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Review Paper

All Species

Organic selenium in animal nutrition – utilisation, metabolism, storage and comparison with other selenium sources

F. W. Edens[1]* and A. E. Sefton[2]

[1]*Prestage Department of Poultry Science, North Carolina State University, Raleigh, NC 27695-7635, USA*
[2]*Alltech, Inc., Nicholasville, KY 40356, USA*

Summary

The importance of selenium as a key component of antioxidant systems in animals is well recognised due to much research about this mineral in many species. Selenium is required as part of the antioxidant enzyme structure and plays a major role in various protective systems in animal physiology, including immunity, cellular stability and DNA protection. The following review is the first in a series of three which details the importance of selenium in animal nutrition, and how the chemically organic form, which is akin to the form of the mineral in natural feed materials, can provide increased benefits in utilisation, storage and metabolism compared to inorganic sources.

Keywords: **Selenium: inorganic: organic: feed: utilisation: tissue storage: metabolism**

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Introduction

Selenium (Se) is an important mineral, which, although required in small amounts in the diet, is a critical component of enzymes involved in specific antioxidant processes. Farm animals, especially those under intensive management, are subject to high levels of oxidative stress that can affect their performance, meat quality, and meat stability. Surai (2002) addressed oxidative damage to lipids in the living animal summarising that the oxidative stress is due to an imbalance between the production of reactive oxygen (ROS) and nitrogen (RNS) species and the animal's defence mechanisms. Surai's review illustrated how oxidative stress might be induced by dietary intake of oxidised lipids and polyunsaturated fatty acids or by lack of intake of nutrients that support the body's many antioxidant systems. He pointed out that in order to improve meat quality, producers had to combat pre- and post-slaughter oxidative stress effects on meat quality and stability. At the time of his review, producers had already begun to explore the use of dietary supplements such as the provision of higher dietary levels of vitamin E or ascorbic acid, which are known to have powerful antioxidant properties and/or pre-slaughter withdrawal of dietary transition trace minerals that have pro-oxidant properties. It has been a long-held belief that non-haem iron and copper have pro-oxidant effects, and many producers have routinely removed iron and copper from finisher diets.

The following review addresses the issue of the various selenium forms (organic Se as a component in cysteine and methionine and incorporated into proteins versus inorganic sodium selenite) that have an influence on antioxidant activity and storage of antioxidants within the body, making it available during times of stress. This is the first part of three papers, which reviews the current research regarding Se activity (specifically Sel-Plex™, Alltech Inc, USA) in animals, especially poultry and also swine and beef. It sets the scene for the second

* Corresponding author: fwedens@mindspring.com

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and third papers, which examine selenium influence, especially in its organic form, on meat quality and stability due to its antioxidant function in pre-harvest muscle cell metabolism and post-harvest meat stability and quality.

Selenium: an essential trace element

The use of organic selenium from yeast cell wall protein (Sel-Plex™) in animal feeds seems, at first, to be outside the primary role of selenium in the integral entity, selenocysteine, in active sites in selenoproteins/enzymes (Holben and Smith, 1999). Edens and Gowdy (2004) assessed selenium sources and selenoproteins in poultry and other food animals, observing that among the known 25–28 selenoproteins and enzymes in animals, many have antioxidant potential, such as the glutathione peroxidases and thioredoxin reductases, and other selenoproteins have functions yet to be determined (Kryukov *et al.*, 2003; Kieliszek and Błażejak, 2013; Brigelius-Flohé and Maiorino, 2013).

In order to address the issue of organic selenium in animal feed, it is important to understand some basic chemical properties of selenium, which is an essential trace element in the diets of all animals. It is required for maintenance of health, growth, and myriad biochemical-physiological functions (Scott *et al.*, 1982). Selenium, which was discovered by the Swedish chemist J. J. Berzelius (1817), did not have a recognised biological significance until it was identified as the toxic agent associated with alkali disease, now called selenosis, in the Dakota and Wyoming territories in the United States in 1856 (Franke, 1934). Later, it was discovered that selenosis was due to extremely high concentrations of selenium in soils and plants, and hence it was considered a dangerous element until 1957. In 1957, Schwarz and Foltz reported that selenium was an essential trace nutrient, and nutritionists then initiated extensive studies to discover its metabolic function and document the consequences of its deficiency in human and animal foodstuffs (Burk, 1983; Combs and Combs, 1984).

Selenium deficiency can manifest itself in many diseases and dysfunctions such as liver necrosis, muscular dystrophy, microangiopathy, exudative diathesis, pancreatic fibrosis, poor feathering, retained placenta, mastitis, cystic ovaries, general unthriftiness, Keshan disease, Kashin-Beck disease, cancer, numerous heart diseases, immune deficiencies, reduced fecundity and many others and can affect humans and animals alike (Combs, 1986; Combs and Combs, 1984; Foster and Sumar, 1997; Levander and Beck, 1997; Schrauzer, 2000; Raiz and Mehmood, 2012).

