Journal of Zhejiang University-SCIENCE B (Biomedicine & Biotechnology) *2024 25(12):1120-1124*
www.jzus.zju.edu.cn; www.springer.com/journal/11585
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https://doi.org/10.1631/jzus.B2400305

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Residual hyperglycemia after successful treatment of a patient with severe copper sulfate poisoning

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Copper sulfate is a frequently used copper compound in laboratory settings, with instances of poisoning being uncommon. A study conducted by the American Association of Poison Control Centers' National Poison Data System found that only 140 individuals were exposed to copper compounds over the course of a year, with five cases being intentional (Gummin et al., 2023). Severe poisoning from copper sulfate can result in isolated gastrointestinal injury (Galust et al., 2023), intravascular hemolysis (Adline et al., 2024), rhabdomyolysis (Richards et al., 2020), and other symptoms documented in the literature. However, there have been no reports of long-term uncontrolled hyperglycemia in patients with copper sulfate poisoning. This case study documents the treatment approach for a patient with unexplained, long-term, uncontrolled hyperglycemia, alongside multiple organ dysfunction resulting from intentional ingestion of a large dose of copper sulfate. This case report details the long-term complications in a patient's recovery from acute copper sulfate, highlighting the significance of ongoing monitoring and intervention.

A 17-year-old female drank 120 mL of a solution prepared with approximately 250 g of copper sulfate at 9:00 p.m., resulting in abdominal pain, diarrhea, and vomiting of blue stomach contents. She was rushed to the hospital, where her creatinine level was 104 μmol/L before transfer to our health facility, and she received 2000 mL of 0.9% (9 g/L) normal saline for gastric lavage. However, the gastric lavage was temporarily stopped because the patient began vomiting blood.

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Received June 11, 2024; Revision accepted Aug. 11, 2024;
Crosschecked Nov. 22, 2024; Published online Dec. 18, 2024

Upon arrival, the patient underwent blood tests to determine the metal levels in her system. There was a significantly elevated copper level of 294.3 μmol/L. Laboratory analysis further identified multiple abnormal indicators (Fig. 1). Concurrently, a computed tomography (CT) scan identified edema and thickening of the antrum, pancreatic swelling, slight mesangial exudation, and minimal fluid accumulation in the pancreas and abdominal cavity (Fig. 2). Based on the clinical presentation and diagnostic findings, the patient received symptomatic supportive therapy, which included sodium thioglycolide detoxification, methylprednisolone for anti-inflammatory purposes, glutathione and glycyrrhizoate monoamine for hepatic protection, pantoprazole for gastric protection, and aggressive fluid resuscitation to maintain water and electrolyte balance.

Seven hours post admission, the patient was transferred to the emergency intensive care unit (EICU) and plasmapheresis and continuous renal replacement therapy (CRRT) were initiated. The plasmapheresis was performed over 4 d with a total volume of 5940 mL, while the CRRT treatment was conducted for 8 d (Fig. 3). On Day 2, the patient developed cyanosis of the lips and cold extremities. Despite a high oxygen flow rate (37%; 40 L/min), there was no clinical improvement, with blood gas oxygen saturation at 99.5%, but percutaneous oxygen saturation was approximately 80%–85%. Consequently, the patient received leukocyte-depleted red cell suspension and methylene blue to address hypoxia, terlipressin to improve microcirculation, and prothrombin complex concentrate to promote coagulation. The patient was transferred to the toxicology observation unit on Day 8 and underwent alternate-day hemodialysis to enhance renal function. By Day 20, the patient exhibited severe non-pitting

