Review: Implication of redox imbalance in animal health and performance at critical periods, insights from different farm species

Denys Durand, Anne Collin, Elodie Merlot, Elisabeth Baéza, Laurence L.A. Guilloteau, Nathalie Le Floc'H, Thomas Armand, Stéphanie Fontagné-Dicharry, Florence Gondret

To cite this version:

Denys Durand, Anne Collin, Elodie Merlot, Elisabeth Baéza, Laurence L.A. Guilloteau, et al.. Review: Implication of redox imbalance in animal health and performance at critical periods, insights from different farm species. Animal, 2022, 16 (6), pp.100543. 10.1016/j.animal.2022.100543 . hal-03681823

HAL Id: hal-03681823
https://hal.inrae.fr/hal-03681823

Submitted on 22 Jul 2024

Review: Implication of redox imbalance in animal health and performance at critical periods, insights from different farm species

D. Durand [a], A. Collin [b], E. Merlot [c], E. Baéza [b], L. A. Guilloteau [b], N. Le Floc'h [c], A. Thomas [a], S. Fontagné-Dicharry [d], F. Gondret [c]

[a] *INRAE, Université Clermont Auvergne, VetAgro Sup, UMR Herbivores, 63122 Saint-Genès-Champanelle, France*

[b] *INRAE, Université de Tours, BOA, 37380 Nouzilly, France*

[c] *PEGASE, INRAE, Institut Agro, 35590 Saint-Gilles, France*

[d] *INRAE, Université de Pau et des Pays de l'Adour, E2S UPPA, NUMEA, 64310, Saint-Pée-sur-Nivelle, France*

Corresponding author: Denys Durand, denis.durand@inrae.fr

Abstract

The process of oxidative stress occurs all over the production chain of animals and food products. This review summarizes insights obtained in different farm species (pigs, ruminants, poultry, and fishes) to underpin the most critical periods for the venue of oxidative stress, namely birth/hatching and weaning/start-feeding phase. Common responses between species are also unravelled in periods of high physiological demands when animals are facing dietary deficiencies in specific nutrients, suggesting that nutritional recommendations must consider the modulation of responses to oxidative stress for optimizing production performance and quality of food products. These conditions concern challenges such as heat stress, social stress, and inflammation. The magnitude of the responses is partly dependent on the prior experience of the animals before the challenge, reinforcing the importance of nutrition and other management practices during early periods to promote the development of antioxidant reserves in the animal. When these practices also improved performance and health of the animal, this further confirms the central role played by oxidative stress in physiologically and environmentally-induced perturbations. Difficulties in interpreting responses to oxidative stress arise from the fact that the indicators are only partly shared between studies, and their modulations may also be challenge-specific. A consensus about the best indicators to assess pro-oxidative and antioxidant pathways is of huge demand to propose a synthetic index measurable in a non-invasive way and interpretable along the productive life of the animals.

Keywords: Oxidative stress, Physiological transition, Inflammation, Challenge, Animal performance.

Implications

The agro-ecological transition in farming practices stimulates natural processes in biological systems. Oxidative stress is considered as a pivotal mechanism underlying the adaptation of animals to management practices and acclimation to environmental constraints. This reinforces the importance of monitoring and understanding the responses to pro-oxidant challenges in farm animals. An overview in different farm species from different ecosystems (terrestrial, aquatic) may be helpful to obtain a consensus on the best biomarkers to measure the redox status and evaluate and propose management practices able to limit the short and long-term consequences of oxidative stress on animal performance, health and welfare.

Introduction

Farm animals are facing many environmental conditions and constraints that challenge their physiology during their whole productive life. Oxidative stress has emerged as an important issue to explain dis-adaptation and dysfunctions (Abuelo et al., 2019) leading to impaired survival, bad production performance or compromised health and immunity (Al-Gubory et al., 2010). Oxidative stress arises from the imbalance between the production of reactive oxygen species (**ROS**) and the neutralizing capacity of the antioxidant system. The ROS family includes free radicals which are often small and diffusible molecules with one or more unpaired electrons (peroxides, superoxide, hydroxyl radical) and no-radical molecules (hydrogen peroxide, peroxinitrite, etc.) which are by-products of the metabolism of oxygen in animal cells. The ROS have beneficial effects for many biological processes such as stem cell differentiation, lineage commitment, self-renewal and cell homeostasis (Ren et al., 2015), because they act as signals inside and between cells to regulate gene expressions involved in cell development and growth (Dalton et al., 2002). However, exaggerated and even uncontrolled ROS production induces oxidative damage to proteins, lipids and DNA, and results in the deterioration of cellular structure and functions, and even cell death. Damaged and destroyed macro-biomolecules can also trigger inflammatory responses as a starting point of altered health. Both enzymatic and non-enzymatic molecules produced by the animal (uric acid, glutathione **GSH**) or brought by the diet (vitamins E and C, carotenoids, flavonoids, polyphenols, selenium, zinc) act as antioxidants to prevent or repair the oxidative damages. Oxidative stress is then defined as a distress situation corresponding to an overexposure to oxidants which results in non-specific oxidation of biomolecules and disruption of redox signalling (Sies and Jones, 2020). This can induce transient or permanent perturbations which generate physiological consequences within the cells and at the whole animal level (Pignatelli et al., 2018).

A better knowledge of the critical periods when exaggerated ROS production occurs and(or) elements in the antioxidant defence system are lacking, is required in farm animals to pay attention on aggravating events during these periods, with the objectives to limit consequences on production performance, health, and welfare. This review enlightens critical periods for the venue of oxidative stress in different farm species, including mammals and oviparous species living in terrestrial or aquatic environments. Detailed mechanisms underlying oxidative issue for a given species can be found in other reviews (Lushchak, 2011; Birnie-Gauvin et al., 2017; Chowdhury and Saikia, 2020; Hoseinifar et al., 2021). However, enlightening common or specific responses across species may allow a better anticipation of the risk events for each species when the conventional management practices must evolve to cope with climatic pressure and environmental or societal expectations. For instance, quality issues for all species can be foreseen when considering meat quality degradation of broilers due at least in part to the physiological challenge imposed by rapid growth on oxidative metabolism. Pastoral ruminant systems can provide examples for risks underlying outdoor productions in pigs or other species. Inter-species comparison in the modulation of pro- and antioxidant molecules and its relationships with variations of performance and health may also underpin the best indicators (when, how, what, where, frequency) to monitor oxidative stress in farm animals.

Critical physiological transition periods in early life

Physiological transition periods are associated with many obligatory changes in types of nutrients, environmental temperature, physical activity, etc..,. These induce many metabolic changes in cell physiology, notably for mitochondria responsible for energy production and controlling many processes from signalling to cell death (Salin et al., 2015; Bottje, 2019).

Birth or hatching and start-feeding phases

Birth in mammals is the most striking shared period for the venue of acute oxidative stress, due to the abrupt switch from a fetal environment with a lower oxygen supply (maternal-mediated respiration in the uterus) than that after birth (autonomous pulmonary respiration). Whereas hypoxia is necessary for the development and growth of the fetus, the aerobic metabolism is needed to efficiently provide enough energy for the newborn to ensure survival and development (Morton and Brodsky, 2016). This switch is obligatory associated with large amounts of ROS generated by the neonatal cells (Friel et al., 2004). This period is also concomitant with a transition in gut activity from amniotic fluid to colostrum feeding, which is another source of oxidative stress (Osorio, 2020; Rosa et al., 2021). In oviparous species, many similarities at hatching are found with these events at birth. In poultry where the embryo derives nutrient requirements from the egg, changes in oxygen availability and nutrition at hatching also induce alterations in the redox status. The role of oxygen in the venue of oxidative stress was proved by the fact that hypoxia/re-oxygenation protocol to pre-hatching ducklings resulted in a higher susceptibility to ROS monitored in red blood cells of these animals (Rey et al., 2010). In situation of aqueous life for fishes, the hatching period is also critical but this is likely more due to the nutritional transition and the dramatic morphological changes in the larvae which both increase the energy demand at this moment, than due to changes in oxygen availability. A specificity of fish is also the high concentrations of long chain n-3 polyunsaturated fatty acids in feed and in animal tissues, which are thus particularly prone to oxidation. In the absence of a suitable antioxidant protection, lipid peroxidation in fish tissues due to the ingestion of oxidized feeds during the early developmental stages thus led to depressed growth and bad survival (Fontagné-Dicharry et al., 2014), inflammatory response (Fontagné-Dicharry et al., 2018) and various pathologies including muscular dystrophy (Boglione et al., 2013).

In all species, internal defence actors against ROS are prepared by the cells in before birth or hatching. For instance in pigs, proteins of the peroxiredoxins family were up-regulated with advancing gestational age in adipose tissue (Gondret et al., 2018). The global antioxidant capacity only slightly increases during the few days after birth, in a moment when plasma concentration of hydroperoxides dramatically increases (Buchet et al., 2017). This explains why newborns suffer from oxidative stress in the days after birth. With the gradual development of the antioxidant system, the oxidative balance can be recovered in 7 days after birth in pigs (Yin et al., 2013). Similarly, most neonatal calves are experiencing oxidative stress during the first few weeks of age (Abuelo et al., 2019). During the early developmental stages in fishes such as trout, the antioxidant protection rather relies on antioxidant vitamins in the earliest embryonic stages, and after first-feeding, of antioxidant enzymes (Fontagné et al., 2008). However, similarly to mammals, the endogenous antioxidant defence system is not fully responsive, leading to pronounced lipid peroxidation when oxidized feed is ingested during this period (Fontagné-Dicharry et al., 2014).

