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From Chilean saltpeter to modern agriculture: navigating nitrate toxicity in ruminants through compartmental modeling

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Nitrate/nitrite poisoning is a significant issue in ruminant livestock health, with historical roots predating the widespread use of nitrogen fertilizers. This review explores the various factors contributing to nitrate toxicity, including natural and anthropogenic sources, metabolic pathways, mechanisms of action, and the variability in reported data. The importance of compartmental modeling in understanding nitrate metabolism dynamics is emphasized. These models provide a framework for simulating the complex processes involved in nitrate intake, conversion, absorption, distribution, and excretion, ultimately informing effective mitigation strategies. The goal of this article is to provide a comprehensive overview of nitrate/nitrite poisoning in ruminants and highlight the role of compartmental modeling in safeguarding animal health, optimizing agricultural practices, and ensuring food safety in the context of modern agriculture.

Key words: nitrate toxicity, ruminants, compartmental modeling, methemoglobinemia, feed management

Introduction

Nitrate/nitrite poisoning has been documented long before the widespread use of nitrogen fertilizers. Acute nitrate poisoning in cattle was reported as early as 1895 [11]. All plants contain some nitrates, and their concentration can be influenced by climatic factors such as cold and drought [14]. The use of nitrogen fertilizers also impacts nitrate levels in plants, with high amounts being a significant factor in nitrate accumulation [3]. Early spring growth usually contains more nitrates than summer plants due to rapid growth [10]. Roots and stems of plants generally have higher nitrate levels than leaves and seeds [10].

Excessive use of poultry litter or animal manure as fertilizers can lead to nitrate accumulation in soil, subsequently affecting plant feeds consumed by herbivores [20]. Nitrates can reach dangerous levels in ponds, shallow wells, or streams due to agricultural runoff and nitrogen fertilizers. Industrial wastewater is another source of nitrates [5]. Plants irrigated with treated wastewater, rich in nitrogen, can accumulate large amounts of nitrates [9].

Ruminant animals, such as cattle and sheep, are sensitive to nitrate poisoning. Bacteria in their rumen convert nitrates to nitrites [19]. Nitrates can be absorbed through the ruminant epithelium via a Cl^-/HCO_3^- exchange mechanism [1]. Nitrate toxicity in ruminants occurs when high nitrate levels in feed overwhelm the animal's digestive system, causing nitrate-to-nitrite conversion to exceed nitrite-to-ammonia conversion, which is part of amino acid and protein synthesis [7]. Nitrate itself has low toxicity compared to nitrite, which causes the formation of methemoglobin (MetHb), a molecule with very limited oxygen-carrying capacity. Methemoglobinemia, resulting from MetHb formation, is a primary adverse effect. MetHb gives blood a brown-black color [18]. Species differences in MetHb formation rates are mainly due to the degree and speed of nitrate-to-nitrite reduction, which is highest in ruminants, lower in horses, and lowest in other monogastric species.

The mechanism of action (MoA) of nitrates and nitrites includes several effects in agricultural and domestic animals, such as increased oxidative stress, thyroid function suppression, and lowered blood pressure. Other effects (e.g., depletion of vitamins A and E, abortions, and fertility impacts) remains to be elucidated [4]. High nitrite levels in the blood cause vasodilation, blood pressure drop, and circulatory shock.

Different authors from various countries report varying nitrate/nitrite content analysis results. This diversity can lead to confusion and misinterpretation of the data. Furthermore, literature sources often employ different methods for nitrite detection, each with varying accuracy and sensitivity, which can further complicate result interpretation. Therefore, standardized recommendations and a unified understanding of laboratory methods are essential for comprehending the impact of nitrates on animal organisms [15].

To address these challenges and enhance our understanding of nitrate metabolism in ruminants, the development and application of compartmental models are crucial. These models provide a framework for simulating the complex processes of nitrate intake, conversion to nitrite, absorption, distribution, and excretion within the animal's body [8].