Rotruck *et al.* (1973) discovered that the antioxidant enzyme glutathione peroxidase (GSHpx) contained an integral and stoichiometric quantity of selenium, which is necessary for activation of the enzyme, demonstrating a biochemical role for this essential trace element as it provided a tool for monitoring its status in all animals. Because of similarities between selenium and sulphur, it has been a long held belief that selenium would follow the sulphur pathways in its metabolism (Franke and Painter, 1937; Painter and Frank, 1940). This concept was strengthened by the discovery that plants and bacteria metabolise selenium to the organic selenomethionine and selenocysteine, which are selenoaminoacid analogues of methionine and cysteine, respectively (Burnell and Whatley, 1977). These selenoaminoacids contain a selenol group in place of the sulphur-containing thiol group. Selenoproteins with catalytic activities and containing one or more selenocysteine residues are called selenoenzymes that are dependent on selenocysteine's incorporation into the enzyme in the active sites (Roy *et al.*, 2005). Selenomethionine is readily utilised as a substrate by enzymes that use methionine, and selenomethionine is more bioavailable than methionine (Pan *et al.*, 1964; Markham *et al.*, 1980). As such, selenomethionine is actively incorporated into proteins substituting for methionine (Hansson and Jacobson, 1966; Ip and Hayes, 1989; Schrauzer, 1998, 2000).

The functionality of natural organic selenium

It has been recognised for more than a quarter century that the selenoaminoacids, selenomethionine and selenocysteine, are the primary sources of naturally occurring selenium in plant-based (Burk and Hill, 2015; Olson and Palmer, 1976) and meat-based (Cai *et al.*, 1995; Whanger, 2002) feed ingredients. These are bound in protein, principally as selenomethionine and selenocysteine and constitute 50 to 80% of the total selenium in plants, grains (Butler and Peterson, 1967) and, in the case of Sel-Plex™, the organic selenium-enriched yeast cell wall protein (Kelly and Power, 1995).

Non-ruminant animals cannot synthesise selenomethionine from either selenite or selenate forms of inorganic selenium (Cummins and Martin, 1967; Olson and Palmer, 1976; Sunde, 1990). However, selenomethionine and inorganic selenate and selenite seleniums can be converted to selenocysteine, which is found in

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body tissues of all animals (Esaki *et al.*, 1981; Beilstein and Whanger, 1986). Selenocysteine is essential in selenoproteins such as selenium-dependent glutathione peroxidases, tetraiodothyronine 5' deiodinases, thioredoxin reductases, formate dehydrogenases, glycine reductases, selenophosphate synthetase 1, methionine-R-sulphoxide reductase B1 (SEPX1), and some hydrogenases (Johansson *et al.*, 2005). In muscle tissue, the appearance of selenocysteine is not unexpected since selenomethionine, selenite selenium and selenate selenium are efficiently converted to selenocysteine and incorporated into proteins substituting for cysteine (Ip and Hayes, 1989; Schrauzer, 1998). Dietary selenomethionine is readily incorporated non-specifically into muscle protein in place of methionine, becoming a structural component of the muscle and serves as a rich source of stored selenium, which can be redistributed to other selenium containing proteins as the original protein degrades (Hansson and Jacobson, 1966; Ip and Hayes, 1989; Schrauzer, 1998, 2000). Selenium from inorganic selenite is incorporated into muscle as only selenocysteine (Olson and Palmer, 1976).

Although selenocysteine can be substituted for cysteine in many proteins, it is not incorporated directly into specific selenoproteins (Sunde, 1990; Daniels, 1996). The selenocysteine from selenomethionine must first react with selenocysteine-β-lyase to release selenide in the presence of reducing agents (Sunde, 1990; Burk, 1991). The hydrogen selenide from this reaction acts as the precursor for the newly synthesised selenocysteine for specific insertion into selenoproteins (Arthur, 1997). Inorganic selenate must be reduced to selenite, which then is metabolised to hydrogen selenide via selenium dependent glutathione peroxidase activity (Ip and Hayes, 1989). The hydrogen selenide from the selenite conversion pathway then becomes the precursor for selenocysteine for specific insertion into selenoproteins (Ip and Hayes, 1989).

The synthesised selenocysteine for specific insertion into selenoproteins involves a unique process in which selenide is phosphorylated under the influence of selenophosphate synthetase to selenophosphate. This is made available to a unique seryl-tRNA^{SEC} that is recognised by selenocysteine synthetase. The selenocysteine synthetase converts seryl-tRNA^{SEC} to selenocysteyl-tRNA^{SEC} that allows specific insertion of co-translationally synthesised selenocysteine into selenoproteins (Burk, 1991). The base triplet UGA that normally functions as a stop codon (Amberg *et al.*, 1996) encodes this process of selenocysteine insertion at its appropriate site in a peptide. The selenocysteine insertion also requires a specific mRNA, an elongation factor, guanosine triphosphate, and the selenocysteine insertion sequence that all interact at the ribosome to read the UGA selenocysteine codon (Low and Berry, 1996).

The conversions of organic and inorganic selenium to selenocysteine is a crucial process in the synthesis of selenoproteins and represents a major form of organic selenium in all animals (Hawks *et al.*, 1985ab). Selenomethionine is a highly available substrate for many proteins and can substitute for methionine in protein structure (Daniels, 1996). In cases where supplementation of selenomethionine is at a high level in feeds, it can be demonstrated that 40 to 50% of total body selenium as selenomethionine can be found in muscle (Daniels, 1996).

Selenocysteine is the pivotal amino acid in the synthesis of selenium-dependent cytosolic glutathione peroxidase (GSHpx-1; Rotruck *et al.*, 1973), but only about 30% of the body's selenium is incorporated into cytosolic GSHpx. About 70% of the body's selenium is incorporated into the other selenoproteins and protein in birds and mammals (Burk and Hill, 1993). These observations have raised a question about the possibility that selenomethionine, due to its natural involvement in the synthesis of selenoproteins, might also be considered an essential amino acid such as selenocysteine, which is considered by many nutritionists as the twenty-first amino acid.