Importantly, the consequences of the redox imbalance during the first days after birth or hatching are more detrimental in situations where prior tissue development is impaired. In pigs, intrauterine growth restriction, a common feature observed in a subset of littermates for sows selected for high prolificacy, was associated with impaired mitochondrial biogenesis and energy homeostasis and with greater hepatic malondialdehyde (**MDA**) concentration, a marker of lipid peroxidation (Zhang et al., 2017). Depressed levels of proteins that regulate oxidative defence and increased levels of proteins involved in the response to oxidative stress have been reported by proteomic studies on intestine, liver and muscle from intrauterine growth retarded piglets (Wang et al., 2008). This means that a particular attention must be paid on stimulating the antioxidant capacities of piglets during the perinatal period, and especially those of the lightest weight. In ruminants, suboptimal intrauterine conditions can similarly affect the foetus (Abuelo et al., 2019). As compared with single foetuses, twinning in ewes led to intrauterine growth restriction, and this was associated with higher oxidative stress monitored in the cord blood (Sales et al., 2018). Artificial feeding after birth to compensate for an insufficient milk production by the ewe in the large litters, further depressed the antioxidant capacity of the lambs when compared with those fed by their mothers, together with other negative indicators of animal health and welfare (Mialon et al., 2021). In poultry, oxidative stress was also increased by management practices before hatch. For instance, egg storage longer than 7 days, which is a common practice in farms for logistical reasons, negatively influenced the embryonic development and resulted in early embryonic mortality and lower hatchability (Fasenko, 2007; Pokhrel et al., 2018). Long egg storage influenced the redox balance, as illustrated by the lower total antioxidant status (**TAS**) in serum (Pertusa et al., 2017) and greater MDA concentrations in the serum and yolk sac (Yang et al., 2020). After hatching, birds have to cope with specific husbandry conditions and transports. Delayed placement in hatchery resulted in an increase in lipid peroxidation as proved by higher thiobarbituric acid reactive substances (**TBARS**) in blood and the liver (Foury et al., 2020), and negatively affected animal performance (Guilloteau et al., 2019). This dis-adaptive oxidative profile was also manifested by altered concentrations in metabolites involved in the antioxidant status and energy metabolism in the fecal metabolome, until at least 13 days after the delayed placement (Beauclercq et al., 2019). Whereas no difference was detected in the redox balance indicators in blood at this time and later in age (Beauclercq et al., 2019; Foury et al, 2020), expression levels of various genes involved in oxidative stress (such as the transcription factors *NFE2L2* and *MEF2A*) were modified. The differences were accentuated for males, which have a lower systemic anti-oxidative activity including lower uric acid concentration, TAS and ferric reducing ability of plasma (**FRAP**) than females.

Altogether, these comparisons between species not only underline birth or hatching as a critical period for the venue of oxidative stress, but they also reveal how selection for reproduction traits and practices to manage it, further accentuate the redox imbalance and consequences in the young animals. Besides identifying these risk factors, possibilities during prenatal/pre-hatching periods may be shared in the different species to sustain the development of antioxidant capacities of animal tissues, and thereby to preserve health. Because intrauterine growth restricted piglets and lambs serve as animal models for a better understanding of the development of the human embryo and complication of pregnancy, there is a considerable literature dealing with orally-treated pups to correct oxidative stress soon after birth. Neonatal formula rich in proteins have been tested to accelerate growth recovery, with consequences in the abundance of redox proteins such as peroxiredoxins, glutathione S-transferase and cyclophilin-A in tissues of growing intrauterine growth restricted piglets (Sarr et al., 2012). In pigs and ruminants as in Humans (Manuelian et al., 2021; Fardet and Chardigny, 2013), other tested solutions include specific aminoacids with antioxidant and functional properties, and plants extracts rich in lipotropic and antioxidant compounds to improve antioxidant capacities during the postnatal period. Dietary antioxidant supplementations than can routinely be used in farms, have been also tested for gestating and lactating females to improve the redox status of their young (Abuelo et al., 2019). However, effects are not always conclusive, depending on the level and timing of supplementation and on the active principles tested. Reducing maternal stress may also have beneficial consequences on oxidative stress in the female and the young (Merlot et al., 2019; see section 5.1). In laying hens, supplying diets with exogenous antioxidants such as vitamin E, has positive effects on antioxidant status of the egg yolks and newly hatched chicks (Yang et al., 2020), showing again the benefit of preparing antioxidant defence through the nutrition of the female. Supplementation of broiler feeds with herbal plant extract like *Melissa officinalis L.* also has beneficial effects on the redox balance, with improved performance during the growth phase and different health effects (Travel et al., 2021). The antioxidant defence system during the early developmental stages in fish can be also sustained by supplementing diets of the broodstock with aminoacids such as methionine (Fontagné-Dicharry et al., 2017) and with selenium (Wischhusen et al., 2019). If the parental selenium supplementation can improve antioxidant status and performance of the progeny, this may however induce a lower stress resistance in the longer term (Wischhusen et al., 2020a) due to alteration of the Methionine cycle and epigenetic changes (Wischhusen et al., 2020b). Therefore, any strategies for parental feeding must be investigated at short and long term before definitive recommendations can be formulated.

Juvenile transitions

Other critical periods for the venue of oxidative stress occur later in the development, when physiological transitions are abruptly imposed to the young animals (Table 2). In these situations, oxidative stress is more likely the consequence of systemic inflammation rather than the cause of systemic disorders. Indeed, in conventional farming systems for pigs and dairy calves, weaning is lived as the abrupt separation from the mother, and this is also associated with a dietary switch from milk to solid feeds rich in plant raw materials. Weaning may generate immune and inflammatory responses that can reach a systemic dimension (McCracken et al., 1999; Gilbert et al., 2019). For instance, intestinal dysfunction is often observed just after weaning and it is clearly associated with inflammatory response and oxidative stress at both the systemic and intestinal levels, which are manifested by changes in the expression levels of cytokines and antioxidant enzymes together with increased concentrations of lipid oxidation markers in pigs (Zhou et al., 2018). In pigs, hydroperoxides concentrations increased whereas the blood antioxidant potential (**BAP**) decreased during the days just after weaning, leading an increase in the oxidative stress index (hydroperoxides / BAP ratio) between 5 and 12 days after weaning (Buchet et al., 2017). Other redox indicators such as plasma MDA, FRAP and erythrocyte GSH content indicate that consequences of oxidative stress may last at least 28 days after weaning (Degroot et al., 2020). The local and systemic inflammatory responses are probably the main cause of the production of oxidation products during the days after weaning. In support, oxidative stress was higher in piglets with post-weaning diarrhoea than in those with no diarrhea (Buchet et al., 2017). Importantly, antioxidant defence and clearance of dysfunctional mitochondria at weaning were more compromised in intrauterine growth restricted piglets than in their normal littermates (Novais et al., 2021), reinforcing the importance of prenatal events in the adaptation capacity to postnatal challenges. Indicators of oxidative stress were also observed in the exhaled breath condensate in calves soon after weaning. Indeed, oxidative stress may result from respiratory infections due to stress-induced alterations in the immune function at this moment (Ranade et al., 2014). In both species, another cause of oxidative stress may be the anorexia observed during the first days after weaning. Anorexia reduces the intake of all nutrients, and among them, of those with antioxidant properties at the time when their use is precisely needed to neutralize the oxidative products generated by inflammation (Amazan et al., 2012). For instance in pigs, blood concentration of vitamin E declined sharply, and to a lesser extent, that of vitamin A (Buchet et al., 2017) in the days following weaning.

Even if oxidative stress might be the consequence rather than the cause of stress and disorders observed just after weaning, it is important to improve antioxidant defence before weaning to limit the post-weaning alterations of performance. Indeed, piglets whose growth was the less affected during the 3 weeks following weaning in commercial farms, were those whose oxidative stress increased the least, and for which blood vitamin E concentration before weaning was the highest (Buchet et al., 2017). Moreover, the oxidative status of piglets was improved thanks to the reduction of hydroperoxides concentration in the blood when the starter diet included a premix combining vitamins E, A, C, polyphenols and trace elements such as zinc and selenium, and this was associated with increased post-weaning growth rate of the supplemented piglets (Robert et al., 2009). In calves, parenteral supplementation of minerals and vitamins with antioxidant effects also prevented the decrease in variables related to the immune system, improved antibody responses and had positive effects on BW (Mattioli et al., 2020). Moreover, monitoring changes in salivary biomarkers of anti-oxidant capacity, such as Trolox equivalent antioxidant capacity (**TEAC**), FRAP and cupric ion reducing antioxidant capacity (**Cuprac**), seems a promising approach to characterize stressful conditions in calves at weaning (Rubio et al., 2021). These examples in the two species suggest that robustness of an animal might be associated, at least in part, with its own ability to limit oxidative stress. In support to this assumption, later in growth, it was observed that BAP as an antioxidant measure in plasma combined with circulating concentrations of metabolic and immune indicators provided an animal-centred index to predict the extent of reduction in growth rate when growing pigs are facing sanitary (inflammatory) challenges (Le Floc'h et al., 2021).