The overarching goal of this article is to present a comprehensive review of nitrate/nitrite poisoning in ruminants, encompassing its historical context, sources of exposure, metabolic pathways, mechanisms of action, and the variability in reported data. Additionally, we aim to highlight the importance of compartmental modeling in understanding nitrate metabolism and its potential for informing evidence-based interventions to safeguard animal health and productivity. This is of paramount relevance in the context of modern agriculture, where nitrogen fertilizer use and intensive animal production practices can inadvertently elevate nitrate levels in the environment, posing a risk to livestock. By unraveling the complexities of nitrate toxicity and leveraging modeling approaches, we can strive towards sustainable agricultural practices that prioritize animal welfare and minimize the adverse impacts of nitrate exposure.

Results and Discussion

1. Physicochemical properties of nitrates, nitrites, and certain specific salts, and their use in animal husbandry, agriculture, and the food industry

On January 19, 2020, the Law of Ukraine "On Feed Safety and Hygiene" came into effect, stipulating that any person can use feed additives provided that such an additive is registered in Ukraine. However, the state registration procedure for feed additives was only unblocked on September 1, 2021. To prevent feed shortages, amendments to the Law of Ukraine "On Feed Safety and Hygiene" were made through the draft Law no. 3672, allowing the unrestricted use of feed additives registered in the European Union. According to the EU Feed Additives Register under Regulation (EC) no. 1831/2003, sodium nitrite (E 250) is a permitted feed additive. Additionally, sodium nitrate (E 251) and potassium nitrate (E 252) are included in the list of food additives approved for use in food products in Ukraine and are part of the EU Feed Additives Register as per Annex II of Regulation (EC) No 1333/2008.

In acidic conditions, nitrite can form N-nitroso compounds (NOCs), including genotoxic and carcinogenic N-nitrosamines, by reacting with certain secondary amines in feed or endogenously in the stomachs of animals.

The physicochemical properties of nitrates, nitrites, and certain specific salts used in food products, feed, and fertilizers are shown in table 1.

The physicochemical properties of these compounds, such as solubility in water and their oxidizing nature, make them versatile in various applications. In the food industry, nitrates and nitrites are used as preservatives to prevent the growth of harmful bacteria and to maintain the color and flavor of processed meats. In agriculture, these compounds are essential components of fertilizers, contributing to the growth and health of plants. Additionally, in animal husbandry, they are used as feed additives to enhance animal growth and health.

Nitrates are ubiquitous in the environment and play a crucial role in the nitrogen cycle, forming significant deposits, particularly as sodium nitrate ($NaNO_3$) in specific regions. The most notable industrial deposit is associated with the accumulation of caliche in the Atacama Desert, Chile, which has led to $NaNO_3$ being sometimes referred to as Chilean saltpeter.

The use of nitrates is extensive. They are employed in animal feeds and food products, notably in the production of fertilizers and food preservatives. Generally, nitrates are highly soluble in water and serve as vital nutrients for plants, being present in all plant species, especially in green leafy vegetables. Sodium nitrate and potassium nitrate are particularly significant for feeds and food products.

Sodium nitrate ($NaNO_3$) is a white, crystalline, slightly hygroscopic powder that serves as an antimicrobial agent, preservative, and color fixative. Sodium nitrate is used in the treatment of cyanide poisoning, in combination with sodium thiosulfate, recommended only for severe cases of cyanide poisoning. Sodium nitrate is also utilized in fertilizers, pyrotechnics, and in the glass industry [2].

Potassium nitrate (KNO_3): this white crystalline powder or transparent prisms have a cooling, salty, pungent taste. It is used as a preservative and in combination with nitrite salts in curing mixtures (e.g., sodium chloride solutions) for meat to develop and fix the color of the meat, inhibit microbial growth, and develop characteristic flavor profiles. In veterinary medicine, potassium nitrate is used as a diuretic for pigs, cattle, and horses.