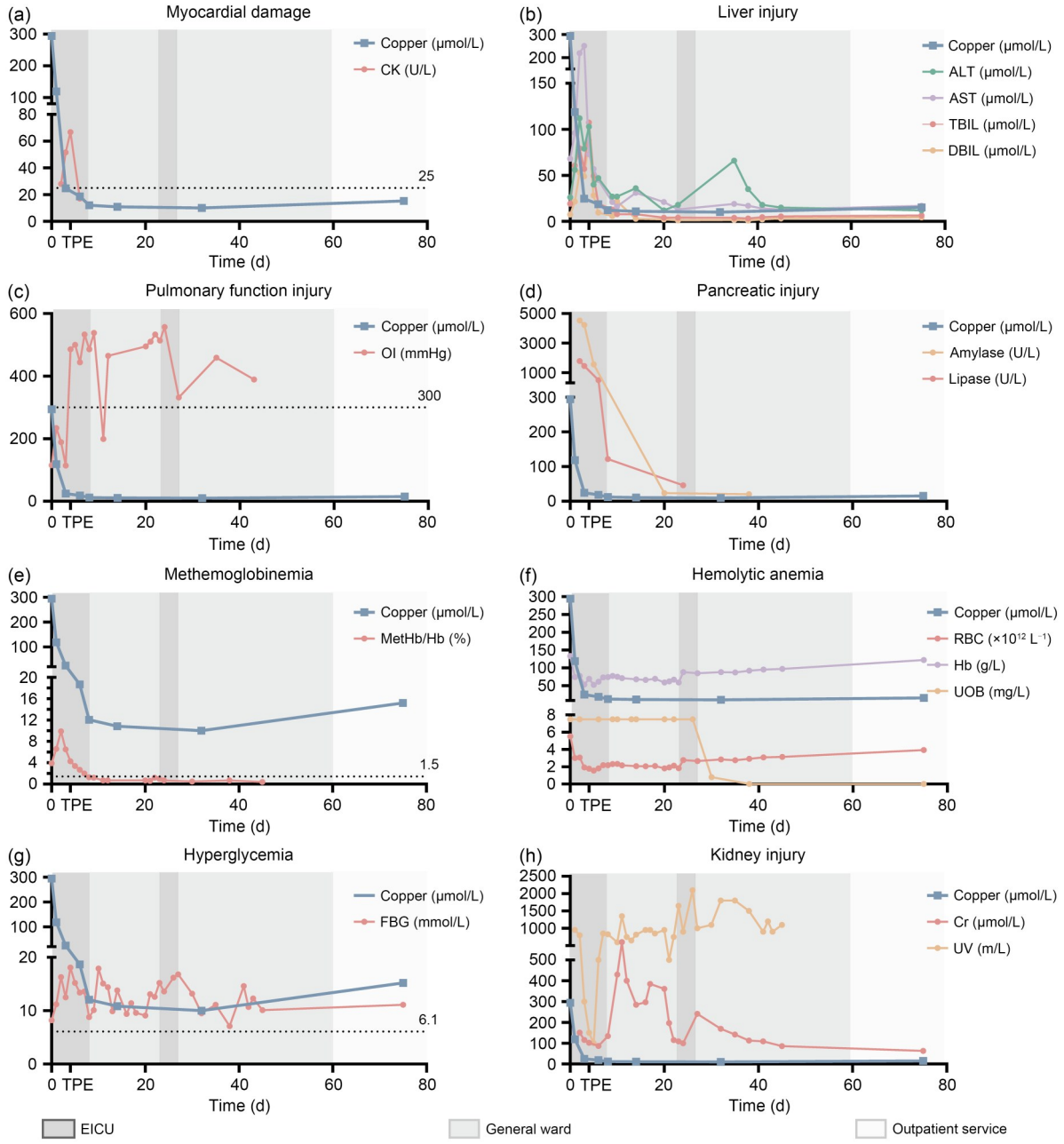

Fig. 1 Laboratory test results for the patient with acute copper sulfate poisoning. (a) Serum CK level (red). (b) Serum indicators related to liver injury: ALT (green), AST (purple), TBIL (red), and DBIL (yellow). (c) Oxygen index (OI, red) (1 mmHg=133.322 Pa). (d) Serum indicators related to pancreatic injury: amylase (yellow) and lipase (red). (e) Serum MetHb/Hb ratio (red). (f) Serum indicators related to hemolytic anemia: RBC (red), Hb (purple), and UOB (yellow). (g) Serum FBG concentration (red). (h) Urine Cr concentration (red) and UV (yellow). Ordinate is laboratory test results; abscissa is days. CK: creatine kinase; TPE: therapeutic plasmapheresis; ALT: alanine aminotransferase; AST: aspartate aminotransferase; TBIL: total bilirubin; DBIL: direct bilirubin; MetHb: methemoglobin; Hb: hemoglobin; RBC: red blood cell; UOB: urine occult blood; FBG: fasting blood glucose; Cr: creatinine; UV: urine volume; EICU: emergency intensive care unit.