Challenges during rearing periods

Physiological challenge: the pro-oxidant effects of high growth rate

Since many decades, farm animals have been selected for productive performance, such as growth rate and yield of edible products (meat or flesh, eggs, milk) which are high-nutrient-demanding processes. At the cellular level, ROS generation takes place at the electron transport chain during the process of oxidative phosphorylation, so that ROS are normal by-products of mitochondrial metabolism associated to energy production. Any increase in cellular metabolism that generates greater energy and oxygen demands would then increase the activity of the mitochondrial respiratory chain and the production of ROS. This suggests that accelerated growth rate would be obligatory associated with accentuated risks for oxidative stress. In support, plasma concentrations of hydroperoxides continuously increased in growing pigs (Buchet et al., 2017). In addition, fast-growing lines and breeds have a deteriorated redox status when compared with slow-growing lines or breeds (Brambilla et al., 2002; Merlot et al., 2012). However, no particular diseases are observed in these situations, although high selected breeds are suggested to be less robust than unselected breeds. On the opposite, the extraordinary achievements of selection for fast growth rate and high breast meat yield in poultry resulted in the apparition of spontaneous myopathies (white striping, wooden breast, spaghetti muscles) in broilers and turkeys (Petracci et al., 2015). In these situations, the breast muscle of the chickens displayed inflammation and oxidative stress (Baéza et al., 2018; Petracci et al., 2019), as revealed by greater levels of lipids (MDA content) and proteins (carbonyls content) oxidation products (Soglia et al., 2016; Baldi et al., 2018). When compared with normal muscles, they also had lower contents in anserine and carnosine, two dipeptides having antioxidant effects (Sundekilde et al., 2017). Comparison between species thus suggests the existence of a physiological limit after which any improvement of growth rate would have detrimental effects on health.

Studies dealing with lines selected for residual feed intake, a measure of feed efficiency, provide more insights on the role of mitochondrial functionalities in managing the balance between oxidative products and antioxidants in animals selected for production performance. In pigs, the protein profile of mitochondria isolated from skeletal muscle in the low residual feed intake pigs (the more efficient) indicated an increase in anti-oxidant defence capacity as compared with high residual feed intake pigs (Grubbs et al., 2017). In good hygiene housing conditions, low residual feed intake pigs have lower antioxidant enzymes activities such as the glutathione reductase and catalase in adipose tissue and superoxide dismutase in muscle, and when reared in degraded hygiene conditions inducing an inflammatory response, the low residual feed intake pigs produced lower ROS than the high residual feed intake pigs (Sierzant et al., 2019). Similarly, low residual feed intake bulls (more efficient) had a lower antioxidant activity in the liver, which is interpreted as the consequence of a lower ROS production in those animals as compared with high residual feed intake bulls (McKenna et al., 2021). Taken together, mitochondrial functionality can modify the venue of oxidative stress, so that there is no absolute relationships high production performance and the venue of oxidative stress.

Dietary challenges: beyond the role of nutrients in growth performance

Due to the close relationships between nutrient use for cellular energy production, oxidative phosphorylation and the oxido-reduction metabolism, any deficiency or excess in macro- and micro-nutrients can generate an imbalance between ROS production and antioxidant defense in tissues. The roles of the sulfur-containing aminoacids such as methionine (Table 3) and cysteine have been particularly examined. Indeed, these aminoacids are limiting for growth and lactation performance due to their involvement in protein synthesis in the different species, and considering that most forages and soybean meal have a low content in methionine. In aquaculture, plant ingredients included in aqua-feeds to reduce the use of ingredients derived from feed grade fisheries (i.e., fishmeal and fish oil) also contain less micronutrients such as methionine. Importantly, these aminoacids can directly modulate the redox status of animal tissues due to their involvement in the synthesis of GSH and taurine, two cellular compounds with antioxidant properties.

In growing pigs, dietary methionine deficiency reduced the GSH content in the muscle and liver, increased the enzymatic antioxidant activities in muscle and adipose tissues, and lowered the total anti-oxidant power (FRAP and 1,1-diphényl-2-picrylhydrazyl) in plasma (Castellano et al., 2015; Conde-Aguilera et al., 2020). Conversely, feeding finishing pigs with extra dietary methionine supply above growth requirements increased the muscle content in total GSH and dipeptides with antioxidant properties such as anserine, but without any changes in the antioxidant enzyme activities in muscle (Lebret et al., 2018; Gondret et al., 2021). In addition, the lower TBARS values generated during a forced oxidation kinetics in muscle of pigs fed extra methionine supply further indicated lower oxidative stress in those pigs (Lebret et al., 2018). In ruminants, a rumen-protected form of methionine may be supplemented to the diet which is of special interest for improving performance of high-yielding dairy cows and liver metabolism (Durand et al., 1992; Bauchart et al., 1998). However, in growing bulls receiving high forage diet supplemented by methionine (Cantalapiedra et al., 2020), there was no improvement in endogenous antioxidants nor changes in the systemic redox status (Durand Denys, unpublished data). In broilers, suboptimum supply of Methionine also resulted in lower antioxidant concentrations in plasma and body tissues. However, although a higher content in GSH in the liver was observed with increased methionine concentrations in the diet (Conde-Aguilera et al., 2016), liver concentrations of TBARS and protein carbonyls were not responsive to dietary methionine concentration (Zeitz et al., 2018).

In various fish species at different life stages, dietary methionine deficiency was also associated with an imbalance between oxidative products and antioxidants, with a decrease in GSH to oxidized gluthatione (**GSSG**) ratio and an increase in lipid peroxidation and protein oxidation observed in rainbow trout juveniles and in the fry fed a deficient methionine diet for 12 weeks (Fontagné-Dicharry Stéphanie, unpublished data). These changes were associated with higher expression levels of genes coding for the antioxidant enzyme glutathione S-transferase π, and for the tumor necrosis factor, a pro-inflammatory cytokine, in the flesh (Alami-Durante et al., 2018). Expression levels of genes coding for antioxidants such as glutathione S-transferase π, glutathione reductase and methionine sulfoxide reductase A1, were induced either directly by dietary methionine deficiency in the liver of the broodstock and in whole fry, or indirectly by the parental methionine intake as observed in the swim-up fry. Long-lasting parental effects of broodstock methionine-intake were observed in the fry, 21 days after first-feeding and irrespective of the fry diet, for the genes coding for methionine sulfoxide reductases A1 and B2 and superoxide dismutase 2 (Fontagné-Dicharry et al., 2017). However, in some studies, dietary methionine deficiency in rainbow trout juveniles decreased rather than increased carbonyls and GSH. This may be due to the sharp increase in mitochondrial degradation through mitophagy which decreased ROS production (Séité et al., 2018). Similarly, feeding extra methionine decreased protein oxidation in rainbow trout juveniles but increased lipid peroxidation and antioxidant genes expression in rainbow trout fry (Fontagné-Dicharry Stéphanie, unpublished data). Discrepancies between studies may be related to the specific needs in methionine depending of age and growth period of the trout.

These experiments illustrate the potential of dietary aminoacid contents for modulating oxidative stress in farm species, and further suggest that nutritional recommendations could be revised to better account for the effects on redox status and not only on growth requirements. Other imbalanced feeding conditions such as glycemic index and balance in polyunsatured fatty acids (n-6 /n-3), can be also concerned, but are not detailed in this review.

Environmental challenges

The environment in which farm animals are reared is subjected to uncontrolled events that tackle the animal physiology. Different situations can be encountered in farm animals.

Maybe not enough considered, the level of oxygen in the environment is of importance due to its role in the venue of oxidative stress. Hypoxia occurs in most aquatic environments, especially those with a high stocking density. In rainbow trout juveniles, chronic hypoxia reduced blood GSH content and increased hepatic activity and transcript expression of the antioxidant enzyme catalase (Fontagné-Dicharry et al., 2020). Acute hypoxic challenge also induced oxidative stress with increased lipid peroxidation and glutathione disulfide content and transcriptional regulation of antioxidant enzymes in rainbow trout fry (Wischhusen et al., 2020a). Water oxygenation is thus a common recommended practice in aquaculture systems. However, if not adequate, it can conversely lead to hyperoxia that also induced physiological stress responses, characterized by a higher TBARS content in flesh and lower antioxidant enzyme activities in the liver of rainbow trout juveniles (Kalinowski et al., 2019). The situation in fish may question the consequences of inadequate oxygen supply in terrestrial species. Although rare, this may concern extensive farming systems in hard mountain conditions (cows or sheep) and poultry houses in altitude. Differences in oxygen availability to tissues can also be due to external and inner events. In poultry, ascites is a frequent metabolic disorder manifested by the abnormal build-up of fluid in the peritoneal spaces, which can be induced by several factors such as continuous light, insufficient ventilation in the poultry house, high altitude and cold environment (Decuypere et al., 2000). Ascites is caused by an imbalance between the oxygen requirement of tissues and the oxygen supply to tissues. In addition, lipid peroxidation further played an important role in the pathogenesis of pulmonary hypertension associated with ascites, since free radicals led to endothelial damage in both heart and lung cells (Aksit et al., 2008). Controlling the early chick embryo environment may be a way to avoid these oxidative damage. The use of cold temperatures during egg incubation was proven to limit cold sensitivity later in age and the incidence of ascites (Shinder et al., 2011). Furthermore, chicks exposed to cyclically cold incubation temperatures exhibited increased antioxidant capacity, such as 8-fold higher catalase activity in the liver at hatch as compared to control-incubated chicks (Loyau et al. 2014).