Two other nitrates widely used, especially as fertilizers, are calcium nitrate ($Ca(NO_3)_2$) and ammonium nitrate (NH_4NO_3). Anhydrous calcium nitrate is colorless and hygroscopic, readily absorbing moisture to form

Table 1. Physicochemical properties and applications of nitrates, nitrites, and certain specific salts

Compound	Empirical formula	Properties	Applications
Nitrate			
Nitrate Sodium (Sodium Nitrate, E 251)	$NaNO_3$	White crystalline solid, highly soluble in water, oxidizing agent	Used as a preservative in food, feed additive, fertilizer
Nitrate Potassium (Potassium Nitrate, E 252)	KNO_3	White crystalline solid, highly soluble in water, oxidizing agent	Used in food preservation, fertilizers, and fireworks
Nitrate Calcium (Calcium Nitrate, anhydrous)	$Ca(NO_3)_2$	White granular or crystalline solid, highly soluble in water	Used in fertilizers, concrete additives, and cold packs
Nitrate Calcium (Calcium Nitrate, tetrahydrate)	$Ca(NO_3)_2 \cdot 4H_2O$	White crystalline solid, highly soluble in water, contains water of crystallization	Used in fertilizers, wastewater treatment, and cold packs
Nitrate Ammonium (Ammonium Nitrate)	NH_4NO_3	White crystalline solid, highly soluble in water, strong oxidizer	Used in fertilizers, explosives, and in veterinary medicine
Nitrite			
Nitrite Sodium (Sodium Nitrite, E 250)	$NaNO_2$	White to slightly yellowish crystalline powder, soluble in water, can act as both an oxidizing and reducing agent	Used as a food preservative, curing agent, feed additive, and in pharmaceuticals
Nitrite Potassium (Potassium Nitrite)	KNO_2	White to yellow crystalline powder, soluble in water, strong reducing agent	Used as a curingagent in the food industry, in pharmaceuticals, and in the production of heat transfer salts, dyes, and other chemicals.

tetrahydrates. Ammonium nitrate is a colorless crystalline salt used in fertilizers and explosives.

Nitrite (NO_2^-): the nitrite anion is present in inorganic nitrite salts. Nitrite naturally occurs in the environment as part of the nitrogen cycle, typically in very low concentrations. It is formed naturally by nitrifying bacteria as an intermediate stage in nitrate formation.

The most important nitrites in feeds and food are sodium nitrite ($NaNO_2$) and potassium nitrite (KNO_2).

Sodium nitrite ($NaNO_2$): this compound appears as a white or slightly yellow crystalline powder, hygroscopic, with a melting point of 270°C, and decomposes above 320°C. It slowly oxidizes to sodium nitrate in the air. Sodium nitrite has various applications, including the production of numerous compounds. In medicine and veterinary practice, it has been used as a vasodilator, bronchodilator, and as an antidote for cyanide poisoning. In veterinary medicine, it is applied topically on the teats of dairy cows post-milking to prevent mastitis. Sodium nitrite is permitted as a food additive (E 250) to stabilize the color of cured fish and meat and to inhibit the growth of *Clostridium botulinum*, the bacterium that produces botulinum toxin.

Nitrate levels and toxicity in unified metrics

Reading reports on nitrate levels in various literatures reveals different parameters for determining nitrate contamination. The results of nitrate analysis can be misleading due to differences in the methods of presenting the results. In chemical analysis of nitrates, the actually determined element is oxidized nitrogen. However, values can be reported as a percentage of nitrates (NO_2^-), nitrate-nitrogen ($N-NO_3$), or as a percentage of potassium nitrate (KNO_3) concentration.

Elevated nitrogen doses and nitrate accumulation in forage are presented as concentration of nitrate nitrogen $N-NO_3$ [6]. Authors [12], accumulation of $N-NO_3$ above 0.07% in dry matter is considered harmful, 0.07–0.2% can lead to poisoning in cattle, and more than 0.25% can be lethal. Other authors determined nitrate concentrations as concentrations of NO_3^- ions [16]. Similarly, nitrate concentrations can be determined as concentrations of potassium nitrate (KNO_3) [21].

For unification and interpretation of the results presented in the literature, formulas are used for converting between different measurement units:

$$KNO_3 = N-NO_3 \times 7.22$$
$$KNO_3 = NO_3 \times 1.63$$
$$NO_3 = N-NO_3 \times 4.43$$
$$NO_3 = KNO_3 \times 0.613$$
$$N-NO_3 = KNO_3 \times 0.139$$
$$N-NO_3 = NO_3 \times 0.226$$

Thus, for accurate interpretation of results in the literature, it must be clearly stated in which units the nitrate concentration was determined. Predominantly, nitrate analysis and information on safe concentrations in feed and water are presented as the concentration of NO_3^- ions (mg per kg dry matter). However, in modern literature, results can also be found in percentages or parts per million (ppm). The following formulas are provided for conversion to interpret the results:

