A Seminar paper

On

Ionophores: The Game-Changer in Future Beef Cattle Production

Course Title: Seminar

Course Code: ASN 698

Term: Winter 2022

Submitted to:

Course instructors

Dr. A.K.M Aminul Islam

Professor

Department of Genetics and Plant Breeding

Dr. Satya Ranjan Saha

Professor

Department of Agroforestry and Environment

Dr. Dinesh Chandra Shaha

Associate Professor

Department of Fisheries Management

Dr. Shaikh Shamim Hasan

Professor

Department of Agricultural Extension

& Rural Development

Major Professor

Dr. Abu Sadeque Md. Selim

Professor

Department of Animal Science and Nutrition

Submitted by

Sabrina Zaman

Reg. No.: 16-05-4030

Program: MS

Department of Animal Science and Nutrition

Bangabandhu Sheikh Mujibur Rahman Agricultural University,

Gazipur- 1706

Ionophores: The Game-Changer in Future Beef Cattle Production[1]

By

Sabrina zaman[2]

ABSTRACT

Right now beef fattening is so popular, but it is harmful for both human and animal health to use steroidal drugs in case of beef fattening. Ionophores are such compound, that binds with specific ion and facilitates transportation through a biological membrane. Ionophores can be used as a feed additive to beef cattle for getting better growth and feed efficiency. It also reduces some rumen disorders like bloat and acidosis. Ionophore is also good source for methane reduction in rumen. The effects of ionophores may vary depending on the animal, diet, and type and dose of ionophore used. In the rumen, they work on specific microorganism and increases feed efficiency. In this paper we discussed the opportunities and challenges of using ionophore in beef cattle diet. Careful management and monitoring are necessary to ensure the safety and efficacy of these compounds. Overall, ionophores are a promising technology that may play a significant role in the future of beef cattle production, helping producers to improve profitability while reducing environmental impact.

Keywords: Ionophore, feed additive, weight gain, methane emission, beef production.

---

[1]A seminar paper for the course ASN 698, winter'22.

[2]MS student, Department of Animal Science and Nutrition, BSMRAU, Gazipur-1706

TABLE OF CONTENTS

LIST OF TABLES

LIST OF FIGURE

CHAPTER 1

INTRODUCTION

Beef cattle production is a crucial component of the global food supply chain and economy. The beef industry faces challenges such as rising demand for beef, struggling for feed resources, and environmental concerns. Therefore, exploring alternative strategies to enhance feed efficiency, animal growth, and productivity is crucial. For this instance, a strategy that has gained significant attention in recent years is the use of ionophores in beef cattle diets.

Ionophores used as feed additives, that have been shown to alter rumen fermentation patterns, leading to improved feed efficiency, average daily gain, and carcass quality in beef cattle (Duffield *et al.*, 2012). The compounds selectively target gram-positive bacteria and ciliate protozoa, reducing competition for nutrients between beneficial and harmful microbial populations in the rumen (Baba *et al.*, 2020). Since their introduction in the 1970s, ionophores have become an essential component of beef cattle diets, and numerous studies have demonstrated their effectiveness in animal performance (Khunchaikarn *et al.*, 2022).

Recently, concerns are growing about the environmental impact of livestock production, particularly the emissions of greenhouse gases such as methane. An approach to solving this issue could involve incorporating ionophores into the diets of beef cattle. By altering the microbial populations in the rumen and improving feed efficiency, ionophores also showed to reduce methane emissions from cattle. Incorporating ionophores in beef cattle diets could have notable impacts on the sustainability of beef cattle farming and its role in mitigating climate change.

However, there are also potential risks associated with the use of ionophores. Some studies have suggested that ionophores may have negative effects on animal health, such as impairing immune function and increasing the risk of coccidiosis. In addition, there are concerns about the development of antibiotic resistance and the potential impact of ionophores on non-target species in the environment. The inclusion of ionophores in the diets of beef cattle has the potential to significantly improve the sustainability of beef cattle production and its ability to address climate change. Modeling is necessary to utilize experimental data to improve our comprehension of the impact of ionophores on ruminant metabolism and to consider their effects in the formulation of diets.

Despite these concerns, ionophores remain a promising tool for improving the efficiency and sustainability of beef cattle production. By providing a balanced review on ionophores, this paper aims to inform and guide future research and policy decisions on their use in beef cattle diets.

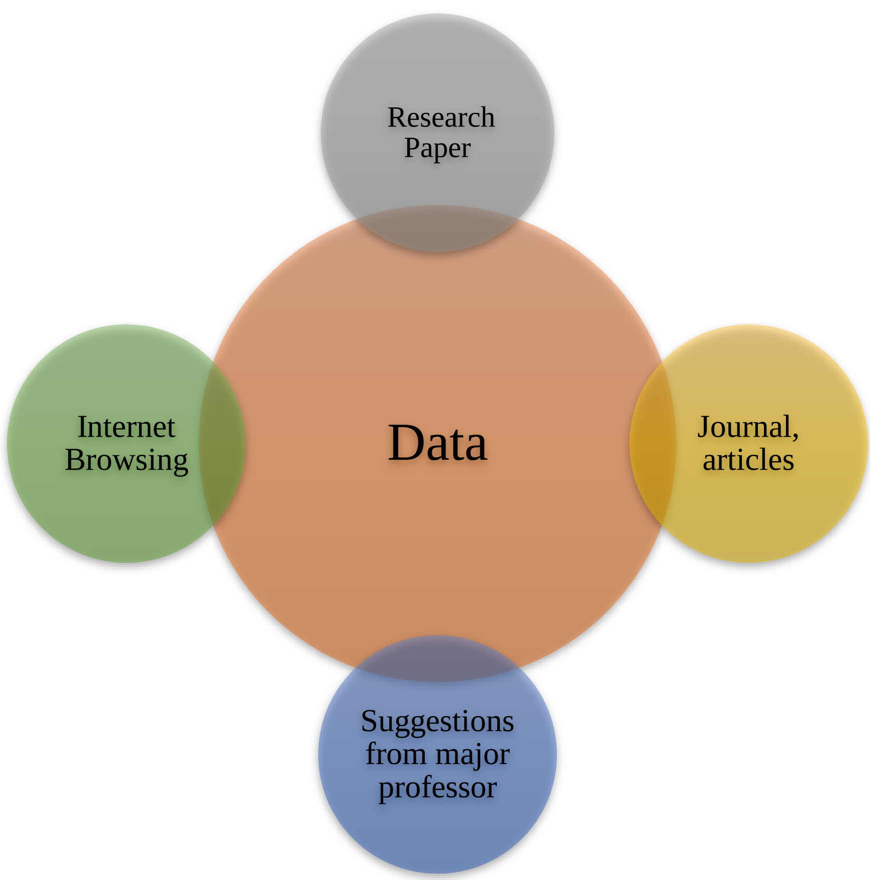
Objectives of the study:

- To evaluate the use of ionophores and their effects on beef cattle production.
- To assess the role of ionophores in minimizing methane production.

CHAPTER 2

MATERIALS AND METHODS

This is ultimately a review paper. So, the data assembled for writing this paper are secondary data collected from different research papers, articles, and reports in various journals and websites available on the internet. I improved this paper with the valuable suggestions from my respected major professor and course instructors. The searched items or publications were thoroughly checked and downloaded for detail and critical reviewing later. Only the original research data containing publications, written in English language, were included for the review. After gathering all relevant information, it was compiled and rationally presented in its present form.