The metabolism of residual selenium from both organic and inorganic selenium sources is excreted from the body as dimethylselenide, mono-, di-, and trimethylselenonium ion (Ip and Hayes, 1989). Trimethylselenonium is excreted via the urine (Palmer *et al.*, 1969, 1970; Ganther, 1986), dimethylselenide is eliminated via the respiratory system (McConnell and Portman, 1952; Ganther, 1986), and selenodiglutathione (GS-Se-SG), the major metabolite of inorganic selenium in mammalian tissues, is converted to hydrogen selenide (Hsieh and Ganther, 1975; Shamberger, 1985) and eliminated via the bile (Ganther, 1986; Gregus *et al.*, 1998; Gyurasics *et al.*, 1998). Both inorganic and organic selenium, that are not absorbed from the gastrointestinal tract, are eliminated in faeces (Ganther, 1986; Gregus *et al.*, 1998; Gyurasics *et al.*, 1998).

Muscle selenoaminoacid accumulation/retention and glutathione peroxidase activity

Deagan *et al.* (1987) found that feeding selenomethionine to selenium-deficient rats resulted in a ten-fold increase in muscle selenium concentration as compared with

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selenium-deficient rats fed either sodium selenite or selenocysteine. Song *et al.* (2015) fed young Boer goats over a 180 day period with a selenium deficient diet supplemented with L-selenomethionine, noting that muscle selenium concentration increased proportionally with dietary L-selenomethionine levels, and at 180 days muscle concentrations were continuing to rise, with the 0.5 ppm L-selenomethionine supplement causing roughly a four-fold increase over controls. After a 10 day selenium-loading period, broiler chickens given selenium yeast (Sel-Plex™) had a breast muscle selenium concentration that was more than two-fold greater than the selenium concentration in breast muscle from broilers fed sodium selenite and four-fold higher than in breast muscle from broilers fed a diet without supplemental selenium (Payne and Southern, 2005ab). Norheim and Moksnes (1985) noted that in laying hens fed either sodium selenite or selenomethionine, accumulation of selenium in muscle was significantly greater in hens fed selenomethionine compared with sodium selenite. Latshaw (1975) fed hens natural selenium (presumably DL-selenomethionine) and sodium selenite and observed significantly greater concentrations of selenium in breast meat, liver, and eggs from hens fed the natural selenium compared to sodium selenite. Latshaw and Osman (1975) reported that selenium retention was greater in hens fed selenomethionine, an observation confirmed later in laying hens by Norheim and Moksnes (1985) and Moksnes and Norheim (1986). Similar observations for selenium concentrations in breast meat, liver, and plasma were reported in broiler chickens fed 0.3 mg/kg selenium in Sel-Plex™, 0.3 mg/kg selenium in sodium selenite, or no supplemental selenium (Payne and Southern, 2005b). Mahan (1995) and Suomi and Alaviuhkola (1992) observed that selenium yeast selenium accumulation and retention in pigs was more effective in muscle, liver, and serum than selenite selenium. Mahan and Parrett (1996) reported that swine muscle concentration of selenium from dietary selenite plateaued between 0.1 and 0.3 ppm, but muscle selenium from the selenomethionine in selenium-enriched yeast continued to increase even at a 0.5 ppm dietary inclusion rate. Mahan and Parrett (1996) also noted that the concentration of selenite selenium in swine pancreas, liver, and kidney was greater than that found in muscle, and with the dietary inclusion of sodium selenite and selenium-enriched yeast, the selenium concentrations in those organs increased in parallel with dietary inclusion rates. Stewart *et al.* (2012) gave oral drenching of solutions containing no selenium, sodium selenate, sodium selenite, or selenium yeast to ewes that were still nursing their lambs. Ewes given selenium yeast provided more selenium to their lambs than did ewes from the other groups, lambs from ewes receiving the selenium yeast accumulated fourfold more skeletal muscle selenium than did lams from ewes given the sodium selenite or sodium selenite (Stewart *et al.*, 2012). Juniper *et al.* (2009) fed sodium selenite or Sel-Plex™ to lambs and found that skeletal muscle selenium content increased with increasing dietary selenium levels, and that lambs given Sel-Plex™ had greater muscle tissue selenium concentrations than those fed sodium selenite. Additionally, they reported no difference in the activity of muscle GSHpx due to either selenium source, but TBARS values (a measure of oxidative stress) were less with the Sel-Plex™ feeding. Wang *et al.* (2011a), using modern fast growing, high-yielding broiler chickens, reported that both dietary L-selenomethionine and D-selenomethionine at 0.15 ppm significantly increased the selenium concentration in serum, liver, kidney, pancreas and breast muscle compared with a comparable level of sodium selenite in the feed. Mahan and Parrett (1996) did not find selenium source-related increases in serum selenium, but Wang *et al.* (2011a) observed significantly greater serum selenium concentrations in broilers fed both D- and L-selenomethionine compared to the feeding of sodium selenite. Mahan and Parrett (1996) noted that serum glutathione peroxidase (GSHpx) correspondingly plateaued when dietary sodium selenite and selenium-enriched yeast were at a level of 0.1 ppm. In broilers, sodium selenite and L-selenomethionine were more effective than D-selenomethionine in the induction of serum GSHpx (Wang *et al.*, 2011a). Wang *et al.* (2011a) noted in broilers that sodium selenite and L-selenomethionine were equally efficient in inducing tissue GSHpx compared with D-selenomethionine.