edema, mainly in the lower extremities, and renal function tests showed a progressive increase in serum creatinine levels, necessitating CRRT in the EICU. Notably, she developed hyperglycemia post poisoning, as detailed in Fig. 1. Initial treatment with conventional insulin was ineffective, prompting the addition of neutral protamine Hagedorn insulin. On Day 42, the patient's poorly controlled hyperglycemia required an adjustment

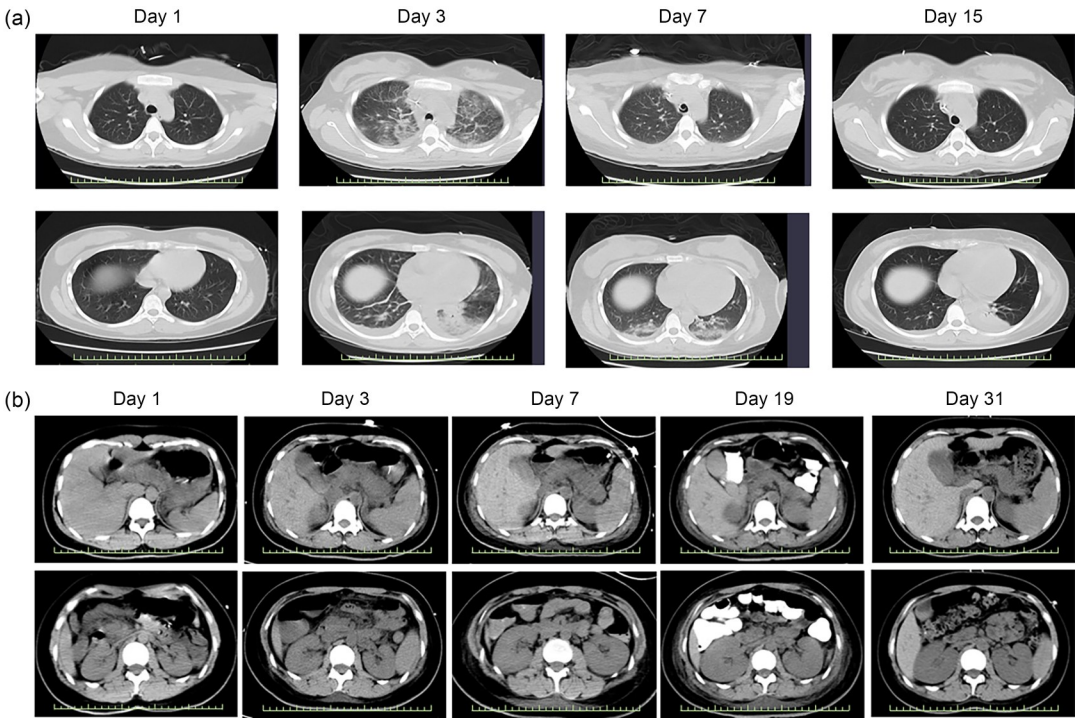

Fig. 2 Changes in the patient's lung and abdominal computed tomography (CT) imaging. (a) Lung CT scans on Days 1, 3, 7, and 15. *Z* slices: −80 mm (top) and −135 mm (bottom). (b) Abdominal CT scans on Days 1, 3, 7, 19, and 31. *Z* slices: −78 mm (top) and −150 mm (bottom).

