1. Description of the Action

1.1. Action and Regulatory Authority

The Food and Drug Administration (FDA) is publishing a notice concerning the regulatory status of certain vitamin K active substances (VKAS) in animal feed. The notice states that some VKAS are required to be marketed under provisions of a food additive regulation.

On July 13, 1990, the United States District Court for the Eastern District of New York issued an order requiring FDA to publish a notice under 21 CFR 570.38, providing for the use of VKAS in accordance with one of the four alternatives listed in 21 CFR 570.38(c). Section 570.38 is a procedural regulation for determination of the food additive status of a substance that is added to animal feed.

The FDA has considered each of its alternatives and issues the notice accompanying this environmental assessment to state that the marketing of VKAS, other than menadione or MSBC for use in poultry feed at 2 to 4 grams per ton and MPB, as covered by Section 573.620 for use in poultry and swine feed, is required to be done under provisions of a food additive regulation.

The action taken in the notice is not a rule or regulation, but instead a declaratory order to terminate controversy or to remove uncertainty about the regulatory status of certain VKAS. This environmental assessment therefore attempts to evaluate the potential environmental consequences of the change in regulatory status of VKAS products.

1.2. Purpose and Need for the Action

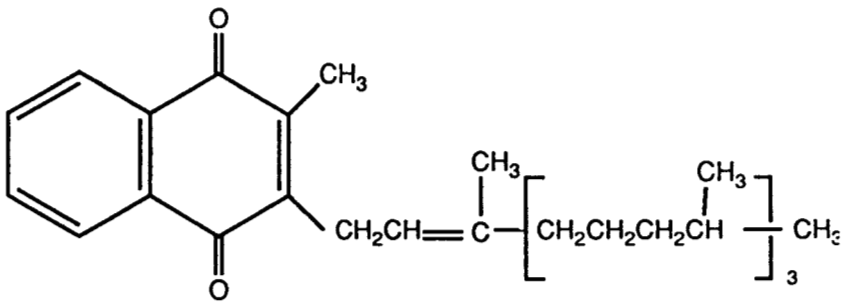
This action is the result of a district court decision resulting from a lawsuit filed by Heterochemical Corporation following publication by FDA of a notice in 1983 (48 FR 16748, April 19, 1983), concerning the regulatory status of VKAS. In the 1983 notice, FDA concluded that none of the VKAS about which it had knowledge were GRAS, but that two VKAS -- menadione and MSBC -- were prior-sanctioned at 2 to 4 grams per ton of poultry feed. Additionally, the agency concluded that it would not propose the issuance of food additive or GRAS affirmation regulations at that time. This decision was based upon

its conclusion that VKAS had been added to animal feed for more than 30 years without apparent animal or human safety problems and its assessment that regulating these substances further was of low priority, given the FDA's resources.

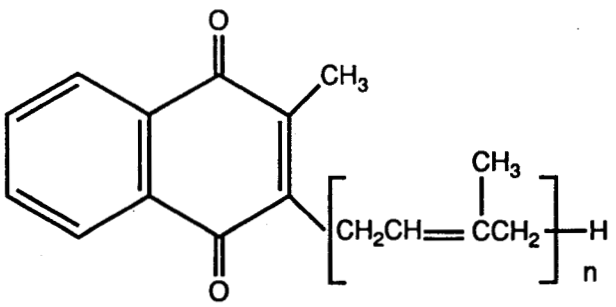
The 1990 district court decision in favor of Heterochemical requires FDA to formalize the regulatory status of VKAS promptly.

2. Environmental Consequences of the Proposed Action

The term vitamin K is used as a generic descriptor for the compound 2-methyl-1,4-napthoquinone and all 3-substituted derivatives which exhibit antihemorrhagic activity in animals fed a vitamin K deficient diet. These include vitamin K_1, also called phylloquinone (2-methyl-3-phytyl-1,4-naphthoquinone), and menaquinone (2-methyl-3-*all-trans* - polyprenyl-1,4-naphthoquinones) or vitamin K_2. The menaquinones, which act as electron carriers in bacteria (Bently and Meganathan, 1982), represent a series of bacterially synthesized compounds in which the phytyl side chain of phylloquinone has been replaced by a side chain of from two to 12 prenyl units (Collins and Jones, 1981). The predominant vitamins of the menaquinone series contain a side chain of from six to ten prenyl units. The parent compound of the vitamin K series is 2-methyl-1,4-napthoquinone, a synthetic lipid soluble product which was once called vitamin K_3 but is now designated as menadione. Water soluble derivatives of menadione, which are used in animal feeds, are known as Vitamin K Active Substances (VKAS).



