# Vitamin E and Se: does 1+1 equal more than 2?

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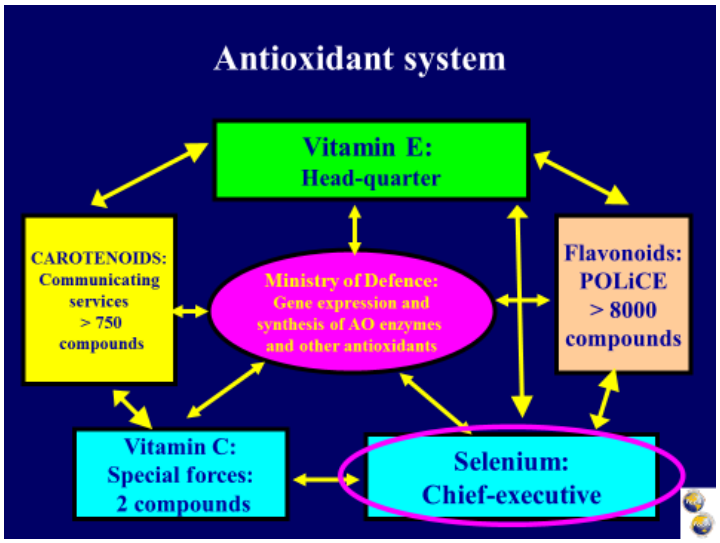
## Introduction

It is well known that animal/poultry production is associated with a range of stresses, including environmental (high or low temperature, dust, not optimal humidity, etc.), technological (bird placement, vaccination, grading, transfer and transportation, etc.), nutritional (mycotoxins, oxidized fat, diet changes, etc.) and biological/internal (disease challenge, peak of production, etc.) stresses. For the last 20 years, it has been proven that at molecular levels major stresses are associated with oxidative stress due to imbalance between free radical production and their detoxification and removal by antioxidant system. In fact, about 20 billion free radicals are produced in every cell every day and this number is substantially increased in stress conditions. The free radicals can damage all types of biological molecules, including polyunsaturated fatty acids in biological membranes, proteins and DNA. This could lead to health problems, including immunosuppression, decreased productive and reproductive performance.

### The antioxidant system network

Indeed, the antioxidant system network in animal/chicken body is responsible for adaptation to various stresses. This network includes a range of antioxidants. Some of them are synthesised in the body and others have to be supplied with the diet.



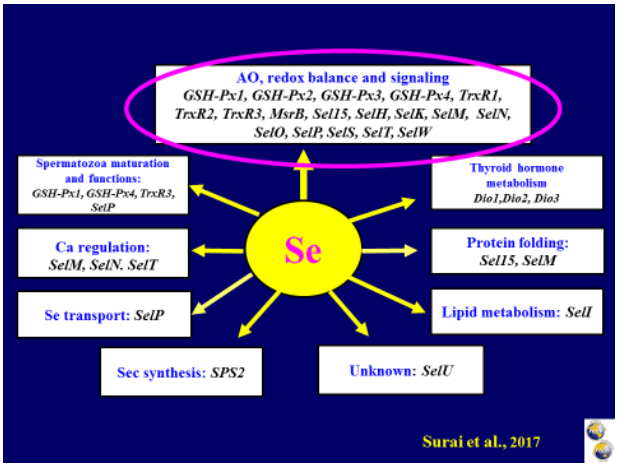

The antioxidant system is a team of various antioxidants working cooperatively and providing an effective antioxidant defences. In the team, vitamin E is called head-quarter of antioxidant defence, since it is located in lipid fraction of the cell and responsible for prevention of lipid peroxidation inside biological membranes, which are a building blocks of every cell and the damages to membranes are detrimental to various physiological functions. Indeed, vitamin E is main fat-soluble antioxidant in biological membranes.

There are at least 750 carotenoids in nature and they also participate in antioxidant defence, but their direct antioxidant properties are not very strong. In many cases carotenoids affect gap junctions in the cell and responsible for cell communication. That is why they are called communicating services of antioxidant defence.

Vitamin C is synthesised in farm animals and poultry, mainly in kidney, but in stress conditions, this synthesis could not cover vitamin C requirement and its dietary supplementation can help to deal, for example, with heat stress. Vitamin C is considered to be Special Forces of antioxidant defence. It acts directly by scavenging free radicals and indirectly by participating in vitamin E recycling.

