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Science & Solutions

Endotoxins in cows

Pro-immune or antagonistic?

China's rising dairy industry

Recovering from recent scandals of producer misconduct, Chinese dairy consumption is set to soar

WORLD NUTRITION FORUM
MUNICH 2014
SUSTAIN: ABILITY

Ruminants in focus

Trends in ruminant technology and management, and a focus on the rumen, udder and uterus

Editorial

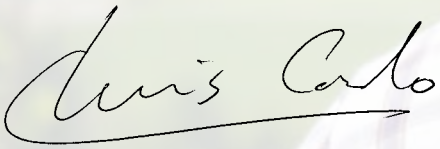
From macro to the molecular

The Global Dairy Outlook by Global Dairy Farmers and Wageningen University forecasts that by 2020, annual milk production will grow to 820 million tonnes, from 754 million tonnes in 2012. It is a global trend that dairy products consumption per capita increases with personal income. With more countries joining the club of the rich, a bigger share of the world population will demand more dairy products and higher quality.

In 2010, the EU-28, India and the US were the largest milk producers. The largest exporters were the EU-28, New Zealand, Australia and the US with Russia, China and Mexico the largest importers. For 2020, nearly all regions are projected to increase absolute volumes, with the shares of India and China forecast to increase. Some uncertainties will undoubtedly add to the mix, such as the disappearance of the quota system in the EU, volatility for both dairy product prices and input prices, and erratic weather patterns.

All these changes, already happening, offer an exciting world of new opportunities and challenges. One of the biggest players in the dairy market, China has one of the fastest-growing dairy markets in the world, with a growing domestic production offering enormous potential and a magnet for imports.

Moving from the market to the molecular level, this issue of **Science & Solutions** also introduces the world of endotoxins. Harmful to all animal species, endotoxins are released from the cell wall of all gram-negative bacteria and are gaining momentum as a key research topic in years to come. Although not much considered until now from a farm efficiency point of view, this looks set to change. Read on to find out more about these interesting compounds!



Luis CARDO
Technical Sales Manager, Ruminants

Contents

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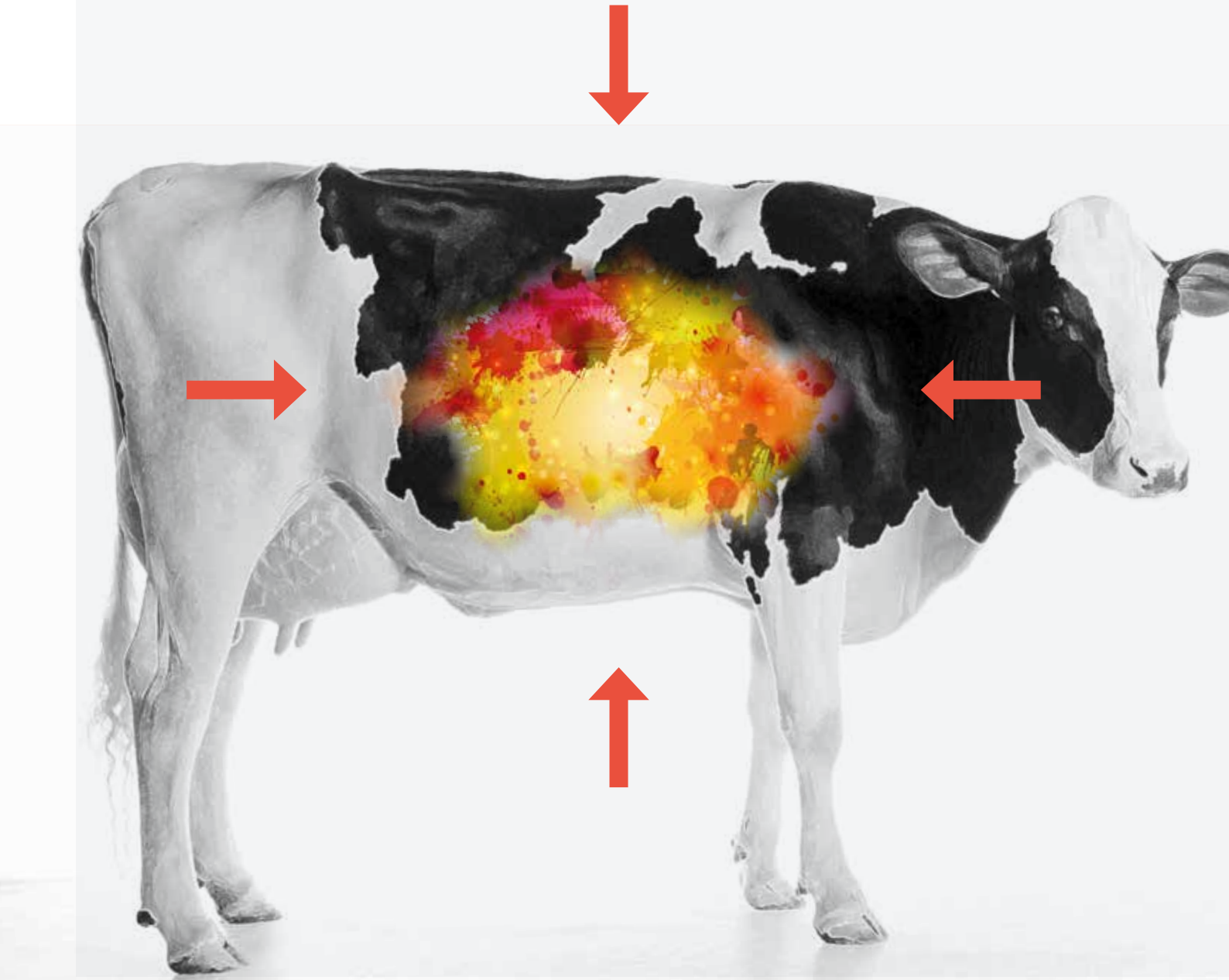
Endotoxins in cows

