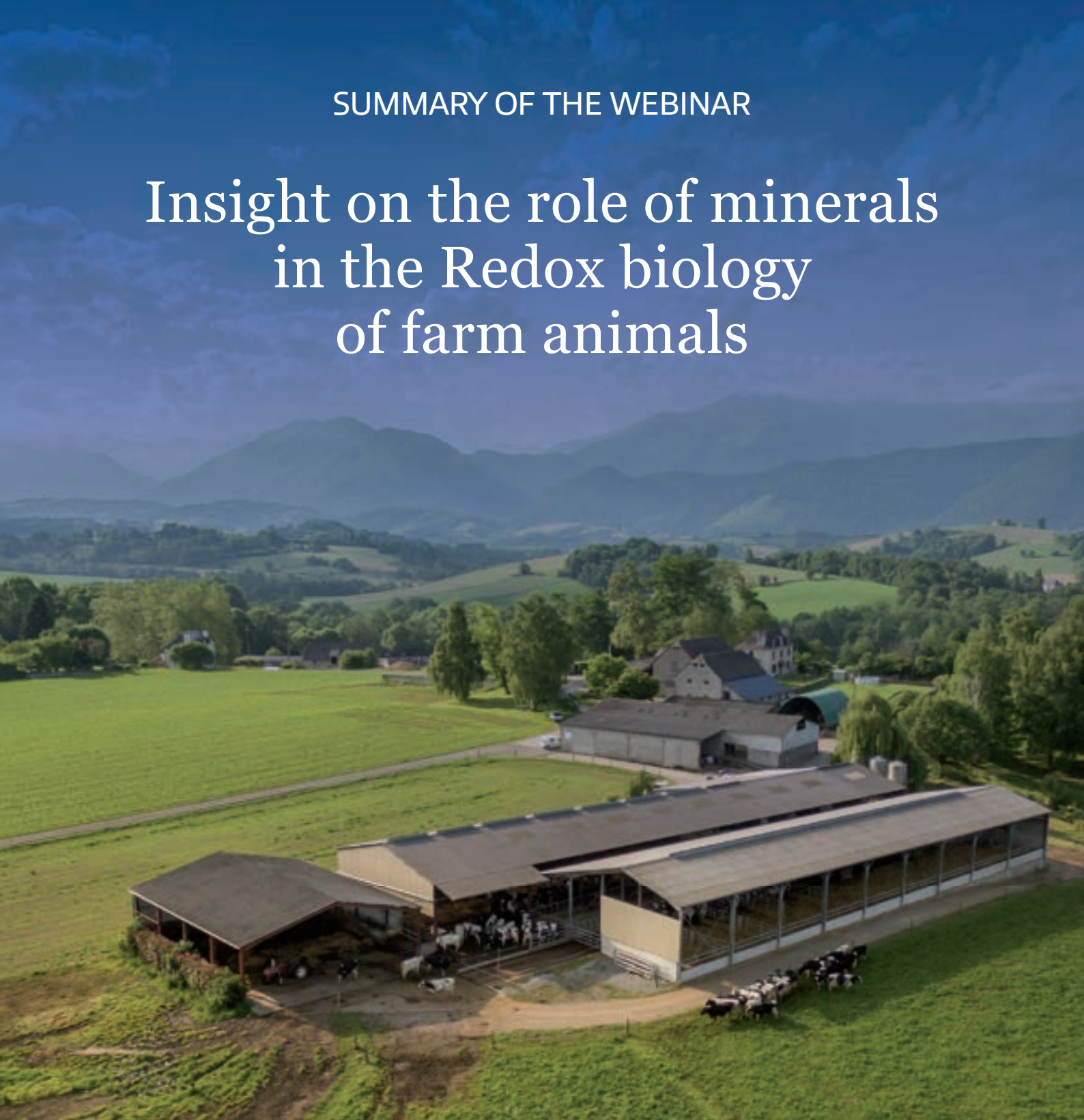
SUMMARY OF THE WEBINAR

Insight on the role of minerals in the Redox biology of farm animals



WEDNESDAY, 25 NOVEMBER
THURSDAY, 26 NOVEMBER
THURSDAY, 3 DECEMBER
2020

Shaping the future of animal health

Virbac

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Points that really matter

1 Injectable mineral supplementation (IMS) is provided in complement of good nutrition. Such supplementation is not an alternative to dietary mineral supplementation, it is a source of supplemental mineral provided to animals fed on a balanced ration. The rule is **oral daily dietary supplementation for the maintenance and injectable supplementation for performance.**