CHAPTER 3

REVIEW OF FINDINGS

3.1 Discovery & development of ionophore

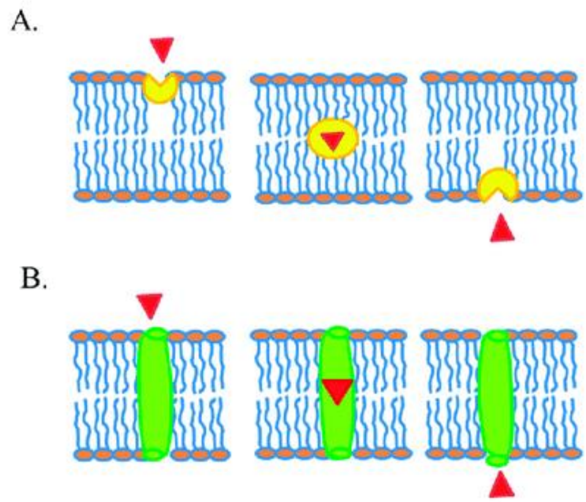
The utilization of ionophores in cattle feed has a lengthy history, dating back to the 1940s. During the initial stages of ionophore investigation, researchers found that specific substances could modify the manner in which bacteria in the rumen of cattle decompose feed (Russell *et al.,* 1960). This led to the development of the first ionophore, called monensin, in the 1960s. Monensin was found to be highly effective at improving feed efficiency in cattle by altering the balance of microorganisms in the rumen and improving the animal's Capacity to break down and assimilate nutrients (Ellis *et al*., 2012).

The adoption of ionophores gained rapid popularity in the cattle sector, and by the 1970s, monensin had become a prevalent feed supplement for both beef and dairy cattle. During the 1980s, alternative ionophores such as lasalocid and laidlomycin were created and authorized for implementation in cattle (Duffield *et al.*, 2012).

Over the years, ionophores have proven to be highly effective at improving feed efficiency in cattle, reducing the amount of feed required to produce a pound of meat or milk. Research has demonstrated that ionophores can diminish the occurrence of disorders like bloat and acidosis, which may arise from disparities in rumen microorganisms (Owens, 2021).

3.2 General properties of ionophore

Ionophores are molecules that selectively bind and transport ions across biological membranes, such as cell membranes or organelle membranes. One of the most remarkable properties of ionophores is their ability to discriminate between different ions, depending on their charge, size, and chemical properties. Ionophores are often classified according to their mode of action, which can be either passive or active (Marques & Cooke, 2021). Another fascinating property of ionophores is their structural diversity, which ranges from small organic molecules, such as valinomycin or gramicidin, to large proteins, such as ion channels or transporters (Kaushik *et al*., 2018). This structural diversity reflects the multiple functions and mechanisms of ionophores in various biological systems, such as signaling, metabolism, osmoregulation, or host defense.



Source: Kaushik *et al*., (2018)

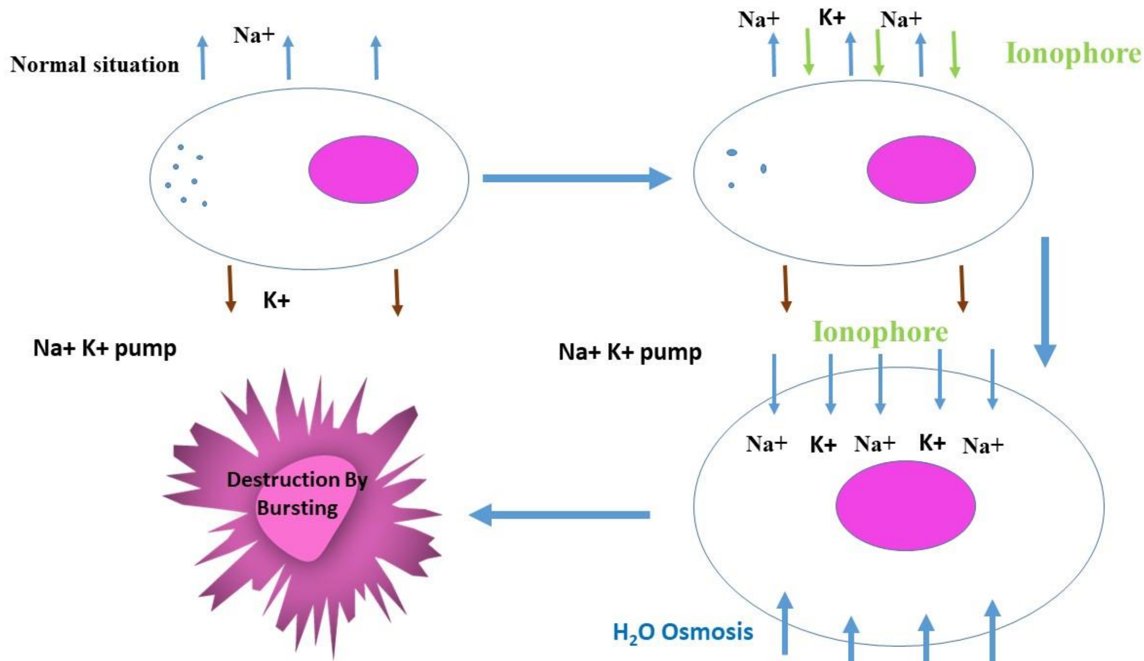
Figure 1. Ionophores assist in the movement of ions through biological membranes.

1(**A)** Ion carriers, also referred to as small ionophores, attach to ions and protect them from the membrane's lipophilic interior. Subsequently, they convey the ions across the membrane and release them on the opposite side; this mechanism is recognized as facilitated diffusion. 1(**B)** In contrast, significant ionophores create ion channels that stretch across the membrane. These channels feature a hydrophilic interior that helps the transportation of ions, while their lipophilic exterior protects the ions from the membrane's repulsive interior. This mechanism is recognized as passive transport.

3.2.1 Mechanism of action of ionophore

Ionophores are a class of carboxylic polyether antibiotics that are naturally produced by *Streptomyces* spp. bacteria. Russell *et al*. (1989) reviewed the mechanism of ionophores in the rumen and their mode of action, as well as their general properties. These antibiotics were found to have a similar mode of action in the rumen environment. Ionophores exhibit a high degree of lipophilicity (Pressman & B.C. 1976) and the vulnerability of bacteria and protozoa in the gastrointestinal tract is determined by how well ionophores can adhere to their membranes. The extent of adherence is influenced by the cell wall structure of the bacteria (Schären *et al.*, 2017; Weimer *et al*., 2008). Gram-positive bacteria, which lack protective membranes, are more sensitive to ionophores. The outer protective membrane of Gram-negative bacteria makes them less susceptible to ionophores. However, the mechanisms underlying this sensitivity are not yet fully comprehended. (Russel *et al*., 1987).

Ionophores possess the unique ability to interact with metal ions and act as carriers for their transport across lipid membranes (Ovchinnikov *et al*., 1979). In the rumen environment, bacteria maintain a more alkaline pH by regulating high intracellular potassium and low intracellular sodium concentrations (Russel *et al*., 1987). However, the ruminal milieu is characterized by elevated sodium and diminished potassium levels, the slightly acidic pH in the rumen is a result of the presence of high concentrations of short-chain fatty acids (SCFAs) (Russel *et al*., 1989). To maintain optimal intracellular environments, rumen bacteria rely on the delicate balance between sodium and potassium ion gradients.



Source: Ekinci *et al*.,(2023)

Figure 2. Mechanism of action of ionophore.

Ionophores function as antiporters of metal and protons, enabling the exchange of hydrogen ions for either sodium or potassium ions (Russel *et al*., 1987; Pressman *et al*., 1976). Ionophores, when administered, incorporate themselves into the lipid membranes of bacteria in the rumen the action of ionophores leads to disruptions in the ionic equilibrium both inside and outside bacterial cells.