An under



Simone Schaumberger Product Manager, Mycotoxin Risk Management
Nicole Reisinger Project Leader, Endotoxins

estimated risk?

Endotoxins are incredibly fascinating substances. On the one hand, they stimulate the immune system in a positive way, yet on the other hand cause endotoxic shock and death.

Toxins are known to have negative effects on rumen fermentation. In general, two types of toxins have drawn much attention within animal health and welfare: toxins from fungi (mycotoxins) and bacterial toxins (endotoxins, exotoxins).

There is growing attention on the issue of increased endotoxin values in the rumen during rumen acidiosis. High carbohydrate diets change the microflora in the rumen, leading to the death of gram-negative bacteria and an increase in gram-positive bacteria. This effect leads to a dysbiosis, which in turn results in ruminitis. Ruminitis consequently increases rumen permeability, allowing endotoxins to enter the organism. But what does this mean for your cow?

About endotoxins

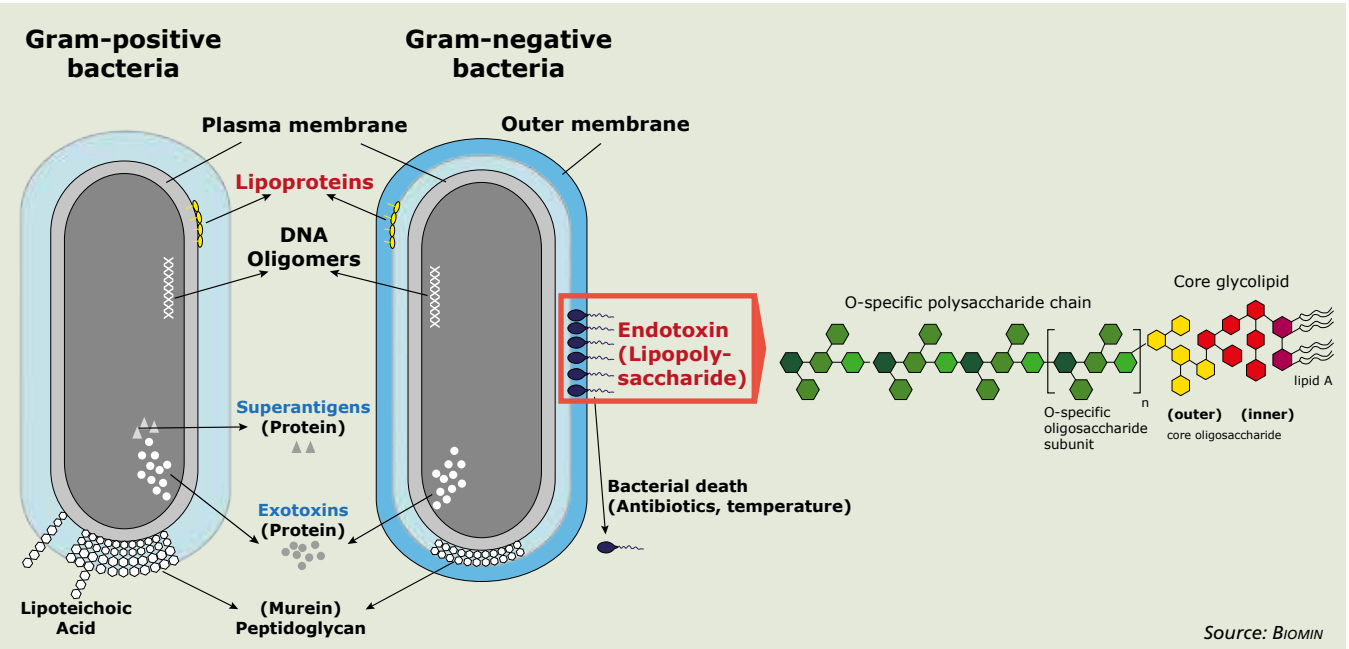
Endotoxins have been known since the early 1900s because of their pyrogenic (fever inducing) effect. In general, endotoxins are parts of the cell wall of all gram-negative bacteria (*Figure 1*) and they are of great interest because of their effect on the immune system. Endotoxins are also called lipopolysaccharides (LPS) as their structure consists of a lipid (lipid A, immunogenic part, lowest variability) and a polysaccharide (species specific part, high variability of chain length).