Phylloquinone: Vitamin K_1



Menaquinone: Vitamin K_2

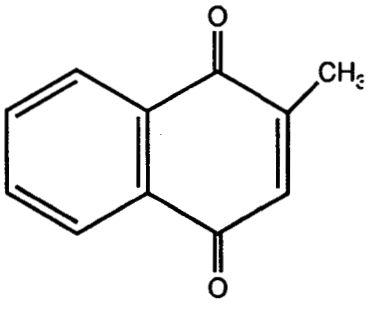
The pharmacological action of vitamin K is related to its normal physiological function, that is, to promote the hepatic biosynthesis of vitamin K dependent blood clotting factors: prothrombin (factor II), proconvertin (factor VII), plasma thromboplastin component (PTC, Christmas factor, factor 9) and the Stuart factor (factor X) (Cohn, 1975). In the absence of adequate levels of vitamin K or in the presence of vitamin K antagonists, animals develop bleeding disorders. These disorders result from an inability of a liver microsomal enzyme (vitamin K dependent-carboxylase) to carry out the post-translational conversion of specific glutamyl residues in the vitamin K dependent plasma proteins to gamma-carboxyglutamyl resides. These residues are essential for the normal Ca^{++}- dependent interactions of the vitamin K-dependent clotting factors with phospholipid surfaces. Insufficient vitamin K to serve as a cofactor for this enzyme results in a decreased rate of thrombin generation. This decrease subsequently results in a decreased rate of fibrin clot formation and an increased susceptibility to hemorrhage (National Research Council, 1987).

2.1. Uses and Magnitude of Uses for VKAS for Which Marketing Would Cease

2.1.1. VKAS for Which Marketing Would Cease

Marketing would cease for MSB and for all non-approved uses of menadione, MSBC and MPB. These include:

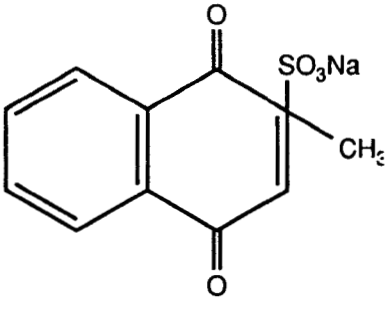
Menadione



Discontinued for all uses other than poultry feed supplementation at 2-4 grams/ton.

CAS Name: 2-Methyl-1,4-naphthalenedione; 2-methyl-1,4-naphthoquinone
CAS #: 58-27-5
Mol. Wt.: 172.17
Structural formula: $C_{11}H_8O_2$
Physical description: Bright yellow crystals. Very faint acrid odor. Stable in air. Decomposes in sunlight. Insoluble in water. Soluble in oil. A synthetic derivative of naphthoquinone having physiologic properties of Vitamin K.

Menadione sodium bisulfite (MSB)



Discontinued for all uses.

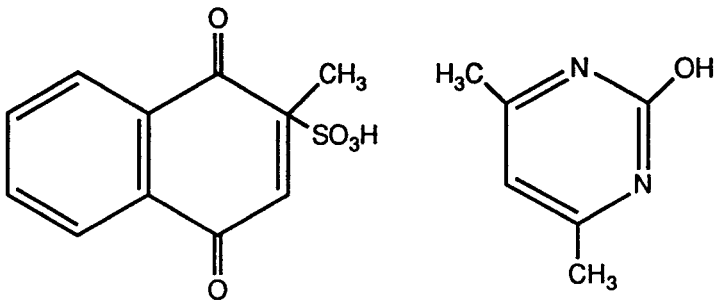
CAS Name: 1,2,3,4-tetrahydro-2-methyl-1,4-dioxo-2-naphthalenesulfonic acid sodium salt
CAS #: 130-37-0
Mol. Wt.: 276.24
Formula: $C_{11}H_9NaO_5S$
Physical Description: Trihydrate, white hygroscopic crystals. Solubility: 1 g/ 2 ml H_2O.
AAFCO Definition: The addition product of menadione and sodium bisulfite containing not less than 50% of menadione (AAFCO, 1990).

Menadione Sodium Bisulfite Complex (MSBC)

Discontinued for all uses other than poultry feed supplementation at 2-4 grams/ton.

Menadione sodium bisulfite plus sodium bisulfite (National Research Council, 1987).
AAFCO Definition: The addition product of menadione and sodium bisulfite containing not less than 30% of menadione (AAFCO, 1990).

Menadione Dimethylpyrimidinol Bisulfite (MPB)



Discontinued for all uses except for the following approved uses: Poultry at 2 grams/ton feed and swine at <10 grams/ton feed (21 CFR 573.620).

CAS Name: 1,2,3,4-tetrahydro-2-methyl-1,4-dioxo-2-naphthalenesulfonic acid compound with 4,6-dimethyl-2(1H)-pyrimidinone (1:1).
CAS #: 14451-99-1
Mol. Wt.: 378.40
Formula: $C_{17}H_{18}N_2O_6S$
Physical description: Crystal powder. Solubility: approx. 1 g/100 ml H_2O.
AAFCO Definition: Crystalline menadione dimethylpyrimidinol bisulfite -commercial feed grade (AAFCO, 1990).