There are more than 8 000 natural compounds belonging to polyphenols with flavonoids to be the major part of polyphenolics. For the last 40 years, flavonoids have been at the front of the antioxidant research and application. There are a lot of papers devoted to antioxidant properties of flavonoids. However, recently it has been shown that flavonoids are not direct antioxidants but rather acting as indirect modulator of antioxidant system by affecting various transcription factors including Nrf2 and NF-kB. In particular it was shown that in in vitro experiments effective doses of flavonoids showing antioxidant properties are 100-1000-fold higher than those achievable in biological tissues. Therefore, low bioavailability dietary flavonoids restrict their usage as feed antioxidants. Depending on conditions, flavonoids can be antioxidants or prooxidants and they are called antioxidant police.

Selenium has a special place in the antioxidant defence network being chief-executive of antioxidant defence. In fact, there are at least 25 selenoproteins in animal/chicken body which are participating in regulation of various physiological functions. Interestingly, more than half selenoproteins participate in redox balance maintenance and antioxidant defences.




**Special role of Se in antioxidant defences**

Selenoprotein expression and synthesis in the body depend on two major factors, namely level of stress and Se status. Therefore, by providing dietary Se in optimal form and concentration it is possible to improve adaptive ability of farm animals and poultry to various commercially-relevant stresses. It is necessary to mentioned that only optimal Se status provides maximal antioxidant protection, since both Se deficiency and excess are detrimental for animal/poultry health and productivity. Selenoproteins are not synthesised in advance since it is very expensive process and they are synthesised as needed. Some of selenoproteins functioning as housekeeping elements and their comparatively low expression can be found in tissues even at low Se status. However, major part of selenoproteins are adaptive molecules synthesised in response to stress conditions and their increase expression and activity parallel level of stress.

## Vitamin E-Se interactions

Historically, antioxidant properties of vitamin E and Se were considered together. In fact, many animal/poultry diseases related to low dietary vitamin E/Se were described in 1980th.

**Table 1 Diseases associated with selenium and vitamin E deficiency in animals (Adapted from Surai, 2006)**

| Syndrome | Tissue or organ affected | Species |
|---|---|---|
| Encephalomalacia | Cerebellum | Chick, turkey, emus, partridges, Quail, pheasant and various zoo species |
| Exudative diathesis | Vascular | Chick, turkey, duck, salmon, catfish |
| Microtic anaemia | Blood, bone marrow | Chick, monkey, pig, rat, salmon, catfish |
| Liver necrosis | Liver | Pig, rat, mouse |
| Pancreatic fibrosis | Pancreas | Chick, salmon, mouse |
| Erythrocyte haemolysis | Erythrocytes | Chick, lamb, monkey, rat |
| Muscular degeneration | Skeletal muscle | Chick, duck, goose, ostrich, flamingo, Monkey, dog, rabbit, guinea pig, horse, calf, lamb, kid, mink, antelope, pig, rodents, salmon, catfish |
| Microangiopathy | Heart muscle | Turkey, pigs, calf, lamb, rat, dog, rabbit, guinea pig, cow, sheep, goat, baboon, antelope, elephant, deer |
| Kidney degeneration | Kidney tubules | Monkey, rat, mouse |
| Embryonic degeneration | Vascular system | Pig, rat, mouse |
| Poor hatchability | Egg embryo | Chick, turkey |
| Steatitis | Adipose tissue | Pig, chick |
| Testicular degeneration | Testes | Pig, calf, chick, pig, monkey, rat, rabbit, guinea pig, hamster, dog |
| Retained placenta | Placenta | Cow |
| Impaired fertility | Spermatozoa | Sheep, cattle, poultry, pig, rat |
| Ill-thrift | Thyroid, pituitary | Lamb, calf |

Interestingly, in the development of most the aforementioned diseases redox balance deterioration and oxidative stress are involved.