2 When it comes to different nutrients (proteins, fats, carbohydrates, minerals), mineral needs count differently from other needs. With respect to energy and protein (and water) supplies, they are fed to farm animals to meet maintenance needs, as well as to cover additional needs resulting from production, and are therefore calculated to maximize animal productivity. In contrast, minerals are provided for **maintaining the mineral status of animals within a physiological range, in compliance with official recommendations, and not for optimization of production.**

3 Mineral recommendations provided by research councils and institutes are developed based on peer reviewed published data. As new data are published, nutritional guidelines are updated. However, there are numerous factors that can impact an animal's response to mineral supplementation such as physiological status of the animal, breed type, the absence or presence of dietary antagonists, age, etc. Also, minerals are not absorbed like common macronutrients. Absorption relies on receptors in the gut that are down or up regulated according to the mineral status. Modification of the mineral uptake capacity needs time, and can result in a temporary or specific deficiency state.

4 To some extent, it can be argued that periods of physiological and metabolic stress increase **nutritional requirements**. These periods of stress relate to the critical periods of the production cycle or high demand periods that will be discussed later on. Therefore the strategic IMS sounds appropriate in providing animals **with additional minerals at the time they need the most.**

Conclusion

IMS is an additional source of minerals, which complement dietary sources and oral daily supplementation. It helps overcoming periods of lower trace mineral supply, lower intake, increasing needs or unavoidable dietary antagonists. **In addition, there is a growing body of evidence that strategic IMS results in a better control of the mineral status across critical periods and helps animals to perform optimally,** talking about production (meat, milk, wool), reproduction, growth, and resistance to production diseases (technopathies).

Critical periods of the production cycle

The life and production cycle of farm animals goes through successive natural, artificial and exceptional circumstances which require a fast adaptation to new living and environmental conditions. Animals deal with these events more or less easily, and animals transition from a steady state to another through critical periods, or transition periods, where homeostasis is maintained at the expense of body reserves in nutrients, the energy balance, and secondary functions, such as the immune system or reproduction. Animal products (food studs, work force, wool) which is the part that can be harvested over the physiological needs are also compromised. The existence and consequences of critical periods are widely substantiated, and they cannot be ignored any longer.

Critical periods are now interpreted as periods of the life cycle where the redox balance is at risk, resulting in an excessive production of free radicals and other pro-oxidant compounds which presence affect the normal cellular activity.

Critical periods include birth, weaning, parturition, periods of intense metabolism such as lactation, fast growth, pregnancy. These periods are associated with an increased output (milk, meat, wool) and they are commonly associated with a compromised appetite and low feed intake. Natural events also included periods of harsh environmental conditions (heat waves).

In the definition of critical periods, we can also include all conditions associated with a serious inflammatory process, infectious disease, although it is unclear still whether the oxidative stress is the consequence of the disease or the redox imbalance the cause. Routine procedures such as vaccination and marking can be considered as critical events since they can temporarily result in reduced feed intake.

Therefore, the critical period refers to the imbalance of the redox balance, and evokes hazards that can arise from these periods. They can be also called periods of high demand, notably in minerals. This phrasing refers to nutritional aspects, and raises the point of supplementation beyond the dietary recommendations. It is generally admitted that IMS shortly before critical events is likely to be beneficial.

An overarching concept: Oxidative stress

The study of redox biology in veterinary medicine is still in the early stages of development, but recent works have shown that oxidative stress (OS), or the imbalance in fundamental oxidation-reduction processes, is associated with numerous adverse health conditions and diseases, providing greater understanding of the significance of Redox biology in ruminant health and production.

The Redox biology, and its dysregulation provide a new frame for the understanding of pathological processes. Therefore, the therapeutic improvement of the redox balance (so-called redox medicine) could be the next step, avoiding the oxidative status from drifting too much under the influence of pro-oxidant factors. In human medicine, redox medicine already plays a role in cancer, and metabolic or chronic inflammatory diseases to name a few. Nevertheless, in veterinary medicine and animal feeding practice, redox biology is recently being studied and the consequences of OS in animal production and health are constantly investigated and, although of inflationary use of the term, the OS is largely misunderstood.

Production of Reactive Oxygen Species (ROS) and other free radicals is a natural process that occurs in many circumstances. Production of ROS is a critical part of the redox biology and not all oxygen metabolites are adverse. Their major role most likely resides in the use of low-level exposure in redox signaling and redox regulation, termed oxidative eustress, whereas higher burden leads to oxidative damage to bio-molecules, oxidative distress or simply oxidative stress.