This results in decreased intracellular levels of potassium and pH, and increased intracellular levels of sodium. These alterations in ion concentrations are caused by the ionophores' ability to affect the transmembrane flux of ions, ultimately resulting in ion imbalances within the bacteria (Russel *et al*., 1987). As a response to the disruption caused by ionophores, rumen bacteria activate ATPase systems for sodium/potassium and hydrogen in order to remove excess protons from the cell (Booth & Ian 1985). Although the ATPase systems help to remove excess protons from the cell in response to ionophores, the antiporter activity can deplete intracellular ATP during hydrogen ion removal. Ultimately, this can result in a decrease in cellular viability. (Russel *et al*., 1989; Russel *et al*., 1987).

Table 1. Ionophore characteristics and ion-bonding selectivity preference

Ionophore	Produce by	Molecular weight	Ion-binding Selectivity Sequence
Monensin	*Streptomyces cinnamonensins*	671	Na+ > K+, Li+ > Rb+ > Cs+
Lasalocid	*Streptomyces lasaliensis*	591	Ba++, K+ >Rb+ > Na+ > Cs+ > Li+
Narasin	*Streptomyces aureofaciens*	765	Na+ > K+, Rb+, Cs+, Li+
Salinomycin	*Streptomyces albus*	751	Rb+, Na+ > K+ >> Cs+, Sr+, Ca++, Mg

Source: Marques & Cooke., (2021)

Specific ions can be selectively bound by ionophores, which belong to a class of compounds with this unique property. This selectivity is a hallmark characteristic of each ionophore and serves as a critical index of their ion-binding preferences. (Nagaraja *et al*., 1995; Painter *et al*., 1982). Although ionophores share a common mode of action, their differences in selectivity can impact their efficacy in achieving effective concentrations in the rumen and causing changes in bacterial populations.

Certain bacteria are capable of producing ionophores, which can disrupt the ion balance of other bacteria and inhibit their growth. Interestingly, these ionophore-producing bacteria themselves are naturally resistant to ionophores, but the mechanisms behind this resistance are not well understood (Russel *et al*., 2003). The initial belief was that ionophores could only permeate the cell membrane of Gram-positive bacteria, rendering them more vulnerable to inhibition by ionophores (weimer *et al*., 2008).

3.3 Inclusion level of ionophore in cattle diet

Table 2. The suggested levels of ionophores to be used in animal feed as well as the duration of withdrawal periods

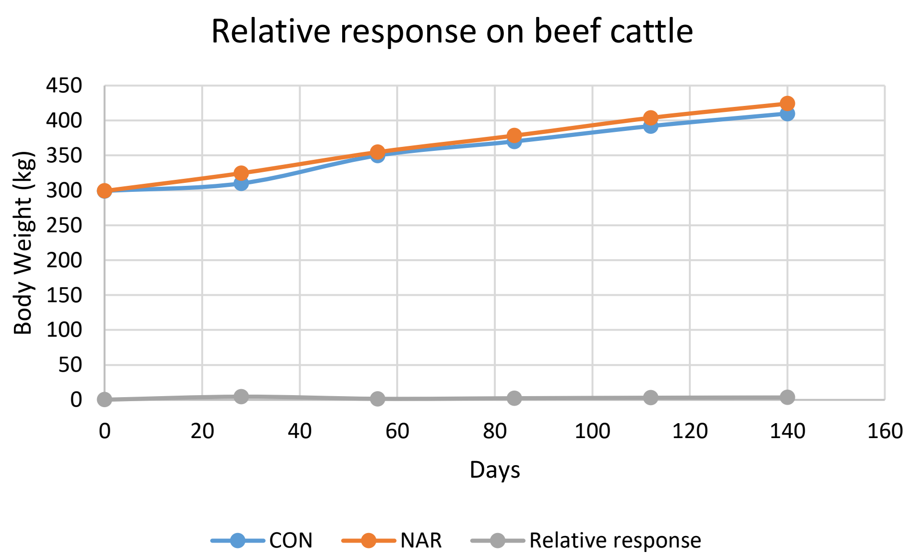
Ionophore	**Producing organism**	**Recommended organism in feed (mg/kg)**	**Withdrawal period**	**Reference**
Salinomycin	*Streptomyces albus*	50-70	1	
Monensin	*Streptomyces cinnamonensis*	100-125	1	
narasin	*Streptomyces aureofaciens*	60-70	0	
Maduramycin	*Actinomadura yumaensis*	Authorization expired on 2021	0	(Ekinci *et al*., 2023)
semduramycin	*Actinomadura roseorufa*	20-25	5	
Lasalocid	*Streptomyces lasaliensis*	75-125	3	

Source: Ekinci *et al*., (2023)

The European Union Register of Feed Additives, Edition 07/2022 provides information on this.

3.4 Ionophores in beef production

Ionophores are commonly used in the beef industry as rumen modulators and coccidiostats. Several meta-analyses on the performance of beef cattle have been done. According to Duffield *et al*. (2012), the use of monensin in feedlot cattle consistently resulted in a 3.1% decrease in dry matter intake (DMI) and a 2.5% increase in average daily gain (ADG), leading to a 1.3% improvement in feed efficiency. This finding is supported by Goodrich *et al*. (1984), who reported a 6.4% reduction in feed intake and a 1.6% increase in average daily gain in cattle fed monensin-containing diets Over the last five decades, the increase in feed efficiency associated with the use of ionophores has declined from 8.1% to 3.5%. This decrease is thought to be a result of advancements in feedlot cattle management, nutrition, and health (Duffield *et al.*, 2012).



Source: Limede *et al.*, (2021)

Figure 3. Performance of *Bos indicus* Nellore bulls receiving control (without feed additive; CON), narasin (NAR) in high forage-based diets for 140 days.

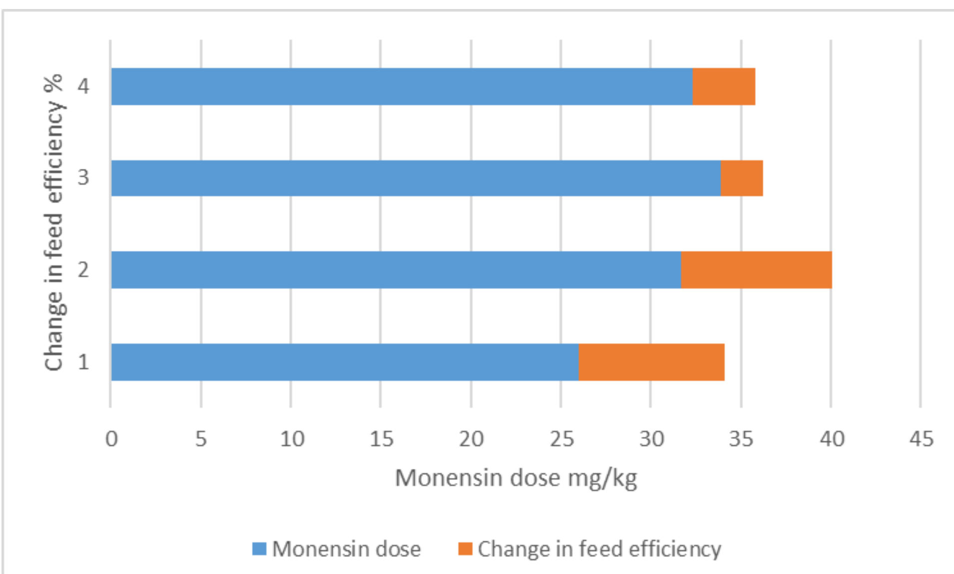
In this study, on day 0, individual body weight was recorded after 14 hours of feed and water withdrawal to determine animal initial BW. Bulls were weighed on days 0, 28, 56, 84, 112, and 140 singly, after 14 hours of feed and water restriction. The study by Limede *et al*. (2021) found that the addition of 13 ppm narasin to a forage-based diet led to a 14.8% increase in average daily gain. As a result, the animals were heavier at the end of the 140-day supplementation period. Beck *et al*. (2011) also found that average daily gain by adding monensin and lasalocid to a corn-based supplement increased in grazing steers. Duffield *et al*. (2012) demonstrated that including monensin in grain-based diets for cattle resulted in a linear effect. Higher doses of monensin led to enhanced efficiency but decreased both intake and average daily response.