In addition, except for the approved compounds and uses listed in section 2.2.1, marketing would cease for all other vitamin K active substances.

2.1.2. Uses and Magnitude of Uses

VKAS are currently primarily incorporated into poultry and swine rations (Madsen and Atwater, 1977). In addition, many prepared foods and feeds are supplemented with VKAS. These include feeds for horses, cattle, fish, mink and domestic pets such as dogs and cats. We have no reliable estimate of the magnitude of VKAS use for which marketing would cease.

2.2. Uses and Magnitude of Uses for Approved VKAS

2.2.1. Approved VKAS

Menadione
Approved use: Poultry at 2-4 grams/ton (prior-sanctioned).

Menadione Sodium Bisulfite Complex (MSBC)
Approved use: Poultry at 2-4 grams/ton (prior-sanctioned).

Menadione Dimethylpyrimidinol Bisulfite (MPB)
Approved uses: Poultry at 2 grams/ton feed and swine at <10 grams/ton feed (21 CFR 573.620).

2.2.2. Uses of Approved VKAS

A limited number of vitamin K active substances are currently available for supplementation of animal feeds. Vitamin K activity is exhibited by a number of naturally occurring and synthetic compounds which exhibit varying degrees of solubility in lipids and water. Two naturally occurring forms are phylloquinone or vitamin K_1 and menaquinone or vitamin K_2. Vitamin K_1 occurs naturally in green plants whereas vitamin K_2 is present in micro-organisms and is synthesized by intestinal bacteria. The structural core of vitamin K is menadione which is formed naturally in the gastrointestinal tract by microbial enzymatic cleavage of the side chains of menaquinone or phylloquinone (Madsen and Atwater, 1977). Menadione is a fat soluble compound that can be considered as the reference standard for vitamin K activity (Griminger, 1966). However, menadione is a strong skin and mucous membrane irritant, is decomposed by sunlight (Merck Index, 1989) and UV light (Madsen and Atwater, 1977) and has a short half-life in animal feeds and thus is not very suitable for feed usage. Because of the expense, chemical instability and lipophilic characteristics of phylloquinone and the menaquinones and the short half-life of menadione in animal feeds, various water soluble forms of menadione are the predominant sources used in animal feed supplementation. Water-soluble forms with improved handling and stability characteristics include MSB, MSBC and MPB. These are the predominate synthetic vitamin K forms used in animal feeds (Madsen and Atwater, 1977). The theoretical activity of these compounds can be calculated on the basis of the proportion of menadione present in the molecule and

water solubilities (National Research Council, 1984a). The requirements for most nonruminant animals ranges from 1 to 10 ug vitamin K/kg of BW/day (50-150 ug/kg of diet), and 50 to 250 ug/kg of BW/day (0.5-1.5 mg/kg of diet) for poultry (National Research Council, 1987).

2.2.2.1. Poultry

Vitamin K requirements of poultry are met primarily by dietary intake. Contrary to most animals poultry have a limited ability for intestinal synthesis and although small amounts of vitamin K_2 may be microbially synthesized in the gut, adequate dietary supplies are of greater importance (Hoffmann-La Roche, 1989). Poultry fed a ration deficient in vitamin K may bleed to death from even slight injury with hemorrhages occurring subcutaneously, intramuscularly or internally (National Research Council, 1984). Mature birds are not as susceptible to acute vitamin K deficiency and chicks showing prolonged clotting time as a result of vitamin K deficiency generally recover spontaneously, provided hemorrhaging is not induced and sufficient levels of vitamin K are available in the feed. It has been shown that breeders fed a diet low in vitamin K may produce eggs that are low in the vitamin. Chicks hatched from such eggs will have low reserves of vitamin K and as a consequence may bleed to death from slight injury (Hoffmann-La Roche, 1989).

Antibacterials in the diet may also suppress intestinal bacteria that synthesize vitamin K and thus the bird may be entirely dependent on the vitamin supplied in the diet. Additionally, arsanilic acid has been shown to increase the need for dietary vitamin K in both breeder and broiler chicken diets (National Research Council, 1984a).

2.2.2.2. Swine

Natural vitamin K present in swine rations and the bacterial synthesis of vitamin K_2 and subsequent absorption, either directly or by coprophagy, often reduces or eliminates the need for supplemental dietary vitamin K. However, the use of rations deficient in vitamin K and use of high levels of antibiotics in the feed, which may act to decrease the level of intestinal vitamin K being synthesized, often make the use of supplemental vitamin necessary. Additionally, hemorrhagic conditions have been observed under field conditions and after the ingestion of mycotoxin-contaminated feeds (National Research Council, 1988).