ROS and free radicals are termed pro-oxidants. OS is a condition that occurs when the production of pro-oxidants exceeds the capacity of the organism to neutralize these compounds, thanks to anti-oxidants, resulting in oxidative damage to lipids, DNA, proteins, and other macromolecules.

The control of excessive production of free radicals is therefore the base of redox medicine. Among antioxidants, enzymatic compounds play a prominent role in the control of OS. The therapeutic intervention can then be seen as a way to lift the limits to the synthesis of these enzymes, or even accelerate their synthesis or their activity. Little is known in veterinary medicine about the way to influence the activity of enzymatic anti-oxidants.

Taking over the redox imbalance raises the question of the diagnostic. Appropriate biomarkers that univocally depict the OS status, cell damage, level of pro-oxidants, etc, remain to be described and popularised. Current biological tests on trace mineral concentrations in liver biopsies, or enzyme activity in the serum provide a quick look at the antioxidant capacity of animals. Among new interesting biomarkers, peroxidation of lipids is an interesting target because phospholipids are the first target of the OS. Prostaglandine-like isoprostane as well as PGE2 level could be regarded as promising indexes of OS. Eventually all of this can combine into an Oxidative Stress Index that could help the clinician. Identification of a consensual set of biomarkers would ease implementing the practice of redox biology in veterinary medicine.

The synergistic role of trace minerals

Control of excessive production of pro-oxidants through a complex machinery of enzymatic and non-enzymatic compounds is a critical part of redox biology. An antioxidant is defined as any substance that significantly delays or inhibits oxidation of oxidisable substrates, which basically include every organic molecule found in vivo. Enzymatic antioxidants play a frontline role in detoxification of free radicals.

All cells in eukaryotic organisms contain powerful antioxidant enzymes. The three major classes of antioxidant enzymes are the superoxide dismutases (SOD), the selenoenzyme family, especially glutathione peroxidase (GSH-Px), and the catalases. They all are trace mineral-dependant proteins.

SOD are some of the most efficient antioxidants and are considered to be the first line of defence against an oxidative challenge. Three different SOD isoforms have been identified: two with Cu and Zn at their catalytic sites, localised either in the cytoplasm or extracellularly, and one with Mn as a cofactor, which is localised in the mitochondria. The trace minerals Cu, Zn and Mn are essential to the normal functioning of these enzymes.

GSH-Px is a family of numerous related proteins. Those Se-dependent antioxidant enzymes are the most widely studied with respect to ruminant reproduction, health and productivity. It is universally recognised that GSH-Px cannot be replaced by any other selenoprotein to protect against generalised oxidative stress, and that GSH-Px has a primary antioxidant function in vivo. Many of the beneficial health effects of Se are mediated by antioxidant selenoenzymes, and cytosolic GSH-Px is the selenoenzyme most often associated with antioxidant function in cattle and sheep.

Catalases are a remarkably large family of compounds found in aerobic organisms. In animals, most catalases have a ferric protoporphyrin, which is similar to the prosthetic group in haemoglobin, at their active centre.

Therefore, Se, Cu, Zn and Mn participate in independent but complementary or cascading antioxidant systems. Consequently , their joint contribution helps mitigating the redox imbalance, and the lack of one of them reduces the overall efficacy of the system. Metal-based antioxidant enzymes act synergistically to some extent, and the concurrent administration of several minerals is expected to enhance the total antioxidant capacity through the potentiation of antioxydant metalo-enzymes.


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Supplying minerals to animals by injection

The IMS is a method of mineral supplementation that complements oral supplies, dietary supply (feedstuff), and supplementation (mineral mix, mineral blocks, rumen reticulum bolus, etc). IMS has unique features that ensure that all targeted animals are dosed with a fixed dose of selected minerals and timed injection.