Table 3. The outcome of two levels of lasalocid and one level of monensin diet in beef cattle

Item	**Control**	**Lasalocid**		**Monensin**
		30 g/ton	45 g/ ton	
Initial weight, kg	347	346	346	346
Final weight, kg	476	479	481	479
Daily gain, kg	.99	1.02	1.04	1.03
Carcass weight, kg	299	297	300	300
Dressing %	62.6	62.4	62.5	62.5
Loin area, cm^2	74.8	77.4	76.1	76.8

Source: Berger *et al*., (1982)

We can evaluate from (Table 4) that daily weight gain, carcass weight and loin area increased in lasalocid and monensin diet.

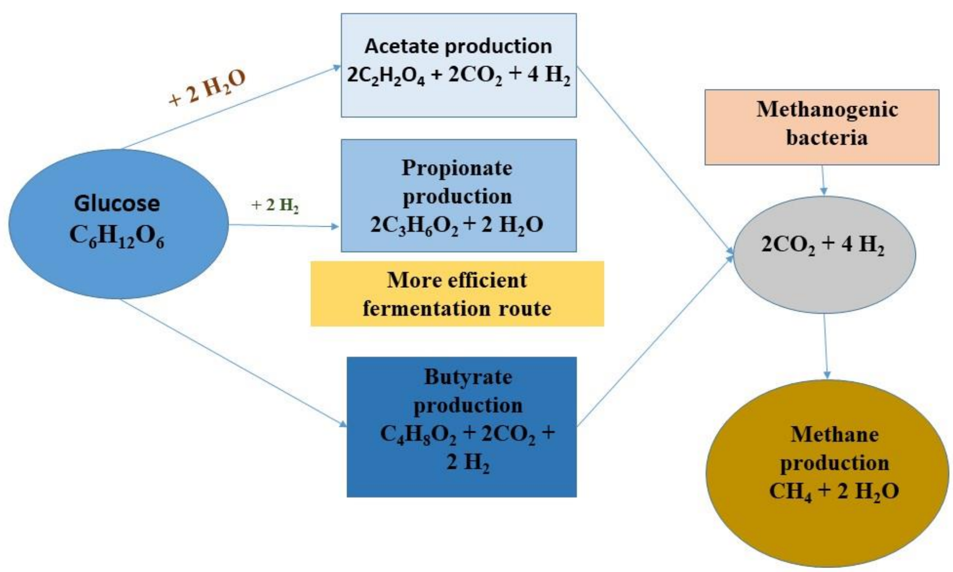


Source: Duffield *et al*., (2012)

Figure 4. Different doses of monensin and the changes in feed efficiency.

3.5 Modulation of Rumen Fermentation by Ionophores

Studies indicate that incorporating ionophores into ruminant diets results in enhanced animal performance and feed efficiency. This is achieved by modifying the rumen microbiome and fermentation pathways (Duffield *et al.*, 2012; Tedeschi *et al.*, 2003; Azzaz *et al.*, 2015) and the passage rate and gut fill of cattle can be affected by various factors, which can consequently impact their intake response (Bretschneider *et al.*, 2008). The inclusion of ionophores in the diet leads to alterations in the ruminal microbiota and fermentation pathways, which is responsible for the observed impacts on animal performance. Rumen converts about 75 to 85% of the energy derived from feed in the diet to ruminal short-chain fatty acids (SCFA), while the remaining energy is lost as heat and methane. Ruminants derive a significant portion, around 60 to 75%, of their digestible energy from the fermentation of carbohydrates in the rumen. This process produces various compounds such as short-chain fatty acids (SCFA), methane, carbon dioxide, ammonia, and microbial cells (Wolin *et al*., 1997). Acetate, propionate, and butyrate are the predominant SCFA in the rumen, and their proportions are influenced by the diet (Wolin *et al*., 1997).



Source: Marques & Cooke., (2021)

Figure 5. Ruminal fermentation routes and short-chain fatty acids (SCFA) and methane production.

Forage-based diets typically have ruminal proportions of acetate, propionate, and butyrate at 70:20:10, with an acetate: propionate ratio of 3:1, while grain-based diets have ruminal proportions of these SCFA at 50:40:10, with an acetate:propionate ratio of 2:1 (Wolin *et al*., 1997).

Propionate represents 27 to 54% of the total glucose synthesized by the liver and is considered the most important SCFA fermented in the rumen (NASEM, 2016). In contrast, acetate and butyrate are hydrogen sources, and hydrogen is the major substrate for methane formation (Ellis *et al*., 2012). Methane production represents an energy loss to the animal, ranging from 2% to 12% of gross energy intake (Ellis *et al*., 2012). Therefore, increasing propionate production and decreasing acetate and butyrate production are positively correlated with greater feed energy utilization and animal performance.

Table 4. Different types of ionophores in propionate and acetate production

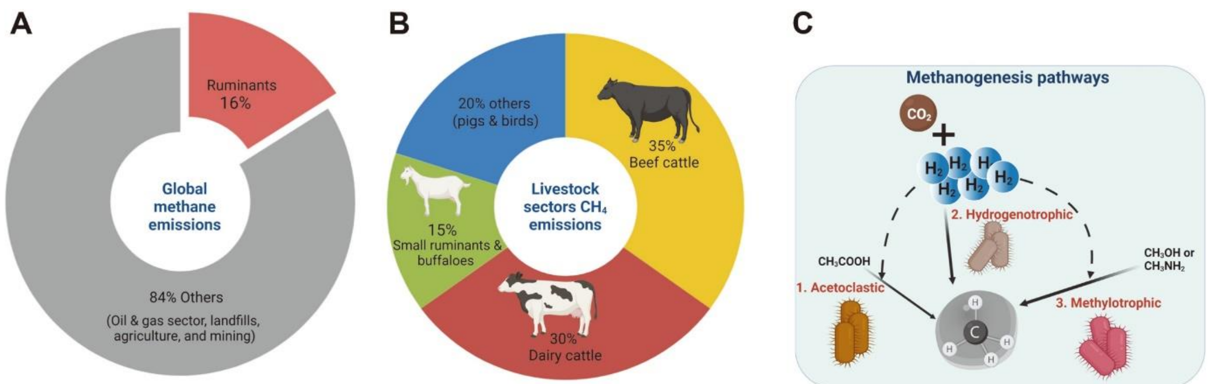
Ionophore	**Diet type**	**Change in propionate%**	**Change in acetate%**	**Source**
Monensin	Feedlot	increased	decreased	Bell *et al*., 2017
Lasalocid	Feedlot	4.6%	-3.2%	Golder and Lean, 2016
Narasin	Forage	enhanced	reduced	Polizel *et al*., 2020 and Limede *et al*.,2021
Monensin	Bermudagrass hay	1.8%	-1.3%	Bell *et al*., 2017

Source: Marques & Cooke., (2021)

Several studies have shown that the inclusion of ionophores in the diet increases the concentration of ruminal propionate and decreases acetate in forage (Bell *et al*., 2017) and grain-based diets (Azzaz *et al*., 2015). For example, Golder and Lean (2016) conducted a meta-analysis of beef cattle supplemented with >200 ppm of lasalocid, showing that ruminal propionate increased by 4.6% and acetate decreased by 3.2%. Similarly, Polizel *et al*. (2020) and Limede *et al*. (2021) reported an enhanced ruminal propionate concentration and reduced acetate and acetate: propionate ratio in beef cattle fed forage-based diets with the addition of narasin.