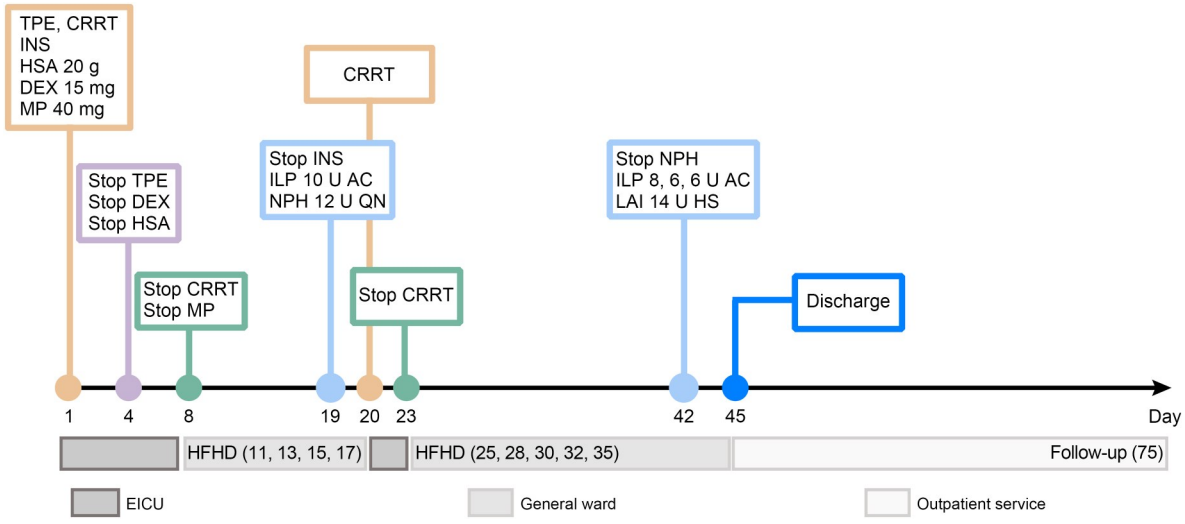

Fig. 3 Timeline of the main treatment regimens received by the patient with acute copper sulfate poisoning. EICU: emergency intensive care unit; TPE: therapeutic plasmapheresis; CRRT: continuous renal replacement therapy; INS: insulin; HSA: human serum albumin; DEX: dexamethasone; MP: methylprednisolone; ILP: insulin lispro; AC: before meals; NPH: neutral protamine Hagedorn; QN: every night; LAI: long-acting insulin; HS: at bedtime; HFHD: high-flux hemodialysis.

in the glycemic management strategy to insulin lispro before meals and long-acting insulin before bedtime. She was discharged on Day 45.

A telephone follow-up one month post discharge revealed a fasting blood glucose level of 210.6 mg/dL while on insulin therapy. By the three-month post-discharge mark, the fasting blood glucose level decreased to 122.76 mg/dL with continued insulin therapy, providing valuable insights into the long-term implications of copper sulfate poisoning.

Copper sulfate is a potent oxidizing agent known to cause severe hemolysis, methemoglobinemia, liver and kidney damage, and significantly higher mortality rates than other poisonous heavy metals (Naha et al., 2012; Wang et al., 2016). The adverse effects of these heavy metals on tissues and organs are frequently associated with oxidative stress and mitochondrial dysfunction (Zhang T et al., 2023; Zhang YL et al., 2023; Jiang et al., 2024). In erythrocytes, renal tubular epithelial cells, and hepatocytes, copper sulfate also induces oxidative stress, mitochondrial autophagy, and endoplasmic reticulum stress (Wu et al., 2020; Tao et al., 2021; Bai et al., 2023), which may collectively contribute to kidney injury and intravascular hemolysis in patients.

Rapid removal of copper ions from circulating plasma by means of plasmapheresis can mitigate damage to the blood system and kidneys (Du and Mou, 2019; Banerjee et al., 2023; Shankar et al., 2023). The early detection, diagnosis, and intervention are of paramount importance, not only for immediate recovery but also to forestall long-term complications (Qin et al., 2023; Wang et al., 2023). In this case, the patient's condition improved following blood dialysis, suggesting that early and continuous blood-purification therapy may be beneficial for severely poisoned patients to optimize treatment outcomes. Timely blood dialysis is equally essential for mitigating long-term complications such as kidney damage. For ongoing management, ongoing monitoring and treatment of potential long-term complications are needed even after controlling the acute poisoning event.