Photo: Eraxion_iStockphoto

Endotoxins are…

- Produced from gram-negative bacteria
- Part of the bacterial cell wall
- Macromolecules with 300,000 to 1,000,000 dalton
- Pyrogens (can induce fever)
- Abundant in the rumen and gastrointestinal tract
- Present in the air, water and feed
- Heat and pH stable

Figure 1. Comparison of gram-positive and gram-negative bacterial cell wall. The location of LPS in the cell wall is circled.



Simone Schaumberger Product Manager, Mycotoxin Risk Management
Nicole Reisinger Project Leader, Endotoxins

Risk factors for endotoxin-related diseases in ruminants

Table 1. Summary of endotoxin activity (endotoxin units, EU/ml) in different parts of the cow in healthy animals and animals with experimentally induced sub-acute ruminal acidosis (SARA) from different studies.

	EU/ml Healthy cow	EU/ml SARA
Blood	< 0.05 EU/ml	0.05 – 1 EU/ml
Rumen	3,700 – 30,000 EU/ml	120,000 – 210,000 EU/ml
Ileum	4,000 EU/ml	110,000 EU/ml
Cecal	18,000 EU/ml	130,000 EU/ml
Fecal	14,000 EU/ml	100,000 EU/ml

Source: Adapted from Plaizier et al., *2013*

The structure of the LPS is crucial for the uptake and detoxification of the molecule. Endotoxins are released during the death or overwhelming proliferation of gram-negative bacteria. The administration of special kinds of antibiotics (for example beta-lactam antibiotics) with bactericidal activity may increase the liberation of endotoxins. This fact should be taken into consideration when treating a cow with antibiotics.

1 Rumen simulation model

The rumen simulation is an important *in vitro* model to test the influence of feed additives on rumen physiology. The model was adapted at the Biomin Research Center (Research Team Analytics) to determine, with the use of natural rumen fluid, the influence of additives on the rumen pH, bacterial number and concentration of fatty acids in a reactor (pictured below). The influence on endotoxin concentration in the rumen can also be tested.

Effects in ruminants

Ruminants are constantly in contact with endotoxins via feed, air and the environment. In healthy animals, only small quantities are absorbed into the blood through the intestine. They are then transported and detoxified in the liver. Due to their structure, endotoxins can also be stored in the fat tissue.

In healthy ruminants, endotoxins are present at certain concentrations in the rumen, intestinal tract and feces. In the case of energy deficiencies or feed imbalances, the rumen or gut wall becomes more permeable, which allows more endotoxins to enter the bloodstream. If the animal lacks sufficient energy, fat is degraded and even more endotoxins can enter the organism.