3.6 Effect of ionophores on methane production

Around two-thirds of the total global methane emissions are caused by human activities, according to research (Saunois *et al*., 2016). The United Nations predicts a global population of 9.8 billion by 2050 and 11.2 billion by 2100, leading to an increase in demand for milk and meat products by 1.04 million tons and 465 million tons, respectively (Barrera *et al*., 2019). However, the rising demand for ruminant livestock could exacerbate the issue of methane production, further contributing to global warming.

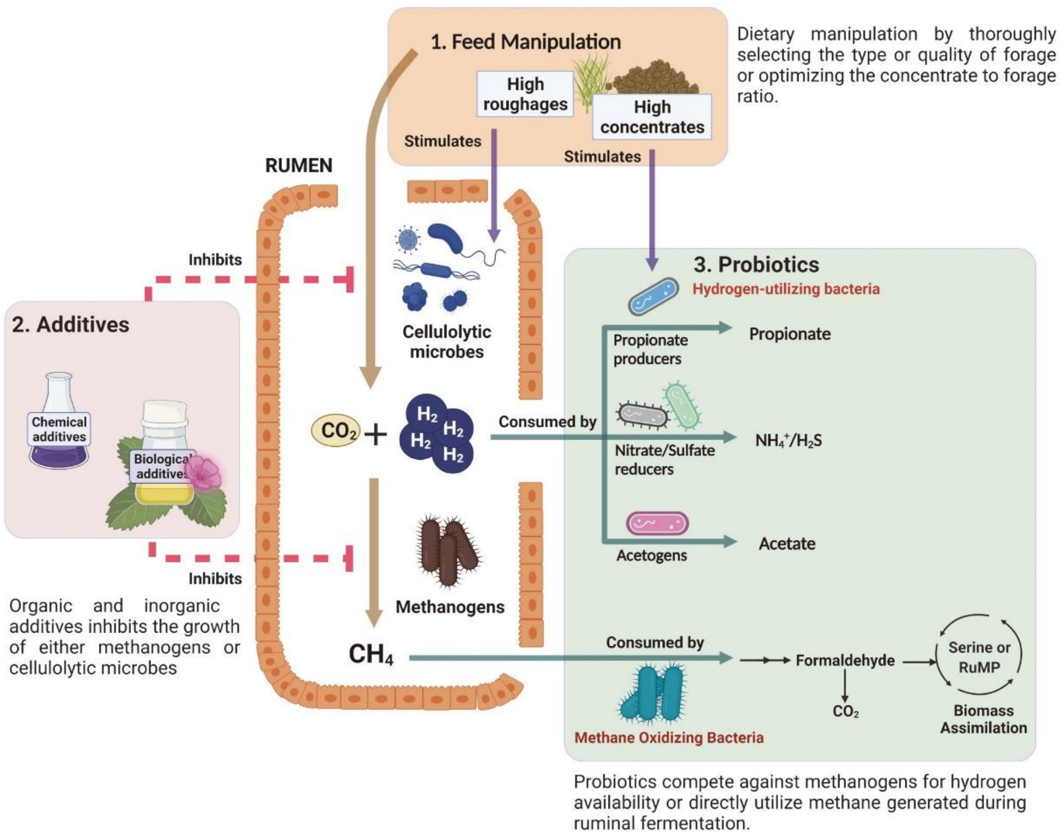


Source: Tseten *et al*., (2022)

Figure 6. Global methane emissions and methanogenesis in rumen.

Figure 5(A) shows the contribution of ruminants and other sectors to global methane emissions. Approximately 16% of global methane emissions can be attributed to ruminant animals. **5(B)** provides a breakdown of the contributions of different animal species to total methane emissions from livestock. Among these species, beef and dairy cattle contribute the most (35% and 30%, respectively), followed by small ruminants and buffalos (15%), and other animals such as pigs and birds (Islam & Lee, 2019). **5(C)** shows the pathways of methanogenesis in the rumen, which involve the breakdown of organic matter by microbes and the production of volatile fatty acids and hydrogen, which are then used by methanogens to produce methane.

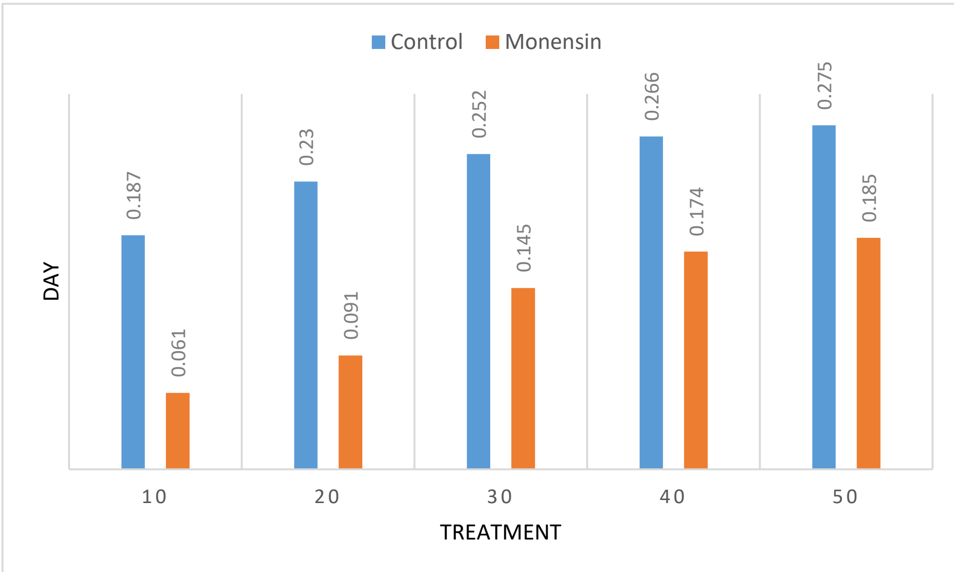
In the rumen, the fermentation process involves the cooperation and competition between different microbial communities, such as protozoa, fungi, bacteria, and methanogens. One important aspect of this process is the transfer of hydrogen between these communities. Methanogens consume hydrogen during methanogenesis, while other microbes produce hydrogen during the fermentation of carbohydrates (Tseten *et al*., 2022). To prevent the buildup of hydrogen, which can inhibit carbohydrate oxidation, the hydrogen must be transferred between the different microbial communities. There are a variety of strategies that can be used to reduce methane emissions from ruminant animals, each with its own benefits and drawbacks. The challenge is to find a balance between reducing emissions and maintaining the health and performance of the animal. Ionophores like monensin (Rumensin), lasalocid (Bovatec), salinomycin (Bio-cox, Sacox), and laidlomycin (Cattlyst) are using in various countries, including the United States, Australia, Argentina, Brazil, Canada, New Zealand, and South Africa. They manipulate ruminal fermentation, leading to improved feed efficiency (Barrera *et al*., 2019).



