Recommendations for Use of

Menadione Sodium Bisulfite Complex (MSBC) in Animal Feed

Editor: Chair of Ingredient Definitions Committee

In 2021 AAFCO convened a panel of experts to provide policy recommendations for the use of Menadione Sodium Bisulfite Complex (MSBC) for intended uses beyond poultry feed. The panel recommended that Menadione Sodium Bisulfite Complex may be used as a safe and suitable source of Vitamin K activity in the food for all animals in the United States in accordance with good manufacturing and feeding practices. To reach their conclusion the expert panel carefully examined:

1. Confidential industry data demonstrating the safety of MSBC in both short- and long-term feeding studies at usual dietary inclusion rates.
2. An independent scientific literature review of MSBC and related compounds.
3. The 2014 European Food Safety Authority (EFSA) publication "Scientific Opinion on the safety and efficacy of vitamin K3 (menadione sodium bisulphite and menadione nicotinamide bisulphite) as a feed additive for all animal species."

In addition to the above, the expert panel noted that MSBC and the structurally related Menadione Nicotinamide Bisulfite (MNB) are authorized for use as vitamin K active substances in food for all animals in the European Union (EU) under Commission Regulation No. 2015/2307 (EC 2015) and in Canada under Schedule IV, Part I of the Feed Regulations, 1983 (CFIA 2020).

Review of Vitamin K and Vitamin K Active Substances[1.]

In his experiments to determine whether cholesterol was a dietary essential, Henrik Dam discovered a new substance, which he named vitamin K. In 1929, he observed a hemorrhagic syndrome in chicks fed a diet from which the sterols were extracted. Eventually, an active, anti-hemorrhagic factor was isolated from alfalfa and was identified as a vitamin K substance. The characterization of this anti-hemorrhagic factor was done by Edward Doisy of St. Louis University. Dam and Doisy shared the Nobel Prize in 1943 for the discovery of vitamin K and its chemical nature (Suttie 2009).

The major clinical sign of vitamin K deficiency noticed in all species is the impairment of blood coagulation. Clinical signs include, but are not limited to, increased clotting time and hemorrhage. Vitamin K deficiency can also lead to impaired bone mineralization due to inadequate levels of osteocalcin, a protein involved in bone mineralization.

Deficiencies may result from inadequate vitamin K in the diet, disruption of microbial synthesis within the gut (e.g., antibiotic use), inadequate absorption from the intestine, ingestion of vitamin K antagonists (substances that counteract the effect of vitamin K), or the inability of the liver to utilize available vitamin K. In many species, under normal health conditions endogenous synthesis of vitamin K is sufficient to meet metabolic needs without the requirement for a dietary source. However, in addition to medical conditions and/or use of therapeutic agents that may result in impaired synthesis, absorption or utilization

of vitamin K, acquired vitamin K deficiencies may also occur due to other dietary factors. For example, cats fed commercial canned diets high in salmon or tuna were found to suffer prolonged coagulation times, gastrointestinal and hepatic hemorrhages and death (Strieker et al., 1996). However, these signs were not observed when the animals were given supplemental phylloquinone (vitamin K_1). High dietary intake of sources of long-chain omega-3 fatty acids may also result in signs of vitamin K deficiency (Mameesh and Johnson, 1959; Saker et al., 1998). Because other fat-soluble vitamins may compete and hence interfere with vitamin K absorption, the addition of high levels of tocopherols to retard oxidation (for either preservative or nutritional reasons) in the food may be an aggravating factor in the development of a vitamin K deficiency. Vitamin K is generally known to exist in three forms, two of them are naturally occurring and one is a synthetic analogue which can be found naturally on normal Vitamin K metabolic pathways:

- **Vitamin K1**, also known as phytonadione or phylloquinone, is the form of vitamin K that occurs naturally in plants.
- **Vitamin K2**, or menaquinone, also naturally occurring, is the fat-soluble form of vitamin K synthesized by the bacteria in the intestinal tract. Bacteria can synthesize a range of related forms of this vitamin. These vitamin K analogues are collectively known as K2 and can be designated by length of sidechain, e.g., MK-4, MK-7, etc.
- **Vitamin K3**, also known as menadione, is the synthetic, water soluble analogue of vitamin K that can be converted to K2 by bacteria in the intestine. Enzymes in mammalian and avian tissues are also capable of converting menadione to the active forms of vitamin K. Menadione is also a metabolite of Vitamin K active substances consumed orally (Thijssen 2006, Hirota 2013).