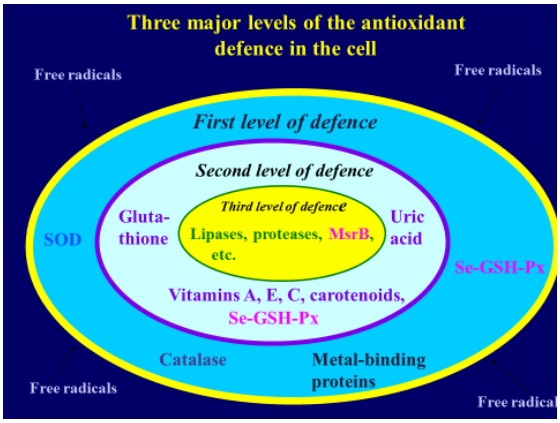
When considering antioxidant properties of vitamin E it is necessary to underline that the major protective reaction of vitamin E is its detoxification of lipid peroxyl radical (LOO*):

**Vit.E + LOO* = Vit.E* + LOOH**

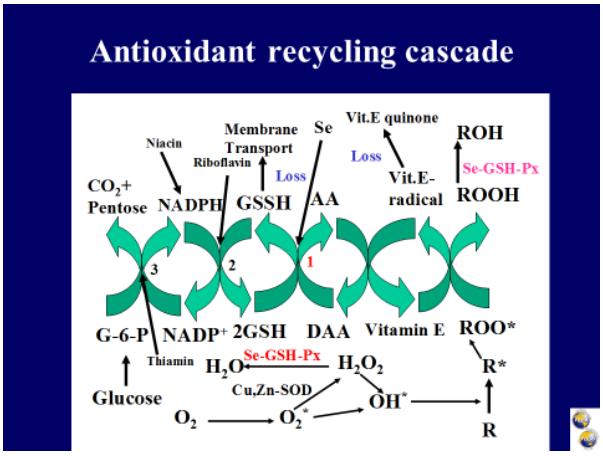
As a result of the lipid peroxyl radical scavenging by vitamin E, a toxic product called lipid hydroperoxide (LOOH) is formed and must be removed from the cell. This is the job for Se-dependent GSH-Px:

**2GSH+ LOOH + GSH-Px = LOH (non-toxic) + H2O + GSSG + GSH-Px**

Therefore, vitamin E and other chain-breaking antioxidants perform only half the job in prevention of lipid peroxidation, and the second half is for GSH-Px. Interestingly, as part of selenoproteins, Se belongs to all major three levels of antioxidant defence in the cell/body:

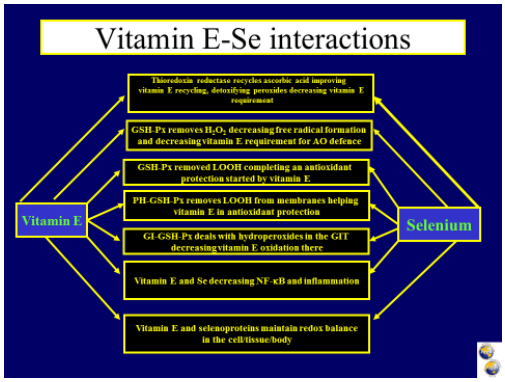



As a result of scavenging free radicals vitamin E is oxidised (vit.E*) and if not reduced back to active form, it is lost. Taking into account a great number of free radicals in the call (20 x $10^9$) it is impossible to get the same number of vitamin E molecules into the cell and vitamin E recycling is considered as the most important mechanism of antioxidant defences in biological systems.



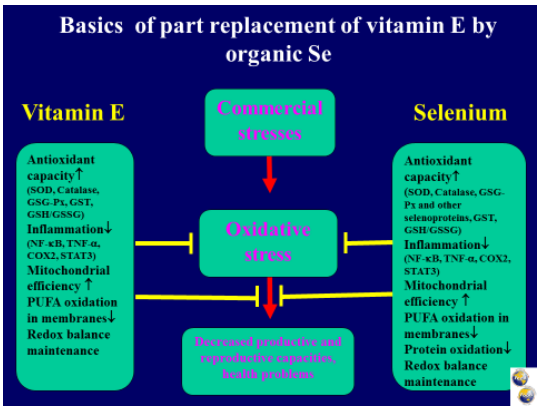
In the vitamin E recycling cascade there is a special role for selenoenzyme thioredoxin reductase (1) which is responsible for recycling ascorbic acid and maintaining the whole chain of vitamin E recycling. Therefore, in many cases when recycling of vitamin E is effective, even low vitamin E concentrations (e.g. brain tissues) can provide an effective antioxidant protection. Indeed, the antioxidant potential of vitamin E is more dependent on efficacy of its recycling than on its concentration and Se has a special role to play in this process.

In general there are at least seven levels of vitamin-Se interactions in the cell and they are shown in the picture.