Source: Tseten *et al*., (2022)

Figure 7. Different schemes that can be used to reduce methane emissions from ruminant animals. These strategies include feed manipulation, supplementation of additives, and probiotics (Tseten *et al*., 2022). The light brown line in the figure represents the flow of rumen fermentation, which is the process by which feed is broken down in the rumen of ruminant animals. Methane is a byproduct of this process, and is released into the atmosphere when the animal exhales or belches. The pink line in the figure represents the use of inhibitors to reduce methane emissions. Inhibitors can be added to the animal's feed to reduce the production of methane during rumen fermentation.

This can be an effective strategy for reducing emissions. The purple line in the figure represents the use of stimulants to increase the production of certain bacteria in the rumen that are less likely to produce methane. This can be a more sustainable strategy than the use of inhibitors, but it requires careful management to ensure that the animal's health and performance are not negatively affected. The green line in the figure represents the use of feed supplements that are consumed by the animal to reduce methane emissions. These supplements can include things like oils or plant extracts that have been shown to reduce methane production.



Source: Junichi & Mitsuhiro, (2020)

Figure 8. Progressive CH4 yield in batch digesters fed manure from steers supplemented with or without monensin.

The suppressive effect of monensin as an ionophore-feed additive on enteric methane (CH_4) emission and renewable methanogenesis were evaluated and methane production was reduced (Junichi & Mitsuhiro, 2020).

3.7 Prevention of rumen disorders with ionophore

3.7.1 Bloat

Excess production of stable foam in the rumen can cause bloat, where gas becomes trapped and causes acute abdominal distension. This disorder is often fatal within hours of ingestion. Research has shown that bloat-susceptible animals have higher viscosity of rumen fluid compared to normal animals on a feedlot diet. During a 30-day feeding period, 86.3% of bloat-susceptible animals experienced bloat (Azzaz *et al*., 2015). However, when monensin was added to their diet at a dose of 40 mg/kg, bloat incidence decreased to 4.2% over the following 36 days (Azzaz *et al*., 2015). Removing monensin from the diet caused bloat incidence to increase to 24.3% for the next 36 days. During monensin supplementation, the viscosity of rumen fluid in bloat-susceptible animals decreased to levels similar to those of normal animals.

3.7.2 Acidosis

Ionophores have the potential to alleviate acidosis in two ways (Baba *et al*., 2020). The first mechanism involves their impact on lactic acid-producing bacteria, such as *Streptococcus bovis*. Research indicates that ionophores like Lasalocid and Monensin can inhibit the growth of many major strains of these bacteria. However, the major strains of lactate-fermenting bacteria are found to be resistant to ionophores. Studies conducted on cattle treated with glucose and ionophore show that colony counts of *S. bovis* and lactobacillus (gram-positive bacteria that produce lactate) were reduced (Azzaz *et al*., 2015). These findings suggest that ionophores may be effective in reducing the growth of lactic acid-producing bacteria in the rumen, which can help alleviate acidosis.

3.8 Performance response of cattle to ionophore

Effective management practices for ruminant growth performance involve ensuring that feed is digested at an appropriate rate. This helps to avoid both digestive problems resulting from excessively rapid digestion, and poor feed efficiency rates due to slow digestion. One way to improve efficiency and profitability of meat production is through the use of rumen metabolic modifiers, or ionophores. Carboxylic polyether ionophores have been shown to positively impact live weight gains, feed conversion, and reduce carcass fatness (Baba *et al*., 2020). However, the effectiveness of these compounds may vary depending on factors such as dietary inclusion level, diet composition, and animal characteristics.

Table 5. Investigate the impact of ionophore technology on average daily gain (ADG) and estimated cost of production in the stocker and feedlot segment

Industry section	ADG,%	Breakeven price %	Cost per head $
Stocker	7.74	1.46	11.51
Feedlot	2.90	1.18	12.43

Source: Hersom & Thrift, (2012)

The study compared the effects of ionophore technology to a control group with no use of ionophores. The use of ionophores in livestock production can result in a reduction in the breakeven price by improving growth performance and feed efficiency, which can lower the overall cost of production per head. Therefore, ionophores can potentially increase profitability in the livestock industry by reducing the breakeven price and increasing revenue. A study indicates that while feeding monensin during finishing cattle resulted in a decrease in feed intake and an improvement in feed efficiency, it did not lead to any significant improvements in body weight gain (Weiss *et al*., 2020).

3.9 Toxicity, safety and environmental factors

3.9.1 Toxicity of ionophore

Ionophores have been shown to be effective in improving cattle performance on grain and forage-based diets, as documented in several studies (Marques & Cooke, 2021). overconsumption of feed additives may result in toxicity in grazing animals. Researchers showed that there is a residual and lasting effect of these molecules on the proportion of SCFA, methane production, and ionophores-insensitive microbe population. Research has suggested that ionophores may impact ruminal microbial adaptation to dietary ionophores if used for an extended period. The administration of ionophores to cattle can result in persistent and consistent changes in ruminal fermentation characteristics for a period of up to 240 days. Some studies have also shown that ionophores may suppress methane production, but the duration of suppression may depend on the type of diet animals receive (Islam & Lee, 2019). Overall, further research is needed to validate the persistence efficacy of it, over a long period on rumen fermentation dynamics. Compared to other species, cattle are less vulnerable to the harmful effects of ionophores, likely due to factors such as ruminal breakdown, reduced absorption, and differences in cell wall structure (Ensley, 2020).

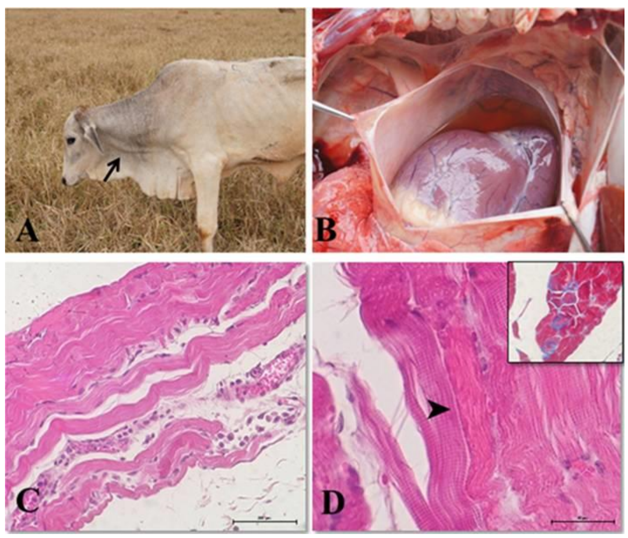
Table 6. Toxicity of ionophore in cattle expressed as median lethal dose

Type of ionophore	LD_{50} (mg/kg body weight)	Reference
Lasalocid	50-150	(Markiewicz *et al*., 2014)
Monensin	20-80	(Ekinci *et al*., 2023)

Source: Ekinci *et al*., (2023)

In some researches we found that overdose of monensin, which is broadly using in developed countries have a harmful effect. Such as, ionophore poisoning detected high levels of monensin in the skeletal muscle (25.5 µg/kg) and liver (209.4 µg/kg) of the affected animal (Brito *et al*., 2020). In this study the clinical sign was included muscle weakness, ataxia, recumbency, bilateral jugular distention, and death.

.