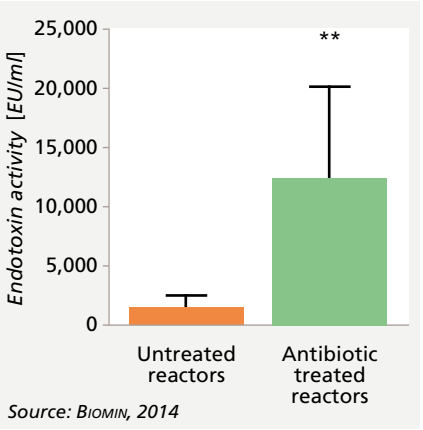
Endotoxin concentrations can increase and can be measured in the blood (*Table 1*). This may trigger a range of diseases such as mastitis, endometritis, laminitis, dermatitis digitalis and endotoxic shock, among others.

In vivo meets *in vitro*

Endotoxins are receptor-mediated agents and hence, their predictive value in animals is uncertain, especially via the oral route. Inducing a controlled *in vivo* oral endotoxin challenge via feed is a difficult task. Therefore, *in vitro* experiments provide an opportunity to explain the mechanism

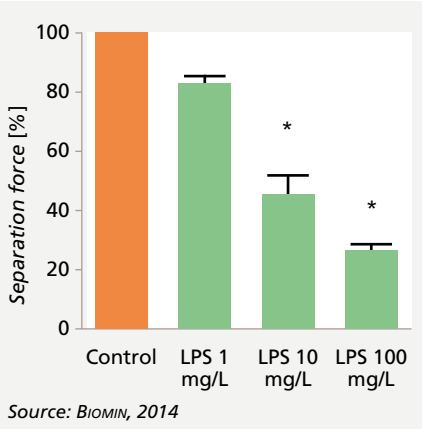
- *Cows in early lactation*
- *Primiparous cows*
- *Cows grazing or fed with rapidly fermentable low fiber grass*
- *High amount of concentrates*
- *Sub-acute acidosis*
- *Management in stables*

Figure 2. Comparison of mean endotoxin values of reactors from the rumen simulation model. The antibiotic treated reactors (green) showed significantly higher endotoxin values after long-term incubation.



Source: Biomin, 2014

Figure 3. Significant decrease in separation force [%] from explants treated with 10 and 100 µgl/ml LPS compared to negative control (green).



Source: Biomin, 2014

induced by endotoxins. The rumen simulation model provides a method to test the effects of feed additives (*Box 1*).

Preliminary results with the rumen simulation model confirmed that antibiotics have a negative effect on endotoxin production in the rumen. After a two-week long incubation, the endotoxin concentration of the reactors treated with antibiotics increased significantly compared to the untreated reactors (*Figure 2*). This shows the need for alternative strategies to positively influence the rumen physiology and control the endotoxin load in the rumen.

Another *in vitro* model is the *ex vivo* laminitis model (*Box 2*), which uses claw tissue to test the effects of endotoxins. This model demonstrates that endotoxins have a negative effect on the claw tissue. Endotoxins significantly decreased the force required to separate the connective tissue from the lamellae (*Figure 3*).

Conclusion

The damages caused by endotoxins are fact and no fiction. They are ubiquitous in the environment and are permanently released. A healthy cow can cope with the normal load of endotoxins by detoxification in the liver or the lymph.

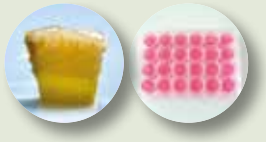
When there is an increase in endotoxins or liver failure, endotoxins can overwhelm the cow's biological function. Inflammation cascades are triggered and result in different diseases, which, in the worst cases, may lead to shock and death.

As endotoxins are ever present in the ruminant environment, control strategies to prevent endotoxin-related diseases among cows are essential, and recommended.

2 ***Ex vivo*** **laminitis model**

(A) **Dissection of the claw**

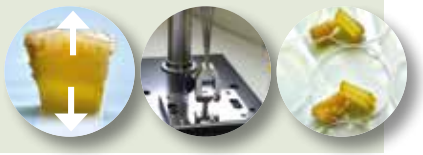
(B) **Cultivation of explants**



Explants of connective tissue, lamellae and claw wall.

- 24 hours
- 37°C, 5% CO_2
- 0 – 100 µg/ml LPS

(C) **Testing of separation force**



Donald Xu
Business Director Dairy China

Part 1 China's rising dairy industry

China's dairy industry is a fast rising one that is developing more rapidly than the local poultry and swine sectors. Today, China is becoming a large and increasingly important global dairy production and trading market.