The patient's elevated blood-glucose level may have been influenced by the stress response induced by the poisoning (Daryagasht et al., 2023). The enlargement of the pancreas we observed in association with the copper sulfate exposure implies potential pancreatic damage and subsequent impairment of insulin secretion. Population-based observational studies have indicated a correlation between dietary copper exposure and the onset of type 2 diabetes (Zhao et al., 2023). Copper exposure disrupts metabolic pathways, impairs glucose metabolism, and induces autophagy through adenosine monophosphate (AMP)-activated protein kinase (AMPK)/mammalian target of rapamycin (mTOR) axis, potentially leading to hyperglycemia (Chen et al., 2024). In pancreatic β cells, copper compounds produce high-molecular-weight covalently linked aggregates that contain the autoantigen glutamic acid decarboxylase, leading to cellular damage (Trigwell et al., 2001). The mechanism of uncontrolled hyperglycemia caused by copper poisoning merits further investigation.

In summary, timely identification and treatment of acute copper sulfate poisoning are crucial for improving patient prognosis. Future research should focus on determining the optimal timing and methods for blood purification, as well as the early identification and management of post-poisoning complications. Additionally, effective strategies for managing long-term complications should be developed to further enhance patient prognosis.

Data availability statement

The data that support the findings of this study are not publicly available due to privacy concerns, but are available from the authors upon request and with the appropriate permissions.

Acknowledgments

This work was supported by the National Key Research and Development Program of China (Nos. 2023YFC3603100 and 2023YFC3603105) and the "Leading Goose" R&D Program of Zhejiang (No. 2022C03076-4), China.

Author contributions

Ting LI performed the experimental research and data analysis, and wrote and edited the manuscript. Yuan-qiang LU contributed to the study design, supervision, and funding acquisition. Both authors have read and approved the final manuscript, and therefore, have full access to all the data in the study and take responsibility for the integrity and security of the data.

Compliance with ethics guidelines

Ting LI and Yuan-qiang LU declare that they have no conflict of interest.

Study has been granted an exemption by Clinical Research Ethics Committee of the First Affiliated Hospital, Zhejiang University School of Medicine (No. 2023-1033). All procedures followed were in accordance with the ethical standards of the responsible committee on human experimentation (institutional and national) and with the Helsinki Declaration of 1975, as revised in 2013. Informed consent was obtained from the patient for being included in the study. Additional informed consent was obtained from the patient for whom identifying information is included in this article.

References

Adline FA, Shanthi R, Sivakumar MR, et al., 2024. *In vitro* immune analysis of serum from the hemolymph of the anomuran crab *Albunea symmysta* (Linnaeus, 1758) displayed

diversified reactions. *J Invertebr Pathol*, 204:108098. https://doi.org/10.1016/j.jip.2024.108098

Bai H, Fang YK, Cao HB, et al., 2023. Inhibition of the BNIP3/NIX-dependent mitophagy aggravates copper-induced mitochondrial dysfunction in duck renal tubular epithelial cells. *Environ Toxicol*, 38(3):579-590. https://doi.org/10.1002/tox.23704

Banerjee P, Mohan AK, Baid H, et al., 2023. Off with the blues: therapeutic plasma exchange in a case of copper sulphate poisoning. *Transfus Apher Sci*, 62(6):103811. https://doi.org/10.1016/j.transci.2023.103811

Chen J, Liao JZ, Yu WL, et al., 2024. Copper toxicity in the liver of broiler chicken: insights from metabolomics and AMPK-mTOR mediated autophagy perspective. *Poult Sci*, 103(9):104011. https://doi.org/10.1016/j.psj.2024.104011

Daryagasht M, Moosavi M, Khorsandi L, et al., 2023. Hepatoprotective and anti-hyperglycemic effects of ferulic acid in arsenic-exposed mice. *Food Chem Toxicol*, 178:113924. https://doi.org/10.1016/j.fct.2023.113924

Du Y, Mou Y, 2019. The role of plasmapheresis in treating lethal cupric sulfate poisoning. *Am J Med Sci*, 357(4):338-342. https://doi.org/10.1016/j.amjms.2018.11.014

Galust H, Seltzer JA, Hardin JR, et al., 2023. Campfire corrosive: isolated gastrointestinal injury following ingestion of copper salts. *Am J Emerg Med*, 70:210.e5-210.e8. https://doi.org/10.1016/j.ajem.2023.05.021