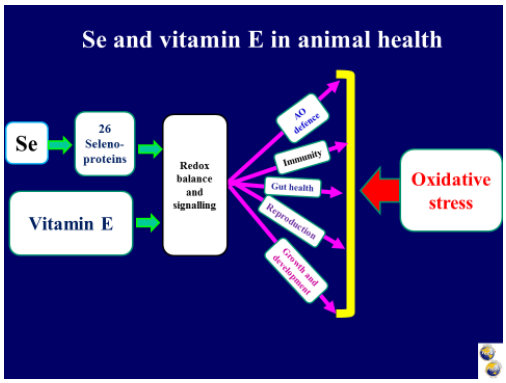

First of all, selenoprotein thioredoxin reductase participates in vitamin E recycling keeping vitamin E in active form. Secondly, GSH-Px removes $H_2O_2$ decreasing free radical formation and decreasing vitamin E requirement for AO defence. Thirdly, GSH-Px removed LOOH completing an antioxidant protection started by vitamin E. Fourthly, PH-GSH-Px removes LOOH from membranes helping vitamin E in antioxidant protection. Fifthly, GI-GSH-Px deals with hydroperoxides in the GIT decreasing vitamin E oxidation there. Furthermore, both vitamin E and Se are able to decrease NF-κB expression and possess anti-inflammatory action. Finally, Vitamin E and selenoproteins maintain redox balance in the cell/tissue/body providing optimal conditions for cell signaling and adaptation to stress. It seems likely that, selenoproteins are more potent than vitamin E in maintaining redox balance of the cell.

Therefore, vitamin E and Se have a lot of similarities in building an effective antioxidant defence network in the body and the general scheme of their action is shown below.



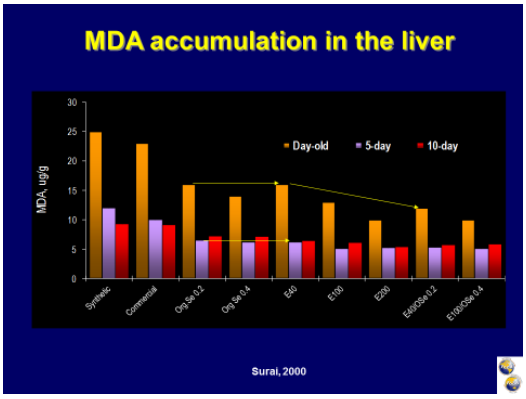

Both vitamin E and Se are important elements of redox balance regulation and this could be related to maintenance of antioxidant defences, immunity/general health, gut

health, reproduction, growth and development of animal/poultry in commercially relevant stress conditions.

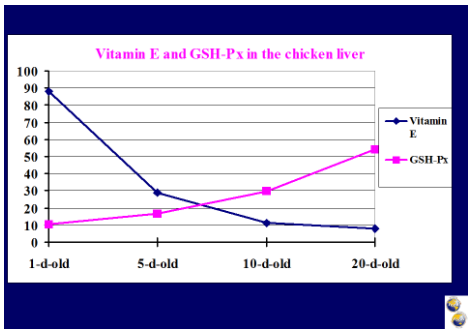



**Is it possible to replace vitamin E by Se?**

The sparing effect of Se on vitamin E has been shown in many various animal/poultry trials. In fact, at the trial conducted at the Scottish Agricultural College it was shown that efficiency of organic Se (0.2 mg/kg diet) in the broiler breeder diet against lipid peroxidation in the liver of newly hatched chicks is similar to vitamin E supplemented at 40 mg/kg (Surai, 2000).




Similar positive effect of dietary Se on vitamin E concentration in the egg was reported later by Skrivan et al. (2008) and Tufarelli et al. (2016). It is important to mention that after chick hatching there are changes in a strategy of antioxidant defences in the postnatal chickens. Since vitamin E is poorly absorbed and assimilated from the diet by newly hatched chicks, its concentration in the liver (main vitamin E reserves in the body) dramatically decrease for the first 9 days posthatch (Surai et al., 1998). At the same time GSH-Px activity increase and therefore this is an adaptive mechanism to deal with postnatal stresses in chicken life.



Indeed, in comparison to sodium selenite, organic Se is more effectively assimilated from the diet, transferred to the egg and newly hatched chicken providing an effective antioxidant defences via expression and synthesis of major selenoproteins.

Similar sparing effect of organic Se has been seen with broilers as well (Markovic et al., 2008). In fact a combination of 20 mg/kg vitamin E with organic Se was shown to have similar protective effect as a combination vitamin E at 100 mg/kg with sodium selenite.