According to Chinese government figures, total cow population in 2013 was 12.6 million. This number includes milking cows, dry cows, heifers and calves, with the actual number of milking cows at about 6.3 million (50% of the total cow population). The overall milk production level in China is low compared with countries with well-developed dairy industries, with an average milk yield of 5,500 kg/cow/year which is half of that in the US and Europe (*Figure 1*).

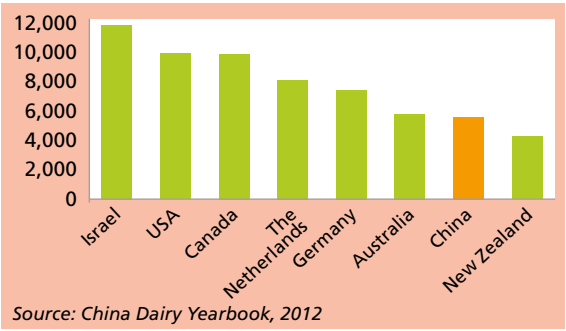
Production and consumption

From 2007 to 2009, milk production in China remained steady at 35.3 million tonnes per year. From 2010, production started to increase to reach up to 38.8 million tonnes in 2012 before dropping to 35.31 million tonnes in 2013 (*Figure 2*). The China Statistics Bureau and China Research Centre for Sustainable Development estimated that milk production will reach 59 and 76 million tonnes by 2020 and 2030, respectively.

The average urban consumption of dairy products per capita per year in 2013 is 28.6 kg. This is only 26% of the global average consumption level of 109 kg and below the consumption level of these countries: Australia 412kg, EU 302.3kg, America 289.5kg, Japan 59.8kg, South Korea 43.2kg (*Figure 3*).

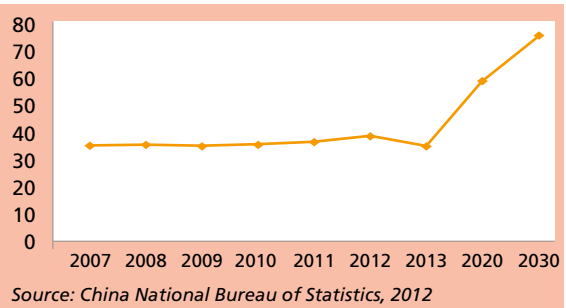
Figure 4 shows dairy consumption falling from 2008 and a declining trend continuing until 2011 due to

Figure 1. Output and world ranking of milk producing countries (kg/cow/year) in 2012



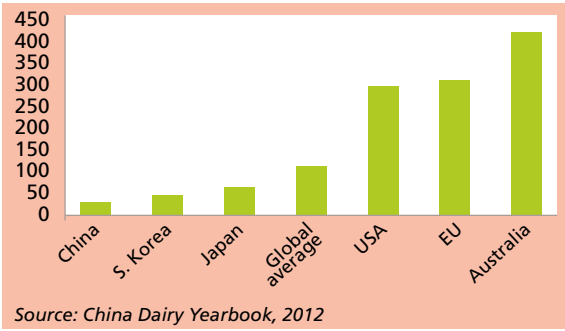
Source: China Dairy Yearbook, 2012

Figure 2. China milk production, 2007 to 2030 forecast (million tonnes)



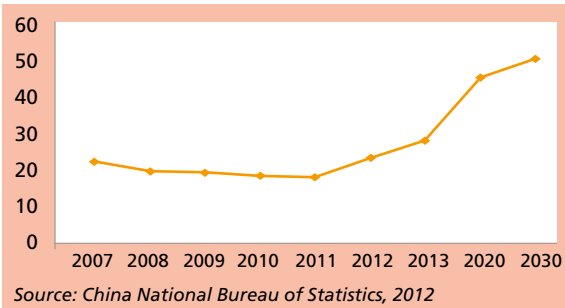
Source: China National Bureau of Statistics, 2012

Figure 3. Urban consumption of dairy products in 2013 (kg/capita/year)