Gummin DD, Mowry JB, Beuhler MC, et al., 2023. 2022 Annual Report of the National Poison Data System® (NPDS) from America's Poison Centers®: 40th Annual Report. *Clin Toxicol (Phila)*, 61(10):717-939. https://doi.org/10.1080/15563650.2023.2268981

Jiang L, Yang F, Liao H, et al., 2024. Molybdenum and cadmium cause blood-testis barrier dysfunction through ROS-mediated NLRP3 inflammasome activation in sheep. *Sci Total Environ*, 906:167267. https://doi.org/10.1016/j.scitotenv.2023.167267

Naha K, Saravu K, Shastry BA, 2012. Blue vitriol poisoning: a 10-year experience in a tertiary care hospital. *Clin Toxicol (Phila)*, 50(3):197-201. https://doi.org/10.3109/15563650.2012.660572

Qin CF, Yang YM, Lu YQ, 2023. Perforation of the esophagus: an overlooked cause of chest pain as a complication of esophageal foreign bodies. *J Zhejiang Univ-Sci B (Biomed & Biotechnol)*, 24(5):455-457. https://doi.org/10.1631/jzus.B2300026

Richards JR, Scheerlinck PH, Owen KP, et al., 2020. Bodybuilding supplements leading to copper toxicity, encephalopathy, fulminant hepatic failure and rhabdomyolysis. *Am J Emerg Med*, 38(11):2487.e2481-2487.e2485. https://doi.org/10.1016/j.ajem.2020.05.096

Shankar JA, Kaur A, Tyagi L, et al., 2023. Severe copper sulphate poisoning: a case rescued with plasmapheresis. *Trop Doct*, 53(2):327-328. https://doi.org/10.1177/00494755231151256

Tao DY, Wang Y, Liu JF, et al., 2021. Mechanism of $CuSO_4$ cytotoxicity in goat erythrocytes after high-level in vitro exposure to isotonic media. *Ecotoxicol Environ Saf*, 208: 111730. https://doi.org/10.1016/j.ecoenv.2020.111730

Trigwell SM, Radford PM, Page SR, et al., 2001. Islet glutamic acid decarboxylase modified by reactive oxygen species is recognized by antibodies from patients with type 1 diabetes mellitus. *Clin Exp Immunol*, 126(2):242-249. https://doi.org/10.1046/j.1365-2249.2001.01653.x

Wang T, Chen XY, Long XH, et al., 2016. Copper nanoparticles and copper sulphate induced cytotoxicity in hepatocyte primary cultures of *Epinephelus coioides*. *PLoS ONE*, 11(2):e0149484. https://doi.org/10.1371/journal.pone.0149484

Wang ZD, Lu X, Yang YM, et al., 2023. Inflammatory granuloma of the trachea: a rare case with Epstin-Barr virus infection. *J Zhejiang Univ-Sci B (Biomed & Biotechnol)*, 24(6):539-542. https://doi.org/10.1631/jzus.B2300024

Wu HB, Guo HR, Liu H, et al., 2020. Copper sulfate-induced endoplasmic reticulum stress promotes hepatic apoptosis by activating CHOP, JNK and caspase-12 signaling pathways. *Ecotoxicol Environ Saf*, 191:110236. https://doi.org/10.1016/j.ecoenv.2020.110236

Zhang T, Yang F, Dai XY, et al., 2023. Role of Caveolin-1 on the molybdenum and cadmium exposure induces pulmonary ferroptosis and fibrosis in the sheep. *Environ Pollut*, 334: 122207. https://doi.org/10.1016/j.envpol.2023.122207

Zhang YL, Li GY, Zhao YQ, et al., 2023. Inhibition of calcium imbalance protects hepatocytes from vanadium exposure-induced inflammation by mediating mitochondrial-associated endoplasmic reticulum membranes in ducks. *Poult Sci*, 102(12):103013. https://doi.org/10.1016/j.psj.2023.103013

Zhao M, Wan J, Qin WZ, et al., 2023. A machine learning-based diagnosis modelling of type 2 diabetes mellitus with environmental metal exposure. *Comput Methods Programs Biomed*, 235:107537. https://doi.org/10.1016/j.cmpb.2023.107537