The structures of the different vitamin K forms are shown in Figure 1. Vitamin K1 and K2 contain a common 2-methyl-1,4-napthoquinone ring but differ in terms

of the length and degree of saturation of the polyisopropenoid side chain at position 3. In vitamin K1 the side chain is a phytyl substituent comprising 4 isoprenyl units of which one is unsaturated, whereas in vitamin K2 a variable number of isoprenyl units are present in the unsaturated form. Vitamin K3 contains the same 2-methyl-1,4-napthoquinone ring but the alkyl side chain is replaced with a hydrogen (menadione) or sulfate derivative (eg, sodium bisulfite). The menadiones must undergo prenylation in the intestinal tract and tissues in order to become a biologically active form (menaquinone form) of vitamin K which can be utilized by the animal.

Figure 1: Structure of the Different Forms of Vitamin K

<table>
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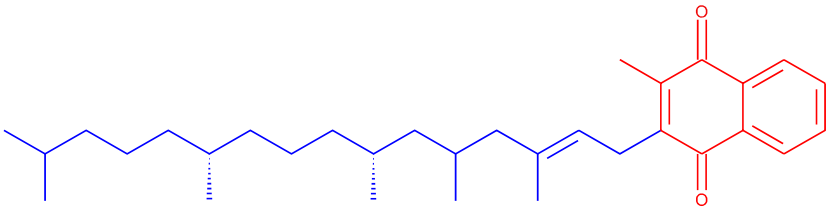
<tr><td colspan="3">  </td></tr>
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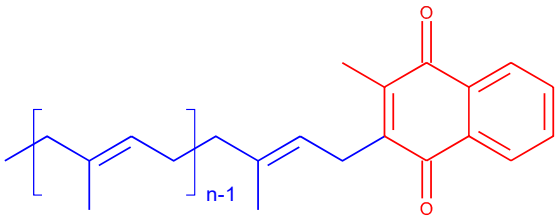
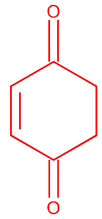
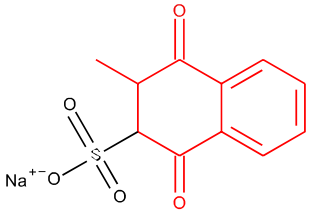
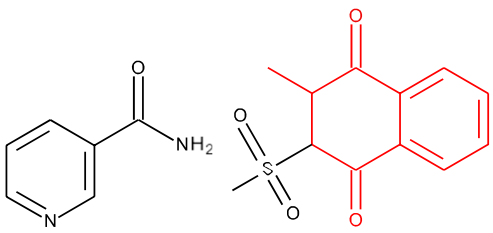
<tr><td colspan="3"> 
</td></tr>
<tr><td colspan="3">Vitamin K3 – menadiones</td></tr>
<tr><td>  </td><td> 
</td><td> 
</td></tr>
<tr><td>Menadione</td><td>Menadione sodium bisulfite complex (MSBC)</td><td>Menadione nicotinamide bisulfite (MNB)</td></tr>
</table>

As mentioned above, Vitamin K3 refers to a group of water soluble menadiones which are converted in the intestinal tract of animals to vitamin K2 (menaquinones) and then absorbed. The menadione content of MSBC is approximately 50% by weight, and that of MNB approximately 44% (EC 2015). This general group of menadiones has been shown to be metabolized by the same pathways in all animals studied (Hirota 2013, Okano 2008, Terachi 2011). Under normal physiological conditions, lipid soluble vitamins K_1 and K_2 can be absorbed in cooperation with bile acid and pancreatic enzymes (Shearer 1975). Absorbed phylloquinone is partly converted to MK-4 consistent with menadione acting as an intermediate metabolite (Thijssen 1996, Okano 2008). The release of menadione can occur in the intestine and it can undergo prenylation both in the intestine and tissues. Menadione is expected to be absorbed from both the small intestine and colon of animals by passive diffusion (NRC 2006).

Ever since its initial discovery, vitamin K has been known to be important in the clotting process of blood, because of its involvement in the synthesis of four plasma clotting proteins. These proteins are factor II (prothrombin) and factors VII, IX, and X. More recent studies have shown that vitamin K also plays a role in calcium metabolism. According to Vitamin Tolerances of Animals (NRC 1987), the dietary adequacy of vitamin K is often defined as the amount of the vitamin needed to maintain normal levels of plasma vitamin K-dependent clotting factors.