Selenocysteine is metabolised similarly to that of sodium selenite and is not retained in the body at levels any greater than selenite selenium (Deagan *et al.*, 1987). In Leghorn chickens on a selenium depletion program, retention of muscle selenomethionine was significantly longer (nine or more weeks) than inorganic selenite selenium retention (five weeks), which is associated with muscle deposition of only selenocysteine (Norheim and Moksnes, 1985; Moksnes and Norheim, 1986). Payne and Southern (2005b) reported that selenium retention of breast muscle from broilers fed Sel-Plex™ was significantly greater than selenium in breast muscles from

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broilers fed sodium selenite or from broilers fed a diet with no supplemental selenium (Payne and Southern, 2005b). Moksnes and Norheim (1986) concluded that selenomethionine served as a mobile pool of selenium that could be recycled into selenoproteins especially during times of selenium restriction. Before the selenium depletion program was initiated, there was no difference between selenite and selenomethionine supplementation on blood and muscle GSHpx activity, but during the depletion period, birds given selenomethionine were able to maintain blood and muscle GSHpx activity for significantly longer times than selenite-fed birds (Moksnes and Norheim, 1986). Payne and Southern (2005a) did not find differences between plasma GSHpx (a marker for body selenium status) in broilers fed either sodium selenite, selenium yeast in Sel-Plex™, or no supplemental selenium, but in a companion paper (Payne and Southern, 2005b) plasma GSHpx was sustained at increased activity in those broilers fed Sel-Plex™ compared with those fed either sodium selenite or no supplemental selenium.

Daun *et al.* (2004) reported that the major selenoaminoacids in poultry meat were selenomethionine and selenocysteine, and that glycolytic meat, represented by light coloured breast meat, contained less selenomethionine and selenocysteine than oxidative meat, represented by dark coloured thigh meat. There appears to be a species difference with duck, turkey, and ostrich binding more of the selenoaminoacids in glycolytic (light in turkey meat) and oxidative (dark in duck and ostrich) meats than in the chicken. It must be kept in mind that, unlike chicken and turkey white breast meats, all the meat from ducks is dark-oxidative, and the there is only the dark-oxidative thigh and drumstick meats (no harvest of breast meat) from ostriches. Daun *et al.* (2001 and 2004) noted that dark oxidative meat (thigh) from chicken had greater GSHpx activity than did the white glycolytic meat (breast), and that duck dark oxidative meats have GSHpx activities that are as much as five fold greater than GSHpx activities in chicken, turkey and ostrich meats. Daun and Åkesson (2004) reported a significant positive correlation between GSHpx activity and soluble selenium content in pork and beef muscle.

A problem with inorganic selenium

Selenium is distributed widely in various forms in soils, water, air, vegetation, and foods. Soils in arid and semi-arid areas have high selenium content, and those soils are often alkaline, favouring the formation of sodium selenate (Moxon *et al.*, 1950; Geering *et al.*, 1968). Selenium as a selenate is in the highest oxidation state (+6) and is stable under alkaline and other oxidising conditions (IPCS, 1987). Selenium in selenite is in the +4 oxidation state and occurs naturally. In alkaline conditions, selenite selenium oxidises slowly to the +6 state becoming the selenate ion, but no oxidation of the selenite selenium occurs in an acidic medium. However, the selenate ion is reduced to the selenite +4 state with the addition of hydrochloric acid (IPCS, 1987), which can occur on contact with the gastric acid produced in the proventriculus of poultry and in the monogastric stomach of mammals. This unstable chemical property of selenite selenium allows it to react with reducing substances such as dietary vitamin C (Ip, 1986; Gonzalez, 1990), ferric and ferrous ions (Rai *et al.*, 1995), and many other reducing agents in a redox type reaction causing oxidation of the reducing agents to a non-active form and reduction of selenite to elemental selenium (0) and selenide (−2), which are relatively unavailable to animals (Leeson and Summers, 1997).

Even though there is an ever-increasing database that shows the essential nature of organic selenium (selenium yeast/ Sel-Plex™) in animals, sodium selenite still is used principally as the source of selenium in many animal feeds. This seems paradoxical because sodium selenite has a documented pro-oxidant property that can oxidise many substances making them non-functional (Hafeman *et al.*, 1974; Csallany and Menken, 1986; Spallholz, 1997; Terada *et al.*, 1999; Schrauzer, 2000). Although selenium is essential for many biochemical and physiological functions in the body, high dietary levels of inorganic selenium often causes toxicity responses.

There are several mechanisms that allow development of selenium toxicity. The most common and important mechanism is the production of the superoxide radical ($O_2^{-\bullet}$) (Stohs and Bagchi, 1995). The superoxide radical has the ability to interact with thiols in mammals (Klaassen *et al.*, 1985) and birds (Hoffman *et al.*, 1991). Reaction of superoxide radicals with thiols can alter the activity of many antioxidant sulphydryl-containing enzymes as well as structural proteins in the body (Spallholz and Hoffman, 2002). When superoxide radicals react with thiols, they can generate additional destructive free radicals that can cause irreversible cellular damage (Spallholz, 1994). Spallholz (1994 and 1997) and Yan and Spallholz (1993) reported that superoxide free radicals (reactive oxygen species, [ROS]) and

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hydrogen peroxide (H_2O_2) generation were induced when selenite selenium interacted with thiol groups on many sulphur containing entities such as glutathione and L-cysteine, and free thiol groups in proteins, but free radical and hydrogen peroxide were not induced by selenomethionine.