- 1000 mg/kg = 0.1%
- 750 mg/kg = 0.075%
- 0.1% = 1000 ppm
- 2100 ppm = 2100 mg/kg
- 300 ppm = 0.3 mg/L (for water)

Calculation examples:

$$0.1\%\ N{-}NO_3 = 0.443\%\ NO_3;$$
$$0.1 \times 4.43 = 4430\ \text{ppm}\ NO_3 = 4430\ \text{mg/kg}$$

$$0.44\%\ NO_3 = 0.099\%\ N{-}NO_3;$$
$$0.44 \times 0.226 = 994\ \text{ppm}\ N{-}NO_3 = 994\ \text{mg/kg}$$

Almost all feeds contain some amount of nitrates. Since herbivores, especially ruminants, consume diets with high levels of nitrates, they are potentially among the most sensitive species to nitrite poisoning due to their inherent microbial ability to convert nitrates to nitrites. However, under normal circumstances, problems do not arise because the resulting nitrite is quickly removed through bacterial fermentation for anabolism, forming ammonia, amino acids, and proteins.

2. Sensitivity of methods for determining nitrates: spectral analysis, nitrite meter, and electrode analysis

The determination of nitrate levels is essential for assessing environmental and agricultural impacts. Various methods are employed to measure nitrates, each differing in sensitivity, accuracy, and application. Here, we discuss the sensitivity of three common methods: spectral analysis, nitrite meters, and electrode analysis.

Spectral analysis

Spectral analysis, including techniques such as UV-Vis spectrophotometry, is widely used for nitrate determination [23]. This method is based on the absorption of light by nitrate ions at specific wavelengths. The advantages of spectral analysis include:

- **High sensitivity**: UV-Vis spectrophotometry can detect nitrates at low concentrations, typically in the range of 0.1 to 5.0 mg/L.
- **Precision**: this method provides precise and repeatable results, making it suitable for laboratory use.
- **Non-destructive**: spectral analysis is a non-destructive technique, preserving samples for further analysis.

However, spectral analysis requires clear, colorless samples and proper calibration to avoid interference from other absorbing species.

Nitrite Meter

Nitrite meters are portable devices designed for field use to measure nitrate levels directly. These meters use colorimetric or electrochemical principles to provide quick and easy readings. Key features include:

- **Moderate sensitivity**: nitrite meters can detect nitrates in concentrations ranging from 0.5 to 100 mg/L, depending on the device.
- **Portability**: these meters are compact and easy to use in various settings, including on-site field measurements.
- **Rapid results**: nitrite meters offer fast results, often within minutes, making them suitable for real-time monitoring.

While convenient, nitrite meters may have limitations in terms of accuracy and potential interferences from other ions present in the sample.

Electrode Analysis

Electrode analysis, such as using ion-selective electrodes (ISEs), is another method for determining nitrate concentrations [17]. This technique measures the potential difference generated by nitrate ions in a solution. Its benefits include:

- **High sensitivity**: ISEs can detect nitrates at very low concentrations, often below 0.1 mg/L.
- **Specificity**: ion-selective electrodes are designed to respond specifically to nitrate ions, reducing the risk of interference from other ions.
- **Versatility**: electrode analysis can be performed in various sample types, including soil, water, and plant tissues.

However, electrode analysis requires regular calibration and maintenance to ensure accurate readings. It may also be influenced by the ionic strength and pH of the sample.

Each method for determining nitrate levels has its strengths and limitations. Spectral analysis offers high sensitivity and precision but is best suited for laboratory environments. Nitrite meters provide rapid and portable measurements but may sacrifice some accuracy. Electrode analysis combines high sensitivity and specificity but requires careful calibration and maintenance.

The choice of method depends on the specific requirements of the analysis, including the desired sensitivity, accuracy, and practicality for field or laboratory use. By understanding the capabilities and limitations of each method, researchers and practitioners can select the most appropriate technique for their needs.

The impact of consuming feeds with significant nitrate concentrations on animals depends on various factors related to the animals' condition.