2.2.3. Magnitude of Use for Approved VKAS

An estimate of the maximum yearly production of menadione and menadione salts which are approved for use in poultry and swine rations is determined by multiplying recommended vitamin K supplement levels by yearly primary feed production levels for poultry and swine (Appendix). Sources for vitamin K supplement levels include: the National Resource Council which provides estimates of the nutrient requirement of domestic animals; Hoffmann-La Roche, a major producer of animal feed supplements; and the permitted use levels as authorized by the FDA. The following tables provide estimates of the yearly production for the approved uses of menadione, MSBC and MPB.

ESTIMATED YEARLY PRODUCTION OF TOTAL VITAMIN K AS MENADIONE

Poultry

National Research Council (1984a):	2.52×10^7 kg
Hoffmann-La Roche (1989):	6.87×10^7 kg
FDA:	1.91×10^8 kg

ESTIMATED YEARLY PRODUCTION OF TOTAL VITAMIN K AS MSBC

Poultry

National Research Council (1984a):	8.94×10^7 kg
Hoffmann-La Roche (1989):	2.08×10^8 kg
FDA :	1.91×10^8 kg

ESTIMATED YEARLY PRODUCTION OF TOTAL VITAMIN K AS MPB

Poultry

National Research Council (1984a):	6.32×10^7 kg
Hoffmann-La Roche (1989):	1.51×10^8 kg
FDA :	9.55×10^7 kg

Swine

National Research Council (1988):	6.45×10^6 kg
FDA:	1.29×10^8 kg

It can be concluded from the above analysis that FDA permitted use levels for menadione, menadione sodium bisulfite complex and dimethylpyrimidinol bisulfite are comparable to, or larger than, levels recommended by the National Research Council and Hoffmann-La Roche. We expect actual usage to be between these values. Since the supplementation of swine and poultry feeds with VKAS will continue to be permitted, no decrease in usage is expected for these applications once the action is in force. However, the total amount of VKAS in use would initially decrease since usage in other feeds and foods would be discontinued.

2.3. Uses of VKAS for Which Substitute VKAS Products Would Not Be Available

Although VKAS are used in a variety of feeds, the importance of these additives has either not been established or VKAS are not required for most species. It has been difficult to clearly demonstrate and to measure vitamin K requirements for many species. A dietary deficiency of vitamin K is unlikely to occur because the vitamin is fairly well distributed in foods and considerable amounts of vitamin K_2 are synthesized by intestinal microorganisms which is subsequently absorbed (Martin, 1983a). Additionally, vitamin K present in fecal material is ingested by animals which are coprophagic.

Ruminants do not appear to need a source of vitamin K in their diet because the vitamin is synthesized by rumen microorganisms in sufficient quantities that is subsequently utilized (National Research Council, 1987). The needs of most dairy cattle with the exception of young calves is met by rumen microbial synthesis of vitamin K_2 (National Research Council, 1989). The requirement for young calves is usually adequately met through vitamin K levels in milk supplied to the calf during early lactation. Vitamin K in pasture and green roughage and/or that is synthesized in the rumen effectively fulfils the requirement for beef cattle (National Research Council, 1984b). The only practical deficiency in cattle occurs in the "sweet clover disease" syndrome. This results from the antagonistic action of dicoumarol that is formed in moldy sweet clover hay. Dicoumarol leads to prolonged blood clotting times and has been responsible for animal deaths from uncontrolled hemorrhages. Immediate correction of the ensuing hypoprothrombinemia and anemia can be accomplished by the administration of whole blood from a healthy animal. The preferred treatment for severely affected animals is treatment with i.m. doses of vitamin K_1 (Merck Veterinary Manual, 1986). A need for dietary supplementation of vitamin K for sheep has not been demonstrated (National Research Council, 1985).

Although vitamins K and VKAS are incorporated into a variety of foods and feeds as described in section 2.1.2., the need for supplemental vitamin K in the diet of animals has not been demonstrated except for swine and poultry. The Merck Veterinary Manual (1986) and National Research Council 'Nutrient Requirements of Domestic Animals' publications do not stipulate dietary supplementation of vitamin K for any of the following animals: dogs, cats, horses, rabbits, beef cattle, dairy cattle, goats, sheep and mink as long as the animals are receiving properly balanced diets.

For conventionally reared laboratory animals, vitamin K is generally not added to natural-ingredient diets. However, vitamin K supplementation may be required for laboratory animals such as rats, gerbils, mice, guinea pigs, hamsters, voles and fishes, which are being maintained on purified and chemically defined diets (National Research Council, 1978). The degree of supplementation is dependent on the amount of vitamin K which is synthesized by the intestinal microbiota of the animal. Thus, variations in diet and experimental treatments that influence intestinal synthesis lead to variable nutrient requirements. For example, animals that ordinarily practice coprophagy may need supplementary vitamin K when this source is made unavailable. Moreover, animals maintained in germ-free, gnotobiotic or specific pathogen-free (SPF) environments, or on antibacterial drugs, may have limited kinds and numbers of intestinal organisms which may have effects on the required dietary concentration of nutrients.