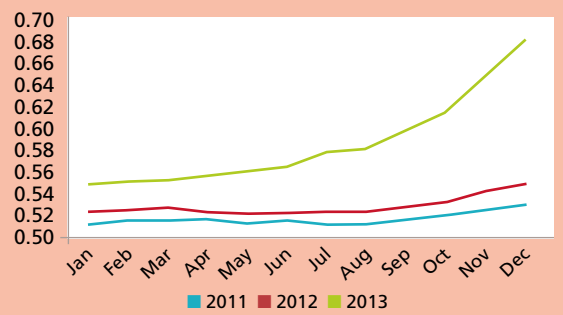
Source: China Dairy Yearbook, 2012

Figure 4. China urban dairy consumption, 2007 to 2030 forecast (kg/capita/year)



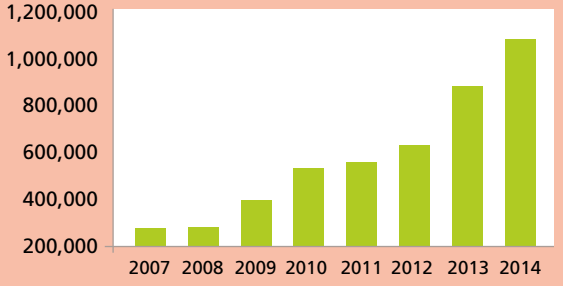
Source: China National Bureau of Statistics, 2012

Figure 5. China average raw milk prices, 2011-2013 (US$/kg)



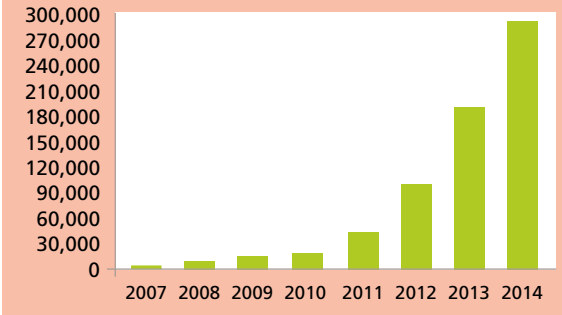
Source: China Orient Dairy Inform. Consulting Company, 2013

Figure 6. Milk powder imports (tonnes)



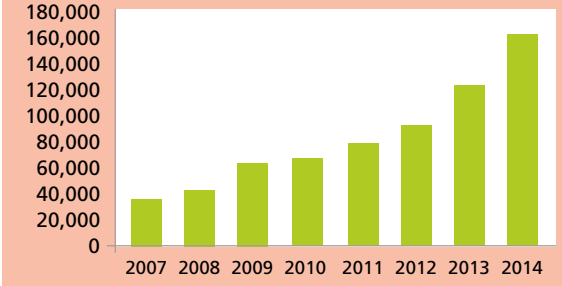
Source: China Customs; Li Shengli (China Agri. University), 2013

Figure 7. Liquid milk imports (tonnes)



Source: China Customs; Li Shengli, 2013

Figure 8. Infant formula milk powder imports (tonnes)



Source: China Customs, 2013

the melamine milk scandal and crisis of trust for dairy products. It was only in 2012 that consumption started to recover and increase. According to the China Statistics Bureau and China Research Centre for Sustainable Development, this level will reach 45 and 50 kg by 2020 and 2030, respectively.

A global business

The milk shortage in 2013 resulted in raw milk prices increasing (*Figure 5*). In some regions, the price of milk even rose to US$0.97/kg, such that most dairy farmers reported the best profits in the last five years. Some top producing farms (over 35kg milk/cow/day) made US$2,500 from each milking cow in 2013.

High demand and steadily increasing consumption levels for dairy products will mean that the gap between supply shortage of raw milk and market demand will continue into 2014.

Together with the rapid development of the dairy industry, there will be many business opportunities for the import of milk powder, liquid milk and materials related to local dairy farming such as alfalfa hay, oaten hay and dairy cattle. As a country with a shortage of inputs for dairy, the trend of China as a net-importer of dairy products will continue to rise.

Milk product imports

Milk imports include powder milk, liquid milk and infant formulas.

China imported 449,542 tonnes, 527,875 tonnes and 854,400 tonnes of milk powder in 2011, 2012 and 2013 respectively. About 85% of these imports were from New Zealand and this is estimated to be over one million tonnes by the end of 2014 (*Figure 6*). The total value of imported milk powder in 2013 is US$3.59 billion.

In 2013, milk powder imported by China reached 20% of the total global trading volume. Of the total domestic supply of dairy products in the market, 28% had to be imported to meet local demand.