Ruminants can tolerate a wide range of nitrate levels depending on several factors. Factors that make nitrates less toxic include:

1. **Gradual adaptation**: animals can be conditioned to consume higher amounts of nitrate-rich feed if the increase is gradual.
2. **Health status**: healthy animals are less susceptible to adverse effects than animals with poor health.
3. **Adequate carbohydrates**: an adequate supply of carbohydrates (grain) allows animals to consume more nitrates, as carbohydrates enhance the conversion of nitrates to microbial protein.

Factors that make nitrates more toxic include [13]:

1. **Rapid dietary changes**: a sudden change in diet can trigger nitrate poisoning.
2. **Parasitism or anemia**: conditions causing anemia or parasitism increase susceptibility.
3. **Multiple sources of nitrates**: nitrates in more than one dietary component (e.g., water and feed).

4. **Rate of feed consumption**: the speed at which feed is consumed can influence toxicity.

Regardless of the nitrate levels present in feeds, there are two types of potential toxicity that cause concern:

1. **Acute or lethal toxicity**: this occurs when daily nitrate concentrations ingested by the animal exceed the conversion rate to nitrites, leading to rapid nitrite accumulation.
2. **Chronic or non-lethal toxicity**: this occurs when prolonged exposure to nitrate-rich feed results in nitrite accumulation and absorption into the bloodstream, causing chronic effects.

These effects depend on the duration of consumption of toxic feed. Specifically, the table 2 presents various effects based on nitrate concentration per kg of body weight ingested daily for cattle.

3. A compartmental model for nitrate metabolism in ruminants: relevance and potential insights

3.1. Relevance of modeling nitrate metabolism

The study of nitrate metabolism in ruminants is crucial due to the significant role these animals play in agriculture and food production. Ruminants, such as cattle and sheep, are particularly sensitive to nitrate toxicity because of their unique digestive systems. The bacteria present in the rumen can reduce nitrates to nitrites, which, in excessive amounts, can lead to methemoglobinemia, a condition that affects the oxygen-carrying capacity of the blood [22].

Modeling nitrate metabolism in ruminants provides several important benefits:

Risk assessment and management: by understanding how nitrates are metabolized and accumulated in ruminants, farmers and veterinarians can better manage feed and forage to prevent nitrate toxicity. This is particularly important in regions where nitrate levels in plants and water can fluctuate significantly.

Optimizing feed composition: a compartmental model allows for the simulation of different dietary scenarios, helping in the formulation of feeds that minimize nitrate accumulation while ensuring nutritional adequacy. This can lead to the development of feeding strategies that enhance animal health and productivity.

Environmental impact assessment: modeling can help assess the environmental impact of nitrate usage in agriculture. By understanding how nitrates are processed in ruminant systems, it is possible to predict the fate of nitrates excreted in manure, which can contribute to nitrate pollution in soil and water.

Guiding agricultural practices: insights from the model can inform agricultural practices, such as the timing and amount of fertilizer application, to ensure that nitrate levels in forage crops remain within safe limits. This can lead to more sustainable farming practices that protect both animal health and the environment.

Public health and food safety: ensuring that nitrate levels in meat and dairy products are within safe limits is essential for public health. Modeling nitrate metabolism helps in understanding how nitrates and their metabolites accumulate in animal tissues, which is vital for food safety regulations and standards.

3.2. Compartmental model for nitrate metabolism in ruminants

Compartmental Model:

- **Rumen compartment C_0:** nitrite concentration in the rumen (mg)
- **Rumen compartment C_1:** this compartment represents the rumen, where nitrates are ingested through contaminated feed or water. In the rumen, nitrates are rapidly reduced to nitrites by microbial action. Nitrate concentration in the rumen (mg)
- **Blood compartment C_2:** this compartment represents the bloodstream, where absorbed nitrites are distributed. Nitrite concentration in the blood (mg)
- **Metabolism and excretion compartment C_3:** this compartment represents the metabolism and excretion of nitrates and nitrites from the body. Nitrite concentration in the tissues (mg)