Due to relationships between environmental availability of oxygen and heat tolerance of the animals, it is also of interest to consider the effects of heat stress on redox status of the animals. Considering the global warming, severity and frequencies of heat waves will be more frequent in the coming years, which further justifies to undergo specific studies to investigate the effects of chronic heat stress on oxidative stress in farm species. As examples, the effects of heat stress on different indicators of oxidative stress have been characterized in chicken and laying hens (Lin et al., 2006; 2008). In laying hens, a moderate heat exposure (32°C during 21 days) at the end of the laying period (60 weeks) increased ROS concentration in blood during heat exposure, and triggered blood antioxidants, on a temporary basis (superoxide dismutase activity) or during the whole period (FRAP) (Lin et al., 2008). In meat type chicken, acute heat stress also led to an increase in TBARS concentrations in the liver but not in the heart (Lin et al., 2006). Solutions to mitigate oxidative stress due to heat conditions can reside in improving the long-term thermo-tolerance of the animals. In poultry, cyclic increases in incubation temperature of the eggs led to a better survival to acute heat exposure at 35-days of age in male chickens (Piestun et al., 2008), and this was associated with many changes in expression levels of genes involved in stress response and vascularization acting in tissue oxygenation (Loyau et al., 2016). These examples obtained in fishes and chicken underline the importance of environmental events in the venue of oxidative stress, and these events may be more frequent in the coming years and have wider effects on a large broad of farm systems, and especially those in loose and harsh conditions.

Pro-inflammatory and stressful conditions

Housing conditions

Poor hygiene conditions and the lack of respecting biosecurity recommendations have been clearly identified as risk factors for health of animals reared indoors. Poor hygiene conditions often induce a systemic inflammatory response due to carbon dioxide, ammonia, temperature and(or) bacterial pressure. Among other problems such as pulmonary diseases, the poor sanitisation levels have been associated with the generation of oxidative stress, as attested by a lower total antioxidant capacity in plasma (FRAP), greater plasma levels of hydroperoxides and an activation of antioxidant enzymes in tissues of growing pigs (Buchet et al., 2018; Sierzant et al., 2019). During reproduction, stressful housing situations can also generate oxidative stress. For example, moving young nulliparous sows from group-housing pens to individual crates increased salivary cortisol, and this was associated with an increased expression of oxidative stress enzymes in serum (Marco-Ramell et al., 2016). Greater plasma concentrations of hydroperoxides were also observed in sows housed in groups on concrete slatted floor during gestation when compared with sows housed in larger pens with deep straw litter favouring animal welfare (Merlot et al., 2019). After farrowing, the one-day old piglets born from the sows housed on concrete slatted floor have a lower blood antioxidant potential than piglets born from mothers that had been housed on straw (Quesnel et al., 2019). The cortisol whose secretion was increased in the group on concrete slatted floor, might play a role in this response, because studies in the avian species showed that glucocorticoids stimulated the production of oxidative products (Lin et al., 2004). In sheep, forced physical activity and transportation led to a higher cortisol concentration, an increase in the metabolism of carbohydrates and lipids; this resulted in the occurrence of oxidative stress proved by an increased MDA production and lower TAS (Gladine Cécile, unpublished data).

Self-medication behavior appears as an interesting strategy to reduce the consequences of production diseases. Self-medication has been defined as the ability of animals to select and use specific plants or substrates with medicinal properties to control or to prevent diseases or situations of discomfort. Self-medication is reported in ruminants which can consume plants associated with anti-parasitic properties to maintain health (Villalba et al, 2014). In cows and sheep, plant extracts rich in polyphenols, vitamin E or the combination of the two additives supplemented to n-3 polyunsaturated fatty acid-rich diets have been tested to reduce the oxidative stress induced by forced physical activity and transport. Although the dietary administration of polyphenols or Vit E did not prevent the induction of lipoperoxidation, the dietary administration of the two antioxidants reduced the increase in MDA production in sheep (Gladine Cécile, unpublished data). This synergic effect of the antioxidants cocktail has been confirmed in dairy cows (Gobert et al., 2009). This can be explain by the dual abilities of the lipophilic (vitamin E) and hydrophilic (polyphenols) antioxidant properties to break the lipoperoxidation chain and reduce the amounts in oxygenated radical species (Delosière et al., 2020). Plant extracts combined with vitamin E can be supplemented to polyunsaturated fatty acid-rich diets to limit oxidative stress in cull cows, even for pre-slaughter animal stress (Gobert et al., 2010; Delosière et al., 2020). Strategies based on self-medication in ruminants have been also tested in poultry. For instance, lame chickens have a preference for a feed supplemented with an anti-inflammatory and analgesic drug rather than the same feed without the drug

(Danbury et al, 2000) and chicks can adjust essential oil consumption after a delayed placement by uptake of lemon verbena essential oil, which is known to have antioxidant, anti-inflammatory, sedative, and digestive effects (Guilloteau et al., 2019).

Surgical procedures

Surgeries are used in farm animals at specific periods for castration, caesarian, visceral interventions, etc. For instance, during a high invasive surgery in sheep, although the antioxidant status estimated by TAS and the lipoperoxidation were not significantly altered, greater nitric oxide and lower GSH/GSSG ratio both indicated that the oxidation was triggered (Faure et al., 2017). To monitor the efficacy of drug-based pain alleviation protocols to surgeries, responses can be followed by using both behavioural and physiological indices. In addition to the most commonly used indicators (cortisol, haptoglobin, clinical signs), oxidative stress indicators are also well correlated with the efficacy of analgesia strategies. For instance, the multimodal analgesia (local anesthesia + non-steroidal anti-inflammatory drug) led to the lowest impact on redox status, thus limiting post-traumatic event (Durand et al., 2019). Painful procedures similarly induce changes in biochemical markers of oxidative stress (Ting et al., 2003), and of inflammation such as haptoglobin and serum amyloid A (Eckersall et al., 2001) in calves and lambs. Oxidative stress markers have also been proposed as relevant indicators of pain in pigs. In this species, salivary cortisol, ferric reducing ability of saliva and advanced oxidation protein products in saliva are correlated with the pain score measured in lame and prolapsed animals (Contreras-Aguilar et al., 2019). These different examples further highlight the close relationships between stress hormones (cortisol or corticosterone depending on the species), inflammation and oxidative stress.

Conclusion

This review highlights several relationships between redox status and animal performance and health at critical periods (Fig. 1). Of note, the level of oxidative stress and its consequences are modulated by additional factors inherent to the animal (genotype, physiological maturity) and to management practices prior, during and after the challenges. The data from different species pointed to the central role of energy metabolism at the origin of pro-oxidative metabolites generation, whereas the antioxidant capacities orchestrated between various tissues are of importance to limit their deleterious effects. Therefore, the evaluation of the redox imbalance can be used as a non-specific but valuable indicator to evaluate the intensity of stressful events encountered by the animals. When measured before a well-known but inevitable challenge, it can be used to predict the robustness and more specifically the resilience of the animal. A synthetic index to estimate oxidative stress would be thus a valuable tool to rank animals according to risk and to evaluate acute or long-term effects of management practices on performance and health. However, this supposes a consensus about the best measures of pro-oxidative and antioxidant pathways and their interpretation along the productive life. It seems premature to identify a simple, generic and robust indicator of oxidative stress. However, specific indicators of the level of oxidative stress and of the level of antioxidants that the animals can mobilise to respond to diverse challenges can be foreseen. They include the measurement of oxidation products such as lipid oxidation products (MDA, lipoperoxides), protein oxidation products (carbonyls) and GSH/GSSG ratio to evaluate the intensity of oxidative processes. Similarly, available antioxidant defence can be assessed by global test (FRAP, BAP, TAS, TEAC, Cuprac) in blood or plasma but must likely be associated with measurements of endogenous (catalase, superoxide dismutase, glutathione peroxidase) enzymatic defenses in different tissues. To data, there is no gold standard approach between species. In humans, considering the complexity of redox status evaluation, the 5R redox principles are recommended with different factors measured at the same time to achieve real precision (Meng et al., 2021). The development of agro-ecological practices in farm animals reinforces the needs to better understand the internal levers from animal physiology to control the level of oxidative stress. Genetic selection for robustness but also the ability of the animals to self-regulate their physiology through feeding preferences are possible strategies to be explored and combined in the future.

Ethics approval

Not applicable

Data and model availability

This review cites data that have been published in peer-reviewed journals or conference proceedings. For the majority of them, they are not deposited in official repositories. For data referred as unpublished, none of these data were deposited in an official repository. The data that support the concepts are available from the authors upon request.

Author ORCIDs

Denis Durand: 0000-0001-8381-8999

Florence Gondret: 0000-0001-7997-1560

Nathalie Le Floc'h: 0000-0001-9858-1584

Elodie Merlot: 0000-0003-2300-0970

Stéphanie Fontagné-Dicharry: 0000-0002-4366-4590

Elisabeth Baéza: 0000-0001-7658-3394

Laurence A. Guilloteau: 0000-0001-7089-2196

Anne Collin: 0000-0002-3410-6108

Author Contributions: D. Durand and F. Gondret conceptualized the review; all co-authors wrote and edited the manuscript. All co-authors read and agreed to the final version of the manuscript.

Declaration of interest

The authors declare no conflict of interest.

Acknowledgements

Not applicable

Financial support statement

Not applicable

References

Abuelo, A., Hernández, J., Benedito, J.L., Castillo, C., 2019. Redox biology in transition periods of dairy cattle: Role in the health of periparturient and neonatal animals. Antioxidants 8, 20. doi: 10.3390/antiox8010020.

Akşit, M., Altan, Ö., Karul, A.B., Balkaya, M., Özdemir, D., 2008. Effects of cold temperature and vitamin E supplementation on oxidative stress, Troponin-T level, and other ascites-related traits in broilers. Archiv für Geflügelk 72, S221-S230. ISSN 0003-9098.