Liquid milk import increased from 4,800 tonnes in 2007 to 194,800 tonnes in 2013, an increase of 40 times. This import volume is estimated to reach 300,000 tonnes by the end of 2014 (*Figure 7*). Eleven EU countries contributed 62% to this milk import volume.

Although it has been six years since the case of melamine-contaminated milk powder, the industry is still reeling from the after-effects and living in the shadow of a crisis of trust in the dairy industry. Consumers continue to demand higher quality and safe dairy products, particularly in infant formula milk powder. A total of 122,000 tonnes of infant formula, valued at US$1.47 billion, were imported in 2013. This import volume was 33.5% more than that in 2012, and 40.7% higher in value terms.

Imports of infant milk formula increased from

Photo: Ivan Cholakov shutterstock

According to the FAO, total global dairy production in 2012 was 784 million tonnes with 33% from Europe and 28% from Asia. China accounted for 6% of global dairy production, ranking third based on a single country contribution. Central and North America accounted for 18% of global total, South America 11%, and 5% each from Africa and Oceania.

35,792 tonnes in 2007, to up to 122,000 tonnes in 2013, an increase of 3.4 times. This import volume is estimated to reach 160,000 tonnes by the end of 2014 (*Figure 8*).

Imports of whey and hay

Whey imports increased from 167,583 tonnes in 2007 to 402,000 tonnes in 2013, an increase of 2.4 times. This import volume is estimated to reach 500,000 tonnes by the end of 2014 (*Figure 9*).

As a country with a shortage of inputs for dairy, the trend of China as a net-importer of dairy products will continue to rise.

The increase in local milk production and market demand for high quality inputs have led to an increase in imports of raw materials such as alfalfa hay and oaten hay as well as breeding stock such as heifers and frozen semen.

China imported 2,088 tonnes of alfalfa hay mainly from the US in 2007. In 2013, imports increased to 755,600 tonnes, valued at US$296.41 million. The 2013 import volume was 362 times more than in 2007, and this volume is expected to be over one million tonnes in 2014 (*Figure 10*).

In 2011, Australian oaten hay was first introduced into Chinese dairy farms with imports starting at 12,700 tonnes. This increased to 42,800 tonnes in 2013 and is predicated to reach 200,000 tonnes in 2014 (*Figure 11*).

Heifer imports

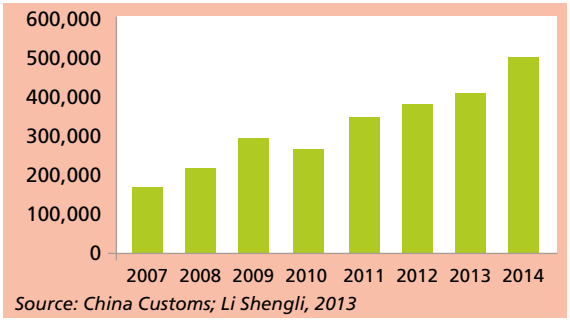
China has been importing large numbers of heifers mainly from New Zealand, Australia and Uruguay to meet the demand coming from newly built commercial farms and expanding ones. Government regulations also stipulate that infant milk powder processors must have their own controlled milk sources (dairy farms). It is estimated that 200,000 heifers will be imported in 2014 (*Figure 12*).

Frozen semen import

To improve the performance of dairy cows, the import of frozen semen has been increasing steadily from 64kg in 2000 up to 7,102kg in 2012 (*Figure 13*). The major foreign players in the market are: World Wide Sires, Alta-Agricorp, ABS Global, Cooperative Resources International (CRI), Semex, Masterind, LIC Semen Paks, Genex Cooperative, CRV (the Netherlands) and Viking Genetics.

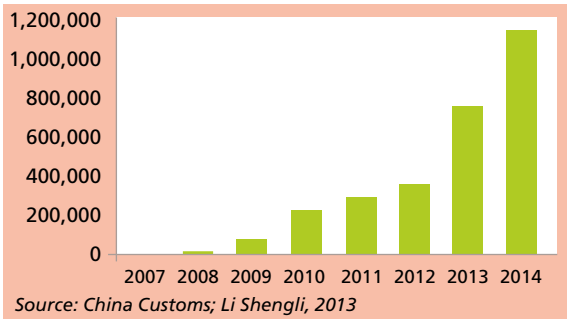
Part 2 will continue (issue 13, October 2014) with an insight on the regional distribution of dairy activities in China and how government policies could shape the future of this industry.