Poultry, such as broiler chickens and turkeys, are more likely to develop signs of vitamin K deficiency than other species of animals, which can be attributed to their short digestive tract and the fast rate of food passage. Ruminant animals such as cattle and sheep do not appear to need a dietary source of vitamin K under normal health conditions due to the microbial synthesis of this vitamin that occurs in rumen. However, a dietary source may be important in preruminant animals (e.g., calves and lambs). Since horses are herbivores, notwithstanding factors that may interfere with synthesis, absorption or

utilization their vitamin K requirements are typically met by consumption of vitamin K sources present in plants and from microbial synthesis in the lower gut. In comparison, omnivorous and carnivorous monogastrics such as swine, dogs, and cats, may be less efficient at gut synthesis as well as less likely to consume large quantities of vitamin K-containing plant materials than horses or ruminants.

Different sources of vitamin K_3, including those that are listed in the Association of American Feed Control Officials' Official Publication as accepted for use in animal feed, are broadly denoted as Vitamin K Active Substances (VKAS). There are two VKAS that are prior sanctioned for use in poultry feed. (Prior sanction means that these vitamin K active substances were used in poultry feeds prior to 1958, so they have a history of safe use, and they are the subject of a formal FDA sanction of the ingredient for a particular use; the sanction is generally in the form of a letter from FDA stating that the use is acceptable.) These prior sanctioned substances are menadione and menadione sodium bisulfite complex (MSBC). These two compounds are also widely used in other types of animal feeds, including pet foods, as animal nutritionists often formulate diets with vitamin K active substances in order to prevent vitamin K deficiencies.

Menadione dimethylpyrimidinol bisulfite and menadione nicotinamide bisulfite are vitamin K active substances that are regulated as food additives for use in animal feed. Federal regulation 21 CFR 573.620 lays out how menadione dimethylpyrimidinol bisulfite must be used in feed. Menadione dimethyl pyrimidinol bisulfite is a nutritional supplement for the prevention of vitamin K deficiency in chicken and turkey feeds at a level not to exceed 2 g per ton of complete feed, and in the feed of growing and finishing swine at a level not to exceed 10 g per ton of complete feed.

Menadione nicotinamide bisulfite is also used as a nutritional supplement for both the prevention of vitamin K deficiency and as a source of supplemental

niacin in poultry and swine. Federal regulation 21 CFR 573.625 states that this substance can be added to chicken and turkey feeds at a level not to exceed 2 g per ton of complete feed, and to growing and finishing swine feeds at a level not to exceed 10 g per ton of complete feed.

Substances with vitamin K activity are often added to animal diets to ensure that animals do not develop vitamin K deficiencies. Even though many vegetable sources, particularly leafy greens (e.g., spinach, kale, and collard) and cruciferous vegetables (e.g., broccoli and Brussels sprouts) contain fairly high amounts of vitamin K, very little is known about the actual bioavailability of the vitamin from these sources. According to Vitamin Tolerances of Animals (NRC 1987), based on the limited amount of available information, vitamin K did not result in toxicity when high amounts of phylloquinone, the natural form of vitamin K, are administered by oral or other means. In human nutrition, the Food and Drug Administration considers the inclusiion of commercially available phylloquinone (chemically synthesized, but identical to that naturally occurring in plants) not only to be "safe and suitable" for its intended use in infant formulas, but also a required component of all formulations (FDA, 1996). Although FDA does not expressly list or affirm this use of phylloquinone in infant formulas (or any other use) to be GRAS (Generally Recognized as Safe), an independent review of the available information did conclude that that phylloquinone, when manufactured in accordance with specifications set forth for use in infant formulas and other foods for human consumption, to be GRAS when fed at nutritional levels for its intended use in foods formulated for dogs and cats (Delaney and Dzanis, 2018),

It is also noted that menadione, the synthetic vitamin K usually used in animal feed, can be added up to levels as high as 1,000 times the dietary requirement without seeing any adverse effects in animals, except when used parentally in horses. Vitamin K and the vitamin K active substances serve important roles in providing an essential nutrient in animal diets.

A survey of the feed industry performed by the American Feed Industry Association found that
MSBC is added to the feed of the following species at the inclusion rates provided in the
following table. The broad use of MSBC in feed for all species has been a common practice for
over 15 years according to the records of one vitamin premix manufacturer.