Alami-Durante, H., Bazin, D., Cluzeaud, M., Fontagné-Dicharry, S., Kaushik, S., Geurden, I., 2018. Effect of dietary methionine level on muscle growth mechanisms in juvenile rainbow trout (Oncorhynchus mykiss). Aquaculture 483 (Suppl. C), 273-285. https://doi.org/10.1016/j.aquaculture.2017.10.030.

Al-Gubory, K.H., Fowler, P.A., Garrel, C., 2010. The roles of cellular reactive oxygen species, oxidative stress and antioxidants in pregnancy outcomes. International Journal of Biochemistry and Cell Biology 42, 1634-1650. doi: 10.1016/j.biocel.2010.06.001.

Amazan, D., Rey, A.I., Fernandez, E., Lopez-Bote, C.J., 2012. Natural vitamin E (D-alpha-tocopherol) supplementation in drinking water prevents oxidative stress in weaned piglets. Livestock Science 145, 55-62. doi:10.1016/j.livsci.2011.12.022.

Baéza, E., Bourin, M., Berri, C., 2018. Etat des lieux sur les défauts de qualité de la viande de poulets. Viandes et Produits Carnés 34, 1-12.

Baldi, G., Soglia, F., Mazzoni, M., Sirri, F., Canonico, L., Babini, E., Petracci, M., 2018. Implications of white striping and spaghetti meat abnormalities on meat quality and histological features in broilers. Animal 12, 164-173. doi: 10.1017/S1751731117001069.

Bauchart, D., Durand, D., Gruffat, D., Chilliard, Y., 1998. Mechanism of liver steatosis in early lactation cows, effects of hepatoprotector agents. Proceedings of Cornell Nutrition Conference for Feed Manufacturers, 20-22 October 1998, Rochester, USA, pp. 27-37.

Beauclercq, S., Lefèvre, A., Montigny, F., Collin, A., Tesseraud, S., Leterrier, C., Emond, P., Guilloteau, L.A., 2019. A multiplatform metabolomic approach to characterize fecal signatures of negative postnatal events in chicks: a pilot study. Journal of Animal Science Biotechnology 10, 1-12. doi: 10.1186/s40104-019-0335-8.

Birnie-Gauvin, K., Costantini, D., Cooke, S.J., Willmore, W.G., 2017. A comparative and evolutionary approach to oxidative stress in fish: A review. Fish 18, 928-942. http://dx.doi.org/10.1111/faf.12215.

Boglione, C., Gisbert, E., Gavaia, P., Witten, P.E., Moren, M., Fontagné, S., Koumoundouros, G., 2013. Skeletal anomalies in reared European fish larvae and juveniles. Part 2: main typologies, occurrences and causative factors. Reviews in Aquaculture 5, S121-S167. http://dx.doi.org/10.1111/raq.12016.

Boivin, X., Malarange, P., Jarousse, A., Gautier, J.M., Mallet, C., Bouvier, F., Richard, M.M., Kling-Eveillard, F., Guilloteau, L., 2017. Farmers' practices and attitudes towards artificial fed lambs and their mortality in meat systems. Proceedings of the 7th International Conference on the Assessment of Animal Welfare at Farm and Group level, 5-8 September 2017, Ede, the Netherlands, pp. 862-869.

Bottje, W.G., 2019. Oxidative metabolism and efficiency: the delicate balancing act of mitochondria. Poultry Science 98, 4223-4230. DOI: 10.3382/ps/pey405.

Brambilla, G., Civitareale, C., Ballerini, A., Fiori, M., Amadori, M., Archetti, L.I., 2002. Response to oxidative stress as a welfare parameter in swine. Redox Reports 7, 159-163. doi: 10.1179/135100002125000406.

Buchet, A., Belloc, C., Leblanc-Maridor, M., Merlot, E., 2017. Effects of age and weaning conditions on blood indicators of oxidative status in pigs. PlosOne 12, e0178487. doi: 10.1371/journal.pone.0178487.

Cantalapiedra-Hijar, G., Ortigues-Marty, I., Sepchat, B., Titgemeyer, E., Bahloul, L., 2020. Methionine-balanced diets improve cattle performance in fattening young bulls fed high-forage diets through changes in nitrogen metabolism. British Journal of Nutrition 124, 273-285. doi: 10.1017/S0007114520001154.

Castellano, R., Perruchot, M. H., Conde-Aguilera, J. A., van Milgen, J., Collin, A., Tesseraud, S., Mercier, Y., Gondret, F., 2015. A methionine deficient diet enhances adipose tissue lipid metabolism and alters anti-oxidant pathways in young growing pigs. PloS ONE 10, e0130514. https://doi.org/10.1371/journal.pone.0130514.

Chowdhury, S., Saikia, S., 2020. Oxidative Stress in Fish: A Review. Journal of Scientific Research 12, 145-160. https://doi.org/10.3329/jsr.v12i1.41716.

Conde-Aguilera, J.A., Cholet, J.C., Lessire, M., Mercier, Y., Tesseraud, S., van Milgen, J., 2016. The level and source of free-methionine affect body composition and breast muscle traits in growing broilers. Poultry Science 95, 2322-2331. doi: 10.3382/ps/pew105.

Conde-Aguilera, J.A., Lefaucheur, L., Gondret, F., Delgado-Andrade, C., Mercier, Y., Tesseraud, S., van Milgen, J., 2020. Skeletal muscle proteome of piglets is affected in a muscle-dependent manner by a limiting total sulfur amino acid supply. European Journal of Nutrition 59, 2939-2951. doi: 10.1007/s00394-019-02133-y.

Contreras-Aguilar, M. D., Escribano, D., Martinez-Miro, S., Lopez-Arjona, M., Rubio, C.P., Martinez-Subiela, S., Ceron, J.J., Tecles, F., 2019. Application of a score for evaluation of pain, distress and discomfort in pigs with lameness and prolapses: correlation with saliva biomarkers and severity of the disease. Research in Veterinary Science 126, 155-163. https://doi.org/10.1016/j.rvsc.2019.08.004.

Dalton, T.P., Shertzer, H.G., Puga, A., 2002. Regulation of gene expression by reactive oxygen. Annual Review of Pharmacology and Toxicology 39, 67-101. https://doi.org/10.1146/annurev.pharmtox.39.1.67.

Danbury, T.C., Weeks, C.A., Chambers, J.P., Waterman-Pearson, A.E., Kestin, S.C., 2000. Self-selection of the analgesic drug carprofen by lame broiler chickens. The Veterinary record 146, 307-311. doi: 10.1136/vr.146.11.307. PMID: 10766114.

De Boyer des Roches, A., Faure, M., Lussert, A., Herry, V., Rainard, P., Durand, D., Foucras, G., 2017. Behavioral and patho-physiological response as possible signs of pain in dairy cows during Escherichia coli mastitis: A pilot study. Journal of Dairy Science 100, 8385-8397. https://doi.org/10.3168/jds.2017-12796.

Decuypere, E., Buyse, J., Buys, N., 2000. Ascites in broiler chickens: exogenous, and endogenous structural, and functional causal factors. World’s Poultry Science Journal 56, 367-378. https://doi.org/10.1079/WPS20000025.

Degroot, J., Vergauwen, H., Wang, W., Ginneken, C.V., De Smet, S., Michiels, J., 2020. Changes of the glutathine redox system during the weaning transition in piglets, in relation to small intestinal morphology and barrier function. Journal of Animal Science and Biotechnology 11, 2-17. https://doi.org/10.1017/S1751731118003166.

Delosière, M., Durand, D., Bourguet, C., Terlouw, C., 2020. Lipid oxidation, pre-slaughter animal stress and meat packaginig: can dietary supplementation of vitamin E and plant extract come to the rescue? Food Chemistry, 309, 125668. doi: 10.1016/j.foodchem.2019.125668.

Durand, D., Chilliard, Y., Bauchart, D., 1992. Effects of lysine and methionine on in vivo hepatic secretion of VLDL in the high yielding dairy cow. Annual Meeting of the American Dairy Science Association, the Ohio State University, Columbus, USA, June 1992. Journal of Dairy Science 75 (Suppl. 1), 279.

Durand, D., Faure, M., de la Foye, A., de Boyer des Roches, A., 2019. Benefits of a multimodal analgesia compared to local anesthesia alone to alleviate pain following castration in sheep: a multiparametric approach. Animal 13, 2034-2043. doi: 10.1017/S1751731119000314.

Eckersall, P.D., Young, F.J., McComb, C., Hogarth, C.J., Safi, S., Weber, A., McDonald, T., Nolan, A.M., Fitzpatrick, J.L., 2001. Acute phase proteins in serum and milk from dairy cows with clinical mastitis. Veterinary Record 148, 35-41. doi: 10.1136/vr.148.2.35.

Faure, M., Paulmier, V., Boissy, A., de Boyer des Roches, A., Durand, D., 2017. A multiparametric approach to discriminate the impacts of different degrees of invasiveness of surgical procedures in sheep. Animal 11, 2275-2284. doi: 10.1017/S1751731117000805.

Fardet, A., Chardigny, J.M., 2013. Plante-based foods as a source of lipotropes for human nutrition: a survey of in vivo studies. Critical review in food science and nutrition 53, 535-590. doi: 10.1080/10408398.2010.549596.

Fasenko, G.M., 2007. Egg storage and the embryo. Poultry Science 86, 1020-1024.