Table 2. Effects of nitrate concentration on cattle

Total daily dose (mg NO_3^-/kg body weight)	Total daily dose (mg $N-NO_3$/kg body weight)	Total daily dose (mg KNO_3/kg body weight)	Effect
<97.7	<22.0	<97.7	Generally safe under all conditions.
97.7–195.3	22.0–44.0	97.7–195.3	Safe for most animals. May be unsafe for pregnant and very young animals.
195.3–293	44.0–66.1	195.3–293	Potentially unsafe for pregnant and young animals. May cause reduced appetite, slow growth, abortions, and decreased milk production. Research suggests a decrease in milk production of approximately 15.9 mg NO_3^-/kg body weight.
293–390.7	66.1–88.2	293–390.7	Unsafe level of intake for all animals. Reduced appetite, vitamin A deficiency, abortions, and overall reduced productivity.
>390.7	>88.2	>390.7	Acute toxicity possible in most animals. In dairy cattle, 45.4 mg NO_3^-/kg body weight can result in 50% mortality.

The kinetic equations for this compartmental model can be described as follows:

1. **Rumen (Nitrite) :**

$$dC_0 / dt = k_{conv} * C_1 - k_{01} * C_0$$

dC_0 / dt — the rate of change of nitrite concentration in the rumen over time;

$k_{conv} * C_1$ — the rate of nitrite formation in the rumen due to the conversion of nitrate.

2. **Rumen (Nitrate):**

$$dC_1 / dt = -k_{12} * C_1 - k_{conv} * C_1$$

dC_1 / dt — the rate of change of nitrate concentration in the rumen over time;

$-k_{12} * C_1$ — the rate of nitrate transfer from the rumen to the blood;

$-k_{conv} * C_1$ — the rate of nitrate conversion to nitrite within the rumen.

3. **Blood:**

$$dC_2 / dt = k_{12} * C_1 + k_{01} * C_0 - k_{23} * C_2$$

dC_2 / dt — the rate of change of nitrite concentration in the blood over time;

$k_{12} * C_1$ — the rate of nitrite entering the blood from the rumen (after nitrate conversion);

$k_{01} * C_0$ — the rate of nitrite entering the blood directly from the rumen;

$-k_{23} * C_2$ — the rate of nitrite absorption from the blood into the tissues.

4. **Tissues:**

$$dC_3 / dt = k_{23} * C_2 - k_{30} * C_3$$

dC_3 / dt — the rate of change of nitrite concentration in the tissues over time;

$k_{23} * C_2$ — the rate of nitrite absorption from the blood into the tissues;

$-k_{30} * C_3$ — the rate of nitrite excretion/metabolism from the tissues.

Description:

- These differential equations describe the dynamics of nitrate and nitrite concentrations in different compartments within the ruminant animal's body.
- The model accounts for the conversion of nitrate to nitrite in the rumen, the transfer of nitrite from the rumen to the blood, the absorption of nitrite from the blood into tissues, and the excretion/metabolism of nitrite from tissues.
- The rate constants (k_{12}, k_{23}, k_{30}, k_{conv}) determine the intensity of each process and can be adjusted based on experimental data or physiological parameters of the animals.

This model is a simplified representation of a complex biological process. For more accurate results, it's essential to consider individual animal characteristics, their diet, and other factors that can influence nitrate metabolism. Using the NumPy-based SciPy library in code written in Python, the proposed system of ordinary differential equations (ODEs), which are the core of our compartmental model, was solved. The results are shown in fig.

The figure displays the change in nitrite concentration within the rumen over a 24-hour period. The model demonstrates the conversion of nitrate to nitrite in the rumen and the subsequent transfer of nitrite to the bloodstream. The initial spike in nitrite concentration is due to the rapid conversion of nitrate, followed by a gradual decrease as nitrite is absorbed into the blood.

$k_{12} = 0$: this eliminates the direct transfer of nitrate from the rumen to the blood, preventing its dilution and potential detoxification in the liver.

$k_{conv} = 0.9$: this significantly increases the rate of conversion of nitrate to nitrite in the rumen, leading to a rapid accumulation of nitrite.

$C_{10} = 400.0$: the high initial dose of nitrate provides ample substrate for the rapid conversion to nitrite.

The combination of these factors results in a scenario where nitrite rapidly accumulates in the rumen and then overwhelms the animal's ability to detoxify it, leading to a dangerous spike in blood nitrite levels and potential fatality.