Table 1 Typical Inclusion Levels

Species	**MSBC mg/Kg dry feed**
Broilers	6 - 8
Layers	6 - 10
Ducks	6 - 7
Geese	6 - 10
Quail, pheasants, partridge	4 - 8
Ostrich, Emu	4 - 8
Turkeys	6 - 8
Swine, grower/finisher	4 - 8
Swine, starter	10 - 12
Bovine calves	1 - 3
Cattle	1 - 5
Cervids	2 - 3
Sheep	0.5 - 1
Goats	0.3 - 1
Salmon & Trout	16 - 24
Tilapia & catfish	10 - 20
Shrimp	8 - 14
Tropical Fish	16 - 24
Horses	6 - 20
Rabbits	2 - 4
Mink	2
Small rodents	0.5 - 1
Dogs	3 -5
Cats	2 - 4

Review of Safety Studies

An important consideration when reviewing adverse effects of menadione and related compounds is the route of exposure; parenteral (especially intravenous) versus oral administration. As previously described, all vitamin K active substances have the same 2-methyl-1,4-napthoquinone ring as part of their chemical structure. Excess exposure of red blood cells (RBC) to menadione can cause methemoglobin formation *in vitro* by an oxidative reaction with hemoglobin with the formation of reactive oxygen species, often resulting in lysis (Winterbourn 1979, Chung 2001). Menadione has also been shown to exert oxidative stress in cells and cause lesions in multiple organs (including heart, lung and kidney) in rats following 5 intravenous injections of menadione at 100 and 150 mg/kg bodyweight, given every other day (Chiou 1997).

From NRC 1987:

> *The toxicity of menadione is undoubtedly not related to its role as a precursor for tissue synthesis of an active form of vitamin K but because of its chemical properties as a quinone.*

The adverse effects of menadione on RBCs (e.g., methemoglobinemia, Heinz Body anemia, hemolytic anemia) have been shown in clinical cases where menadione has been given by the intravenous route (Rebhun 1984, Maxie 1992, Fernandez 1984) with kidney damage and death reported in some animals.

Under experimental conditions, animals have been shown to tolerate great excesses of menadione when administered by the oral route, with extreme levels of menadione (when compared with nutritionally adequate levels) causing similar adverse effects to RBCs in animals as was observed *in vitro* as well as that seen when menadione was administered by the intravenous route.

In a repeated dose oral toxicity study, rats were provided by gavage 0 (control), 250, 350 or 500 mg/kg bodyweight menadione daily suspended in acacia gum for 30 days (Molitor 1940). The weight of the animals was recorded daily and blood was sampled at weekly intervals. Administration of menadione had no effect on the growth of the rats, and levels of up to 350 mg/kg bodyweight/day were not associated with any adverse effects on overall health. Menadione was reported by the authors to be lethal at 500 mg/kg bodyweight, with animals dying sporadically over the 30-day feeding period. No adverse effects on blood parameters were reported in rats provided 250 mg/kg bodyweight/day of menadione but a dose of 350 mg/kg bodyweight/day was associated with a notable decrease in erythrocyte count and hemoglobin concentrations (Molitor 1940). The apparent No-Observed-Adverse-Effect-Level (NOAEL) from this 30-day study was 250 mg menadione/kg bodyweight/day. Assuming the rats consumed 50 g DM (dry matter)/kg bodyweight/day (5% body weight as DM intake), the equivalent dietary level of menadione would equal 5,000 mg/kg DM food.

In a series of studies that were broad based but limited in design and detail, Ansbacher 1942 evaluated the acute and chronic oral toxicity of menadione in several different species, specifically mice, chickens, rats, rabbits, cats, dogs and monkeys. Acute oral toxicity studies were conducted in mice, chicks and rabbits and median lethal doses (LD50) of 620 mg/kg bodyweight, 804 mg/kg bodyweight and between 230 and 280 mg/kg bodyweight, respectively, were determined. Two cats were provided menadione daily at 2 mg/kg bodyweight orally for 72 days without adverse effects to blood parameters or tissue pathology. Two additional cats were given menadione daily orally at 50 mg/kg bodyweight for 13 days, again without adverse effects to blood or tissues. Assuming a cat consumes 15 -50 g DM/kg bodyweight/day (depending on life stage), the dose of 2 mg/kg bodyweight/day of menadione is equivalent to a dietary level of 40 -133 mg menadione/kg DM food. Similarly, the menadione dose level of 50 mg/kg bodyweight/day tolerated by cats for 13 days, equates to a dietary menadione

level of 1,000 mg/kg DM food. For comparison, the AAFCO Cat Food Nutrient Profiles consider 0.1 mg/kg DM of food as adequate for nutritional purposes.,

In an analogous study (Ansbacker 1942), two dogs were provided a daily 2 mg/kg bodyweight of menadione orally for 73 days with no reports of adverse effects. Assuming a dog consumes 15-40 g DM/kg bodyweight/day (depending on life stage), the menadione dose level of 2 mg/kg bodyweight/day tolerated by dogs over the 73-day period is equivalent to a menadione dietary level of 50 - 128 mg/kg DM food.