The need for vitamin K supplementation and the use of VKAS in aquaculture is unclear. Knowledge of the vitamin requirements of fish is very limited. A specific need for vitamin K has been demonstrated for trout (National Research Council, 1981), however, no dietary requirement for vitamin K could be demonstrated under experimental conditions for common carp (National Research Council, 1984). Compared with most mammals, the gastro-intestinal tract of fish does not contain a typical pattern of established microorganisms and therefore it cannot be assumed that fish obtain vitamin K from the intestinal microbiota. It appears that in extensive culture and low-density intensive culture, fish are able to meet their dietary requirements from natural foods (National Research Council, 1981; 1984). However, vitamin supplementation may be required under intensive high density culture such as in heavily stocked ponds, or in cages or races where waters are low in natural feeds.

Alternative vitamin K sources are available for incorporation into laboratory animal and fish diets. For both fish and laboratory animals natural feeds with high vitamin K levels can be utilized. Knowledge of the dietary requirements of the animal in question and of the nutrient

content of available feedstuffs can be used to formulate a diet which provides all of the essential nutrients without supplementation.

For animals involved in research, the use of natural-ingredient diets may not be compatible with the experiment and vitamin supplementation may be required. The use of vitamin K_1 and/or vitamin K_2 supplementation of such diets may ensue even though these compounds do not have GRAS or FAP status. Although these sources may be more expensive on a weight basis, vitamin K_1 is considered to be approximately 10 times more active than menadione or menadione derivatives (National Research Council, 1978).

If such feed formulation changes are inconvenient for any segment of the animal industry, a food additive or GRAS affirmation petition for any important use of VKAS can be prepared and submitted to the FDA.

2.4. Environmental Impact of Substitutions of VKAS

2.4.1. Introductions Into the Environment Through Manufacturing and Use

2.4.1.1. Introductions Due to Manufacturing

All the vitamin K active substances discussed here are menadione (2-methyl-1,4-napthoquinone) derivatives and therefore share similar chemical synthesis pathways:

Menadione is prepared by the oxidation of 2-methylnaphthalene by chromic anhydride under acid conditions (Merck Index, 1989). Menadione sodium bisulfite is prepared by the reaction of menadione with sodium bisulfite in the presence of sodium bicarbonate (Moore and Kirchmeyer, 1945). Menadione sodium bisulfite (bisulfite adduct of 2-methyl-1,4-napthoquinone) can also be synthesized by a one-step method. The adduct is produced in an alcoholic medium by the reaction of sulfurous acid with 2-methyl-naphthoquinone dissolved in an alcohol while maintaining pH value between 1.5 and 5 with the simultaneous addition of an aqueous sodium hydroxide solution (Pomot, 1986).

Menadione dimethylpyrimidinol bisulfite is prepared from urea, acetylacetone and menadione sodium bisulfite. Urea, concentrated sulfuric acid and H_2O are added to acetylacetone, the mixture is stirred and an aqueous solution of menadione sodium bisulfite is added. The precipitate is collected, washed with H_2O and dried at 50°C to give menadione

dimethylpyrimidinol bisulfite (Madjar, 1967; Nanninga, 1969). Menadione sodium bisulfite is stabilized by an excess of sodium bisulfite to prepare menadione sodium bisulfite complex which consists of approximately 63% menadione sodium bisulfite and 37% sodium bisulfite or a molar ratio of menadione sodium bisulfite to sodium bisulfite of approximately 1:2 (Boehme, 1970).

Any of the added reagents and reactants named in the synthesis of VKAS could be potentially released in wastewater. Because the FDA has not regulated these materials through a food additive petition since the advent of environmental information requirements, FDA does not have any information on the pollutants that are released or discharged in the workplace or into the environment.

2.4.1.2. Introduction Through Use in Target Animals

2.4.1.2.1. Absorption and Metabolism of VKAS by Target Animals

The lipid soluble vitamins K (phylloquinone and menaquinone) are absorbed from the gastrointestinal tract in the presence of bile salts and pancreatic juices (Olsen, 1980). Menadione and its water soluble derivatives are absorbed even in the absence of bile directly into the blood stream. In the gastrointestinal tract, microbial enzymatic cleavage of the side chains of menaquinone or phylloquinone can also occur to yield free menadione (Madsen and Atwater, 1977). Once absorbed, hepatic enzymes in mammalian and chicken microsomes have been shown to alkylate menadione to active forms of the vitamin. Menaquinone-4 appears to be the predominant species formed (National Research Council, 1987: Olsen, 1980). Experiments have demonstrated that menadione is converted in the animal to the menaquinone series. For example, labeled menadione was converted to menaquinone-4 in the rat and vitamin K biological activity depended on this conversion (Taggart and Matschiner, 1969). The conversion of menadione to menaquinone has also been demonstrated in birds (Olsen, 1980). Water-soluble forms of menadione, such as MSB,MSBC and MPB are similarly converted in the body to menadione (Cohn, 1975; Hoffmann-La Roche, 1976).