Figure 9. Whey imports (tonnes)



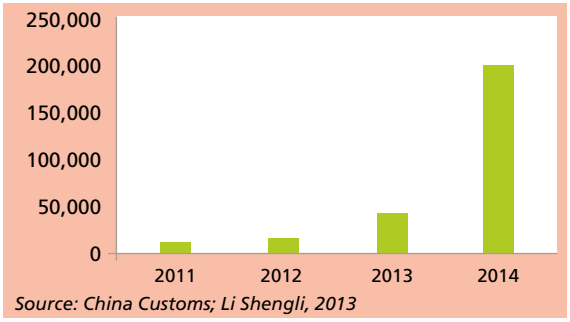
Source: China Customs; Li Shengli, 2013

Figure 10. Alfalfa imports (tonnes)



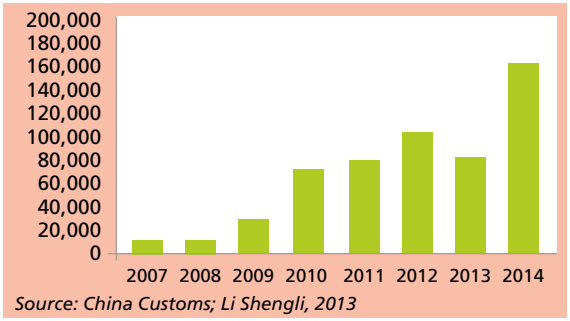
Source: China Customs; Li Shengli, 2013

Figure 11. Oaten hay imports (tonnes)



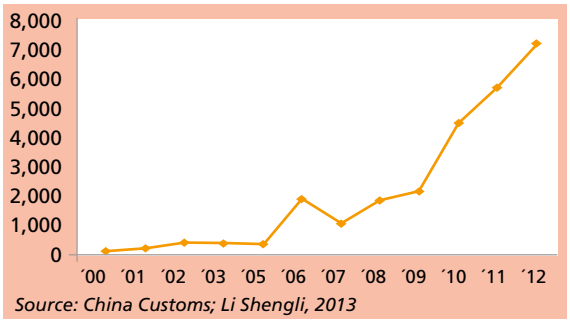
Source: China Customs; Li Shengli, 2013

Figure12. Heifer imports (head)



Source: China Customs; Li Shengli, 2013

Figure 13. Frozen semen imports (kg)



Source: China Customs; Li Shengli, 2013

WORLD NUTRITION FORUM

MUNICH 2014

SUSTAIN:ABILITY

RUMINANT Breakout Session

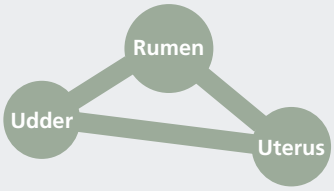
What to expect

1. Behind the scenes: Agricultural breakthroughs the public does not see

Ever heard a comment about livestock farming which you know to be untrue? The fact is: the general public is more readily influenced by attention-grabbing news than science-based findings.

As consumer perceptions continue to drive retail demand, this topic explores the advancements and trends in the use of technology and ruminant management that should not remain only as insider knowledge.

So the next time you hear something erroneous about cattle production, you'll know how to respond!



2. This triad for sustainable production—the rumen, udder and uterus—form the core of long-term cattle health and profitability.

Dedicated to dairy cows, the presentations in this topic cover the impact of feeding on dairy health and welfare; "Ruminomics"; nutrient losses during digestion and metabolism; and issues related to high performance fertility in dairy cows.

A tradition of the **World Nutrition Forum (WNF)** since 2010, the species-specific Breakout sessions address timely topics in ruminant farming and other animal production sectors.

Each four-hour long Breakout session covers two topics. Sessions for each species are held in parallel on the afternoon of the first day (Thursday, 16 October 2014).

The World Nutrition Forum, sponsored by Biomin, is a premier biennial industry event where leading professionals, scientists and decision-makers gather to brain-storm and exchange ideas and strategic prospects on the future of animal nutrition. Held in Munich, Germany, the WNF 2014 will explore the theme of "sustain:ability".

For up-to-date information, please visit **www.worldnutritionforum.info**.

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