Fontagné-Dicharry, S., Alami-Durante, H., Aragão, C., Kaushik, S.J., Geurden, I., 2017. Parental and early-feeding effects of dietary methionine in rainbow trout (Oncorhynchus mykiss). Aquaculture 469, 16-27. http://dx.doi.org/10.1016/j.aquaculture.2016.11.039.

Fontagné-Dicharry, S., Larroquet, L., Dias, K., Cluzeaud, M., Heraud, C., Corlay, D., 2018. Effects of dietary oxidized fish oil supplementation on oxidative stress and antioxidant defense system in juvenile rainbow trout (Oncorhynchus mykiss). Fish and Shellfish Immunology 74, 43-51. https://doi.org/10.1016/j.fsi.2017.12.039.

Fontagné, S., Lataillade, E., Brèque, J., Kaushik, S., 2008. Lipid peroxidative stress and antioxidant defense status during ontogeny of rainbow trout (Oncorhynchus mykiss). British Journal of Nutrition 100, 102-111. http://dx.doi.org/10.1017/S0007114507876215.

Fontagné-Dicharry, S., Lataillade, E., Surget, A., Larroquet, L., Cluzeaud, M., Kaushik, S., 2014. Antioxidant defense system is altered by dietary oxidized lipid in first-feeding rainbow trout (Oncorhynchus mykiss). Aquaculture 424, 220-227. http://dx.doi.org/10.1016/j.aquaculture.2014.01.009.

Fontagné-Dicharry, S., Véron, V., Larroquet, L., Godin, S., Wischhusen, P., Aguirre, P., Terrier, F., Richard, N., Bueno, M., Bouyssière, B., Antony Jesu Prabhu, P., Tacon, P., Kaushik, S.J., 2020. Effect of selenium sources in plant-based diets on antioxidant status and oxidative stress-related parameters in rainbow trout juveniles under chronic stress exposure. Aquaculture 529, 735684. https://doi.org/10.1016/j.aquaculture.2020.735684.

Foury, A., Collin, A., Helbling, J.C., Leterrier, C., Moisan, M.P., Guilloteau, L.A., 2020. Spontaneous intake of essential oils after a negative postnatal experience has long-term effects on blood transcriptome in chickens. Scientific Reports 10, 20702. doi:10.1038/s41598-020-77732-5.

Friel, J.K., Friesen, R.W., Harding, S.V., Roberts, L.J., 2004. Evidence of oxidative stress in full-term healthy infants. Pediatric Research 56, 878–882. https://doi.org/10.1203/01.PDR.0000146032.98120.43.

Gilbert, H., Ruesche, J., Muller, N., Billon, Y., Begos, V, Montagne, L., 2019. Responses to weaning in two pig lines divergently selected for residual feed intake depending on diet. Journal of Animal Science 97, 43–54. doi: 10.1093/jas/sky416.

Gobert, M., Gruffat, D., Habeanu, M., Parafita, E., Bauchart, D., Durand D., 2010. Plant extracts combined with vitamin E in PUFA-rich diets of cull cows protect processed beef against lipid oxidation. Meat Science 85, 676-683. doi: 10.1016/j.meatsci.2010.03.024.

Gobert, M., Martin, B., Ferlay, A., Chilliard, Y., Graulet, B., Pradel, P., Bauchart, D., Durand, D., 2009. Plant polyphenols associated with vitamin E can reduce plasma lipoperoxidation in dairy cows given n-3 polyunsaturated fatty acids. Journal of Dairy Science 92, 6095-6104. doi: 10.3168/jds.2009-2087.

Gondret, F., Guével, B., Père, M.C., Quesnel, H., Billon, Y., Com, E., Canario, L., Louveau, I., Liaubet, L., 2018. Proteomic analysis of adipose tissue during the last weeks of gestation in pure and crossbred Large White or Meishan fetuses gestated by sows of either breed. Journal of Animal Science and Biotechnology 9, 28. https://doi.org/10.1186/s40104-018-0244-2.

Gondret, F., Le Floc'h, N., Batonon-Alavo, D.I., Perruchot, M.H., Mercier, Y., Lebret, B., 2021. Flash dietary methionine supply over growth requirements in pigs: Multi-facetted effects on skeletal muscle metabolism. Animal 15, 100268. doi: 10.1016/j.animal.2021.100268.

Gondret, F., Vincent, A., Houée-Bigot, M., Siegel, A., Lagarrigue, S., Causeur, D., Gilbert, H., Louveau, I., 2017. A transcriptome multi-tissue analysis identifies biological pathways and genes associated with variations in feed efficiency of growing pigs. BMC Genomics 18, 244. https://doi.org/10.1186/s12864-017-3639-0.

Grubbs, J.K., Fritchen, A.N., Huff-Lonergan, E., Dekkers, J.C., Gabler, N.K., Lonergan, S.M., 2013. Divergent genetic selection for residual feed intake impacts mitochondria reactive oxygen species production in pigs. Journal of Animal Science 91, 2133-2140. https://doi.org/10.2527/jas.2012-5894.

Guilloteau, L.A., Collin, A., Koch, A., Leterrier, C., 2019. Spontaneous intake and long-term effects of essential oils after a negative postnatal experience in chicks. Frontiers in Veterinary Science 6, 72. https://doi.org/10.3389/fvets.2019.00072.

Hoseinifar, S.H., Yousefi, S., Van Doan, H., Ashouri, G., Gioacchini, G., Maradonna, F., Carnevali, O., 2021. Oxidative Stress and Antioxidant Defense in Fish: The Implications of Probiotic, Prebiotic, and Synbiotics. Reviews in Fisheries Science and Aquaculture 29, 198-217. https://doi.org/10.1080/23308249.2020.1795616.

Kalinowski, C.T., Larroquet, L., Véron, V., Robaina, L., Izquierdo, M.S., Panserat, S., Kaushik, S., Fontagné-Dicharry, S., 2019. Influence of dietary astaxanthin on the hepatic oxidative stress response caused by episodic hyperoxia in rainbow trout. Antioxidants 8, 626. https://doi.org/10.3390/antiox8120626.

Lebret, B., Batonon-Alavo, D.I., Perruchot, M.H., Mercier, Y., Gondret, F., 2018. Improving pork quality traits by a short-term dietary hydroxy-methionine supplementation at levels above growth requirements in finisher pigs. Meat Science 145, 230-237. doi: 10.1016/j.meatsci.2018.06.040.

Le Floc'h, N., Gondret, F., Resmond, R., 2021. Identification of blood immune and metabolic indicators explaining the variability of growth of pigs. BMC Veterinary Research 17, 166. https://doi.org/10.1186/s12917-021-02872-3.

Lin, H., Decuypere, E., Buyse, J., 2004. Oxidative stress induced by corticosterone administration in broiler chickens (Gallus gallus domesticus): 1. Chronic exposure. Comparative Biochemistry and Physiology Part- B Biochemistry and Molecular Biology 139, 737-744. https://doi.org/10.1016/j.cbpc.2004.09.013.

Lin, H., Decuypere, E., Buyse, J., 2006. Acute heat stress induces oxidative stress in broiler chickens. Comparative Biochemistry and Physiology Part- A: Molecular and Integrative Physiology 144, 11-17. https://doi.org/10.1016/j.cbpa.2006.01.032.

Lin, H., De Vos, D., Decuypere, E., Buyse, J., 2008. Dynamic changes in parameters of redox balance after mild heat stress in aged laying hens (Gallus gallus domesticus). Comparative Biochemistry and Physiology Part- C: Toxicology and Pharmacology 147, 30-35. https://doi.org/10.1016/j.cbpc.2007.07.005.

Loyau, T., Hennequet-Antier, C., Coustham, V., Berri, C., Leduc, M., Crochet, S., Sannier, M., Duclos, M.J., Mignon-Grasteau, S., Tesseraud, S., Brionne, A., Métayer-Coustard, S., Moroldo, M., Lecardonnel, J., Martin, P., Lagarrigue, S., Yahav, S., Collin, A., 2016. Thermal manipulation of the chicken embryo triggers differential gene expression in response to a later heat challenge. BMC Genomics 17, 329. https://doi.org/10.1186/s12864-016-2661-y.

Loyau, T., Collin, A., Yenisey, Ç., Crochet, S., Siegel, P.B., Akşit, M., Yalçin, S., 2014. Exposure of embryos to cyclically cold incubation temperatures durably affects energy metabolism and antioxidant pathways in broiler chickens. Poultry Science 93, 2078-2086. http://dx.doi.org/ 10.3382/ps.2014-03881

Lushchak, V.I., 2011. Environmentally induced oxidative stress in aquatic animals. Aquatic Toxicology 101, 13-30. http://dx.doi.org/10.1016/j.aquatox.2010.10.006.

Manuelian, C.L., Pitino, R., Simoni, M., Mavrommatis, A., De Marchi, M., Righi, F.,Tsiplakou, E., 2021. Plant feed additives as natural alternatives to the use of synthetic antioxidant vitamin on livestock mammals' performances, health and oxidative status: a review of the literature in the last 20 years. Antioxidants 10, 1461-1483. https://doi.org/10.3390/antiox10091461.

Marco-Ramell, A., Arroyo, L., Pena, R., Pato, R., Saco, Y., Fraile, L., Bendixen, E., Bassols, A., 2016. Biochemical and proteomic analyses of the physiological response induced by individual housing in gilts provide new potential stress markers. BMC Veterinary Research 12, 265. https://doi.org/10.1186/s12917-016-0887-1.