Menadione is rapidly metabolized and excreted. Phosphate, sulfate and glucuronide conjugates of menadiol have been identified in the urine (National Research Council, 1987). Moreover, one report indicates that only a small percentage of menadione (0.05-1.0%) is

converted to the active vitamin, menaquinone-4 (Olsen, 1980). Thus, although menadione is well absorbed, it is apparently poorly retained in the body (Griminger, 1966).

2.4.1.2.2. Catabolism of 2-Hydroxy-4,6-Dimethylpyrimidine from MPB

MPB would be expected to replace some restricted uses of VKAS. MPB contains in addition to menadione, a pyrimidine moiety. Such pyrimidine bases which occur predominantly in nucleotides are important intracellular molecules of low molecular weight which participate in a wide variety of biochemical processes (Martin, 1983). The best known role of the pyrimidine nucleotides is to serve as the monomeric precursors of RNA and DNA. The three major bases found in the nucleotides of both prokaryotes and eukaryotes are cytosine, thymine and uracil. The pyrimidine base which most closely approximates 2-hydroxy-4,6-dimethylpyrimidine is the lactim form of thymine (2,4-dihydroxy-5-methylpyrimidine). Additionally, substituted bases are found in the nucleic acids of bacteria and viruses and in transfer RNA of both prokaryotes and eukaryotes. The catabolism of pyrimidines occurs mainly in the liver and results in the production of highly soluble end products. In most species pyrimidines are degraded to urea and ammonia. They may also be utilized as precursors in the biosynthesis of B-alanine (Lehninger, 1975; Martin, 1983). Although the FDA lacks specific information for the metabolic fate of the pyrimidine in MPB, it is reasonable to speculate that its fate is similar to other substituted pyrimidines.

2.4.2. Environmental Fate of Introduced Substances

The metabolic fate of menadione and menadione salts appears to take two major pathways. Menadione is either transformed to menaquinone and utilized as active vitamin K in the animal body, or is rapidly metabolized and excreted as phosphate, sulfate and glucuronide conjugates of menadiol (National Research Council, 1987). The conjugates appear to be the primary forms that reach the environment through animal wastes and are available for further metabolism by soil and water microorganisms. Such conjugates would be expected to readily hydrolyze in the environment to yield free menadione. Because menadione salts are unstable in the presence of heat, moisture and trace minerals (Hoffmann-La Roche, 1989; Nanninga, 1969), water-soluble menadione salts that enter the environment would be expected to decompose into free menadione and sodium bisulfite or dimethylpyrimidinol. Additionally, menadione is decomposed by sunlight (Merck Index, 1989) and UV light (Madsen and Atwater, 1977) and would be expected to degrade on soil surfaces. There is

little information available on the mechanisms by which substances with vitamin K activity, and specifically menadione, are taken up by bacterial cells and the subsequent transformations that occur. Experimental results show menadione [(methyl-^{14}C) menadione] to be incorporated into bacterial menaquinones by *Aerobacter aerogenes , Bacillus megaterium, Bacteriodes melaninogenicus, Staphylococcus aureus* and other microorganisms (Bently and Meganthan, 1982). Other bacteria with vitamin K requirements have been shown to be capable of fulfilling this need when grown in the presence of menadione. Additionally, the incorporation of vitamin K as menadione is recommended for broth medium prepared for the isolation of anaerobes from various clinical specimens (Bently and Meganthan, 1982).

As discussed above, the dimethylpyrimidinol salt of MPB would be expected to degrade to urea and ammonia in the animal body and excreted as such. The pyrimidine moiety may also be utilized as precursors in the biosynthesis of B-alanine (Lehninger, 1975; Martin, 1983). We speculate that the free pyrimidine moiety in the environment would be readily utilized or degraded by microorganisms present in soils, waters and waste.

Menaquinones and menaquinone excretory products are expected to be degraded or utilized readily by soil and water bacteria. Menaquinones are synthesized and excreted by bacteria and the metabolic pathways are well described (Bently and Meganthan, 1982).

