929.
- *Surreptitious Ingestion of a Long-Acting Vitamin K Antagonist/Rodenticide, Brodifacoum: Clinical and Metabolic Studies of Three Cases | Elsevier Enhanced Reader*. https://doi.org/10.1182/blood.V76.12.2555.2555.
- Patočka, J.; Petroianu, G.; Kuča, K. TOXIC POTENTIAL OF SUPERWARFARIN: BRODIFACOUM. *MMSL* 2013, *82* (1), 32–38. https://doi.org/10.31482/mmsl.2013.003.
- US EPA. Office of Pesticide Programs. US EPA - Pesticides - Reregistration Eligibility Decision (RED) for Pival and Salts, 1998. https://www3.epa.gov/pesticides/chem_search/reg_actions/reregistration/red_G-69_1-Sep-97.pdf.
- Yip, L.; Stanton, N. V.; Middleberg, R. A. Vitamin K_1 Treatment Duration in Patients with Brodifacoum Poisoning. *N Engl J Med* 2020, *382* (18), 1764–1765. https://doi.org/10.1056/NEJMc1916199.

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