Yet, the pro-oxidant potential associated with sodium selenite in animal feeds is not the only problem. Vitamin C is not routinely added to poultry diets because it can be synthesised readily by animals (McDowell, 2000), but it is used extensively as an anti-stress agent, especially during times of high temperature exposure (Kolb, 1984; Mahmoud *et al.*, 2004). Heat is a strong stimulus that induces oxidative stress that can cause damage to many different tissues and skeletal muscles in broiler chickens (Mahmoud and Edens, 2003; Azad *et al.*, 2010). Induction of oxidative stress requires greater antioxidant activity, and organic selenium is more effective than sodium selenite in the maintenance of antioxidant activity via the maintenance of the activity of GSHpx (Mahmoud and Edens, 2003).

Leeson and Summers (1997) have stated that ferrous salts are preferred to ferric salts as a source of dietary iron in poultry feeds, but ferrous salts can be oxidised to ferric salts by selenite during feed storage at a moderate ambient temperature of 25 °C. Eisenberg (2007) described the effect of water activity in feeds that results in the reduction of the very hygroscopic sodium selenite to the elemental form of selenium. The process of reduction of sodium selenite to elemental selenium is facilitated by the presence of reducing agents such as vitamin C, ferrous salts, iodides and other reducing agents in premixes and feeds with high water activity.

Additionally, it is likely that sodium selenite, which is hygroscopic, will dissolve to form selenous acid and disappear as a vapour. Eisenberg (2007) demonstrated that even if poultry feeds are formulated with low water activity, it readily absorbs moisture from the environment allowing sodium selenite to become reactive- only to be reduced to elemental selenium or to be converted to volatile selenous acid.

Thus, selenite is likely to be at a level less than nominal in poultry feeds, especially in feeds stored in warm humid conditions, but the residual sodium selenite would still have the potential to act as a pro-oxidant in the feed and in the animal. In a reactive state, the pro-oxidant property of inorganic selenium would be capable of oxidising many ingredients in the feed and would attack such ingredients as vitamins, fats, and even proteins (Davies, 1987). Oxidised products in feed are known to have significant negative effects on meat quality (Igene and Pearson, 1979; Asghar *et al.*, 1989; Buckley *et al.*, 1989; Sheehy *et al.*, 1993b). Nevertheless, supplementation of poultry diets with vitamin E has the effect of reducing lipid peroxidation and increasing shelf-life of poultry meat (Sheehy *et al.*, 1993a). However, supplemented vitamin E will have a limited time of effectiveness without dietary selenium in adequate concentrations. The interaction between selenium and vitamin E requires a cascading oxidation reduction pathway. Vitamin E reduction is dependent upon oxidative decarboxylation of 6-phosphogluconate to ribulose-5-phosphate in the pentose phosphate pathway and two selenoprotein antioxidant enzymes (glutathione peroxidase [GSH-px] and thioredoxin reductase, [TrxR]). TrxR reduces dehydroascorbic acid. The reduced ascorbic acid recycles the oxidised α-tocopheroxyl back to the reduced α-tocopherol (Vitamin E). Without GSHpx and the TrxR-facilitated reduction of oxidised ascorbate to reduced ascorbate, the recycling of Vitamin E would be minimal.

Although selenium is an essential trace element, high dietary levels of inorganic selenium cause toxicity. Toxicity of selenium is related to the concentration of the selenium, duration of exposure, and the form that is ingested (Spallholz and Hoffman, 2002). Most toxicity studies have examined the effects of sodium selenite in poultry and other livestock. Spallholz and Hoffman (2002) provided a list of selenium compounds known to have the ability to generate superoxides. Among those compounds important to the issue of oxidation, as influenced by dietary selenium, were selenite, selenium dioxide, and selenocysteine, and selenium compounds that did not generate superoxides were elemental selenium, selenate, selenomethionine, selenium-methylselenocysteine, and selenobetaine.

Ort and Latshaw (1978) fed graded levels of sodium selenite to laying hens, finding that selenite selenium was toxic at 5 mg/kg feed. Adult male albino rats were found to become intoxicated from sodium selenite at 6 and 8 mg/kg (Kaur and Kaur, 2000). Gowdy (2004) reported that in the modern fast growing, high yielding broiler chicken, signs of toxicity to sodium selenite could be detected when the broilers were fed as little at 1 mg/kg in their feed, but up to 20 mg/kg of organic selenium as selenium yeast (Sel-Plex™) did not cause signs of toxicity.

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Mice exposed to L-selenomethionine or inorganic sodium selenite at 0, 0.1, 0.3, or 0.9 mg/l of drinking water did not express any signs of toxicity at any level of L-selenomethionine but not the case for sodium selenite, indicating that inorganic sodium selenite is more toxic than organic selenium (Johnson *et al.*, 2000). Selenomethionine and selenocysteine at 2.5, 5, and 12.5 μM/l, did not induce cytoxicity, oxidative DNA lesions, or apoptosis (Stewart *et al.*, 1999). However, Lowry and Baker (1989) showed that pure selenomethionine at high dietary incorporation was toxic in avian species. In mallard duck embryos, pure L-selenomethionine was significantly more toxic than DL-selenomethionine (Heinz *et al.*, 1996).

Neither organic selenium as L-selenomethionine nor organic selenium yeast were found to generate superoxides, and it was hypothesised that organic selenium is less toxic than inorganic forms in waterfowl (Spallholz and Hoffman, 2002). *In vitro* studies with human lymphocytes have established a toxicity level of sodium selenite at 5μM/l, but that was not the situation with the addition of selenomethionine (Kelly and Powers, 1995). Similar results were seen in an *in vivo* study in which male BALB/c mice were given 0, 1, 3 or 9 ppm of selenium as sodium selenite or L-selenomethionine in the drinking water for 14 days. The thymus/body weight ratio was significantly reduced at 3 ppm of sodium selenite. Selenite at 9 ppm also significantly increased the production of proinflammatory cytokines in LPS stimulated macrophages, which has greater impact due to the potential production of both ROS and RNS by the activated macrophages and the potential for their interaction to form peroxynitrite. Induction of peroxynitrite represents a very serious free radical problem that could result in wide-spread cellular damage.