2.4.3. Environmental Effects

2.4.3.1. Occupational Safety of Menadione and Derivatives

Menadione is irritating to mucous membranes, the respiratory tract and to the skin and a solution of it in alcohol is a vesicant (Hoover, 1975). Menadione can induce hemolysis in individuals who have a glucose-6-phosphate dehydrogenase deficiency in their erythrocytes (Cohn, 1975). When menadione is heated to decomposition it emits acrid smoke and fumes and menadione sodium bisulfite emits toxic fumes of SO_x (Sax, 1984).

2.4.3.2. Animal Toxicity

Phylloquinone and menaquinone are nontoxic to animals even when given in large doses. For example, mice receiving a single oral dose of 15-25 g phylloquinone/kg BW showed no adverse effects (Molitor and Robinson, 1940). The administration of large doses of menadione and its derivatives to animals has resulted in the production of anemia,

polycythemia, splenomegaly, renal and hepatic damage and death (Cohn, 1975). The LD_{50} for a single oral dose is 600 to 800 mg/kg of BW for chicks and mice (National Research Council, 1987). Menadione has a reported mouse dermal toxicity (TDLo) of 1860 mg/kg BW and an oral-mouse lethal dose (LD_{50}) of 1250 mg/kg BW. Menadione sodium bisulfite has a reported oral-mouse LD_{50} of 1250 mg/kg BW (Sax, 1984).

The toxicity of menadione is not related to its role as a precursor for tissue synthesis of an active form of vitamin K, but due to its chemical properties as a quinone. The basis for the adverse reactions is not clear but is thought to be related to an influence on cellular redox state or sulfhydryl metabolism (National Research Council, 1987).

From the limited amount of information available on the toxicity and metabolic fate of VKAS it appears that all the menadione-based VKAS have similar potential for toxic effects in the environment. Given the low exposures that would occur in animal wastes and the probable degradation of these residues, the potential for adverse effects on exposed organisms in the environment appear to be low and similar for all VKAS. As the available information is very limited, considerable extrapolation is required. More information is needed to better define the magnitude of effects and the potential differences among the various VKAS.

3. Mitigation Measures

The action to require FDA pre-market approval of certain VKAS prior to further marketing may result in a shift in products used in animal feeds as sources of vitamin K activity; including use of MPB, natural vitamin K substances, or the inclusion of feed ingredients, like alfalfa, that are a good source of plant-produced vitamin K. While this shift may be inconvenient, and possibly more costly, there do not appear to be any adverse environmental effects associated with the change which require mitigation.

Manufacturing sites producing affected VKAS should be able to shift fairly easily to approved forms, assuming there are no patent infringement issues. Based on the limited information available to FDA on the manufacture of these substances, the procedures used are very similar. If the restricted VKAS are important for certain uses about which FDA does not have enough information, it should be possible to gather information to support those uses in either a GRAS affirmation or food additive petition.

4. Regulatory Alternatives to the Action

As stated in the notice that this EA accompanies and in Section 1, above, the FDA has four alternatives that may or may not apply to this situation.

First, the FDA could issue a food additive regulation that would permit the use of some or all of the VKAS that would be restricted by the declaratory order. Unfortunately, the FDA does not have in its possession enough information to meet the statutory requirements for such an order. FDA does not know all the ingredients and stabilizers used in the unapproved VKAS products, and therefore cannot show that the various products are safe. In fact, FDA does not know all the companies who may manufacture or re-formulate VKAS or even all the VKAS types in use.

Second, an interim regulation is also not a viable option because such a regulation is for those situations where *new* data raise questions about a substance's safety or functionality. We have no such data.

Third, the FDA could take the action that is described in the declaratory order, that is, requiring the approval of either a food additive petition or a GRAS affirmation petition for each of the unapproved VKAS.

Fourth, a combination of one, two or three above, is not feasible, since only alternative three can be supported with the information currently available to the FDA.

No action, which is ordinarily required to be considered by the Council on Environmental Quality regulations, 40 CFR 1500-1508, when preparing an environmental assessment, is also not feasible. FDA was ordered by a District Court to take one of the four alternatives described above, as detailed in 21 CFR 570.38(c). It should be noted that FDA attempted a no action alternative in 1983 (48 FR 16748), by not proposing the issuance of food additive or GRAS affirmation regulations at that time. It was this "no action" decision that was overturned by the district court. "No action" is the state of affairs prior to this declaratory order, however, and is the baseline for comparisons for potential environmental effects throughout this environmental assessment.

5. Comparative Analysis of the Action and Regulatory Alternatives

As discussed in 4. above, there does not appear to be any regulatory alternative other than the declaratory order that will satisfy the legal requirements with which the FDA must comply. Comparison will be made between the declaratory order and no action for gauging possible environmental impact.