In other additional studies of menadione given orally (Ansbacher 1942), two 18-day old puppies provided daily with 40 or 80 mg/kg bodyweight of menadiol dipropionate (an alternative source of menadione) exhibited temporary anemia. When repeated oral doses of menadione were administered to rabbits, 28-36 daily doses of 4 mg/kg body weight were well tolerated. Also, monkeys (1/group) provided with 1 mg/kg bodyweight of menadione for 12 or 50 days did not exhibit any treatment-related effects.

The effects of menadione on the cardiovascular system of rats was evaluated in a study by Melgar et al. (1991). Sprague-Dawley rats received gradually increasing oral doses of menadione for 6 weeks, starting at 5 mg/kg bodyweight per day and increasing to 20 mg/kg bodyweight per day in the third week and 40 mg/kg bodyweight per day in the fifth week of treatment. An electrocardiogram, blood pressure change, and hematological analysis were performed in weeks 2, 4 and 6 as well as before and after treatment. At the end of the experiment, the hearts of 2 rats/group were processed for electron microscopy. Heart, spleen and liver weights were determined and subjected to histopathological examinations. The administration regime was generally well tolerated with no effects of menadione on growth or hematology parameters. Some alternations in blood pressure were reported as well as an increase in spleen weight.

Summary of Safety Review

Taken together, the available toxicological data indicate that under the conditions of intended use in the diet as a vitamin K active substance at levels consistent with the nutritional requirements of the animal, menadione and by extrapolation, MSBC is not expected to be associated with any adverse effects.

LD50 values of greater than 200 mg/kg bodyweight and up to 804 mg/kg bodyweight were determined for a range of different animal species. An apparent 30-day rat NOAEL of 250 mg menadione/kg bodyweight/day was shown, equal to dietary level of 5000 mg/kg DM.

By comparison, supplementation of the diet of cats with 0.1 mg menadione/kg DM food ("0.1 mg Vitamin K/kg DM in diets containing >25% fish on a DM basis. ", AAFCO 2021) is equivalent to an intake of approximately 2 µg/kg body weight/day. The NRC 2006 recommends the diets of adult dogs and growing puppies are supplemented with 22 µg and 44 µg menaquinone/kg bodyweight/day, respectively, well below levels tolerated in experimental diets. Similarly, 72- and 73-day feeding studies in cats and dogs, respectively, reported that intakes of 2 mg menadione/kg bodyweight/day were not associated with any adverse effects, which is around 1,000 time higher than the nutritional level of vitamin K supplementation in cats, and 90 and 45 times higher than for adult dogs and growing puppies, respectively. See Table 1 for typical use levels.

The primary adverse effects observed at high levels of oral supplementation with menadione in rats and other animals were decreases in red blood cell count and blood hemoglobin levels.

EFSA Review Summary:

The safety of MSB (identical to MSBC, but not complexed with additional bisulfite in the final product) and MNB for use as vitamin K active substances in feed for all animal species was evaluated by the European Food Safety Authority in 2014 (EFSA, 2014). On the basis that vitamin K1, K2 and K3 share a common metabolic fate in animals, EFSA considered the body of available published and unpublished absorption, distribution, metabolism and excretion (ADME) and toxicology data on all forms of vitamin K in its evaluation. Overall, EFSA concluded that acute toxicity of menadione or its derivatives is reached at levels exceeding the requirements of animals for vitamin K by a factor of at least 1,000, and therefore, MSBC and MNB does not pose a safety concern for target animals under practical conditions of use.

Conclusion

The expert panel recommended that Menadione Sodium Bisulfite Complex may be used as a safe and suitable source of Vitamin K activity in the food for all animals in the United States in accordance with good manufacturing and feeding practices.

Footnotes

1. Majority of content, unless specifically referenced, taken from (FDA 2008): https://www.fda.gov/animal-veterinary/safe-feed/vitamin-k-substances-and-animal-feed Accessed October 5, 2021.

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