Given the provided parameters and initial conditions, let's analyze the expected outcome of the simulation in terms of nitrate and nitrite levels in a ruminant animal. With the modified parameters, the animal is exposed to a high initial dose of nitrate (400 mg) and a rapid conversion rate of nitrate to nitrite ($k_{conv} = 0.9$). Simultaneously, the direct transfer of nitrate from the rumen to the blood is blocked ($k_{12} = 0$), while the absorption of nitrite from the blood to tissues and its excretion are relatively slower ($k_{23} = 0.1$, $k_{30} = 0.2$). Since the animal received a lethal dose of nitrate, we can expect a rapid accumulation of nitrite in the rumen due to the high conversion rate and lack of direct nitrate transfer. This will subsequently lead to a significant increase in nitrite levels in the blood, exceeding toxic thresholds, and potentially causing acute toxicity. To confirm this, let's run the simulation without plotting the graph and examine the peak nitrite concentrations in the blood.

With the modified parameters, the simulation results in a maximum nitrite concentration in the blood of 256.56 mg. This high level of nitrite in the blood, likely exceeding the toxic threshold, would be consistent with a lethal dose of nitrate leading to acute toxicity in the ruminant animal.

3.3. Insights from the model

A compartmental model for nitrate metabolism in ruminants can provide detailed insights into several key aspects:

1. **Kinetics of nitrate reduction**: the model can elucidate the rates at which nitrates are reduced to nitrites and further to ammonia in the rumen. Understanding these kinetics is essential for predicting the conditions under which toxic levels of nitrites might accumulate.