**Effect of vitamin E and Se on chickens**

TBARS (indicator of oxidative stress)

| Parameter | day | 20 IU Vitamin E | | 100 IU Vitamin E | |
|---|---|---|---|---|---|
| | | Selenite | Org. Se | Selenite | Org. Se |
| Plasma i mmol MDA/L | 1 | 7.43 | | | |
| | 21 | 6.81 | 6.70 | 6.12 | 6.80 |
| | 42 | 6.88 | 6.44 | 6.79 | 6.71 |
| Breast, mg MDA/kg | 1 | 0.53 | | | |
| | 21 | 0.82 | 0.56 | 0.70 | 0.43 |
| | 42 | 1.09$^{aA}$ | 0.62$^{aB}$ | 1.03$^{b}$ | 0.68$^{d}$ |
| Liver, mg MDA/kg | 1 | 0.56 | | | |
| | 21 | 1.12 | 0.75 | 1.01$^{a}$ | 0.73$^{b}$ |
| | 42 | 0.59 | 0.57 | 0.66 | 0.74 |
| Breast, mg MDA/kg | frozen | 1.69 | 0.78 | 1.03 | 0.72 |

$^{A,B}$ Means differ, p<0.01 $^{a,b}$ Means differ, p<0.05

Markovic et al., 2008

Similarly, in growing chickens a combination of vitamin E at 50 mg/kg with organic Se was shown to have similar protective antioxidant effect to a combination of higher vitamin E level (200 mg/kg) with sodium selenite (Ozkan et al., 2007).

**Effect of vitamin E and Se on broilers**

Liver biochemistry

| | 50 IU Vitamin E | | 200 IU Vitamin E | |
|---|---|---|---|---|
| | Selenite | Org. Se | Selenite | Org. Se |
| GSH-Px, mU/mg protein | 3.19 | 2.65 | 3.72 | 2.83 |
| Catalase, U/mg protein | 17.98 | 16.71 | 16.10 | 16.38 |
| GSH, mmol/mg protein | 7.95 | 6.16 | 6.33 | 7.03 |
| MDA, nmol/g | 21.07 | 25.62 | 25.09 | 24.96 |

Ozkan et al., 2007

Interestingly, a protective effect of a combination of organic Se with lower vitamin E dose was shown to be more pronounced in cold-stressed broiler chickens (Ozkan et al., 2007).

**Effect of vitamin E and Se on cold-stressed broilers**

Liver biochemistry

| | 50 IU Vitamin E | | 200 IU Vitamin E | |
|---|---|---|---|---|
| | Selenite | Org. Se | Selenite | Org. Se |
| GSH-Px, mU/mg protein | 3.53 | 4.69 | 3.77 | 3.32 |
| Catalase, U/mg protein | 13.37 | 14.03 | 12.26 | 15.93 |
| GSH, mmol/mg protein | 7.75 | 12.07 | 11.20 | 8.45 |

Ozkan et al., 2007

It is important to mention that in many cases when vitamin E or Se individually do not improve animal/chicken performance, a combination of vitamin E with organic Se can improve it. For example, inclusion of vitamin E and organic selenium in layer diet had a significant effect on production performance of laying hens and improved their immunity (Ziaei et al., 2013), while individually these antioxidant were not effective. It seems likely that by using organic Se in optimal form it is possible to reduce vitamin E level in poultry and farm animal diets.

**Practical recommendations**

1. **Poultry breeders:** current vitamin E supplementation – 100 mg/kg

*Recommended: 75 mg/kg vitamin E + 0.2-0.3 mg/kg Se in the form of pure form of organic selenium (OH-SeMet)*

2. **Layers:** current vitamin E supplementation – 10-20 mg/kg

*Recommended: 10 mg/kg vitamin E + 0.2-0.3 mg/kg Se in the form of pure form of organic selenium (OH-SeMet)*

3. **Broilers:** current vitamin E supplementation – 20-30 mg/kg

*Recommended: 20 mg/kg vitamin E + 0.2-03. mg/kg Se in the form of pure form of organic selenium (OH-SeMet)*

4. **Farm animals**
   Pigs, sows, boars, Cows, calf, etc.

*Recommended: 75% current supplementation of vitamin E + 0.2-03 mg/kg Se in the form of pure form of organic selenium (OH-SeMet)*