Appropriate dietary mineral supplementation can be calculated by animal nutritionists according to national/international recommendations, and from the mineral content of feed, which is generally estimated from published data, rarely from analysis. Calculation does not take in account the seasonality of the green fodder, changes in the vegetative phase of plant development, presence of antagonists in the feed, and fluctuations in the stational geochemistry. The situation is particularly critical in tropical countries such as southern Africa and Australia. In addition, trace mineral supplements should be tailored to the specific farm needs and should involve minerals with a high biodisponibility. Inorganic salts, such as sulphates, carbonates, chlorides, and oxides, are compounds commonly used as mineral supplements. These salts form free ions which are both readily absorbed and react easily with other dietary molecules, then impairing the absorption. Large quantities of undigested minerals are then excreted and cause environmental pollution.Therefore, the management of oral supplementation remains a question mark. There is a significant discrepancy between what is calculated, what is actually fed to animals, and what is ingested. Also, what is in soils cannot help predicting what will be in plants and forages, and what is in pastures does not reflect what reaches animals eventually. Finally, respectless of the nutritional status of target animals, IMS is almost always advisable, at least for grazing areas of the intertropical band.

In a critical situation or a situation which requires a quick restoration of the mineral status animals, it is advisable to use IMS. This strategy ensures that all animals that need it receive the correct dose of minerals, the same dosage, at the same time. Finally, provided that minerals are given in a bioavailable form, IMS allows a rapid restoration of body reserves.

ITM supplementation is particularly beneficial to:

- grazing animals, fed on green fodder with little or no concentrates at all. Content in minerals fluctuates and the presence of mineral antagonists is not quantifiable, when it is known. Pastures do not benefit from fertilisation, or fertilisation is recommended on very general bases.
- animals/herds under organic management, because of the restriction of use of plant fertilizers.
- all ruminant operations where it is not possible to analyse all minerals in the diet.
- all small / medium-size operations where it is not possible to set groups of animals fed on a specific diet that matches evolving physiological requirements.

Finally, thanks to its finely-tuned formulation nature, blanket injectable mineral supplementation results in low dose of minerals spread across the environment, and contributes to lowering the ‘mineral footprint’ of farm animals, an issue that should emerge in the years to come.

Medical benefits of injectable mineral supplementation

The OS (OS-eustress) is part of many natural processes critical to life. Excessive free radical production (OS-distress) hampers the functioning of many metabolic pathways, then impairs the performance of body systems and organs. Through antioxidant metalloenzymes, trace elements play an important role in the modulation of the redox balance and prevent it from dangerously drifting to OS. In this sense, ITM may contribute to preventing disorders related to excessive free radical production or OS during high demand periods of the life cycle of production animals.

The described medical benefits raise several questions. Indications related to the resistance of animals to diseases in general, and the improvement of zootechnical performances particularly. It is perilous to say that IMS is always beneficial and can be recommended in all circumstances. Every medical indication must be substantiated specifically. Identification of target animals raises the point of the collective nature of IMS cannot be ignored because we are not talking about individual on-demand supplementation, based on a diagnosis, but group preventive therapy. Depending on circumstances, IMS can be regarded as a prophylactic intervention (supply of minerals before animals need it) or metaphylactic response (need is identified on a subset of animals). Consequently, the timing of IMS refers to as the critical periods of the life cycle. IMS is a treatment given to a group of animals, regardless of their mineral status, before a critical period of their productive life. We assume that critical periods are common to all animals in the same category, then IMS is both prophylactic and collective.

The remaining points are the identification of treatment periods and the assessment of health or production effects. Research has shown that even animals with an adequate trace mineral status can temporarily transition into a suboptimal state due to increased demand during critical stages of production or reproduction. Regardless of the cause, these losses can easily go unnoticed as they do not usually present obvious clinical signs, but they can still have a significant effect on key profit drivers on the farm. An extensive and rapidly expanding list of peer-reviewed literature demonstrates the beneficial effect of strategically timed trace mineral supply on financially important aspects of livestock production.

Although further research is still needed, a solid body of empirical studies have already demonstrated the impact of IMS in maintaining correct immune system functioning. In cows, IMS in late pregnancy generally results in a better health status during the transition period and early lactation, including mastitis. It also influences the mineral status of the newborn through the transfer to the foetus in the last weeks of pregnancy, and the enrichment of the colostrum. In recent research, IMS at the time of vaccination enhances the immune response, after vaccination and after a subsequent challenge.

Application of IMS to cows before insemination or at the time of the initiation of fixed-timed artificial insemination (FTAI) also results in an improved conception rate and reduced embryonic mortality. The calving pattern is improved in block calving herds. In bulls, optimum redox status and trace minerals are required to complete the maturation processes of spermatozoa. Application of IMS, between 8-4 weeks for females and between 12 and 8 weeks for males, before the beginning of the mating season contributes to improved conception rates and sperm quality as a consequence of improved embryo survival and less spermatozoa defects and a better motility.

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