All of these studies have led to the conclusion that high levels of selenium in diets may be detrimental to health, but certain forms are more toxic than others. Thus, it was concluded by Spallholz and Hoffman (2002) that pure L-selenomethionine (SeMet) has a problem with toxicity when given into embryonated mallard eggs due to an unusual metabolism of that selenium form, which leads to accumulation of hydrogen selenide. L-selenomethionine deposited in mallard eggs from the dam's dietary intake was not toxic since that L-selenomethionine was complexed with protein, which rendered it a non-toxic entity in the egg white proteins. Furthermore, it has been reported that selenite selenium is more toxic to mallard ducklings than L-selenomethionine (Heinz *et al.*, 1988)

Following the publication of the observation that selenium is an essential micro-trace element (Schwarz and Foltz, 1957 and 1958), intensified research revealed that selenium was a factor needed for the nutrition and normal metabolism in chickens, turkeys, pigs, cattle, sheep and all other animals (Scott, 1973). However, the US Food and Drug Administration delayed the approval of selenium as an essential trace mineral for a period of 17 years before it responded to the well documented problems associated with deficiency of selenium in animal feeds. Finally, in 1974 the US Food and Drug Administration (1974) approved the use of selenium as a supplement to poultry and animals feeds, with a stipulation that either sodium selenite or sodium selenate were allowed at levels not to exceed 0.1 mg/kg for chickens and swine and 0.2 mg/kg for turkeys. In 1987 the US Food and Drug Administration modified the Federal Code, which allowed the use of 0.3 mg/kg of feed.

Since 1974, many studies have been conducted to ascertain the many roles played by selenium in poultry and livestock nutrition and biochemistry. In addition to the study of sodium selenite, which was chosen as the primary selenium form for poultry and livestock feeds, a second research branch has developed for the elucidation of the importance of selenomethionine as a free selenoaminoacid or in selenium yeast as an alternative to sodium selenite as a source of dietary selenium (Schruazer, 2000).

Functions of organic and inorganic selenium as antioxidants

The use of dietary selenium as an element necessary to support the glutathione-glutathione peroxidase (GSH-GSHpx) antioxidant system has greatly influenced poultry and livestock nutrition. A recent meta-analysis (Bermingham *et al.*, 2014) demonstrated that dietary selenomethionine and selenium-yeast in particular can increase GSHpx in selenium-enriched muscle foods more efficiently than selenite selenium. Generally, there are no differences in GSHpx activity in various tissues including muscle tissue of broilers given either Sel-Plex™ as a source of organic selenium or the inorganic sodium selenite (Mahmoud and Edens, 2003 and 2005; Wang *et al.*, 2011ab). Nevertheless, retention of organic selenium is longer in poultry given organic selenium than for those fed sodium selenite, and under long-term

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depletion due to consumption of a selenium deficient diet, increased GSHpx activity can be maintained in all tissues, including muscle, of broilers (Zhang *et al.*, 2014) and layers (Moksnes and Norheim, 1986) previously fed organic selenium.

There are six known selenium-dependent glutathione peroxidases (GSHpx), which include GSHpx-1 in the cell cytosol, GSHpx-2 in the gastrointestinal tract, GSHpx-3 in plasma, GSHpx-4 in the cell membranes and spermatozoa, GSHpx-5 in the epididymus, and GSHpx-6 in olfactory epithelium and embryonic tissues (Pappas *et al.*, 2008; Brigelius-Flohe and Maiorino, 2013).

The role played by selenium-dependent GSHpx in maintaining a cellular environment favouring a reduced state is well documented as reported above. However, the relationship between GSHpx activity and GSH is often relegated to a secondary level of importance. Nevertheless, GSH is the most abundant of all of the non-protein thiols found in cells (Dickenson and Forman, 2002) and promotes the general antioxidant status within cells acting as a co-factor for all GSHpx activities (Sies, 1999; Arteel and Sies, 2001). It functions directly in the neutralisation of free radicals and serves in the maintenance of the reduced forms of the antioxidant vitamin C (Hughes, 1964) and vitamin E (Scholz *et al.*, 1989). Vitamin E is vitally important in preservation of meat quality. Other functions in which GSH is used include metabolic and biochemical reactions such as DNA synthesis and repair, gene expression, protein synthesis, prostaglandin synthesis, amino acid transport, and enzyme activation (Sies, 1999; Arteel and Sies, 2001; Dickenson and Forman, 2002; Pompella *et al.*, 2003). The indirect antioxidant activity of GSH in combination with GSHpx involves its use as a substrate by GSHpx in the reduction of hydroperoxides and lipid peroxides (Cohen and Hochstein, 1963). In addition to the role played by GSH as an antioxidant against reactive oxygen radicals, it interacts with peroxynitrite to reduce it to nitrite in an interaction with GSHpx (Radi *et al.*, 1991; Sies *et al.*, 1997). Peroxynitrite is a potent RNS radical that can cause oxidation of membrane lipids, which can affect the oxidative stability of lipids, flavour, colour and functional properties of meat (Brannan *et al.*, 2001).