Source: Brito *et al*., (2020)

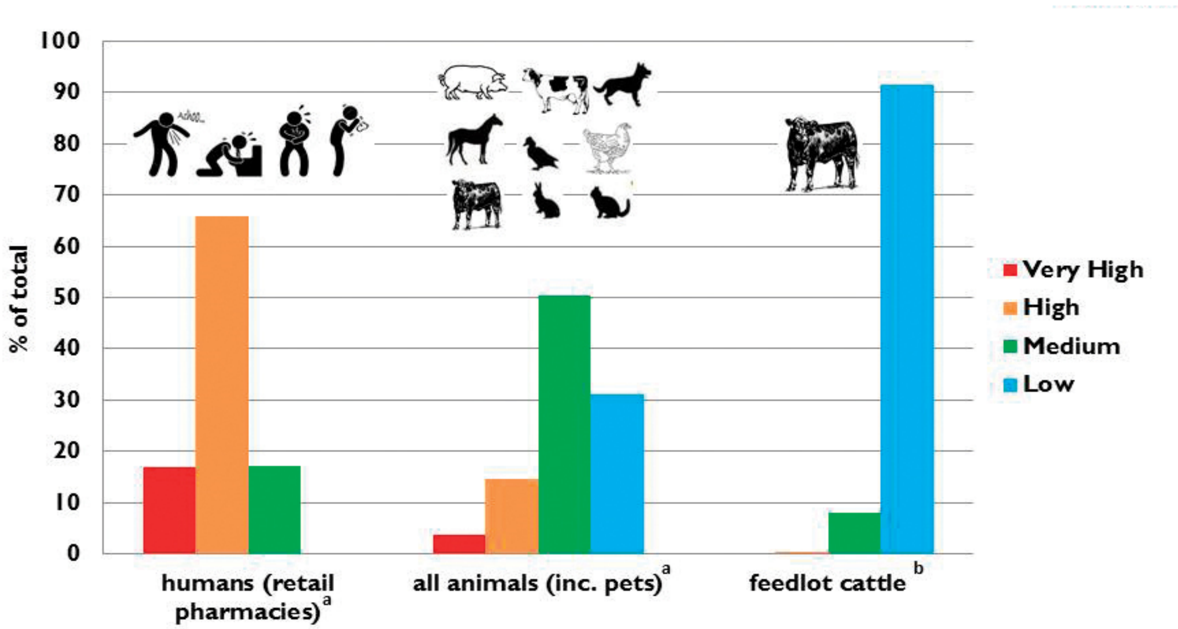
Figure 9. Toxicity of ionophore in cattle.

In the state of Goiás, Brazil cattle diagnosed with monensin poisoning showed in Figure 7(A) distended jugular vein. 7(B) during necropsy they found 100 mL of serous fluid in the pericardium. 7(C) Diaphragm tissue from a bovine intoxicated by monensin displayed signs of myocyte degeneration, loss of cellular details, and a mononuclear inflammatory cell infiltrate. D. necrotic muscle fibers were observed with fragmented eosinophilic cytoplasm and loss of transverse striations. Multifocal fibrosis in cardiomyocytes was also observed, which appeared as blue areas under Masson's trichrome staining.

3.10 Safety and environmental concerns of using ionophore

Ionophores are a type of antibiotic that inhibit the reproduction of certain disease-causing organisms, such as coccidia, which can cause bloody diarrhea in poultry and cattle. They are derived from naturally occurring bacteria, but work differently than antibiotics used in human medicine. Ionophores do not kill bacteria, but restricts their multiplication to control disease. While resistance can develop but it does not jeopardize the effectiveness of antibiotics used in human medicine. Due to their specificity, ionophores are not used in medically relevant human applications and are not currently regulated under the U.S. Veterinary Feed Directive, allowing them to be fed to cattle to improve feed efficiency (Clarke Ron, 2019).

.



Source: (BeefResearch.ca)

Figure 10. Antimicrobial use by category.

Canadian integrated program for antimicrobial surveillance (CIPARS) annual report, 2009 developed a longitudinal antimicrobial resistance and antimicrobial surveillance program for the feedlot sector in Western Canada.

A study found that some bacteria, such as *Enterococcus faecium*, have developed resistance to ionophores commonly used in cattle feed (Holman *et al*., 2021). Studies have shown that resistance to ionophores is highly complex and specific, and unlikely to contribute to the development of antibiotic resistance in humans. Therefore, the use of ionophores in animal feeds is still considered safe (Clarke Ron, 2019).

3.11 Current status & future direction of ionophore use

Currently, ionophores are approved for use in the United States and many other countries, but their use is subject to regulatory scrutiny. There is growing concerns about the use of ionophores and other antimicrobials to promote growth in food animals due to the potential development of antibiotic resistance. Despite this concern, the Canadian Food Inspection Agency categorizes ionophores as a low-importance antimicrobial in human medicine. This is because ionophores have a unique mode of action and are not used in human medicine, nor do they affect the shedding of pathogens in production facilities. As a result, the use of ionophores in animal agriculture is closely monitored and regulated by government agencies such as the United States Food and Drug Administration (FDA) and the European Union (EU). Ionophores are generally considered a good investment for cattle regardless of diet fed, but are used most extensively in feedlot cattle diets. In fact, it is estimated that 90 per cent of the cattle on feed in North America are fed ionophores. One of the reasons for the tremendous adoption of this particular technology is the consistent return on investment. The net return when ionophores are fed to cattle similizes to approximately $20 per head (Elanco Animal Health, 2015).

Some consumer groups have expressed concerns about the potential health and environmental impacts of ionophores, which may lead to increased pressure on regulators to limit their use. the future of using ionophores in cattle production will depend on a variety of factors, including regulatory policies, consumer demand, and advances in alternative technologies. As research continues to uncover new information about the benefits and potential drawbacks of ionophores, it is possible that their use in cattle production will evolve or even be phased out over time. Feeding policies should be maintained to have the benefits of ionophore in future beef industry. In Bangladesh, there are no researches regarding ionophore diets on cattle. So, we should start researching about this issue.

CHAPTER 4

CONCLUSION

Ionophores have been extensively studied and used as feed additives in beef cattle diets, consistently showing positive effects on rumen microbiome, fermentation, digestive disorders, and methane production reduction. However, research suggests that ionophores on ruminal fermentation remain consistent even with prolonged feeding periods. These lasting effects may help beef producers define nutritional strategies that can enhance productivity and profitability in cattle systems utilizing this dietary technology. Ionophores also reduces some digestive disorders that are common in cattle by disrupting bacterial cell wall and ion balance. Based on this review, we can tell that ionophore has a beneficial effect on weight gain and feed efficiency.

Over and above that, it can reduce global warming by reducing methane emission from rumen. It ferments feeds by the propionate production route, which is more preferable to reduce methane production. So, with proper implementation of ionophores into diet we can make better cattle farms for future beef production. It is already eminent in USA, Canada, Austrailia and Europe, so it is high time to apply ionophore based diet in Bangladesh.

REFERENCES

Azzaz, H. H., Murad, H. A., & Morsy, T. A. (2015). Utility of ionophores for ruminant animals: a review. *Asian Journal of Animal Sciences*, *9*(6), 254-265.

Baba, M., Baso, Z., Ubayi, Y. K. M., & Sariyyu, S. (2020). The Roles of Ionophores in Ruminant Animalsnutrition. *Journal of Agriculture and Veterinary Science (IOSR-JAVS), 30*, 46-5.

Barrera, O. R., Salinas-Chavira, J., & Castillo, Y. C. (2019). Yeasts as Dietary Additives to Manipulate Ruminal Fermentation: Effect on Nutrient Utilization and Productive Performance of Ruminants. *Yeasts in Biotechnology*. *10*.5772-82769.

Bell, N., Wickersham, T., Sharma, V., & Callaway, T. (2015). Ionophores: a tool for improving ruminant production and reducing environmental impact. In *Livestock production and climate change*, 263-272.

Berger, L. L., Ricke, S. C., & Fahey Jr, G. C. (1981). Comparison of two forms and two levels of lasalocid with monensin on feedlot cattle performance. *Journal of animal science, 53(6),* 1440-1445.