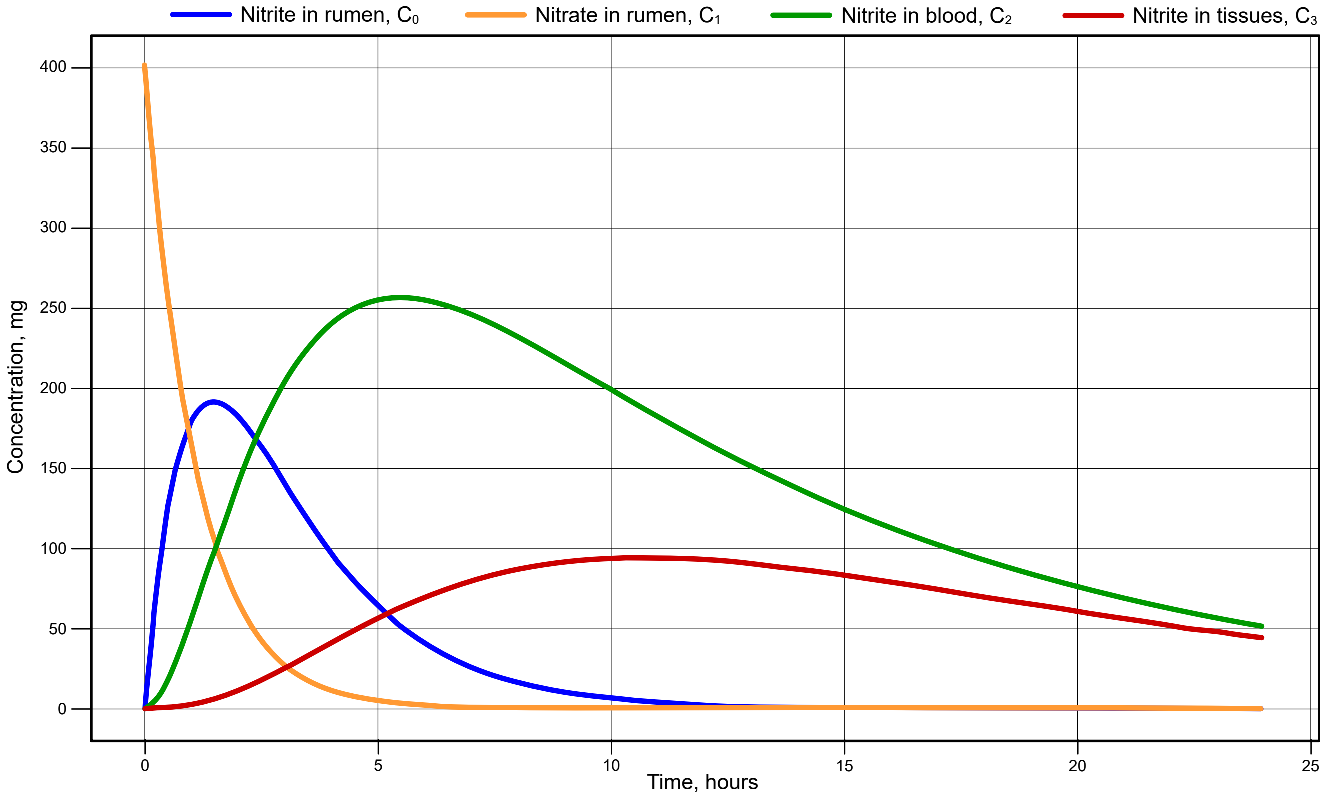

Fig. Nitrite concentration in the rumen over time (results of the proposed model implemented in Python)

2. **Distribution of nitrate metabolites**: by modeling different compartments within the animal's body (e.g., rumen, blood, tissues), it is possible to track the distribution and concentration of nitrate metabolites. This helps in identifying critical points where interventions can be made to reduce toxicity.
3. **Impact of diet and environment**: the model can simulate how different dietary components and environmental conditions (such as water nitrate levels and forage type) affect nitrate metabolism. This can guide the selection of optimal feeding practices and environmental management.
4. **Inter-species variability**: The model can be adapted to study different ruminant species, allowing for comparisons and the development of species-specific recommendations. This is particularly useful for mixed farming operations.
5. **Predictive tool for management decisions**: by integrating real-time data and scenario analysis, the model can serve as a predictive tool for making informed management decisions. This can help in preemptively addressing potential issues related to nitrate toxicity.

In summary, a compartmental model for nitrate metabolism in ruminants is a valuable tool for improving animal health, optimizing agricultural practices, and ensuring food safety. By providing detailed insights into the complex processes involved in nitrate metabolism, the model supports the development of effective strategies for managing nitrates in ruminant production systems.

Nitrate/nitrite poisoning poses a significant threat to ruminant livestock, necessitating a comprehensive understanding of its multifaceted nature. This article has provided an in-depth overview of the historical context, diverse sources of exposure, intricate metabolic pathways, and varied mechanisms of action associated with nitrate toxicity. The complexity of this issue is further compounded by the variability in reported nitrate/nitrite levels and the diversity of analytical methods employed.

Compartmental modeling emerges as a crucial tool in navigating these complexities. By simulating the dynamic processes of nitrate intake, conversion to nitrite, absorption, distribution, and excretion, these models offer valuable insights into the factors that influence nitrate toxicity in ruminants. This knowledge can be leveraged to develop evidence-based interventions, optimize feeding practices, and guide agricultural management decisions to mitigate the risks associated with nitrate exposure. Ultimately, the integration of research, modeling, and practical application holds the promise of fostering sustainable agricultural practices that prioritize animal welfare, environmental health, and food safety.

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Від чилійської селітри до сучасного сільського господарства: дослідження нітратної токсичності в жуйних тварин за допомогою компартментального моделювання

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Отруєння нітратами/нітритами є значною проблемою для здоров'я жуйних тварин, з історичними коренями, що передують широкому використанню азотних добрив. Цей огляд досліджує різні фактори, які сприяють нітратній токсичності, зокрема природні та антропогенні джерела, шляхи метаболізму, механізми дії та варіабельність у наявних даних. Підкреслюється важливість компартментального моделювання для розуміння динаміки метаболізму нітратів. Ці моделі надають основу для моделювання складних процесів, пов'язаних зі споживанням, перетворенням, абсорбцією, розподілом та виведенням нітратів, що зрештою сприяє розробці ефективних стратегій пом'якшення наслідків. Метою цієї статті є надання всебічного огляду отруєння нітратами/нітритами в жуйних тварин та підкреслення ролі компартментального моделювання для збереження здоров'я тварин, оптимізації сільськогосподарських практик та забезпечення безпеки харчових продуктів у контексті сучасного сільського господарства.

Ключові слова: нітратна токсичність, жуйні тварини, компартментальне моделювання, метгемоглобінемія, управління кормами

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