The tissue concentration of GSH is altered by its redox status in the cell and its organelles (Lu, 2013; Aoyama and Nakaki, 2015). As an antioxidant, GSH interacts with GSHpx in catalysed reactions in which hydroperoxides and lipid peroxides are reduced while GSH is oxidised to glutathione disulphide (GSSG). The oxidation of GSH to GSSG is reversible through the action of GSSG reductase (GR) at the expense of NADPH, which yields reduced GSH (Lu, 2009). It is the ratio between GSH to GSSG that sets the redox state in a cell (Forman *et al.*, 2009). Under severe oxidative stress, cellular GSH can be decreased when the oxidative stressor overcomes the cell's ability to reduce GSSG back to GSH. When this occurs, the excess GSSG is exported actively from the cell, or it is bound reversibly to cellular protein sulphhydryl groups (Lu, 2013). A very important observation made by Mahmoud and Edens (2003) was that in Sel-Plex™-fed broilers subjected to a heat stressor (an inducer of oxidative stress), the reduction of GSSG to GSH was increased to meet the demands associated with the increased oxidative stress associated with the heating episode. Liver GSH and GSSG were in greater concentrations, respectively, than their concentrations in selenite and control fed broiler chickens (Mahmoud and Edens, 2003). This demonstrated that the redox balance in Sel-Plex™-fed broilers was improved compared to selenite and control fed broilers experiencing oxidative stress.

The primary source of GSH is the liver, which secretes large amounts into the plasma, where it is then used to maintain inter-organ GSH homeostasis (Bartoli and Sies, 1978; Ookhtens and Kaplowitz, 1998). The phospholipid hydroperoxide glutathione peroxidase (GSHpx-4) activity that inhibits lipid peroxidation in membranes requires the presence of both GSH and vitamin E in order for the enzyme to inhibit the rate of the initiation reactions (Ursini *et al.*, 1986; Ursini and Bindoli, 1987; Maiorino *et al.*, 1989 and 1991; Nomura *et al.*, 2000). In plasma membranes, the GSHpx-4 interaction with GSH only accounts for partial inhibition of lipid peroxidation, but the presence of vitamin E in the membrane allows for nearly complete inhibition of lipid oxidation (Ursini and Bindoli, 1987). By preventing the free radical generation from lipid hydroperoxides, GSHpx-4 activity can reduce the vitamin E requirement necessary to inhibit lipid peroxidation (Ursini and Bindoli, 1987).

The antioxidant selenoenzyme GSHpx-4 is unique in that it has a primary residence in cell membranes where it, along with GSH, targets peroxidised phospholipids (Ursini *et al.*, 1982 and 1985). All GSHpx's have the ability to reduce hydrogen peroxide, alkyl peroxide, and fatty acid hydroperoxides, but GSHpx-4 is special in that it alone can reduce hydroperoxides in lipoproteins and other complex lipids associated with cholesterol, cholesteryl esters and phospholipids in conjunction

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with α-tocopherol (Maiorino *et al.*, 1991; Liang *et al.*, 2007). The presence of GSHpx-4 in cell membranes is very important since it reduces lipid hydroperoxides and provides protection for the integrity and stability of the cell plasma and subcellular membranes (Maiorino *et al.*, 1991), which is vitally important in oxidative stability. As a selenoprotein, GSHpx-4 is sensitive to tissue selenium status. Zoidis *et al.* (2010) fed Sel-Plex™ (0, 0.15, 0.3, or 3.0 ppm supplemental selenium/kg) to broiler chickens and quantified the selenium concentration in blood and liver. Increasing levels of Sel-Plex™ caused a progressive parallel increase in selenium in both blood and liver, but unlike GSHpx-1, which can be elevated in parallel with dietary selenium forms, in chickens GHSpx-4 will down regulate its expression when dietary selenium exceeds 0.15 ppm (Zoidis *et al.*, 2010). In another study, Wu *et al.* (2010) examined the effect of no selenium, sodium selenite, DL-selenomethionine, or κ-selenocarrageenan (another source of organic selenium) on cultured chicken hepatocytes' ability to express GSHpx-1 enzyme and GSHpx-4 mRNA. The GSHpx-1 activity increased with increasing selenium concentration in the incubation media, but when the incubation medium selenite selenium concentration exceeded 2 μmol/l, the GSHpx-1 activity decreased. Nevertheless, hepatocytes exposed to DL-selenomethionine continued to maintain significantly greater GSHpx-1 activity compared to sodium selenite or κ-selenocarrageenan. Wu *et al.* (2010) noted that chicken hepatocyte GSHpx-4 mRNA expression was maximised when selenium sources were at 0.5 μmol/l in the incubation media and decreased with increasing selenium concentrations in the incubation media. However, hepatocytes exposed to DL-selenomethionine expressed significantly more GSHpx-4 mRNA than hepatocytes exposed to either sodium selenite or κ-selenocarrageenan. In the turkey poult GSHpx-4 enzyme activity often can be an interfering factor to accurate measurement of GSHpx-1 since up to 47% of the GSHpx-1 activity can be contributed by GSHpx-4 (Sunde and Hadley, 2010). However, unlike the chicken, increasing selenium intake does not appear to depress turkey liver GSHpx-4 activity (Sunde and Hadley, 2010). It has been reported that the selenium requirement for turkey GSHpx-4 is less than the requirement for GSHpx-1 and was variable among different tissues of the turkey (Sunde and Hadley, 2010). A similar observation was made in the *in vitro* chicken hepatocyte study, which revealed maximised GSHpx-4 mRNA expression at 0.5 μmol/l (Wu *et al.*, 2010). The low selenium requirement for GSHpx-4 expression appears to be the reason why very small amounts of dietary selenium could spare the dietary requirement for the lipid bound antioxidant vitamin E (Ursini *et al.*, 1985). Thus, it appears that GSHpx-1 and GSHpx-4, GSH, and vitamin E are necessary for maintenance of oxidative stability in muscle cells and in the maintenance of meat quality.