The products affected by this order will, at least temporarily, not be approved for the uses in animal feeds. They will be replaced, in all probability, by MSBC, MPB, and natural sources of vitamin K. MSBC and MPB are both salts of menadione, just as are the restricted products. Their manufacture all seem to be similar, as do their metabolism and excretion by animals. Consequently, the FDA does not expect that there will be any significant change in the introduction of VKAS-related residues into the environment as the result of the declaratory order. VKAS and feed manufacturers may shift from affected products to the approved products and it is anticipated that their use will be in similar quantities and the environmental effects due to the shift in products will be small, if any.

6. List of Preparers

Dr. Raanan A. Bloom co-authored the Environmental Assessment. He has recently joined CVM's Environmental Sciences Staff as an Environmental Scientist. He holds a Bachelor of Science Degree in Nutrition and Food Science (1982) and a Master of Science Degree in Environmental Science (1985), both from Drexel University, Philadelphia, PA. He received a Ph.D. in Soil Microbiology (1988) from Rutgers University, New Brunswick, NJ. Prior to joining the FDA, he completed a postdoctoral fellowship in the Department of Soil, Crop and Atmospheric Sciences at Cornell University, Ithaca, NY, under a training grant from the National Institute of Environmental and Health Sciences.

Mr. John C. Matheson III co-authored the Environmental Assessment and assisted in the editing of the document. He has been the Chief of the CVM Environmental Sciences Staff since 1980 and is currently the acting Director of the Division of Toxicology and Environmental Sciences. He has served with the FDA as an environmental scientist since 1975. He holds a Master of Science Degree in Public Health (1975) and a Bachelor of Science Degree in Biology, both obtained from the University of North Carolina, Chapel Hill, where he studied in the Department of Environmental Sciences and Engineering and the Department of Biology.

7. Limited Information

The information used to prepare this EA is extremely limited. The Center lacks resources to carry out studies to provide data that are not available from the scientific literature or from information supplied by applicants. Where information is incomplete or unavailable, and assumptions, estimates, and calculations have been necessary, these have been so identified. Information used to support this environmental assessment has been gathered and evaluated in compliance with guidance on incomplete or unavailable information contained in the Council on Environmental Quality's regulations for implementing the procedural provisions of the National Environmental Policy Act (40 CFR 1502.22).

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Appendix:

VITAMIN K (MENADIONE) REQUIREMENTS FOR POULTRY

1. National Resource Council Recommendations (1984a)

Chickens:	mg menadione/kg diet
Growing (0-20 weeks) birds, Laying and Breeding Hens:	0.50
Broilers (0-8 weeks):	0.50
Turkeys:	
0-8 weeks (male, female):	1.0
8-24 weeks (male):	0.8
8-20 weeks (female):	0.8
Holding birds:	0.8
Breeding Hens:	1.0
Geese:	
No requirement listed	
Ducks (Pekin):	
Starting (0-2 weeks), Growing (2-7 weeks), Breeding:	0.4
Japanese Quail:	
Starting, Growing and Breeding:	1.0

2. Hoffmann-La Roche Recommendations (1989)

Chickens	
Starting (0-8 weeks; Broilers, Roasters):	2.0
Growing (8-18 weeks; Replacements):	1.1
Laying Hens:	1.1
Breeding Hens (Broiler and Layer):	2.0
Turkeys	
Starting (0-8 weeks):	1.2
Growing Turkeys (8 weeks-market):	0.9
Turkey Breeders:	1.4

VITAMIN K (MENADIONE) REQUIREMENTS FOR SWINE

1. National Resource Council Recommendations (1989)

Live Weight (kg)	mg menadione /kg diet
1-5	0.5
5-10	0.5
10-20	0.5
20-50	0.5
50-110	0.5

PRIMARY FEED PRODUCTION

Source: Feedstuffs 1990 Reference Issue (1990)

Type of Feed	kg Feed
Starter/grower/layer/breeder:	1.23×10^{10}
Broiler:	2.38×10^{10}
Turkey:	7.11×10^{9}
Swine:	1.29×10^{10}

VITAMIN K (MENADIONE) INCORPORATED INTO FEED

1. National Resource Council Recommendations (1984a)

	mg menadione/kg diet	kg menadione
Chickens (Starter, grower, layer, breeder, Broiler):	0.5	1.80×10^{7}
Turkey:	1.0	7.11×10^{6}
Swine:	0.5	6.47×10^{6}
Total:		3.16×10^{7}

2. Hoffmann-La Roche Recommendations (1989)

	mg menadione/kg diet	kg menadione
Chickens (Starter, grower, layer, breeder, Broiler):	1.50 (Ave)	5.96×10^{7}
Turkey (Starting, Grower, Breeder):	1.16 (Ave)	9.07×10^{7}
Total:		6.87×10^{7}

CONVERSION FACTORS (Hoffmann-La Roche, 1989)

Menadione Salt	Menadione Activity
MSBC	33%
MPB	45.4%