Mattioli, G.A., Rosa, D.E., Turic, E., Picco, S.J., Raggio, S.J., Minervino, A.H.H, Fazzio, L.E., 2020. Effects of parental supplementation with minerals and vitamins on oxidative stress and humoral immune response of weaning calves. Animals 10, 1-9. doi/10.3390/ani100811298.

McCracken, B.A., Spurlock, M.E., Roos, M.A., Zuckermann, F.A., Gaskins, H.R., 1999. Weaning anorexia may contribute to local inflammation in the piglet small intestine. Journal of Nutrition 129, 613-619. https://doi.org/10.1093/jn/129.3.613.

McKenna, C., Keogh, K., Porter, R.K., Waters, S.M., Cormican, P., Kenny, D.A., 2021. An examination of skeletal muscle and hepatic tissue transcriptomes from beef cattle divergent for residual feed intake. Scientific Reports 11, 8942. https://doi.org/10.1038/s41598-021-87842-3.

Meng, J., Lv, Z., Zhang, Y., Wang, Y., Qiao, X., Sun, C., Chen, Y., Guo, M., Han, W., Ye, A., Xie, T., Chu, B., Shi, C., Yang, S., Chen, C., 2020. Precision redox: the key for antioxidant pharmacology. Antioxidants and Redox Signaling 34, 1069-1082. doi:10.1089/ars.2020.8212.

Merlot, E., Pastorelli, H., Prunier, A., Père, M.C., Louveau, I., Lefaucheur, L., Perruchot, M.H., Meunier-Salaün, M.C., Gardan-Salmon, D., Gondret, F., Quesnel, H., 2019. Sow environment during gestation: Part I. Influence on maternal physiology and lacteal secretions in relation with neonatal survival. Animal 13, 1432-1439. doi: 10.1017/S1751731118002987.

Merlot, E., Vincent, A., Thomas, F., Meunier-Salaün, M.C., Damon, M., Robert, F., Dourmad, J.Y., Lebret, B., Prunier, A., 2012. Health and immune traits of Basque and

Large-White pigs housed in a conventional or enriched environment. Animal 6, 1290-1299. doi: 10.1017/S1751731112000080.

Mialon, M.M., Boivin, X., Durand, D., Boissy, A., Delval, E., Bage, A.S., Clanet, C., Cornilleau, F., Parias, C., Foury, A., Moisan, M.P., Fassier, T., Marcon, D., Guilloteau, L.A., Nowak, R. 2021. Short and mid-term effects on performance, health and qualitative behavioral assessment of Romane lambs in different milk feeding conditions. Animal 15, 100157. https://doi.org/10.1016/j.animal.2020.100157.

Morton, S.U., Brodsky, D., 2016. Fetal physiology and the transition to extra-uterine life. Clinics in Perinatology 43, 395-407. doi: 10.1016/j.clp.2016.04.001.

Novais, A.K., Deschêne, K., Martel-Kennes, Y., Roy, C., Laforest, J.P., Lessard, M., Matte, J.J., Lapointe, J., 2021. Weaning differentially affects mitochondrial function, oxidative stress, inflammation and apoptosis in normal and low birth weight piglets. PloS ONE 16, e0247188. doi: 10.1371/journal.pone.0247188.

Osorio, J., 2020. Gut health, stress, and immunity in neonatal dairy calves: the host side of host-pathogen interactions. Journal of Animal Science and Biotechnology 11, 105-120. doi: 10.1186/s40104-020-00509-3.

Petracci, M., Mudalal, S., Soglia, F., Cavani, C., 2015. Meat quality in fast-growing broiler chickens. World’s Poultry Science Journal 71, 363–374. https://doi.org/10.1017/ S0043933915000367.

Petracci, M., Soglia, F., Madruga, M., Carvalho, L., Ida, E., Estevez, M., 2019. Wooden-Breast, White Striping, and Spaghetti Meat: Causes, Consequences and

Consumer Perception of Emerging Broiler Meat Abnormalities. Comprehensive Reviews in Food Science and Food Safety 18, 565-583. https://doi.org/10.1111/1541-4337.12431.

Pertusa, M., Skiba, F., Godfrain, B., Guilloteau, L., Cailleau-Audouin, E., Chartrin, P., Travel, A., Quentin, M., 2017. Comparaison de l'effet de différents additifs alimentaires en production de poulets label Rouge. Proceedings of the 12èmes Journées de la Recherche Avicole et Palmipèdes à Foie Gras, 5-6 April 2017, Tours, France, pp. 844-848.

Piestun, Y., Shinder, D., Ruzal, M., Halevy, O., Brake, J., Yahav, S., 2008. Thermal manipulations during broiler embryogenesis: effect on the acquisition of thermo-tolerance. Poultry Science 87, 1516-1525. doi:10.3382/ps.2008-00030.

Pignatelli, P., Menichelli, D., Pastori, D., Violi, F., 2018. Oxidative stress and cardiovascular disease : new insights. Kardiologia Polska 76, 713-722. doi:10.5603/KP.a2018.0071.

Pokhrel, N., Cohen, E.B., Genin, O., Ruzal, M., Sela-Donenfeld, D., Cinnamon, Y., 2018. Effects of storage conditions on hatchability, embryonic survival and cyto-architectural properties in br2015oiler from young and old flocks. Poultry Science 97, 1429-1440. https://doi.org/10.3382/ps/pex393.

Quesnel, H, Père MC, Louveau I, Lefaucheur L, Perruchot MH, Prunier A, Pastorelli H, Meunier-Salaün MC, Gardan-Salmon D, Merlot E, Gondret F., 2019. Sow environment during gestation: part II. Influence on piglet physiology and tissue maturity at birth. Animal 13, 1440-1447. doi: 10.1017/S1751731118003087.

Ranade, R., Talukder S., Muscatello, G., Celi P., 2014. Assessment of oxidative stress biomarkers in exhaled breath condensate and blood of dairy heifer calves from birth to weaning. Veterinary Journal 202, 583-587. https://doi.org/10.1016/j.tvjl.2014.10.025.

Ren, F., Wang, K, Zhang, T., Jiang, J., Nice, E.C., Huang, C., 2015. New insights into redox regulation of stem cell self-renewal and differentiation. Biochemica Biophysica Acta 1850, 1518-1526. https://doi.org/10.1016/j.bbagen.2015.02.017.

Rey, B., Spée, M., Belouze, M., Girard, A., Prost, J., Roussel, D., Duchamp C., 2010. Oxygen recovery up-regulates avian UCP and ANT in newly hatched ducklings. Journal of Comparative Physiology B 180, 239–246. Doi: 10.1007/s00360-009-0409-6.

Robert, F., Bebin, K., Garrau, J.M., Gueriot, J.F., Foret, R., Brack, M., Garrel, C., 2009. Evaluation et correction du stress oxydatif du porcelet en post-sevrage. Journées de la Recherche Porcine 41, 173-178.

Rosa, F., Michelotti, T.C., St-Pierre, B., Trevisi, E., Osorio, J.S., 2021. Early life fecal microbiota transplantation in neonatal dairy calves promotes growth performance and alleviates inflammation and oxidative stress during weaning. Animals, 11, 2704. https://doi.org/10.3390/ ani11092704.

Sales, F., Peralta, O.A., Narbona, E., McCoard, S., De Los Reyes, M., Gonzales-Bulnes, A., Parraguez, V.H., 2018. Hypoxia and oxidative stress are associated with reduced fetal growth in twin and undernourished sheep pregnancies. Animals 8, 217. https://doi.org/10.3390/ani8110217.

Salin K., Auer S.K., Rudolf A.M., Anderson G.J., Cairns A.G., Mullen W., Hartley R.C., Selman C., Metcalfe N.B., 2015. Individuals with higher metabolic rates have lower levels of reactive oxygen species in vivo. Biology Letters 11, 20150538. http://dx.doi.org/10.1098/rsbl.2015.0538.

Sarr, O., Louveau, I., Le Huërou-Luron, I., Gondret, F., 2012. Adipose tissue proteomes of intrauterine growth-restricted piglets artificially reared on a high-protein neonatal formula. Journal of Nutritional Biochemistry 23, 1417-1424. doi:10.1016/j.jnutbio.2011.09.002.

Séité, S., Mourier, A., Camougrand, N., Salin, B., Figueiredo-Silva, A.C., Fontagné-Dicharry, S., Panserat, S., Seiliez, I., 2018. Dietary methionine deficiency affects oxidative status, mitochondrial integrity and mitophagy in the liver of rainbow trout (Oncorhynchus mykiss). Scientific Reports 8, 10151. https://doi.org/10.1038/s41598-018-28559-8.

Shinder, D., Ruzal, M., Giloh, M., Druyan, S., Piestun, Y., Yahav, S., 2011. Improvement of cold resistance and performance of broilers by acute cold exposure during late embryogenesis. Poultry Science 90, 633-641. doi: 10.3382/ps.2010-01089.

Sierzant, K., Perruchot, M.H., Merlot, E., Le Floc'h, N., Gondret, F., 2019. Tissue-specific responses of antioxidant pathways to poor hygiene conditions in growing pigs divergently selected for feed efficiency. BMC Veterinary Research 15, 341. https://doi.org/10.1186/s12917-019-2107-2.

Sies, H., Jones D.P., 2020. Reactive oxygen species (ROS) as pleiotropic physiological signalling agents. Nature Review of Molecular and Cellular Biology 21, 363-383. doi: 10.1038/s41580-020-0230-3. Epub 2020 Mar 30. PMID: 32231263

Soglia, F., Laghi, L., Canonico, L., Cavani, C., Petracci, M., 2016. Functional property issues in broiler breast meat related to emerging muscle abnormalities. Food Research International 89, 1071–1076. https://doi.org/10.1016/j.foodres.2016.04.042.