It has been hypothesised that poultry meat quality is improved with the use of diet-supplied antioxidants (Delles *et al.*, 2014, 2015). Delles *et al.* (2014) noted that breast meat from broilers had significantly higher GSHpx activity and selenium content after antioxidant supplementation. They also observed that high levels of oxidised fat in the diet caused decreased GSHpx activity, which was corrected by antioxidant supplements. Upton *et al.* (2009) noted that both sodium selenite and Sel-Plex™ increased GSHpx activity in the red blood cells and liver of broilers fed oxidised fat. However, in sodium selenite fed broilers, hepatic GSHpx was decreased by highly peroxidised dietary fat, while in broilers fed Sel-Plex™, the GSHpx activity was maintained at an elevated activity.

Fellenberg and Speisky (2006) noted that feed-grade antioxidants generally improved systemic oxidative stability in broilers and that oxidative stability, related to oxidation of polyunsaturated fatty acids (PUFA), extended into the post-mortem conversion of muscle to meat. The Fellenberg and Speisky (2006) review focused on the antioxidant functions of α-tocopherol forms, β-carotene, BHA/BHT, tea catechins, ethyoxyquin, and the plant extracts of rosemary, sage, green tea powder, and dried tomato pulp. Each of the aforementioned antioxidants has a different mechanism of action, but the ultimate mode of action is to remove free radical initiators of oxidative stress and the free radical propagators of oxidative stress in muscles before and after the animal has been slaughtered. Underlying the different mechanisms of action of the antioxidants is the fact that each will act as a donor of a proton reducing equivalent to bind and inactivate free radicals while becoming an oxidised free radical themselves. However, the oxidised form of the primary antioxidant can regenerate back to the reduced form via acceptance of another reducing equivalent from another antioxidant donor.

The supplementation of L-selenomethionine, which is the major selenoaminoacid in Sel-Plex™, to broiler breeders had major effects in their progeny. Zhang *et al.* (2014) found increased GSHpx activity in breast muscle of 56-days old progeny and noted that the

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supplementation of L-selenomethionine to the breeder caused stabilisation of the nucleus, cellular organelles and membranes of cells in several organs in the progeny. The observations by Zhang *et al.* (2014) are rather intriguing. Biological membranes are targets for reactive oxygen species (ROS) and reactive nitrogen species (RNS) that often interact to produce peroxynitrite, which then induces lipid peroxidation of membrane phospholipid unsaturated fatty acids causing alterations in the membrane physical properties such as changes in membrane fluidity causing alterations on cell permeability and enzyme activities (Horan *et al.*, 1994; Ahsan *et al.*, 2003; de Lima *et al.*, 2004). RNS are produced in animals starting with the reaction of nitric oxide (•NO) with superoxide ($O_2^{-\bullet}$) to form peroxynitrite ($ONOO^-$; Blough and Zafiriou, 1985), which might be the most damaging of all the free oxygen/nitrogen radicals (Roussyn *et al.*, 1996). Roussyn *et al.* (1996) reported that peroxynitrite caused single strand breaks in DNA, which could be effectively blocked (75%) by selenomethionine. Briviba *et al.* (1996) reported that sodium selenite had no protective effects against oxidation and nitration reactions of peroxynitrite differing from the protective properties of selenomethionione. Walter and Roy (1971) reported that selenomethionine had a GSHpx property, which allowed it to act in an antioxidant manner. Sies *et al.* (1997 and 1998) further noted that in addition to selenomethionine, selenium-containing enzymes catalyse peroxynitrite reduction and that GSHpx-1 played a dual role in its ability to act as a peroxynitrite reductase. Later, Sies and Arteel (2000) reported that selenoaminoacid residues in proteins had the potential to protect against peroxynitrite (RNS). Thus, it appears that selenomethionine, either as a free amino acid, as a component in selenium yeast, or as a residue in protein in muscle, could act as an antioxidant against ROS and RNS, which would ultimately protect muscles from oxidative damage. Sel-Plex™, which contains organic selenium as selenomethionine, is known to improve antioxidative status of broilers via their increased selenium content in muscle and via increased activity of enzymes such as GSHpx-1 and GSHpx-4, and their interaction with both GSH and vitamin E in cell membranes to decrease the potential for phospholipid oxidation in the membrane.

Conclusions

The purpose of this review was to examine the role of organic selenium, and specifically Sel-Plex™, which provides an organic form of selenium in yeast protein, in animal nutrition. The interaction between selenium, which forms the basis of many antioxidant enzymes and proteins, and vitamin E, which is known to have a powerful function in preventing lipid and poly-unsaturated fatty acid oxidation, seems to be the ultimate focus, perhaps justifiably. The observation that most researchers have potentially measured the wrong selenium dependent antioxidant enzyme in GSHpx-1, whereas information delineated in this review holds that GSHpx-4, which resides within cell membranes along with GSH and vitamin E, is the form that should be measured relative to antioxidant influence by selenium in poultry meat. Use of commercial products such as Sel-Plex™ appears to provide a more reliable source of natural organic selenium compared to other forms, especially inorganic selenite and selenates.

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Declaration of interest

Dr. A. E. Sefton is an employee of Alltech, Inc. USA.

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