Booth, I. R. (1985). Regulation of cytoplasmic pH in bacteria. *Microbiological reviews*, *49*(4), 359-378.

Bretschneider, G., Elizalde, J. C., & Pérez, F. A. (2008). The effect of feeding antibiotic growth promoters on the performance of beef cattle consuming forage-based diets: A review. *Livestock Science*, *114*(2-3), 135-149.

Brito, E. S. A., Andrade, T. G., Oliveira, C. H. S. D., & Moura, V. M. B. D. D. (2020). Outbreak of monensin poisoning in cattle due to supplementation error. *Ciência Rural, 50*.

Callaway, T. R., Edrington, T. S., Rychlik, J. L., Genovese, K. J., Poole, T. L., Jung, Y. S., ... & Nisbet, D. J. (2003). Ionophores: their use as ruminant growth promotants and impact on food safety. *Microbial, 4*(2)*,* 43-51.

Clarke Ron. (2019, July 13). The complicated life of an ionophore - Canadian Cattlemen. Retrieved from https://www.canadiancattlemen.ca/features/the-complicated-life-of-an-ionophore.

Ekinci, İ. B., Chłodowska, A., & Olejnik, M. (2023). Ionophore Toxicity in Animals: A Review of Clinical and Molecular Aspects. *International Journal of Molecular Sciences*, *24*(2), 1696.

Ellis, J. L., Dijkstra, J., Bannink, A., Kebreab, E., Hook, S. E., Archibeque, S., & France, J. (2012). Quantifying the effect of monensin dose on the rumen volatile fatty acid profile in high-grain-fed beef cattle. *Journal of Animal Science*, *90*(8), 2717-2726.

Ensley, S. (2020). Ionophore use and toxicosis in cattle. *Veterinary Clinics: Food Animal Practice*, *36*(3), 641-652.

Golder, H. M., & Lean, I. J. (2016). A meta-analysis of lasalocid effects on rumen measures, beef and dairy performance, and carcass traits in cattle. *Journal of Animal Science*, *94*(1), 306-326.

Goodrich, R. D., Garrett, J. E., Gast, D. R., Kirick, M. A., Larson, D. A., & Meiske, J. C. (1984). Influence of monensin on the performance of cattle. *Journal of animal science*, *58*(6), 1484-1498.

Hersom, M., & Thrift, T. (2012). Application of Ionophores in Cattle Diets: AN285/AN285, 12/2012. *EDIS*, *2012*(12).

Holman, D. B., Klima, C. L., Gzyl, K. E., Zaheer, R., Service, C., Jones, T. H., & McAllister, T. A. (2021). Antimicrobial resistance in Enterococcus spp. isolated from a beef processing plant and retail ground beef. *Microbiology Spectrum*, *9*(3), e01980-21.

Islam, M., & Lee, S. S. (2019). Advanced estimation and mitigation strategies: a cumulative approach to enteric methane abatement from ruminants. *Journal of animal science and technology*, *61*(3), 122.

Kaushik, V., Yakisich, J. S., Kumar, A., Azad, N., & Iyer, A. K. (2018). Ionophores: Potential use as anticancer drugs and chemosensitizers. *Cancers*, *10*(10), 360.

Khunchaikarn, S., Mankeb, P., & Suwanmaneepong, S. (2022). Economic efficiency of beef cattle production in Thailand. *Journal of Management Information & Decision Sciences*, *25*(2).

Limede, A. C., Marques, R. S., Polizel, D. M., Cappellozza, B. I., Miszura, A. A., Barroso, J. P. R., ... & Pires, A. V. (2021). Effects of supplementation with narasin, salinomycin, or flavomycin on performance and ruminal fermentation characteristics of Bos indicus Nellore cattle fed with forage-based diets. *Journal of Animal Science, 99*(4), skab005.

Markiewicz, W., Barski, D., Burmanczuk, A., & Tomaszewska, E. (2014). Toxicity of salinomycin and narasin in turkeys. *Journal of Elementology*, *19*(3).

Marques, R. D. S., & Cooke, R. F. (2021). Effects of ionophores on ruminal function of beef cattle. *Animals*, *11*(10), 2871.

Takahashi, J., & Iwasa, M. (2021). Entomological approach to the impact of ionophore-feed additives on greenhouse gas emissions from pasture land in cattle. Journal of Animal Science and Technology, 63(1), 16.

Nagaraja, T. G. (1995). Ionophores and antibiotics in ruminants. *Biotechnology in animal feeds and animal feeding*, *174*.

Ovchinnikov, Y. A. (1979). Physico-chemical basis of ion transport through biological membranes: ionophores and ion channels. *European Journal of Biochemistry*, *94*(2), 321-336.

Owens, F. Ionophores for growing and finishing beef cattle: History, benefits, challenges, and global warming. *Journal of Animal Science, 60*(2).

Painter, G. R., Pollack, R., & Pressman, B. C. (1982). Conformational dynamics of the carboxylic ionophore lasalocid A underlying cation complexation-decomplexation and membrane transport. *Biochemistry*, *21*(22), 5613-5620.

Russell, J. B., & Houlihan, A. J. (2003). Ionophore resistance of ruminal bacteria and its potential impact on human health. *FEMS microbiology reviews*, *27*(1), 65-74.

Russell, J. B., & Strobel, H. (1989). Effect of ionophores on ruminal fermentation. *Applied and environmental microbiology*, *55*(1), 1-6.

Saunois, M., Jackson, R. B., Bousquet, P., Poulter, B., & Canadell, J. G. (2016). The growing role of methane in anthropogenic climate change. *Environmental Research Letters*, *11*(12), 120207.

Schären, M., Drong, C., Kiri, K., Riede, S., Gardener, M., Meyer, U., & Dänicke, S. (2017). Differential effects of monensin and a blend of essential oils on rumen microbiota composition of transition dairy cows. *Journal of dairy science*, *100*(4), 2765-2783.

Stahl, D. A., Flesher, B., Mansfield, H. R., & Montgomery, L. (1988). Use of phylogenetically based hybridization probes for studies of ruminal microbial ecology. *Applied and Environmental Microbiology*, *54*(5), 1079-1084.

Sutton, J. D. (1979). Carbohydrate fermentation in the rumen—variations on a theme. *Proceedings of the Nutrition Society*, *38*(3), 275-281.

Tedeschi, L. O., Fox, D. G., & Tylutki, T. P. (2003). Potential environmental benefits of ionophores in ruminant diets. *Journal of environmental quality*, *32*(5), 1591-1602.

Tseten, T., Sanjorjo, R. A., Kwon, M., & TT, S. W. K. (2022). Strategies to mitigate enteric methane emissions from ruminant animals. *Journal of Microbiology and Biotechnology*, 32(3): 269–277.

Weimer, P. J., Stevenson, D. M., Mertens, D. R., & Thomas, E. E. (2008). Effect of monensin feeding and withdrawal on populations of individual bacterial species in the rumen of lactating dairy cows fed high-starch rations. *Applied Microbiology and Biotechnology*, *80*, 135-145.

Weiss, C. P., Beck, P. A., Gadberry, M. S., Richeson, J. T., Wilson, B. K., Robinson, C. A., ... & Hubbell III, D. (2020). Effects of intake of monensin during the stocker phase and subsequent finishing phase on performance and carcass characteristics of finishing beef steers. *Applied Animal Science*, *36*(5), 668-676.

Wolin, M. J., Miller, T. L., & Stewart, C. S. (1997). Microbe-microbe interactions. *The rumen microbial ecosystem*, 467-491.