Sundekilde, U.K., Rasmussen, M.K., Young, J.F., Bertram, H.C., 2017. High resolution magic angle spinning NMR spectroscopy reveals that pectoralis muscle dystrophy in chicken is associated with reduced muscle content of anserine and carnosine. Food Chemistry 217, 151-154. doi: 10.1016/j.foodchem.2016.08.104.

Ting, S.T.L, Earley, B., Hughes, J.M.L., Crowe, M.A., 2003. Effect of ketoprofen, lidocaine local anesthesia, and combined xylazine and lidocaine caudal epidural anesthesia during castration of beef cattle on stress responses, immunity, growth, and behavior. Journal of Animal Science 81, 1281-1293. https://doi.org/10.2527/2003.8151281x.

Travel, A., Petit, A, Parat, P., Collin, A., Bourrier-Clairat, C., Pertusa, M., Skiba, F., Crochet, S., Cailleau-Audouin, E., Chartrin, P., Guillory, V., Bellenot, D., Guabiraba, R., Guilloteau, L.A., 2021. Methodologies to assess the bioactivity of an herbal extract on immunity, health, welfare and production performance in the chicken: the case of Melissa officinalis L. extract. Frontiers in Veterinary Science (in press) doi: 10.3389/fvets.2021.759456.

Villalba JJ, Miller J, Ungar ED, Landau SY, Glendinning J. 2014. Ruminant self-medication against gastrointestinal nematodes: evidence, mechanism, and origins. Parasite 21, 31. doi: 10.1051/parasite/2014032. Epub 2014 Jun 30. PMID: 24971486; PMCID: PMC4073621.

Wang, J, Chen, L, Li, D., Li, D., Wang, X., 2008. Intrauterine growth restriction affects the proteome of the small intestine, liver and skeletal muscle in newborn pigs. Journal of Nutrition 138, 60-66. doi: 10.1093/jn/138.1.60.

Wischhusen, P., Larroquet, L., Durand, T., Oger, C., Galano, J.-M., Rocher, A., Vigor, C., Jesu Prabhu, P.A., Véron, V., Briens, M., Roy, J., Kaushik, S.J., Fauconneau, B., Fontagné-Dicharry, S., 2020a. Oxidative stress and antioxidant response in rainbow trout fry exposed to acute hypoxia is affected by selenium nutrition of parents and during first exogenous feeding. Free Radical Biology and Medicine 155, 99-113. https://doi.org/10.1016/j.freeradbiomed.2020.05.006.

Wischhusen, P., Parailloux, M., Geraert, P.A., Briens, M., Bueno, M., Mounicou, S., Bouyssiere, B., Antony Jesu Prabhu, P., Kaushik, S.J., Fauconneau, B., Fontagné-Dicharry, S., 2019. Effect of dietary selenium in rainbow trout (Oncorhynchus mykiss) broodstock on antioxidant status, its parental transfer and oxidative status in the progeny. Aquaculture 507, 126-138. https://doi.org/10.1016/j.aquaculture.2019.04.006.

Wischhusen, P., Saito, T., Heraud, C., Kaushik, S.J., Fauconneau, B., Antony Jesu Prabhu, P., Fontagné-Dicharry, S., Skjærven, K.H., 2020b. Parental selenium nutrition affects the one-carbon metabolism and the hepatic DNA methylation pattern of rainbow trout (Oncorhynchus mykiss) in the progeny. Life 10, 121. https://doi.org/10.3390/life10080121.

Yang, J., Ding, X., Bai, S., Wang, J., Zeng, Q., Peng, H., Xuan, Y., Su, Z., Zhang, K., 2020. The effects of broiler breeder dietary vitamin E and egg storage time on the quality of eggs and newly hatched chicks. Animals 10, 1409. https://doi.org/10.3390/ani10081409.

Yin, L., Ren, W., Liu, G., Duan, J., Yang, G., Wu, L., Li, T., Yin, 2013. Birth oxidative stress and the development of an antioxidant system in newborn piglets. Free Radical Research 47, 1027-1035. doi: 10.3109/10715762.2013.848277.

Zeitz, J.O., Mohrmann, S., Fehse, L., Most. E., Helmbrecht, A., Saremi, B., Eder, K., 2018. Tissue and plasma antioxidant status in response to dietary methionine concentration and source in broilers. Journal of Animal Physiology and Animal Nutrition 102, 999-1011. https://doi.org/10.1111/jpn.12909.

Zhang, H., Li, Y., Su, W., Ying, Z., Zhou, L., Zhang, L., Wang, T., 2017. Resveratrol attenuates mitochondrial dysfunction in the liver of intrauterine growth retarded suckling piglets by improving mitochondrial biogenesis and redox status. Molecular Nutrition and Food Research 61, 10.1002/mnfr.201600653. doi: 10.1002/mnfr.201600653.

Zhou, X., Zhang, Y., Wan, X., Yin, Y. 2018. Effects of dietary serine supplementation on intestinal integrity, inflammation and oxidative status in early-weaned piglets. Cellular Physiology and Biochemistry 48, 993-1002. DOI: 10.1159/00049196.

Table 1

Post-natal period events with increased oxidative process in pigs, ruminants, poultry and fishes.

Species[1]	Critical stage	Main challenge	Additional challenge	Redox status involvement	Aggravating factors	Levers to limit oxidative stress
Pig	Birth	Hypo- to hyperoxia	Amniotic fluid to colostrum feeding	Blood hydroperoxides ↑ Expression of peroxiredoxins in adipose tissue ↑ Hepatic MDA content ↑	Low BW of piglets	Neonatal diet rich in proteins
Ruminant	Birth	Hypo- to hyperoxia	Amniotic fluid to colostrum feeding	Blood ROS ↑	Feeding newborns with milk replacer	Dietary supplementation of lactating females and calves with antioxidants and selenium
Poultry	Hatching	Hypo- to hyperoxia	Yolk sac to concentrate diet feeding	Lipid peroxidation in skeletal muscles and heart	Long egg storage before incubation Delayed placement of chicks in farms	Short egg storage before incubation Short delay between hatching and placement in farms Dietary supplementation of breeders with antioxidants
Fish	Hatching	Active feeding	Egg yolk to larval diet	Lipid peroxidation ↑ Vitamins A, C and E ↓ GSH/GSSG ↓ Antioxidant enzyme activities ↑	High concentration of long chain n-3 polyunsaturated fatty acids in diet and animal tissues. Incomplete development of the endogenous antioxidant	Dietary supplementation of broodstock with vitamin A, methionine, selenium

system

Abbreviations: GSH = reduced glutathione; GSSG = oxidized glutathione disulphide; MDA = malondialdehyde; ROS = Reactive oxygen species.

[1] Examples in different species are mainly based on our own works, and not an overview of all references. This underlines that depending of the lab history and skills, the used indicators may vary and no systematic studies have been considered for one or more challenges.

Table 2

Juvenile transition events with increased oxidative process in pigs and ruminants.

Species[1]	Critical stage	Main challenge	Additional challenge	Redox status involvement	Aggravating factors	Levers to limit oxidative stress
Pig	Weaning	Dietary transition, separation from the mother, social stress	New environment, high rearing density, animal mixing, cold stress	Hydroperoxides in blood and liver ↑ Hepatic MDA content ↑ Glutathione peroxidase activity in liver ↓ Vitamins A and E in blood ↓	Early stage, low BW, additional gut health disorders	Dietary supplementation with antioxidants
Ruminant	Weaning	Dietary transition, separation from the mother	New environment, social stress	Hydroperoxides in exhaled breath condensate ↑		Dietary supplementation with minerals and antioxidants

Abbreviations: MDA = malondialdehyde.

[1] Examples in different species are mainly based on our own works, and not an overview of all references. This also underlined that depending of the labs history and skills, indicators may vary and no systematic studies have been considered for one or more challenges

Table 3

Synthesis on dietary methionine deficiency and redox status of pigs, ruminants, poultry and fishes.

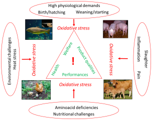
Species[1]	Redox status
Pig	Glutathione content in muscles and liver ↓
	Antioxidant enzyme activities (catalase, superoxide dismutase or glutathione peroxidase) in muscle and adipose tissues ↑
Ruminant	glutathione peroxidase and glutathione reductase mRNA in placenta
Poultry	Glutathione and vitamin E contents in liver ↓
	TBARS value and carbonyl contents in blood ↑
	Vitamin E in blood ↓
	Antioxidant enzyme activities (Catalase, superoxide dismutase, and glutathione peroxidase) in jejunum ↑
Fish	Glutathione content in plasma and liver ↓
	Protein carbonyls in liver ↑
	Glutathione transferase-π transcript expression in liver, muscle and fry ↑

Abbreviations: TBARS = thiobarbituric acid reactive substances.

[1] Examples in different species are mainly based on our own works, and not an overview of all references. This also underlined that depending of the labs history and skills, indicators may vary and no systematic studies have been considered for one or more challenges

Figure captions

Fig. 1. Schematic representation of the main internal and external factors inducing oxidative stress in pigs, ruminants, poultry or fishes.


High physiological demands
Birth/hatching
Weaning/starting
Oxidative stress
Environmental challenges
Heat stress
Oxidative stress
Welfare
Product qualities
!
Health
Performances
Oxidative stress
Slaughter
Inflammation
Pain
Oxidative stress
Aminoacid deficiencies
Nutritional challenges